The Ability of Functional Magnetic Resonance Imaging Responses to Alcohol and Different Emotional Challenges to Predict Escalating Drinking in Different At-Risk Individuals

Malak Abu Shakra

Department of Psychology
McGill University
Montreal, Canada

October 2016

A thesis submitted to McGill University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

To those who live with doubt in the service of understanding.

Abstract

Alcohol use disorders (AUDs) are among the top two most prevalent psychiatric conditions in the Americas. Their expression is complex and their developmental pathways are varied. Understanding how individual differences in these pathways lead to the full pathology is imperative for designing and implementing effective therapeutic and preventative interventions. To investigate these pathways to alcohol use disorders, we studied healthy young adult male and female social drinkers who scored high in either sensation-seeking or anxiety-sensitivity traits. All subjects had two functional magnetic resonance imaging (fMRI) sessions following the ingestion of either ethanol (g/kg) or placebo given in a double-blind, counter-balanced repeated-measures design. During both sessions, subjects underwent an emotional challenge paradigm consisting of the Face Emotion Processing Task (FEPT) and the Montreal Imaging Stress Task (MIST). Behavioral (performance), subjective mood, and endocrine response profiles were assessed throughout. Two to three years later, subjects were re-contacted and clinically assessed for substance use and mental health status. Seven propositions were made and defended: (1) anxiety sensitive subjects (ASSs) were hyper-vigilant toward facial stimuli signaling threat, whereas sensation seeking subjects (SSSs) were hypo-responsive or unresponsive to these stimuli; (2) the social evaluative component of the MIST procedure induced arousal and a threat to social standing in ASSs, especially males, whereas in SSSs, particularly males, it was perceived primarily as a stimulating challenge eliciting energetic arousal; (3) alcohol intoxication blunted responses to aversive faces in ASSs but had no effect in SSSs; (4) alcohol-induced effects on social stress (MIST) reactivity differed as a function of personality profile, consistent with the pathways of risk; (5) escalation to alcohol misuse at follow-up was seen in ASSs who had previously exhibited the largest amygdalae activations to threatening faces

under placebo and deactivation under alcohol; (6) escalation to misuse of alcohol or other drugs (typically cocaine) at follow-up was seen in SSSs who had previously exhibited marked medial orbitofrontal activations to social stress (MIST) under placebo and diminished responses under alcohol; and (7) the predictive power of these neural responses was above and beyond other measured risk factors and occurred absent statistical differences at study entry between subjects who showed later escalating use and their same-personality counterparts who did not in terms of the behavioral, subjective mood and endocrine responsiveness to emotional challenge. Together, these results suggest that at-risk individuals with distinct personality profiles respond differently to alcohol and stressful events, with the response patterns predicting their alcohol and illicit drug use behaviors two to three years later. Some effects were sex-dependent.

Abrégé

Les troubles liés à la consommation l'alcool, constituant la plus importante condition prévalant en Amérique, ou la seconde, sont éminemment complexes et leur développement est sujet á une variabilité inter-individuelle. Comprendre comment ces développements ménent la pathologie à SA pleine expression, en fonction des personnes, est impératif pour modeler et déployer des thérapies efficaces et des interventions préventives. Le travail ci-présent se référe á une importante étude d'une population d'hommes et de femmes adultes en santé constituée de consommateurs sociaux et qui expriment fortement des traits relatif à la recherche de sensation ou bien une sensibilité á l'anxiété. Cette étude posséde deux parties: la premiére est une étude d'imagerie par résonance magnétique fonctionnelle (IRMf) présentant un groupe-contrôle placebo, en double aveugle, employant un défi d'alcohol. Dans le scanner, les sujets sont exposés un paradigme de challenge émotionnel consistant en deux tâches qui différent dans la forme et l'affect: the Face Emotion Processing Task (FEPT) et la Montreal Imaging Stress Task (MIST). Le profil de réponse a été conjointement investigué du point de vue comportemental, de la description subjective de l'humeur et du systéme endocrinien. La deuxiéme partie est une étude de suivi dans laquelle lesdits sujets ont été contactés 2 ou 3 ans aprés et ont été cliniquement testés á propos déventuelles habitudes d'utilisation de drogues et de maladie mentale. Sept propositions ont été posées et défendues: (1) les sujets sensibles á l'anxiété (ASS) sont négativement biaisés pour l'hypervigilance envers les signaux faciaux de menace, alors que les individus recherchant de sensations (SSS) étaient hyporéactifs ou non réactifs á ces signaux. (2) la composante socio-évaluative de la procédure du MIST induit un éveil soutenu et un intense sens de menace sociale s'observe chez les ASS, spécialement les hommes AS, alors que chez les SSS, particuliérement les hommes SS, elle étaient percue davantage comme un challenge que comme une menace, suscitant conséquemment une

intense stimulation et un éveil énergique; (3) l'intoxication par l'alcool émousse passablement la capacité de réaction aux visages provoquant l'aversion mais n'a pas causé de changement chez les SSS; (4) les effets, induits par l'alcool, sur la réaction au stress social (MIST) sont particuliérement prononcés chez les sujets masculins mais différent substantiellement de pattern en fonction du profil de personnalité, oú l'on observe une cohérence entre les réponses des hommes intoxiqués AS et SS avec (respectivement) la régulation négative des affects et les voies désinhibitrices du risque; (5) parmi les ASS, ceux exprimant l'activation la plus prononcée de l'amygdale au visage menaçant VS neutre, sous placebo et la désactivation sous l'influence de l'alcool, ont abouti á l'abus d'alcool durant le suivi; (6) parmi les SSS, ceux affichant une activation substantielle de l'orbitofrontal médial au stress social (MIST), sous placebo et sous l'émoussement résultant de l'alcool lors de cette activation, sont ceux qui sont sujets á l'abus d'alcool et/ou d'autres drogues (typiquement la cocaïne) durant les 2-3 années suivantes; (7) la puissance prédictive des réponses neurales susnommées était supérieure á tout autres facteurs de risques mesurés. Nous concluons que les individus á risque selon les profils de personnalités distinctes répondent différemment aux différents stresseurs, et á l'alcool selon le sexe et ces stresseurs, et que la nature et l'ampleur de leur réponse prédit la réponse de la tâche liée á la consommation d'alcool et á l'abus de drogues illicites á l'égard des habitudes durant les 2-3 années suivantes.

Acknowledgments

The process leading up the completion of this thesis has been nothing short an emotional roller coaster. One that I know would not have gone or ended well was not for my mentor and supervisor, Prof. Robert Pihl. His sharp and fascinating intellect have helped me become an independent thinker, and a better researcher and therapist because of that. His continuous understanding and unwavering support of me at times where I found myself most vulnerable, insecure and overcome with my lack of self-esteem and irrational fears (which has been often), is the main reason I found the strength in me to keep going in a tunnel that seemed as dark as it was endless.

I would also like to thank my family, my father, Said Abu Shakra especially, who I love more than anything and who inspires me everyday. I know that I would have not been at the place I am at now was not for his tremendous love and constant presence in my life.

I am so thankful to Dr. Hussein Moghnieh, the genius software engineer who made the process of automating a large number of scripts for a massive set of data as smooth as it could possibly have gotten. Thanks to Kevin Larcher for technical assistance as well.

I would also like to express my profound gratitude to Bogdan Rotaru. To say nothing of Bogdan's kindness, generosity, and unconditional support, his reading through my introduction chapter is the reason it has as few typos and other sorts of errors as it does not (and why other chapters that he did not read have way more). As well, I am grateful for my Dr. Annie Duchesne, for being such a good friend and great help for me in writing this thesis, as well as for Frenching up my abstract. And for my honor students, research assistants and volunteers, from all of whom I continue to learn.

My thanks also goes to the wonderful Giovanna LoCascio, who has been extremely helpful in facilitating my completion of the necessary forms to submit this thesis, and

has been so kind and patient with me throughout. Thanks additionally to Chantale Bousquet, who has also been quite helpful throughout this process.

I would finally like to thank my committee members, Profs. Marco Leyton, Jens Pruessner and Alain Dagher for their brilliant insights and consistently helpful advice, and for being ever so professional, kind, and generous to me throughout the years. I am honored to have had the opportunity to learn from each of these extraordinary people.

Preface and Contribution of Authors

The work presented in this thesis makes an original contribution to the current knowledge concerning the distinct typologies for alcoholism and risk thereof: how they respond to differentially aversive stimuli, when sober and alcohol intoxicated, behaviorally, subjectively, endocrenologically and neurally, and what prospectively predicts their escalating drinking.

The study in both of its parts was designed by myself and my supervisor, Professor Robert O. Pihl. I recruited subjects, was responsible for administering the testing protocol, completed behavioral, subjective, endocrine, and fMRI data analyses, and written manuscripts (in preparation).

Contents

1 Introduction **1**

1.1 Thesis Rationale and Objectives 2

1.2 Some Perspective 3

1.3 Statement of Problem 6

1.4 The Importance of Aetiology 11

1.5 Problems with Current Nosology 14

1.6 Distinct Typologies for Alcoholism 16

1.7 The Need for Markers 20

1.7.1 High Heart Response 22

1.7.2 Stress Response Dampening 24

1.8 Two Predominate Risk Trajectories 29

1.8.1 The Anxiety-Sensitive Phenotype 30

1.8.2 The Sensation-Seeking Phenotype 32

1.9 The Importance of Delineating Neurophenotypic Markers of Risk of AUDs and related SUDs 36

1.9.1 Functional Neuroimaging Markers 40

1.9.1.1 Executive Function 41

1.9.1.2 Reward sensitivity 49

1.9.1.3 Emotional processing 52

1.9.2 Structural Neuroimaging Markers 55

1.9.2.1 White Matter Maturation 55

1.9.2.2 Grey Matter Maturation 58

1.10 Using Emotional Challenge Paradigms to Delineate Risk Pathways for AUDs 61

1.10.1 Face Emotion Processing 61

1.10.1.1 Alcohol-Induced Modulation of Face Emotion Processing 72

1.10.2 Acute Social Stress . . . 74
1.10.2.1 Alcohol-Induced Modulation of Social Stress Reactivity 89

2 Methods 91

2.1 Screening and Characterization . . . 92
2.2 Design and Testing Procedure . . . 105
2.2.1 Alcohol Challenge . . . 107
2.2.2 MRI Scanning . . . 108
2.2.2.1 Face Emotion Processing Task . . . 109
2.2.2.2 Montreal Imaging Stress Task . . . 111
2.2.3 Behavioral Measurements . . . 114
2.2.3.1 Face Emotion Processing Task . . . 114
2.2.3.2 The Montreal Imaging Stress Task . . . 115
2.2.4 Psychological Measurements . . . 116
2.2.5 Physiological Measurements . . . 116
2.3 Follow-Up Assessment . . . 118
2.4 MRI Data Acquisition . . . 119
2.5 MRI Data Preprocessing . . . 120
2.5.1 Face Emotion Processing Task . . . 121
2.5.1.1 Exploratory whole-brain analyses . . . 121
2.5.1.2 Regions of interest analyses . . . 124
2.5.2 Montreal Imaging Stress Task . . . 126
2.5.2.1 Exploratory whole-brain analyses . . . 126
2.5.2.2 Regions of interest analyses . . . 128
2.6 Statistical Analyses . . . 131
2.6.1 Face Emotion Processing Task . . . 131
2.6.1.1 Behavioral Analyses . . . 131
2.6.1.2 Endocrine Analyses . . . 132

2.6.1.3 Correlational analyses . . . 133
2.6.2 Montreal Imaging Stress Task . . . 134
2.6.2.1 Behavioral Analyses . . . 134
2.6.2.2 Subjective Mood Analyses . . . 135
2.6.2.3 Endocrine Analyses . . . 137
2.6.2.4 Correlational analyses . . . 139

3 Results **142**

3.1 Demographic and Clinical Characteristics . . . 143
3.2 Face Emotion Processing Task . . . 147
3.2.1 Placebo Condition . . . 147
3.2.1.1 Behavioral Results . . . 147
3.2.1.2 Endocrine Data . . . 148
3.2.1.3 Neurofunctional Results . . . 149
3.2.2 Alcohol Condition . . . 160
3.2.2.1 Behavioral Results . . . 160
3.2.2.2 Endocrine Results . . . 162
3.2.2.3 Neurofunctional Results . . . 162
3.2.3 Summary of Results . . . 178
3.3 Montreal Imaging Stress Task . . . 179
3.3.1 Placebo Condition . . . 179
3.3.1.1 Behavioral Results . . . 179
3.3.1.2 Subjective Mood Results . . . 181
3.3.1.3 Endocrine Results . . . 183
3.3.1.4 Neurofunctional Results . . . 185
3.3.2 Alcohol Condition . . . 197
3.3.2.1 Behavioral Results . . . 197
3.3.2.2 Subjective Mood Results . . . 199

3.3.2.3 Endocrine Results . . . 200
3.3.2.4 Neurofunctional Results . . . 203
3.3.3 Summary of Results . . . 209
3.4 Follow-up Assessment . . . 210
3.4.1 Face Emotion Processing Task . . . 215
3.4.2 Montreal Imaging Stress Task . . . 219
3.4.3 Summary of Results . . . 221

4 Discussion **222**

4.1 Face Emotion Processing Task . . . 223
4.2 Montreal Imaging stress Task . . . 241
4.3 Follow-up Assessment . . . 283
4.4 Strengths and Limitations . . . 294
4.5 Summary and Perspective . . . 298

List of Figures

2.1 Flow Chart of Screening and Experimental Procedures. 107
2.2 Flow Chart of MRI Testing Procedure. 109
2.3 Graphic User Interface of the Face Emotion Processing Task. 111
2.4 Graphic User Interface of the Montreal Imaging Stress Task 112

3.1 Personality Groups Comparisons on Behavioral Response Indices to Emotional and Neutral Faces Under Placebo. 148
3.2 The Effects of Personality Risk Profile on Whole-Brain Activation to Emotional Faces Under Placebo. 150
3.3 Personality-Based Differences in Whole-Brain Activation to Specific Face Emotions 152
3.4 Activation of Regions of Interest to Specific Emotional Faces. 157
3.5 The Association Between Threat-Related AMYG Activation and AS Scores Under Placebo. 158
3.6 Pre-Task Cortisol Association with Threat-Related AMYG Activation Under Placebo 159
3.7 The Effects of Alcohol Intoxication on Behavioral Indices of Detection Speed, Identification Accuracy and Appraisal of Facial Affect. 161
3.8 Effects of Alcohol and its Interaction with Personality risk Profile on Whole-Brain Response to Emotional Face Expressions. 163
3.9 The Effects of Alcohol on Whole-Brain Activation to Specific Face Emotions as a Function of Personality Risk Profile 171
3.10 Effects of Alcohol on Threat-Related AMYG Activation. 178
3.11 Personality Groups Comparisons on Performance Outcome in the Context of an Acute Psychosocial Stressor Under Placebo. 180
3.12 Pre-stressor self-ratings of states embarrassment and anger under placebo by personality group. 181

3.13 Subjective mood reactivity profiles of AS and SS male and female subjects during stress session under placebo. 182
3.14 Time-Adjusted Pre-Stressor Cortisol Levels under Placebo. 183
3.15 Time-Adjusted Effect of Personality-by-Sex Interaction on Stress Reactive Cortisol Production Under Placebo. 184
3.16 Time-Adjusted Cortisol AUCi Association with Stress-Related Subjective Embarrassment Under Placebo. 185
3.17 Main Effects of Acute Psychosocial Stress. 186
3.18 The Effects of Personality Risk Profile on Whole-Brain Activation to Acute Psychosocial Stress Under Placebo. 188
3.19 The Effects of Sex and Personality-by-Sex Interaction on Whole-Brain Activation to Acute Psychosocial Stress Under Placebo. 193
3.20 Medial Orbitofrontal Activation Differences and its Relatio to Stress-Related Subjective Anger in the Context of Acute Psychosocial Stress Under Placebo. 196
3.21 Anterior insular Activation Differences and Its Relationship with Sensation-Seeking Scores In the Context of Acute Psychosocial Stress Under Placebo. 197
3.22 Condition Differences in Performance Outcomes on the MIST by Personality Group. 198
3.23 Changes in Subjective Mood Throughout the Course of the MIST Under Alcohol. 200
3.24 Effect of Alcohol on Stress-reactive Cortisol Level as a Function of Personality and Sex in the Context of Acute Psychosocial Stress. 202
3.25 Effects of the Interaction of Condition with Personality Risk Profile and Sex on Whole-Brain Response to Acute Psychosocial Stress. 204
3.26 Effects of the Interaction of Condition with Personality Risk Profile and Sex on ROIs Response to Acute Psychosocial Stress. 207

3.27 Linear relationships between between neural and subjective responding to acute psychosocial stress under the influence of alcohol. 209

3.28 Prospective Association Between AMYG Activation to Socioaffective Signals of Threat and Escalating Use 217

3.29 Prospective Association Between Medial Orbitofrontal Activation to Acute Psychosocial Stress and Escalating Use 220

List of Tables

2.1 Demographic Characteristics of the Recruited Sample by Personality Group. 96
2.2 Bivariate Pearson Correlation Matrix of Personality Screening Measures. 97

3.1 Means, Standard Deviations, and Group Comparisons of Demographic Data and Rating Scale Scores. 145
3.2 Personality-Based Differences in Whole-Brain Activation to Specific Face Emotions 153
3.3 Personality-based comparisons in ROI activation to specific facial emotions under placebo 155
3.4 Raw means of behavioral responses to the FEPT by personality group in under alcohol and placebo. 161
3.5 Conditition-by-Personality Interaction Effect on Brain Response to Negatively Valent > Neutral Faces. 164
3.6 Condition-by-Personality Interaction Effect on Brain Response to Specific Emotional Faces. 165
3.7 The effect of personality by condition interaction on brain response to aversive (minus neutral) faces. 167
3.8 Condition Differences in Whole-Brain Response to Negative versus Neutral Faces by Personality Group. 169
3.9 The Effects of Alcohol on Whole-Brain Response to Specific Face Emotions by Personality Group. 172
3.10 The effect of alcohol on brain response to Specific Facial Expressions in the personality groups. 175
3.11 Personality Groups Comparisons for Performance Outcomes on the MIST Under Placebo 180

3.12 Whole-Brain Response of the Entire Sample Combined to Acute Psychosocial Stress Under Placebo. 186
3.13 Effects of Personality on Whole-Brain Activation to Acute Psychosocial Stress Under Placebo. 189
3.14 Whole-Brain Response to Acute Psychosocial Stress Under Placebo by Personality Group. 190
3.15 The Effects of Sex and Personality-by-Sex Interaction on Whole-Brain Activation to Acute Psychosocial Stress Under Placebo. 193
3.16 Condition Differences in Performance Outcomes on the MIST by Personality Group. 198
3.17 Time- and BAC- adjusted means of pre-stressor cortisol as a Function of Personality and Sex under alcohol and placebo conditions. 201
3.18 Time- and BAC- adjusted means of stress-reactive cortisol as a Function of Personality and Sex under alcohol and placebo conditions. 202
3.19 Main effect of alcohol and its interaction with either and both personality and sex on Brain Response to Acute Psychosocial Stress. 203
3.20 Decomposition of the Condition-by-Personality-by-Sex Effect on Whole-Brain Activation to Acute Psychosocial Stress. 205
3.21 The Condition Difference in ROIs Activation to Acute Psychosocial Stress. 208
3.22 Means, Standard Deviations, and Group Comparisons of Demographic Data and Rating Scale Scores. 211
3.23 The condition difference in threat-related AMYG activity as a function of Personality Profile and Transitioning Status. 218
3.24 The Condition Difference in mOFG Activation to Acute Psychosocial Stress as a Function of Personality Profile and Transitioning Status. . . 220

List of Acronyms

a.u.	arbitrary units
AA	alcohol abuse
ACC	anterior cingulate cortex
ACTH	adrenocorticotrophic hormone
AD	alcohol dependence
aINS	anterior insula
AMYG	amygdala
ANCOVA	analysis of covariance
ANOVA	analysis of variance
APA	American Psychiatric Association
AS	anxiety-sensitivity
ASFSs	anxiety sensitive female subjects
ASMSs	anxiety sensitive male subjects
ASPD	antisocial personality disorder
ASSs	anxiety sensitive subjects
AUC	area-under-the-curve
AUCg	area-under-the-curve ground
AUCi	area-under-the-curve-increase
AUDs	Alcohol Use Disorders
BA	brodmann's area
BAC	Blood Alcohol Concentration
BLA	basolateral nucleus of the amygdala
BMI	body mass index
BNST	Bed Nucleus of the Stria Terminalis
BOLD	blood oxygen level–dependent
CAU	caudate

CeA	Central nucleus of the amygdala
CeM	Centromedial nucleus of the amygdala
CER	cerebellum
CG	cingulate gyrus
CNc	Cuadate Nucleus
CNVs	Common Variants
COGA	Consortium on the Genetics of Alcoholism
CPT	cold pressor test
CRH	corticotropin releasing hormone
CU	callous-unemotional
DA	Dopamine
dACC	dorsal anterior cingulate cortex
DALYs	disability-adjusted life years
dlPFC	dorsolateral PFC
DMN	default mode network
DSM	Diagnostic and Statistical Manual of Mental Disorders
DTC	drinking to cope
DTI	diffusion tensor imaging
EEG	electroencephalogram
FEPT	Face Emotion Processing Task
FL	frontal lobe
fMRI	Functional Magnetic Resonance Imaging
$FWE - corr$	family-wise error corrected
GABA	gamma-aminobutyric acid
GG	Greenhouse Geisser
GM	grey matter
GR	glucocorticoid receptors

h	Hour(s)
h^2	heritability
HC	hippocampus
HDs	Heavy Drinkers
HHRR	high heart rate response
HPAA	Hypothalamic-Pituitary-Adrenal Axis
IFG	inferior frontal gyrus
IL	infralimbic prefrontal cortex
INS	insula
IU	intolerance of uncertainty
LC	locus coeruleus
LING	lingual gyrus
LL	limbic lobe
lPFC	lateral PFC
MANOVA	multivariate analysis of variance
MCC	mid-cingulate cortex
MDN	medial dorsal nucleus
MFG	middle frontal gyrus
MI	motivational interviewing
MIST	Montreal Imaging Stress Task
MNI	Montreal Neurological Institute
mOFC	medial orbitofrontal cortex
mOFG	medial orbitofrontal gyrus
mPFC	medial prefrontal cortex
MR	mineralocorticoid
MTG	middle temporal gyrus
NAc	Nucleus Accumbens

NESARC	National Epidemiologic Survey on Alcohol and Related Conditions
NIMH	National Institute of Mental Health
OFC	Orbitofrontal Cortex
OOA	offspring of alcoholics
PAG	periacqueducal grey
PCC	posterior cingulate cortex
PES	Partial eta-squared
PET	positron emission tomography
PFC	Prefrontal Cortex
pgACC	perigenual anterior cingulate
PHG	parahippocampal gyrus
POMS	Profile of Mood State
PostcG	postcentral gyrus
PPI	psychophysiological interaction
PrecG	precentral gyrus
PTSD	Post-Traumatic Stress Disorder
PUT	putamen
PVN	paraventricular nucleus
rCBF	resting cerebral blood flow
RDoC	Research Domain Criteria
ROI	Region of interest
s	Second(s)
SA	Social anxiety
SCID	Structured Clinical Interview for DSM
SCR	skin conductance response
SD	Standard Deviation
SDs	Social Drinkers

SE	Standard Error
SEM	Standard Error Mean
S-G	subgyral
S-L	sub-lobar
SOA	sons of alcoholics
SPM	Statistical Parametric Mapping
SR	subjective response
SRD	stress response dampening
SS	sensation-seeking
SSET	subjective social evaluative threat
SSFSs	sensation-seeking female subjects
SSMSs	sensation-seeking male subjects
SSSs	sensation-seeking subjects
STG	superior temporal gyrus
SUDs	Substance Use Disorders
SURPS	Substance Use Risk Profile Scale
THAL	thalamus
TSST	Trier Social Stress Test
vACC	ventral anterior cingulate cortex
vlPFC	ventrolateral PFC
VMPFC	ventral/infralimbic of medial PFC
VTA	Ventral tegmental area
WM	white matter

Notations

η_{p}^2	Partial eta-squared
p	The degree of statistical significance
K_E	cluster size in voxels
$FWE - corr$	family-wise error corrected
°C	Degrees Centigrade
t	t-test value
y	Vertical axis on a graph
x	Horizontal axis on a graph
$\tilde{\chi}^2$	Chi square test value
%	Percentage
n	Number in subsample
F	F-ratio (used in ANOVA, ANCOVA and MANOVA)
d	Cohen's measure of effect size
df	degrees of freedom
r	Pearson's correlation
α	alpha, the probability of making a Type 1 error in hypothesis testing
β	beta, the probability of making a Type 2 error in hypothesis testing
LSD	Fisher's Least Significant Difference
SEM	Standard Deviation Standard Error Mean
M	mean
SD	standard deviation

Chapter 1

Introduction

Contents

1.1 Thesis Rationale and Objectives 2

1.2 Some Perspective 3

1.3 Statement of Problem 6

1.4 The Importance of Aetiology 11

1.5 Problems with Current Nosology 14

1.6 Distinct Typologies for Alcoholism 16

1.7 The Need for Markers 20

1.7.1 High Heart Response 22

1.7.2 Stress Response Dampening 24

1.8 Two Predominate Risk Trajectories 29

1.8.1 The Anxiety-Sensitive Phenotype 30

1.8.2 The Sensation-Seeking Phenotype 32

1.9 The Importance of Delineating Neurophenotypic Markers of Risk of AUDs and related SUDs 36

1.9.1 Functional Neuroimaging Markers 40

1.9.2 Structural Neuroimaging Markers 55

1.10 Using Emotional Challenge Paradigms to Delineate Risk Pathways for AUDs 61

1.10.1 Face Emotion Processing 61

1.10.2 Acute Social Stress 74

1.1 Thesis Rationale and Objectives

It is indisputable that while most people consume alcohol and other drugs, only some are at-risk of ever coming to abuse either or both. Also indisputable is that addiction is not the destiny of the vulnerable, just as the absence of predisposition does not imply immunity against it; some at-risk individuals will experiment with but never misuse licit and/ or illicit substances, while others will never even use them. It is additionally clear that the pathways leading up to and causing alcoholism are divergent. In a sample of individuals with or at-risk for the condition, the only common denominator that is certain to exist is respectively drinking to excess, or having the propensity to come to do so. Otherwise, explanations as to why risk exists, and how it is expressed, what unfolds when the explosion eventually ensues and how it is different when it does not, are neither collectively exhaustive nor mutually exclusive. They vary substantially across individuals and critically depend upon and are largely determined by who the vulnerable person is, and just what it is that alcohol ingestion acutely does to and for her, subjectively and objectively.

The work presented in this thesis is predicated on the above mentioned. Its primary goal is two-fold: (1) to differentiate otherwise healthy young adults who are putatively at-risk of AUDs based on their behavioral, subjective, endocrine and neurofunctional response patterns to negative socioaffective signals and an acute psychosocial stressor, and the extent to which these responses are influenced by acute alcohol intoxication; and (2) to identify neural phenotypes that predict drug-use status 2-3 years later.

Based on the background presented in the first chapter, we expected to find behavioral, subjective, endocrine and fMRI evidence to support three primary working hypotheses. The first hypothesis was that ASSs would be biased towards hypervigilance for potential threat as signalled by socioaffective stimuli (negative and surprised faces) and that this bias would be substantially reduced by acute alcohol intoxication. This is contrarily to SSSs, who were expected to be unresponsiveness to said stimuli,

be they sober or intoxicated.

The second hypothesis was that in the context of a performance-based acute social stressor (MIST), ASSs, especially ASMSs, would be tensely aroused, intensely threatened and emotionally involved, whereas SSSs, especially SSMSs, would be energetically aroused and motivationally engaged, without necessarily feeling 'stressed' in the aversive sense of the term. Alcohol was expected to dampen and stimulate the reactivity of (respectively) the AS and SS groups, relative to placebo, with the magnitude of those effects corresponding to the extent of reactivity to said procedure under placebo.

The third and final hypothesis was that distinct neural phenotypes would predict escalating drinking 2-3 years later in the distinct personality groups. Specifically, we expected that (a) a particularly robust stimulation of a phylogenetically archaic danger-recognition system (amygdala) in response to threatening faces under placebo, and substantial inactivation of this system by alcohol intoxication, would predict escalating alcohol and/ or illicit drug consumption in ASSs; and (b) marked activation of a comparatively younger system (medial orbitofrontal cortex) to acute psychosocial threat (MIST) under placebo, and substantial inactivation of this system by alcohol intoxication, would predict escalating use in SSSs.

1.2 Some Perspective

Human beings have been using alcohol and other drugs to elevate mood or otherwise alter experience since they have existed (Austin, 1985). Beer receives prominent mention in early Sumerian texts and is portrayed in Egyptian pictographs dating back to 4000 BC. The ancient Egyptians heavily drank and used other psychoactive substances (Rudgley et al., 1994) and the Babylonians worshipped *Siduri*, a Goddess of wine and beer, and regularly offered both alcoholic beverages to their gods (Sasson 1994; recently reviewed in Nathan et al. 2016). It has additionally been suggested that it was

Fly Agaric, a hallucinogenic mushroom, that inspired Palaeolithic rock art festooning the dark and dank anteriors of caves throughout southern Europe (Rudgley et al., 1994). Many, if not most, nonhuman animals, too, "do drugs" for seemingly the same and other reasons, consequently showing acute signs of intoxication that strikingly resemble humans' (see Mantegazza, 1871; Samorini, 2002; McGrew, 2011; Pihl and Abu Shakra, 2014). Elephants have a strong preference for and proclivity to binge on alcohol, man-made or otherwise (e.g, fermented fruit; Carrington, 1959; Sikes, 1971; Winfrey, 1980; Lewis and Fish, 1978; Siegel and Brodie, 1984; Siegel, 1989) and when drunk, they "[stagger] about, playing huge antics, screaming so as to be heard miles off, and not seldom having tremendous fights" (Drummond, 1875, p. 223). There are birds that actively search for and seek to self-indulge on hallucinogenic berries, upon the ingestion of which uncoordinated movement is acutely triggered, leading said birds to frequently smash into windows and their death along with that (see Pihl and Abu Shakra, 2014; Pihl, 2014). And there are ants that host in their nests a species of beetle whose intoxicating abdominal secretions are so attractive and rewarding (in the unconditioned sense) to the ants that when distribution of the colony occurs, they would forgo rescuing their own larvae just to safeguard the beetle (Samorini, 2002). The affinity for recreational drug use is a fundamental, even if an unnecessary, part of who we are; it is neither aberrant nor uniquely exhibited by the human species, and this is what previously mentioned information goes to suggest. Epidemiological reality concurs; according to national surveys, some 20% of American teens report having ever drank or gotten drunk before the age of 13 (Eaton et al., 2012a; SAMHSA, 2011), and about 10%, 16%, and 29% of respectively 4^{th}, 5^{th} and 6^{th} graders admit to trying more than a sip of alcohol at least once before (Donovan et al., 2004). In the year 2015, lifetime prevalence of, respectively, alcohol and illicit substance use was reported by 26% and 21% of 8^{th} graders, 47% and 35% 10^{th} graders, 64% and 49% 12^{th} graders, 81% and 54% college students, and 86% and 63% young adults (ages 19 to 28; Miech et al. 2015). Based on these numbers alone, there really is no explaining away that in

relatively open societies like ours, self-drugging for recreational purposes is a behavior so prevalent that it is, at least statistically, normative, though a slight downward trend in illegal drug use in recent years, among all age groups, is notable (Miech et al. 2015; de Looze et al. 2015; but see Burcu et al. 2016).

It is true that when the rates of drug use increase, so do those of misuse and abuse, and obviously, one cannot misuse what is unavailable. Also true, however, is that drug abuse is not an automatic outcome of experimental use, otherwise the former would have been an epidemic (it is not). In fact, among individuals encapsulated in the aforementioned statistical figures, only a fraction (10%−20%) will ever come to abuse either or both alcohol and illicit substance(s) (Weber et al., 1989; Moss, 2013), and it is precisely this small minority of cases that accounts for the preponderance of vagaries brought on by the problematic consumption of alcohol. There is more. The beneficial effects of drugs have been quantified and empirically, if still neither consistently nor conclusively, substantiated. A number of studies have linked lifetime or classic psychedelic use to a range of, often sustained, beneficial effects (McGlothlin and Arnold, 1971; Doblin, 1991; Griffiths et al., 2008, 2011; Morgan et al., 2009; Carhart-Harris and Nutt, 2010; Jónsson, 2015), including better mental well-being (Krebs and Johansen, 2013; Johansen and Krebs, 2015) and reduced suicidality (Hendricks et al., 2015). Numerous others have found that moderate alcohol use was associated with positive health outcomes (Gepner et al. 2015, 2016; Sayed and French 2016; Keller 2016; but see Chikritzhs et al. 2015; Goulden 2016), psychological benefits (Baum-Baicker, 1985; Peele and Brodsky, 2000) and, in some cases, higher cognitive function (Reas et al., 2016). And so it is not the question of why drugs are recreationally used, it is why not (Pihl and Peterson, 1995).

Despite, and perhaps in recognition, of all of the above, any society can and all do curtail the use and availability of some drugs in some way. They do so for a myriad of reasons that almost always have much to do with religion and tradition and nothing the scientifically proven harm of the drug. Irrespective, the most relevant question with

regard to such an approach is whether it is sustainable and effective in obviating rates of disordered drug use, and the answer to that, based on the previously mentioned statistics and countless historical examples is, unequivocally, a resounding no.

1.3 Statement of Problem

According to epidemiological surveys, and depending on which one, alcohol use disorders (AUDs) are the most or second most prevalent psychiatric condition in the Americas and most developed countries (Grant et al., 2004b; Kessler et al., 2005b; Hasin et al., 2007; Wittchen et al., 2011; Roerecke and Rehm, 2013; Haberstick et al., 2014; Rehm et al., 2015c; Manthey et al., 2016; Slade et al., 2016; Delker et al., 2016). Estimated 12-month and lifetime prevalence rates in the general American population are, respectively, 13.9% (17.6% for men and 10.4%, women) and 29.1% (36% for men and 22.7%, women; Grant et al. 2015a). Prevalence rates for developing countries are lower but still substantial (for details, see UNODC, 2011).

Rates of alcohol use and onset of misuse and abuse peak between late adolescence and young adulthood (Fillmore et al., 1991; Naimi et al., 2003; Hasin et al., 2007; Abuse, 2012; Organization, 2012; Merikangas and McClair, 2012; Sathe et al., 2013; Paksarian et al., 2016). Some 50% of adult alcoholics initially become symptomatic between 15 and 19 years of age (Kessler et al., 2005a), and 80% of all alcoholics develop the full-blown condition before the age of 30 (Helzer et al., 1991; Chambers et al., 2003). A recent national epidemiological survey reported a mean age of 26.2 years at AUDs onset, which rose to 30.1 years for mild cases and decreased to 25.9 and 23.9 years for, respectively, moderate and severe cases[1] (Grant et al., 2015a).

The individual and societal costs associated with excess and disordered alcohol consumption are staggering (Lim et al., 2013; Whiteford et al., 2013; Rehm et al., 2015c; Fuehrlein et al., 2016). Related yearly deaths worldwide total nearly 3.3 mil-

[1] In DSM-5, mild, moderate and severe AUDs are characterized by, respectively, two to three, four to five, and six or more behavioral and/or physiological symptoms.

lion, making alcohol responsible for 5.9% of the global mortality rate (roughly one in every twenty deaths; WHO 2014), and 9% of deaths among individuals aged 15 to 29 (UNODC 2011; Marshall 2014; for rates within Canada, see Shield et al. 2012). In the year 2000, excessive drinking claimed 85,000 lives in the United States (U.S) alone, representing the third leading preventable cause of death (Mokdad et al. 2004; for meta-analyses, see Roerecke and Rehm 2013, 2014). Loss of life due to alcohol-related causes has additionally contributed to the spike in all-cause deaths in U.S white non-Hispanic men from 1999 to 2013 (Case and Deaton, 2015). Studies generally agree that between the ages of 15 and 70 years, disordered alcohol use is associated with an approximately 6-fold rise in all-cause mortality (Pell and D'alonzo 1973; Lindberg and Ågren 1988; Chou 1994; Haver et al. 2009; Kendler et al. 2016c; although see Roerecke and Rehm 2013; Laramée et al. 2015, for lower estimates). Several lines of evidence also suggest that the link between AUDs and mortality is direct and causal (Leon et al., 1997; Dills and Miron, 2004; Rehm and Roerecke, 2013; Laramée et al., 2015; Kendler et al., 2016c), and the recent work of Kendler et al. (2016c) demonstrates that causality of said association increases with age, specifically from age 40 years onwards, on account of shared familial factors become increasingly less relevant.

When alcohol misuse does not kill, it disables, and much more pronouncedly so (Dawson et al., 2009; Hasin et al., 2007; Samokhvalov et al., 2010; Collins et al., 2011; Lim et al., 2013; Rehm et al., 2014, 2015b). Being implicated, directly or indirectly, in the aetiology of upwards of 200 diseases and injury conditions, some of which are trivial and many life-threatening (WHO 2014; Eriksson 2015; Praud et al. 2016; also see Rehm et al. 2009; Smyth et al. 2015), problem drinking is responsible for a considerable amount of hospital admissions (Verelst et al., 2012; Liang and Chikritzhs, 2016; Nunn et al., 2016), and Emergency Room (ER) visits (Cherpitel, 2009; Parkinson et al., 2016; Castle et al., 2016), particularly among adolescents (Sindelar et al., 2004). In Canada alone, alcohol causes some 6% of all hospital days, triple the rate caused by all illegal drugs, combined (Rehm et al., 2006b). Further, according to a

recent epidemiological report, between the years 2001 and 2011, alcohol-related ER visits increased at a greater rate than overall ER visits (Mullins et al., 2016). It is additionally clear that for many alcoholics, particularly women with early onset alcoholism (i.e. rapid course), the health sequelae of disordered drinking tend to be enduring and potentially permanent, ceasing to desist even after purported 'recovery' has occurred (Foster et al., 2014). Alcohol-related global DAILYs[2] (disability-adjusted life years) are estimated at a 139 million, a number corresponding to 5.1% of the global disease and injury burden (WHO 2014; also see Rehm et al. 2014). Consequently, AUDs rank seventeenth on the list of leading causes of DAILYs in high-income countries, and it is projected that by the year 2030, this pathology will have come to rank fourth (Mathers and Loncar, 2006). According to the most recent World Health Organization (WHO)[3] report (2014), excessive drinking is the most prominent risk factor for preventable/ premature death and disability among individuals aged 15–49 in large parts of the world, claiming more lives than HIV/AIDS, violence or tuberculosis, and causing greater disability than these three conditions combined (WHO 2014; also see Shlosberg and Shoval 2015; recently reviewed in Medina-Mora et al. 2016).

Other related costs are as startling; compared with non-pathological individuals, alcoholics are disproportionately likely to struggle financially, be absent from and unproductive at work, lose their employment and retire prematurely due to health problems (Romelsjö et al., 2004). Their interpersonal relationships are hijacked by their alcoholism and close ones (see Peirce et al. 2000), including but not restricted to family members, often beset by substantial distress that often contributes to the manifestation, exacerbation or maintenance of stress-related pathologies and/ or psychopathologies that ultimately necessitate seeking treatment.

General societal ills are illustrated in involvement of alcohol in nearly 50% of acts

[2]A measure of disease burden, expressed as the number of years lost owing to ill-health, disability or early death.

[3]The WHO is a specialized agency of the United Nations that is concerned with global public health.

of violence (Murdoch et al., 1990; Arseneault et al., 2000; O'Farrell et al., 2003; Elbogen and Johnson, 2009; Harford et al., 2013; Shlosberg and Shoval, 2015), be the perpetrator psychiatrically disordered or not (Conner et al., 2001; Elbogen and Johnson, 2009; Wintemute, 2015). These include incidences of suicide (Conner et al., 2001; Borges and Loera, 2010; Branas et al., 2011; Bagge et al., 2013; Kaplan et al., 2013), homicide (Darke, 2010; Kuhns et al., 2014), domestic violence (Murdoch et al., 1990; Murphy et al., 2005; Afifi et al., 2012), child abuse (Kelleher et al., 1994), armed assault and rape (Collins and Messerschmidt, 1993; Chermack and Giancola, 1997), the latter wherein the victim, too, is typically intoxicated or drunk (Abbey et al., 2004; Reed et al., 2009; Pihl and Sutton, 2009; Abracen and Looman, 2016). In the U.S alone, the previous statistic translates into roughly 3 million reported violent assaults each year (Nasby et al., 1980). It is also the case that relative to psychopathology-free individuals, alcohol abusers are more prone to commit crimes and lead crime-related careers (Swanson et al., 1990; Arseneault et al., 2000; Rehm, 2011; Bouchery et al., 2011; Moffitt et al., 2011; Marmot, 2014), as well as intentionally or unintentionally injure themselves and others (Coid et al. 2006; for recent reviews, see Kuramoto and Wilcox 2016; Medina-Mora et al. 2016). Relatedly, lifetime alcohol and illegal drug abuse is much more prevalent amongst teens with access to firearms, compared with teens without (Simonetti et al., 2014). According to longitudinal and epidemiological data, the association of alcohol misuse, acute or chronic, with aggression and violence is direct (O'Farrell et al., 2003; Boden et al., 2012), and stronger than that of any other psychoactive substance (Organization, 2007; Nutt et al., 2010; UNODC, 2011; Boden et al., 2012). Consequently, problematic alcohol intake accounts for 85% of the collective mayhem caused by all drugs of abuse, and generates a crime rate that costs twice as much as that attributable to all other psychoactive substances, combined (reviewed in Pihl and Sutton, 2009).

Furthermore, children placed under the care of an alcoholic, which is not at all uncommon in Canadian societies, often fall victims to his or her alcohol-related abuse

including neglect (Kelleher et al., 1994). Left unattended to and its aftermath unmitigated, this can seriously hinder the neurobiological development of the innocent (Teicher and Samson, 2016), predisposing to the full panoply of psychopathologic manifestations (Green et al. 2010; Scott et al. 2010; Teicher and Samson 2013; Geoffroy et al. 2016; González et al. 2016; Skinner et al. 2016; Taillieu et al. 2016; reviewed in Nemeroff 2016), including even psychotic symptoms (Janssen et al. 2004; Arseneault et al. 2011; DeRosse et al. 2014; Post et al. 2015; Yung et al. 2015; Matheson et al. 2016; Begemann et al. 2016; for reviews, see Morrison et al. 2003; Read et al. 2005; Bendall et al. 2008 ; for meta-analyses, see Varese et al. 2012; Agnew-Blais and Danese 2016). Such outcomes have been invoked as a plausible explanatory mechanism for why risk of premature death is much higher among victims of childhood abuse (Chen et al. 2016; also see Shalev et al. 2016). This phenomenon additionally tends to set off a vicious self-perpetuating intergenerational cycle of abuse of both individuals and drugs (Widom et al., 2015; Leve et al., 2015), along with their concomitant consequences (e.g, dysfunctional parenting; Treit et al., 2013; Bowers and Yehuda, 2016; Bosquet Enlow et al., 2016), reminiscent of the saying that "what is done to children they will do to society" (see Theresa and Betancourt, 2008; Betancourt et al., 2013; Oshri et al., 2015; Bijleveld et al., 2016; González et al., 2016). Various studies have collectively estimated the rate of violence among alcoholics to fall somewhere between 20% and 50% (Nicol et al., 1973; Mayfield, 1976; Schuckit and Russell, 1984; Jaffe et al., 1988; Giancola et al., 2009).

A final illustrative example relates to in-uteri alcohol exposure, another prevalent phenomenon in Western populations (O'Keeffe et al., 2016). We know that the misuse of alcohol during pregnancy may impinge on fetal growth (Linnet et al., 2003; McGrath et al., 2014), engendering, though not necessarily causally, decrements that vary in nature, severity and reversibility (Elkins et al., 2004; Lebel et al., 2012b; Gautam et al., 2014; Van Dam et al., 2014; Hannigan et al., 2015; Gautam et al., 2015; Ware et al., 2015; Lundsberg et al., 2015; Bazinet et al., 2016), and frequently manifest as

the well-characterized fetal alcohol syndrome (Treit et al. 2013; also see Charness et al. 2016). There are also indications that neonates prenatally exposed to alcohol exhibit a pattern of neuroanatomical aberrations (Donald et al., 2016; Paquola et al., 2016) that have previously been found to presage psychopathologic outcomes (Romano et al., 2015; Jabbar et al., 2016), including AUDs (Van Dam et al., 2014), and early-onset-persistent conduct problems (Murray et al., 2015). In fact, recent evidence suggests that risk of the latter condition is ostensibly increased, directly and through causal mechanisms, by moderate drinking in pregnancy (Murray et al., 2015).

Estimated total yearly billion dollar figure costs are for, Canada 14.6 (Rehm et al., 2006a, 2009), the U.S 223 (Eaton et al., 2008; Bouchery et al., 2011; Sacks et al., 2013) and Great Britain 55.1 (Balakrishnan et al., 2009), making alcohol misuse the most expensive psychiatric disorder known (Eaton et al., 2008; Mathers et al., 2008; Sullivan et al., 2012). But considering that much of the devastation related to excessive drinking is unquantifiable and/ or goes unnoticed or unreported (e.g, $\sim$ 90% of child abuse cases), one could reasonably conclude that the aforementioned financial expenditures, as immense as they truly are, in all likelihood represent but the tip of an iceberg.

1.4 The Importance of Aetiology

It needs no explanation that when working with individuals who have or are at risk of alcoholism, the priority should be to (respectively) treat or prevent. Unfortunately, despite massive study and assiduous effort to improve it, the treatment state for AUDs remains bleak and problematic (Pihl and Abu Shakra, 2014; Wallhed Finn et al., 2014; Bujarski and Ray, 2016; Heilig and Leggio, 2016). Alcoholism is a problem often masked, missed and misunderstood (for other problems, see e.g, Lane et al., 2016). More than 68% of lifetime cases of AUDs are misdiagnosed or never diagnosed, and well over 80% ($\sim$ 60% of the serious cases; Demyttenaere et al. 2004) never treated

(Alonso et al., 2004; Drummond et al., 2011; Rehm et al., 2012, 2013; Grant et al., 2015a; Rehm et al., 2015a). It is nonetheless notable that these non-treated individuals frequently utilize medical services, and are often treated for other pathologies and/ or psychopathologies as alcoholism never, or almost never occurs in isolation (Kessler et al., 1997; Hasin et al., 2007; Cargiulo, 2007; Rehm, 2011; Grant et al., 2015a; Odlaug et al., 2016). For example, data from a nationally representative sample indicate that in 96% of the cases in which AUDs co-occurred with depression, the latter was granted deference in terms of both diagnosis and treatment (Edlund et al., 2012). This is troubling and significant, considering that the comorbidity between two conditions is rather high and far from coincidental (Grant and Harford 1995; Hasin et al. 2007; Hill et al. 2008; Conner et al. 2009; Boschloo et al. 2011; Brière et al. 2014; Hasin and Grant 2015; McBride et al. 2016; Conway et al. 2016; Karpyak et al. 2016; Jung et al. 2016, reviewed in Morisano et al. 2014), and depression treatment efficacy is hindered by the presence of an AUD (Hashimoto et al. 2015; also see Morley et al. 2015). "Diagnostic deference might be given to the personality, affective, or anxiety disorders, more mysterious, intrinsically rewarding, and seductive to the diagnosing professional, as they appear more theoretically explicable, and more clearly amenable to respectable and traditional treatment", Pihl and Peterson (1995) noted. Perhaps this is why it has been recently found that three out of four persons who reported visiting a primary care physician in the past year in the U.S were not screened for alcohol misuse (Denny et al., 2016) – a problem so prevalent it is hardly noticeable anymore.

It gets worse. Even when treatment is sought and received, effect sizes for over 60% of the cases are modest at best (Morgenstern and Longabaugh, 2000; Rubak et al., 2005; Ferri et al., 2006; Anton et al., 2006; Magill and Ray, 2009; Rösner et al., 2010a,b; Litten et al., 2012, 2016; Huhn et al., 2014; Bujarski and Ray, 2016; Heilig and Leggio, 2016), and relapse within 2- or 3- months of treatment termination is the rule rather than the exception (McLellan et al. 2000; Hyman and Malenka 2001; Dawson

et al. 2007; Brandon et al. 2007; Heilig and Leggio 2016; although see Heyman 2013, for a counter-argument), especially among those whose need to quit is most urgent and symptom severity worst (Chiappetta et al., 2014). These clinical outcomes are strikingly similar those reported in the early 1970s (Hunt et al., 1971), and their trends almost identical to those of supposedly different treatments targeting other drug addictions (Stark, 1992; Sandler et al., 2014), alluding to (respectively) ineffectiveness and unspecificity. More egregiously, even when symptomatic or syndromatic remission occurs, risk of relapse remains unabated long after withdrawal symptoms have cleared, and sometimes for a lifetime (Wise and Bozarth, 1987; Hyman, 1995; O'Brien et al., 1998; Wise, 2000). Extant evidence indicates a mean duration of nearly 4 years with respect to AUDs (Hasin et al., 2007), and the prevailing view is that alcohol addiction has become full-blown, a downward spiral of chronicity dooms, hence the oft-repeated mantra "once an alcoholic always an alcoholic". A related concern is that where treatment is sought and received, it is typically after long (average 6 to 9) years of delay (Wang et al., 2005b; Shoham and Insel, 2011; Chapman et al., 2015). This is highly problematic because alcoholism treatment seeking is consistently proportional to symptom severity and the latter strongly correlates with greater psychiatric comorbidity (Salom et al. 2014; also see Ilgen et al. 2011), and just as is the case for medical diseases (Shoham and Insel, 2011), reversing the addiction trajectory so long after initial onset of symptoms is exceedingly difficult to achieve (Wang et al. 2005b, 2007b; Kalivas and O'Brien 2008; Shoham and Insel 2011; Chiamulera and Cibin 2014; although see Lopez-Quintero et al. 2011; Heyman 2013). This also explains why the risk of alcohol-related mortality is much higher among individuals who underwent treatment than those with AUD from the general population (Roerecke and Rehm, 2013).

An even graver concern relates to the predication of almost all available treatments on minimal or no etiological insight, the good intentions behind many of those

notwithstanding. Alcoholics Anonymous (AA)[4] is a good example. Ubiquitous in location and brand and with some degree of success (Dawson et al., 2012; Hasin and Grant, 2015), this treatment program is straitjacketed by the ideology of its administrators, being implemented under the aegis of recovered addicts proselytizing whatever general approach that seems to have worked for them. These individuals are typically nonprofessionals whose efforts and techniques "are seldom granted medical or psychological legitimacy, often for valid reasons" (Pihl and Peterson, 1995). Another example relates to generalized prevention programs (e.g. Drug Abuse Resistance Education [DARE]). Predicated on resisting social influence and aimed at decreasing drug abuse by preaching abstinence, the DARE has been factually found to produce a iatrogenic effect - i.e, increase drug use (reviewed in Werch and Owen 2002; also see Lilienfeld 2007; Schuckit et al. 2015).

Starkly stated, many available interventions for AUDs, be they ameliorative or preventative, appear to be heavily infused with the values and beliefs of their designers, as opposed to the characteristics of the addicted individual, no matter how clinically germane (Emrick and Hansen, 1983; Pihl and Peterson, 1995; Miller and Heather, 2013; Miller and Hester, 1986; Hester and Miller, 1989; Vaillant, 1983), and they are generally ineffective[5] because of that. This makes the dearth of resources deployed to deliver available interventions a problem that readily pales in comparison.

1.5 Problems with Current Nosology

The term 'alcoholism' describes a psychiatric condition in which alcohol is persistently and compulsively imbibed, unnecessarily leading to adverse outcomes in terms of one's health, interpersonal relationships and daily functioning. The "bible" of mod-

[4]Founded in 1935, AA is a fellowship of recovering addicts, who support one another other as they try to achieve abstinence; the 12 Steps Toward Recovery is a primary defining feature of AA. References of Higher Power, which is to be trusted by the abstaining alcoholics, are frequently made by AA members.

[5]Effective interventions are those that successfully obviate either or both alcohol-related morbidity and mortality rates remains

ern psychiatry, namely the Diagnostic and Statistical Manual (DSM), had up until and including its 4th version (DSM-IV-TR), discriminated between alcohol abuse and alcohol dependence (respectively, AA and AD). AD was defined as persistent and excessive use of alcohol despite significant negative consequences, in addition to physical dependence (tolerance or withdrawal) on the drug, whereas AA was described as a milder version of AD minus the dependence. This distinction, however, came to an end after empirical evidence had consistently left it unjustified (Kahler and Strong, 2006; Saha et al., 2006, 2010, 2012; Lynskey and Agrawal, 2007; Dawson et al., 2010; Borges et al., 2010; Kerridge et al., 2011; Hasin et al., 2013; Hicks and Zucker, 2014; Blanco et al., 2014).

In the latest edition of the DSM, DSM-5, the term 'Alcohol Use Disorders' (AUDs) is used to describe a continuum along which alcohol intake ranges from heavy and excessive to profoundly disordered (APA, 2013). Qualification for an AUD is satisfied when two or more of 11 listed behavioral diagnostic criteria are met during the same 12-month period, with the number of criteria endorsed corresponding to disorder severity[6]. While the unidimensional structure of AUDs is robust (Lane et al., 2016), and congruent with both theoretical (Martin et al., 2008, 2011, 2014) and empirical arguments (Cooper and Balsis, 2009; Casey et al., 2012; Hagman and Cohn, 2013; Rutter, 2013; Lane and Sher, 2015), meta-analytic evidence has suggested that replicability across studies is low and generalizability from any particular one lacking (Lane et al. 2016; also see Haeny et al. 2016).

This problem is a signature of a conceptual conundrum. Behavioral descriptors, which are all that the DSM uses to define mental disorders, do not explain psychological phenomena. Meaning, the DSM, a self-proclaimed explanatory system, essentially fails to explain (for recent reviews, see Mullins-Sweatt et al., 2016; Wakefield, 2016; Baglama, 2016). Responsible for this problem is the use of the medical model, whereby

[6]In the DSM-5, mild, moderate and severe AUDs are characterized by, respectively, two to three, four to five, and six or more behavioral and/or physiological symptoms (APA, 2013).

a set of symptoms is given a name (e.g."AUD"), the name called an "illness", and the "illness" presumed to be "curable" by the resolution its symptoms, with which it is equated and to which it is reduced, despite the fact that absolute deficiencies and causal mechanisms remain completely obscure and fundamentally untreated.

A detailed discussion of why despite - or in recognition of - the previously mentioned information, the field is yet to abandon the medical model, along with the biological reductionism originating from it, is beyond the scope of this thesis. The most salient point, nevertheless, is that ironically, American psychiatrists have purportedly always been philosophically opposed to the medical model (Hyman, 2010), which continues to be alive and well in psychiatry due to its dubious ties with the health insurance industry, and the prominence ascribed to the two systems associated with it, namely medicine and science, in a society like ours (see Pihl, 2010; Hyman, 2010; Kendler et al., 2011; Rutter and Uher, 2012; Kendler, 2016; Maj, 2016; Zachar and Kendler, 2007; Kendler, 2005a; Morgan, 2015; Lilienfeld and Treadway, 2016; Rose, 2016, for thoughtful essays).

No matter, the unalterable fact remains that "nosology necessarily precedes aetiology" (Cattell, 1940), and such could not be truer in the case of alcoholism, were the underlying pathways are divergent and disordered drinking is the only common denominator guaranteed to be seen in a group of individuals diagnosed with what the DSM portrays as being (but is not) the same (alcohol use) disorder.

1.6 Distinct Typologies for Alcoholism

The notion of distinct typologies for alcoholism or risk thereof has been around for decennia. From the earliest of Bowman and Jellinek (1941), to the more recent dimensional approach of Cloninger et al. (1988), the symptom cluster approach of Babor et al. (1992), and latent analysis approach of Bucholz et al. (1996), the focus has been on the differentiation by, among other theoretically germane variables, childhood and/ or

adolescence precursors, familial characteristics, patterns of, motives for and sensitivity to alcohol as well as personality profile and temperamental dispositions (Jellinek 1960; Cloninger et al. 1981; Babor et al. 1992; Del Boca and Hesselbrock 1996; Bucholz et al. 1996; Cloninger 1987a,b; Babor et al. 1992; Windle and Scheidt 2004; Vyssoki et al. 2011; Hesselbrock and Hesselbrock 1993; Kendler et al. 2015a; reviewed in Leggio et al. 2009; Lesch et al. 2011). Distinct inter-subtype definitional descriptors purportedly reflect and are governed by unique etiopathogenic mechanisms (Babor and Caetano, 2006; Kendler et al., 2012; Pombo et al., 2015; Litten et al., 2015), and if accurately characterized, should or would aid in predicting clinical outcomes (e.g, responsiveness to and/ or compliance with treatment), thus allowing that each subtype be matched for the most precise behavioral and pharmacotherapeutic intervention (Kadden et al., 1989; Litt et al., 1992; Mattson et al., 1994; Potgieter et al., 1999; Addolorato et al., 2005a,b; Bogenschutz et al., 2009; Leggio et al., 2009; Pettinati et al., 2010; Johnson, 2010; Meier et al., 2013; Litten et al., 2015; Pombo et al., 2015).

The current thesis is predicated on the concept of how alcohol consumption affects different motivational systems in different individuals, portends to specific pathways to abuse. According to the pharmacological vulnerability model (Sher, 1991), the subjective response to alcohol (SR)[7] significantly differs across individuals, and such differences are potentially relevant to the development of disordered drinking (see Sher and Vieth, 1999; Ray et al., 2016, for more details).

SR differs by a range of established risk factors for the development of AUDs (e.g, familial alcoholism; Morean and Corbin, 2010; Morean et al., 2015; Rueger et al., 2015; King et al., 2016; Trela et al., 2016; Morris et al., 2016), and as a function of personality profile (McDougall, 1929; Cleckley, 1982). Variations in personality profile correspond to distinct motivational systems (Pihl and Peterson, 1995; Conrod et al., 2000a; Castellanos-Ryan and Conrod, 2012; Blevins et al., 2016a; Wardell et al.,

[7]SR reflects individual differences in sensitivity to alcohol's pharmacological properties (see Quinn and Fromme, 2016), and is implicated in the panoply of theoretical accounts of problem drinking (Newlin and Renton, 2010)

2016), and predict the nature of drunken comportment and alcohol-related outcomes (for reviews, see Lejuez et al., 2010; Stautz and Cooper, 2013), with extant evidence suggesting that alcohol use in early teens is best explainble by personality profile (Heinrich et al., 2016). This predictive power is, in large part, driven by the ability of personality to determine susceptibility to the reinforcing effects of addictive substances, as per motivational accounts of drug abuse vulnerability (McDougall, 1929; Cleckley, 1982; Cox and Klinger, 1988; Cooper, 1994; Cooper et al., 1995; Pihl and Peterson, 1995; Conrod et al., 2000a). That is, how and to what extent one responds to an intoxicating dose of alcohol, subjectively and objectively, and what it is that alcohol does to and for him or her that significantly determines risk status (Erblich and Earleywine, 2003; Littlefield and Sher, 2010; Littlefield et al., 2013; Scott and Corbin, 2014; Leeman et al., 2014; Blevins et al., 2016a). Accordingly, alcoholism typologies that emphasize and classify persons with or at risk of alcoholism based on motivational systems "provide a particularly useful framework for examining the association between personality and SR to alcohol" (Morris et al., 2016).

Pihl and Peterson (1995) originally hypothesized four psychobiological systems that mediated the response to alcohol. These four neural systems, each with some degree of anatomical and biochemical uniqueness, were the psychomotor/ cue for reward system, the anxiety system, the analgesia system, and a cognitive control system. Each of these motivational pathways are putatively associated with distinct personality profiles that differentially predispose for AUDs and related SUDs (Castellanos-Ryan and Conrod, 2012; Littlefield and Sher, 2016; O'Leary-Barrett and Conrod, 2016; Cooper et al., 2016; Skinner and Veilleux, 2016; Viana and Stevens, 2016; Pedersen, 2016; King et al., 2016). Validation of the motivational hypothesis later came from a study by Pihl's group, in which 293 drug addicted women underwent an extensive battery of personality and symptom inventories and were found to classify according to relatively unique personality clusters (namely, anxiety sensitivity (AS), introversion-hopelessness, impulsive sensation-seeking (SS) and non-impulsive SS), and manifest distinct patterns of

addictive and nonaddictive psychopathology and coping skills deficits (Conrod et al., 2000a). Specifically, those in the AS cluster were likely to be diagnosed with specific phobia, somatization disorder, and dependence on anxiolytic substances. Those in the introversion hopelessness cluster were more likely to be depressive, socially phobic and opioid-abusing. Those with an impulsive personality profile were likely antisocial personality disordered with a dependency on both cocaine and alcohol. Those in the non-impulsive SS cluster were more likely to have an AUD that interestingly manifested itself in isolation from other psychopathologies (Conrod et al., 2000a). From the standpoint of pathology, these findings suggest that the form of drug abuse and co-occurring disorders may have the same underlying aetiology and it is what the drug does for the individual that produces differential effects that explains the commonality (Conrod et al., 2000a). In a subsequent laboratory study, Conrod et al. (2000b) randomly assigned of 1 to 3 brief (90-min) motivational interventions to 198 community-recruited substance abusing women. The interventions differentially targeted subject's personality profile and reasons for addictive substance use, and included (1) a personality-specific motivation-matched intervention; (2) a motivational control intervention; and (3) a motivation-mismatched intervention targeting a putatively different personality profile (Conrod et al., 2000b). A follow-up assessment at six months revealed that only the matched intervention was superior to the control intervention in ameliorating symptoms of alcohol and illicit substance misuse and averting utilization of numerous medical services (Conrod et al., 2000b). Similar result patterns have been obtained since by studies targeting motives to reduce problem use (Conrod et al. 2006, 2011; LaBrie et al. 2008; Banes et al. 2014; Blevins and Stephens 2016; Blevins et al. 2016b; Gilmore and Bountress 2016; also see McCarter et al. 2016; reviewed in Conrod and Nikolaou 2016; O'Leary-Barrett and Conrod 2016). Further, a brief and screening questionnaire, the Substance Use Risk Personality Profile (SURPS), has been developed, also by Pihl's group, to assess variation in preparedness for alcohol and other drug misuse as well as non-substance psychopathology along 4 dimensions: AS, hope-

lessness, SS and impulsivity (Conrod et al. 2000a; Woicik et al. 2009; for more details, see section 2.1). This instrument, with established psychometric properties and up to 91% in identifying individuals who would come to develop substance misuse or other psychiatric problems within the subsequent 1.5 years (Castellanos-Ryan et al., 2013), has been used in a series of targeted preventative interventions with youth, where both substance use and co-occurring pathology have been significantly reduced (e.g, Conrod et al. 2008, 2010, 2013; O'Leary-Barrett et al. 2013; reviewed in Conrod and Nikolaou 2016; O'Leary-Barrett and Conrod 2016). Moreover, the SURPS is particularly advantageous in that it is neither time consuming nor resource exhaustive (see section 2.1), whereas many of the instruments used to delineate other typologies are both, with some of them requiring as many as 17 assessment measures (Babor, 1996).

The above mentioned points to the promise for personalized interventions that target personality-specific motives for drug misuse (Conrod et al., 2000b), and suggests that reliance on the SURPS in differentiating at-risk persons is particularly opportune. Notwithstanding, the aforementioned studies, while supporting the need to differentiate abusers, are not instructive as to understanding the differential mechanisms involved.

1.7 The Need for Markers

The marked heterogeneity among individuals with or at-risk for AUDs provides a solid rationale for the search for endophenotypic markers (i.e, quantifiable biological markers of the genetic risk for the disorder; see Gottesman and Shields 1972; Gottesman and Gould 2003). For a marker[8] to classify as an endophenotype[9], it must meet a number of criteria: (1) it is exhibited by non-disordered individuals at-risk for the

[8] A marker refers to a pattern or component that is both sensitive and specific to one psychological state and therefore allows that reverse inference about that state be made based on the activation of said pattern.

[9] Note that the endophenotype concept is analogous to, but distinct from two other concepts with which it is sometimes interchangeably used and conceptually conflated, namely biomarkers and intermediate phenotypes. For an extended discussion of this issue, see Lenzenweger (2013).

condition at a higher rate than in the general population. That is, the presence of the marker predates and does not represent aftermath of the explosion and is a quantifiable phenotypes; (2) it correlates with theoretically relevant variables such as severity, gender and age of onset; and (3) it provides specific biological manifestations and is prospectively predictive (Gottesman and Gould 2003; also see Almasy and Blangero 2001; Cannon and Keller 2006; for critical reviews of the endophenotype concept, see Kendler and Neale 2010; Miller and Rockstroh 2013; Salvatore et al. 2015; Iacono et al. 2016). Satisfying these demands necessarily requires that at-risk persons be studied, the putative marker specific, and subjects prospectively followed. The advantages of the at-risk paradigm are many. Chief among them is that cause can be separated from the consequence, predictive factors clarified and the heterogeneity of the outcome and interactive factors studied. Just how one differentially responds to a drug before abuse develops, represents the window of opportunity to ascertain the involvement of potential mechanisms (for reviews of candidate endophenotypic markers for AUDs, see Hines et al., 2005; Porjesz and Rangaswamy, 2007; Rangaswamy and Porjesz, 2008; Karoly et al., 2014; Salvatore et al., 2015; Belin et al., 2016).

Earlier laboratory studies marshaled by, among other prominent researchers, Robert Pihl, have delineated two predisposing response profiles using samples of high-risk individuals, predominantly sons of alcoholics (SOA) who have a 4 to 9 times increased risk of the disorder (Goodwin, 1985; Cloninger et al., 1988; Mellentin et al., 2016). These were, respectively, the high heart rate (HHR) and the stress dampening responses to alcohol challenge.

The alcohol challenge paradigm[10] is of particular import as it is just what ingestion of the drug acutely does to and for one, both subjectively and objectively that should be fundamental to understanding why the drug is misused (see Pihl and Peterson, 1995; Strang et al., 2015; Bujarski and Ray, 2016), and such is especially true in the

[10]Procedurally, an alcohol challenge paradigm involves the administration of a standardized dose of alcohol as well as a placebo to the same individual on two separate occasions.

case of alcohol, a drug of abuse that unlike others, has no unique molecular targets in the central nervous system (Heilig and Spanagel, 2015). This explains why alcohol can act as an "upper" in some individuals and as a "downer" in others, something that cannot really be said of, for example, cocaine or heroin.

To the extent that the HHR and stress response dampening (SRD) represent two mutually exclusive phenotypes, they may be understood as phenomenologically distinct characteristics.

1.7.1 High Heart Response

When challenged with an intoxicating dose of alcohol, some SOA typically respond with a greater increase of heart rate versus controls, relative to their respective sober baselines (Levenson et al., 1987; Finn and Pihl, 1987, 1988; Finn et al., 1990; Wilson and Nagoshi, 1988; Pihl et al., 1989; Newlin and Thomson, 1991; Peterson et al., 1993, 1996; Conrod et al., 1997b,a, 1998, 2001; Newlin and Thomson, 1999; Carlson et al., 2002). This occurs on the rising limb of the blood alcohol curve and the curve itself is extended. That is, the excitatory response is maintained for almost three hours (Brunelle et al., 2007; Pihl et al., 2003). Throughout this period, the response positively correlates with scales that assess aspects of positive mood, in particular reports of increased energy, confidence and elation (Peterson et al., 1993; Pihl and Peterson, 1994; Conrod et al., 2001; Brunelle et al., 2004, 2005; Assaad et al., 2006; Corr, 2008; Fillmore et al., 2009). A large body of research has lent direct support to the proposition that this HHR response is an endophenotypic physiological of alcohol-produced rewarding stimulation ("high"; Fowles et al. 1982; Pihl et al. 2003; although contradictory findings have been reported by Marc Schuckit's group and others', e.g, Schuckit 1980, 1984; Schuckit and Smith 1996; Pollock et al. 1986; Pollock 1992; Neale and Martin 1989; Moss et al. 1989; McCaul et al. 1991; Heath and Martin 1992; Morzorati et al. 2002). Specifically the Pihl studies have demonstrated the reinforcing effect of said stimulatory response with alcohol, showing, for example, that when HHR respon-

ders (HHRRs) and healthy controls learned lists of words sober and then drank to intoxication and were asked on the following day (a second testing session) to recall the words learnt when sober, it was the HHRRs who recalled the most positive words (Bruce et al., 1999). Further, it is individuals who show heightened Behavioral Activation System (BAS) sensitivity (Dawe et al., 2004), and characteristics of aggression (Assaad et al., 2006), past delinquency (Assaad et al., 2006) and relative deficits on prefrontal neuropsychological tests (Pihl and Peterson, 1994; Harden and Pihl, 1995), and traits impulsivity and sensation seeking (Assaad et al., 2003; Peterson et al., 1996) that are most likely to demonstrate this response (also see King et al., 2002, 2011), and it is people demonstrating this response that are most likely to engage in risk-taking behavior after drinking (Goudriaan et al., 2007; Yan and Li, 2009; Huang et al., 2010; Gilman et al., 2012b; Kruschwitz et al., 2012).

Correspondingly, when alcohol challenged and then PET[11] (Positron Emission Tomography) scanned, it was the HHRRs who, compared to controls, demonstrated the greatest mesolimbic dopamine (DA)[12] activation (Boileau et al. 2003, 2007; Brunelle et al. 2004; for supporting evidence from animal research, see Nadal et al. 2002; Jupp and Dalley 2014). The Brunelle study also found that the HHR positively correlated with trait SS scores (Brunelle et al., 2004), and the same pattern of enhanced dopamine activation was later replicated in a study of subjects selected *a priori* for trait SS (Setiawan et al., 2011). These findings are consistent with those of other stimulant substances, such as amphetamines (Hutchison et al. 1999; Leyton et al. 2002; Riccardi et al. 2006; Kelly et al. 2006; Stoops et al. 2007; Carmen Arenas et al. 2016; Smith et al. 2016a; although see Zheng and Liu 2015), and cocaine (Martinez et al. 2004; Cox et al. 2009; although see Casey et al. 2014), which also preferentially af-

[11] A functional imaging technique that is used to observe metabolic processes in the body. The system detects pairs of gamma rays emitted indirectly by a positron-emitting radionuclide (tracer), which is introduced into the body on a biologically active molecule. If the biologically active molecule chosen for PET is fludeoxyglucose (FDG), an analogue of glucose, the concentrations of tracer imaged will indicate tissue metabolic activity as it corresponds to the regional glucose uptake.

[12] DA is the brain's neurotransmitter that predicts reward (see Leyton et al. 2007; Leyton 2010; although without necessarily directly enhancing subjective positive mood; Liggins et al. 2012).

fect the striatum in humans (Nutt et al., 2015), as well as drugs that may indirectly target the DA system, e.g, oxycodone (Zacny, 2010), non-substance related rewards (e.g, monetary; Weiland et al., 2016) and cues of forthcoming rewards (nb the former associated has to date only been documented in men; O'Sullivan et al. 2011; Milella et al. 2016; Leyton 2016).

These findings also reinforce the notion that hyper-dopaminergic function (in terms of DA release), in primarily the striatum, may contribute to the heightened reactivity to novelty and reward observed in individuals high in the aforementioned trait characteristics (Zuckerman 1990; Bardo et al. 1996; Krebs et al. 2009; reviewed in Norbury and Husain 2015; for animal evidence, see Piazza et al. 1989b; Hooks et al. 1991b,a, 1992, 1994), and resonate with explanations of addiction involving positive reinforcement (Wise, 1988; Koob et al., 1998; Leyton and Vezina, 2013, 2014; Wiers et al., 2016). Prospective investigations now show that precisely this rewarding stimulation profile that predicts later escalating use in the aforementioned segment of the population, above and beyond other measured risk factors, e.g, familial alcoholism (Hendershot et al., 2016; King et al., 2016; Jünger et al., 2016).

In sum, the HHR typically exemplifies externalizing high-risk persons. It is specifically rewarding stimulation (i.e, positive reinforcement) that this responding pattern signifies, and it is precisely through these positive reinforcement mechanisms that drinking behavior in these individuals is promoted and the path to escalating use paved (Pihl and Peterson, 1995).

1.7.2 Stress Response Dampening

When drinking behavior attenuates reactivity to subjective stress or perceived threat, it is viewed as negatively reinforcing, and in comparison to the HHR response, in a sense, can be seen as pain avoiding rather than pleasure inducing, and as a 'downer' rather than an 'upper'. Stress response dampening (SRD; Sher and Walitzer, 1986; Sher, 1987) represents a concept with considerable heritage, having morphed from

the tension reduction theories and studies that has begun in the 1950's (Conger 1956; Kingham 1958; also see Cappell and Herman 1972; Cappell 1987; Kushner et al. 1990). Many studies have demonstrated that this SRD effect is particularly pronounced in victims of fear (Levenson, 1980; Sher, 1987; Stewart and Pihl, 1994; Stewart, 1996; Cooper et al., 1995; Schroder and Perrine, 2007; Hefner et al., 2013), which has been commonly invoked as an explanatory mechanism for the frequent co-occurrence between alcohol problems and certain anxiety (and mood) disorders (Kushner et al., 2000, 2013; Wolitzky-Taylor et al., 2011; Karpyak et al., 2016; Stewart et al., 2016). For example, odds ratios for co-occurrence, have been reported as 1.64 for any anxiety disorder (Lai et al., 2015), 3.3 for PD, for GAD, and 2.5 for SAD (Regier et al., 1990; Himle and Hill, 1991; Naragon-Gainey, 2010). Anxiety-disordered persons are 2.6 times more likely to be alcohol dependent (Grant et al., 2004a; Hall et al., 2009), and more than a third of alcoholic adults are anxiety- (or mood-) disordered (Grant et al. 2004a; Hall et al. 2009; although see Cyders et al. 2016b).

Especially predictive of the SRD are dimensions of anxiety hallmarked by experiential avoidance and a markedly increased sensitivity to uncertainty (Hefner et al., 2013; Gorka et al., 2013, 2016b; Gorka, 2016). These are considered core aspects of specific anxious pathologies, namely SAD, PD and GAD, which explains why a recent meta-analysis of 22 epidemiologic comorbidity surveys found that among all anxiety-disordered, lifetime (and 12-month) prevalence of AUDs was highest in those with specifically, SAD ($\sim$ 25%), PD and GAD, in descending order (Lai et al., 2015). Chief among the aforementioned dimensions is AS ("fear of fear"; Reiss 1991; detailed in section 1.8.1). This trait has been consistently shown to predict motives for, patterns of and outcomes related to alcohol use (Brandon 1994; Breslau and Klein 1999; Stewart and Zeitlin 1995; Stewart et al. 1997a, 1999, 2001, 2002; Kushner et al. 2001; Schmidt and Zvolensky 2007; Goldstein and Flett 2009; Brandt et al. 2013; Chandley et al. 2014; Keough et al. 2015; Chavarria et al. 2015; Allan et al. 2015; Kraemer et al. 2015; reviewed in Samoluk and MacDonald 2014), including AUDs 2-years later

(Schmidt and Zvolensky, 2007). High anxiety sensitivity scores additionally correlate, positively and substantively, correlate with marked alcohol-produced anxiolysis (Conrod et al., 1998; MacDonald et al., 2000a; Stewart and Pihl, 1994; Stewart and Kushner, 2001; Stewart et al., 1999; Brown et al., 2001, 2002, 2009; Zack et al., 2007), and with using alcohol to decrease aversive affect, particularly that brought on bodily autonomic arousal (Stewart and Zeitlin 1995; Pihl and Peterson 1995; Stewart et al. 2001; Kushner et al. 2001; Chandley et al. 2014; Goldstein and Flett 2009; Novak et al. 2003; Kuntsche et al. 2006; for a critical review, see DeMartini and Carey 2011). As such, by drinking under stressful situations, anxiety-sensitive persons are effectively self-medicating (Quitkin et al., 1972; Stewart and Zeitlin, 1995). This drinking to cope (DTC) motive is also often endorsed by individuals high in either or both traits intolerance of uncertainty (IU; i.e, the tendency to find the possibility of an aversive event occurring to be, no matter how minute; Carleton et al. 2007; Oglesby et al. 2015; Kraemer et al. 2015; also see Banducci et al. 2016) and social anxiety (SA; i.e, the tendency to experience paramount concerns about being scrutinized by others; Watson and Friend 1969; Thomas et al. 2003; Carrigan and Randall 2003; Buckner et al. 2006; Stewart et al. 2006; Ham et al. 2007; Battista et al. 2010; also see Keough et al. 2016; Mulligan et al. 2016; Ham et al. 2016), two constructs that are very highly interrelated with anxiety-sensitivity and in which experiential avoidance and uncertainty are central elements (Kashdan et al. 2013, 2014; Wong and Rapee 2016; Torvik et al. 2016; Heeren and McNally 2016; Evans et al. 2016b; Thai et al. 2016; for more details, see section 1.8.1).

This information accords with the premise that it is individuals who display avoidant coping styles and hypersensitivity and exaggerated reactivity to uncertain threats that are most prone to DTC (Grant et al., 2007b; Field and Quigley, 2009; Moberg and Curtin, 2009; Moberg et al., 2011; Hefner and Curtin, 2012; Hefner et al., 2013; Gorka et al., 2013, 2016b) and to the most pronounced SRD under the influence of alcohol (Rousseau et al., 2011; Hefner et al., 2013). More broadly, this information is con-

sistent with a framework in which a hypersensitive Behavioral Inhibition (avoidance) system (BIS) marks individuals high in any or all of the aforementioned anxiety dimensions (Clauss and Blackford, 2012; Thai et al., 2016), making them attentionally biased for signals of potential punishment (Bantin et al., 2016), and more prone to drink because of that (Pihl and Peterson, 1995; Corr, 2008). Importantly, it is precisely the DTC motive that seems to predict and have been consistently linked to increased levels of both alcohol consumption and related consequences among persons who display the aforementioned response pattern under alcohol intoxication (Cooper et al., 1988, 1992b; Cooper, 1994; Cooper et al., 1995; Allan, 1995; Carey and Correia, 1997; Kushner et al., 2000; Kassel et al., 2000; Holahan et al., 2001; Park and Levenson, 2002; Ham and Hope, 2003; Baker et al., 2004; Kuntsche et al., 2005; Bolton et al., 2006; Kuntsche et al., 2008; Martens et al., 2008; Robinson et al., 2009; Merrill and Read, 2010; Chandley et al., 2014; Merrill et al., 2014; Blevins et al., 2016a), with some findings showing that DTC motive predicted alcohol related consequences, with drinking levels controlled for (Cooper et al., 1992a; Carpenter and Hasin, 1999) and above and beyond alcohol expectancies, depressive mood and perceived coping ability (Park and Levenson, 2002). Consistently, a large scale epidemiological study of a prospective and nationally representative sample (NESARC; $N = \sim 44,000$) demonstrated that among anxiety-disordered individuals, those who endorsed DTC motive, compared with those who did not, drank more heavily, and were more likely to classify as disordered drinkers at initial assessment and to develop a new one within the subsequent 3 years (Menary et al. 2011; also see Crum et al. 2013b,a). Even though the subjects with clinically anxiety conditions who reported no DTC motives exhibited some elevation in cross-sectional vulnerability for disordered drinking at baseline relative to those free of anxious psychopathologies, their prospective disposition was comparable and their daily alcohol intake was comparatively lower (Menary et al., 2011). Along these same lines, Wolitzky-Taylor et al. (2015) noted that it was anxiety sensitivity, but not distress tolerance that accounted for (i.e., statistically mediated) the relation-

ship between manifest indicators of the 3 anxiety phenotypes namely GAD, SAD and PD in a sample of high-schoolers aged 14-15. Thus, while AUDs and anxiety-disorders occur in frequent association, clinically anxious persons do not uniformly endorse DTC motives (for reviews, see Battista et al. 2010; Becker et al. 2011).

Note that the linkage between alcohol intake and negative affect is a two-way street, in which DTC is a central goal-oriented behavior with concomitant negative reinforcement perpetuating and fostering further alcohol use. This, in turn, worsens anxiety and other negative affect via neurobiological dysregulations and environmental disruptions/ consequences (the "vicious cycle") (Anker et al., 2016), as per the neurobiological model of allostatic adaptation in addiction (Koob, 2013; Koob and Le Moal, 2006). A final noteworthy piece of information is that whereas the aforementioned associations between trait AS and drinking-related outcomes are significant for both males and females (although see Stewart et al., 1997b, 2001, for null findings in men), they have generally been found to be comparatively larger in the latter (also see Stewart and Zeitlin, 1995; Pettinati et al., 1997; Conway et al., 2006; Karpyak et al., 2016; McHugh et al., 2016), with some indications that the link between AS, coping motives and heavy drinking (and incidentally benzodiazepines abuse; McHugh et al., 2016) is perhaps particularly pertinent for females (Chandley et al., 2014), although reports of males endorsing DTC motive more than females notably exist (Lawyer et al. 2002; reviewed in Nolen-Hoeksema 2012). This fact is in agreement with the National Co-Morbidity data (Kessler et al., 2005a), which shows approximately double the odds ratios for women with panic, phobia and general anxiety for alcohol dependence (also see Karpyak et al., 2016). Numerous studies have indicated that female alcoholics report drinking in response to unpleasant emotions more often than males (Pettinati et al., 1997; Conway et al., 2006; Karpyak et al., 2016) and many others have documented sex differences in fear/ anxiety processing, including brain structures and pathways involved in emotional processing (Grossman and Wood, 1993; Bettencourt and Miller, 1996; Asthana and Mandal, 1998).

In sum, the SRD pathway for escalating alcohol use typifies individuals whose personality style is avoidant, reactivity to uncertain threats exaggerated, and coping their primary motive for drinking. Because of that, they are more likely to drink when stressed, and have more to gain by procuring anxiolytic drugs including alcohol, relative to individuals not displaying said response profile under alcohol intoxication.

1.8 Two Predominate Risk Trajectories

The background research presented in the previous sections is broadly consistent with two alternative risk pathways that cut across conventionally defined AUDs: "internalizing" and "externalizing". These two phenotypes, roughly denoting the (respectively) inward and outward expression of emotional dysregulation (see Freud, 1965; Novick and Kelly, 1970; Furman, 1980; Liu, 2004; Rice, 2016), map onto distinct, albeit overlapping, brain systems and embody differential risk mechanisms (Cooper et al., 1995; Hussong et al., 2011; Lazareck et al., 2012; Nichter and Chassin, 2015; Strang et al., 2015; Farmer et al., 2016; O'Leary-Barrett et al., 2016), although the two phenotypic expressions occasionally coincide. The genetic, neurobiological and experiential signifiers reflected in this differentiation can and do predict the nature and degree of susceptibility and responsiveness to the ingestion of different substances of abuse. As such, the discussion here is not merely of new semantics but also of explanatory ones that more successfully capture the biological reality of the risk profile displayed by a given individual. Distinctions have also been made between constructs layered underneath each of the two aforementioned spectrums and their particularities on the aforementioned levels. It is additionally notable that while the externalizing trajectory has been extensively investigated and is considered to be the most prominent pathway to AUDs (Edwards et al. 2016; also see Squeglia et al. 2016), the internalizing pathway has received much less attention and seems to have been relegated to secondary status.

Of particular relevance to this thesis are two specific phenotypes, one internalizing,

namely anxiety-sensitive, and another externalizing, namely sensation-seeking.

1.8.1 The Anxiety-Sensitive Phenotype

Anxiety is experienced and expressed in multiple fashions. While anxiety related to external stressors is rather prevalent, it is the physical sensations and cognitive symptoms that emerge during a bout of anxiety which some persons fear most. This "fear of fear" is secondary to the belief that disastrous physical, psychological, or social consequences such as fainting, serious medical illness, death, insanity, or social humiliation and ostracism will potentially ensue (Reiss and McNally, 1985; McNally, 1989; Reiss, 1991; Taylor et al., 1992b; Taylor, 1993, 1999; Taylor et al., 2007; McNally, 1999; Adams et al., 2012; Battista et al., 2008; Allan et al., 2014; Stewart and Kushner, 2001).

The proclivity to specifically dread and catastrophically misappraise one's anxiety-related symptoms or sensations (e.g, heart palpitations, trembling, dizziness, sweating, muscle tension and inability to concentrate) is conceptualized within the anxiety sensitivity (AS) construct (Reiss et al., 1986; Reiss, 1991; Peterson and Reiss, 1992; Taylor, 1993). This trait has both heritable[13] (h^2 = 45%; Stein et al. 1999; Taylor et al. 2008) and developmental (e.g, childhood trauma; Scher and Stein, 2003) components. AS scores predict self-reported anxiety in response to laboratory biological challenges (e.g., carbon dioxide inhalation) independently from actual physiological arousal changes (Forsyth et al., 1999; Asmundson et al., 1994; Zvolensky and Eifert, 2001; Melzig et al., 2011), and severity of laboratory-elicited panic (Schmidt, 1999; Zinbarg et al., 2001). This trait also potentially serves as a cognitive predisposing and maintaining factor in multiple clinical anxiety conditions (Reiss and McNally, 1985; Reiss, 1991; Maller and Reiss, 1992; Taylor, 1999; Barlow, 2002; Schmidt et al., 2006; Schmidt and Zvolensky, 2007; Wheaton et al., 2012; Viana et al., 2016; Velasco et al.,

[13] h^2 refers to the proportion of total phenotypic variance that can be accounted for by genetic factors.

2016; Bakhshaie et al., 2016), especially those where fear of the unknown features heavily, specifically SAD (Kimbrel, 2008; Carleton et al., 2010), GAD (Viana and Rabian, 2008; Naragon-Gainey, 2010) and PD (Clark, 1986; McNally, 1990; Stewart et al., 1992; Taylor et al., 1992b; McNally, 2002; Pérez Benítez et al., 2009; Naragon-Gainey, 2010; Poletti et al., 2015). This is because, AS serves as an anxiety amplifier and tense arousal catalyst, as per the expectancy theory of anxiety; when persons high in this trait become anxious, they become preoccupied with the aversiveness of physical symptoms or sensations related to anxiety (e.g., palpitations), thus further perpetuating their anxious suffering (Reiss and McNally, 1985; Reiss, 1991).

Despite inconsistencies within the literature (Taylor, 1999), the most widely replicated factor solution of AS consists of three interrelated phenotypic but conceptually distinct subscale factors labeled Physical Concerns, Cognitive Concerns, and Social Concerns (for an illustration, see section 2.1; Zinbarg et al. 1997; Taylor 1999; Taylor et al. 2007; Sandín et al. 2004). There are indications that the three dimensions mat be related to specific psychopathologic manifestations (Zinbarg et al., 2001; Rodriguez et al., 2004; Grant et al., 2007a).

Trait AS is directly linked to SA (Watson and Friend, 1969; Asmundson et al., 1994; Orsillo et al., 1994; Ball et al., 1995; Anderson and Hope, 2009), and may be causally dependent on IU (Carleton et al., 2007; Carleton, 2016a,b; Wright et al., 2016; Ursa, 2016; Shihata et al., 2016), the latter having also been (independently) related to GAD (Ladouceur et al., 2000; Dugas et al., 1998; Dugas and Ladouceur, 2000; Dugas et al., 2004, 2005; Dugas and Robichaud, 2007; Holaway et al., 2006; Boelen and Reijntjes, 2009; Koerner and Dugas, 2006; Yook et al., 2010; Gentes and Ruscio, 2011; Zlomke and Jeter, 2014), SAD (Boelen and Reijntjes, 2009; Boelen et al., 2010; Carleton et al., 2010; Khawaja and McMahon, 2011; Teale Sapach et al., 2015; Hearn et al., 2016) and PD (Dugas et al., 2005; Simmons et al., 2008a; Buhr and Dugas, 2009; Fetzner et al., 2013; Carleton et al., 2013, 2014; Boelen et al., 2016). Importantly, the three aforementioned constructs and anxious pathologies share the same foundational

aspects and primary defining characteristics of experiential avoidance (Reiss, 1991; Carver and White, 1994; Fialko et al., 2012; Kaldewaij et al., 2016) and pronounced reactivity to uncertainty (McNally, 1990; Reiss, 1991; Taylor, 1995a; Clark, 1986; Neal and Edelmann, 2003; Barlow et al., 2004; Taylor et al., 1992b; Stewart, 1996; Grosse Holtforth, 2008; Kimbrel, 2008).

AS rates are higher in females than males (Stewart et al., 1997a, 2001; Bernstein et al., 2006; O'connor et al., 2008), which explains the female preponderance shown by the aforementioned anxiety disorders (Kessler et al., 2005a; McLean et al., 2011; Eaton et al., 2012b; Xu et al., 2012; Baxter et al., 2013). There is also evidence to suggest that the importance of genetic influences on the trait vary as a function of sex and are greater in the female sex (Taylor et al., 2008).

As a continues trait that predisposes for AUDs (see section 1.7.2), while also participating in the development, maintenance and/ or perpetuation of a set of highly debilitating and burdensome internalizing pathologies, AS makes for an appealing target for human high-risk research.

1.8.2 The Sensation-Seeking Phenotype

Sensation-seeking (SS) is a multifaceted personality trait that subsumes the generalized tendency to seek out and engage in experiences that are varied, novel and emotionally intense - even when an element of significant risk is involved (Zuckerman, 1979, 1994, 2007). Other researchers have used different terms to characterize what is essentially the same construct or components thereof (e.g. novelty seeking, arousal seeking, thrill seeking, experience seeking, disinhibition, venturesomeness, excitement seeking, fun seeking, susceptibility to boredom; Zuckerman 1994, 2005; Bardo et al. 1996; Arnett 1994; Wohlwill 1984). SS is an aspect of extroversion (Zuckerman et al., 1972; Aluja et al., 2003; Whiteside et al., 2005). It is a moderately heritable trait ($h^2 = 40\% - 60\%$; Eysenck 1983; Fulker et al. 1980; Koopmans et al. 1995; Hur and Bouchard Jr 1997), with genetic influences primarily accounting for the inter-correlation between its facets

(Koopmans et al., 1995). Twin studies indicate no sex differences in the magnitude or nature of genetic effects on sensation seeking (Eysenck, 1983; Koopmans et al., 1995), although males who score high in SS measures outnumber females (Kramer et al. 2008; Shulman et al. 2015; also see Cyders et al. 2016a; Smith et al. 2016c).

Individuals high in SS generally perceive the world as 'non-threatening' (Franken et al., 1992; Mujica-Parodi et al., 2014; Norbury and Husain, 2015), and underestimate physical risk incurred by various activities (e.g, sky-diving; Mujica-Parodi et al., 2014; Zheng et al., 2015), as indicated by behavioral, electrophysiological, endocrine and neurofunctional data. When challenged and/ or faced with aversive information, they (compared with non-SS controls) are (1) less subjectively anxious or not at all anxious (Blankstein, 1975; Schwarz et al., 1978; Franken et al., 1992; Mujica-Parodi et al., 2014); (2) less physiologically responsive or prone to defensive reactions (e.g, cortisol, affective startle reflex, skin conductance and HR; Schulkin et al., 1994; Herman et al., 2003a; Sorocco et al., 2006; De Pascalis et al., 2007; Mujica-Parodi et al., 2014); and (3) neurally hyposensitive or insensitive altogether (e.g, weaker AMYG response, reduced error-related negativity (ERN) amplitude and diminished P300[14]; Santesso and Segalowitz 2009; Cservenka et al. 2013; Zheng et al. 2014; Mujica-Parodi et al. 2014; Zheng et al. 2015; Zheng and Liu 2015; also see Orsini et al. 2015). The opposite is however true when it comes to reward cues (e.g, greater NAc activation Kruschwitz et al. 2012) and high-arousal material (e.g, stronger aINS response Joseph et al. 2009).

Furthermore, healthy SS young adults are highly susceptible to experimentally elicited alcohol-related aggression (Cheong and Nagoshi, 1999; Joireman et al., 2003; Dahlen et al., 2005; Pihl and Sutton, 2009), and to report "angry driving" (Dahlen et al., 2005), drive under the influence and engage in risky sexual behavior (Donohew et al., 2000; Gonzalez et al., 2005; Spitalnick et al., 2007). Moreover, when given the

[14]P300 component is "a positive-going waveform in the electroencephalogram that occurs approximately 300 ms after the onset of a stimulus, and is related to the attentional and working memory demands of a task" amplitude (Donchin and Coles, 1988; Castellanos and Tannock, 2002).

opportunity to self-administer unusual sensory stimulation that non-SS persons find aversive and avoid, sensation-seekers find it intrinsically rewarding and behaviorally invigorating, seeking to administer it at increasing intensities if at the cost of monetary loss, a behavior diminishable by antagonism at the D2 receptor (Norbury et al., 2015). The aforementioned outcomes that can be understood within a framework in which individuals high (versus low) on SS trait display a hyperactive approach system (Joseph et al. 2009; Kruschwitz et al. 2012; Manzo et al. 2014; also see Kelly et al. 2006; Stoops et al. 2007) and a hypoactive avoidance system (Lissek et al., 2005; Lang et al., 2005; Santesso and Segalowitz, 2009; Zheng et al., 2014; Manzo et al., 2014).

Interestingly, there are indications that the predilection of SS persons for arousal tends to obviate valence in the face of intensely arousing material, contrarily to non-SS individuals who tend to be more focused on emotional content than arousal (Feldman, 1995; Joseph et al., 2009; Norbury et al., 2015). For example, when exposed to high-arousal pictorial stimuli, healthy SS adults have been found to more strongly activate neural structures associated with reinforcement and (e.g, insula) than their low-SS peers, irrespective of emotional content (Joseph et al., 2009). Consequently, high SS individual are more prone to misuse licit and illicit drugs and are more likely to engage in risky sexual behaviors or excessive gambling compared with individuals low in this trait (Bardo et al., 1996; Roberti, 2004). Animal models of addiction support the premise that SS is associated with the use of psychostimulants (Blanchard et al., 2009). In humans, SS trait predicts risk for the initiation of drug use (Stephenson and Helme, 2006; Sargent et al., 2010; Spillane et al., 2012; Nees et al., 2012), is a powerful predictor of drug use among adolescents (Martin et al., 2002; Hampson et al., 2008) and adults (Crawford et al., 2003; Gerra et al., 2004; Hittner and Swickert, 2006), and differentiates between students who self-drug and those who do not. This increased tendency to engage in use of addictive psychoactive substances appears to be a fundamental, even if an unnecessary part of a broader tendency to seek novel experiences (Ersche et al., 2013a), with converging lines of evidence suggest that exposure to nov-

elty and addictive drugs may involve overlapping neural networks (Bunzeck and Düzel, 2006; Reichel and Bevins, 2008; Gabbay et al., 2010; Fukushiro and Frussa-Filho, 2011). Importantly, Holmes et al. (2016) have recently established the presence of links between SS and neuroanatomical features in a large cohort ($n > 1000$) of healthy drug-naïve young adults. Indeed, SS contributes to the escalation into externalizing psychopathologies and worse symptom severity, and in fact its genetic influences have been found to be largely shared with AUDs and conduct disorder (Slutske et al., 2002). As such, high levels of SS trait have been documented in individuals with (Gerra et al., 2004; Hittner and Swickert, 2006; Noël et al., 2011; Jupp and Dalley, 2014) or at risk of SUDs (Pascual et al., 2006), including pathological gamblers (Fortune and Goodie, 2010). Notably, SS frequently co-presents with impulsivity (see Finn et al., 1992; Conrod et al., 1997a; Whiteside and Lynam, 2001), a well-established endophenotype for AUDs (Ersche et al., 2010b), and the aetiological mechanisms of the two considerably overlap (Jupp and Dalley, 2014). SS and impulsivity are however not synonymous or interchangeable and important distinctions between their developmental trajectories (Collado et al., 2014) abound neurobiological underpinnings (Ersche et al., 2013a; Jupp and Dalley, 2014; Holmes et al., 2016). Importantly, SS arguably possesses explanatory power, separate from that of impulsivity (Norbury and Husain, 2015; Holmes et al., 2016; Mann et al., 2017), and extant evidence appears to support of the premise that this trait is a promising endophenotypic marker for fundamentally disinhibitory/externalizing psychopathologies, including (externalizing forms of) SUDs and AUDs (Benjamin et al., 2001; Gottesman and Gould, 2003; Krueger et al., 2007; Derringer et al., 2010).

Notwithstanding, findings that call into question the notion that SS truly represents an endophenotype of addiction risk have also been reported (e.g, Whiteside and Lynam, 2001; Ersche et al., 2010b). For example, Ersche's group found that (1) both psychostimulant (cocaine) addicts and their non-drug using siblings were highly impulsive but only the former were also high in SS (Ersche et al., 2010a, 2013a); and

(2) both psychostimulant (cocaine) addicts and recreational cocaine users who have been regularly consuming said drug (for 8 years) were high in SS but only the former were impulsive (Ersche et al., 2013a). The investigators argued that the non-SS personality profile of the unaffected siblings may have protected them from engaging in drug-taking behaviors, and that while high sensation seekers seem more likely to experiment with drugs, they are not necessarily at risk for abusing them if they have no familial vulnerability, despite continuous use (Ersche et al., 2013a). Animal models of addiction also support the proposal that sensation-seeking traits are associated with the use of stimulant drugs (Belin et al. 2008; Marinelli and White 2000; Piazza et al. 1989a; also see Flagel et al. 2010; Saunders and Robinson 2010; Beckmann et al. 2011), but not necessarily escalation into compulsive use (Belin et al., 2008), although escalating cocaine self-administration has been found in rats selectively bred for novelty preference (but not assessed for impulsivity prior to drug exposure; Belin et al. 2011; reviewed in Blanchard et al. 2009; Jupp and Dalley 2014). It is possible that in rodents, reactivity to novelty and impulsivity contribute to distinct phases of cocaine self-administration[15] (initiation and persistence; Dalley et al., 2011). It is also conceivable that impulsivity and sensation-seeking traits interact with each other to drive risk for addiction (Jupp and Dalley, 2014). More research is however needed to sort out alternative explanations.

1.9 The Importance of Delineating Neurophenotypic Markers of Risk of AUDs and related SUDs

Ever since the start of the Decade of the Brain, the field has been in a headlong rush to identify the genetic and neurobiological causes of AUDs and SUDs. Thus far, it has delineated none, and very little remains known about why and how disordered use develops and in whom. Enough "lessons" have nonetheless been learned and

[15] A form of operant conditioning using a drug as a reward, generally by administration through an intravenous line that is controlled directly by the animal's actions.

discoveries made to provide valuable topographical information to indicate where the further research for aetiological knowledge is likely to pay off (see Suckling and Nestor, 2016; Ekhtiari et al., 2016). First, while alcoholism is at least moderately heritable (∼ 50%–60%; Sullivan et al. 2012; Ystrom et al. 2014; Enoch 2014; Verhulst et al. 2015; Kendler et al. 2016d,a; Huibregtse et al. 2016), it is not advisable to search for genes that singularly cause AUDs, or endophenotypic markers thereof, because such genes (almost) certainly do not exist[16] (Hamer 2002; Kendler 2005b; Miller 2010; Dick et al. 2010; Kendler 2013; Pihl and Abu Shakra 2014; Pihl 2014; Clarke et al. 2015). No argument against this is defensible based on available data, and by logical deduction necessarily assumes that the extraordinary complexity of alcoholism is reducible to some simple linear and powerful associations between single genetic loci and alcohol-related phenotypes (it is not; Hamer, 2002; Kendler, 2005b; Kendler et al., 2016b; Edwards et al., 2016), and that genes function to cause a mental disorder (they do not, genes alter biochemical processes; Pihl and Abu Shakra, 2014; Salvatore et al., 2015).

Second, the genetics of AUDs may, after all, be the genetics of neural development (Pihl 2010; Insel and Wang 2010; Insel 2010; Labonté et al. 2012; also see Barsky and Gaysina 2016). Meaning, early brain development is arrested in a fashion that sets the stage, without necessarily dooming one, for alcohol abuse. In otherwise slightly overlapping - or not at all overlapping - lists of 'candidate genes'[17] identified across molecular genetic studies of (risk of) AUDs, functional involvement in neurodevelopmental nervous-system related processes is the common denominator (see van den Oord et al. 2008; Calboli et al. 2010; Verweij et al. 2010; Terracciano et al. 2010;

[16] The one exception to this statement is variations in genes encoding alcohol metabolizing enzymes, namely aldehyde dehydrogenase (Harada et al., 1982; Dick, 2011; Wu et al., 2016a) and alcohol dehydrogenase (Whitfield, 1997, 2002; Thomasson et al., 1991; Luczak et al., 2006; Edwards et al., 2015), which have been robustly associated the initial sensitivity to alcohol, a known risk marker for AUDs (also see Hart et al., 2015; Edwards et al., 2015; Salvatore et al., 2015). These variations are determined by ethnicity (Thomasson et al., 1995; Mulligan et al., 2003; Birley et al., 2009; Bierut et al., 2012; Hurley and Edenberg, 2012; Morozova et al., 2014; Hart et al., 2015).

[17] A candidate gene is a gene thought to contribute to a certain phenotypic manifestation.

De Moor et al. 2012; Service et al. 2012). Such processes are pivotal for the orchestration of neurogenesis and include neural cell adhesion, signal transduction, axonal pathfinding and synaptic plasticity, to name a few (see Joslyn et al., 2010, 2011; Morozova et al., 2012; Rietschel and Treutlein, 2013; Morozova et al., 2014; Edwards et al., 2015; Salvatore et al., 2015). Pathways subserving those processes involve hundreds of genes (Walsh et al., 2008), and interruption of anyone of those genes could confer vulnerability for the same phenotypic expression (e.g, AUD).

The story of schizophrenia (SZ), a neurodevelopmental disorder with heritability estimated at upwards of 85% (Cardno and Gottesman, 2000; Sullivan et al., 2003; Purcell et al., 2009), is illustrative and constructive. Across families with high genetic loading of the disorder ("multiplex"[18] pedigree), affected probands are 3-fold richer in rare copy number variants (CNVs, also known as genomic microduplications and microdeletions) than their ancestry-matched controls (Walsh et al., 2008; Kirov et al., 2009; Buizer-Voskamp et al., 2011). However, the genetic fingerprints of the CNVs disposing to SZ are unique to single cases or families and specific genes that "code for" SZ have been hunted for, but are yet nowhere to be found (reminiscent of Tolstoy's famous saying What is critically shared across said "private mutations", nevertheless, is the capacity to stunt brain development, through disrupting genes that are substantially overrepresented in pathways of neural maturation and regulation (Walsh et al. 2008; also see Ahn et al. 2014; Hall et al. 2015; Singh et al. 2016).

There is more. The same rare CNV that disposes for SZ in one family member can predispose for bipolar disorder in another and autism in yet another (Walsh et al., 2008; Friedman et al., 2006; Szatmari et al., 2007; Kirov et al., 2008; Kumar et al., 2008; Rees et al., 2016). This piece of information resonates with indications within a body of literature indicating that AUDs share their genetic underpinnings with other addictive (Rietschel and Treutlein, 2013) and non-additive psychopathologies (Dick et al., 2009;

[18]Multiplex pedigree is a family constellation containing two or more affected probands (for more details, see Sullivan et al., 2012).

Dick, 2011; Khemiri et al., 2016; Verweij et al., 2016; Ashenhurst et al., 2016), and that the same genetic influences can be associated with differential behavioral expressions within the same individuals across the developmental trajectory, manifesting e.g, as conduct problems earlier in development, before playing a role in adult alcohol abuse (i.e, heterotypic continuity; Dick 2011; Ormel et al. 2014). Such is a testament to how severely current classification systems blur the picture, as mental disorders are dimensional, multilevel, fuzzy and messy phenomena, and the DSM obscures all of the above (Kendler, 2005a; Kendler et al., 2011; Nesse and Stein, 2012; Heinz et al., 2016; Stephan et al., 2016).

Another important fact to consider is that the nature versus nurture debate - ongoing, heated and frequently contentious - is inherently sterile, ideologically driven and highly irrelevant (Dick et al., 2010; Pihl, 2010; Insel and Wang, 2010). Because the heritability of AUDs is not 100%, and human beings do not exist in a vacuum, nongenetic (or environmental) effects must matter (Pihl, 2010; Dick et al., 2010; Schellekens, 2016), and they do in more ways than one. For example, environmental influences (e.g, parental monitoring during adolescence) can modulate the relevance of the genetic (and vice versa), and even turn specific genes "on" or "off", much like a light bulb on a dimmer switch (see Dick, 2011; Pihl and Abu Shakra, 2014). This is not only true of AUDs. Even the genes involved in tumorigenesis have been shown to be down-regulated, numbered in the hundreds, as a result of making lifestyle modifications (i.e, diet; Ornish et al. 2008). The point being, genes are not static and they are certainly not destiny.

A final "lesson" that helps further narrow the search field is this: while most of what is known about AUDs and SUDs derives from studying the lifetime disordered, drawing legitimate causal inferences with respect to causation using this approach and absent a snapshot of the brain prior to the development of the full-blown condition is a virtual impossibility (see Bjork and Gilman, 2014; Xiao et al., 2015; Dupuy and Chanraud, 2016). The ability of alcohol to impinge on the psychology and biology of the organism

is well-documented (Goodlett and Horn, 2001; Oscar-Berman and Marinković, 2007; Schulte et al., 2012; Baker et al., 2013; Gulley and Juraska, 2013; Petit et al., 2014; Squeglia et al., 2014a; Spear and Swartzwelder, 2014; Spear, 2014, 2015; Fauth-Bühler and Kiefer, 2016; Volkow et al., 2016; Silveri et al., 2016; Cservenka and Nagel, 2016; Shokri-Kojori et al., 2016), and there is now sufficient evidence to corroborate addiction models whereby the chronic misuse of alcohol or other drugs culminates in unremitting neuroadaptations (McEwen and Gianaros, 2011; Hefner et al., 2013). Given that, and the apparent fact that neuroanatomical and neurofunctional irregularities are often present in high-risk persons before their drug use 'career' has even begun, it is exceedingly difficult, if at all logically plausible, to determine by studying those who chronically drink to excess or used to, whether and to what whether and to what extent observed neural dysfunction and/ or dysmorphology predated, resulted from or got exacerbated by the explosion.

Taking note of the above mentioned, individuals who are at-risk for alcoholism but otherwise psychopathology-free and ideally, with little or no addictive substance experience, seem to be, in many respects, the perfect subjects for researchers interested in investigating and elucidating the causal mechanisms underlying AUDs. The succeeding sections are therefore dedicated to the neuroimaging studies of those individuals.

These studies are classified according to their outcome measures (functional versus structural) and design: cross-sectional, whereby data collected at one specific point in time is analyzed, versus the more recently emerging prospective studies, in which baseline brain imaging data is used to predict subsequent alcohol use or misuse, therefore allowing for a comparatively more definitive link between neural signaling patterns and vulnerability to be established.

1.9.1 Functional Neuroimaging Markers

The heritability of brain function has been generally estimated at $\sim$ 40% (Jansen et al., 2015).

Functional Magnetic Resonance Imaging (fMRI) studies have identified a number of neurofunctional aberrations in high-risk individuals, those often a positive family history of alcoholism (FHP)[19] adolescents with minimal to no prior drug use, contrasted against matched family history negative (FHN)[20] controls (for a meta-analysis, see Mackey et al. 2016).

1.9.1.1 Executive Function

Response inhibition and working memory are two aspects of executive functions that predict the first alcoholic drink and first binge drinking episode in alcohol naïve young adolescents (Peeters et al. 2015; although see Boelema et al. 2016; reviewed in Takagi et al. 2016).

Inhibitory control. Inhibitory control, the ability to suppress ill advised impulses and behave in accord with age appropriate socially defined norms (Stevens et al., 2007; Luna et al., 2010), and can be considered a top-down system that dramatically matures during adolescence (Durston et al., 2006; Velanova et al., 2008). This development occurs alongside and symbiotically with a transition of the neural activation patterns seen during response inhibition, purportedly, from diffuse prefrontal and parietal to localized prefrontal activation (Luna and Sweeney, 2004; Luna et al., 2010; Wetherill et al., 2013b). This characteristic is a core neurocognitive dimension that predicts key alcohol and other drug related outcomes (Wills et al. 1996; Rohde et al. 1996; Miller and Plant 2002; Young et al. 2009; recently reviewed in Moeller et al. 2016).

Cross-sectional studies. Consistent with earlier laboratory-based reports of impulsive characteristics in high-risk offspring (Aronson and Gilbert 1963; Saunders

[19]FHP is often defined as at least one biological parent or two or more second-degree relatives diagnosed with AUDs (e.g, Schweinsburg et al., 2004; Andrews et al., 2011; Cservenka and Nagel, 2012; Sjoerds et al., 2013).

[20]Individuals classify as FHN if they have an absence of familial alcoholism in first (e.g, Heitzeg et al., 2010) or first and second-degree relatives (e.g, Cservenka and Nagel, 2012; Squeglia et al., 2014b).

and Schuckit 1981; Knop et al. 1985; Schulsinger et al. 1986; Pihl et al. 1990; Nigg et al. 2004; Saunders et al. 2008; also see Ryan et al. 2016), numerous studies have established the presence of early-occurring neurofunctional irregularities connoting cognitive dyscontrol in this vulnerable population (recently reviewed in Heitzeg et al., 2015; Cservenka, 2016; Moeller et al., 2016). Such aberrations have often been shown using the Go/no-Go task[21], and typically absent observable behavioral differences as a function of risk status. For example, Schweinsburg et al. (2004) FHP alcohol-naïve teens aged 12-14 underactivated, among other frontal areas, the left middle frontal gyrus (MFG) during response inhibition ('no-Go') trials, relative to matched controls, despite comparable task performances and verbal intelligence scores in the two groups (Schweinsburg et al., 2004). Heitzeg et al. (2010) found that unlike their low-risk counterparts, offspring of alcoholics (OOA, age 16-21) did not deactivated the ventral caudate during successful response inhibition, and the worse their externalizing symptoms, the weaker the deactivation (Heitzeg et al., 2010). This sort of aberration suggests OOA had to exert greater neural effort so as to successfully performed on the task, and is likely a signature of a defective affective neurocircuitry that might deter proper motivational responding (Heitzeg et al. 2010; also see Hardee et al. 2014). The same study also showed, nonetheless, that OOA who were heavy drinkers ('vulnerable') also failed to deactivate orbital and (left) medial prefrontal sites, a response that low-risk controls and OOA without drinking problems ('resilient')[22] both showed, with less deactivation corresponding to greater alcohol and other drug use (Heitzeg et al., 2010). This observation could suggest that heavy alcohol consumption on part of genetically liable persons impinges on prefrontal "control" mechanisms, causing fur-

[21]The Go/no-Go is neuropsychological task that is widely used to assess inhibitory control of behaviour. Subjects are required to rapidly respond (by pressing a button) to one stimulus type (frequently appearing 'go' signals) while refraining from responding to another (infrequently appearing 'no-go' signals).

[22]Resilience means to most people "achieving a positive outcome in the face of adversity". This can involve "bending and not breaking," that is, recovering from a bad experience. Or it can involve an "active resistance" to adversity through coping mechanisms that operate at the time of trauma (Karatsoreos and McEwen, 2011) (McEwen et al., 2015; McEwen, 2016).

ther aggravation and dysregulation of the frontostriatal motivational circuitry (Heitzeg et al., 2010).

In the same vein, DeVito et al. (2013) found that FHP young adults were as successful as FHN controls matched on drinking characteristics at withholding proponent responses ('no-Go'), but more robustly activated the (left) anterior insula (aINS) and inferior frontal gyrus (IFG) during successful inhibitions. This effect was primarily driven by FHP males, and correlated with higher self-reported trait impulsivity scores (DeVito et al., 2013). Collectively, the aforementioned findings point to a pattern of blunted frontal activity during inhibitory control as a precursor of escalating drinking in FHP persons (Heitzeg et al., 2015).

Exceptions in the literature, however exist, albeit in the context of comparatively more complex inhibitory control tasks, such as the Stroop[23] task. Specifically, greater temporo-parietal activity has been found in FHP young adults in response to the "incongruent versus congruent trials" contrast (Acheson et al., 2014), and hyperactivation in frontal sites subserving response inhibition (e.g. middle frontal and cingulate gyri) in FHP youngsters (age 8-19 years) during Stroop interference (Silveri et al., 2011), relative to FHN matched controls, perhaps alluding to compensatory mechanisms stemming from the lacking refinement and efficacy of said neural network. The inconsistency of aforementioned findings is explainable in a number of non-mutually exclusive nor collectively exhaustive ways. First, the Stroop task is, by design, more complex and cognitively demanding than the Go/no-Go task as well as most other tasks used to probe inhibitory control (Jacobus and Tapert, 2013), and might thus uncovers neurofunctional differences in more effortful contexts. A second, source of variability potentially relates to different developmental epochs under study.

[23] A neuropsychological task commonly utilized to investigate response conflict. Respondents view words printed in colors that are are either congruent with the word meaning (e.g, blue printed in blue) or incongruent (eg., blue printed in red), and have to name the color of ink in which a word is printed. Doing so correctly would require that on incompatible trials, subjects successfully inhibit the proponent tendency to read the word's text in order to correctly report the colour of the word. Impaired performance on Stroop task is associated with prefrontal cortex dysfunction.

As pointed out previously, the capacity to suppress inappropriate responses improves throughout childhood into early adolescence (Tottenham et al., 2011), a phenomenon that occurs alongside and symbiotically with the maturation of the neurocircuitry governing impulse control (Rubia et al., 2006; Heitzeg et al., 2015). On these bases, it may be speculated that the wide age range exemplifying the sample ascertained by Silveri et al. (2011) somehow and to some extent obscured highly relevant developmental variations (Heitzeg et al., 2015). This supposition finds support in the recent work of Hardee et al. (2014), in which FHP and FHN youngsters with minimal or no prior drug use were MRI scanned during the Go/no-Go task at age 7-12 and then again every 1 to 2 years up to and including age 17 (Hardee et al., 2014). These researchers found that age interacted with risk status to significantly influence neural signaling within caudate, middle cingulate, and middle frontal gyrus during successful response inhibition: at baseline testing, comparably blunted activation evinced in FHP subjects Hardee et al. 2014; consistent with prior evidence Schweinsburg et al. 2004; McNamee et al. 2008). With age, caudate and MFG activity decreased in FHN but not FHP subjects, with the latter additionally exhibiting enhanced middle cingulate activity (Hardee et al., 2014). It is therefore plausible that the pattern of differences in neural activation as a function of familial alcoholism changes across the developmental trajectory over the course of development (Hardee et al., 2014). A third possibility is that, the increased BOLD activation seen in FHP persons during successful inhibition within frontal (DeVito et al., 2013) and parietal regions (Acheson et al., 2014) reflects a protective neural mechanism against the development of AUDs and efficient cognitive control functioning in these individuals (Cservenka, 2016).

Prospective studies. A recently emerging body of neuroimaging research has established the ability of early inhibitory functioning in adolescents with minimal to no lifetime drug use to prospectively predict escalating use. The first prospective study to do so was conducted by Norman et al. (2011) on a sample of youngsters 12-14

year-olds. At baseline, subjects performed the Go/no-Go task in the MRI scanner. At a 4-year follow-up, subjects were assessed for potential changes in drinking habits and accordingly divided into two groups: TRAs (those who escalated into heavy drinkers) and abstainers/ controls. Analyzing the neural responding patterns by transitioning status, the researchers found extensive underactivation in frontal, parietal, and temporal and striatal sites during response inhibition at baseline among 'TRAs' (Norman et al., 2011). Similarly, in a latter study of high- and low-frequency substance users, hypoactivity of the ventromedial prefrontal cortex (vmPFC) during response inhibition at study entry (age 16-19) predicted more drug and alcohol dependency symptoms 1.5 to 3 years later, above and beyond baseline symptoms and lifetime drug use, particularly in high-frequency users (Mahmood et al., 2013). The sane study also found that enhanced (left) angular and supramarginal gyri activity during response inhibition ('no-Go') trials predicted more total drug use occasions at follow-up, an effect that was also most evident in high-frequency users (Mahmood et al., 2013). This response pattern hints at deployment of an alternate strategy to compensate for a relative weakness in said function (Mahmood et al., 2013; Heitzeg et al., 2015), as the left angular and supramarginal gyri are not among brain regions commonly linked inhibitory control (Grabner et al., 2007; Hartwigsen et al., 2010). Left unanswered, however, was the question of whether the emergence of heightened risk-related activation is a developmental effect related to the older age of subjects (e.g., compared with Norman et al. 2011; Schweinsburg et al. 2004) as the previously cited study of Hardee et al. (2014) might suggest, or whether it is accounted for by the inclusion of high-frequency drug users (Mahmood et al., 2013). In another study, subjects performed theGo/no-Go task task while undergoing fMRI scanning twice: once at 12-17 years of age when they were drug-naïve, and again $\sim$ 3 years later, after some of them had come to classify as heavy drinkers ('TRAs') (Wetherill et al., 2013b). The investigators found that during response inhibition ('no-Go' trials) at baseline, 'TRAs' and 'non-TRAs' (respectively) deactivated and activated neural structures that foster inhibition (e.g,

middle frontal gyri and inferior parietal lobule; congruent with results described earlier Hardee et al. 2014; Schweinsburg et al. 2004; Norman et al. 2011; Mahmood et al. 2013). At follow-up, however, the picture completely shifted such that 'TRAs' displayed activation and 'non-TRAs', deactivation (Wetherill et al., 2013b). The authors went to suggest that initiation of heavy drug use during adolescence may hamper the efficiency of the response inhibition circuitry, as indexed by overactivation (Wetherill et al., 2013b). Thusly, diminished inhibitory control functioning could be related to risk prior to escalating into heavy use, while after escalation has occurred, ineffective allocation of "neural resources" may become more relevant (Wetherill et al., 2013b; Heitzeg et al., 2015).

Other prospective investigations using the same paradigm have alternatively focused on brain functioning during inhibition control errors (as opposed to successful inhibitions) as a potential marker of risk (Heitzeg et al. 2014a; Whelan et al. 2014; reviewed in Heitzeg et al. 2015). Specifically, a study by Heitzeg et al. (2014a), showed that at baseline, drug-naïve 9-12 year-olds who classified as 'TRAs' 4 years later underactivated the neural circuitry that promote error monitoring (e.g, middle frontal gyrus) to inhibitory errors, relative to 'non-TRAs'. This response pattern was associated with worse severity of externalizing symptom at a 2-year follow-up (age 11-14) later, predicted drug misuse at a 4-year follow-up (age 13–16) over and above externalizing symptom profile, and interestingly occurred in the absence of differential neural responding during successful inhibition (no-go trials) at baseline as a function of transitioning status (Heitzeg et al., 2014a). Said inactivation conceivably underlies a compromised capacity to properly adapt ones actions and reactions, resulting in behavioral dyscontrol, one manifestation of which being early-onset drug misuse (Heitzeg et al., 2014a, 2015). Along the same lines, the large-scale multi-cite work from IMAGEN, particularly notable for its methodological rigor (e.g, cross-validation and replication) demonstrated that the extent of prefrontal activity during failed inhi-

bitions at 14 years of age significantly predicted binge drinking[24] within the subsequent 2 years (Whelan et al., 2014).

Summary. Taken together, the bulk of extant research supports the presence of altered neural responding patterns, prior to significant drug use, in non-using or non-abusing FHP individuals in the context of inhibition tasks relative to matched FHN controls, and establishes the ability of such aberrations to differentiate teens who later show escalating use from those who do not, although the nature and extent of these affects are likely developmentally modulated.

Summary To summarize, altered patterns of neural functioning in the context of inhibition tasks among teens with non-using or non-abusing teens have been found to prospectively predict escalating use, with the specific pattern of predictive markers likely depending on age and likely other variables.

Working memory. Working memory refers to a set of processes involved in actively rehearsing and/ or manipulating information held in conscious awareness during experiences or after retrieval from long-term memory, typically in the service of goal-directed behaviour. Deficient working memory could compromise decision-making skills, thereby augmenting risk of a host of psychopathologies including AUDs (Nagel et al., 2012).

Cross-sectional studies. Consistent with numerous neuropsychological findings of working memory problems in FHP individuals (Hegedus et al., 1984; Tarter et al., 1984; Peterson et al., 1992; Harden and Pihl, 1995; Finn and Hall, 2004; Lovallo et al., 2006b; Nagel et al., 2012), especially those with a personal history of heavy drug use (Weiland et al. 2012; for reviews, see Pihl et al. 1990; Nixon and Tivis 1997),

[24] A drinking pattern in which high quantities of alcohol are consumed in a short amount of time (typically four drinks for women or five drinks for men consumed over approximately 2 hours) that brings blood alcohol concentration (BAC) levels to 80 mg per 100 ml.

neurofunctional abnormalities during working memory tasks have been demonstrated in high-risk individuals. For example, whereas FHN teens show stronger frontal activation during verbal (Cservenka et al., 2012) or spatial (Mackiewicz Seghete et al., 2013) working memory vs vigilance control conditions, no such contrast is displayed by their FHP peers (Cservenka et al., 2012; Mackiewicz Seghete et al., 2013). This lack of frontal disengagement during vigilance indicates that these high risk persons still allocate "neural resources" under a relatively simple attentional and motor response condition, which could explain visuospatial and visuomotor deficits reported in this population (Hegedus et al., 1984; Tarter et al., 1984; Schaeffer et al., 1984; Aronson et al., 1985; Tarter et al., 1989; Garland et al., 1993; Ozkaragoz et al., 1997). These findings resonate with reports of comparatively weaker fronto-parietal connectivity in drug-naïve FHP teens during a visual working memory task (Wetherill et al., 2012), alluding to possible asynchrony in the functioning of the neural structures subserving working memory (also see Rangaswamy et al., 2004). Conflicting reporting on this issue nonetheless exists, with some studies finding that youth whose history of familial AUDs was densest activated cingulate and medial frontal gyri least during a simple vigilance condition relative to spatial working memory and most during rest[25], perhaps signifying a difficulty regulating the default mode network (DMN)[26] (Spadoni et al. 2008; also see Correas et al. 2016). This inconsistency with the literature could be attributable to the different task features, which ostensibly engage different neuronal substrates (Spadoni et al., 2008). The authors of the latter study also noted ineffective disengagement of the DMN in denser FHP teens in response to the spatial working memory relative vs vigilance contrast (Spadoni et al., 2008), an irregularity that, given the importance of working memory in the maintenance and updating of information, could contribute to maladaptive- and risky- decision making in this vulnerable pop-

[25] A cognitive state in which a subject is quietly awake and alert but does not engage in or attend to a specific cognitive or behavioral task.

[26] The DMN is a collection of midline and parietal brain regions that show more activity when people are constructing representations of the past and the future, simulating the present or processing semantic and conceptual content.

ulation, especially those with denser familial alcoholism (Spadoni et al., 2008; Nagel et al., 2012; Cservenka, 2016).

Prospective studies. A relationship between altered neural functioning under working memory conditions and subsequent change in drug use habits has been established. For example, reduced resting state regional cerebellar blood flow (rCBF)[27] to the (inferior) parietal cortex at age 12–15 can predict the onset of disordered drug use over a 3 year follow-up period (Ramage et al., 2015). In the latter study, the marker was specific to the inferior parietal cortex, an area previously found to show decreased rCBF in young alcoholic women (Clark et al., 2007; Gordon et al., 2011), weaker BOLD activation during a spatial working memory task in adolescent binge drinkers (Squeglia et al., 2011), and atrophy in long-term abstinent alcoholic men (Fein et al., 2006; Jolles et al., 2011). Other studies have similarly suggested that studies suggest that having less brain activation relative to comparison subjects during tasks of working memory can be used to predict which youths will initiate alcohol use during adolescence and less BOLD response contrast to a cognitive challenge by age 14 contributed to risk of moderate to heavy drinking by age 18 (Squeglia et al., 2016), consistent with previous findings (Brown et al., 2008; Squeglia et al., 2012b; Whelan et al., 2014).

1.9.1.2 Reward sensitivity

Cross-sectional studies. While reports of null results exist (e.g, Munro et al., 2006; Bjork et al., 2008; Müller et al., 2015), findings of aberrant mesolimbic circuitry functioning, and reward-related responding, particularly in the nucleus accumbens (NAc[28]), have generally been a recurring theme across studies of alcoholics (Beck

[27] rCBF is a measure used to characterize tonic neural activity, allowing for inference to maturation given the need for blood flow to support processes like neuronal proliferation and pruning (Uhlhaas et al., 2010).

[28] The NAc is a major site of dopamine release in the mesolimbic pathway (Oades and Halliday, 1987).

et al., 2009a; Makris et al., 2008; Wrase et al., 2007), and their unaffected first degree relatives (Andrews et al., 2011; Yau et al., 2012). This has led for the proposition that said characteristic as a precursive neurophenotypic marker of risk (reviewed in Heitzeg et al., 2015).

The specific pattern of this aberration, nonetheless, has been subject to debate, and evidence of pre-existing differences reward-related processing between FHP and FHN persons has been mixed (reviewed in Cservenka, 2016). While some researchers have noted comparatively weaker NAc activity during monetary reward anticipation in non-abusing FHP adults (Andrews et al., 2011), others have found that this diminished activation in FHP younger adults was conditional on the absence of a personal history of problem drinking (Yau et al., 2012), and still others have shown greater striatal DA release when tasting beer (versus Gatorade) in FHP adults compared with matched low-risk controls (Oberlin et al., 2013). From the perspective of typical neurodevelopmental trajectory of the reward neurocircuitry, this discrepancy could be accounted for by the ascertainment of different age groups across studies, as neural reactivity to reward likely differs from one neurodevelopmental stage (e.g., age) to another, and interacts with environmental influences (Yau et al., 2012; Bjork et al., 2008; Jacobus and Tapert, 2013). It is additionally conceivable that said phenotype reflects a resilience mechanism, as Yau et al. (2012) did not detect its presence in problem drinker FHP persons and in fact demonstrated an association between NAc activity during incentive anticipation and externalizing symptom severity as well as lifetime drinking (also see Lopez et al., 2014; Cservenka, 2016). This premise is also supported by a recent report describing greater NAc activity in association with a greater propensity for self-dyscontrol (Lopez et al., 2014), another finding that greater striatal activation to pictures of alcohol in younger adults predicted subsequent escalating use of alcohol (Dager et al., 2014), and yet another showing that age of drunkenness onset and dopamine release to monetary reward outcome were inversely correlated in a cohort of PFH young adults (Weiland et al., 2016). A third possible scenario is that said

discrepancy is driven, at least partly, by a lack or absence of emphasis on the personality composition of ascertained samples (Cservenka, 2016). Numerous illustrations of the importance of personality profiling have been made by functional neuroimaging studies. For example, Yarosh et al. (2014) showed that behavioral risk-taking scores were proportional to NAc activation in the context of a decision-making paradigm (i.e, Domino[29] task), but bore no association with FH status. Nees et al. (2012) noted that whereas reward-related behavior and neural activity contributed to early-onset alcohol use in healthy 14-year olds ($N = 324$), a comparatively greater proportion of the variance was explainable by personality risk traits (i.e, sensation seeking, novelty seeking, impulsivity and extroversion). Weiland et al. (2013) found that attenuated functional connectivity of the NAc with regions ascribed to the DMN and sensorimotor areas contribute to habit formation, observed in FHP persons during incentive anticipation (MIDT), mediated the link between trait SS and alcohol intake (Weiland et al., 2013). Moreover, Cservenka et al. (2014a) showed that stronger functional coupling between the NAc and regions subserving top-down cognitive control processing (e.g, IFG), displayed by FHP vs FHN youngsters (age 10–16) during resting state, positively correlated albeit at a trend level, with trait sensation-seeking scores (also see Galvan et al., 2006; Qiao et al., 2015). Such outcomes suggest that inter-individual variations in reward-related neural activation may be better explainable by personality or behavioral phenotypes than FH status (Cservenka, 2016).

Prospective studies. Prospective studies have persuasively made the case that heightened reward-related brain activation (e.g., VS) early in the drug use trajectory can predict subsequent alcohol-related phenotypes, and thus single out those who are most susceptible to escalating use (reviewed in Heitzeg et al., 2015; Cservenka, 2016). For example, enhanced NAc activity during monetary reward anticipation in 8-13

[29]In this task, subjects are informed that they are playing a competitive game against another human opponent, when in fact they are competing against a computer, in which they have to make risky or safe decisions to dispose of all of their domino chips.

year-olds positively correlates with the number of drinking-related problems reported over the next 3–6 years, even when controlling for lifetime drinking at time of the scan (Heitzeg et al., 2014b). Similarly, greater engagement of the cue-reactive neurocircuitry components (e.g, caudate, vmPFC, ACC, OFC, and insula; see Schacht et al. 2013; Heinz et al. 2009) during the processing of alcohol vs non-alcohol cues in 18-21 year-olds predicts escalating alcohol use and more drinking-related consequences within the next 3 years, above and beyond baseline level of alcohol intake and impulsivity scores (Dager et al., 2014). Further, increased BOLD activation within the superior frontal gyrus to monetary reward at age 14 significantly predicted binge drinking by age 16, as found in the IMAGEN sample (Whelan et al., 2014). Such findings are compatible with an addiction model whereby heightened motivation for substances of abuse over-engages networks dedicated to reward and motivation (Volkow et al., 2011). It is also notable that Dager et al. (2014) found that having a positive family history of AUDs was related to neither drinking levels at baseline nor subsequent change in this behavior, which recapitulates the previously made point about the importance of personality profiling samples ascertained to study this topic.

Summary In sum, while the picture is far from clear, family history cross-sectional studies (Yau et al., 2012; Ivanov et al., 2012; Stice and Yokum, 2014), and prospective studies (Heitzeg et al., 2014b; Dager et al., 2014; Whelan et al., 2014) generally concur with the premise that hyperactivation of reward-related circuitry represent a neurophenotypic precursive risk of AUDs and related SUDs, with some indications that this relationship may be subject to developmental modulation (Heitzeg et al., 2014b).

1.9.1.3 Emotional processing

Cross-sectional studies. Studies of alcoholics have documented the presence of both difficulties with socioemotional communication (Thoma et al., 2013) and aber-

rations in the functioning of the brain's emotional systems under aversive conditions (Marinkovic et al., 2009). Similar findings have been yielded by studies on non-using or non-abusing FHP persons (reviewed in Cservenka, 2016). For example, Cservenka et al. (2014b) noted that largely alcohol-naïve FHP teens unactivated the temporal lobe among other neural structures involved in socio-emotional processing during the presentation of appetitive stimuli (i.e, happy faces). Hill et al. (2007a) found diminished BOLD activation within the right middle temporal gyrus during a theory of mind task in FHP young adults, although their sample was not completely psychopathology-free. Glahn et al. (2007) described AMYG hyporesponsiveness to negatively valent signals, namely fearful faces in FHP young adults, and directly linked it to impulsive temperament. This finding resonates with a report linking genetic vulnerability for drug use (Sipe et al., 2002) to attenuated AMYG activation to threatening material in a normative cohort of middle-aged adults (Hariri et al., 2009). In a similar fashion, Heitzeg et al. (2008) noted diminished AMYG activation to passively viewed negative vs neutral words in OOA ages 16-20, although the manifestation of this aberration was conditional on the presence of a personal history of excessive alcohol use and was not demonstrated by non-problem drinking OOA.

Considered in combination with other work demonstrating a relationship between relatively reduced threat-related AMYG (and relatively enhanced reward-related VS activity) and problem drinking in university undergraduates (Nikolova and Hariri, 2012; Nikolova et al., 2016) that was mediated by impulsivity (Nikolova et al., 2016), the study off Heitzeg et al. (2008) raises the possibility that absence of said premorbid phenotype in OOA reflects a protective mechanism against the disorder (Cservenka, 2016), and could explain why some studies showed no evidence of blunted AMYG responding to threatening faces in high-risk individuals (e.g, Cservenka et al., 2014b). Other patterns of neural deactivation have also been documented using FHP teens during the processing of subliminal emotional faces (Peraza et al., 2015). It is possible that attenuated limbic activation to information signaling threat propels one to engage

in risky behaviors (Glahn et al., 2007), as AMYG activation to fearful faces ostensibly signifies a "breaking" mechanism, through which engagement in risky behaviors might be diminished (Amaral, 2002; Ernst et al., 2006). Notwithstanding, an association between heightened AMYG reactivity to threat signals and problem drinking that is mediated by anxious/ depressive symptomatology has also been established in young adult university students (Nikolova and Hariri, 2012; Nikolova et al., 2016). This observation resonates with reports of heightened AMYG responsiveness to threat-related stimuli in individuals with clinical anxiety and mood dysregulation conditions (Stein et al., 2002; Etkin and Wager, 2007), those occurring in frequent association with and contributing to the development of disordered drinking (Conway et al., 2006; Boschloo et al., 2011). Therefore, both hyper- and hypo-activation of the AMYG to threatening stimuli may dispose for alcohol misuse, if through differential risk pathways, one internalizing and another externalizing, respectively (Nikolova and Hariri, 2012; Nikolova et al., 2016).

Prospective studies. Relative to inhibitory control and reward processing, emotional processing has received much less attention from prospective investigations and the number of studies conducted on this topic has been extremely small. Nonetheless, the previously cited Nikolova studies indicated that relatively exaggerated and diminished threat-related AMYG activation predicted escalating drinking 3-months later via, respectively, anxiety and impulsivity (Nikolova and Hariri, 2012; Nikolova et al., 2016).

Summary. Two diametrically opposing patterns of aberration in threat-related AMYG responsiveness appear to be associated with distinct risk pathways of AUD development: AMYG hyperactivation is related to AUDs through the internalizing pathway whereby one drinks to cope with stress, via anxiety symptoms, while AMYG hypoactivation is conversely associated with the disorder through the externalizing

pathway, whereby one drinks to enhance one's mood as part of a general disinhibitory proclivity cope with stress, via impulsivity.

1.9.2 Structural Neuroimaging Markers

Brain structure is substantially genetic, certainly much more so than its function (Jansen et al., 2015). Heritability of GM volume has been conservatively estimated at 70% (Gilmore et al., 2010) and of WM volume > 96% (Bohlken et al. 2014; see Jansen et al. 2015 for a comprehensive review). A burgeoning research has identified abnormalities in brain morphology in non-disordered FHP persons. A full treatment of this literature is beyond the scope of this thesis (reviewed in Heitzeg et al., 2015). Rather, the goal here is to highlight the main findings.

1.9.2.1 White Matter Maturation

Cross-sectional studies. While the picture is far from clear and reports of null findings exist (e.g, Squeglia et al., 2015), it generally appears to be the case, based on diffusion tensor imaging (DTI)[30] investigating the presence of altered WM macrostructure (e.g, volume, track strength, and architectural complexity) and/ or microstructure in teens with minimal to no prior drug use, that youth with familial alcoholism tend to display both atypical WM microstructure and in the presence of multiplex familial loading of the condition (Herting et al., 2011; Jacobus and Tapert, 2013), and/ or a personal history of heavy drug use (Bava et al., 2013a; Jacobus et al., 2013; McQueeny et al., 2009), perturbed WM macrostructure (i.e, volume) as well. This pattern of findings resonates with reports of describing reduced volume, particularly in the OFC, in association with self-dyscontrol and trait impulsivity (Hill et al., 2009), as these characteristics are more likely to be present at higher levels in those with multigenerational

[30] An MRI technique that enables the measurement of the diffusion properties of water molecules in brain tissues. Since the diffusion properties of water differ between different types of brain tissues, DTI can be used to measure the microstructural properties of these tissues. The most common use of DTI is to evaluate white matter tracts, which have greater diffusion along the WM tract compared with tangential to the WM tracts.

as opposed to unigenerational familial AUDs (Conrod et al., 1997a; Finn et al., 1992; Sanchez-Roige et al., 2016; Acheson et al., 2016).

Specifically, Squeglia et al. (2015) found no WM mactrostructural aberrations in reward-related regions, namely NAc and OFC or alterations in their corresponding WM tracts in FHP teen. They also found no significant associations between WM indices and behavioral phenotypes (Squeglia et al., 2015). Atypical WM microstructural characteristics of the aforementioned regions were nonetheless seen, and indicated an abnormally precocious development, such that WM integrity within the NAc and OFC was better compared with the control group (Squeglia et al., 2015). This irregularity, the authors postulated, potentially influences behaviors and cognitive functions that emerge alongside typical white matter maturation in youth (Bava et al., 2010; Yap et al., 2013). Consistently, Squeglia et al. (2014b) detected the same pattern of irregular WM maturation in nearly 20 WM tracts throughout the brain in OOA (Squeglia et al., 2014b), an observation congruent with a report of functional frontoparietal dysconnectivity absent disruption of corresponding WM tracts in substance-naïve FHP teens (Wetherill et al., 2012).

Along similar lines, aberrations in frontal WM tracts have been identified in youth liable for SUDs (Lee et al., 2011; Charach et al., 2011; Shollenbarger et al., 2015), diagnosed with ADHD (Li et al., 2010) or conduct disorder (Sarkar et al., 2013), alcohol-abusing juvenile offenders (Thayer et al., 2013), or have a marked proclivity to engage in particularly risky and dangerous behaviors (Berns et al., 2009). It is possible that WM maturation begins comparatively earlier and/ or is more precipitous in said vulnerable teen population, probably instilling/ unmasking a latent predilection to engage in risky behaviors, even before behavioral alterations have become readily apparent (Squeglia et al., 2015). This proposition is congruent with fMRI studies linking more "mature" BOLD response patterns to greater rates of drug misuse (Wetherill et al., 2013b; Heitzeg et al., 2014a; Squeglia et al., 2012b, 2016). Early and precocious neurodevelopment might be a risk factors that propels teens to initiate and escalate

in, among other risky behaviors, addictive substance use, as compared to normative peers (Squeglia et al., 2016). At the same time, they might also have a predilection for earlier autonomy, behavioral exploration, and prosocial behaviors, all characteristics that might make them superior to their peers in some respects (e.g, more resilient), barring engagement in risky behavior (Squeglia et al., 2015). This alludes to a window of opportunity as opposed to mere vulnerability (Squeglia et al., 2015). Importantly, whereas the picture emerging from the above mentioned suggests that the trajectory of WM maturation, in at risk teens, goes from being catalyzed prior to initiating drug use to paralyzed after ("pseudo-maturity"; Squeglia et al., 2016), it remains to be determined whether this association is causal or like alcoholism itself, a mere consequence of the actual cause.

With respect to WM macro-structural aberrations, worse WM integrity in tracts corresponding to fronto-cerebellar regions has been detected in the drug-naïve teen OOA, and found to co-occur greater impulsivity, as indexed by poorer performance on a task of delay discounting[31]. Importantly, these alcohol-related disturbances are seen as unfolding during a time when the typically developing adolescent brain (healthy non-using and/ or low-risk) is showing increasing WM coherence and more mature neural processing (Giorgio et al., 2008; Schmithorst and Yuan, 2010; Stiles and Jernigan, 2010; Lebel et al., 2012a; Wandell, 2016; Krogsrud et al., 2016).

Prospective studies. Perturbed WM integrity has been found to prospectively predict risky behaviors including delinquency/ aggression and substance use measured over 1.5 years (Bava et al. 2013b; also see Jacobus et al. 2012; reviewed in Jacobus and Tapert 2013; Squeglia and Gray 2016).

[31]The reduced ability to choose larger but delayed rewards compared with smaller but earlier rewards (seen as an index of impulsive tendencies) (Heinz et al., 2011).

1.9.2.2 Grey Matter Maturation

Volumetric GM aberrations and architectural alterations in number of brain regions have been documented in people with AUDs/ SUDs and their first degree relatives, with some findings being more consistent than others (for recent reviews, see Hill and O'Brien, 2015; Heitzeg et al., 2015; Cservenka, 2016). The list of regions include but is not limited to the cerebellum (Bellis et al., 2005; Benegal et al., 2007; Hill et al., 2007b, 2011; Squeglia et al., 2014c), ACC (Benegal et al., 2007; Squeglia et al., 2012a; Cheetham et al., 2014), HC (De Bellis et al. 2000; Nagel et al. 2005; Medina et al. 2007; Hanson et al. 2010; Van Dam et al. 2014; Grodin and Momenan 2016; Mole et al. 2016; although see Hill et al. 2001), NAc Cservenka et al. 2015; Urošević et al. 2015; Grodin and Momenan 2016; although see Mole et al. 2016), putamen (Ersche et al., 2013a), thalamus (Bellis et al., 2005; Benegal et al., 2007; Grodin and Momenan, 2016), insula (Chung and Clark, 2014) and of the particular relevance to this thesis, the AMYG (Hill et al., 2001, 2013, 2010; Benegal et al., 2007; Dager et al., 2015; Wrase et al., 2008; Zhang et al., 2013; Durazzo et al., 2016) and OFC (Hill et al. 2010, 2009; Lyoo et al. 2015; Ersche et al. 2011; Franklin et al. 2002; Alia-Klein et al. 2011; Matochik et al. 2003; Sim et al. 2007; Moreno-López et al. 2012; Hanlon et al. 2011; Parvaz et al. 2012; Ersche et al. 2013b; for reviews, see Jacobus and Tapert 2013; Hill and O'Brien 2015; Heitzeg et al. 2015; Salvatore et al. 2015; Squeglia and Gray 2016; Brooks and Stein 2016).

AMYG. Smaller AMYG GM volume has been noted in individuals with current (Wrase et al., 2008; Zhang et al., 2013; Dager et al., 2015) and past (Dager et al., 2015) AUD, and shown to predict craving and relapse after undergoing treatment (Wrase et al. 2008; Zhang et al. 2013; also see Durazzo et al. 2016). The same anomaly has also been documented in high-density (multiplex[32]) FHP adults (Hill et al., 2001, 2013,

[32]Multiplex or multigenerational familial alcoholism is defined as having multiple alcoholic biological relatives, with persons who classify as such being typically considered at ultra-high risk for developing alcoholism.

2010; Benegal et al., 2007), adolescents (Hill et al., 2001; Benegal et al., 2007) and children (Benegal et al., 2007), in unaffected first degree adult relatives of alcoholics (Benegal et al., 2007; Dager et al., 2015) and in infants prenatally exposed to alcohol (Donald et al., 2016). The previously mentioned information suggests that AMYG GM volumetric shrinkage presages and perpetuates risk of the explosion. Said dysmorphology purportedly connotes precursive externalizing risk in general as opposed to susceptibility for specifically alcoholism, as it has been found to correlate with a dose-dependent increase in trait impulsivity scores (Tajima-Pozo et al., 2016), and externalizing symptoms severity (Benegal et al., 2007), to predict escalating psychostimulants use (Becker et al., 2015), and to manifest itself in ADHD-disordered (unmedicated) adults (Tajima-Pozo et al., 2016) and conduct-disordered teens (Sterzer et al. 2007; Huebner et al. 2008; Fairchild et al. 2011, 2013; although see for null results in children Fairchild et al. 2013), especially those with callous-unemotional (CU)[33] traits (Cope et al., 2014; Cohn et al., 2016), relative to their typically developing peers (for meta-analyses, see Rogers and De Brito 2016; Noordermeer et al. 2016; for a systematic review, see Noordermeer et al. 2016). The aforementioned externalizing disorders frequently co-occur and share their aetiology (Slutske et al., 1998; Edwards and Kendler, 2012; Salvatore et al., 2015) with AUDs. Notwithstanding, while the regional structural dysmorphology exemplifying both the AMYG meets many of the endophenotype criteria (Salvatore et al., 2015), its causal status remains to be definitively determined.

OFC. Significantly reduced OFC GM volume has been observed in youth and young adults with multiplex familial alcoholism (Hill et al. 2010, 2009; also see Lyoo et al. 2015), and described in prospective association with escalation into drug abuse in younger teens (e.g, at a 4-year follow-up; Cheetham et al., 2012), with the possible confounding of personal history of alcohol and other drug use controlled for (see Hill and O'Brien, 2015). Such effects have often been specific to the right hemisphere (Hill

[33] CU traits index diminished empathy and remorse, a proclivity to manipulate and be unconcerned with others (Essau et al., 2006).

et al., 2010, 2009; Cheetham et al., 2012), which resonates with indications that the right OFC is particularly important (Tessner and Hill, 2010) in the association between this region and disordered drug use (Lubman et al., 2004; Volkow and Fowler, 2000; Goldstein and Volkow, 2002; Dom et al., 2005; Schoenbaum and Shaham, 2008). This observation is additionally congruent with reports of unique associations between unilateral damage to the right OFC (in humans) and profoundly disturbed socioaffective processing (Tranel et al., 2002; Hill and O'Brien, 2015) and decision-making ability (Bechara et al. 1994; reviewed in Gordon 2015).

As such, even though the contemporary literature suggests that chronic and excessive drug use might be particularly neurotoxic to the OFC (Hill and O'Brien, 2015), and links orbitofrontal volume decline to prolonged stimulant use (Ersche et al. 2011; Franklin et al. 2002; Alia-Klein et al. 2011; Matochik et al. 2003; Sim et al. 2007; Moreno-López et al. 2012; Hanlon et al. 2011; Parvaz et al. 2012; for a meta-analysis, see Ersche et al. 2013b), reduced OFC volume does appear to presage the onset of disordered-drug use, if it is dose-dependently perpetuated by it. Fascinatingly, volumetric enlargement of the OFC GM has been found in casual cocaine users who have regularly consumed cocaine for 8 years while managing to not abuse, compared with non-using low-risk matched controls, cocaine addicts and their unaffected biological siblings, suggesting that this atypical volume increase conceivably denotes resiliency to the effects of cocaine and possibly reflects advantageous decision-making abilities or inhibitory control and might have been serving to protect these individuals against drug abuse throughout their years of recreational and regular use (Ersche et al., 2013a). This notion is supported by reports of enhanced attentional bias to cocaine cues in stimulants (cocaine) addicts but not recreational users (Smith et al., 2014). This response, or lack thereof, on part of longtime casual users co-occurs with comparatively significant underactivation of both the orbitofrontal and anterior cingulate cortices (Smith et al., 2014) - the latter being, like the formers, vitally involved in inhibitory control and reward-based decision-making (Lubman et al. 2004; Ridderinkhof et al.

2004; for more information on the OFC and ACC, see sections 1.10.2 and 1.10.2, respectively) Finally, it is notable that as in the case of AMYG, said OFC volumetric perturbation likely predisposes for a host of externalizing problems, having has also been documented in adult ADHD patients (Hesslinger et al., 2002) and in conduct-disordered compared with typically developing children (Sebastian et al. 2016; for a systematic review and meta-analysis, see Noordermeer et al. 2016).

In sum, it appears that OFC GM volume reduction potentially serves as a familial vulnerability marker for externalizing psychopathologies, the abuse of alcohol and psychostimulants amongst them.

1.10 Using Emotional Challenge Paradigms to Delineate Risk Pathways for AUDs

1.10.1 Face Emotion Processing

A facial expression can be viewed as an environmental "canvas", from which information reflecting the internal emotional states and intentions of others is consistently extracted to help us predict their responses to events and adjust ours accordingly (Darwin, 1965, 1872; Schwanenberg, 1974; Ekman, 1993, 2007; Frith, 2009). This makes face emotions "the most immediate and important social signals for the human species" (LeDoux, 1998a), and places the ability to (accurately) identify and appropriately respond to them at the crux of human social interactions (Marsh 2015; also see Adolphs 2003; Kemmis et al. 2007; Verdejo-García et al. 2007; Fairchild et al. 2009; Kim et al. 2011b; Blair 2012; Collin et al. 2013; Hopfer et al. 2013; Morgan and Marshall 2013; Ersche et al. 2015; Bora and Zorlu 2016). How we respond to facial affect is determined by innate predilections and/ or quickly learnt associations (Bruce and Young, 1986; Stenberg et al., 1998; Haxby et al., 2000; LeDoux, 2000b; Öhman and Mineka, 2001; Myers and Davis, 2002; Weymar and Schwabe, 2016). As such, face emotions can be

usefully thought of as a naturally conditioned stimuli[34], in the sense that the subjective, physiological and neural responses they trigger have come to approximate those evoked by whatever events or occurrences these stimuli had predicted for us in the past (Hariri and Whalen 2011; Whalen and Phelps 2009; also see Bouton 2007). Based on this and compelling evidence suggesting the ecological validity of positive and negative facial expressions exceeds that of other emotional stimuli (e.g, words; reviewed in Heinrichs and Hofmann 2001), facial displays of affect have been widely utilized by studies aimed at capturing individual differences in emotion processing (Ekman et al., 1987; Hamann and Canli, 2004). In this context, the most prevalent use has been of basic emotions, which total six: fearful, angry, disgusted, surprised, sad and happy faces (Ekman 1994; Dubois and Adolphs 2015; although presentations of more complex emotions, e.g, moral emotions[35] have also been used and become increasingly popular in recent years). Facial displays of fear signal direct, albeit unspecified, environmental threat against the individual (Anderson et al., 2003), and relative to other basic emotions, they are consistently the most commonly misrecognized (Elfenbein et al., 2002), with identification accuracy relating to, among other variables, indices of intelligence (Amlerova et al., 2014; Simon et al., 1996; Kessels et al., 2014). Angry faces may, too, be perceived as immediately threatening as they potently signal social disapproval (Blair, 2003a). Because of that, facial displays of covert fear and anger, and perhaps other negative emotions, can also instigate a critical component of anxious psychopathologies, namely the anticipation of impending threats (Taylor and Whalen, 2015), leading individuals with or at-risk for these disorders to respond with hypervigilance (Etkin et al., 2004; Williams et al., 2007; Eisenegger et al., 2011). This

[34] A previously neutral stimulus that comes to acquire aversive or rewarding properties following its co-occurrence with a naturally (respectively) aversive or rewarding stimulus (i.e, unconditioned stimulus).

[35] Moral emotions include guilt, shame, embarrassment, jealousy, pride and other states that depend on a social context. They arise later in development and evolution than the basic emotions and require an extended representation of oneself as situated within a society. They function to regulate social behaviours, often in the long-term interests of a social group rather than the short-term interests of the individual person Adolphs 2002).

concept has representation in the defensive survival circuit" (LeDoux, 1996; Ledoux, 2002; LeDoux, 2012, 2013, 2014a,b,b, 2015), which primarily encompasses the AMYG, insula (aINS) and ventral anterior cingulate cortex (vACC), although other regions such as the HC are also certainly involved (Martin et al. 2009; reviewed in Posamentier and Abdi 2003).

The AMYG. Often referred to as the amygdaloid complex, the AMYG is a small almond-shaped medial temporal lobe structure (Swanson and Petrovich, 1998). This region comprises two subdivisions: the basolateral (BLA) and centrocorticomedial (CeA), with multiple functionally segregated and morphologically heterogeneous nuclear divisions totalling ~ 12 (see Amaral et al., 1992; Kim et al., 2011a; Grant et al., 2015b; Tye et al., 2011; Sah et al., 2003; LeDoux and Schiller, 2009; De Francesco et al., 2015). The AMYG is one of the most heavily interconnected neural structures (Kubota and Niki 1971; Swanson 2003; Davis and Whalen 2001; Pessoa 2008; although it is notable that the AMYG projects to the cortex much more than it receives Freese and Amaral 2009; LeDoux and Schiller 2009), and is regarded as the epicenter for fear conditioning (which signifies learning to predict immediate danger; LeDoux et al., 1990; LeDoux, 2003, 2007; Quirk et al., 1995; Gallagher and Chiba, 1996; Rogan et al., 1997; LaBar et al., 1998; Whalen, 1998; Whalen et al., 1998b; Whalen and Phelps, 2009; Adolphs et al., 1995; Adolphs, 2008, 2013; Haxby et al., 2002; Davis et al., 2010; Davis and Whalen, 2001; Davis et al., 2010; Zald, 2003; Collins and Paré, 2000; Wilensky et al., 2006; Duvarci and Pare, 2014; Fox et al., 2015; Johnson and Casey, 2015; Duits et al., 2015; Rigoli et al., 2016; Felix-Ortiz et al., 2016). Its heightened reactivity appears to causally contribute to threat-induced negative affect (Shackman et al., 2016a), is inducible by stress and adversity (Dannlowski et al., 2012), and can predict subsequent development of internalizing symptamology (Swartz et al., 2015). Specifically, the BLA is primarily glutamatergic (Smith and Pare, 1994; Carlsen, 1988; Tye et al., 2011), projects to the BNST, NAc, HC and cortex (Pitkänen, 2000; Tye et al.,

2011) and is critical for threat detection and the consolidation of learnt states of fear (Quirk et al., 1995; Collins and Paré, 2000; Hobin et al., 2003; LeDoux, 2007; Sangha et al., 2013; Johnson and Casey, 2015; Felix-Ortiz et al., 2016; Beyeler et al., 2016). It is on this subnucleus that sensory thalamic inputs during fear learning converge (Quirk et al., 1995; Collins and Paré, 2000; Johnson and Casey, 2015). Conversely, the CeA, is mainly gamma-aminobutyric acid (GABA)-ergic (McDonald, 1982; LeDoux, 2007; Tye et al., 2011) and particularly the CeM (which is the primary output subterritory of the AMYG; Krettek and Price, 1978a,b; Tye et al., 2011), receives gluatamatergic projections from BLA (Grant et al., 2015b). The latter subnucleus has generally been linked to the expression of anxiety (Kalin et al. 2004; Etkin et al. 2009; Lyons and Thiele 2010; Tye et al. 2011; Gilpin et al. 2015; Oler et al. 2015; Shackman and Fox 2016; also see Paton et al. 2006; Gore et al. 2015; Beyeler et al. 2016; Maren 2016; reviewed in Shackman and Fox 2016), activating upon threat detection and thereby precipitously eliciting autonomic and behavioral (defensive) reactions associated with fear and anxiety states via projections to the hypothalamus (autonomic responses such as heart rate and respiration), PVN (PVN; GCs), and PAG (somatomotor reactions such as freezing) (Swanson and Petrovich, 1998; Davis, 2000b; Tye et al., 2011; Mcdonald, 1998; Armony and LeDoux, 1997; Walker et al., 2003; Maren, 2001; Johnson and Casey, 2015). Such responses are, at least temporarily, adaptive in that they allow the organism to learn best (Weisz et al., 1992; Whalen, 1998; Gallagher and Holland, 1994; Kapp et al., 1992).

It has long been speculated, but only recently directly substantiated that there exists a phylogenetically ancient subcortical pathway conveying rapid, yet coarse, threat-related information to human AMYG (Méndez-Bértolo et al., 2016), with this pathway becoming quickly operative when fearful, but not neutral or happy, nor highly arousing pictorial stimuli, are unconsciously processed (Méndez-Bértolo et al., 2016). This implies that the centrality of the AMYG to fear may not necessarily generalize to other emotions (Marsh, 2015), without suggesting that subserving fear is all that the

AMYG does (it is not, see below). Indeed, extensive evidence indicates that focal bilateral AMYG damage hinders the recognition of and sensitivity to fear-signaling stimuli (Adolphs et al. 1994, 1999, 2002, 2005; Young et al. 1995; Anderson and Phelps 2001; Sato et al. 2002; Wiest et al. 2006; Scheele et al. 2012; Feinstein et al. 2013; Bach et al. 2015; Dal Monte et al. 2015; Amaral and Adolphs 2016; Khalsa et al. 2016; De Winter et al. 2016; Pishnamazi et al. 2016; Claire et al. 2016; but see Becker et al. 2012), and the capacity to experience any sort of subjective fear (Feinstein et al. 2011; Klumpers et al. 2015; but see Tranel and Damasio 1989; Meadows and Kaplan 1994; Anderson and Phelps 2002; Becker et al. 2012).

It has been argued that the AMYG drives reflexive orienting to facial features (Gamer et al., 2013) and operates based on a set of implicit principles (reviewed in Hariri and Whalen, 2011). Substantive evidence comes from the work of Todorov's group (Engell et al., 2007; Said et al., 2009), in which healthy subjects were presented with many ambiguously valent (i.e, neutral) face photographs and instructed to verbally indicate to the investigators the level of perceived trustworthiness of each face based on their "gut" reaction (Engell et al., 2007; Said et al., 2009). These researchers found that AMYG activation to said faces corresponded to subjects verbal assessments, but was even more strongly related to the consensus ratings (i.e, mean trustworthiness score) for each face (Engell et al., 2007; Said et al., 2009). Along the same lines, a study by Mujica-Parodi et al. (2009) found that when exposed to sweat samples obtained from individuals who had either just undergone their first ever sky dive or a treadmill exercise, subjects showed greater AMYG activation to samples from the first-timer sky-divers, despite having no way of knowing which sample belonged to whom.

The aforementioned outcomes adhere with a massive literature indicating that in both animals and humans, the AMYG functions as a monitoring and protection device, being designed to automatically detect and evade danger (LeDoux 1998b, 2015; Whalen 1998; Hariri and Whalen 2011; Grant et al. 2015b; also see Madarasz et al.

2016). These outcomes additionally resonate with the prevailing view of fear as an innate (or quickly learnt), universal and highly evolutionary conserved experience (LeDoux, 2000b; Myers and Davis, 2002) that requires no (or very little Weymar and Schwabe, 2016) prior learning (Öhman and Mineka, 2001).

Though a somewhat oversimplified view, initial enhanced AMYG reactivity can be overridden and regulated automatically by the hippocampus (Maren et al., 2013; Keding and Herringa, 2014) or cognitively by the prefrontal cortex, specifically vmPFC[36]/ medial OFC (Hariri et al., 2000; Ochsner et al., 2002; Milad and Quirk, 2002; Kim et al., 2003; Phelps et al., 2004; Van Reekum et al., 2007; Hare et al., 2008; Sotres-Bayon and Quirk, 2010; Whalley, 2014; Abiri et al., 2014; Johnson and Casey, 2015; Powers and Casey, 2015; Baratta et al., 2015; Motzkin et al., 2015; Shiba et al., 2016). The latter region projects directly and densely to the AMYG and is regarded as it chief regulatory structure (Porrino et al., 1981; Amaral and Price, 1984; Ghashghaei et al., 2007), and the two work alongside of each other to decode and represent affectively laden information (Bechara et al., 2000; Blair, 2003b; Price, 2003; Ochsner et al., 2004; Stein et al., 2007a; Ghashghaei et al., 2007; Murray and Izquierdo, 2007; Gorka et al., 2013).

Failure of this regulatory function can translate into mishandling of the calculation of actual threat, leading to and causing failure of AMYG reactivity to subside when threat ceases to exist and signaling danger no longer warranted, which is precisely what appears to be the case in conditions of clinical and subclinical anxiety (Shin et al., 2005; Whalen, 2007; Tottenham et al., 2009; Casey et al., 2011a; Sladky et al., 2015; Etkin et al., 2015; Geiger et al., 2016; Shackman et al., 2016b; Bas-Hoogendam et al., 2016). There is extensive evidence of AMYG hyperactivity during the conscious or non-conscious processing of threatening versus neutrally (or positively) valent faces among individuals with SAD (social phobia; Stein et al. 2002; Straube et al. 2004; Phan

[36]The vmPFC corresponds to regions of the cerebral cortex on the ventral and medial surfaces of the frontal lobes, including the OFC, gyrus rectus and ACC.

et al. 2006; Blair et al. 2008; Evans et al. 2008; Shah and Angstadt 2009; Klucken et al. 2009; Kleinhans et al. 2010; Freitas-Ferrari et al. 2010; Demenescu et al. 2013; Fouche et al. 2013; Brühl et al. 2014; Binelli et al. 2014; Fonzo et al. 2015; Blair et al. 2016; Charpentier et al. 2016; but see Klumpp et al. 2013b), GAD (McClure et al. 2007; Monk et al. 2008a; Fonzo et al. 2015; but see Whalen et al. 2008), PD (Poletti et al. 2015; Sakai et al. 2005; Ottaviani et al. 2012; Fonzo et al. 2015; but see Demenescu et al. 2013; Pillay et al. 2006; Poletti et al. 2015; Etkin and Wager 2007), PTSD (Fredrikson and Faria 2012; Rauch et al. 2000; Fonzo et al. 2010; Armony et al. 2005; Mahabir et al. 2015; Rabellino et al. 2016; also see Diener et al. 2016), OCD (Via et al., 2014; Weidt et al., 2016), specific (simple) phobias (Wright et al. 2003; Schienle et al. 2005b; Straube et al. 2007b; Fredrikson and Faria 2012; for reviews, see Brooks and Stein 2015; Taylor and Whalen 2015; Britton and Rauch 2008; Shin and Liberzon 2010; Holzschneider and Mulert 2011; Blackford and Pine 2012; Paulus 2008; Etkin and Wager 2007; Mochcovitch et al. 2014; Brühl et al. 2014; Stern and Taylor 2014; Bas-Hoogendam et al. 2016; Habecker et al. 2016; Ducharme et al. 2016; Hendler and Admon 2016), in addition to depressives (Hamilton et al., 2012; Groenewold et al., 2013; Mattson et al., 2016; Beesdo et al., 2009) and mood disordered persons (Tseng et al., 2016).

An equally solid body of evidence has extended this phenomenon to nonclinical cohorts of individuals characterized as "phobia-prone" (Bertolino et al., 2005), neurotic (Etkin et al. 2004; Barrett and Armony 2009; Phan et al. 2006; Rauch et al. 2000; Stein et al. 2007b; Paulus 2008; also see Haas et al. 2007), anxiety-sensitive (Stein et al. 2007b; although see Killgore et al. 2011), socially anxious (Killgore and Yurgelun-Todd, 2005; Ball et al., 2012), threat-sensitive (Cools et al., 2005), dispostionally-negative (Shackman et al., 2013), harm-avoidant, uncertainty intolerant (reviewed in Schienle et al., 2010).

The INS. The INS is a small island of cerebral cortex buried in the Sylvian fissure, and extensively connected with cortical and subcortical neural structures (e.g, OFC, ACC, AMYG and ventral striatum; Augustine 1996; Cavada et al. 2000; Reynolds and Zahm 2005). By virtue of its anatomical position and connectivity pattern, the INS plays a vital role in emotional processing and reactivity (Kelly et al., 2012; Chang et al., 2012; Ryali et al., 2013; Uddin et al., 2014).

The INS divides into two subregions: posterior and anterior, the latter being of particular focus in this thesis. The posterior INS (pINS) bears functional connections to primary and secondary somatomotor cortices (Deen et al., 2011), and receives basic sensory information (e.g, regarding pain and visceral changes; Craig 2009; Grupe and Nitschke 2013)

The comparatively larger anterior INS (aINS), on the other hand, is functionally and structurally connected with the AMYG (Deen et al., 2011; Baur et al., 2013). The evidence implicating the INS in affective processing is broad and deep. This region is chiefly involved in subjective interoception and more broadly contributes to promoting subjective awareness of emotionally potent stimuli (Critchley et al., 2002, 2004; Gray et al., 2007; Craig, 2009, 2011; Paulus and Stein, 2006; Garfinkel et al., 2015; Haase et al., 2016; Kuehn et al., 2016; Li et al., 2016a; Nguyen et al., 2016). It activates during the processing of negative emotions and events (e.g, monetary loss cues; Knutson and Greer, 2008), the anticipation of aversive stimuli (e.g, negative images; Paulus and Stein, 2006; Simmons et al., 2006, 2008a; Grupe and Nitschke, 2013; Shankman et al., 2014; Eisenberger, 2015b) and to risk risk aversion (Kuhnen and Knutson, 2005). Damage to the aINS has been found to result in acquired alexithymia (i.e, a difficulty in identifying and/ or describing one's own feelings; Hogeveen et al. 2016) a condition hallmarked by impaired interoceptive awareness (Longarzo et al., 2015; Shah et al., 2016; Morie et al., 2016; DuBois et al., 2016). Interestingly lesioning the aINS in rats has also been recently shown to diminish impulsive behavior, suggesting that the aINS is a causal contributor to individual vulnerability to impulsive-compulsive phenotypic

manifestations (Belin-Rauscent et al., 2016), consistent with extensive evidence implicating this region in addiction (Naqvi et al., 2007; Naqvi and Bechara, 2009, 2010; Paulus and Stewart, 2014; Belin-Rauscent et al., 2016).

The aINS consistently activates during the anticipation of pain (Wager et al., 2004; Paulus and Stein, 2006; Simmons et al., 2006; Drabant et al., 2011; Eisenberger, 2015b), imagining oneself experiencing pain (Carlsson et al., 2006; Ogino et al., 2007; Ploghaus et al., 1999), and intensity encoding of pain (Peyron et al., 1999; Craig et al., 2000; Bantick et al., 2002), which has led to its proposal as a "pain" site (Eisenberger, 2015b). The INS, particularly the aINS, has been ascribed to and is considered to be at the core of the "salience network" of brain function (Seeley et al., 2007), which is dedicated to the detection of salient sensory material (Critchley et al., 2004; Craig, 2009; Iannetti and Mouraux, 2010; Grupe and Nitschke, 2013), and additionally encompasses, among other regions, the midcingulate cortex (MCC; reviewed in Vogt 2016) particularly its anterior division (aMCC = MCC, BA 24), and the thalamus (see Kinomura et al., 1996; Purpura and Schiff, 1997; Portas et al., 1998; McAlonan et al., 2008). Activation of the "salience network" has been extensively debated in the context of social (and physical) pain (and its anticipation), which is why it is regarded as the 'medial pain system' or the classic pain matrix (see Peyron et al., 2000; Casey, 1999; Ingvar, 1999; Davis, 2000a; Wager et al., 2004; Eisenberger, 2012b; Christoffel et al., 2015).

Unlike the AMYG, which is consistently responsive to both masked and unmasked threatening faces in normal persons (Critchley et al., 2002), the INS activates to the latter but not the former and necessarily as a function of conscious awareness of said stimuli (Critchley et al., 2002). That said, like the AMYG, the INS has also been repeatedly implicated in the aetiology of anxious psychopathologies (reviewed in Etkin and Wager, 2007; Damsa et al., 2009; Taylor and Whalen, 2015), with heightened INS, especially aINS activation to aversive versus neutral (or happy) faces being one of the more consistent findings across studies of SAD (Stein et al. 2002; Shah and Angstadt 2009; Klumpp et al. 2013b; also see van Tol et al. 2012), PD (Fonzo et al.,

2015), specific phobia (Wright et al., 2003) and OCD (Schienle et al., 2005a) relative to matched controls. This phenomenon has also been extended to nonclinical cohorts that classify as anxiety-prone, being frequently described, in a typically dose-dependent association with symptoms of trait anxiety (Stein et al., 2007b; Engel et al., 2009), anxiety-sensitivity (Stein et al. 2007b; Killgore et al. 2011; but see Ball et al. 2012), SA (Ball et al., 2012) and IU (Simmons et al., 2008a)).

Such outcomes are compatible with the view that subjective anxiety emerges when the bodily arousal sensations represented by the aINS are misrepresented/ inaccurately categorized, leading for an over prediction of future aversive interoception (Paulus and Stein, 2006; Paulus, 2008).

It is notable that the aINS has been theorized to be a central underpinning of anxiety-sensitivity (Paulus and Stein, 2006), as AS persons are particularly prone to experiencing greater aINS "anticipatory prediction error signal" (Harrison et al., 2015), which result in a predilection for tense hyperarousal and catastrophic appraisals of anxiety-related symptoms, as per Paulus and Stein (2006). Though findings lending support to this hypothesis have been preliminary Stein et al. 2007b; Killgore et al. 2011, inconsistencies within the the literature on this topic exist (e.g, Ball et al., 2012), and slightly different perspectives have been proposed (e.g, Harrison et al., 2015). Further, an abundance of evidence now implicates the INS in addiction (Naqvi et al., 2007; Naqvi and Bechara, 2009, 2010; Paulus and Stewart, 2014; Belin-Rauscent et al., 2016), primarily on the basis of its purported participation in translating the visceral responses to addictive substances into subjective emotion states (Critchley et al., 2004; Everitt and Robbins, 2005, 2016).

The vACC. Human ACC, lying at the midline and corresponding to BAs 24, 25 and 32 (Vogt and Paxinos, 2014), divides into five subregions: caudal, dorsal, perigenual, subgenual and ventral/ rostral, with each of these being functionally dissociable (see Bush et al., 2000; Paus, 2001; Holz et al., 2015). The prevailing view has been that

the functions covered by the more posterior aspects are predominantly cognitive (e.g, error monitoring), and the anterior regions, social and emotional (e.g, stress down-regulation; Bush et al. 2000, 2002; Eldreth et al. 2004; Margulies et al. 2007; Kelly et al. 2009; Clark and Beck 2010), although legitimate concerns about this influential model have been raised (Straube et al., 2009a). The ventral (subgenual and pregenual), regions of the ACC, often referred to in the literarture as vmPFC or medial PFC, and are of particular interest here, maintains connections with the AMYG and aINS (Amaral and Price, 1984; Price, 2003; Ghashghaei and Barbas, 2002; Ghashghaei et al., 2007), and has a long recognized role in disposing for mood and anxiety disorders (Etkin and Wager, 2007; Drevets and Savitz, 2008; Caseras et al., 2013), given its purported contribution to conscious aspects of anxiety, such as catastrophizing and worry (Etkin and Wager, 2007; Ball et al., 2012).

The vACC has been found to increase its activation to threat (Etkin and Wager, 2007; Straube et al., 2007b, 2009a; Ball et al., 2012; Müller-Pinzler et al., 2016b), although this response appears to follow an inverted U-function rather than to a linear gradient (Straube et al., 2009a), and dynamically vary with the (objective) level of (Straube et al., 2009a) and distance to (Mobbs et al., 2007) the threat. The vACC also activates during anticipation of noxious stimuli (Wager et al. 2004; Butler et al. 2005; Nitschke et al. 2006; Ploghaus et al. 2003; Straube et al. 2009b; but see Ploghaus et al. 1999; Simpson et al. 2001), and it has been shown that the most anxious subjects exhibit the strongest activation/ weakest deactivation in the vACC under such conditions (Simpson et al., 2001; Shin et al., 2004; Straube et al., 2007a), a response likely reflecting effortful control of attention to threat or suppression of externalized attention (Mogg and Bradley, 1998; Shin et al., 2004; Bishop et al., 2004; Etkin et al., 2006; Straube et al., 2009a). Specific links to AS have also been made, with scores on this trait dose-dependently increasing rACC activation to emotional versus neutral faces (Ball et al., 2012). This over-engagement of the rACC in AS persons might be based on their bias for hypervigilance towards arousal and could engender dysregula-

tion of stress and catastrophic misappraisals of physical arousal symptoms (Ball et al. 2012; also see Harrison et al. 2015). Interestingly, in the previously discussed study by Ball et al. (2012), both AS and rACC activity were inversely associated with accuracy of matching emotional facial expressions, leading the authors to speculate that the experimentally-evoked anxiety symptomalogy could have been more distracting to AS individuals, which may have produced higher inacuracy. However, it is important to point out that the literature on the role of the vACC (relative to the AMYG and aINS) in anxiety and affective processing in general is much smaller and fragmented, with diametrically opposite results being frequently reported (Straube et al., 2009a). The aforementioned findings and documented associations notwithstanding, the mechanism governing the functional involvement of this region in the conscious aspects of anxiety and specific components of trait anxiety (e.g, anxiety sensitivity) is unclear and needs to be more carefully and extensively scrutinized (Ball et al., 2012).

1.10.1.1 Alcohol-Induced Modulation of Face Emotion Processing

The first pharmaco-fMRI study investigating the acute effects of alcohol intoxication on the neural correlates of face emotion processing was carried out by Gilman et al. (2008). In this study, healthy young adult social drinkers were intravenously administered alcohol and saline (placebo) on two separate occasions, prior to undergoing an MRI session, in which set of fearful and neutral faces was passively viewed (Gilman et al., 2008). Findings revealed that under the influence of alcohol (BAC $\sim$ 0.08 g%) relative to placebo, (1) decreased BOLD activation within the AMYG and other limbic and higher-order visual areas (e.g, lingual and superior temporal gyri and ventral ACC) to fearful versus neutral expressions; and (2) enhanced AMYG reactivity to neutral faces, thus dwarfing its response to the "Fearful versus Neutral face" contrast, suggesting that alcohol hampered the capacity of the AMYG to serve as a threat detector, perhaps by rendering it less able or unable to reliably discriminate threatening socioaffetive signals (i.e, fearful faces) from neutrally valent ones (Gilman et al., 2008).

This finding of alcohol-induced attenuation of AMYG and other limbic regions activity during the presentation of threatening versus non-threatening socioaffective stimuli of was later replicated by the same research group (Gilman et al., 2012a) and others (Sripada et al., 2011; Gorka et al., 2013), in analogous samples and under roughly the same levels of alcohol intoxication, although it is notable that the aforementioned investigations were either underpowered to assess potential sex differences (Gilman et al., 2008; Sripada et al., 2011; Gorka et al., 2013), or ascertained an all-male sample (Gilman et al., 2012a), and none of them personality profiled their subjects, *a priori* or otherwise. Notably, in their previously cited study, Gorka et al. (2013) also examined functional connectivity and found that reduced AMYG reactivity to threatening (fearful and angry) faces occurred alongside, albeit independent from, reduced AMYG-OFC coupling relative to placebo, purportedly connoting alcohol-elicited disruption of communication between the aforementioned regions (Gorka et al., 2013). Importantly, there are indications that individuals who display heightened alcohol-induced stimulation, such as *non-dependent* heavy drinkers and the disinhibited OOA, tend to display none of the aforementioned effects of alcohol (Gilman et al., 2012a), as their AMYG is unresponsive to threatening face presentions even when they are sober (Glahn et al., 2007; Gilman et al., 2012a). The aforementioned findings converge with those of experimental studies in animals (Blanchard et al., 1993; Spanagel et al., 1995; Nie et al., 2004; Pandey et al., 2006) in providing strong support for an anxiolytic interpretation of alcohol's effect and the premise that the locus of action for alcohol's anxiolytic involves limbic fear circuitry (e.g., GABA pathway, central and/ or medial amygdaloid nuclei; Allan et al., 1987; Möller et al., 1997; Sommer et al., 2001; McBride, 2002; Pandey et al., 2006).

The picture emerging from the previously mentioned observations reinforces the notion that the acute negative affect reduction and/ or curtailed scanning of the environment for signals of danger and curtailed salience of otherwise threatening information elicited under the influence of alcohol ostensibly occurs via decreased threat-related

processing within the AMYG (Gilman et al., 2008, 2012a; Sripada et al., 2011; Gorka et al., 2013) and, conceivably, in combination with reduced functional coupling between the AMYG and its chief regulatory structure, the OFC (Porrino et al., 1981; Amaral and Price, 1984; Ghashghaei et al., 2007).

It is, however, notable that a study by Padula et al. (2011) found that the (bilateral) INS, particularly the aINS, but not AMYG demonstrated sensitivity to the inhibitory effects of alcohol during emotional face processing, alluding to alcohol-induced anxiolysis via a region (aINS) that is tightly interconnected with the AMYG and largely involved in introceptive awareness. Nevertheless, the above described research corroborates theoretical models of alcohol use whereby drinking blunts anxiety and attenuates fear and aversive affect by hampering attention to the perceived salience of threat cues (Hull, 1987; Steele and Josephs, 1990; Sayette, 1993; Curtin et al., 2001), and converges with laboratory-based investigations indicating that alcohol use that occurs before exposure to, and thus prior to appraisal of, stressors or threat signals is more robustly anxiolytic than drinking that occurs after the fact (Sayette et al., 2001) and that such is especially or specifically the case when said aversive stimulus is temporally unpredictable and the threat it signals uncertain (Moberg and Curtin, 2009; Hefner and Curtin, 2012).

1.10.2 Acute Social Stress

Human beings are abundantly social animals, with an innate need to belong, be (and feel) accepted by others and maintain good and lasting' social relationships (Baumeister and Leary 1995; MacDonald and Leary 2005; Kawamoto et al. 2015; also see Meuret et al. 2016). This need, found across phylogeny and by no means uniquely human (Sapolsky, 1993; Cacioppo et al., 2015b) is jeopardized in momentary instances of subjective social evaluative threat (SSET; Bowlby, 1969; Baumeister and Leary, 1995; Dickerson and Kemeny, 2004; Smart Richman and Leary, 2009; Baumeister et al., 2007; Cacioppo et al., 2011). The latter typically arises when social connectedness and in-

teractions are prioritized, but one perceives oneself as being ineffective at negotiating them, as per the social self-preservation theory (Schlenker and Leary, 1982; Dickerson and Kemeny, 2004). Based on this, situations that evoke SSET are considered to be an important source of stress (Baumeister and Leary, 1995; Cacioppo et al., 2015a). Situations of this sort pose a threat to central goals, such as social self-presentation (Lazarus and Folkman, 1984; Dienstbier, 1989; Blascovich and Tomaka, 1996; Carver and Scheier, 1999; Lazarus, 1999; Lovallo and Thomas, 2000; Sapolsky, 2000; Dickerson and Kemeny, 2004), typically by involving elements of (1) public failure or inferior performance (Baumeister and Leary, 1995; Dickerson and Kemeny, 2004; Foley and Kirschbaum, 2010; Cacioppo et al., 2015a); (2) uncontrollability of failure outcomes (Breier, 1989; Henry and Grim, 1990; Kirschbaum et al., 1993; Sapolsky, 1993; Croes et al., 1993; Peters et al., 1998; Dickerson and Kemeny, 2004; Dedovic et al., 2005; Wang et al., 2005a, 2007a; Ying et al., 2011); and (3) novelty/ unpredictability (Mason, 1968, 1971). (Weiner, 1992; Dickerson and Kemeny, 2004) (Blascovich and Tomaka, 1996; Carver and Scheier, 1999; Dienstbier, 1989; Lazarus and Folkman, 1984; Lazarus, 1999)

In the aftermath of this, subjective stress is often elicited and negative affect amplified (Baumeister and Leary 1995; also see Taylor and Brown 1988; Baumeister et al. 2002; DeWall and Baumeister 2006; Williams 2007; Stillman et al. 2009; Muscatell and Eisenberger 2012; Lehman et al. 2015; Wagels et al. 2016; Will et al. 2016; van der Meulen et al. 2016; Baddam et al. 2016; Wagels et al. 2016), and hypothalamic-pituitary-adrenal axis (HPAA)[37] activation stimulated, leading to the increased secretion of stress hormones, cortisol (corticosterone in rodents) - the major physiological end product of the HPAA (Dickerson et al., 2004a; Brkic et al., 2016). The purpose of this physiological stress response response is to rapidly mobilize the organism's energy and allocate the necessary resources so as to promote coping with danger and, ultimately, survival (Cannon, 1932; Mason, 1968; Sapolsky, 1992; Linden et al., 1997;

[37]The HPAA is the neuroendocrine core of the stress system.

McEwen, 1998b; Sapolsky et al., 2000; Koolhaas et al., 2011). The production of stress-reactive cortisol is known to influence approach-avoidance behavior (Kaldewaij et al., 2016; Feng et al., 2016) by shifting the threat neurocircuitry "from passive fear to active escape" (Montoya et al., 2015), and it is bidirectionally (and complexly) linked to state affect (Hoyt et al., 2016).

Indeed, acute psychosocial stress paradigms that effectively induce the aforementioned response profile have been developed (Foley and Kirschbaum, 2010). Chief among these are the well-established, standardized and widely utilized laboratory-based Trier Social Stress Paradigm (TSST; Kirschbaum et al., 1993), and the latter's neuroimaging analogue, Montreal Imaging Stress Task (MIST; Dedovic et al., 2005). In the context of the TSST, subjects are asked to prepare and undergo a mock job interview, in addition to performing mental arithmetic in front of an evaluative audience (Kirschbaum et al., 1993). In a similar fashion, the MIST, performed in the scanner environment, requires respondents to perform of mathematical problems under pressure of both time and psychosocial evaluation (for more information, see section 2.2.2.2). Studies incorporating either of these experimental manipulations or comparable forms thereof have reported decrements in state self-esteem and increments in self-reported states embarrassment, shame, anxiety, nervousness, depression and anger (Nezlek and Leary 2002; Lewis and Ramsay 2002; Nolan et al. 2003; Gruenewald et al. 2004; Dickerson et al. 2004a; Schulz et al. 2008; Dedovic et al. 2013, 2014; Achterberg et al. 2016; Sznycer et al. 2016; Wagels et al. 2016; reviewed in MacDonald and Leary 2005; Williams 2007; Allen et al. 2014; Leary 2015; Kawamoto et al. 2015), with increase in some emotions (e.g, in anger) being greater and more frequently instigated than others (e.g, embarrassment; reviewed in Lehman et al., 2015). Reactive aggression in subset of individuals has been documented as well (Twenge et al., 2001; Leary et al., 2006; DeWall and Bushman, 2011; Chester et al., 2013; Riva et al., 2014; Chester and DeWall, 2015; Achterberg et al., 2016). It is thought that any one of the aforementioned emotional experiences can instigate SSET, although there are indications

that the association between SSET and said physiological parameters might piggyback on the erosion of perceived self-worth and mastery and induction of the family of so-called self-conscious emotions such as embarrassment[38] and shame (Lewis and Ramsay 2002; Gruenewald et al. 2004; Weitzman et al. 2004; Dickerson et al. 2004a; Sznycer et al. 2016; for a review, see Lehman et al. 2015; for a meta-analysis, see Dickerson and Kemeny 2004), and negative emotions, such as anger[39] have factually been found to decrease cortisol production (Lundberg and Frankenhaeuser, 1980; Lovallo et al., 1985).

Of course, stress is a highly personalized experience (Kudielka et al., 2009; Lecic-Tosevski et al., 2011; Wu et al., 2013; Choi et al., 2014), which substantially varies, along with its physiological and psychosocial manifestations, as a function of endogenous[40] and exogenous[41] factors (Kumsta et al., 2007; Back et al., 2008; Shalev et al., 2009; Heim et al., 2009; Edelman et al., 2012; Kinner et al., 2016; Herman et al., 2016;

[38]Embarrassment can be understood as prototypical self-conscious, lower activation and avoidance-oriented emotion (Lehman et al., 2015), the experience of which necessarily requires that an evaluating audience be present and results from an undesirable act being publicly displayed by one, leading him or her to implicitly or explicitly reflect about how this norm transgression will damage his or her image in the "eye of others" (Tangney et al., 2007; Krach et al., 2011; Paulus et al., 2013, 2014; Jankowski and Takahashi, 2014; Müller-Pinzler et al., 2015, 2016a). Empirical evidence has directly linked the family of so-called self-conscious emotions (in relation to the potential for critique) with psychosocial evaluative stress/ pressure (Lewis and Ramsay, 2002; Gruenewald et al., 2004; Weitzman et al., 2004; Dickerson et al., 2004a; Sznycer et al., 2016; Lehman et al., 2015).

[39]Anger is generally considered to be a more active feeling (Smith and Ellsworth, 1985; Mackie et al., 2000; Lerner and Keltner, 2001) directly related to heightened sensitivity of the BAS (Harmon-Jones and Allen 1998; Smits et al. 2004; Smits and Kuppens 2005; Cooper et al. 2008; Habib et al. 2015; Rajchert and Winiewski 2016; also see Carver and White 1994; Costa and MacCrae 1992; Berkowitz 2000; Watson 2000).

[40]The list of endogenous factors includes polymorphisms of glucocorticoid and CRH receptors (reviewed in Lamberts and Rossum, 2004) and personality traits (Pruessner et al., 2004; Tyrka et al., 2007; Henckens et al., 2016).

[41]The list of environmental (exogenous) factors includes developmental experiences or attachment style (Witek-Janusek, 1988; Del Giudice et al., 2011; Gunnar et al., 1992; Nachmias et al., 1996; Oberlander et al., 2008; Obradović, 2012; Tarullo and Gunnar, 2006), early life adversity (Bremner et al., 2003; Yoon and Weierich, 2016; Rao et al., 2008; Harkness et al., 2011; Grimm et al., 2014; Voellmin et al., 2015; Nemeroff, 2016; Klengel et al., 2015; Bowers and Yehuda, 2016; Chang and Debiec, 2016; Houtepen et al., 2016; Barton et al., 2016; Winzeler et al., 2016; Kasanova et al., 2016), parental, especially maternal caregiving (Tyrka et al., 2012; Witek-Janusek, 1988; Gunnar et al., 1992; Nachmias et al., 1996; Tarullo and Gunnar, 2006; Howell et al., 2016b), parenting behavior (Carlson and Earls, 1997; Gunnar et al., 2001), familial alcoholism (Schuckit et al., 1987, 1988; Waltman et al., 1994; Dai et al., 2002a; Zimmermann et al., 2004; Dai et al., 2007), life habits (e.g., heavy drinking; Dai et al., 2007; Starcke et al., 2013) and social relationships (e.g., social support; Kudielka et al., 2009).

Lupien et al., 2016), and there are key situational elements to which the physiological stress system is sensitive, and there are inter-individually varied psychological factors, by which the physiological (and also affective) response profile is influenced (Lazarus and Folkman, 1984; Lazarus, 1993). Two out of these factors are particularly relevant to this thesis, namely personality profile and sex.

Acute social stress response modulation by personality profile. Prior research has demonstrated cortisol hyper-responsiveness to acute stress in persons bearing characteristics that amplify sensitivity to social evaluation and public mistakes (e.g, low social-competence: Schmidt et al. 1999; behavioral shame-proneness: Tops et al. 2006; Lupis et al. 2016; low self-esteem: Seeman et al. 1995; Kirschbaum et al. 1995b; Pruessner et al. 1999b; Ford and Collins 2010; depressive tendencies: Kirschbaum et al. 1995b; Powers et al. 2016; dysphoria: Hankin et al. 2010; social phobia: Van West et al. 2008; Roelofs et al. 2009; clinical anxiety in general Powers et al. 2016; and general internalizing problems Hartman et al. 2013), and hypo-responsiveness in individuals with disinhibitory traits (general externalizing symptoms Hartman et al. 2013; Evans et al. 2016a; SS: Zuckerman 1994; Netter et al. 1996; Wang et al. 1997; Rosenblitt et al. 2001; impulsivity: Moss et al. 1995; Dawes et al. 1999; Hardie et al. 2002; antisociality: Vanyukov et al. 1993; Sorocco et al. 2006; and psychopathy: O'Leary et al. 2007).

It has additionally been suggested that more 'resilient' endocrine profiles tend to evince in those who might experience more positive affect (Lazarus and Folkman, 1984) in the sense that they perceive the stress manipulation primarily as a challenge as opposed to a threat (Epel et al., 1998; Buchanan and Preston, 2014).

Acute social stress response modulation by sex. While the picture is far from clear and reports of inconsistent and negative findings exist (e.g, Gruenewald et al., 2004; Kelly et al., 2007, 2008; Youssef et al., 2012; Izawa et al., 2013; Kogler

et al., 2015a, 2016), males clearly appear to be the more physiologically responsive sex to acute performance-based psychosocial stressors (Kirschbaum et al. 1992, 1995a; Kudielka et al. 2004; Rohleder et al. 2003; Lovallo et al. 2006a; Kumsta et al. 2007; Childs et al. 2010; Cornelisse et al. 2011; Schoofs and Wolf 2011; Hidalgo et al. 2012; Edelman et al. 2012; Marin et al. 2012; Lovallo et al. 2015; Stephens et al. 2016; also see Lovallo et al. 2006a). This is contrarily to contexts of physical stressors (e.g, noxious stimulation or exercise; Kirschbaum et al., 1992; Lovallo et al., 2006a; Mather et al., 2010; Felmingham et al., 2012; Bentz et al., 2013) and pharmacological stimulation (Kirschbaum et al. 1992; Born et al. 1995; Luisi et al. 1998; although see Young et al. 2008, for an exception), where the response profiles of the sexes have rarely been found to differ.

The aforementioned sex differences are compatible with the previously made argument that whereas young women are generally socialized for a relational orientation by authority figures and peers, there exists a sociocultural emphasis on instrumentality and physical dominance for young men (Crick and Zahn-Waxler, 2003), as the performance-based threat component marking the TSST and MIST procedures is more sensitive to an instrumental as opposed to a relational orientation (Stroud et al., 2002).

It is important to note, though, that where the cognitive performance and social evaluation components have been examined separately, opposite patterns of sex differences generally stood out, with males showing greater responsiveness to the former (Steptoe et al., 1996; Stroud et al., 2002), and females doing so the latter (Kiecolt-Glaser et al. 1996; Stroud et al. 2002; but see Linnen et al. 2012). Therefore, men's HPAA appears to be particularly sensitive to performance stressors, whereas women's seems particularly responsive to the interpersonal elements of a stressor (also see Andrews et al., 2007; Wadiwalla et al., 2010), although a recent report found greater physiological responsivity to social evaluation (giving a public speech) in men compared with women when subjects were exposed to the a panel of all-female judges (Duchesne et al., 2012). The aforementioned outcomes resonate with the gender gap

in the incidences of anxious psychopathologies (Javidi and Yadollahie, 2011; Bekker and van Mens-Verhulst, 2007; Maeng and Milad, 2015) and major depression (Parker and Brotchie, 2010; Schuch et al., 2014), with disordered females outnumbering males approximately two to one. The above mentioned findings notwithstanding, there are indications that personality composition of the subject groups under study might override sex variability in contexts of acute social stress, which could explain, at least partly, the frequent reporting of null findings with respect to sex variability under the aforementioned conditions (e.g, Gruenewald et al., 2004; Kelly et al., 2007, 2008; Youssef et al., 2012; Izawa et al., 2013; Kogler et al., 2015a, 2016). For example, in a sample of internalizing and externalizing teens, exposure to the TSST triggered a greater increase in cortisol release in internalizing boys relative to internalizing girls, but left the externalizing sexes comparably unresponsive (Hartman et al., 2013). The same result patterns have been reported in nonclinical samples of highly and lowly (trait) anxious young adults exposed to a psychological stressor (a 15-min video of corneal surgery; Takai et al., 2007), and college students high and low in psychopathic personality traits in the context of the TSST (O'Leary et al., 2007), such that males were more responsive than their personality-matched females counterparts only when they were (respectively) highly anxious (Takai et al., 2007) and low in psychopathic personality (O'Leary et al., 2007). Such outcomes allude to the importance of personality profiling selected subjects *a priori* instead of treating personality traits as mere noise. In sum, males generally appear to be the more reactive sex to acute psychosocial stressors such as the TSST and the MIST, although these sex differences might be accounted for by the cognitive performance component, and appear to be overridden by the presence of an externalizing disposition and/ or absence of an internalizing disposition.

Neural correlates of acute psychosocial evaluative stress In contrast to extant research on face emotion processing, the literature on the neurofunctional correlates of

social stress processing is rather small, inconsistent and unrobust. Whereas virtually all brain imaging studies agree that the experience of SSET has neural representation in the top regulator of HPAA reactivity, namely the limbic system (de Kloet et al., 1999; Veenema et al., 2004), conflicting reporting with respect to the particularities of this phenomenon is frequent, even across studies using the same paradigm (e.g, MIST). Even when studies concur with respect to the gross anatomical locations involved, many of them describe "activations" (e.g, Davidson, 2002; Dedovic et al., 2013, 2014; Grimm et al., 2014; Cacioppo et al., 2013; Eisenberger et al., 2003; Sebastian et al., 2011; Wagels et al., 2016), but many others report "de-activations" (i.e, negative changes from baseline of BOLD fMRI signal; Critchley et al., 2000; Pruessner et al., 2004, 2008; Wang et al., 2005a, 2007a; Soliman et al., 2008; Dagher et al., 2009; Dedovic et al., 2009b; Onoda et al., 2009; Gradin et al., 2012; Moor et al., 2012) which is especially true for brain cites such as the HC, AMYG ACC and OFC (Kogler et al., 2015b). By comparison, the deactivation phenomenon is not as well understood (Arsalidou et al., 2013; Kogler et al., 2015b), and underscoring the uncertainty and controversy concerning its interpretation is therefore warranted. Contrarily to an elevation of BOLD signal response relative to baseline, which almost certainly signifies enhanced neural firing (activation), a negative change from baseline may, but does not necessarily, index attenuated synaptic activity (deactivation; Harel et al., 2002; Heeger and Ress, 2002; Czisch et al., 2004; Ernst et al., 2005). Among possible explanations, outside the realm of BOLD signaling suppression (Raichle, 1998), are "vascular stealing phenomena and reversed baseline state" (Czisch et al., 2004). A related concern is that where meta-analyses of neuroimaging studies on social stress or emotion processing in general are performed, studies referring to "deactivations" are typically excluded (e.g, Stevens and Hamann 2012; Lindquist et al. 2012b, 2016; although see Ernst et al. 2005; Kogler et al. 2015b, for exceptions). Then there is the fact that variables such as personality traits and sex have scarcely been addressed in the literature on said topic, despite ample evidence that the nature and extent of the subjective social stress varies

with both, as does its concomitants endocrine response profile.

Bearing those caveats in mind, three regions that have been more consistently found to significantly change their activation (irrespective to direction) in contexts of acute psychosocial stress, with this change in signalling response purportedly being specifically stress-related, namely the hippocampus, perigenual ACC and medial OFC.

Hippocampus (HC). The HC is a highly complex and intricately organized medial temporal lobe (Derdikman and Moser, 2010; Maras and Baram, 2012), with a vital role in leaning and memory (Fedulov et al., 2007; Squire et al., 2007; Maras and Baram, 2012), and a longstanding connection to emotion that historically owes itself to the central position occupied by HC in Papez's limbic circuit and its postulated involvement in affect modulation. Human HC divides into three functionally segregated territories: dorsal, intermediate and ventral, the dorsal being primarily cognitive and the ventral, affective (for more details, see Fanselow and Dong, 2010). Afferent projections to the HC relay signals that carry information concerning changes in one's surrounding environment (Vinogradova, 2001; Maras and Baram, 2012). The HC recognizes the biological significance of incoming new signals, stores them, and reacts to the ones it deems to be crucial - that is, potentially threatening (Maras and Baram, 2012). This section focuses primarily on the relationship between the HC and emotion, which has been supported since the early seminal work of Klüver and Bucy (1937), in which monkeys were found to exhibit profound emotional disturbances consequent to medial temporal lobe ablation (also see Gray and Jeffrey, 1971; Gray and McNaughton, 2003; Sokolov et al., 1975). The HC acts to (automatically) quell fear reactivity via its connections to the AMYG and vmPFC (Maren et al., 2013; Keding and Herringa, 2014; Engin et al., 2016), although the mechanisms underlying this effect are incompletely understood. The HC exerts a potent down-regulatory influence on the HPAA basal activity and reactivity to certain stress modalities, through its primarily inhibitory trans-synaptic effects on the PVN (paraventricular nucleus of the

hypothalamus; Sapolsky et al. 1986; Jacobson and Sapolsky 1991; Jacobson 2005; Herman and Cullinan 1997; Herman et al. 2003b, 2005; Raison and Miller 2003; Dedovic et al. 2009a; Jankord and Herman 2008). Correspondingly, stimulation of the HC, in humans and animals, inhibits cortisol secretion (Dunn and Orr, 1984; Rubin et al., 1966; Herman et al., 2005), while its surgical lesioning or ablation, in animals, results in HPAA overactivation to stressors (Kant et al., 1984; Herman et al., 1998, 2005). This latter effect is also inducible by hippocampal glucocorticoid receptor (GR)[42] blockade (Ratka et al., 1989; Feldman and Weidenfeld, 1999; Herman et al., 2005) or deletion (Boyle et al., 2005; Jankord and Herman, 2008).

In turn, the HC is a prominent target for stress. Mild or transient stressors typically improve hippocampal function by increasing synaptic plasticity, likely suggestive of the adaptive import of being able to recall threatening events or situations (Joëls and Baram, 2009; Joëls et al., 2011; McEwen and Gianaros, 2011; Maras and Baram, 2012). However, if repeatedly activated in excess, these same mechanisms, can erode the functional and structural integrity of this system, leaving it vulnerable to the deleterious effects of prolonged and/ or severe stress (Sapolsky and McEwen, 1986; Issa et al., 1990; Magarin et al., 1995; McEwen, 1999; McEwen and Gianaros, 2011; McEwen et al., 2016; Kim and Diamond, 2002; Raison and Miller, 2003; McLaughlin et al., 2007; Joëls et al., 2007; Zoladz and Diamond, 2009; Joëls et al., 2011; Krugers et al., 2010; Schwabe et al., 2011; Teicher et al., 2016; Maras and Baram, 2012). Indeed, hippocampal dysfunction and dysmorphology have been linked to human anxiety (and mood) disorders (Frey et al., 2007; Bonne et al., 2008; Karl et al., 2006; Woon et al., 2010; Kühn and Gallinat, 2013; Pitman et al., 2012; Keding and Herringa, 2014; Morey et al., 2016; Teicher et al., 2016; Culig and Belzung, 2016), and, interestingly, it is the hippocampal function and physiology that effective pharmacological interventions for

[42] GRs are activated by glucocorticoids, are expressed in most cells throughout the body, and are richly present in the HC (Reul and Kloet, 1985; Reul and De Kloet, 1986; Aronsson et al., 1988; Arriza et al., 1988; Herman et al., 1989b,a; Herman, 1993). GRs modulate genes governing development, metabolism and the immune response neuroadaptation (Lupien et al., 2009).

these disorders primarily target (Vermetten et al., 2003; Levy-Gigi et al., 2013; Soares et al., 2016). The aforementioned findings notwithstanding, HC-stress relationship is highly complex, and dynamically varies in both nature and extent varying with stress modality (Joëls and Baram, 2009; Zoladz and Diamond, 2009; McEwen and Gianaros, 2011; Schwabe et al., 2011; Maras and Baram, 2012; Herman et al., 2005, 2016). For example, whereas restraint and novelty (open field) can trigger corticosterone secretion (Herman et al., 1998, 1995), inhalation and hypoxia[43] cannot or do not (rinos et al., 1987; Mueller et al., 2004). Similarly, hippocampal ablation alters endocrine responding to some stressors (e.g, ether stress; Feldman and Conforti, 1980; rinos et al., 1987), but not others (e.g, restraint or hypoxia; Bradbury et al., 1993; Herman et al., 1998). Moreover, the HC inhibits HPAA activity in some situations, yet boosts it in certain others (Feldman and Weidenfeld, 1993, 2001; Dunn and Orr, 1984), and there is evidence to indicate that hippocampal lesions may exert diametrically opposing effects on distinct stress modalities (Mueller et al., 2004).

In humans, it is often assumed, and frequently supported, that the HC is prominently involved in responding to acute psychosocial stressors. In the context of the MIST (Dedovic et al., 2005), hippocampal deactivation to the "stress versus nonstress" contrast has often been described in cohorts of healthy young adults (Pruessner et al., 2008; Dedovic et al., 2009b,a; Dagher et al., 2009; Khalili-Mahani et al., 2010; Soliman et al., 2011; Lederbogen et al., 2011; Grimm et al., 2014; Albert et al., 2015), typically in association with a dose-dependent increase in stress-reactive cortisol secretion (e.g, Pruessner et al., 2008; Dedovic et al., 2009b,a; Lederbogen et al., 2011; Grimm et al., 2014), and often as part of more widespread limbic deactivation, although reports of increased activation also exist (Dedovic et al., 2013, 2014; Eckstein et al., 2014). This "deactivation" phenomenon reinforces the premise that some stressors curtail hippocampal activation, thereby leading to HPAA stimulation and stress hormone secretion initiation (Pruessner et al., 2008; Jacobson, 2005; Herman et al., 2005). As

[43] A condition in which oxygen in blood or tissue is insufficient.

initially proposed by Pruessner et al. (2008), hippocampal deactivation in the context of an acute psychosocial stressor such as the MIST constitutes a specific element of the stress response, ostensibly promoting stress-reactive cortisol production via disinhibition of the PVN (also see Dedovic et al., 2009a; Dagher et al., 2009). In detail, the HC is constantly active by default because the function it covers, namely evaluation of new incoming messages and singling out those indicating potential danger, is highly prioritized (Pruessner et al., 2008) (also see Gusnard and Raichle, 2001). This ongoing activation mode tonically inhibits the HPAA, but is interrupted and blunted when threat is perceived, consequently stimulating the endocrine stress responding and ultimately secretion of the stress surrogate marker cortisol (Pruessner et al., 2008).

Hippocampal functioning in the context of the MIST or comparable stress paradigms has been linked to self-esteem related behavioral phenotypes (Pruessner et al., 2005a), and there are some indications that it might be more pronounced in men than women (Duchesne et al., in preparation), and have the opposite association patterns with perceived stress in the sexes[44] (Wang et al., 2007a). However, the mechanisms governing the previously mentioned differences remain unclear and understudied, as sample ascertainment across studies employing the said procedures has largely been male-biased, and often oblivious to personality traits.

Perigenual anterior cingulate cortex (pgACC). The pgACC (caudal-dorsal ACC) is a paralimbic region spatially encompassing BAs 24 and 32 (Gianaros et al., 2007). It is an important component of the limbic stress modulation system (LeDoux, 2000b), with an extensively described key role in regulating and ultimately quelling stress-related AMYG activity (Pezawas et al., 2005; Pessoa, 2008; M.L. et al., 2003; Diorio et al., 1993; Vogt, 2005; Vogt et al., 1992; Devinsky et al., 1995; Bush et al., 2000; Gianaros et al., 2007), cortisol reactivity (Diorio et al., 1993) and autonomic responsivity (e.g, increases in blood pressure; Benarroch, 1997; Lovallo and Gerin, 2003;

[44] Using a serial subtraction stress paradigm, Wang et al. (2007a) found that hippocampal activation was positively (vs negatively) associated with perceived stress during the task in women (vs men).

Soufer et al., 2002; Gianaros et al., 2005). Such functions resonate with the richness of the pgACC in neuronal glucocorticoid receptors (Herman et al., 2005), its powerful interconnections with the NAc, AMYG, HC, PAG as well as the aINS and OFC (Carter et al., 1998; MacDonald et al., 2000b; Meyer-Lindenberg and Tost, 2012; Shiba et al., 2016), and its reciprocally inhibitory connections (anticorrelation) to the MCC (Shulman et al., 1997; Drevets and Raichle, 1998; Whalen et al., 1998a), the latter, as pointed out in a previous section (see 1.10.1), a key functional element of the "classic pain matrix" (Peyron et al., 2000; Casey, 1999; Ingvar, 1999; Davis, 2000a; Wager et al., 2004) subserves the emotional aspect of pain processing (Rainville et al., 1997). As such, pgACC activation has consistently been described during the modulation of experimentally-induced pain (e.g, heat) under conditions of increased cognitive load, and in association with a dose-dependent decrease of perceived pain intensity and unpleasantness, alluding to enhanced pgACC activation by attentional reorientation away from the aversiveness of the situation (Bush et al., 2002; Bantick et al., 2002; Büchel et al., 1999; Petrovic et al., 2002; Peyron et al., 1999; Ploghaus et al., 2001; Rainville et al., 1999; Valet et al., 2004; Wager et al., 2004). Conversely, ACC deactivation has often been found in the context of the MIST and correspondingly with SSET (Pruessner et al. 2004, 2008; Wang et al. 2005a, 2007a; Soliman et al. 2008; Dedovic et al. 2009b; Dagher et al. 2009; Akdeniz et al. 2014; but see Lederbogen et al. 2011; Wagels et al. 2016). It has been suggested that the pgACC is part of a system that represents a target for the modulatory effects of 'prosocial' neuropeptides (Zink et al., 2010), and on which social-environmental risk and protective factors might thus converge (Zink et al., 2010; Lederbogen et al., 2011; Holz et al., 2016). In line with this view, altered pgACC responsiveness to acute psychosocial stress (MIST) has been described in association with urban upbringing[45] (Lederbogen et al., 2011), and with ethnic minority status, the latter which corresponded to greater self-reported expo-

[45]Early life urbanicity has been established as a causal risk factor of various psychopoathologic manifestations (Krabbendam and Van Os, 2005; Peen et al., 2010; van Os et al., 2010; Newbury et al., 2016).

sure to chronic stress (Akdeniz et al. 2014; for a review, see Tost et al. 2015). Further, pgACC GM volume covaries with coping styles (Holz et al., 2016), perceived social standing (Gianaros et al., 2007), and potentially the capacity to modulate fear (Milad et al., 2005). As well, synaptic and neuronal remodelling of the pgACC has been found in rats exposed to prolonged social stress (Poeggel et al., 2003), and pgACC dysmorphology in persons directly exposed to 3-year long harsh corporal punishment (Tomoda et al., 2009), 9/11 (Ganzel et al., 2008) and cumulative adverse life events (Ansell et al., 2012). The aforementioned outcomes illustrate the potential importance of the pgACC in mediating threatening experience, and amplifying (as well as buffering) against risk of psychiatric disorders.

Medial orbitofrontal cortex (mOFC). The OFC (BA 10, 11) is a multifaceted prefrontal structure with intimate anatomical and functional (inter)connections with, among other regions, the AMYG, ACC and INS (Amaral and Price, 1984; Barbas, 2007; Barbas et al., 2011; Carmichael and Price, 1995; Cho et al., 2013a; Rolls, 2005; Price, 2007). Extensive extant evidence suggests that the OFC is necessary for inhibitory control, affective decision-making and goal-directed action (Bechara et al., 2000; Kringelbach and Rolls, 2004; Saddoris et al., 2005; Beer et al., 2006; Goldstein and Volkow, 2011; Motzkin et al., 2015; Jackson et al., 2016; Dalton et al., 2016; Amodeo et al., 2016; Wikenheiser and Schoenbaum, 2016). This region additionally contains neurones responsive to negatively valent material, as electrical stimulation of the (medial) OFC, in both animals and humans, is analgesic (Oleson et al., 1980; Thorpe et al., 1983) and increased OFC activation during laboratory pain modulation corresponds to reduced intensity and unpleasantness of perceived pain (e.g, Derbyshire et al., 1997; Petrovic et al., 2000; Bantick et al., 2002). Particularly the mOFC plays a pivotal role in decoding and responding to socioaffective stimuli (Adolphs, 2002; Mah et al., 2004; Kringelbach and Rolls, 2004; Ohira et al., 2006; Angrilli et al., 2008; Spikman et al., 2012; Takahashi et al., 2004; McCloskey et al., 2016), especially stim-

uli signaling provocation (e.g, angry faces; Blair et al., 1999; Davidson et al., 2000; Coccaro et al., 2007; Gorka et al., 2013; Attwood and Munafò, 2014; Fabiansson et al., 2012; Beyer et al., 2015), and is key for the down-regulation of impulsive aggression through top-down limbic response suppression (McDonald, 1991; Anderson et al., 1999; Davidson et al., 2000; Rule et al., 2002; Izquierdo et al., 2005; Coccaro et al., 2007; Joseph et al., 2009; Márquez et al., 2013; Attwood and Munafò, 2014; Amodeo et al., 2016). Indeed, failure in this system (e.g, underreactivity to emotionally salient material) in often seen in cohorts of pathologically aggressive individuals, such as those with intermittent explosive, conduct, and antisocial personality disorders (Davidson et al., 2000; Herpertz et al., 2001; Pol et al., 2001; Donegan et al., 2003; Dougherty et al., 2004; Schmahl et al., 2004; Coccaro et al., 2007; Blair, 2008; Schulze et al., 2011; Passamonti et al., 2012; Huang et al., 2014; Herpers et al., 2014; Rolls and Deco, 2016; Angus et al., 2016), alluding to centrality of said deficit as a mechanism governing reactive aggression (Coccaro et al., 2007; Marsh et al., 2008; Jones et al., 2009; Jonker et al., 2015). Such outcomes resonate with reports implicating the mOFC in reward and punishment expectancy (Plassmann et al., 2010; Metereau and Dreher, 2015), regulation of sensitivity to outcome value (Gourley et al., 2016; Forscher et al., 2016) and processing of risk-related signals under conditions of uncertainty (Fiorillo et al., 2003; Hsu et al., 2005; McCoy and Platt, 2005; Preuschoff et al., 2006; Christopoulos et al., 2009; Tobler et al., 2009; O'Neill and Schultz, 2010).

In the context of the MIST, the mOFC has often been found to deactivate, a finding consistent with the notion that threat appraisal can compromise top-down regulatory functions (Pruessner et al., 2004, 2008; Soliman et al., 2008; Dedovic et al., 2009b; Dagher et al., 2009). The same pattern of results has been found in studies employing other serial subtraction tasks (Wang et al., 2005a, 2007a).

1.10.2.1 Alcohol-Induced Modulation of Social Stress Reactivity

To our knowledge, no neuroimaging studies of the effect of alcohol on the response to acute social stress have been performed to date and generally speaking, the relationship between alcohol and stress remains poorly understood (e.g, Cappell and Herman 1972; Hodoson et al. 1979; Cappell 1987; Pohorecky 1991; Croissant and Olbrich 2004; Cobb and Thiel 1982; Elias et al. 1982; Rivier et al. 1984; Merry and Marks 1969; Dai et al. 2007; Välimäki et al. 1984; Magrys et al. 2013; for a review, see Becker et al. 2011).

For example, Sayette et al. (1994) found that when young adult male and female social drinkers drank to intoxication in the context of a public speech task, their self-reported anxiety and negative self-appraisal decreased, with differential effects of alcohol on subjective mood ratings evincing as a function of familial AUDs. In a similar vein, de Wit et al. (2003) showed that exposure to the TSST procedure modestly increased alcohol intake in healthy social drinkers, although this increase was not directly linked to alcohol's pharmacological properties. On the other hand, Thomas et al. (2014) observed that social drinkers who endorsed DTC motives were not different from those who did not in terms of drinking behavior (and did not significantly increase their drinking) in response to acute social stress (TSST), though differences between the groups in the stress experiences were noted. Along similar lines, Buckingham et al. (2016) demonstrated that hazardous drinkers did not differently experience simulated social ostracism when moderately intoxicated versus sober.

A similar incoherent picture emerges from the literature on the relationship between acute alcohol intoxication and endocrine stress responding. Neither the question of how alcohol acutely influences the HPAA has been uniformly answered across studies, nor is the subjective effect of a given endocrine responding pattern under intoxication entirely clear. The work of Brick's group for example, showing that among FHP individuals, it was those who were high cortisol responders to acute stress (when sober) that drank most (Brkic et al., 2015), and displayed the most pronounced sensitivity to

alcohol's sedative properties (Brkic et al., 2016), alludes to alcohol-induced anxiolysis by HPAA inhibition. At the same time, there are indications in the human and animal literatures that for certain subjects, stimulation of the stress systems along with resultant increase in glucocorticoid secretion might signify alcohol-produced energetic arousal and euphoria (see Piazza et al. 1993; Deroche et al. 1993; Fahlke et al. 1994a,b, 1995, 1996; Fahlke and Hansen 1999; Lamblin and De Witte 1996; for reviews, see Miczek et al. 2008; Sinha 2008; Cleck and Blendy 2008; Uhart and Wand 2009; Melis et al. 2009; Becker et al. 2011).

These inconsistencies are likely explainable by inter-study methodological discrepancies in terms of alcohol dose (Klatsky et al. 1977; DeTurck and Vogel 1982; Kelbaek et al. 1985; reviewed in Pohorecky 1981, 1990, 1991), the nature and intensity of the stressor (Moberg and Curtin 2009; Moberg et al. 2011; Hefner and Curtin 2012; Hefner et al. 2013; reviewed in Kopin 1995; Pacak and Palkovits 2001; Miczek et al. 2008; Becker et al. 2011) and the order in which stress and alcohol are administered (Sayette et al., 2001), likely compounded by a host of individuals-related factors, such prior exposure to alcohol (Ireland et al., 1984; Marmot, 1984), the subjective state of the individual at the time of testing (Pohorecky, 1981, 1991) and personality profile (see Greeley and Oei 1999; Bradford et al. 2013; Gorka et al. 2016b,a; Gorka 2016; reviewed in (Curtin and Lang, 2007)). Additional research that accounts for these and other variables known to alter the physiological phenotype (e.g, familial alcoholism: Schuckit et al. 1987, 1988; Waltman et al. 1994; Dai et al. 2002a; Zimmermann et al. 2004; Dai et al. 2007; and developmental experiences Bremner et al. 2003; Yoon and Weierich 2016; Rao et al. 2008; Harkness et al. 2011; Grimm et al. 2014; Voellmin et al. 2015; Nemeroff 2016; Klengel et al. 2015; Bowers and Yehuda 2016; Chang and Debiec 2016; Houtepen et al. 2016; Barton et al. 2016; Winzeler et al. 2016; Kasanova et al. 2016) is therefore needed to provide a more cohesive understanding of the aforementioned topics.

Chapter 2

Methods

Contents

2.1 Screening and Characterization 92

2.2 Design and Testing Procedure 105

2.2.1 Alcohol Challenge 107

2.2.2 MRI Scanning 108

2.2.3 Behavioral Measurements 114

2.2.4 Psychological Measurements 116

2.2.5 Physiological Measurements 116

2.3 Follow-Up Assessment 118

2.4 MRI Data Acquisition 119

2.5 MRI Data Preprocessing 120

2.5.1 Face Emotion Processing Task 121

2.5.2 Montreal Imaging Stress Task 126

2.6 Statistical Analyses 131

2.6.1 Face Emotion Processing Task 131

2.6.2 Montreal Imaging Stress Task 134

This study was approved by the McGill Institutional Review Board. The design was a double-blinded, counter-balanced, placebo-controlled, repeated-measures study of responses to alcohol challenge and different types of emotionally challenging tasks, with longitudinal follow-up of alcohol and illicit substance use and misuse in otherwise psychopathology-free social drinkers who are putatively at-risk of developing AUDs. The 'baseline' testing phase included three sessions, one laboratory and two MRI. Subjects who completed those and were not excluded from MRI data analyses entered the prospective follow-up phase. Follow-ups were conducted at the end of year 2-3 after 'baseline' testing.

2.1 Screening and Characterization

A group of young adult social drinkers, who are putatively at-risk for AUDs but otherwise healthy was recruited via advertisements posted in classified listings around Montreal and on-line. One thousand, five hundred volunteers completed a of an on-line survey (surveymonkey) that indicated whether or not they were initially eligible to participate. The survey included a series of pre-screening questionnaires, namely the Michigan Alcohol Screening Test (MAST), Substance Use Risk Profile (SURPS), Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) and Anxiety Sensitivity Index (ASI), in addition to a list of questions assessing whether any of our exclusion criteria were met.

Cutoff scores for inclusion into one of the two personality risk were set based on the Woicik et al. (2009) report of normative data for the SURPS. Cutoff scores required for inclusion into the sensation-seeking (SS) group were a minimum score of 18 on the SS subscale, a maximum score of 6 the AS subscale and a score of 12 or higher on the SR subscale of SPSRQ. The cutoff scores required for inclusion into the anxiety-sensitive (AS) group were: a minimum score of 15 on the AS and a maximum score

of 12 on the SS subscales of the SURPS, a score of 21 or higher on the ASI, and of 11 or less on the SPSRQ-SR subscale. All this to ensure that our subjects were very clearly differentiated in terms of their personality risk profiles and latent dispositions. Individuals who classified as high in both AS and SS traits were excluded. Individuals scoring 3 or higher on the MAST were, too, excluded.

Exclusion criteria were as follows: meeting diagnostic lifetime criteria for active medical illness, lifetime history for one or more psychiatric disorder, including illicit drug abuse, chronic use of prescription medication (other than contraceptives), pregnancy, breastfeeding, a history of head injury, claustrophobia, having a night job that required one to work during the night and abnormally high or abnormally low body mass index (BMI; normal BMI is $18.5 - 23.5$ for men and $19.5 - 24.5$ women; overweight is $> 23.5 - 29.5$ for men and $> 24.5 - 29.5$ women, and underweight is < 18.5 for both men and women Bray 1979). Of individuals who completed the online questionnaires, 88, whose scores indicated initial eligibility to participate in the study, were subsequently contacted and underwent a short (15-min) phone interview. In the latter, assessment for trait impulsivity (using the 5-item Impulsivity subscale of the SURPS), drinking habits and general sleep patterns was conducted. This interview additionally involved assessing whether prospective subjects met all the usual safety requirements for the MRI environment, whether they were confident they would not experience excessive discomfort being in the MRI scanner for 50 plus minutes, whether they underwent any type of brain imaging study in the past and finally, whether prospective female subjects were normally cycling. Subjects were thanked for their time and excluded if they: (1) surpassed the cutoff score of 14 for impulsivity; (2) were unfamiliar with the alcohol dose to be administered in the study (i.e, have not consumed 5 alcoholic drinks[1] (4 for females) or more in the past month; (3) classified as regular binge drinkers (i.e, binge-drinking[2] episodes on weekly bases (+5 drinks per occasion

[1] A standard alcoholic drink is 12 oz of beer, 5 oz of wine, or 1.5 oz (one shot) of liquor (ICAP, 1998).

[2] A drinking pattern in which high quantities of alcohol are consumed in a short amount of time

for men; 4+ drinks for women; of Alcohol Abuse and Alcoholism 2004; of Health et al. 2005) or heavy drinkers (i.e, consuming more than 15 alcoholic drinks per week); (4) had irregular or dysregulated sleep patterns (awakening time after 10); (5) were abnormally cycling women; (6) did not meet all the safety requirements to undergo MRI scanning; (7) expressed concern about possibly experiencing excessive discomfort in the scanner given the length of scanning; (8) reporting experiencing a traumatic event or unusually high levels of psychological stress during the last month; (9) have in the past underwent a brain imaging study of a similar nature, as this raises the possibility that said individual might not be completely or at all naïve to the currently employed emotional challenge paradigm; or (10) reported having any sort of learning disability (this will become relevant in the context of the MIST). Otherwise, an invitation for an interview at the alcohol research lab was extended. Individuals undergoing this additional testing session totalled 49.

In the lab, subjects first underwent a structured clinical interview, conducted by a trained doctoral student in clinical psychology, using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, non-Patient Edition (SCID-I/NP; First et al. 2002) in the context of a relatively extensive clinical interview, to rule out manifestation of major psychiatric disorders (lifetime criteria). On the basis of this interview, one individual was suspected of misreporting and probably underreporting both psychiatric symptoms as well as alcohol and drug use patterns (primarily due to inconsistent reporting). This person was provided with a list of mental health referrals, thanked and compensated 20 dollars for his time and excluded. The remaining 48 individuals neither indicated nor were suspected of being and/ or having ever been psychologically disordered, and all were therefore deemed to be eligible for the fMRI study. These subjects were then familiarized with the experimental procedure that was to take place on the upcoming two scanning sessions. Subjects were informed they will need

(typically four drinks for women or five drinks for men consumed in the span of a 2-hour period) that brings BAC levels to 80 mg per 100 ml. (Ron and Barak, 2016)

to commit to approximately 7 hours for each scanning days, and that they would not be released from the lab until and unless their blood alcohol limit is below 0.02. Subjects were instructed to refrain from physical exercise, caffeine, licit and illicit substances, and larger (especially high-fat) meals on MRI testing days and were advised to get at least 6 hours of sleep the night before. Either or both MRI scanning sessions were then scheduled (when possible). For the remaining part of this lab session, subjects filled out a series of questionnaires meant to assess several variables that might require covariation, namely current and past polydrug use, familial history of alcoholism, developmental experiences (i.e, early life trauma and parental abuse including neglect), self-esteem and internal locus of control and alcohol-expectancy. Measures used to quantify these variables are described below.

The final recruited sample consisted of 48 putatively at-risk for alcoholism but otherwise healthy subjects, 23 females and 25 males (41 university undergraduates), with a mean $\pm$ standard deviation (SD) age of 20.4 ± 1.87 years (range $= 18 - 24$ years). that divided into two groups, one scoring high in measures of SS and another, AS. Table 2.1 presents the characteristics of this recruited sample.

Study protocols were approved by the Institutional Review Board (IRB) of the McGill University, and written informed consent form was obtained prior to participation in accordance with the the McGill IRB requirements from all subjects. The same consent form, we note, contained a question inquiring as to whether subjects would agree to being contacted in the future concerning this study. Participation in the study, it was made clear to the subjects, was not conditional in anyway on them answering yes to the latter question. All subjects consented to being contacted again in the future for a follow-up assessment. All subjects were fully debriefed at the end of their third testing day.

Table 2.1 Characteristics of the Recruited Sample by Personality Group.

	ASSs	**SSSs**	***P*-value**[†]
Age (years, $M \pm SD$)	20.52 ± 1.65	20.4 ± 2.20	*ns*
Sex, Women, *n* (%)	11 (47.8)	11 (44.0)	
Race, *n* (%)			
Caucasian	21 (91.3 %)	18 (75.0%)	–
Black	0	0	–
Asian	0	2 (8.3%)	–
Other	2 (8.7%)	4 (16.7%)	–
Education (years, $M \pm SD$)	14.17 (.89)	14.18 (1.07)	*ns*
Weight (Kg, $M \pm SD$)	66.57 ±18.62	69.64 ± 12.84	*ns*
Height (Cm, $M \pm SD$)	170.79 ± 10.32	175.61 ± 12.27	*ns*
SURPS score ($M \pm SD$)			
AS scale	16.95 ± 1.70	6.20 ± 1.25	.000
SS scale	10.35 ± 1.22	22.37 ± 1.95	.000
ASI total score ($M \pm SD$)	34.60 ± 6.61	10.45 ± 4.73	.000
Physical Concerns score	17.58 ±5.35	3.45 ± 3.00	.000
Mental Incapacitation Concerns score	5.64 ±2.87	3.62 ± 1.66	.006
Social Concerns score	7.17 ±2.12	4.79 ± 1.91	.000
SPSRQ score ($M \pm SD$)			
SP scale	13.40 ± 4.79	6.21 ± 4.03	.000
SR scale	10.90 ± 3.27	16.04 ± 2.82	.000
MAST score	.57 ± 1.46	.24 ± .88	*ns*
Alcoholic drinks per week	8.20 ± 4.10	± 10.54 ± 7.27	*ns*
Lifetime regular smokers[a](n (%))	0	0	–

Abbreviations: ASSs = anxiety-sensitive subjects; SSSs = sensation-seeking subjects; ASI = Anxiety-Sensitivity Index; SURPS = Substance Use Risk Profile Scale; AS = Anxiety-Sensitivity; SS = Sensation-Seeking; SPRSQ = Sensitivity to Reward and Punishment Questionnaire; SP = Sensitivity to Punishment and SR = Sensitivity to Reward; M = mean and SD = standard deviation

No effects of sex and personality-by-sex interaction on any of the presented variables showed or trended towards (i.e, $p \leq .1$) significance.

[†] *P*-value for personality group difference found using GLM univariate testing with personality and sex and fixed factors.

Bivariate Pearson correlation coefficients for the personality screening measures are presented in Table 2.2. As shown, scores on the different personality measures were very strongly correlated.

Table 2.2 Bivariate pearson correlation matrix of personality screening measures ($N = 44$).

	ASI	SURPS-SS	SURPS-AS	SPRSQ-SP	SPRSQ-SR
ASI	1	$-.902^{**}$	$.886^{**}$	$.697^{**}$	$-.543^{**}$
SURPS-SS	$-.902^{**}$	1	$-.930^{**}$	$-.687^{**}$	$.630^{**}$
SURPS-AS	$-.886^{**}$	$-.930^{**}$	1	$.647^{**}$	$-.633^{**}$
SPRSQ-SP	$.697^{**}$	$-.687^{**}$	$.647^{**}$	1	$-.537^{**}$
SPRSQ-SR	$-.543^{**}$	$.630^{**}$	$-.633^{**}$	$-.537^{**}$	1

ASI = Anxiety-Sensitivity Index; SURPS = Substance Use Risk Profile Scale; AS = Anxiety-Sensitivity; SS = Sensation-Seeking; SPRSQ = Sensitivity to Reward and Punishment Questionnaire; SP = Sensitivity to Punishment and SR = Sensitivity to Reward.

** Correlation is significant at $P_{(2-tailed)} \leq .001$.

Following is a description of the screening questionnaires that were administered in the present study, and all of which were scored based on the guidelines of the respective authors.

Substance Use Risk Profile Scale (SURPS). The SURPS (Woicik et al., 2009) is a 23-item questionnaire measuring variation in personality risk for drug misuse and non-substance related psychiatric conditions along 4 dimensions: hopelessness, anxiety sensitivity, sensation seeking and impulsivity. This instrument is administered in a paper/pencil format on which respondents can endorse statements about themselves by selecting one of four response options (strongly disagree [1], disagree [2], agree [3] and strongly agree [4]. The psychometric properties of the SURPS, including its concurrent, predictive and incremental validity (relative to other personality measures) in identifying and differentiating persons predisposed to reinforcement-specific drug use profiles has been established in multiple samples of both teens and adults (Conrod et al., 2008, 2010; Woicik et al., 2009; Krank et al., 2011; Castellanos-Ryan et al., 2013; Jurk et al., 2015; O'Leary-Barrett et al., 2015). It has additionally been recently shown that the sensitivity of the SURPS' subscales in identifying a high number of individuals who would come to develop substance misuse or other psychiatric

problems within the subsequent 1.5 years, ranges between 72% and 91% (Castellanos-Ryan et al., 2013). Each of the four subscales differentially correlate, and with a good degree of specificity with specific psychiatric manifestations. Specifically, the internalizing anxiety sensitivity traits is associated with "drinking to forget" - that is, using alcohol to self-medicate and manage anxiety or depressive symptamology. The same traits also represents a risk factor that more than triples the odds for developing anxious pathologies (relative to individuals low in this trait; Stewart and Kushner 2001; Woicik et al. 2009), especially GAD, SAD and PD. Conversely, high levels of the externalizing sensation seeking trait are associated with risk-taking behaviors, heavy drinking chief among them, for enhancement purposes, and is not related to particular forms of non-substance related psychopathologic expression *per se*. Importantly, the SURPS is practically advantageous over other personality measures such as the NEO, the latter including 240 items (versus 23 in SURPS), and hence the feasibility of completion of the SURPS and potential for its utilization as a systematic screening instrument.

Each of the AS and SS subscales had good internal reliability in the current study (Swailes and McIntyre-Bhatty, 2002), with Cronbach alpha coefficients being α = .915 for AS (5 items) and α = .933, SS (6 items). Averaged inter-item correlations were, respectively, .710 and .705 for the AS and subscales, which are considered high High-risk individuals were partially defined as those scoring at least 1 SD above the normative mean on either the AS or SS subscales of the SURPS.

Anxiety Sensitivity Index (ASI). The ASI (Reiss et al., 1986) is the most widely used measures in empirical investigations for the quantification of the construct of anxiety sensitivity construct: the dispositional proclivity to fear anxiety-related symptoms secondarily to the belief that their consequences will potentially be catastrophic (Reiss et al., 1986; Peterson and Reiss, 1992). This questionnaire consists of 16-items (e.g, "When I begin to sweat in a social situation, I fear people will think negatively of

me"), each self-rated assessed on a five-point Likert scale ranging from 0 (very little) to 4 (very much). The psychometric properties and predictive validity of the ASI have been well-documented (Peterson and Reiss, 1992; Peterson and Plehn, 1999).In a non-pathological sample Peterson and Reiss (1992) indicated a mean of 19.1 ($SD = 9.11$) and internal consistency ranging from $\alpha = .82$ to .91, and correlations from .71 to .75 between administrations. In the current study, the ASI and its subscales had good internal reliability (Swailes and McIntyre-Bhatty, 2002), with a Cronbach alpha coefficient being $\alpha = .927$ and averaged inter-item correlations, .453 which is considered acceptable. We used the total score within our sample as has been previously suggested since studies have found that the subscales are highly correlated, and a greater percentage of items load higher on the general domain factor rather than on the domain-specific factors (Osman et al., 2010). While intended by its developers to assess AS as a unitary construct, and several studies factor analyzing this it have reported a one-factor solution (Reiss et al., 1986; Sandin et al., 1996; Taylor et al., 1991, 1992a; Taylor, 1996) , other studies have challenged the factor structure of the ASI, with a two-factor solution being found by some (e.g, Cox et al., 2001), a three-factor solution by others (Taylor et al., 1996; Stewart et al., 1997a; Zinbarg et al., 1997), and as many as four factors by still others (Telch et al., 1989; Wardle et al., 1990; Cox et al., 1996). Notwithstanding, based on the work of Zinbarg et al. (1997), most seem to agree that the structure of the ASI is perhaps best explainable by three lower order factors assessing fear of anxiety-related the physical symptoms ("Physical Concerns"), fear of cognitive dyscontrol ("Mental Incapacitation Concerns") and fear of adverse social consequences of anxiety ("Social Concerns"), all loading on one factor of global AS (Stewart et al., 1997a; Rodriguez et al., 2004).

In the present study, we used the total score on the ASI to screen subjects but also looked at the three subscales separately when analyzing the data. Cronbach's alpha coefficients for the physical, mental incapacitation and social concerns subscales were, respectively, .928 (9-items),.835 (4-items) and .510 (4 items), and averaged inter-item

correlations, .587, .570 and .204.

Sensitivity to Punishment Sensitivity to Reward Questionnaire (SPRSQ). The SPSRQ is a 48 yes/no response item, self-report questionnaire (Torrubia et al., 1995, 2001) containing two orthogonal subscales, namely Sensitivity to Punishment (SP, $\alpha = .84$) and Sensitivity to Reward (SR, $\alpha = .70$). This instrument is a proposed measure of Gray's motivational systems, namely the Behavioral Inhibition and Behavioral Activation Systems (respectively, BIS and BAS; assessed by 24 SP and 24 SR items), such that SP and SR items describe, respectively, responsiveness in situations where punishment and reward are predominant (Gray, 1975, 1981, 1982, 1987b,a; Beck et al., 2009b). Even and odd items are ascribed to, respectively SR and SP. Scores for each scale equal the sum of the "yes" answers to their respective items. Both scales have good reliability ($.76 - .84$; Torrubia et al. 1995, 2001) and convergent validity (Caseras et al. 2003; also see O'Connor et al. 2004). An exploratory factor analysis (EFA; principal components analysis) of the SPRSQ, performed in an earlier study by Torrubia et al. (1995) reportedly revealed that all items loaded adequately and as expected on two factors (24 items on each factor; Torrubia et al. 1995).Cronbach's alpha coefficients for the SP and SR subscales in the present study were, respectively, .886 and .697, and averaged inter-item correlations, .243 and .089

SP trait has been shown to negatively correlate with extroversion ($r = -0.50$), and positively neuroticism ($r = 0.54$), while the opposite pattern of these association is shown by SR (where did I get this?- cite). Further, whereas SR is positively associated with Sensation Seeking Scales ($r = .45$ in males, $r = .21$ in females) and scales assessing closely related constructs (e.g, Thrill and Adventure Seeking; Experience Seeking; disinhibition and Boredom Susceptibility), SP is inversely related to all of those, often to a significant extent (Torrubia et al., 2001).

Michigan Alcoholism Screening Test (MAST). The MAST is a 25 yes/ no response item self-report questionnaire that has been widely used to assess the presence and extent of drinking problems (Selzer, 1971; Storgaard et al., 1994) and previously shown to reliability discriminate between casual alcohol users and abusers (Brady et al., 1982). The cutoff score for mild-to-moderate problem drinking on the MAST is 4 (Selzer, 1971) and individuals scoring 3 or higher on this instrument were excluded, so as to ensure that the recruited sample was not in any way alcohol use disordered.

Structured Clinical Interview for DSM-IV-TR Axis I Disorders - Non–Patient Version (SCID-I/ NP). The SCID-I/ NP (First et al., 2002) is a diagnostic exam used to assess mental health status and determine DSM-IV-TR Axis I disorders (major mental disorders)

Individuals meeting the diagnostic lifetime criteria for a major psychiatric disorder were excluded, so as to ensure that the recruited sample was psychologically "pristine".

Current and past Polydrug use. Subjects were asked to list all the licit and illicit substances they have ever used in their lifetime. The experimenter then read from a standard list of substances to ensure the subject had not forgotten to mention any. The standard list is as follows: Tobacco, Alcohol, Cannabis, LSD, Psilocybin, Cocaine, Mescaline, Amphetamine, Methylphenidate, Phencyclidine, Ketamine, GHB, MDMA, Heroin, Ephedrine, Amphetamine-Dextroamphetamine, Dextroamphetamine, other. Subjects were then required to state the age of first use and use of the substances during the 30 days prior to the study. For each substance, subjects were required to state if they had mixed substances and list all the combinations. Subjects were then asked to recall the last time they used each substance, the date and an estimate of the amount used.

Family Tree Questionnaire. The potential presence of AUD cases in first-degree and second-degree relatives was assessed for using the Family Tree Questionnaire

(Mann et al. 1985; also see Kendler et al. 2015b). Subjects were asked to specify who, if any, among their relatives, in immediate family, paternal side and maternal side, has ever been diagnosed or suspected of alcoholism or suffered from a drinking problem (lifetime criteria).

The definitions of family history of alcoholism have varied across studies (see Alterman, 1988; Cservenka, 2016). That said, previous neuroimaging research has largely classified individuals as FHP if either or both biological parents had AUDs, or two or more second-degree relatives did (e.g, Schweinsburg et al., 2004; Andrews et al., 2011; Cservenka and Nagel, 2012; Sjoerds et al., 2013). Conversely, FHN individuals have no cases of AUDs in first (e.g, Heitzeg et al., 2010) or first and second-degree relatives (e.g, Cservenka and Nagel, 2012; Squeglia et al., 2014b). We therefore relied on these (dichotomous) definitions plus two others, one of mild family history for alcoholism (FHM), which we defined, as have previously others, as having one second degree relative with an AUD or two second degree relatives on different sides of the family with the condition. The second definition we used was of multigenerational family history for alcoholism (MFH): having at least one alcoholic parent plus two alcoholic relatives on the same side of the family.

Rosenberg Self-esteem Scale (RSE). We administered the RSE (Rosenberg, 1965, 1979), which is currently the most commonly utilized and well-validated self-report instrument for evaluating global self-esteem. This tool quantifies perceptions of global self-worth and -acceptance. The scale's items total 10 (e.g, "I feel that I'm a person of worth"), and each is self-rated on a 4-point Likert scale (1, "strongly agree" to 4, "strongly disagree"; see Crandal 1973; Wylie 1974; Martín-Albo et al. 2007 for psychometric properties and further characteristics of the scale).

Self-efficacy questionnaire. The locus of control measure (Krampen, 1991) was administered on account of its well-established strong power in predicting stress re-

active cortisol production (e.g, Pruessner et al., 2005b). This instrument consists of subscales assessing internal locus of control (e.g., "What happens to me is my own doing") and external locus of control (e.g., "Sometimes I feel that I don't have enough control over the direction my life is taking"). The validity of this questionnaire for the assessment of locus of control has been demonstrated and its scores are generally independent of affective state (Bachman and O'Malley, 1977).

Alcohol-Expectancy Questionnaire (AEQ). It has been previously suggested that the tension-reducing/ stress-dampening effect of alcohol in anxiety-inducing contexts occur only if the person ingesting said drug expects it to (Buckner et al., 2013). Given this, and considering that the route of alcohol administration in our study was oral as opposed to intravenous, we reasoned that expectancy of alcohol effects, if statistically different across subjects as a function of personality, sex and/ or their interaction, would require co-variation. As such, we used the AEQ (Brown et al., 1980), a well-validated (Rohsenow and Bachorowski, 1984) and widely used instrument that provides a means of quantifying one's beliefs about the expected effects of alcohol.

This questionnaire contains 40-items and comprises 7 subscales (respectively, Global Positive, Careless Unconcern, Cognitive Impairment, Power and Aggression, Sexual Enhancement, Social and Physical Pleasure, Social Expressiveness and Tension Reduction), with 5-6 items addressing each (e.g, e.g, "drinking makes it easier to concentrate on the good feelings I have at the time"). Each item is self-rated on a 6-point Likert scale (1, "disagree strongly" to 6, "agree strongly").

Childhood trauma questionnaire (CTQ). This 28-item self-report measure (Bernstein et al., 2003) is widely to assess for the presence of a history of childhood maltreatment. A total of subscales (5-items each) measure five forms of maltreatment, namely (respectively): emotional abuse (e.g, "People in my family called me stupid, lazy, or ugly"), sexual abuse (e.g, "Someone tried to make me do sexual things or watch sexual

things"), physical abuse (e.g, "People in my family hit me so hard that it left bruises or marks"), emotional neglect (e.g, "There was someone in my family who helped me feel that I was important or special" inverse item), and physical neglect (e.g, "There was someone to take me to the doctor if I needed it", inverse item). (Heim et al., 2013) Each phrase is rated on a 5-point Likert scale (1, "never true" to 5, "very often true").

The psychometric properties of the CTQ are well-established. Its internal consistency is good (Crohnbach's $\alpha = 0.63 - 0.95$) and so is its criterion-related validity ($r = 0.50 - 0.75$) in pathological and community-recruited samples. Convergent reliability with clinical psychologist assessments of childhood maltreatment is high, and considerable specificity and sensitivity of cutoff scores to to distinguishing respondents who were abused as children from those who were not has also been noted (see Heim et al., 2013). The cutoff scores for moderate to severe abuse are 13 for emotional abuse, 8 sexual abuse, 10 physical abuse, 15 emotional neglect, and 10 physical neglect (Heim et al., 2013).

Parental Bonding Instrument (PBI). Th PBI is retrospective self-report questionnaire (Parker et al., 1979), used to asssess care and overprotection received independently from mother and father during the first 16 years of life. This scale, extensively used, has good reliability (e.g, internal consistency and re-test reliability). In fact, the test-retest reliability of this instrument has even been established over extended time periods that can be as long as twenty years (Wilhelm et al., 2005). The validity of the PBI has also been well-established by numerous investigations, with satisfactory construct and convergent validity and independence of mood effects (see Parker, 1983).

Two forms, the mother form and father form, consist of 25 item each. 12 of these quantify 'care' and 13 'overprotection'. Items are endorsed by respondents on 4-point Likert scale (very like, moderately like, moderately unlike and very unlike). Normative

scores, as established by Parker (1983) range between 0 and 26 for low maternal care, 0 and 23, low paternal care, 27 and 36, high maternal care and 24 and 36, high paternal care.

Notably, the PBI additionally allows that parents be effectively "assigned" to one of four quadrants, namely "affectionless control" (high *protection* and low *care*), "optimal parenting" (high *care* and low *protection*) and, finally, "neglectful parenting" (low *care* and low *protection*; Parker et al. 1979). Assignment to "high" or "low" categories is based on the following cut-off scores: for mothers, a care *care* of 27.0 and a *protection* score of 13.5 and for father, a *care* score of 24.0 and a *protection* score of 12.5 (Parker et al., 1979).

2.2 Design and Testing Procedure

This fMRI study featured a repeated-measure, randomized, double-blind, placebo-controlled counter-balanced design (Figure 2.1). Both MRI testing occasions entirely took place at the Montreal Neurological Institute (MNI). We attempted to the best of our ability to schedule MRI sessions for the afternoon, when baseline cortisol levels are relatively low, and all subjects included in the final analyses underwent and completed two MRI testing sessions, separated by approximately 14 days. The study coordinator was the same throughout the entire duration of the study, as was the MRI scanner used and software version in operation. Acquisition parameters, processing and statistical analysis of any and all physiological, neural and behavioral data obtained throughout the study were identical for all subjects.

Subjects reported to the scanning unit at least one hour prior to the start of MRI session. Arrival and awakening times on that day were recorded. Subjects were asked to change their clothing (into scrubs) and then seated in a comfortable quite room, where they rested for 45 minutes. This was done to ensure that by the time MRI testing has started, cortisol levels would have had returned to baseline/ resting levels.

After resting period salivary cortisol and blood alcohol curve (BAC) readings were obtained through, respectively, a swab and breathalyzer. Next, the tasks that subject would be required to perform in the scanner were clearly explained and their duration and order of presentation laid out. Subjects briefly practiced the MIST (control trials only) prior to being alcohol/ placebo challenged.

The alcohol/ placebo challenge (15 minutes) and absorption period (15 minutes) followed, in chronological order. BAC and salivary cortisol readings were obtained and placement in the scanner occurred, in chronological order, immediately after (precisely 30 minutes after subjects received the drink challenge of alcohol or the control placebo condition), at or near the height of the blood alcohol curve (BAC = .08; range .075 − .10).

Inside the scanner, subjects held a socket USB in their right hand, which technicians illustrated for them how to use as they underwent a emotional challenge paradigm. The latter consisted, a Face Emotion Processing Task and then the Montreal Stress Imaging Task (MIST), administered identically and chronologically on both scanning days, with salivary cortisol measurements, BAC readings and subjective mood assessments being recorded at multiple time points throughout. After the MIST, subjects underwent a 10-minute structural scanning period as they rested. Once the MRI scan has ended, subjects were placed in a comfortable and quite room, given a blanket, served a hot meal and offered a laptop and a set of movies on DVDs. BAC and salivary cortisol readings were obtained at 10-minutes interval until subject was sent home, approximately 1.5-2 hours after end of scanning session. For subjects receiving placebo on their first day, they were kept in the scanning unit for at least one hour before being sent home so as to try and prevent them from seeing through the placebo condition. Once both scanning sessions and data collection have been completed, subjects were debriefed about the testing procedure.

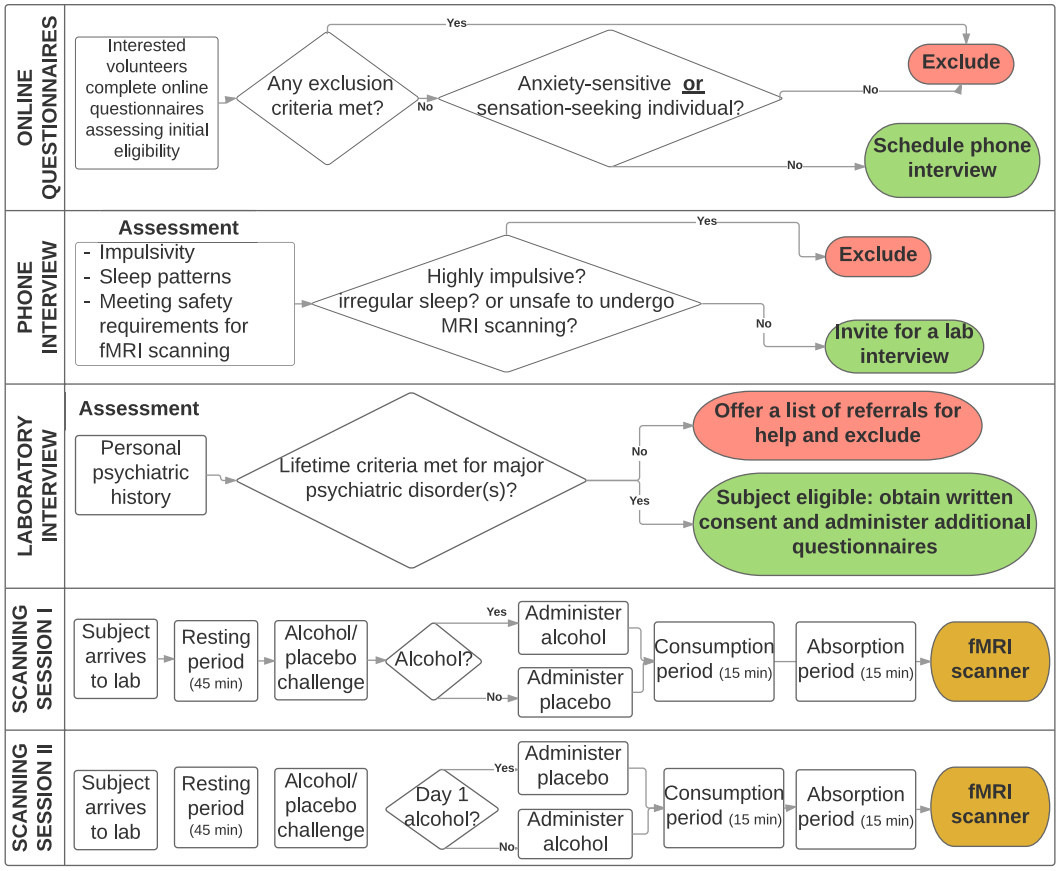


Figure 2.1 Flow chart of screening and experimental procedures.

Explication of the previously mentioned steps and experimental procedures follows.

2.2.1 Alcohol Challenge

Female subjects received a dose of alcohol which was 12.5% less alcohol per kilogram of body weight than men. Due in part to sex differences in total body water content and different rates of elimination, numerous studies have shown women to display more cognitive impairment than men at the same dose. Men received an alcohol dose of 1 ml/kg of 95% USP alcohol. For both sexes the alcohol was mixed with room temperature orange juice (3:1 of alcohol: juice ratio) and administered prior to scanning. Both dosages of alcohol have been reliably shown to achieve a target blood alcohol level of .08 (range .075 – .10) in 15 minute period (Schuckit et al., 1997a,b),

a concentration maintained for approximately 30 minutes. The placebo beverage was the room temperature orange juice, with drops of 95% USP ethanol poured on the surface of the drink just before being served and on a terry cloth drink holder, so that subjects would smell and taste alcohol without ingesting enough to alter BAC. The drink volumes were equal and subjects were told they received two different dosages of alcohol on each day. Each of the three drink glasses was consumed within a 5-minute period (total consumptions time is 15 minutes) and drinking was paced to standardize ingestion rates and to maximize experimental control across subjects (Schuckit et al. 1997a,b; also see Ramchandani et al. 2009). While aware that compared to oral alcohol administration, intravenous infusion is more accurate, we avoided this approach given that one of our groups is highly anxious and it is precisely anxiety and stress related neural BOLD responses that we were aiming at measuring shortly after the alcohol challenge was completed.

15 minutes after subjects have completed their last drink have elapsed, they were placed in the scanner so that testing could occur at or near the height of the blood alcohol curve. After the alcohol-placebo challenge administration was completed, serial breathalyzer readings were recorded every 8 to 10 minutes until BrAC fell below 0.02 g%, after which subjects were sent home.

2.2.2 MRI Scanning

In the MRI scanner, subjects were exposed to an emotional challenge paradigm, administered identically on both days. This paradigm involved the administration of two tasks, in chronological order, namely a Face Emotion Processing Task (FEPT) and the MIST (Dedovic et al., 2005). The latter was followed by a 10-minute resting period, during which an anatomical scan was obtained. Total scanning time was approximately 55 minutes (Figure 2.2).

All fMRI scans were done on a Siemens 3T TIM Trio scanner. The visual tasks

were viewed by a mirror above the participant inside the scanner, from a projector. Subjects submit their answers during the tasks using a socket placed in their hand.

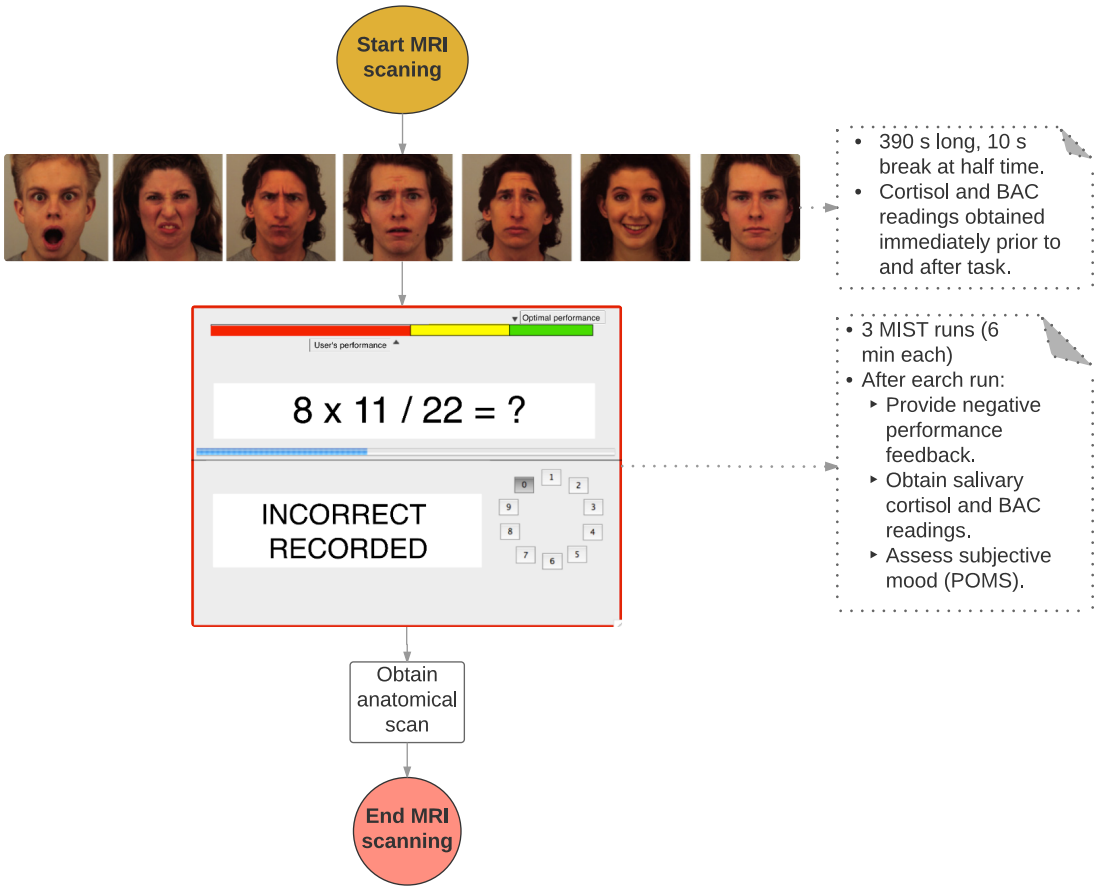


Figure 2.2 A flow chart of MRI testing procedure, conducted identically on both scanning days. MRI scanning session involved, in chronological order, administration of the FEPT and the MIST and obtaining an anatomical scan. BAC = blood alcohol curve; s = seconds; min = minutes

2.2.2.1 Face Emotion Processing Task

In the Face Emotion Processing Task (FEPT), subjects identify a target emotion displayed as a face stimulus. Fearful, angry, disgusted, surprised, sad, happy and neutral facial expressions were used as stimuli. All stimuli were presented using a Mac laptop computer with in-house stimulus delivery software.

The task was designed in our lab and created with a code written in MATLAB (The Mathworks, Natick, MA, USA), using the Psychophysics Toolbox extensions

and a standardized set of photographs of said emotional (Disgusted, Surprised, Angry, Sad, Fearful, Happy) and neutral faces, taken from the Karolinska Directed Emotional Faces set (KDEF; Lundqvist et al. 1998), presented in an event-related design that lasted 6 min 30s (Figure 2.3). Overall, there were seven different faces expressing each of the seven emotions (49 pictures in total). The photographs, all unfamiliar to subjects, were of Caucasian young adult males and females. They were static, projected through a mirror mounted onto the headcoil, on a dark grey background, displayed in horizontal positions and shown centrally for a duration of 2.5 seconds. Photographs of facial expressions appeared in a pseudo-randomized fashion such that subject viewed each of 7 facial expressions (these were randomly selected) within each 'cycle', and none of them could re-appear within the same 7 emotion cycle. Subjects were instructed to focus on the face and label the perceived emotional expression being displayed by choosing one of 7 options ("Fearful", "Angry", "Disgusted", "Surprised", "Sad", "Happy" and "Neutral"). The task was carried out in a single continuous trial that persisted for 390 seconds, with a 10-second break at half time. The time it took subject to label the emotion served at the interstimulus interval, the latter which varied across and within subjects. Naturally, as a result of that, the number of face photographs viewed and emotions identified varied across subjects and within the same subjects between the two testing occasions. A script was yielded for each subject at the end of his or her FEPT, indicating, for each stimulus presented (in chronological order) the face photographs displayed, as well the actual and perceived emotional expression of target face. The FEPT and the code written to create it are freely available for use upon contacting thesis author.

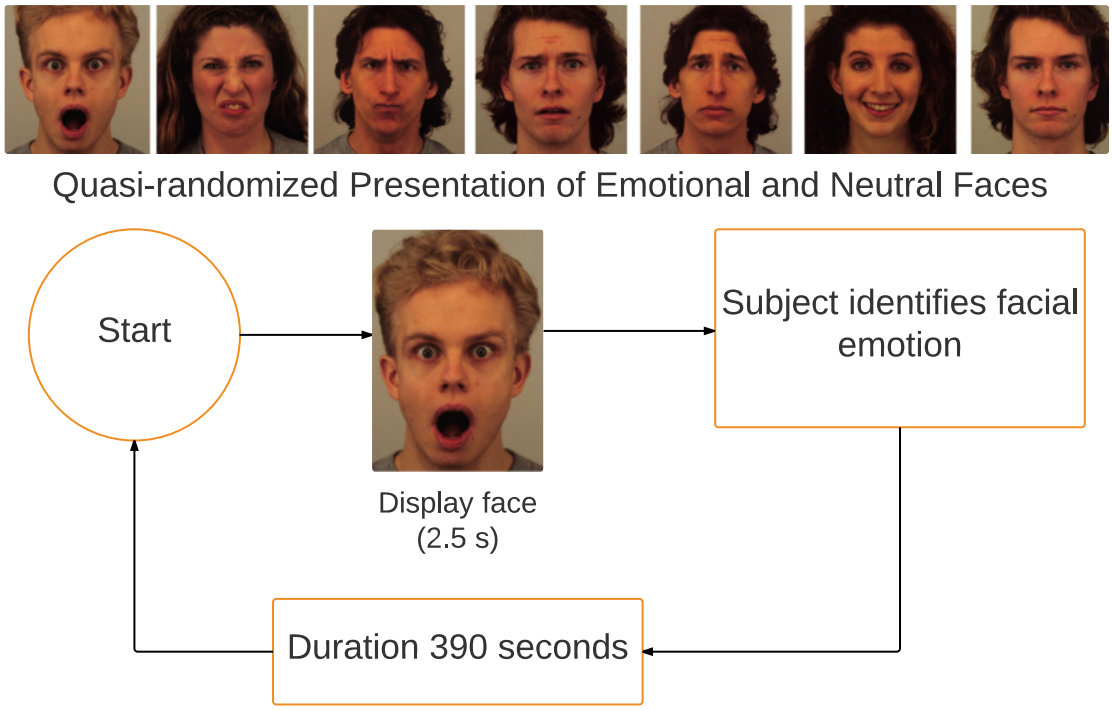


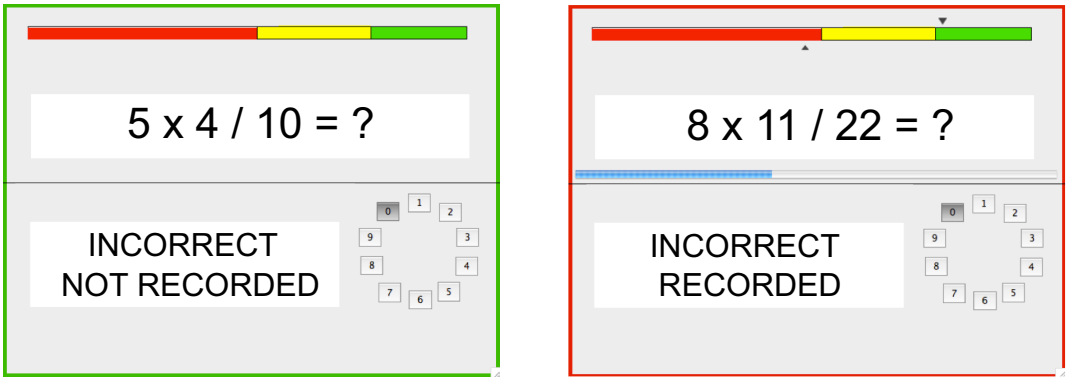
Figure 2.3 Graphic User Interface of the FEPT. Depicted are the seven types of basic emotions presented (top row, from left to right, fearful, disgusted, angry, surprised, sad, happy and neutral faces). Faces are presented in a pseudo-randomized fashion for a fixed duration of 2.5 seconds per face. Subjects then have to label the emotional displayed by target face (by choosing from seven options). Response latency serves as interstimulus interval (see text for additional detail).

2.2.2.2 Montreal Imaging Stress Task

The Montreal Imaging Stress Task (MIST; Dedovic et al. 2005) is a psychosocial evaluative stress paradigm wherein subjects are asked to solve arithmetic tasks under time pressure. The task featured a block design included three conditions: rest, control and experimental. Each condition was presented in a fixed order that was repeated three times within each one of a total of 3 runs ("Experimental": 72 s, "Control": 36 s and "rest": 12 s), resulting in a duration of 6-minutes per run.

Under the experimental (stress) condition, mental arithmetic problems are to be solved by subject under the pressure of time and psychosocial evaluation (Figure 2.4**B**). Under the control (nonstress) condition, mental arithmetic is performed under a significantly less strict time limit and absent the psychosocial evaluative pressure element

(Figure 2.4**A**). During rest, subjects were shown neutral surface and asked to keep their eyes open. The computer algorithm has been designed such that the answer for any arithmetic problem will always be an integer between 0 and 9, thus requiring a single keystroke to submit the response (see Figure 2.4).



(A) **(B)**

Figure 2.4 Graphic user interface of the MIST (Dedovic et al., 2005). **(A)**, In the experimental (stress) condition, mental arithmetic is performed under psychosocial evaluative pressure: a performance color bar reflecting the individual subject's performance (bottom arrow) in contrast to a mock 'average performance' (top arrow), a progress bar displaying elapsed time, a performance feedback text field emphasizing that subject's poor performance was recorded. **(B)**, In, the control (nonstress) condition, mental arithmetic problems are to be solved under a significantly less strict time limit and absent the psychosocial evaluative pressure components.

Psychosocial evaluative pressure is induced through a scripted investigator interaction slightly adapted from the originally proposed one (Dedovic et al., 2005; Pruessner et al., 2008). Subjects are told, when introduced with the MIST prior to entering the MRI scanner, that performing "at par" was attainable for anybody with average intelligence and did not require that one has advanced math abilities. Subjects were also told that their performance would be closely monitored real time by everyone in the scanner room (investigator, assistants, MRI technicians), and had to be at least "average" for their MRI data to be usable. The "average" performance, we falsely claimed, was based on the performance of a large sample of their peers, whose IQ was average and math abilities not necessarily advanced. Unbeknown to the subject is

the fact that, by design, the algorithm contained in the MIST generates a script that automatically manipulate either or both the arithmetic problem difficulty and allotted time depending on subject's "aptitude", such that his or her performance would be suboptimal irrespective of math skills and a failure rate of 40%-50% is enforced (Dedovic et al., 2005).

After each test run, a female confederate enters the room with a female assistant wearing a lab coat and holding a notebook, both looking puzzled and surprised by the subject's "unusually bad" performance. The confederate informs the subject that he or she was not performing well and if such continued to be the case, the experiment would be unsuccessful and subject's data unusable, which would be unfortunate on account of MRI scans are associated with great costs and are very time-exhaustive. The confederate then tried to "explore" with the subject possible explanations for their performance (can you see the numbers well, did u use drugs last night). Meanwhile, the assistant looks concerned as she continuously writes notes. It is notable that our style in providing the feedback was slightly different from the original approach, whereby negative feedback is provided by a lab coat-wearing investigator who did not meet subject before: here the confederate conveying the evaluative feedback to subjects was always the same doctoral student who interviewed them on their first testing day (in the lab), familiarized them with the testing procedure and the tasks they would be performing in the scanner and established good rapport with them. It would be this doctoral student's dissertation work that suffers if a subject performed below "average" on the MIST, subjects were told. At no point did this said confederate wear lab coat. This was done with the purpose of making the situation seem as natural and least staged as possible.

Negative performance feedback was followed by obtaining BAC and salivary cortisol readings, and completion of a brief self-report mood questionnaire immediately after the confederates have left the room.

2.2.3 Behavioral Measurements

2.2.3.1 Face Emotion Processing Task

Response latency. The speed with which an individual identified facial emotion has been suggested to correspond to the degree of vigilance displayed by that individual to socioaffective signals (e.g, Doty et al., 2013). As such, response latency was an outcome measure of interest in the present work. Values for this behavioral index were obtained through the following expression: duration in seconds spent by subject rating all faces/ total number of faces rated $\times$ 100.

Response accuracy. It has been suggested that persons high in trait SA might more accurately identify facial emotions, especially the negatively valent ones than would individuals low in this trait. Whether they were intoxicated to the point of distorted perception and whether such an effect would differ as a function of personality and sex or their interaction. Measures of identification accuracy of any facial expression (i.e, number of faces labelled correctly/ number of faces labelled $\times$ 100) and negatively valent expressions (i.e, number of fearful, angry, disgusted and sad faces labelled correctly/ number of fearful, angry, disgusted and sad faces labelled $\times$ 100) were thus obtained. Accuracy in identifying positively valent faces was also measured to serve as some sort of control/ baseline measure (i.e, number of happy faces labelled correctly/ number of happy faces labelled $\times$ 100).

Appraisal bias. Previous research has gone to compellingly suggest that neutral faces are not really neutral, at least as far as high trait anxiety subjects are concerned. Rather, neutral faces might be best conceptualized as ambiguously valent (expand on this a but and cite ref from my discussion section); Socially anxious individuals, pathological or not, have been shown to demonstrate a proclivity to interpret faces of

this sort in a negative light, as opposed to anxiety-normative individuals who typically tend to perceive them as unambiguous signals of neutrality.

It has additionally been shown that high- sensation seeking individuals are in fact positively biased, being more likely to perceive stimuli that others would find to potentially signal threat as less or not at all threatening. Based on the previously mentioned information, we assessed potential differences between personality groups and within them (by alcohol) in terms of negativity bias in rating a) neutral faces (i.e, neutral faces rated as emotional; number of neutral labelled as negative or surprised/number of neutral faces labelled $\times$ 100) and positivity bias in rating emotional faces (i.e, fearful, angry, disgusted, sad and surprised faces rated as neutral/number of fearful, angry, disgusted, sad and surprised faces labelled $\times$ 100).

Finally, facial displays of surprise can be distinguished from those signaling direct threat against the individual (e.g, fearful and angry) in that the former can be interpreted as predicting either a negative or positive outcome (Tomkins and McCarter, 1964; Kim et al., 2003). Therefore, if BOLD activation to surprised faces were to differ across subjects (as a function of either or both personality and sex) and within the same subjects (as a function of alcohol intoxication), it would be important to determine whether such differences are accompanied with differential interpretations of such faces. We therefore examined the tendency to rate surprised faces rated as harsh (i.e, surprised faces rated as harsh; number of surprised labelled as fearful, angry or disgusted/ number of surprised faces labelled $\times$ 100).

2.2.3.2 The Montreal Imaging Stress Task

While it is true that by virtue of the MIST's algorithm design, any and all individuals undertaking this task (referring here to its original version) will, at best achieve a success rate between 40% and 60%, we wanted to assess whether subjects, still, statistically differed in their performances. Performance outcome on the MIST has notably been shown to be inversely associated with stress-induced increments in self-

rated anger (Kazén et al., 2012) as well as cortisol secretion (Kazén et al., 2012). Further, performance on cognitive tasks administered within the fMRI scanner have been found to be modulated by the degree of engagement of higher-order cognitive functioning and emotion-responsive brain regions. These findings suggest that information on whether and to what degree the performance outcome on the MIST differs across different subjects or within the same subjects would be highly relevant to and important to consider when interpreting our findings. Performance outcomes of interest were correct responses (number of arithmetic problems presented/ number or correct answers submitted × 100), incorrect responses (number of arithmetic problems presented/ number or incorrect answers submitted × 100) and time overshoots (i.e, questions for which no answer was submitted within allotted time, "time out"; number of arithmetic problems presented/ number or time overshoots × 100).

2.2.4 Psychological Measurements

Profile of Mood States (POMS). Subjective mood was assessed at multiple points throughout the course of the MIST using a brief versions of the Profile of Mood State (POMS; McNair et al. 1971). Subjects visually rated, on a scale of 0 to 10, states cheerfulness, relaxation, confidence, efficiency, embarrassment, anger, relaxation, tension and confusion at the moments immediately prior to the beginning of the MIST, immediately after the negative feedback that followed each of the three runs and once again at 10 min after the completion of the task.

2.2.5 Physiological Measurements

Salivary cortisol sampling To assess cortisol levels, every subject provided saliva samples at 11 time points over the course of experiment on each MRI testing day, starting at the moment immediately prior to start of alcohol/ placebo challenge. The

second cortisol reading was obtained immediately after absorption period a and just before the start of MRI session, when subjects were seated at the scanning bench prior to the FEPT ($\sim$ 30 minutes following the first sample). Subsequently, salivary cortisol readings relevant for the MIST occurred at, as follows: times 0 (immediately prior to start of the MIST), $\sim$ +10 min (after the first run has ended and performance feedback received, prior to start of the second run), +20 (after the second run has ended and performance feedback received, prior to start of the third run), +30 (after the third run has ended and performance feedback received, prior to start of the structural scanning) and +40 minutes (after the structural scan). Outside of the scanner (after scanning session), saliva samples were collected at 10 min intervals while subjects were resting until semi complete descendance of the BAC ($\sim$ 1 hour after completion of scanning session; same was done for placebo days).

Salivary cortisol readings were ascertained using the salivette sampling device (Sarstedt Inc, Quebec City, Quebec, Canada) and stored shortly thereafter in the laboratory freezer at $-20°$C (Degrees Centigrade) until they were sent for analysis using time-resolved fluorescence immunoassay. Intra- and inter-assay variability have been found to less than 10% and 12%, respectively (Dressendörfer et al., 1992).

Blood Alcohol Curve Blood alcohol curve (BAC) level was first measured upon subject arrival to the scanning unit (to ensure subject was sober) and then again after the absorption period. After that, BAC level was recorded at 10 minutes intervals, each time just prior to collection of the salivette sample (see previous section for specificity time points) and until semi-complete descendance of the BAC (i.e, 0.02 level).

One very notable fact is that the use of breathalyzer in the MRI scanning room is not allowed, for safety and other reasons. To avoid the caveat of having to estimate BAC during scanning based on time spent in the scanner (as is typically done by others; e.g., Padula et al. 2011; Sripada et al. 2011), we resorted to an approach that was suggested and implemented by an engineer in our team: the plastic tube meant to

be attached to the breathalyzer for the subject to breathe in was attached to a closed Ziploc, so that half of the tube is inside the Ziploc. In the scanner room, subject would breathe into the closed Ziploc through the tube, and the latter is then immediately attached to the breathalyzer just outside the scanner room, the Ziploc bag is deflated and BAC reading is obtained. Each Ziploc bag used to obtain a BAC reading was used only once. We tested this method on a total of 10 subjects undergoing a different study in our lab, wherein they, too, were alcohol challenged, with a 100% test-retest reliability.

2.3 Follow-Up Assessment

Within a time range of 2-3 years, 9 out of out 44 subjects were lost to follow-up. The remainder 35 underwent a short interview a phone ($n = 14$) or skype interview ($n = 21$).

DSM-V AUDs or SUDs. The DSM-V criteria for AUDs, total 11 and come in the form of yes/no questions (e.g, "in the past year, have you continued to drink even though it was causing trouble with your family or friends?"). Those meeting 2 or more, 4 to 5 and 6 or more of said criteria classified as, respectively, mildly, moderately and profoundly/ severely disordered alcohol users.

Michigan Alcoholism Screening Test (MAST). Description of the MAST and its psychometricproperties (Selzer, 1971; Storgaard et al., 1994) was provided in an earlier section, given that this same instrument was initially used to exclude individuals who classified (or almost classified) as problem drinkers (using a cutoff score of 3; see Section 2.1).

The incorporation of this instrument in our follow-up assessment procedure was meant to corroborate the findings of the DSM-V criteria in relation to subject's drinking status. Again, the MAST has consistently proven to reliability discriminate be-

tween casual alcohol users and abusers (Brady et al., 1982). Those scoring 4 to 5 on this measure classified as mildly-to-moderately alcohol use disordered while those scoring 6 or higher classified as severely alcohol use disorder. (Selzer, 1971; Storgaard et al., 1994).

Structured Clinical Interview for DSM-IV-TR Axis I Disorders - Non–Patient Version (SCID-I/ NP). A description of the SCID-I (First et al., 2002) was provided in an earlier section, given that this same examination was initially used to exclude individuals meeting the diagnostic criteria for a major psychiatric disorder (lifetime criteria) so as to ensure that the recruited sample was psychopathology-free (see Section 2.1). The same instrument was re-administered at follow-up in order to determine in whom among our subjects major psychiatric illness has come to develop. Specific emphasis was placed on assessing anxious pathologies, on account of the frequent association in which those and AUDs appear among high-AS persons.

2.4 MRI Data Acquisition

MRI data of all subjects were acquired using a 3.0 T Siemens Magnetom Trio Tim (Erlangen, Germany) MRI scanner at the Montreal Neurological Institute. Subjects were positioned in a 12-channel transmit-receive headcoil and stabilized by padding to reduce motion-related artifacts. Subjects laid supine in the scanner with a response box in their right hand which they have been shown how to use by the technicians and were asked to try and avoid head movement to the best of their ability. Duration of the two tasks performed by subjects (namely Face Recognition and MIST) totalled approximately 40 minutes and was followed by a 10 minute period of anatomical scanning. T2*-weighted images sensitive to the blood oxygenation level-dependent (BOLD) signal (repetition time [TR] = 2000 ms, echo time [TE] = 30 ms, flip angle = 90°, filed of view (FOV) = 224 m) were used to acquire 210 whole-brain volumes for the Face recognition task (38 slices, voxel size isotropic = 3.5 × 3.5 × 3.5 mm)

and 540 whole-brain volumes for the MIST (180 volume each round; 38 slices, voxel size isotropic = 3.5 × 3.5 × 3.5 mm). A T1-weighted high-resolution image of the brain with a rapid gradient echo sequence (MP-RAGE) was additionally obtained for anatomical reference were additionally obtained (176 slices FOV = 256, slice thickness = 1.00 mm, "repetition time = 2300 ms,echo time = 2.98 ms,flip angle = 9°,voxel size isotropic 1.0 × 1.0 × 1.0 mm).

2.5 MRI Data Preprocessing

Preprocessing of the structural and functional images was performed using using MATLAB (The Mathworks, Natick, MA, USA) and the Statistical Parametric Mapping software package (SPM8)

(http://www.fil.ion.ucl.ac.uk/spm/;WellcomeTrustCenterforNeuroimaging, London,UK) implemented in MATLAB 7 (Mathworks, Inc, Natick, MA) under Ubuntu Linux 10.04.4 Lucid Lynx. All imaging data for obtained from all subjects was preprocessed and then analyzed using the same machine.

All imaging data obtained from each subject on each testing day was preprocessed all at once using the same batch automated MATLAB (The Mathworks, Natick, MA, USA) script and same machine. The raw data were converted into DICOM format. The first six volumes of each fMRI run were discarded on account of unsteadiness of the MRI signals. Slice timing correction was performed for each of the four sets of functional volumes (3 volumes for each of the three MIST runs plus one for the Faces Task). The next preprocessing steps involved, in chronological order, correction of head movement using rigid body transformations and least sum of squares minimization, spatial coregistration of the T1- weighted image to the mean of the functional images, segmentation of the anatomical image, then transformation and resampling of the fMRI time series at an isotropic voxel size of $2mm \times 2mm \times 2mm$ and spatial normalization into to the standard stereotactic space (template provided by the Mon-

treal Neurological Institute (MNI) template), and finally, spatial smoothing (to reduce noise) with a an isotropic 6-mm full-width half-maximum Gaussian kernel. This software identified head movement outliers in the fMRI data that could go undetected or not fully corrected by realignment. The EPI data was inspected volume by volume, and volumes with extreme motion artifact were specified as no-interest regressors in the in the design matrix.

The above was performed automatically using in-house built MATLAB (The Mathworks, Natick, MA, USA) scripts to preclude the possibility of human error. These scripts will be made available for free online and can be obtained by contacting the first author. Modeling and analyses of imaging data was carried out using SPM8 and in-house MATLAB (The Mathworks, Natick, MA, USA) scripts to automate process and thereby preclude the possibility of human error. These scripts will be made freely available for use online and upon contacting the corresponding author.

2.5.1 Face Emotion Processing Task

2.5.1.1 Exploratory whole-brain analyses

Standardized whole-brain voxel-by-voxel analyses of imaging data were carried out using SPM8 and the tools contained within it. Functional images were processed using MATLAB 7. 9. 0 (The Mathworks, Natick, MA, USA) and SPM8 (Statistical parametric mapping software, SPM; Wellcome Department of Imaging Neuroscience, 2008, London, UK; http://www.fil.ion.ucl.ac.uk).

The General Linear Model (GLM) was used to analyze preprocessed EPI images in order so as to examine effects of interest in individual-level analysis.

GLM was built with seven event-related orthogonal regressors of interest, those modelling the neural activation signals that corresponded to the passive viewing trials for neutral, disgusted, surprised, angry, sad, fearful and happy faces, respectively. Specifically, the regressors of interest were engendered by convolving the onset times

of each of the seven events with a canonical hemodynamic response functions (HRF). The six head motion parameters were additionally built into the GLM to account for motion artifacts that realignment did not fully correct. These were specified as regressors of interest in the design matrix. Also included as regressors of no interest were the volumes identified by ART software as outliers (i.e, extreme motion artifact).

The following six corresponding contrasts were created for the first-level analysis for each subject to isolate neural circuits subserving the passive vieweing of emotional face processing: (1) Fearful minus Neutral Face; (2) Angry minus Neutral Face; (3) Disgusted minus Neutral Face; (4) Sad minus Neutral Face; (5) Surprised minus Neutral Face; (6) Happy minus Neutral Face.

These individual contrast images would later be used to generate group-level statistical results (second-level analyses). Spatial normalization of anatomical maps of t-statistics was carried out by warping to MNI space, and followed by their combination into a group map.

The above mentioned steps were performed twice for each subject, once for placebo day and again for alcohol day. We must note here that given that the face identification time (not modelled here) varied across subjects, and because of that so did the total numbers of faces viewed and rated, and considering that the lowest ever/ minimum number of faces viewed and rated by any participant, under the placebo or alcohol conditions, totalled 35, only the first 35 face trials for each participants were analyzed. This was done for the obvious reason that legitimately comparing the brain activation of subjects to the averaged trials of a face necessarily requires exposure to the same stimulus for the same time period across subjects. Each emotional face had 5 trails (12.5 s total; Huettel and McCarthy 2001).

A statistical map of the main effect of personality, sex and their interaction on brain activation at baseline, that is, under the placebo condition was then computed using a voxel-wise full factorial GLM random effects analysis of the event-related β coefficients. In this model, personality (anxiety-sensitive or sensation-seeking) and

sex (male or female) were specified as between-subject factors, each with independent observations and unequal variance. In case of significant main or interaction effects, the full factorial analysis was followed by voxel-wise simple main effects tests. Activation maps were overlaid on subjects' mean structural image.

Clusters forming 10 or more contiguous voxels ($k = 10$) at an individual voxel level of $p \leq 0.05$, familywise error (FWE) corrected for whole brain, were considered significant, to minimize the risk of false positives (i.e, Type I errors). Coordinates for activation were reported in the standardized MNI space. using SPM8 and Functional Imaging Visualization Environment

(nmr.mgh.harvard.edu/harvardagingbrain/People/AaronSchultz/OrthoView.html).

Corresponding axial, sagittal and coronal slice levels were recorded directly from the screen at high resolution using a Mac screen capture software SnagIt (TechSmith Corp., Okemos, MI, USA).

Next, we wanted to assess the main effects of alcohol and its interaction with either and both personality and sex. Typically for the assessment of within-subject effects, analysis featuring a flexible factorial model would be required on account of the latter includes a subject factor (while the full-factorial model does not), which results in an increase in the degrees of freedom. That being said, a limiting feature in SPM is that it does not allow for the inclusion of more than one between-subject factor (we had two). One way around this caveat would be to substract the contrast image of interest produced for a given subject one day (alcohol or placebo) from that produced for the same subject on the other, subsequently feeding resultant contrast image to a full-factorial analysis. Technically, results unravelled by contrasts assessing personality, sex and interaction effects using this model would be identical to those produced by the flexible factorial model in response to contrasts assessing, respectively, condition-by-personality, sex-by-personality and emotion-by-personality-by-sex interaction effects. As such, we adopted precisely this approach in the context of

this investigation; each of the six contrast images produced for each subject under placebo day was substracted from that produced on alcohol day, using the ImCalc feature in SPM8 and the expression $i1 - i2$. Resultant contrast images for each participants were then fed to the full-factorial model, with personality and sex as between-subject factors (each with independent observations and unequal variance). Here, too, clusters equal to or larger than 10 voxels at an individual voxel thresholded level of $P \leq 0.05$, FWE-corrected for whole brain were considered significant. In case of significant results, this analysis would be followed by whole-brain paired-sample t-tests. Coordinates for activation were reported in the standardized MNI space. using SPM8 and Functional Imaging Visualization Environment (nmr.mgh.harvard.edu/harvardagingbrain/People/AaronSchultz/OrthoView.html). Corresponding axial, sagittal and coronal slice levels were recorded directly from the screen at high resolution using a Mac screen capture software SnagIt (TechSmith Corp., Okemos, MI, USA).

2.5.1.2 Regions of interest analyses

Region Of Interest (ROI) analysis refers to an (f)MRI analysis methodology whereby one or more regions of interest is (are) identified, and analyses is restricted to this(these) region(s) Though we did plan on exploring BOLD response changes, we were especially interested emotional faces across the entire brain, response change in specific neural structures that previous research has identified as playing important roles in the processing of socioaffective signals or aetiology of disordered drinking and/ or anxious pathologies. These regions, selected *a priori*, included the bilateral AMYG, aINS and vACC, and were all spherically defined based on results from previous studies investigating processing of socioaffective signals and performed by other research groups. For the AMYG, MNI coordinates, centering at $x = \pm\ 18\ mm$, $y = -6\ mm$ and $z = -18\ mm$, with a 10mm radius sphere, based on the work of Williams et al. (2006b). For the aINS, MNI coordinates, centering at $x = \pm\ 44\ mm$, $y = 22\ mm$ and $z = -2\ mm$

with the extent set to 12 mm radius sphere, based on a study by Toller et al. (2015) Finally, the vACC ROI was predicated on the work of Williams et al. (2006b). MNI coordinates for this region centered at $x = \pm\ 22\ mm$, $y = 10\ mm$, $z = -18\ mm$, with an extent of 8 mm radius sphere.

Mean parameter estimates (arbitrary units; referred to by others as beta weights or BOLD signal intensity) of activity in response to each of the six contrasts generated in first level analyses were extracted from these ROIs at the individual subject level using MarsBar (`http://www.marsbar.sourceforge.net`) and exported to SPSS20 (SPSS, Inc., Chicago, Illinois) for further analyses.

Main effects of personality, sex and their interaction under placebo were assess by performing a series of two-way between-subjects ANOVAs, each time with the values obtained for one of the three ROI (in either the left or right hemisphere) in response to one of the six contrasts of interest as the dependent variable and personality and sex as fixed factors. To correct for multiple comparisons[3], alpha level was adjusted from .05 to .0083 (i.e, 0.05/6). Significances that survived before (i.e, $p \leq .05$) but not after correction for multiple comparisons, if and when found, were, nonetheless, reported and some of them discussed. When a significant personality-by-sex interaction was found, two-way between-subjects ANOVA was followed up by two-sample t-tests thresholded at a Bonferroni corrected alpha of $P \leq .025$ (.05/2).

To assess main effects of condition (alcohol or placebo) and its interaction with either and both personality and sex, 3-way mixed-design ANCOVAs were carried out, with mean parameter estimates of a ROI activity in response to a contrast of interest as repeated measures, and personality and sex as between-subject factors, and always including BAC just before the start of the FEPT as a covariate. To correct for multiple comparisons, an adjusted alpha of $p \leq .0083$ was employed (although, again, significances that survived before but not after alpha adjustment were reported, if and when

[3]Here and elsewhere, Bonferroni alpha adjustment was conducted by dividing a p value of .05 by the number of tests conducted on the same measurement.

found). 2-way or 3-way interactions that reached statical significance, were followed by by two-tailed paired-sample t-tests, thresholded at, respectively, $p \leq .025$ and $p \leq .0125$.

Output of ROI analyses, was depicted in barplot figures produced using MATLAB 7. 9. 0. software (The Mathworks, Natick, MA, USA).

2.5.2 Montreal Imaging Stress Task

2.5.2.1 Exploratory whole-brain analyses

Standardized whole-brain analyses of imaging data were carried out using SPM8 and the tools contained within it. Functional images were processed using MATLAB 7. 9. 0 (The Mathworks, Natick, MA, USA) and SPM8 (Statistical parametric mapping software, SPM; Wellcome Department of Imaging Neuroscience, 2008, London, UK; http://www.fil.ion.ucl.ac.uk). For each participant, two GLMs featuring a block-design, one for each testing day, were defined containing regressors for experimental (stress) and control (nonstress) condition of each MIST segment leading to a total of 6 condition regressors. To account for motion artifacts which were not fully corrected by realignment, 6 motion regressors were also included. Six head motion parameters were additionally built into the GLM to account for motion artifacts that realignment did not fully correct.These were specified as regressors of interest in the design matrix. Also included as regressors of interest were the volumes identified by ART software as outliers (i.e, extreme motion artifact).

The main and only contrast of interest was the stress > nonstress for the averaged three MIST runs. As such, the final contrast, which was -1 1 and additionally padded with zeros for the movement parameters was replicated and created per session (an SPM8 feature that allows that the contrast of interest be averaged over sessions).

The "stress > nonstress" contrast image (corresponding to the three MIST runs averaged), was then used in whole-brain and ROI, group-level random-effects analyses

across subjects. (second-level analyses).

To assess the main effect of personality, sex and their interaction on brain activation to said contrast of interest under the placebo condition, the contrast images were introduced to a voxel-wise full factorial GLM random effects analysis. In this full factorial model, personality (anxiety-sensitive or sensation-seeking) and sex (male or female) were specified as between-subject factors, each with independent observations and unequal variance. In case of a significant interaction effect, performing whole-brain two-sample t-tests would follow. Linear contrasts computed were as follows: SSSs minus ASSs, ASSs minus SSSs. Activation maps were overlaid on mean structural image of all participants. Clusters equal to or larger than 20 voxels ($k = 20$) at an individual voxel level of $p \leq 0.005$, uncorrected, were considered significant. Coordinates for activation were reported in the standardized MNI space. using SPM8 and Functional Imaging Visualization Environment

(nmr.mgh.harvard.edu/harvardagingbrain/People/AaronSchultz/OrthoView.html). Corresponding axial sagittal and coronal slice levels recorded directly from the screen at high resolution using a Mac screen capture software SnagIt (TechSmith Corp., Okemos, MI, USA).

In accordance with previous studies using the same stress paradigm (e.g, Dedovic et al., 2013, 2014), and as per the recommendations of Lieberman and Cunningham (2009), we employed a threshold of $P \leq .005$, and cluster extent (K) of 20 voxels for establishing significance, so as to achieve an ideal balance the rates of both false positives and false negatives.

Obviously, this is a much more liberal cutoff threshold compared to that employed when analyzing imaging data for the Emotional Facial Processing Task (i.e, $P_{FWE-corrected} \leq .05$). However, the functional neuroimaging literature on the MIST is, at least when compared to that on emotional face processing, both recent and small (albeit growing), with inconsistent and even contradictory results being frequent. This means that in studies employing this stress paradigm are carried out false negatives

would likely have worse repercussions than would false positives on account of the latter would self-erase when meta-analyses on the topic are performed while the former would remain obscure (Lieberman and Cunningham, 2009). On these bases, we argue that the use of a relatively more relaxed threshold in the current analyses is defensible and perhaps even preferable.

Next, to assess the main effects of alcohol and its interaction with either and both personality and sex, the contrast image of interest obtained for each subject on placebo day was substracted from that obtained for the same subject on alcohol, using the ImCalc feature in SPM8 and the expression $i1 - i2$. Resultant contrast image of each subject was then entered into a full-factorial analysis, with personality and sex as between-subject factors (each with independent observations and unequal variance; see section 2.5.1.1 for why the full- instead of flexible- factorial model was selected to investigate within-subject effects). Here, too, clusters equal to or larger than 20 voxels at an individual voxel activation maps were thresholded at $P_{uncorrected}$ 0.005 (k= 20). In case of significant results, this analysis would be followed by whole-brain paired-sample t-tests.

Coordinates for activation were reported in the standardized MNI space. using SPM8 and Functional Imaging Visualization Environment

(nmr.mgh.harvard.edu/harvardagingbrain/People/AaronSchultz/OrthoView.html).

The axial and corresponding sagittal and coronal slice levels and positions were recorded directly from the screen at high resolution using a Mac screen capture software SnagIt (TechSmith Corp., Okemos, MI, USA).

2.5.2.2 Regions of interest analyses

While planning to explore changes in BOLD activation in response to negative performance feedback across the entire brain, we were particularly interested in examining those changes in five brain structures, namely the bilateral hippocampus (HC), an-

terior insula (aINS), the more anterior vmPFC subregion, the medial orbitofrontal cortex (mOFC) and perigenual anterior cingulate cortex (pgACC) and nucleus accumbens (NAc). Each of these ROIs, selected *a priori*, has previously been identified as being involved in the neural circuitry underlying the processing of psychosocial evaluative stress, including that elicited by the MIST (Dedovic et al., 2009b, 2013, 2014; Dagher et al., 2009) in healthy (e.g, Albert et al. 2015; Dagher et al. 2009), subclinical (e.g, Dedovic et al. 2013, 2014) and clinical (e.g, Soliman et al. 2011) populations. As well, the aINS was shown to increase its activation in the face of intensely arousing material, irrespective of valence, as a function of high levels of sensation-seeking trait (Joseph et al., 2009).

A mask for the analyses for subcortical ROIs, namely the HC and NAc, were anatomically defined for each individual subject with the current Harvard–Oxford subcortical atlas (http://www.fmrib.ox.ac.uk/fsl/data/atlas-descriptions.html#ho), provided by the Harvard Center for Morphometric Analysis (http://www.cma.mgh.harvard.edu/) with the probability threshold at .25 included in the FSL software package (http://www.fmrib.ox.ac.uk/fsl/), which has been widely used in human neuroimaging studies wherein main interest was in specifically investigating these regions (e.g, Pejic et al. 2013).

For the aINS, mOFG and pgACC, functional spheres were constructed, using the SPM extension utility, MarsBaR (Brett et al. 2002; http://marsbar.sourceforge.net/), based on results of previous studies assessing processing of social evaluative components (e.g, Dedovic et al. 2009b, 2013, 2014). For the aINS, MNI coordinates, centering at $x = \pm\ 44\ mm$, $y = 22\ mm$ and $z = -2\ mm$ with the extent set to 12 mm radius sphere, based on a study by Toller et al. (2015). The mOFC was defined using a 12 mm radius sphere centered at MNI coordinates $x = \pm\ 0.3\ mm$, $y = 43\ mm$, $z = -20\ mm$, based on the results of a previous study employing the same stress task and contrast of interest (Dedovic et al., 2009b). For the pgACC, an 8mm radius sphere was built around the MNI coordinates $x = \pm\ 9\ mm$, $y = 23\ mm$

$z = -9\ mm$]. This definition was adopted from a recent study which, also involving the MIST and same contrast of interest, demonstrated a local activation maximum at the previously mentioned coordinates in response to social exclusion compared with inclusion (Akdeniz et al., 2014).

Mean parameter estimates (arbitrary units) of activity in response to the contrast of interest were extracted from the four ROIs at the individual subject level using MarsBar (http://www.marsbar.sourceforge.net) and exported to SPSS 20 (SPSS, Inc., Chicago, Illinois) for further analyses.

After checking the data for outliers and ensuring normal distribution ..(reword) no $>$ 1.5 SD from mean, the main effects of personality, sex and their interaction under placebo were assess by performing a series of two-way between-subjects ANOVAs, each time with the values obtained for one of the three ROI (in either the left or right hemisphere) as the dependent variable and personality and sex as fixed factors. To correct for multiple comparisons, alpha level was adjusted from .05 to .0062 (i.e, .05/8). That said, significances that survived before (i.e, $p \leq .05$) but not after correction for multiple comparisons, if and when found, were reported. In case of significant personality-by-sex interactions, univariate analysis was followed up by two-sample t-tests, thresholded at $p \leq .025$ (i.e, .05/2).

To assess main effects of alcohol and its interaction with either and both personality and sex, 3 -way mixed-design ANOVAs were carried out, with mean parameter estimates of a ROI activity as repeated measures, and personality and sex as between-subject factors. In these analyses, case of significant 2-way or 3-way interactions,the ANOVA analysis was followed up by two-tailed paired-sample t-tests, thresholded at, respectively, $p \leq .025$ and $p \leq .0125$.

Results were expressed as means $\pm$ standard error means (SEM) effect sizes are expressed as partial eta-squared (η_{p}^2). Where graphs and figures depicting the output of ROI analyses were produced, this was done using MATLAB 7. 9. 0. software (The Mathworks, Natick, MA, USA).

2.6 Statistical Analyses

All statistical analyses were carried out using SPSS 20 for Macintosh osx (SPSS, Inc., Chicago, Illinois). For all statistical analyses, effect size was calculated using partial eta-squared (η_p^2).

2.6.1 Face Emotion Processing Task

2.6.1.1 Behavioral Analyses

Behavioral outcome measures of interest for the Faces task totalled four. These were: (1) response latency (i.e, the average duration,in seconds, subject takes to label a facial affect; (duration in seconds spent by subject rating all faces/ total number of faces rated $\times$ 100), ostensibly a measure of the degree of vigilance to socioaffective threat signals; (2) identification accuracy of (a) any facial expression (i.e, number of faces labelled correctly/number of faces labelled $\times$ 100), (b) negatively valent faces (i.e, number of fearful, angry, disgusted and sad faces labelled correctly/ number of fearful, angry, disgusted and sad faces labelled $\times$ 100) and (c) positively valent faces (i.e, number of happy faces labelled correctly/ number of happy faces labelled $\times$ 100); and (3) negativity bias in rating (a) neutral faces (i.e, neutral faces rated as emotional; number of neutral labelled as negative or surprised/number of neutral faces labelled $\times$ 100), and (b) surprised faces (i.e, surprised faces rated as harsh; number of surprised labelled as fearful, angry or disgusted/number of surprised faces labelled $\times$ 100).

To investigate potential differences on the previously mentioned behavioral indices as a function of personality, sex and their interaction under the placebo, a series of two-way between-subjects ANOVAs was carried out, with the outcome measure of interest as the dependent variable, and personality and sex, always, as fixed factors. In case of significant interaction, the analysis was followed with simple main effect

t-tests were performed, thresholded at 0.0125 to correct for multiple comparisons.

To investigate the effects of alcohol and its interaction by either and both personality and sex, 3-way mixed-design ANOVAs were conducted, with behavioral response levels as repeated-measures and always with personality and sex, always, as between-subjects factors. In case of 2-way or 3-way significant interactions, 3-way mixed-design ANOVAs were followed by two-tailed paired-sample t-tests thresholded at, respectively, 0.025 or 0.0125 to correct for multiple comparisons.

2.6.1.2 Endocrine Analyses

Endocrine data were tested for normal distribution using Kolmogorov-Smirnov test. The latter indicated cortisol values were not normally distributed, leading us to apply logarithmic transformation to them. All computations of hormonal measures of interest were performed on these log-transformed data. One saliva cortisol reading was of interest to us in the context of the FEPT, namely cortisol values measured immediately prior to the start of task (referred to from hereon as pre-FEPT cortisol).

To assess the effects of personality, sex and their interaction on pre-FEPT cortisol, a two-way between-subjects ANCOVA was conducted, with said endocrine measure as the dependent variable, personality and sex as fixed factors and "session time" (i.e, the time of day at which cortisol reading was obtained) as a covariate, so as to control for circadian variability in cortisol level, and ensure that any observed effects on cortisol in the context of the MIST were not attributable to time of start of testing session. An analogous two-way between-subjects ANCOVA was then repeated, this time the composite score for parental care[4] and paternal overprotection assigned as additional covariates, so as to preclude contamination of results by possible confounding effects of variables known to carry considerable influence on the physiological phenotype and shown here to significantly differ as a function of personality risk profile.

[4]Extracted from Mother Form and Father Form (PBI) scores. For subjects raised by a single parent ($n = 3$), the one score obtained was, instead, used.

Statistically significant main and interaction effects were decomposed using pairwise comparisons thresholded at an alpha adjusted to correct for multiple comparisons.

To examine the effect of condition (alcohol or placebo) and its interaction with either and both personality and sex on pre-FEPT cortisol, a 3-way mixed-design ANCOVA was performed, with said cortisol values for alcohol and placebo days as repeated measures, personality and sex as between-subjects factors, and always with "testing times" for both alcohol and placebo days and the BAC just prior to the task as covariates. An analogous 3-way mixed-design ANCOVA was then repeated, but this time while additionally assigning parental care and paternal overprotection as covariates.

Statistically significant main and interaction effects were decomposed using pairwise comparisons thresholded at an alpha adjusted to correct for multiple comparisons. In case of violation of sphericity assumption, computed Greenhouse Geisser corrections (GG corrected) were conducted. Post hoc, within-subject differences were assessed using 2-paired samples t-tests and using Bonferroni corrected alpha level per test. For all statistical analyses, effect size was calculated using partial eta-squared (η_{p}^2).

2.6.1.3 Correlational analyses

Two correlations of interest, both under placebo condition, were examined. The first correlation of interest was between bilateral amygdalae reactivity to "Fearful > Neutral face" contrast and anxiety sensitivity levels (indexed by, respectively the SURPS-AS subscale and ASI). This was assessed using Pearson correlation coefficients (bivariate correlations) and then linear regression analyses, the latter with AS or ASI score as an independent variable and functional ROI (namely amygdalae) reactivity as a dependent variable. The second correlation of interest was between bilateral amygdalae reactivity to the "Fearful > Neutral face" contrast and pre-FEPT cortisol levels, adjusting for time of testing. This relationship was assessed using partial correlation coefficients (controlling for "session time").

The previously mentioned associations of interest were assessed for the entire sample combined, using an alpha level of $p \leq .05$ as well as for personality groups and personality-by-sex subgroups separately using a Bonferroni corrected alpha of respectively, .025 (.05/2) and .0125 (.05/4) per test.

Significant relationships were shown using scatter diagrams. Note that the diagram depicting the association between two pre-FEPT and amygdalae activity with (i.e, "session time") controlled for reflects the unstandardized residuals [5]. The latter were obtained for individual subjects by regressing mean parameter estimates of amygdalae activity (under placebo day) in response to the "Fearful > Neutral face" onto "session time" and then doing the same for pre-FEPT cortisol values, so as to obtain the unstandardized residuals for both associated variables. This was done using linear regression analyses, with the associated variable as the dependent variable and "session time" as an independent variable. Scatter diagrams were produced using MATLAB 7. 9. 0. software (The Mathworks, Natick, MA, USA).

2.6.2 Montreal Imaging Stress Task

2.6.2.1 Behavioral Analyses

Performance outcome measures of interest for the MIST task were two three: 1) correct responses (number of correct answers on all runs/number of mental arithmetic problems carried out in all runs× 100), b) frequency of time overshoots (number of time overshoots on all runs/number of mental arithmetic problems carried out in all runs× 100).

To examine potential differences on these outcomes as a function of personality, sex and their interaction under the placebo, two two-way between-subjects ANOVAs were conducted, with the performance outcome of interest as the dependent variable, and personality and sex, as fixed factors. In case of significant interaction, the analysis was followed with simple main effect t-tests were performed, thresholded at 0.0125 to

[5] In essence, partial correlation analysis is a Pearson correlation of the unstandardized residuals.

correct for multiple comparisons.

For the assessment of the main effect of alcohol and its interaction with either and both personality and sex, two 3-way mixed-design ANOVAs were conducted, with performance levels as repeated-measures, personality and sex, always, as between-subjects factors and the averaged BAC throughout the MIST as a covariate. In case of 2-way or 3-way significant interactions, 3-way mixed-design ANOVAs were followed by two-tailed paired-sample t-tests thresholded at, respectively, 0.025 or 0.0125 to correct for multiple comparisons.

2.6.2.2 Subjective Mood Analyses

To assess the main effect of personality, sex and their interaction on self-rated mood immediately at the moment prior to the MIST under placebo, a univariate analysis was carried out, with the self-rating of the emotion (on a scale of 0 to 10) obtained at time 0 as the dependent variable and personality and sex as fixed factors. This analysis was ran twice, on respectively, embarrassment and anger. Where a significant personality-by-sex interaction effect was found, a two-sample t-tests on the variable showing said effect were ran twice, once comparing the same-sex oppposite-personality subgroups and again comparing the opposite-sex same-personality subgroups (by splitting file). To correct for multiple comparisons, alpha level was adjusted from 0.05 to 0.025 (i.e, 0.05 divided by number of t-tests ran on same variable)

To explore potential differences in experiencing negative (self-rated) mood induction by the MIST as a function of personality, sex and their interaction under placebo, repeated measures (time point 0 as factor 1 and time points 1, 2 and 3 averaged as factor 2) GLMs were utilized for the 7 POMS subscales (cheerful, relaxed, angry, efficient, confident, embarrassed and confused) assessing subjective mood states.

Repeated measures GLMs with personality and sex as fixed factors, averaged BAC throughout the MIST, as a covariate were used to examine effects of alcohol and its interaction by either and both personality and sex. These 3 -way mixed-design

ANCOVAs were then carried out again, but this time while additionally covarying for early life history parental neglect neglect.

Due to the fact that the POMS during the scanning session was only incorporated in the testing paradigm after 7 subjects have undergone either or both testing sessions, subjective mood data were only available for 34 subjects on placebo day and 36 subjects, placebo day. To assess the main effect of personality, sex and their interaction on stress-induced change in mood state under placebo, a 3 -way mixed-design ANOVA was carried out, with the self-rating of the emotion at time 0 and throughout the task as the within subject factors and personality and sex as between-subject factors. This analysis was ran three times, on respectively, embarrassment, cheerfulness and anger.

Where a significant time-by-personality or time-by-sex effects were found, two-tailed paired-sample t-tests were ran twice, once on each personality or sex group, respectively. These were thresholded at $p \leq .025$ (obtained by diving a p value of .05 by the number of tests ran) so as to correct for multiple comparisons. This alpha adjustment is known to be more strict that Bonferroni correction, but doing the latter was not an option that SPSS offers.

Where a significant time-by-personality-by-sex unravelled, two-tailed paired-sample t-tests were ran four times, once on each subgroup (respectively, ASMs, ASFs, SSMSs and SSFs). These tests were thresholded at $P \leq .0125$ (.05/4) in order to, again, correct for multiple comparisons.

To assess the main effect of alcohol and its interaction with either and both personality and sex on stress-related changes in self-rated mood, three 3 -way mixed-design ANOVAs, one for each mood state of interest, were ran, each time with the net stress-related change in a given mood state self-rating (i.e, relative to placebo) under alcohol and under placebo as the within-subject factor (with 2 levels) and personality and sex as between-subject factors. Where a significant time-by-personality or time-by-sex effects were found, two-tailed paired-sample t-tests were ran twice, once on each personality or sex group, respectively. These were thresholded at $P \leq .025$ (obtained

by diving a P value of .05 by the number of tests ran) so as to correct for multiple comparisons. Significances at $.1 > p > .05$ prior to the alpha adjustment were reported as showing or trending towards significance before, but not after adjusting alpha to correct for multiple comparisons.

2.6.2.3 Endocrine Analyses

Endocrine data were tested for normal distribution using Kolmogorov-Smirnov test. The latter indicated cortisol values were not normally distributed, leading us to apply logarithmic transformation to them. All computations of hormonal measures of interest were performed on these log-transformed data (n/mol).

Two endocrine measures of interest, namely pre-MIST cortisol (i.e, cortisol reading obtained just prior to start of the MIST; referred to from here on as pre-stressor) and stress-reactive cortisol (referred to from here on as cortisol AUC [area-under-the-curve]) were investigated. AUC captures the dynamic fluctuation of a system from baseline Pruessner et al. 2003, and with respect to cortisol was here computed using samples surrounding the stress reactivity component of the cortisol assessment; i.e. at times 0, +8, +16, +24, +32 and +40 minutes of the MIST (Pruessner et al., 2003; Juster et al., 2012). This is given the apparent fact that cortisol levels begin to show gradual elevation within a few minutes after stress onset, and reach peak levels 10–30 min after stressor termination (Kirschbaum et al., 1993; Dedovic et al., 2005; Wang et al., 2005a, 2007a; Foley and Kirschbaum, 2010; Qi et al., 2016).

To assess the effects of personality, sex and their interaction on both pre-MIST cortisol levels (i.e, cortisol reading obtained just prior to start of the MIST; referred to from here on as pre-stressor) and cortisol AUC increase (AUCi), two-way between-subjects ANCOVAs, with the endocrine measure of interest as the dependent variable, personality and sex as fixed factors and "session time" (i.e, the time of day at which the MIST started) as a covariate, so as to control for circadian differences in cortisol level.

Analogous two-way between-subjects ANCOVAs on said hormonal variables were then conducted again, but this time while additionally incorporating a composite score for parental care[6] and paternal overprotection as covariates so as to preclude contamination of results by possible confounding effects of variables known to considerably alter the physiological phenotype and shown here to significantly differ as a function of personality risk profile. Statistically significant main and interaction effects were decomposed using pair-wise comparisons thresholded at an alpha adjusted to correct for multiple comparisons. The same analyses were then repeated again, but this time covarying for, in addition to "session time", variables that has been previously demonstrated to significantly alter the physiological phenotype and found to differ between our subjects as a function of either or both personality and sex. Candidate covariates incorporated in these analyses were 1) a childhood history of low parental care (one composite score entered for maternal and paternal care), a childhood history neglect (one composite score entered for physical and emotional neglect).

Data were also calculated as the area-under-the-curve (AUC) within the 40-min interval following the start of the MIST. We also conducted a GLM ANCOVA with the area-under-the-curve-increase (AUCi) of cortisol as a dependent measure, personality and sex as fixed factors and "session time" as covariate.

To examine the effect of condition (alcohol or placebo) and its interaction with either and both personality and sex on pre-stressor cortisol and cortisol AUC, 3-way mixed-design ANCOVAs were carried out, with cortisol readings (of either pre-stressor cortisol or cortisol AUCi) obtained under alcohol and placebo conditions as repeated measures, personality and sex as between-subjects factors, and always with "session times" for both alcohol and placebo days and the BAC throughout the MIST on alcohol day (calculated by averaging BAC readings at times 0, +10, +20 and +30 minutes) as covariates.

[6]Extracted from Mother Form and Father Form (PBI) scores. For subjects raised by a single parent ($n = 3$), the one score obtained was, instead, used.

Analogous 3-way mixed-design ANCOVAs were then repeated, but this time while additionally assigning parental care and paternal overprotection as covariates.

Time- and BAC- adjusted means and SEM were included in a table and values were exported to MATLAB software (The Mathworks, Natick, MA, USA), where they were plotted using barplot figures.

Statistically significant main and interaction effects were decomposed using pairwise comparisons thresholded at an alpha adjusted to correct for multiple comparisons. In case of violation of sphericity assumption, computed Greenhouse Geisser corrections (GG corrected) were conducted.

Post hoc, within-subject differences were assessed using 2-paired samples t-tests and using Bonferroni corrected alpha level per test. For all statistical analyses, effect size was calculated using partial eta-squared (η_p^2).

2.6.2.4 Correlational analyses

Of particular interest to us was investigating the relations of the psychological, endocrine and neurofunctional components of anxious anticipation and stress reactivity with each other and with specific personality dimensions, in the context of the MIST.

Associations of interest, under both alcohol and placebo days, were between (1) pre-stressor mood self-rating (embarrassment and anger) and anxiety-sensitivity [7], controlling for "session time" with the association between specifically pre-stressor embarrassment and the social concerns dimension of the anxiety-sensitive construct[8] being of highly particular interest; (2) self-rated mood (embarrassment and anger) AUC and cortisol AUC, controlling for "session time"; (3) pre-stressor cortisol and cortisol AUC, controlling for "session time"; (4) trait SS [9] and aINS reactivity (bilaterally, but especially in the right hemisphere) to the "Stress > Nonstress" contrast; (5) self-rated embarrassment AUC and aINS reactivity to the "Stress > Nonstress"

[7] Assessed using the SURPS-AS subscale and ASI
[8] Measured by the Social Concern subscale of ASI.
[9] Assessed using the SURPS-SS subscale

contrast; (6) self-rated anger AUC and mOFG reactivity (bilaterally, but especially in the left hemisphere) to the "Stress > Nonstress" contrast and finally; (7) self-rated embarrassment AUC and pgACC reactivity to the "Stress > Nonstress" contrast. The first three associations of interest, on account of involving cortisol measurements (psychoendocrine covariance), were assessed by calculating partial correlations with "session time" plus BAC throughout the course of the MIST if the association was being assessed under alcohol intoxication controlled for. The fourth to seventh associations of interest were assessed using bivariate correlations if they were being assessed under placebo condition and using partial correlation analyses, controlling for BAC throughout the task when assessed under the alcohol condition. Also, where one of the variables being analyzed was anger or embarrassment, additional partial correlation analyses controlling for self-ratings of the other mood states (i.e, confidence, confusion, relaxation, efficiency and cheerfulness). All associations of interest were assessed for the entire sample combined, using an alpha level of $p \leq .05$ as well as for personality groups and personality-by-sex subgroups separately using a Bonferroni corrected alpha of respectively, .025 (.05/2) and .0125 (.05/4) per test. Where significant relationships were found they were often depicted using scatter diagrams. Note that showing relationships of which significance unravelled with one or more variables controlled for (i.e, partial correlations) using such diagrams requires that the unstandardized residuals of whatever two variables are being correlated be used. As such, when we were interested in depicting a significant partial correlation using a scatter diagram, we first regressed the two associated variables onto the factor(s) that said partial correlation analysis had controlled for. This was done using linear regression analyses, with the factor to be controlled for as an independent variable and measurement of interest as a dependent variable. This step enabled us to obtain unstandardized residuals for individual subjects and it is precisely these values that scatter diagrams depicting a correlation between two variables while controlling for another (or others) reflect.

Values were plotted in scatter diagrams using MATLAB 7. 9. 0. software (The

Mathworks, Natick, MA, USA).

Chapter 3

Results

Contents

3.1 Demographic and Clinical Characteristics 143

3.2 Face Emotion Processing Task 147

3.2.1 Placebo Condition 147

3.2.2 Alcohol Condition 160

3.2.3 Summary of Results 178

3.3 Montreal Imaging Stress Task 179

3.3.1 Placebo Condition 179

3.3.2 Alcohol Condition 197

3.3.3 Summary of Results 209

3.4 Follow-up Assessment 210

3.4.1 Face Emotion Processing Task 215

3.4.2 Montreal Imaging Stress Task 219

3.4.3 Summary of Results 221

3.1 Demographic and Clinical Characteristics

The first MRI scanning session of three subjects (2 ASFSs[1] and one ASMS[2] was interrupted, resulting in their exclusion. One SSFS was a no show for her second scanning session twice without giving prior notice, and one SSMS reported, after completion of his first scanning session (placebo day) having seen through the MIST by the time its second run had started (and then looking it up on-line and confirming his suspicions). Both of these subjects were therefore, too, excluded. Due to a technical error[3], the script produced for individual subjects at the end of the Face Emotion Recognition Task was improperly produced and saved for 3 SSSs (1 female), therefore precluding their inclusion of imaging data analyses for this task. One ASFS was identified as an outlier with respect to her performance outcome on the MIST and was therefore excluded from analyses of this specific measure. Subjective mood data during the MIST was not obtained for a total of three (one ASM and two SSF) subjects on placebo condition and four (two ASM, one ASF and one SSF) subjects on alcohol condition. This is because said subjective mood measure was incorporated in the study design after few subjects have already been tested. Cortisol data was missing for three subjects (one ASM and two SSM) due to practical issues reported by the lab to which saliva samples were sent to for analyses. Last but not least, two SSSs (one female) showed excessive head movement[4] that could not be corrected for using currently available artifact detection and correction tools, leading to their exclusion from MRI data analyses.

Final AS and SS groups were composed of, respectively, 20 and 24 subjects (9 and 10 females). Clinical and demographic characteristics of these personality risk groups are displayed in Table 3.1. Basically, AS and SS subjects were characteristically

[1] Respectively, for expressing intolerable distress as a result of the MIST, and for having artificial hair integrations that created too much artifact in the acquired brain images.
[2] For not being MIST-naïve while falsely claiming that he was.
[3] Related to the code written for the task.
[4] Under placebo condition.

similar in some ways and different in several others. Similar in that neither of the two included any regular cigarette smokers[5] (lifetime criteria), and both reported closely similar means of alcoholic drinks consumed per week as well as comparable onsets of lifetime alcohol and, where applicable, illicit drug use. Familial alcoholism[6] was reportedly present for roughly half ($n = 23$ (52.3%)) of the entire sample, but equally distributed across the personality and sex groups. The frequencies of mild, positive and multinational family history for the condition also did not statistically vary between the personality group nor as a function of sex. Scores on a measure of childhood trauma[7] were also comparable between the groups and, notably, well below the cutoff for mild or more severe forms of developmental experiences of this sort. Further, scores on a measure of trait self-esteem did not statistically differ as a function of personality, sex or an interaction, nor did scores on a self-report measure tapping eight domains of alcohol-expectancy. Finally, the personality groups did not statistically differ on BMI and general sleep patterns including typical awakening time nor did female subject subgroups on menstrual cycle length and consumption of birth control hormones.

Where the personality groups differed was as follows: trait internal locus of control was higher in SS than AS subjects, as indicated by a self-efficacy measure and early-life[8] parental *care* and *protection*, the reported absence of childhood trauma notwithstanding. Specifically, ASSs' scores on the PBI were indicative of low and high levels of respectively parental *care* and *protection*, while SSSs' score indicated the opposite of just that. On these bases, ASSs classified as individuals developmentally exposed to parental "affectionless control" (high protection[9] and low care) while SSSs classified as persons who received "optimal parenting" (high care[10] and low protection[11]).

[5] Classification as a regular cigarette smoker required smoking an average of 12 cigarettes per day.
[6] Having ≥ 1 identifiable [suspected or diagnosed] cases of an AUD in 1^{st} and/ or 2^{nd} degree relatives.
[7] Abuse in all of its forms, including neglect.
[8] Refers to ages 0 to 16 years.
[9] A score of ≥ 13.5 for mother and ≥ 12.5, father.
[10] A score of ≥ 27 for mother and ≥ 24, father.
[11] A score of ≤ 13.5 for mother and ≤ 12.5, father.

Given these differences in developmental experiences, and considering the influence that early-life parental, especially maternal care and protection can carry on the endocrine and other response profiles (reviewed in Curley and Champagne, 2016), two composite scores that would be parsimonious and theoretically representative of the parental *care* and *protection* variables were extracted, the former from maternal and paternal *care* scores[12] and the latter from maternal and paternal *protection* scores[13]. These composite scores would later be assigned as covariates in ANCOVA analyses of endocrine measures so as to preclude the contamination of results by said possible confounding variables[14].

With respect to testing variables, the groups did not significantly differ on start of MRI sessions, length of period separating the two scanning days or percent subjects receiving alcohol on day 1 and BAC at the start of MRI session (Table 3.5).

Finally, data were checked for normal distribution salivary cortisol values were not normally distributed and therefore log-transformed for the statistical analyses. Normal distribution of all data points for each group was seen after this transformation, and it is these log-transformed values that the figures presented in the Results section reflect.

Table 3.1: Means, Standard Deviations, and Group Comparisons of Demographic Data, Rating Scale Scores and Testing Variables

	ASSs	**SSSs**	***P*-value**
Psychological Measures			
RSES Score[a]($M \pm SD$)	21.28 ± 4.53	22.91 ± 4.13	*ns*
CCQ Score[a]($M \pm SD$)			
Self-esteem	28.39 ± 5.26	32.96 ± 5.66	.012
Internality	31.17 ± 4.66	34.22 ± 4.06	.031
Perceived Control of Others	28.22 ± 4.29	26.17 ± 3.63	*ns*
Chance	23.83 ± 5.17	21.3 ± 3.64	*ns*
AEQ Score[a]($M \pm SD$)			

Continued on next page

[12]Correlation coefficient between maternal and paternal *care* scores was $r = .488$.

[13]Correlation coefficient between maternal and paternal *protection* scores was $r = .708$

[14]The advantage of using one (composite) scores that represents two variables is that it helps avoid unnecessarily loss of degrees of freedom when ANCOVA analysis is carried out with these variables assigned as covariates.

Table 3.1 – continued from previous page

	ASSs	SSSs	*P*-value
Careless Unconcern	17.56 ± 2.94	17.78 ± 3.27	*ns*
Cognitive and Physical Impairment	45.72 ± 5.64	43.17 ± 10.98	*ns*
Global Positive	18.00 ± 4.73	15.13 ± 5.74	*ns*
Power and Aggression	23.00 ± 4.10	23.26 ± 4.76	*ns*
Sexual Enhancement	18.44 ± 4.13	19.09 ± 3.98	*ns*
Social and Physical Pleasure	24.89 ± 3.25	24.70 ± 2.62	*ns*
Tension Reduction	20.94 ± 3.61	21.48 ± 4.56	*ns*
Developmental History			
CTQ Score[a]($M \pm SD$)			
Phyisical Abuse	5.22 ± 0.73	5.24 ± 1.61	*ns*
Physical Neglect	6.28 ± 1.78	5.71 ± 1.74	*ns*
Emotional Abuse	7.44 ± 2.12	6.43 ± 2.42	*ns*
Emotional Neglect	9.67 ± 4.16	7.81 ± 5.38	*ns*
Sexual Abuse	5.00 ± 0.00	4.76 ± 1.09	*ns*
PBI Score ($M \pm SD$)			
Maternal Care[b]	23.58 ± 6.51	29.25 ± 2.64	.002
Maternal Overprotection[b]	13.95 ± 6.90	10.92 ± 6.66	*ns*
Paternal care[c]	20.84 ± 5.47	25.61 ± 6.50	.015
Paternal Overprotection[c]	12.11 ± 5.75	7.48 ± 5.85	.014
Alcohol and Polydrug Use History[d]			
Onset age drinking	15.55 ± 1.82	15.13 ± 1.30	*ns*
Onset age illicit drug use	16.12 ± 1.93	15.82 ± 1.65	*ns*
Number of illicit drugs ever used	1.60 ± 1.39	3.46 ± 3.87	.048
Family History of AUDs[d]**(n, %)**			
Negative	14 (60.9%)	10 (40.0%)	–
Mild	3 (13.0%)	7 (28.0%)	–
Positive	5 (21.7%)	7 (28.0%)	–
Multigenerational	1 (4.3%)	1 (4.0%)	–
Testing Variables			
Time of start of scanning session[d]			
Placebo day[d]	13.34 ± .54	12.68 ± .49	*ns*
Alcohol day	12.78 ± .50	12.70 ± .46	*ns*
BAC at start of scanning[d]	0.08 ± 0.01	0.07 ± 0.01	*ns*
Typical awakening time[d]	9.19 ± 0.77	9.08 ± 1.15	*ns*
Subjects receiving alcohol on day 1[d]	10 (50%)	12 (50%)	*ns*

Significant differences were found using independent-samples t-testing.

Abbreviations: ASSs = anxiety-sensitive subjects; SSSs = sensation-seeking subjects; RSES = Rosenberg Self-Esteem; AEQ = Alcohol Expectancy Questionnaire; CTQ =

Childhood Trauma Questionnaire; PBI = Parental Bonding Instrument; BAC = blood alcohol curve; AUDs = alcohol use disorders and*ns* = non-significant difference (at $p < .05$).

No sex differences within either personality group for any of the variables presented approached statistical significance.

[a] nASSs= 18, nSSSs= 23; data were missing for 2 ASSs (females) and 1 SSS (male).

[b] nASSs= 19, nSSSs= 24; one ASS (female) was raised by a single father and therefore did not fill out a Mother Form.

[c] nASSs= 19, nSSSs= 23; one ASS (female) and one SSS (male) were raised by a single mother and therefore did not fill out a Father Form.

[d] nASSs = 20 (9 females); nSSSs = 24 (10 females).

3.2 Face Emotion Processing Task

3.2.1 Placebo Condition

3.2.1.1 Behavioral Results

Two-way between-subjects ANOVA, assessing the effects of personality, sex and their interaction on behavioral responses during the FEPT, indicated a significant main effect of personality on face emotion identification latency, referred to from hereon as response latency (i.e, the time it took subject to identify facial affect), $F_{(1,37)} = 4.15$, $p = .049$, $\eta^2_{\mathrm{p}} = .101$, with shorter response latency being shown by the AS ($M = 2.99$, $SD = .70$) relative to SS group ($M = 3.88$, $SD = 1.74$; Figure 3.1**a**). No statistical effects of sex or an interaction on this measure were found.

An analogous analysis showed no significant results with respect to negative[15] face emotion identification accuracy ($p > .1$; Figure 3.1**b**). As to appraisal bias[16], two-way between-subjects ANOVA found a significant main personality effect on the tendency to identify neutral faces as emotional[17], $F_{(1,37)} = 4.45, p \leq .042, \eta^2_{\mathrm{p}} = .107$ (Figure 3.1**c**), and surprised faces as harsh[18], $F_{(1,37)} = 5.66, p = .023, \eta^2_{\mathrm{p}} = .133$ (Figure 3.1**d**), with

[15] Fearful, angry, disgusted or sad.

[16] As previously noted, appraisal bias is used here to refer to a tendency to perceive/ interpret and rate ambiguously valent (i.e, neutral) or surprised faces negatively or positively.

[17] Fearful, angry, disgusted, SAD or surprised.

[18] Fearful, angry or disgusted.

greater rates of both in the AS group (respectively, $M = 12.69$, $SD = 14.74$ and $M = 6.78$, $SD = 10.26$) relative to SS personality group (respectively, $M = 4.90$, $SD = 8.18$ and $M = .96$, $SD = 3.03$). No statistical differences in the rate of emotional faces identified as neutral (a measure of positivity bias) stood out as a function of personality, sex or an interaction. In sum, personality profile significant exerted a significant effect on how rapidly facial emotion was decoded and how ambiguously valent faces were interpreted, with a shorter response latency and interpretative negativity bias being evident in ASSs relative to SSSs.

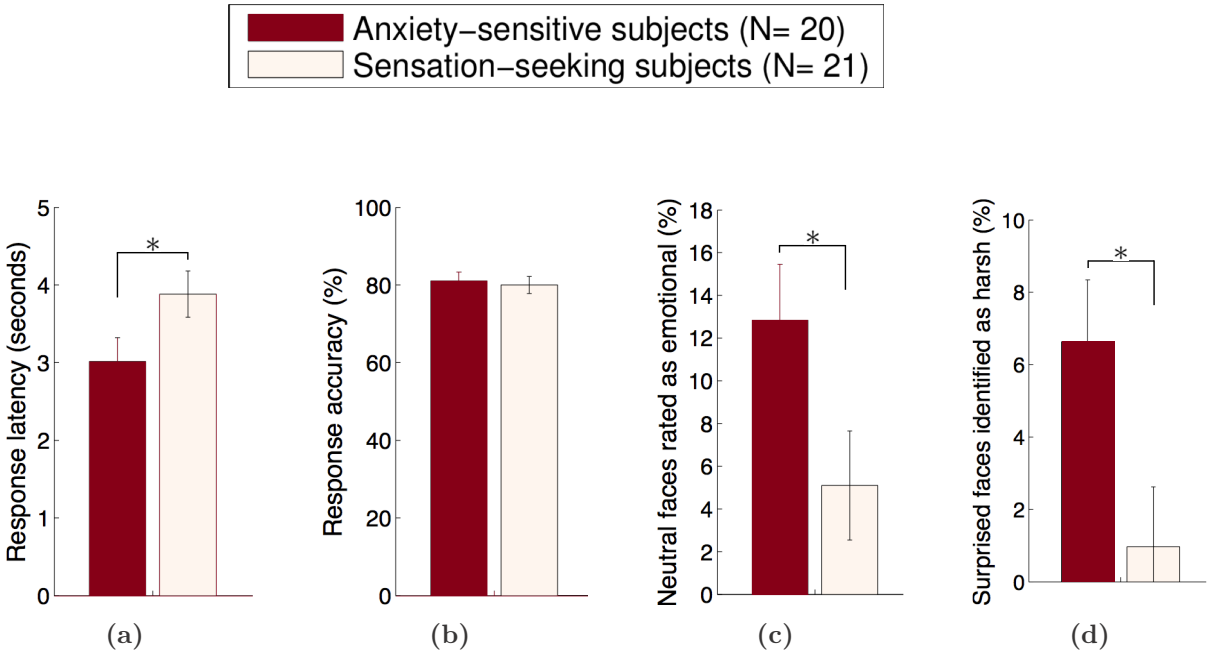


Figure 3.1 ***a-d***, Personality group means for facial emotion identification latency (***a***) and accuracy (***b***), as well as negativity bias in appraising neutral (***c***) and surprised (***d***) faces in anxiety-sensitive (dark bars) and sensation-seeking (light bars) subjects under placebo. Values were entered into the GLM two-way between-subjects ANOVA to test for main effects of personality, sex and an interaction. An asterisk (*) indicates a significant difference ($p \leq .05$) as a function of main personality effect. See text for additional details. Error bars indicate SEM.

3.2.1.2 Endocrine Data

Two-way between-subjects ANCOVA, controlling for "session time" found no significant effects of personality, sex or an interaction on pre-FEPT cortisol levels.

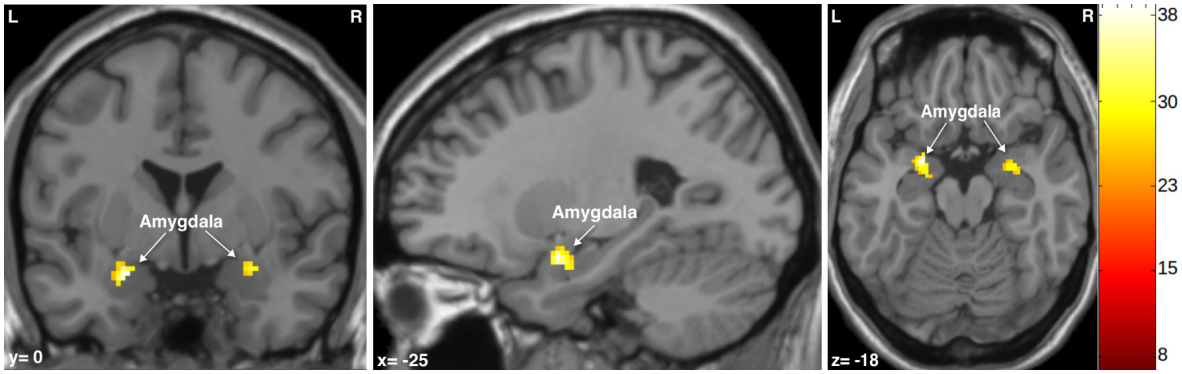
3.2.1.3 Neurofunctional Results

Exploratory voxel-wise analyses. A whole-brain full-factorial GLM random effects analysis of the event-related β coefficients, thresholded at $p \leq .05$, family-wise error corrected for whole brain ($k = 10$), revealed significant main effects of personality on brain response to the "Emotional[19] > Neutral face" contrast. These effect were seen in two brain clusters, localized to the left AMYG [$x = -26$, $y = 0$, $z = -18$, cluster size (K_E) = 63, F-value: 37.81, $P_{FWE-corrected} = .000$] and right AMYG [$x = 26$, $y = -2$, $z = -16$, cluster size (K_E) = 47, F-value: 33.13, $P_{FWE-corrected} = .002$]. These results are visually displayed in Figure 3.2**A**.

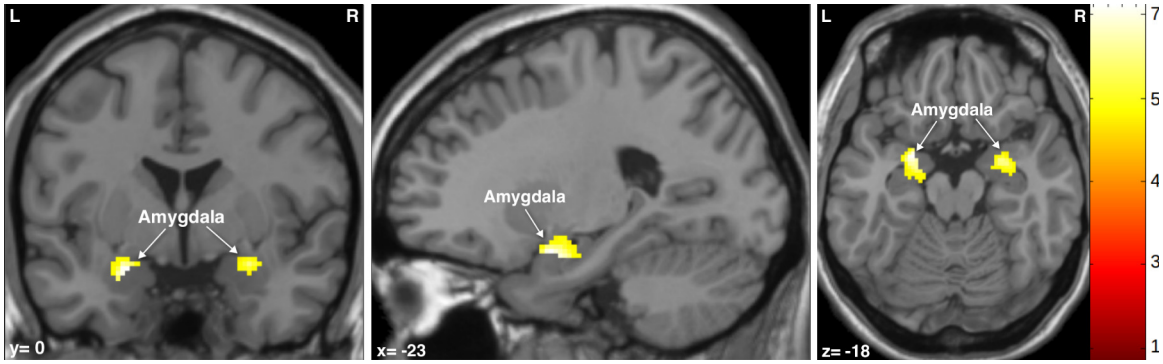
Similar results were obtained when directly contrasting the personality groups in response to the combination of negatively valent relative to neutral faces: compared to SSSs, ASSs more strongly activated the left AMYG [$x = -24$, $y = 0$, $z = -18$, $K_E = 151$, T-score: 6.58, $P_{FWE-corrected} = .000$] and right AMYG [$x = 26$, $y = -2$ $z = -16$, $K_E = 108$, T-score: 6.09, $P_{FWE-corrected} = .000$]. These results are visually displayed in Figure 3.2**B**.

Directly contrasting the response of the two personality groups to the same contrast revealed that the previously mentioned activation differences, favored the AS group (Table 3.2, Figure 3.2**B**).

[19] Averaged fearful, angry, disgusted, surprised, sad and happy faces trials.



(A) Main Effect of Personality Risk Profile



(B) Anxiety Sensitive Subjects > Sensation Seeking Subjects

Figure 3.2 The effects of personality risk profile on whole-brain activation to emotional faces under placebo. ***(A)***, Main effects of personality on regional brain activation to Emotional versus Neutral faces under placebo. Color map represents the corresponding F values; ***(B)***, Linear contrast between the personality groups (ASSs > SSSs) in response to the "Negative > Neutral face" contrast under placebo. The reverse contrast (SSSs > ASSs) yielded no significant results. Color coding represents the t-score. Activation maps were thresholded at $P_{FWE-corrected} \leq .05$ ($k = 10$), superimposed on the mean structural image of all subjects. x, y, z = sagittal, coronal and horizontal view in MNI coordinates. L and R correspond to, respectively, the left and right sides of the brain. For values and additional details, see section 3.2.1.3

The same pattern of findings stood out as contrasts comparing the personality groups' reactivity to individual emotional (relative to neutral) faces were introduced to the model. In response to both "Fearful > Neutral face" and "Angry > Neutral face" contrasts, two brain clusters, in the right and left AMYG, demonstrated stronger BOLD activation in AS compared to SS subjects. In response to the "Disgusted >

Neutral face" and "Sad > Neutral face" contrasts, one brain cluster localized to the left AMYG activated more strongly in the AS compared to SS group. Finally, in response to the "Surprised > Neutral face", three brain cluster, localized to, respectively and in descending order of corresponding t-value, the right parahippocampal gyrus (PHG; corresponding to BA 28), right PHG/ AMYG (corresponding to BA 34) and left PHG/ HC, showed greater activity in the AS than SS group. These results are summarized in Table 3.2 and displayed in Figure 3.3. The "Happy > Neutral face" contrast was the only one to which both personality groups responded comparably at the currently employed threshold. No effects of sex or personality-by-sex on the response to any of the previously discussed contrasts approached significance. Finally, no significant differences were found at the currently employed threshold between the brain activation patterns shown in response to specific face emotions.

Taken together, these results suggest that personality profile had a significant and pronounced effect on whole-brain response during the presentation of negative (assessed separately and together) and surprised versus neutral faces. These effects were chiefly localized to the bilateral AMYG and always favored the AS over SS group.

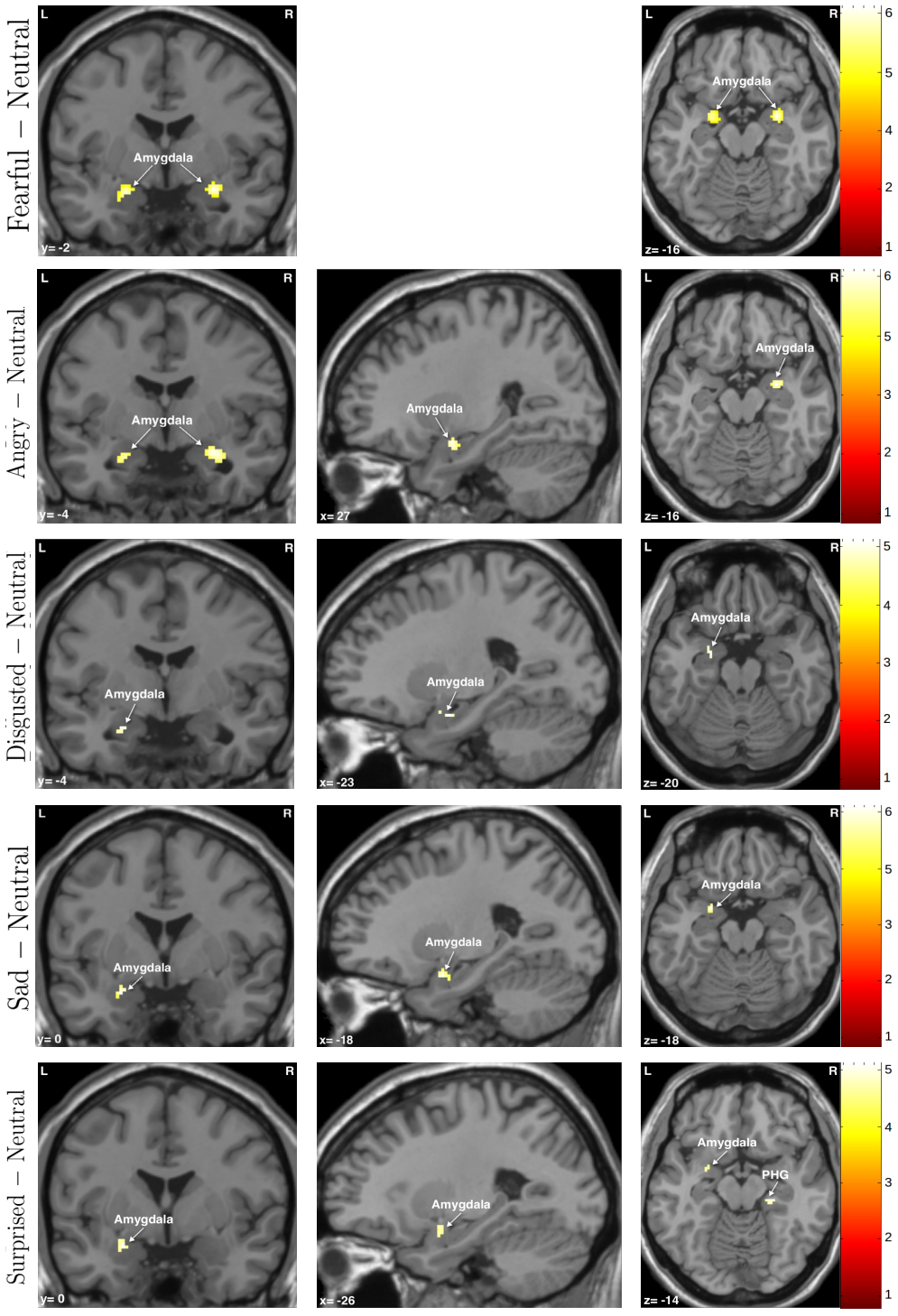


Figure 3.3 Personality-based differences in whole-brain activation to specific face emotions. Linear contrasts between the personality groups (ASSs > SSSs) under each face emotion (versus neutral), computed using a full-factorial GLM random effects analysis of the event-related β coefficients. Each panel shows in a coronal (y), sagittal (x) and axial (z) view (in MNI coordinates), activation maps thresholded at $P_{FWE-corrected} \leq .05$ ($k = 10$), superimposed on the mean structural image of all subjects. The reverse contrast (SSSs > ASSs) yielded no significant results. Color map represents the corresponding t-score. For values, see Table 3.2. L = left hemisphere; R = right hemisphere; and PHG = parahippocampal gyrus.

Table 3.2 Personality-Based Differences in Whole-Brain Activation to Specific Face Emotions. Brain regions showing significantly higher activation during specific emotional versus neutral (peak level $p \leq .05$ FWE-corrected for whole brain)

Region (BA)	x	y	z	K_E	***F* value**	$P_{FWE-corr}$
Fearful: ASSs > SSSs						
R AMYG	26	−2	−16	70	6.15	0.000
L AMYG	−24	0	−18	56	5.92	0.000
Fearful: SSSs > ASSs[a]						
Angry: ASSs > SSSs						
R AMYG	26	−4	−16	47	5.68	0.001
L AMYG	−24	−4	−20	23	5.19	0.010
Angry: SSSs > ASSs[a]						
Disgusted: ASSs > SSSs						
L AMYG	−24	−6	−20	13	5.22	0.009
Disgusted: SSSs > ASSs[a]						
Sad: ASSs > SSSs						
L AMYG	−24	2	−18	20	5.71	0.001
Sad: SSSs > ASSs[a]						
Surprised: ASSs > SSSs						
R PHG (28)	20	−28	−12	22	5.33	0.005
R AMYG (34)	26	0	−16	17	5.24	0.008
L PHG/ HC	−20	−14	−18	10	5.04	0.018
Surprised: SSSs > ASSs[a]						
Happy: ASSs > SSSs[a]						
Happy: SSSs > ASSs[a]						

K_E = cluster volume in voxels; BA = Brodmann's area; ASSs = anxiety-sensitive subjects; SSSs = sensation-seeking subjects; L = left; R = right; AMYG = amygdala, HC = hippocampus; PHG = hippocampal gyrus.
Coordinates refer to the cluster peak voxel in mm (MNI). BA estimated from mni2tal conversion with positive = right (x), anterior (y), and superior (z).

† Relative to neutral faces.

[a] No significant clusters detected.

Regions of interest analyses. Two-way between-subjects ANOVA, assessing the effects of personality, sex and their interaction on BOLD signal intensity within our

functional ROIs, our findings were, as follows: for the "Fearful versus Neutral face" contrast, personality had a main effect on the activation of the bilateral AMYG (L: $F_{(1,36)} = 19.49, p = .000$, $\eta^2_p = .351$; R: $F_{(1,36)} = 23.07, p = .000$, $\eta^2_p = .391$), left aINS ($F_{(1,36)} = 22.10, p = .000$, $\eta^2_p = .380$) and bilateral vACC (L: $F_{(1,36)} = 7.75, p = .009$, $\eta^2_p = .177$; R: $F_{(1,36)} = 10.85, p = .002$, $\eta^2_p = .232$). These activation differences favored the AS group, and all remained significant after adjusting alpha to correct for multiple comparisons.

For the "Angry > Neutral face" contrast, personality had a main effect on the activation of the bilateral AMYG (L: $F_{(1,36)} = 13.82, p = .001$, $\eta^2_p = .277$; R: $F_{(1,36)} = 15.74, p = .000$, $\eta^2_p = .304$) and vACC (L: $F_{(1,36)} = 4.57, p = .039$, $\eta^2_p = .113$; R: $F_{(1,36)} = 10.96, p = .002$, $\eta^2_p = .233$). These activation differences favored the AS group. The difference within the left vACC did not withstand correction for multiple comparisons.

For the "Disgusted versus Neutral face" contrast, personality had a main effect on the activation of the bilateral AMYG (L: $F_{(1,36)} = 11.511, p = .002$, $\eta^2_p = .242$; R: $F_{(1,36)} = 12.576, p = .001$, $\eta^2_p = .259$), left aINS ($F_{(1,36)} = 6.033, p = .019$, $\eta^2_p = .144$) and left vACC ($F_{(1,36)} = 5.665, p = .023$, $\eta^2_p = .136$). These activation differences favored the AS group, and only those with in the the AMYG, bilaterally, remained significant after adjusting alpha to correct for multiple comparisons.

For the "Sad versus Neutral face" contrast, personality had a main effect on the activation of the bilateral AMYG (L: $F_{(1,36)} = 17.66, p = .000$, $\eta^2_p = .329$; R: $F_{(1,36)} = 15.73, p = .000$, $\eta^2_p = .304$) and vACC (L: $F_{(1,36)} = 10.84, p = .002$, $\eta^2_p = .231$; R: $F_{(1,36)} = 7.15, p = .011$, $\eta^2_p = .166$). These activation differences favored the AS group. The difference within the right vACC did not withstand correction for multiple comparisons.

For the "Surprised versus Neutral face" contrast, personality had a main effect on the activation of the bilateral AMYG (L: $F_{(1,36)} = 19.51, p = .000$, $\eta^2_p = .351$; R: $F_{(1,36)} = 24.81, p = .000$, $\eta^2_p = .408$), left aINS ($F_{(1,36)} = 4.69, p = .037$, $\eta^2_p = .115$) and vACC

(L: $F_{(1,36)} = 8.14, p = .007$, $\eta_p^2 = .184$; R: $F_{(1,36)} = 14.92, p = .000$, $\eta_p^2 = .293$). These activation differences favored the AS group. The difference within the left aINS did not withstand correction for multiple comparisons.

Finally, for the "Happy versus Neutral face" contrast, personality had a main effect on the activation of the bilateral aINS (L: $F_{(1,36)} = 10.55, p = .003$, $\eta_p^2 = .227$; R: $F_{(1,36)} = .6.04, p = .019$, $\eta_p^2 = .144$). These activation differences favored the AS group, and only those in the left aINS survived correction for multiple comparisons.

Personality group means of parameter estimates (arbitrary units) of ROIs activity are displayed in Table 3.3 and Depicted in Figure 3.1.

Table 3.3: Parameter estimates (arbitrary units) of region-of-interest activity in response to specific facial emotions* for anxiety sensitive subjects ($N = 21$) and sensation-seeking subjects ($N = 20$) under placebo (standard error means are shown in parentheses).

ROI	ASSs	SSSs	Mean Differences
Negative > Neutral			
L AMYG	1.21 (.21)	−.12 (.21)	**1.3**[a](.29)
R AMYG	1.30 (.19)	−.06 (.20)	**1.4**[a](.28)
L aINS	.70 (.18)	−.09 (.18)	**0.8**[a](.25)
R aINS	.56 (.12)	.16 (.12)	**0.41**[c](.17)
R vACC	.68 (.16)	−.07 (.17)	**0.75**[a](.23)
L vACC	.76 (.14)	.05 (.15)	**0.7**[a](.21)
Fearful > Neutral			
L AMYG	1.35 (.22)	−0.09 (.22)	**1.44**[a](.31)
R AMYG	1.44 (.22)	−0.11 (.22)	**1.55**[a](.31)
L aINS	0.82 (.18)	−0.36 (.18)	**1.18**[a](.25)
R aINS	0.51 (.15)	0.14 (.15)	**0.37**[d](.21)
R vACC	0.75 (.19)	−0.06 (.19)	**0.80**[b](.27)
L vACC	0.86 (.16)	0.08 (.16)	**0.79**[b](.23)
Angry > Neutral			
L AMYG	1.19 (.25)	−0.13 (.25)	**1.32**[b](.35)
R AMYG	1.29 (.23)	−0.08 (.23)	**1.37**[a](.33)
L aINS	0.70 (.22)	0.05 (.28)	**0.64**[d](.32)
R aINS	0.56 (.14)	0.35 (.14)	**0.22** (.203)
L vACC	0.62 (.21)	−0.05 (.22)	**0.67**[c](.30)
R vACC	0.83 (.18)	−0.07 (.19)	**0.89**[b](.26)

Continued on next page

Table 3.3 – continued from previous page

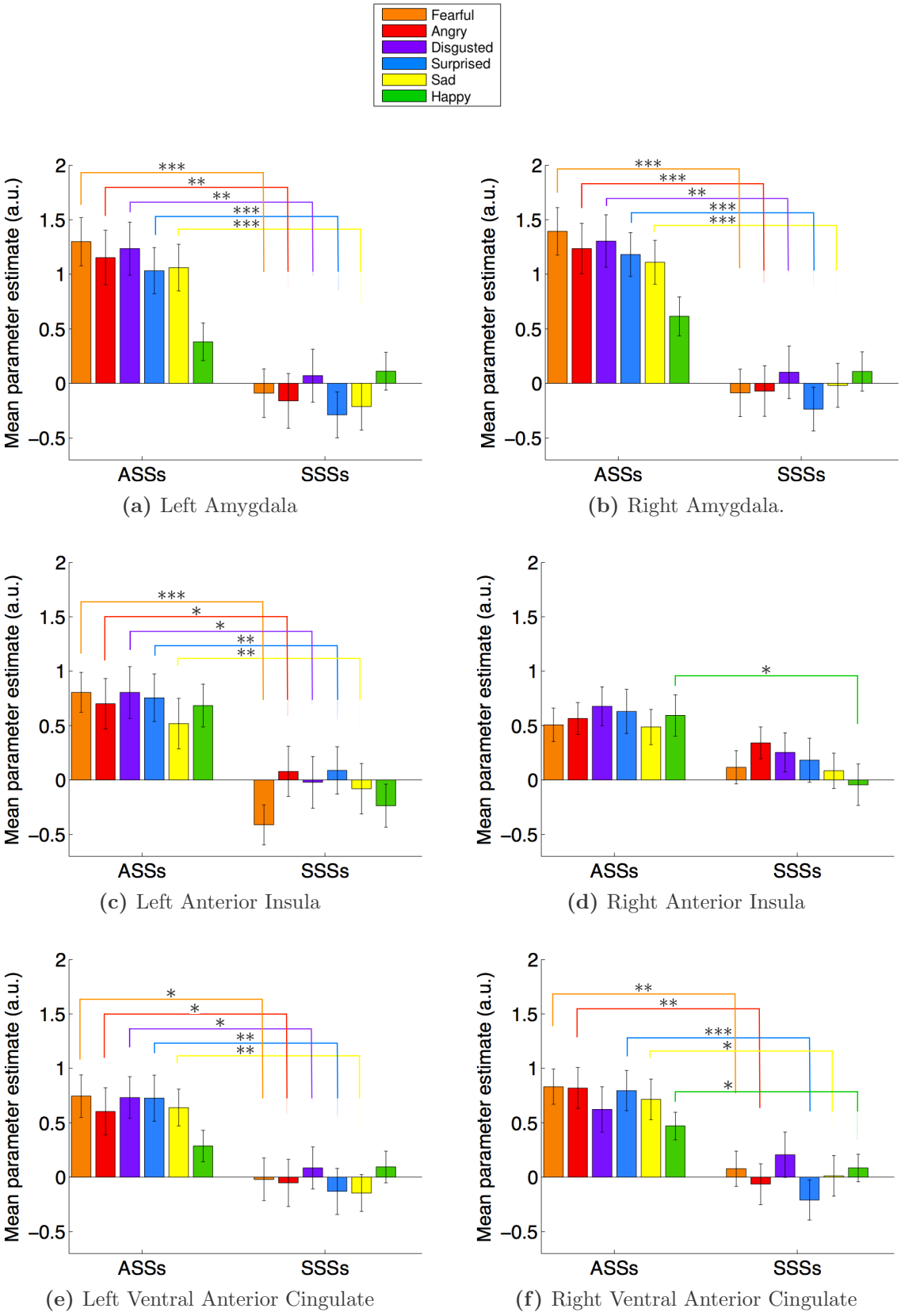
ROI	ASSs	SSSs	Mean Differences
Disgusted > Neutral			
L AMYG	1.24 (.24)	0.07 (.24)	**1.17**[b](.34)
R AMYG	1.34 (.23)	0.10 (.24)	**1.24**[b](.33)
L aINS	0.78 (.23)	−0.02 (.24)	**0.80**[c](.33)
R aINS	0.68 (.17)	0.25 (.18)	**0.43**[d](.25)
L vACC	0.73 (.19)	0.09 (.19)	**0.64**[c](.27)
R vACC	0.64 (.20)	0.21 (.21)	**0.43** (.29)
Sad > Neutral			
L AMYG	1.05 (.21)	−0.21 (.21)	**1.26**[a](.30)
R AMYG	1.12 (.20)	−0.02 (.20)	**1.14**[a](.28)
L aINS	0.52 (.22)	−0.08 (.23)	**0.60**[d](.32)
R aINS	0.50 (.16)	0.09 (.16)	**0.41**[d](.22)
L vACC	0.63 (.16)	−0.15 (.17)	**0.77**[b](.23)
R vACC	0.73 (.18)	0.01 (.18)	**0.71**[b](.26)
Surprised > Neutral			
L AMYG	1.05 (.209)	−0.22 (.21)	**1.27**[a](.30)
R AMYG	1.19 (.20)	−0.24 (.20)	**1.43**[a](.28)
L aINS	0.71 (.21)	0.10 (.22)	**0.61**[d](.31)
R aINS	0.59 (.20)	0.17 (.20)	**0.42** (.285)
L vACC	0.73 (.21)	−0.14 (.21)	**0.86**[b](.29)
R vACC	0.82 (.18)	−0.20 (.18)	**1.02**[a](.26)
Happy > Neutral			
L AMYG	0.31 (.18)	0.11 (.18)	0.20 (.25)
R AMYG	0.58 (.18)	0.11 (.18)	**0.47**[d](.25)
L aINS	0.61 (.20)	−0.24 (.20)	**0.85**[b](.29)
R aINS	0.53 (.19)	−0.04 (.19)	**0.58**[c](.27)
L vACC	0.24 (.15)	0.10 (.15)	0.14 (.21)
R vACC	0.45 (.12)	0.09 (.13)	**0.36**[c](.18)

ROI = region of interest; M = mean; SEM = mean square error; L = left; R = right; AMYG = amygdala; aINS = anterior insula; vACC = ventral anterior cingulate cortex. Significant mean differences are printed in bold.

[a] $P \leq .001$

[b] $P \leq .0083$ (alpha adjusted to correct for multiple comparisons)

[c] $P \leq 0.05$



(a) Left Amygdala

(b) Right Amygdala.

(c) Left Anterior Insula

(d) Right Anterior Insula

(e) Left Ventral Anterior Cingulate

(f) Right Ventral Anterior Cingulate

Figure 3.4 ***a-f***, Mean parameter estimates (arbitrary units) of ROIs activity (y-axes) in response to fearful, angry, disgusted, surprises, sad, and happy versus neutral faces (orange, red, purple, blue, yellow and green bars, respectively) by personality group (x-axes) under placebo. *p $\leq$.05; **p $\leq$.0083; ***p $\leq$.001. For values and additional details, see Table 3.3 and section 3.2.1.3, respectively. Error bars indicate SEM.

Correlational analyses. Pearson correlation linear regression analyses of the relationship between trait anxiety -sensitive levels and functional regions-of-interest activation to emotional face stimuli found a highly significant inverse association betweentrait anxiety sensitivity levels, as measured by the SURPS-AS subscale and the parameter estimate (arbitrary units) of mean amygdalae activity in response to the "Fearful > Neutral" faces contrast, bilaterally (L: $r(39) = .64$, $p_{(2-tailed)} = .000$ and R: $r(39) = .67$, $p_{(2-tailed)} = .000$). This association, however, remained significant only in ASSs when the personality groups were analyzed separately (L: $r(17) = .84$, $p_{(2-tailed)} = .000$ and R: $r(17) = .85$, $p_{(2-tailed)} = .000$; Figure 3.5).

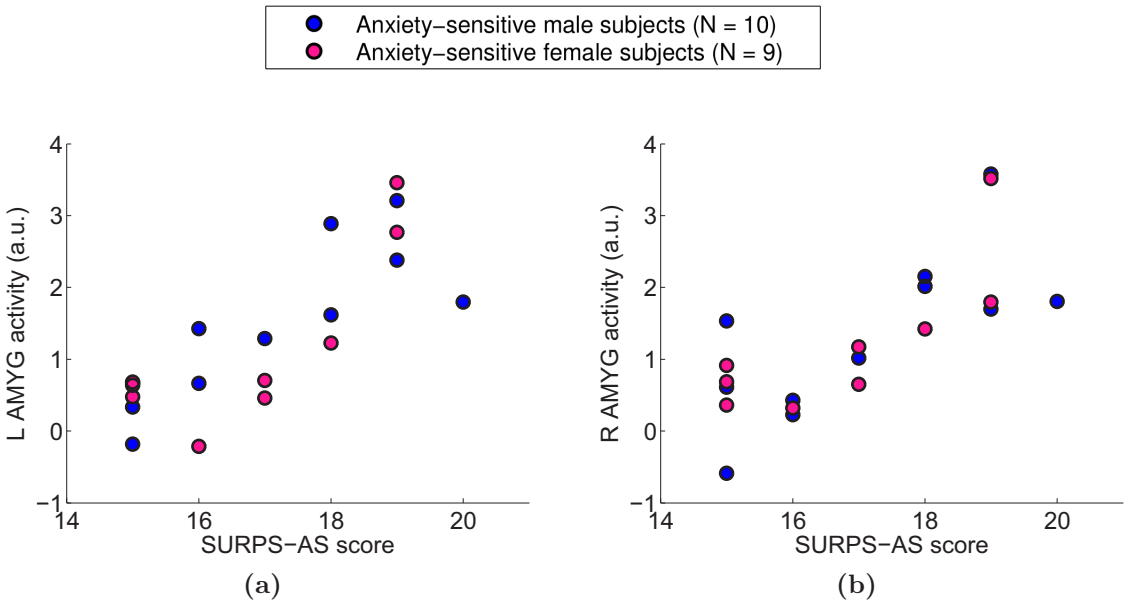
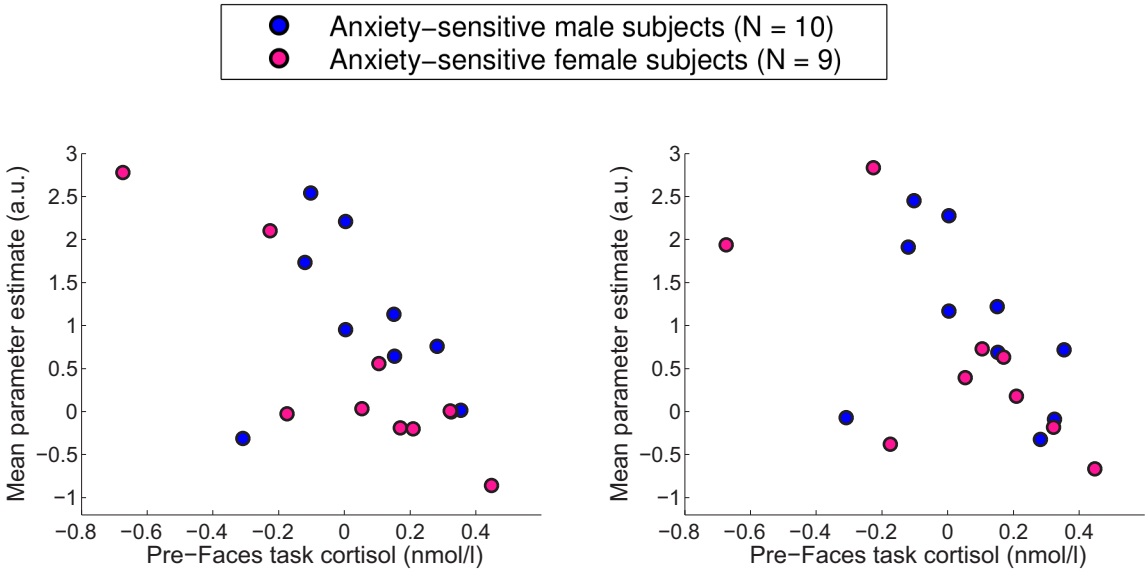


Figure 3.5 Significant linear relationships between AS scores (SURPS; x-axes) and mean parameter estimates (arbitrary units; y-axes) of left ***(a)*** and right ***(b)*** AMYG activation to "Fearful > Neutral face" contrast under placebo in ASMSs (blue circles) and ASFSs (pink circles). Significance of association was unique to the AS group.

Further, testing the association between pre-FEPT and amygdalae activity in response to "Fearful > Neutral face" contrast separately for each personality group, partial correlation analyses controlling for time of testing and thresholded at a Bonferroni adjusted alpha level of .0125 each (.05/4) were conducted. These analyses showed, in broad consistency with our initial expectation, that pre-FEPT cortisol levels were

inversely associated with mean parameter estimate of left and right AMYG activity, bilaterally, but that this was true only for the AS group and only in the left AMYG after adjusting alpha level to correct for multiple comparisons (L: $r(19) = -.600, p = .008$, Figure 3.6**a**; R: $r(19) = -.520, p = .027$, Figure 3.6**b**).

Also, in accordance with our working hypothesis, the significance of this amygdala-cortisol association was not only specific to ASSs but also exclusively displayed in response to "Fearful > Neutral face" contrast, diminishing when other emotional faces (relative to neutral) are viewed. The same association was also insignificant in response to averaged trials of emotional (fearful, angry, disgusted, SAD and surprised), relative to neutral, face trials and after correcting for multiple comparisons.



(a) Pre-task association with left amygdalae reactivity.

(b) Pre-task association with right amygdalae reactivity.

Figure 3.6 ***a-b***, Significant time-adjusted correlations between pre-FEPT cortisol levels (x-axes) and percent activation (arbitrary units; y-axes) in the in left ***(a)*** and right ***(b)*** AMYG in response to the "Fearful versus Neutral faces" contrast under placebo in in ASMSs (blue circles) and ASFSs (pink circles). Significance of association was unique to the AS group. See text for values.

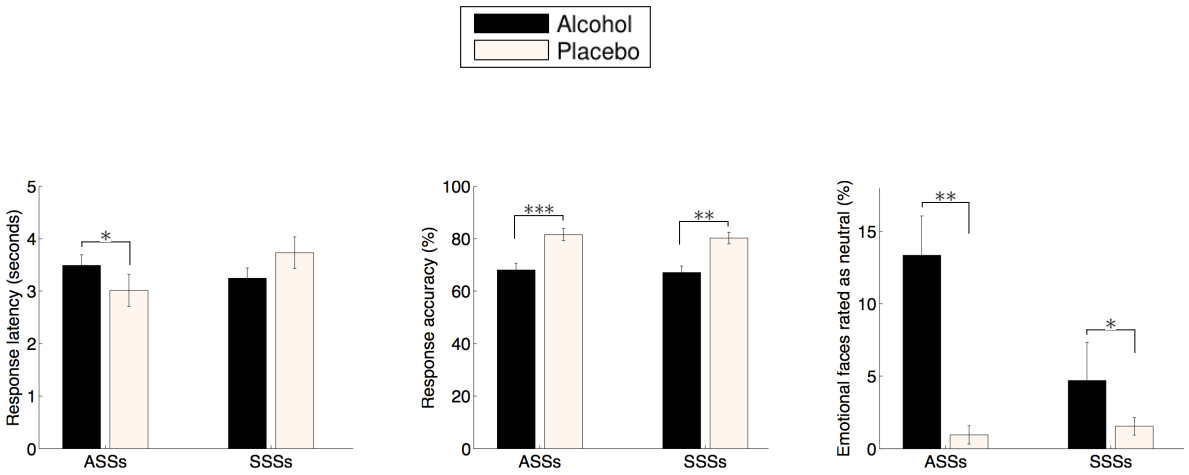
3.2.2 Alcohol Condition

3.2.2.1 Behavioral Results

Three-way mixed-design ANOVA, assessing the effect of condition (alcohol or placebo) and its interaction with either and both personality and sex on the behavioral correlates of facial emotion processing, revealed a significant condition-by-personality interaction effect on response latency ($F_{(1,37)} = 5.59, p = .023$, $\eta^2_{\text{p}} = .131$). Decomposing this 2-way interaction (using paired-sample t-tests and a Bonferroni adjusted thresholded of $p_{(2-tailed)} \leq .025$ ($.05/2 = .025$) revealed, as would be expected, a significantly greater response latency on part of ASSs when alcohol intoxicated relative to when sober: $t_{(19)} = 2.34, p = .030$), but no statistical condition difference within SSSs ($p_{(2-tailed)} > .1$, *ns*; Figure 3.7**a**).

With response to negative or surprised face emotion identification accuracy, there was a main effect of condition such that alcohol, relative to placebo, significantly decreased accuracy level in the entire sample: $F_{(1,37)} = 29.45, p = .000$, $\eta^2_{\text{p}} = .443$ (Figure 3.7**b**). No significant interaction effects on this behavioral measure stood out, indicating that the entire sample was intoxicated to the point of significant, but not differentially altered perception, relative to placebo.

Finally, a significant condition-by-personality effect on the rate of emotional (i.e, negatively valent or surprised) faces identified as neutral also stood out: $F_{(1,37)} = 7.12, p = .011$, $\eta^2_{\text{p}} = .161$. Decomposing this effect using paired-sample t-tests and a Bonferroni corrected 2-tailed alpha of $p \leq .025$ per test, we found that relative to placebo, said rate was significantly dampened by alcohol in both the AS and SS groups (respectively, $t_{(19)} = 3.98, p = .001$ and $t_{(20)} = 2.25, p = .036$) groups, but that this significance did not survive Bonferroni's correction for multiple comparisons in the SS group (by adjusting alpha to $p \leq .025$ per test). Results displayed in Figure 3.7**c** and Table 3.4.



(a) Response Latency **(b)** Response Accuracy **(c)** Negativity Bias

Figure 3.7 ***a-c,*** The condition differences in behavioral performance on the FEPT by personality group (x-axes). On y-axes are face emotion recognition latency (seconds) ***(a)***, percent of accurately identified negatively valent faces ***(b)***, and percent negative and surprised faces mislabeled as neutral ***(c)***. An asterisk (*) denotes a significant condition difference at $p_{(2-tailed)} \leq .05$; $^{**}p_{(2-tailed)} \leq .025$ (Bonferroni corrected); $^{***}p_{(2-tailed)} \leq .001$. For values, see Table 3.4. Error bars indicate SEM.

Table 3.4: Raw means (standard error means) of behavioral responses to the FEPT by personality group in under alcohol and placebo.

Behavioral Index	Alcohol	Placebo	Mean Difference
Response Latency (seconds)			
ASSs	3.49 (.20)	3.01 (.31)	**.46**[a](.19)
SSSs	3.25 (.20)	3.73 (.30)	−.48 (.34)
Correctly identified negative emotions (%)			
ASSs	68.06 (2.55)	81.61 (2.29)	− **13.33**[c](2.97)
SSSs	67.16 (2.42)	80.25 (2.18)	**−13.22**[b](3.57)
Neutral faces identified as emotional			
ASSs	12.83 (3.78)	11.65 (3.58)	−.06 (3.21)
SSSs	10.18 (3.58)	6.92 (3.42)	7.13 (3.86)
Surprised faces identified as harsh			
ASSs	6.78 (2.68)	6.64 (1.71)	.12 (3.67)
SSSs	3.89 (2.60)	.96 (1.66)	2.82 (2.01)
Emotional faces identified as neutral (%)			
ASSs	13.34 (2.71)	.96 (.63)	**12.72**[b](3.2)
SSSs	4.70 (2.63)	1.55 (.61)	**3.18**[a](1.41)

Abbreviations: ASSs = anxiety sensitive subjects; SSSs = sensation seeking subjects. Significant mean differences are printed in bold.

[a] Significant at $p_{2-tailed} \leq .05$

[b] Significant at $p_{2-tailed} \leq .025$ (Bonferroni adjusted)

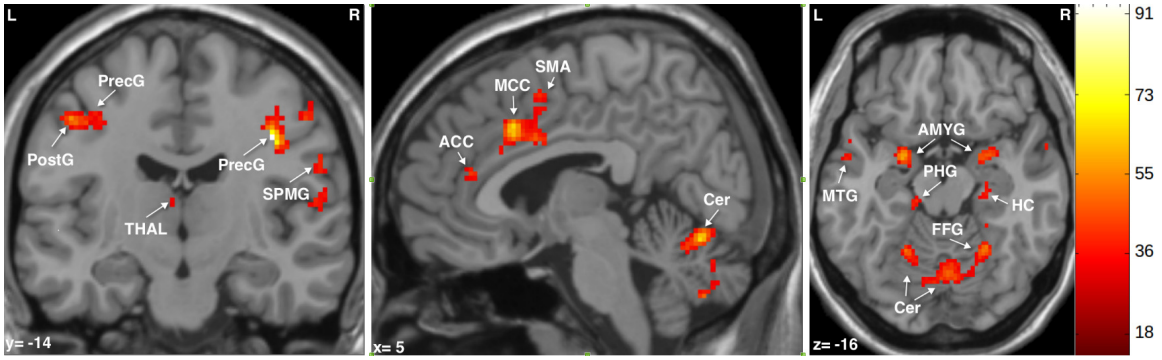
[c] Significant at $p_{2-tailed} \leq .001$

3.2.2.2 Endocrine Results

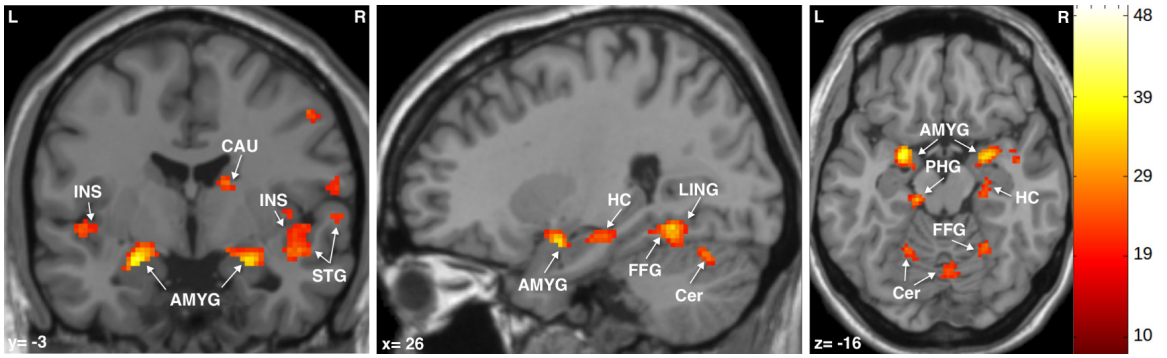
Three-way mixed-design ANCOVA assessing for the effects of condition (alcohol or placebo) and an interaction with either and both personality and sex on pre-FEPT cortisol values, with "session time" controlled for, revealed no significant results.

3.2.2.3 Neurofunctional Results

Exploratory voxel-wise analyses. Assessing the main effect of alcohol and its interaction with either and both personality and sex on neural correlates of emotional (> Neutral) face processing, emotion processing brain response to emotional (> Neutral) faces, separately and together, whole-brain analyses, thresholded at $P \leq .05$, FWE corrected ($k = 10$) showed main effects of alcohol (Table 3.5, Figure 3.8**A**) and its interaction with personality in response to all emotional (relative to neutral) except for happy faces, both separately and combined together. Note that we consider the unravelling of a significant condition-by-personality interaction effect as arguably undermining the importance of the main effect of alcohol. Results for the latter are therefore not reported here and can be found in appendix. A personality-by-condition interaction effect on the brain response to aversive (relative to neutral) faces (Figure 3.8**B** and Table 3.5.



(A) Main effect of alcohol intoxication



(B) Interaction between alcohol and personality profile

Figure 3.8 ***A-B,*** Main effect of alcohol (***A***), and its interaction with personality risk profile (***B***) on regional brain activation to emotional (−neutral) faces. Anatomical maps of t statistics were spatially normalized by warping to MNI space and combined into a group map. A statistical map of the main effect of personality was computed by conducting a voxel-wise flexible-factorial GLM random effects analysis of the event-related β coefficients. In this model, personality (AS or SS), and condition (alcohol or placebo) were fixed factors and individual subject was a random factor. The main effects of alcohol were notably observed in, among other areas, core limbic structures (e.g, AMYG, HC and thalamus), the FFG, PHG, MCC and ACC. The condition-by-personality interaction effect, however, was comparatively more noticeably and selectively localized to the previously mentioned core limbic regions and other subcortical (e.g, caudate) cites and the insular cortex. x, y, z = sagittal, coronal and horizontal view in MNI coordinates. The color map represents the corresponding F value (see Table 3.5). L and R indicate, respectively, the left and right sides of the brain; AMYG, amygdala, CAU, caudate; INS, insula; PrecG, precentral gyrus;

Table 3.5: The Effect of condition-by-Personality Interaction on Brain Response to Negatively Valent > Neutral Faces.

Region (BA)	x	y	z	K_E	F**-value**	$P_{FWE-corr}$
R FL/ subgyral	36	−14	38	60	48.43	0.000
L AMYG	−24	0	−16	140	40.94	0.000
L Putamen	−26	−6	−8		23.11	0.013
L STG (38)	−32	4	−18		20.82	0.033
R MCC	6	18	36	245	40.26	0.000
L MCC	−6	18	34		30.09	0.001
R MCC (24)	4	8	32		25.05	0.006
L MFG	−38	48	22	96	35.19	0.000
R AMYG	22	−2	−16	101	34.36	0.000
R S−L	14	−4	−12		25.70	0.005
R PHG (19)	24	−52	−10	100	33.88	0.000
R Cerebellum	10	−70	−38	31	32.61	0.000
R Cerebellum	4	−68	−14	83	32.16	0.000
L PHG	−16	−26	−16	63	31.09	0.001
L PHG/ HC	−24	−24	−12		24.76	0.007
R Cerebellum	18	−70	−26	94	30.00	0.001
L Cerebellum	−4	−76	−36	32	29.73	0.001
L Cerebellum	−8	−74	−28		21.10	0.029
R INS (13)	44	6	−4	436	29.59	0.001
R INS(21)	42	−4	−12		29.28	0.001
R STG	48	14	−12		27.63	0.002
L PostcG	−46	−12	44	55	29.37	0.001
L PrecG (6)	−36	−12	50		20.82	0.033
R Cerebellum	36	−56	−28	27	29.02	0.001
L STG	−54	10	−10	52	28.95	0.001
R MFG	36	50	22	59	28.53	0.002
R MFG	40	50	12		22.78	0.015
R PrecG (43)	54	−12	12	172	28.47	0.002
R PrecG (4)	58	−4	16		24.35	0.008
R STG	62	−10	8		24.30	0.008
R PrecG (6)	48	−4	44	35	28.34	0.002
R PrecG (4)	50	−14	46		21.26	0.027
R MFG	38	44	−4	20	27.86	0.002
L Cerebellum	−32	−56	−26	25	26.31	0.004
R Caudate body	14	−2	16	17	26.16	0.004
L Cerebellum	−16	−60	−22	109	25.94	0.004
L Cerebellum	−22	−54	−16		25.71	0.005
L Cerebellum	−20	−72	−22		23.01	0.014
R PHG/ HC	24	−22	−14	46	25.48	0.005
R INS	40	−6	4	16	25.28	0.006
L Cerebellum	−12	−34	−22	17	25.24	0.006

Continued on next page

Table 3.5 – continued from previous page

Region (BA)	x	y	z	K_E	F-value	$P_{FWE-corr}$
R Midbrain	14	−26	−8	15	25.11	0.006
R MFG	28	16	60	15	24.80	0.007
R SFG	26	8	56		21.04	0.030
L PHG/ FFG (19)	−28	−52	−8	12	24.77	0.007
R PHG/ LING	14	−46	2	23	24.63	0.007
L STG	−48	−2	−4	33	24.57	0.007
L LING	−12	−66	2	24	23.45	0.011
R IFG	54	8	30	10	23.19	0.013
R CG (32)	8	4	46	12	22.42	0.017

FL = frontal lobe; MFG = middle frontal gyrus, IFG = inferior frontal gyrus; CG = cingulate gyrus; MCC = mid-cingulate cortex; ACC = anterior cingulate cortex; PrecG = precentral gyrus; PostcG = postcentral gyrus; AMYG = amygdala, INS = insula; MTG = middle temporal gyrus; STG = superior temporal gyrus; HC = hippocampus; PHG = parahippocampal gyrus; LING = lingual gyrus. TL = frontal lobe;

Table 3.6: Condition-by-personality interaction effect on brain response to fearful (relative to neutral) Specific Emotional.

Region (BA)	x	y	z	K_E	$\boldsymbol{F}$ value	$P_{FWE-corr}$
Fearful > Neutral						
L ACC (24)	−6	22	26	87	39.74	0.000
R ACC (24)	4	24	26		25.20	0.006
L MFG	−42	46	20	45	33.00	0.000
R MCC (32)	6	14	34		31.89	0.001
L HYP	−22	0	−16	75	30.71	0.001
L PUT	−28	−6	−8		21.63	0.023
R AMYG	26	2	−16	29	26.86	0.003
R INS (13)	44	6	−4	27	24.37	0.008
L STG	−54	10	−8	25	23.79	0.010
R MFG	38	48	20	26	23.77	0.010
L PrecG	−48	−8	44	11	23.68	0.010
Angry > Neutral						
R MCC	6	20	36	57	33.50	0.000
L AMYG	−26	−2	−18	29	29.12	0.002
R STG	62	−10	8	75	28.77	0.002
R PostcG	62	−14	20		25.86	0.005
R PrecG (43)	54	-12	12		21.26	0.030
R MCC	2	0	30	10	27.78	0.003
L PHG	−14	−26	−16	50	27.63	0.003
L Cerebellum	−12	−34	−22		26.94	0.004
L HC	−22	−26	−12		22.60	0.018

Continued on next page

Table 3.6 – continued from previous page

Region (BA)	x	y	z	K_E	F value	$P_{FWE-corr}$
L cuneus	−12	−64	6	38	27.34	0.003
L PrecG	−20	−24	58	17	25.37	0.006
L STG (38)	−46	14	−10	17	24.89	0.008
R PrecG (4)	54	−10	48	32	23.83	0.011
R Cerebellum	20	−72	−24	18	23.45	0.013
R Cerebellum	16	−62	−16		20.95	0.035
R INS (13)	38	14	−4	23	22.43	0.020
R STG	48	14	-6		22.18	0.022
R FL/ sub-gyral	36	−12	42	10	21.89	0.024
Disgusted > Neutral						
R Cerebellum	6	−70	−12	11	23.40	0.013
R INS (13)	42	2	−6	15	21.89	0.024
R STG	50	12	−12	15	21.39	0.029
Sad > Neutral						
L PHG (34)	−22	2	−14	25	28.30	0.002
L PHG (19)	−28	−52	−8	34	26.32	0.005
L Cerebellum	−22	−54	−14		25.24	0.007
L Cerebellum	−4	−76	−30	31	26.23	0.005
R Caudate head	8	16	4	37	25.16	0.008
R Caudate	18	22	-6		24.01	0.012
L Cerebellum	−20	−74	−24	18	24.19	0.011
L Cerebellum	−14	−34	−20	17	23.65	0.013
Surprised > Neutral						
L MFG	−38	46	22	21	28.62	0.002
L STG	−48	16	−12	36	25.53	0.006
L AMYG	−18	0	−12	23	23.50	0.012
R AMYG	24	2	−14	10	23.04	0.014
R STG (38)	46	12	−8	18	22.64	0.017

ASSs = anxiety sensitive subjects; SSSs = sensation-seeking subjects; FL = frontal lobe; MFG = middle frontal gyrus, IFG = inferior frontal gyrus; CG = cingulate gyrus; MCC = mid-cingulate cortex; ACC = anterior cingulate cortex; PrecG = precentral gyrus; PostcG = postcentral gyrus; AMYG = amygdala, INS = insula; MTG = middle temporal gyrus; STG = superior temporal gyrus; HC = hippocampus; PHG = parahippocampal gyrus; LING = lingual gyrus.

Condition-by-personality effects were decomposed by directly contrasting the alcohol against placebo condition within each personality group.

For aversive (minus neutral) faces, the placebo minus alcohol contrast for ASSs generated activation in brain clusters, with those showing the strongest and second

strongest activations being localized to, respectively, the left ACC (BA24) and amygdala. SSSs showed no signficant effect of alcohol (Table 3.8)

Table 3.7: The effect of personality by condition interaction on brain response to aversive (minus neutral) faces. Whole-brain activations are thresholded at $P_{FWE-corrected} \leq .05$, with a cluster size $k \geq 10$ voxels. A negative t-value indicates that there was greater activation to placebo than to alcohol. Coordinates refer to the MNI system.

Region (BA)	x	y	z	K_E	***F* value**	$P_{FWE-corr}$
R FL/ Sub-Gyral	36	−14	38	60	48.43	0.000
L PHG/ AMYG	−24	0	−16	140	40.94	0.000
L PUT	−26	−6	−8		23.11	0.013
L STG (38)	−32	4	−18		20.81	0.033
R MCC	6	18	36	245	40.26	0.000
L MCC	−6	18	34		30.09	0.001
R MCC (24)	4	8	32		25.05	0.006
L MFG	−38	48	22	96	35.18	0.000
R PHG/ AMYG	22	−2	−16	101	34.36	0.000
R S−L/ E−N	14	−4	−12		25.70	0.005
R PHG/ LING (19)	24	−52	−10	100	33.87	0.000
R Cerebellum	10	−70	−38	31	32.61	0.000
R Cerebellum	4	−68	−14	83	32.16	0.000
L PHG	−16	−26	−16	63	31.09	0.001
L PHG/ HC	−24	−24	−12		24.75	0.007
R Cerebellum	18	−70	−26	94	29.99	0.001
L Cerebellum	−4	−76	−36	32	29.72	0.001
L Cerebellum	−8	−74	−28		21.09	0.029
R INS (13)	44	6	−4	436	29.59	0.001
R TL/ INS (21)	42	−4	−12		29.28	0.001
R STG	48	14	−12		27.63	0.002
L PrecG	−46	−12	44	55	29.37	0.001
L PrecG (6)	−36	−12	50		20.82	0.033
R Cerebellum	36	−56	−28	27	29.01	0.001
L STG	−54	10	−10	52	28.95	0.001
R MidFG	36	50	22	59	28.52	0.002
R MidFG	40	50	12		22.78	0.015
R PrecG	54	−12	12	172	28.47	0.002
R PrecG (4)	58	−4	16		24.34	0.008
R STG	62	−10	8		24.30	0.008
R PrecG (6)	48	−4	44	35	28.33	0.002
R PrecG (4)	50	−14	46		21.25	0.027
R MidFG	38	44	−4	20	27.85	0.002
L Cerebellum	−32	−56	−26	25	26.31	0.004

Continued on next page

Table 3.7 – continued from previous page

Region (BA)	x	y	z	K_E	***F* value**	$P_{FWE-corr}$
R Caudate Body	14	−2	16	17	26.15	0.004
L Cerebellum	−16	−60	−22	109	25.93	0.004
L Cerebellum/ FFG	−22	−54	−16		25.70	0.005
L Cerebellum	−20	−72	−22		23.01	0.014
R PHG/ HC	24	−22	−14	46	25.47	0.005
R INS	40	−6	4	16	25.27	0.006
L Cerebellum	−12	−34	−22	17	25.24	0.006
R Midbrain	14	−26	−8	15	25.11	0.006
R MFG	28	16	60	15	24.80	0.007
R SFG	26	8	56		21.04	0.03
L PHG/ FFG (19)	−28	−52	−8	12	24.76	0.007
R PHG/ LING	14	−46	2	23	24.63	0.007
L STG	−48	−2	−4	33	24.56	0.007
L LING	−12	−66	2	24	23.45	0.011
R IFG	54	8	30	10	23.19	0.013
R CG (32)	8	4	46	12	22.41	0.017

ASSs = anxiety sensitive subjects; SSSs = sensation-seeking subjects; FL = frontal lobe; MFG = middle frontal gyrus, IFG = inferior frontal gyrus; CG = cingulate gyrus; MCC = mid-cingulate cortex; ACC = anterior cingulate cortex; PCC = posterior cingulate cortex; thalamus PrecG = precentral gyrus; PostcG = postcentral gyrus; AMYG = amygdala, INS = insula; MTG = middle temporal gyrus; STG = superior temporal gyrus; HC = hippocampus; PHG = parahippocampal gyrus; LING = lingual gyrus; ; MDN = medial dorsal nucleus; VLN = ventral lateral nucleus.

Peak MNI coordinate region.

Cluster size in voxels.

[a] No clusters detected.

Table 3.8: Condition differences in whole-brain response to negative versus neutral faces by personality group at $P_{FWE-corrected} \leq .05$ ($k = 10$). A negative t-value is indicative of greater BOLD activity under the placebo than to alcohol condition. Coordinates refer to the MNI system.

Region (BA)	x	y	z	K_E	t-value	$P_{FWE-corr}$
ASSs: alcohol > placebo						
L AMYG	−24	0	−16	493	−8.99	0.000
L PHG	−16	−26	−16		−7.86	0.000
L cerebellum	−12	−34	−22		−7.07	0.001
R FL/ subgyral	36	−14	38	70	−8.75	0.000
R AMYG	22	−2	−16	1750	−8.25	0.000
R INS (21)	42	−4	−12		−7.56	0.000
R PrecG (43)	54	−12	12		−7.41	0.000
R MCC	6	18	36	371	−7.56	0.000
L MCC	−6	18	34		−6.68	0.002
R MCC (24)	4	8	32		−6.43	0.003
L STG	−50	10	−8	278	−7.41	0.000
L STG	−48	−2	−4		−6.78	0.001
L STG	−44	16	−16		−5.93	0.013
R PHG/ LING (19)	26	−54	−8	286	−7.28	0.000
R cerebellum	22	−66	−22		−7.13	0.000
R cerebellum	34	−54	−26		−6.80	0.001
R caudate body	14	−2	16	45	−6.87	0.001
R thalamus −VLN	14	−10	14		−5.67	0.027
R PHG/ LING	14	−46	2	174	−6.79	0.001
R LING (19)	12	−56	−4		−6.19	0.007
R OL/ subgyral	16	−62	16		−6.13	0.008
L cerebellum	−18	−58	−18	164	−6.66	0.002
L cerebellum	−28	50	−18		−6.29	0.005
L PHG/ FFG (19)	−28	−52	−8		−5.97	0.012
L TL/ subgyral	−40	−4	−16	56	−6.59	0.002
L MTG	−56	0	−18	13	−6.58	0.002
R MFG	36	44	−2	37	−6.57	0.002
R MFG	46	42	−2		−5.78	0.020
R MFG	−38	46	24	58	−6.53	0.003
L LING	−12	−66	2	55	−6.40	0.004
L LING	−12	−58	0		5.96	0.012
R PostcG (3)	44	−24	58	33	6.37	0.004
R PostcG	46	−24	50		−5.72	0.024
L cerebellum	−4	−76	−36	21	−6.34	0.004
R PostcG	52	−28	38	32	−6.31	0.005
R PostcG	58	−28	44		−5.57	0.035
L PrecG	−46	−12	44	57	−6.23	0.006
L PrecG (6)	−36	−12	50		5.70	0.025

Continued on next page

Table 3.8 – continued from previous page

Region (BA)	x	y	z	K_E	***t*-value**	$P_{FWE-corr}$
R PCC	2	−72	12	77	−6.21	0.006
R CUN/ LING (30)	6	−68	6		6.05	0.010
L thalamus − MDN	−6	−16	6	41	−6.15	0.007
R cerebellum	2	−66	−14	52	−6.08	0.009
L S−L/ E−N	−18	−4	18	14	−6.08	0.009
L STG	−60	−14	8	21	−6.05	0.010
L FFG	−28	−36	−22	16	−6.03	0.010
R Putamen	22	22	−8	27	−6.02	0.010
R caudate	14	18	−2		−5.93	0.013
R MCC	12	−30	38	13	−5.89	0.015
L CG	−16	−32	38	11	−5.83	0.018
L cerebellum	−20	−72	−22	12	−5.70	0.025
SSSs: alcohol > placebo[a]						

ASSs = anxiety sensitive subjects; SSSs = sensation-seeking subjects; FL = frontal lobe; MFG = middle frontal gyrus, IFG = inferior frontal gyrus; CG = cingulate gyrus; MCC = mid-cingulate cortex; ACC = anterior cingulate cortex; PCC = posterior cingulate cortex; thalamus PrecG = precentral gyrus; PostcG = postcentral gyrus; AMYG = amygdala, INS = insula; MTG = middle temporal gyrus; STG = superior temporal gyrus; HC = hippocampus; PHG = parahippocampal gyrus; LING = lingual gyrus; ; MDN = medial dorsal nucleus; VLN = ventral lateral nucleus.

Peak MNI coordinate region.

Cluster size in voxels.

[a] No clusters detected.

In response to fearful faces, there was a significant personality-by-condition interaction effect on the brain response to fearful versus neutral faces (Figure 3.9) and Table 3.9.

The placebo minus alcohol contrast for ASSs generated activation in a total of 8 brain clusters, with those showing the strongest and second strongest activations being localized to, respectively, the left ACC (BA24) and AMYG (Figure 3.9), Table 3.9). These results indicate, as was expected, that the current condition-by-personality interaction effect was mainly driven by the AS group. SSSs showed no significant effect of alcohol.

Similar results patterns were obtain in response to other negative face emotions (assessed separately), and those are depicted in Figure 3.9 and displayed in Table 3.9.

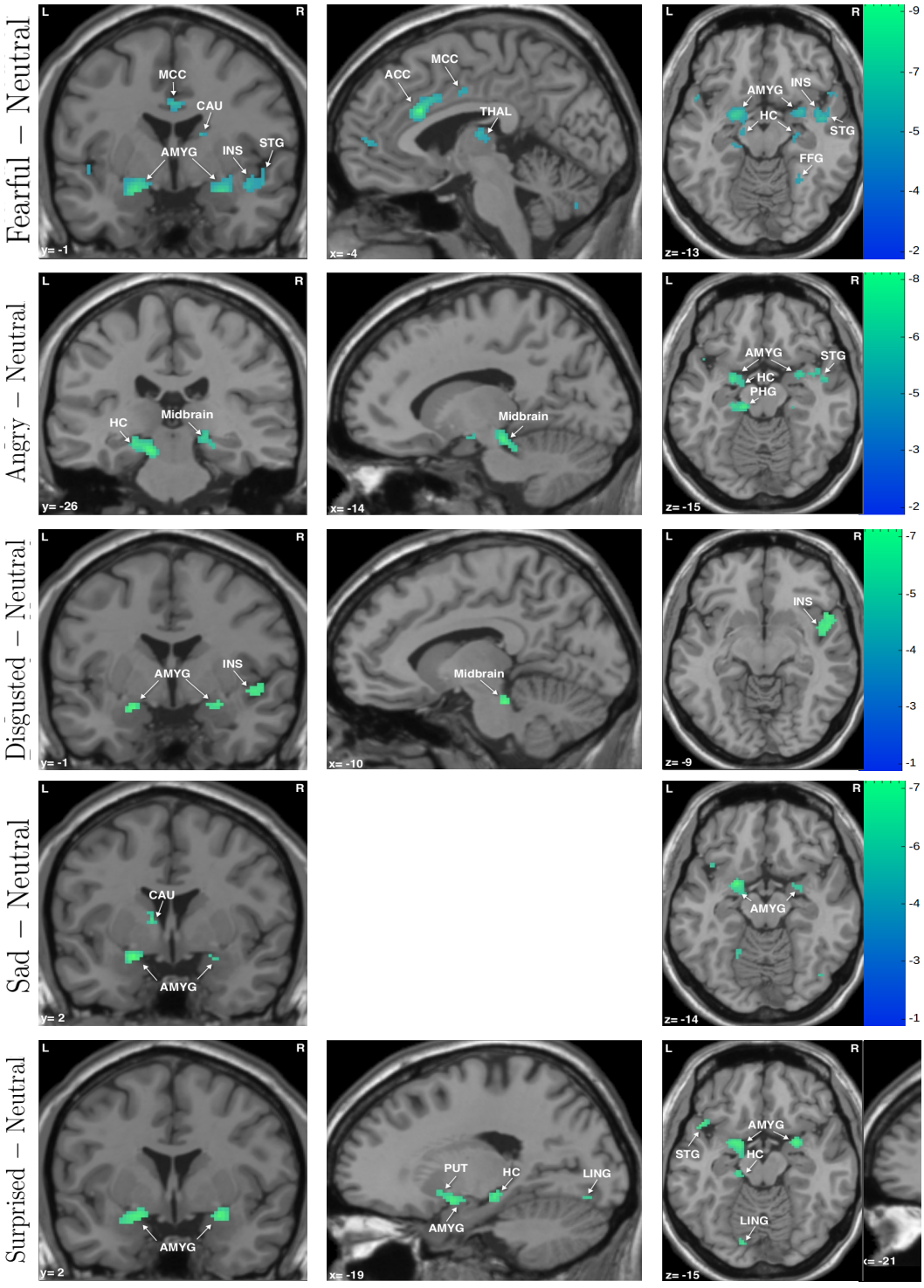


Figure 3.9 The effects of alcohol on whole-brain activation under specific face emotions in ASSs. Each panel shows in a coronal (y), sagittal (x) and axial (z) view activation maps thresholded at $P_{FWE-corrected} \leq .05$. Negative t-values (shown by color map), indicate greater activation to placebo than to alcohol. Alcohol-induced deactivation is, as illustrated, is primarily subcortical, with the dampening of AMYG activation being the common denominator in all of five face emotions shown. Results for SSSs (Alcohol versus Placebo) were not significant. For values, see Table 3.9.

Table 3.9: The effects of alcohol on whole-brain response to specific face emotions by personality group at $P_{FWE-corrected} \leq .05$ ($k = 10$). A negative t-value is indicative of greater BOLD activity under the placebo than to alcohol condition. Coordinates refer to the MNI system.

Region (BA)	x	y	z	K_E	$\boldsymbol{F}$ value	$P_{FWE-corr}$
Fearful > Neutral						
Alcohol > placebo: ASSs						
L ACC (24)	−6	22	26	347	−8.80	0.000
R MCC (32)	6	14	34		−7.51	0.000
R ACC (24)	4	24	26		−6.84	0.001
L AMYG	−22	0	−16	183	−7.77	0.000
L AMYG/ HC	−16	−8	−14		−6.23	0.006
L midbrain	−18	−16	−10		−5.86	0.016
R AMYG	26	2	−16	87	−7.27	0.000
R IFG	32	10	−14		−5.97	0.012
L STG (22)	−52	12	−8	91	−6.67	0.002
R PrecG (4)	56	−6	16	82	−6.51	0.003
R TL/ INS (21)	42	−4	−12	201	−6.51	0.003
R INS (13)	44	8	−4		−6.35	0.004
R STG (38)	50	14	−10		−5.88	0.015
R caudate	14	18	−4	18	−6.44	0.003
L Cerebellum	−4	−74	−36	11	−6.35	0.004
R caudate body	14	−2	16	19	−6.31	0.005
R HC	24	−20	−16	59	−6.30	0.005
R midbrain	14	−26	−8		−6.08	0.009
L PrecG	−48	−8	44	36	−6.29	0.005
L PrecG	−36	−14	42		−5.84	0.017
L thalamus - MDN	−6	−14	12	37	−6.03	0.01
L MedFG	−6	56	6	15	−5.91	0.014
L PHG	−18	−26	−14	18	−5.87	0.016
R Cerebellum	32	−56	−26	14	−5.85	0.016
R LING	14	−52	2	16	−5.81	0.018
R PHG/LING (19)	24	−52	−10	14	−5.75	0.021
Alcohol > placebo: SSSs						
L MFG	−44	46	18	18	−6.79	0.001
Angry > Neutral						
Alcohol > placebo: ASSs						
L AMYG	−26	−2	−18	82	−7.56	0.000
L AMYG/ HC	−18	−6	−14		−5.87	0.017
R STG	62	−10	8	193	−7.54	0.000
R PostcG	60	−14	16		−6.43	0.004
R PostcG (43)	56	−6	14		−5.69	0.028
L PHC	−14	−26	−16	152	−7.39	0.000

Continued on next page

Table 3.9 – continued from previous page

Region (BA)	x	y	z	K_E	$\boldsymbol{F}$ value	$P_{FWE-corr}$
L Cerebellum	−12	−34	−22		−7.24	0.000
L PHG/ HC	−22	−26	−12		−6.60	0.002
R MCC	6	20	36	79	−7.10	0.001
L CG (32)	−2	18	40		−5.61	0.035
L CG (24)	−6	12	34		−5.49	0.047
R MCC	2	−2	30	22	−6.81	0.001
R PHG/ AMYG	28	0	−16	40	−6.79	0.001
L CUN	−12	−64	6	43	−6.57	0.003
L STG (38)	−46	14	−10	44	−6.44	0.004
R S-L	38	2	−12	76	−6.36	0.005
R PHG/ LING (30)	20	−52	2	30	−6.15	0.008
R Midbrain	16	−26	−8	21	−6.08	0.010
R PCC/ PrecG	18	−58	14	12	−6.07	0.010
R INS (13)	38	14	−4	22	−6.01	0.012
R STG	48	14	−12	17	−5.97	0.013
L FFG	−28	−36	−20	12	−5.91	0.016
Alcohol > placebo: SSSs[d]						
Disgusted > Neutral						
Alcohol > placebo: ASSs						
L Midbrain	−10	−30	−22	28	6.54	0.003
R INS (13)	44	4	−6	184	6.32	0.005
R STG	50	12	−12		6.26	0.006
R IFG (47)	50	16	0		5.75	0.023
L PHG/ AMYG	−22	0	−16	31	6.25	0.006
R PHG/ AMYG	22	−4	−16	29	6.14	0.008
R S-L/ E-N	14	−4	−12		5.63	0.032
Alcohol > placebo: SSSs[d]						
Sad > Neutral						
Alcohol > placebo: ASSs						
L PHG (34)	−22	2	−14	96	7.40	0.000
R AMYG	−20	−6	−12		6.31	0.006
R PHG/ AMYG	−28	−4	−20		5.90	0.018
L Cerebellum	−14	−34	−20	59	6.70	0.002
L Cerebellum	8	−70	−28	19	6.61	0.003
L caudate	18	22	−6	70	6.57	0.003
L Caudate	14	16	0		6.38	0.005
L PHG/ AMYG	22	−2	−16	28	6.51	0.003
L Caudate Body	−8	10	10		5.74	0.026
R IOG	36	−72	−10	14	6.20	0.008
L Cerebellum	−20	−56	−16	25	6.08	0.011
L Cerebellum	−22	−72	−22	14	5.85	0.02

Continued on next page

Table 3.9 – continued from previous page

Region (BA)	x	y	z	K_E	$\boldsymbol{F}$ value	$P_{FWE-corr}$
R PUT	−16	14	−2	17	5.80	0.023
Alcohol > placebo: SSSs[d]						
Surprised > Neutral						
Alcohol > placebo: ASSs						
L STG (38)	−48	14	−8	100	7.05	0.001
R PHG/ AMYG	24	2	−14	49	6.76	0.001
R STG/ INS	46	12	−8	110	6.70	0.002
L AMYG	−18	0	−12	114	6.62	0.002
L PUT	−20	8	−10		5.91	0.014
L PHG/ HC	−20	−24	−12	32	6.47	0.003
L LING (18)	−18	−80	−12	22	6.31	0.005
L ACC	−2	36	30	79	6.28	0.005
L ACC (32)	−10	36	28		6.23	0.006
L ACC	-4	26	22		5.91	0.015
R Midbrain/ HC	16	−28	−8	18	6.19	0.007
L Midbrain	−12	−30	−4	17	6.18	0.007
L MFG	−38	46	22	11	6.10	0.009
R Caudate	14	18	−2	26	5.90	0.015
R Putamen	24	16	−8		5.76	0.022
R Caudate (17)	6	−86	4	13	5.77	0.021
R PHG/ HC	22	−18	−14	11	5.69	0.026
Alcohol > placebo: SSSs[d]						

ASSs = anxiety sensitive subjects; SSSs = sensation-seeking subjects; FL = frontal lobe; MFG = middle frontal gyrus, IFG = inferior frontal gyrus; CG = cingulate gyrus; MCC = mid-cingulate cortex; ACC = anterior cingulate cortex; PCC = posterior cingulate cortex; thalamus PrecG = precentral gyrus; PostcG = postcentral gyrus; AMYG = amygdala, INS = insula; MTG = middle temporal gyrus; STG = superior temporal gyrus; HC = hippocampus; PHG = parahippocampal gyrus; LING = lingual gyrus; ; MDN = medial dorsal nucleus; VLN = ventral lateral nucleus.

Peak MNI coordinate region.

Cluster size in voxels.

[a] No clusters detected.

ROI analyses. Repeated-measures ANOVAs assessing the effects of condition and its interaction with either and both personality profile and sex on functional ROIs activation to emotional faces revealed the following:

For the "Fearful versus Neutral face" contrast, there was condition-by-personality effects on the bilateral AMYG (L: $F_{(1,36)} = 11.60, p = .002$, $\eta_{\mathrm{p}}^2 = .244$; R: $F_{(1,36)}$

$= 11.18, p = .002$, $\eta_p^2 = .237$), left aINS ($F_{(1,36)} = 9.22, p = .004$, $\eta_p^2 = .244$) and bilateral vACC (L: $F_{(1,36)} = 5.67, p = .023$, $\eta_p^2 = .163$; R: $F_{(1,36)} = 5.79, p = .021$, $\eta_p^2 = .139$) activation (Figure 3.10).

For the "Angry versus Neutral face" contrast, there was condition-by-personality effects on the bilateral AMYG (L: $F_{(1,36)} = 8.37, p = .006$, $\eta_p^2 = .189$; R: $F_{(1,36)} = 9.18, p = .005$, $\eta_p^2 = .203$) and vACC (L: $F_{(1,36)} = 4.43, p = .042$, $\eta_p^2 = .110$; R: $F_{(1,36)} = 5.56, p = .024$, $\eta_p^2 = .134$) activation.

For the "Disgusted versus Neutral face" contrast, there was condition-by-personality effects on the bilateral AMYG (L: $F_{(1,36)} = 8.00, p = .008$, $\eta_p^2 = .182$; R: $F_{(1,36)} = 10.80, p = .002$, $\eta_p^2 = .229$) activation.

For the "Sad versus Neutral face" contrast, there was condition-by-personality effects on the bilateral AMYG (L: $F_{(1,36)} = 10.04, p = .003$, $\eta_p^2 = .218$; R: $F_{(1,36)} = 11.54, p = .002$, $\eta_p^2 = .243$) and vACC activation (L: $F_{(1,36)} = 8.45, p = .006$, $\eta_p^2 = .190$; R: $F_{(1,36)} = 15.36, p = .026$, $\eta_p^2 = .130$).

For the "Surprised versus Neutral face" contrast, there was condition-by-personality effects on the bilateral AMYG (L: $F_{(1,36)} = 8.65, p = .006$, $\eta_p^2 = .194$; R: $F_{(1,36)} = 10.25, p = .003$, $\eta_p^2 = .222$) and aINS (L: $F_{(1,36)} = 7.29, p = .011$, $\eta_p^2 = .168$; R: $F_{(1,36)} = 6.07, p = .014$, $\eta_p^2 = .156$) activation.

For the "Happy versus Neutral face" contrast, there was condition-by-personality effects on the left aINS activation ($F_{(1,36)} = 5.04, p = .031$, $\eta_p^2 = .123$).

Values for the above mentioned are displayed in Table 3.10 and depicted in.

Table 3.10: The effect of alcohol on brain response to Specific Facial Expressions in the personality groups. Whole-brain activations are thresholded at $P_{FWE-corrected} \leq .05$ ($k = 10$). A negative t-value is indicative of greater BOLD activity under the placebo than to alcohol condition.

Region of Interest	Alcohol	Placebo	Paired t-tests
Fearful > Neutral: ASSs			
L AMYG	−.99 (.29)	1.35 (.22)	**−5.18**
R AMYG	−1.07 (.29)	1.44 (.22)	**−5.05**
L aINS	−.68 (.24)	.82 (.18)	**−4.45**

Continued on next page

Table 3.10 – continued from previous page

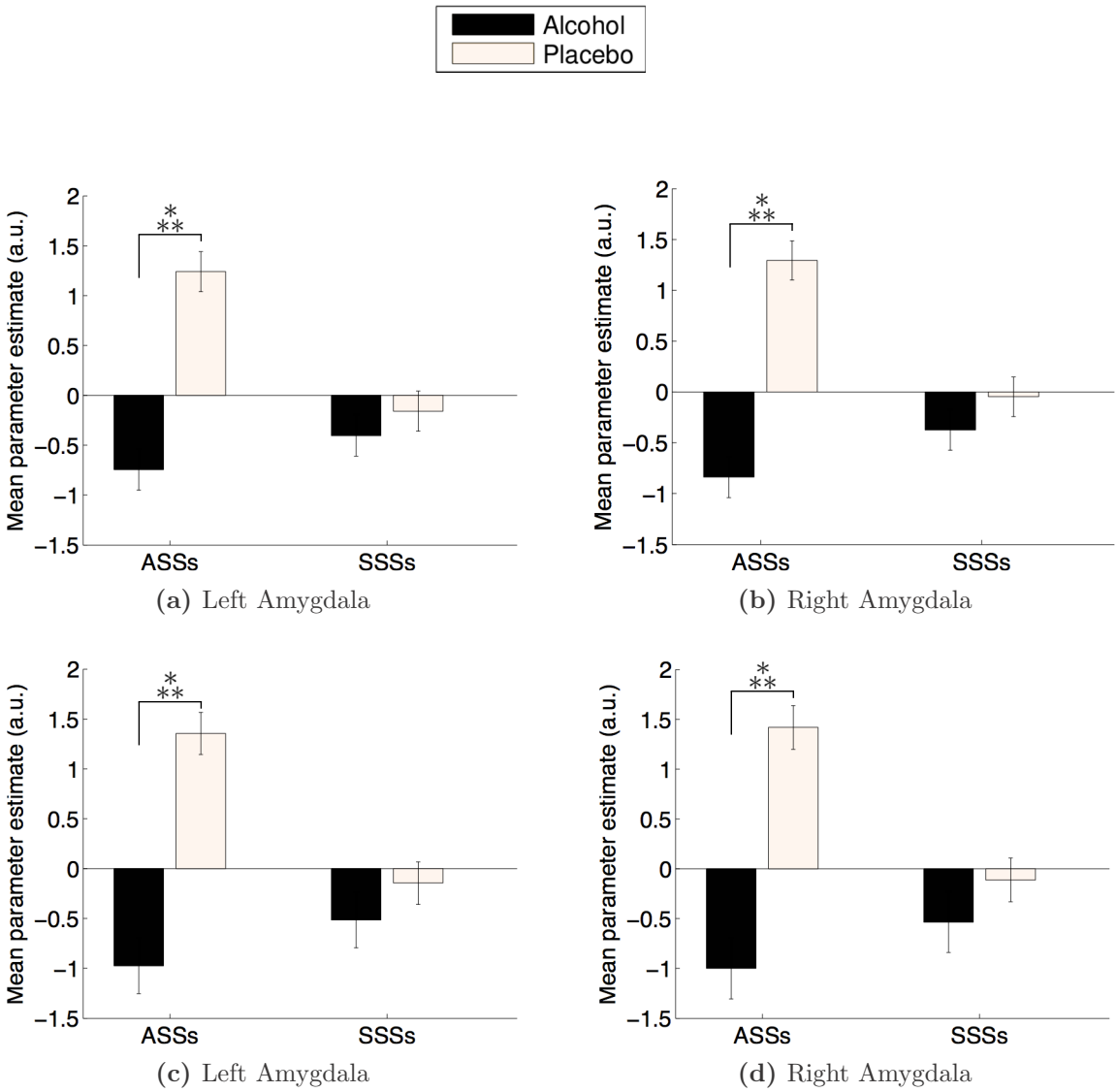
Region of Interest	Alcohol	Placebo	Paired t-tests
R aINS	−.8Q (.24)	.51 (.15)	**−4.72**
L vACC	−.74 (.22)	.75 (.19)	**−3.94**
R vACC	−1.00 (.23)	.86 (.16)	**−5.29**
Fearful > Neutral: SSSs			
L AMYG	−.47 (.27)	−.09 (.22)	−1.58
R AMYG	−.54 (.30)	−.11 (.22)	−1.66
L aINS	−.54 (.25)	−.36 (.18)	−0.78
R aINS	−.47 (.25)	.14 (.15)	**−2.25**
L vACC	−.37 (.23)	−.05 (.19)	−1.43
R vACC	−.66 (.24)	.08 (.16)	**−3.01**
Angry > Neutral: ASSs			
L AMYG	−.86 (.25)	1.19 (.24)	**−4.82**
R AMYG	−.94 (.25)	1.29 (.23)	**−5.29**
L aINS	−.76 (.27)	.70 (.22)	**−4.31**
R aINS	−.85 (.23)	.56 (.14)	**−4.80**
L vACC	−.65 (.18)	.62 (.21)	**−3.86**
R vACC	−.80 (.23)	.83 (.18)	**−4.61**
Angry > Neutral: SSSs			
L AMYG	−.57 (.25)	−.13 (.25)	−1.64
R AMYG	−.57 (.26)	−.08 (.23)	−1.73
L aINS	−.49 (.27)	.05 (.23)	−1.72
R aINS	−.36 (.23)	.35 (.14)	**−2.59**
L vACC	−.34 (.18)	−.05 (.21)	−1.18
R vACC	−.57 (.23)	−.75 (.19)	−1.94
Disgusted > Neutral: ASSs			
L AMYG	−.547 (.22)	1.24 (.23)	**−4.44**
R AMYG	−.679 (.20)	1.34 (.23)	**−5.03**
L aINS	−.341 (.20)	.78 (.23)	**−3.00**
R aINS	−.500 (.16)	.68 (.17)	**−4.70**
L vACC	−.396 (.19)	.73 (.19)	**−3.13**
R vACC	−.628 (.19)	.64 (.20)	**−3.92**
Disgusted > Neutral: SSSs			
L AMYG	−.18 (.23)	.07 (.24)	−0.99
R AMYG	−.20 (.20)	.10 (.24)	−1.29
L aINS	−.12 (.20)	−.02 (.23)	−0.40
R aINS	−.26 (.17)	.25 (.18)	**−2.38**
L vACC	−.22 (.19)	.09 (.19)	−1.222
R vACC	−.55 (.19)	.21 (.20)	**−2.55**
Sad > Neutral: ASSs			
L AMYG	−.71 (.23)	1.05 (.21)	**−4.71**
R AMYG	−.82 (.23)	1.12 (.19)	**−5.11**
L aINS	−.66 (.19)	.52 (.22)	**−3.55**
R aINS	−.69 (.19)	.50 (.16)	**−3.72**

Continued on next page

Table 3.10 – continued from previous page

Region of Interest	Alcohol	Placebo	Paired t-tests
L vACC	−.66 (.18)	.63 (.16)	**−4.80**
R vACC	−.80 (.22)	.73 (.18)	**−5.38**
Sad > Neutral: SSSs			
L AMYG	−.345 (.23)	−.21 (.21)	−0.50
R AMYG	−.217 (.24)	−.02 (.20)	−0.82
L aINS	−.48 (.19)	−.08 (.23)	−1.30
R aINS	−.43 (.19)	.09 (.16)	−2.01
L vACC	−.28 (.19)	−.15 (.17)	−0.69
R vACC	−.43 (.23)	.01 (.18)	−1.47
Surprised > Neutral: ASSs			
L AMYG	−.71 (.29)	1.05 (.21)	**−4.94**
R AMYG	−.67 (.31)	1.19 (.20)	**−4.97**
L aINS	−.67 (.31)	1.19 (.20)	**−5.31**
R aINS	−.85 (.18)	.59 (.20)	**−5.95**
L vACC	−.76 (.22)	.73 (.21)	**−4.48**
R vACC	−.76 (.25)	.82 (.18)	**−6.49**
Surprised > Neutral: SSSs			
L AMYG	−.41 (.30)	−.22 (.21)	−0.50
R AMYG	−.29 (.32)	−.24 (.20)	−0.12
L aINS	−.29 (.32)	−.24 (.20)	−1.32
R aINS	−.27 (.18)	.17 (.20)	−1.38
L vACC	−.17 (.23)	−.14 (.21)	−.177
R vACC	−.25 (.25)	−.20 (.18)	−.193
Happy > Neutral: ASSs			
L AMYG	−.11 (.21)	.31 (.18)	−1.68
R AMYG	.05 (.22)	.58 (.18)	−2.00
L aINS	−.52 (.20)	.61 (.20)	**−4.19**
R aINS	−.50 (.20)	.53 (.19)	−3.55
L vACC	−.29 (.18)	.24 (.15)	−2.64
R vACC	−.02 (.27)	.45 (.12)	−2.00
Happy > Neutral: SSSs			
L AMYG	−.19 (.21)	.11 (.18)	−0.94
R AMYG	.01 (.22)	.11 (.18)	−0.25
L aINS	−.42 (.20)	−.24 (.20)	−0.55
R aINS	−.34 (.21)	−.04 (.19)	−1.04
L vACC	−.25 (.18)	.10 (.15)	−1.47
R vACC	−.35 (.27)	.09 (.13)	−1.23

ASSs = anxiety sensitive subjects; SSSs = sensation-seeking subjects; L = left; R = right; AMYG = amygdala, aINS = anterior insula; vACC = ventral anterior cingulate cortex. Significant mean differences are printed in bold.



(a) Left Amygdala **(b)** Right Amygdala

(c) Left Amygdala **(d)** Right Amygdala

Figure 3.10 Effects of Alcohol on Threat-Related AMYG Activation. ***a*−*d***, Mean parameter estimates (arbitrary units) of mean AMYG activation (y-axes) to negative ***(a*−*b)*** and fearful ***(b*−*c)*** versus neutral faces by personality group (x-axes) under the under alcohol (dark bars) and placebo (light bars) conditions. Significant condition × personality interaction effects were indicated by 3-way mixed-design ANOVAs and survived alpha adjustment to correct for multiple comparisons. ***, $p_{(2-tailed)} \leq .001$ (paired t-test). Error bars indicate SEM. For values, see Table 3.10.

3.2.3 Summary of Results

Under placebo, the personality groups showed distinct behavioral and neural response profiles to face emotion processing: behaviorally, ASSs identified face emotion faster

and a greater rate of neutral faces as emotional and surprised faces as harsh than did SSSs. Neurofunctionally, ASSs reacted to negatively valent and surprised (relative to neutral) faces with greater subcortical, most prominently amygdalar activation. The magnitude of the latter, in response to fearful faces, positively correlated with anxiety sensitivity levels and negatively, pre-FEPT cortisol levels, in ASSs.

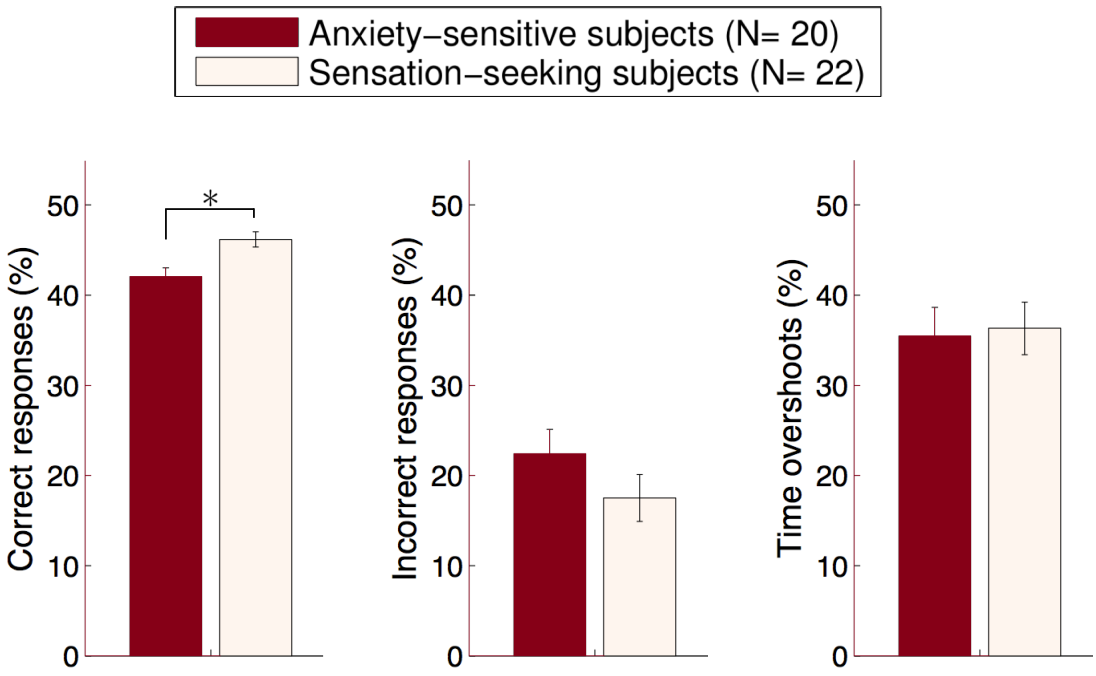
Relative to placebo, alcohol hindered negative face emotion identification accuracy in the entire sample, and resulted in a proclivity to identify emotional faces as neutral in both personality groups but to a greater extent . On a neurofunctional level, alcohol subtantially blunted amygdalae reactivity to negative face emotions in ASSs but left it unaltered in SSSs.

3.3 Montreal Imaging Stress Task

3.3.1 Placebo Condition

3.3.1.1 Behavioral Results

Assessing the effect of personality, sex and an interaction on the performance outcome of the MIST under placebo, two-way ANOVA revealed a significant personality effect on percent correct responses ($F_{(1,37)} = 10.68$, $p = .002$, $\eta^2_{\mathrm{p}} = .224$, Figure 3.11**a**), with SSSs scoring higher on this measure ($M = 46.01, SD = 4.64$) than ASSs ($M = 42.09, SD = 3.31$). Analogous analyses on percent incorrect responses and time overshoots revealed no significant results (Figures 3.11**b** and 3.11**c**, respectively). Means and standard error means are shown in Table 3.11, Figure 3.11.



(a) Correct Responses **(b)** Incorrect Responses **(c)** Time Overshoots

Figure 3.11 ***a-c***, Raw mean scores on performance outcomes, namely correct responses ***(a)***, incorrect responses ***(b)***, and time overshoots ***(c)*** for anxiety sensitive and sensation-seeking subjects (dark and light bars, respectively) under placebo condition. *A significant difference difference at $p \leq .01$. For values, see Table 3.11 below. Error bars indicate SEM.

Table 3.11 Raw mean scores for performance outcomes under placebo by personality groups (standard errors are shown in parentheses).

Performance Outcome	**ASSs**	**SSSs**	**Mean Difference**[†]
Correct Responses[a](%)	42.08 (0.91)	46.17 (0.84)	−4.08[*](1.25)
Incorrect Responses[b](%)	22.41 (2.79)	17.50 (2.58)	4.91 (3.80)
Time Overshoots[c](%)	35.49 (3.15)	36.32 (2.90)	−0.83 (4.28)

Abbreviations: ASSs= anxiety sensitive subjects and SSSs= sensation-seeking subjects.

[*] $p = 0.002$

[†] ASSs > SSSs

[a] Number of correct responses/ number of arithmetic problems presented×100

[b] Number of incorrect responses/ number of arithmetic problems presented×100

[c] Number of time overshoots/ number of arithmetic problems presented×100

3.3.1.2 Subjective Mood Results

Pre-stressor mood. Assessing the effect of personality, sex and an interaction on pre-stressor[20] embarrassment and anger self-ratings under placebo, two-way ANOVAs found significant main personality effects on both mood states: $F_{(1,34)} = 5.07$, $p = .031$, $\eta_p^2 = .130$; and $F_{(1,34)} = 13.85$, $p = .001$, $\eta_p^2 = .289$, respectively. Specifically, greater levels of embarrassment and anger were self-reported by ASSs (respectively, $M = 3.28, SD = 2.46$ and $M = 2.50, SD = 2.04$) than SSSs (respectively, $M = 1.68, SD = 2.17$ and $M = .51, SD = 1.34$). These results are displayed in Figure 3.12. Subsequent correlational analyses (linear regression) revealed that pre-stressor embarrassment self-rating significantly correlated with ASSs' scores on the ASI-Social Concerns subscale ($r(17) = .535, p = .018$).

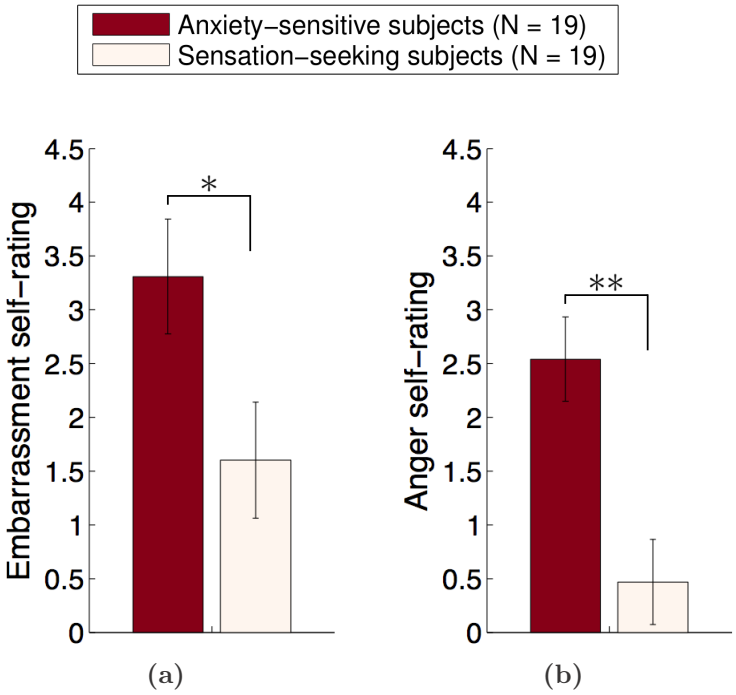
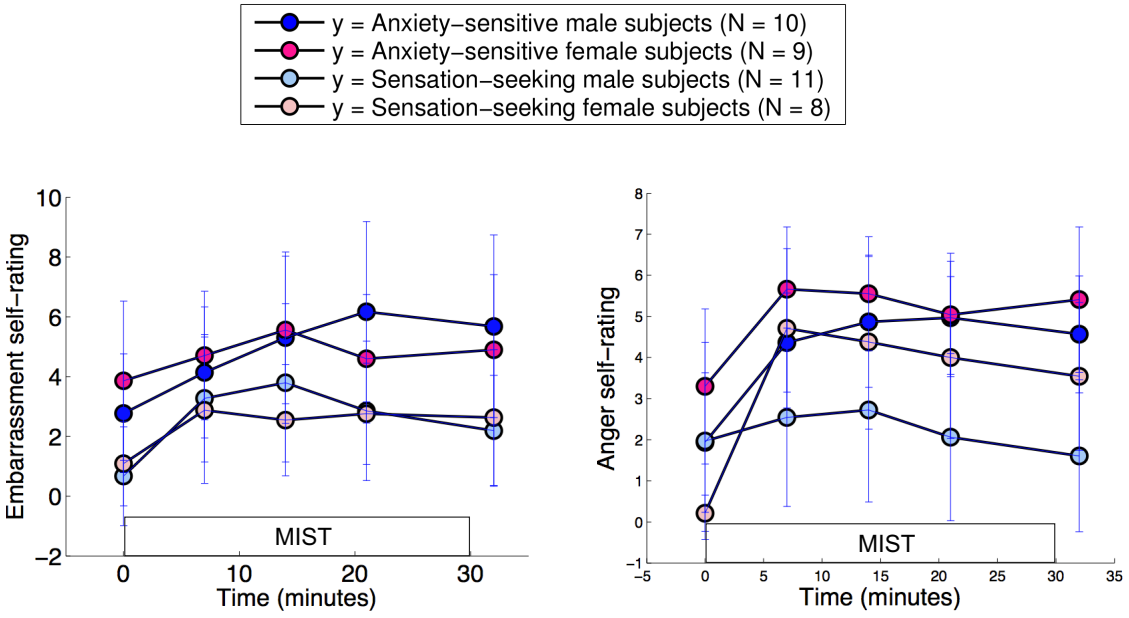


Figure 3.12 ***a-b***, Pre-stressor self-ratings (y-axes) of states embarrassment ***(a)*** and anger ***(a)*** under placebo in the anxiety sensitive (dark bars) and sensation-seeking (light bars) personality groups (x-axes). * and ** signify, respectively, significant main personality effects at $p \leq .05$ and $p \leq .01$.Error bars indicate SEM.

[20] Assessed immediately prior to the beginning of the MIST.

Mood changes related to stress induction. Three-way mixed-design ANOVA assessing the effect of time[21] and its interaction with either and both personality and sex on mood self-ratings revealed a time-by-personality-by-sex effect on embarrassment self-ratings: $F_{(1,32)} = 4.74, p = .037, \eta^2_{\mathrm{p}} = .129$. Decomposition of this 3-way interaction using paired-sample t-tests and an adjusted alpha level of $p = .0125$ (.05/4) per test revealed significant increments in embarrassment for AS male subjects ($t_{(9)} = 3.02, p = .003$) but no significant time effects in the other three subgroups. As for stress-induced increments in self-rated anger, only a main effect of time was found ($F_{(1,32)} = 29.37, p = .000, \eta^2_{\mathrm{p}} = .497$).

Subsequent correlational analyses (linear regression) revealed that embarrassment AUC significantly correlated with ASSs' scores on the ASI-Mental Incapacitation ("Cognitive Dyscontrol") Concerns subscale ($r(17) = .555, p = .014$).



(a) State Embarrassment **(b)** State Anger

Figure 3.13 Subjective mood reactivity profiles of AS and SS male and female subjects during stress session under placebo. a-b, Self-rated intensity on a scale of 0 (not at all) to 10 (very much so) of embarrassment ***(a)*** and anger ***(b)*** states (y-axes) throughout the course of the MIST (x-axes) in ASMs, ASFs, SSMSs and SSFSs (respectively, dark blue, dark pink, light blue and light pink) under placebo.

[21] Throughout the course of the MIST relative to pre-stress (time 0).

3.3.1.3 Endocrine Results

Pre-stressor cortisol levels. Two-way between-subjects ANCOVA, assessing the effect of personality, sex and an interaction on pre-stressor cortisol, with "session time" assigned as a covariate revealed a highly significant personality-by-sex effect: $F_{(1,36)} = 15.11, p = .000, \eta_p^2 = .296$ Decomposition of this 2-way interaction, using two-sample t-tests and an adjusted alpha threshold of .0125 per test (.05/4) showed greater pre-stressor cortisol values in SSM ($M = 0.92$) compared to SSF ($M = 0.53$) subjects ($t_{(20)} = 3.73, p = .001$) and also compared to ASM ($M = 0.54$) subjects ($t_{(20)} = 3.74, p = .001$). Further, ASFSs ($M = 0.83$) also showed greater levels relative to ASMSs ($t_{(17)} = 2.25, p = .038$) and relative to SSFSs ($t_{(17)} = 2.25, p = .038$), but the significance of these differences did not survive correction for multiple comparisons. These results are displayed in Figure 3.14. Significance of the current personality-by-sex effect survived and even increased as a result of additional covariation for parental *care protection*: $F_{(1,34)} = 18.17; p = 0.000, \eta_p^2 = .348$.

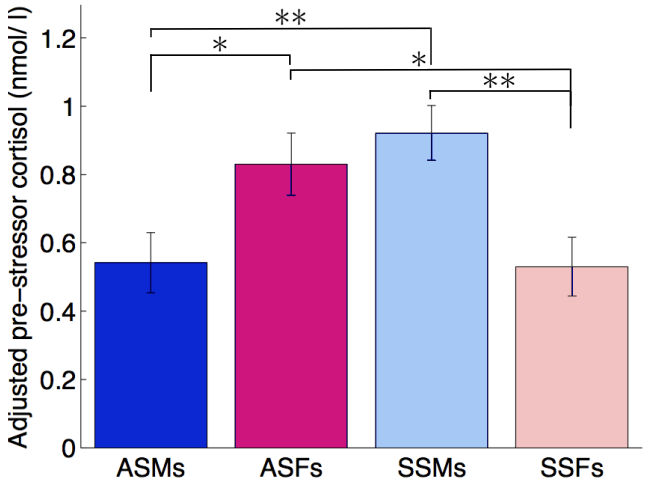


Figure 3.14 Time-adjusted pre-stressor mean cortisol (n/ nmol) levels (y-axis) under placebo in anxiety sensitive and sensation-seeking male and female subjects (x-axis; dark and light blue and pink bars, respectively). A significant personality-by-sex interaction effect was shown by a two-way between-subjects ANCOVA. *, $p < .05$ and **, $p < .01$. Error bars indicate SEM.

Cortisol area-under-the-curve (AUC). Conducting an ANCOVA with cortisol AUC as the dependent variable, personality and sex as fixed factors and "session time" as a covariate, we found a significant main effect of personality ($F_{(1,36)}$) $= 9.49; p = 0.004, \eta_p^2 = .209$); The AS group was more physiologically responsive ($M = .35$ nmol/ l, $SD = 1.22$) than the SS group ($M = -.52$ nmol/ l, $SD = .74$). A significant personality-by-sex interaction effect was also found ($F_{(1,36)} = 6.75; p = 0.014, \eta_p^2 = .158$), and decomposition of this 2-way interaction, using independent-samples t-tests and a Bonferroni adjusted alpha level of .0125 per test (.05/4) showed greater cortisol AUC (nmol/ l) in ASMSs ($M = .90$, $SD = 1.29$) compared to SSMSs ($M = -.62$, $SD = .56$); ($t(20) = 3.65; p = .005$) and also compared to ASFSs), although the latter difference did not survive after adjusting alpha for multiple comparisons; $t(17) = 2.19; p = .043$. These results are displayed in Figure 3.15. Significance of the current personality and personality-by-sex interaction effects held and even increased after assigning *care protection* as additional covariates: $F_{(1,34)} = 14.24; p = 0.001, \eta_p^2 = .295$ and $F_{(1,34)} = 9.06; p = 0.005, \eta_p^2 = .348$, respectively.

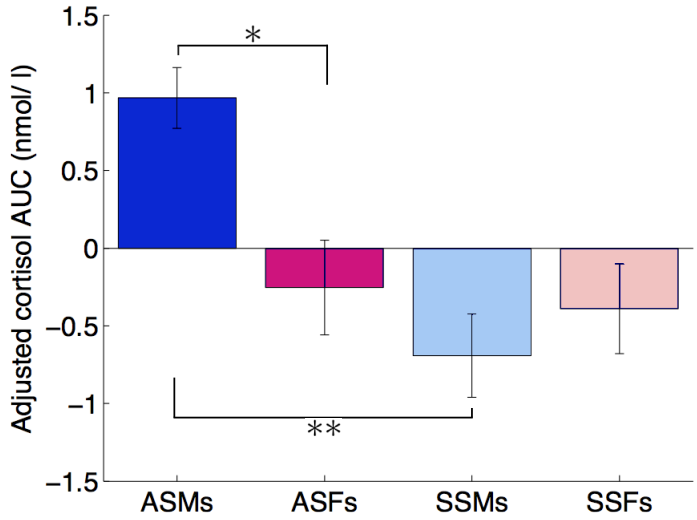


Figure 3.15 Time-adjusted cortisol AUC (n/ nmol) (y-axis) under placebo in anxiety sensitive and sensation-seeking male and female subjects (x-axis; dark and light blue and pink bars, respectively). The personality-by-sex interaction effect, as indicated by two-way between-subjects ANCOVA, was significant at $p < .01$. Error bars indicate SEM.

Psychoendocrine Covariance. Partial correlation analyses, controlling for "session time" indicated a highly significant association between stress-reactive cortisol production (i.e, cortisol AUC) and self-rated embarrassment AUC in the entire sample ($r(33) = .688, p = .000$) under placebo (Figure 3.16). This association, too, remained significant when anger, efficiency, confidence, cheerfulness, relaxation and confusion self-ratings AUC were also controlled for.

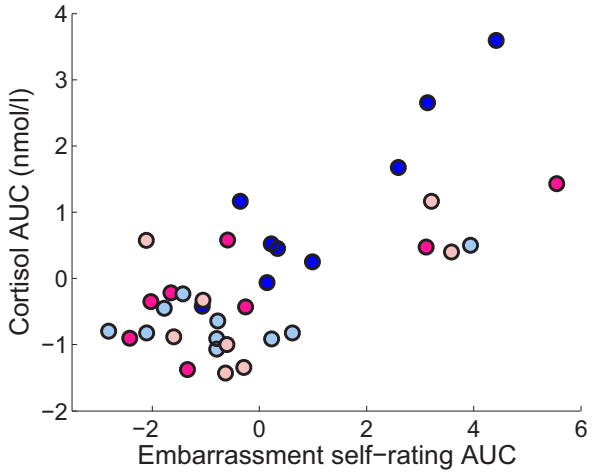


Figure 3.16 Time-adjusted cortisol AUC (n/ nmol; y-axis) positive association with stress-induced increments in subjective embarrassment under placebo, for the entire sample combined ($r(33) = .688, p = .000$). Significant coefficients for these correlations were found using partial correlation analyses (SPSS). Vales displayed scatter graph represent standardized residuals of the correlated variables obtained after regressing values of each participant onto "session time" using linear regression analysis. Scatter graph was produced using Matlab software.

3.3.1.4 Neurofunctional Results

Exploratory voxel-wise analyses. A whole-brain full-factorial GLM random effects analysis thresholded at $p \leq .05$, FWE-corrected for whole brain ($k = 10$), revealed significant main effects of acute psychosocial stress on brain response to the "stress versus nonstress" contrast. These effect were seen in many clusters throughout the brain, and those are depicted in Figure 3.17 and listed in Table 3.12 below.

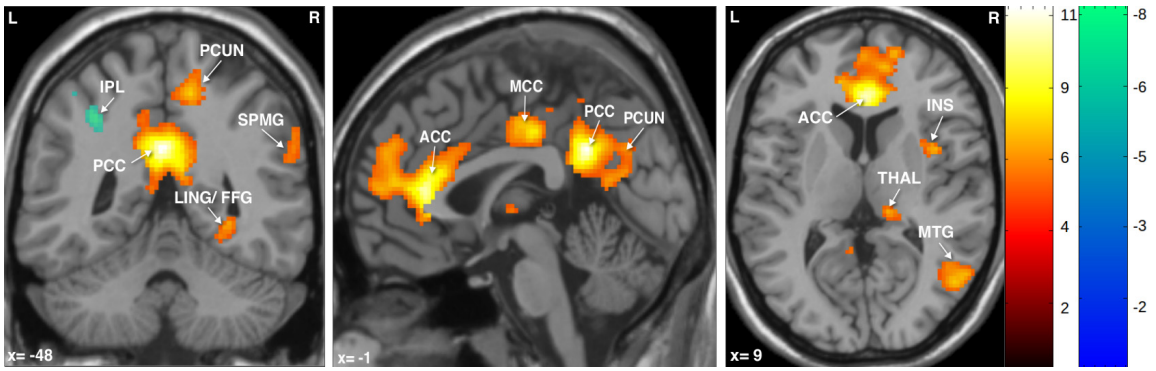


Figure 3.17 Main effects of acute psychosocial stress. $x, y, z =$ sagittal, coronal and horizontal view in MNI coordinates. Activation map was thresholded at $P_{uncorr} < .005$ superimposed on the mean structural image of all subjects. Main effects of acute psychosocial stress were substantially present in the 'salience network'. The color map represents the corresponding F-score. L and R denote, respectively, the left and right sides of the brain.

Table 3.12: Whole-brain response of the entire sample combined to acute psychosocial stress under placebo, at $P_{FWE-corrected} \leq .05, k = 10$

Region (BA)	x	y	z	K_E	***F* value**	P
L CG/ PCC	−4	−46	28	1180	110.56	0.000
L Precuneus (7)	−8	−62	30		66.00	0.000
L PCC (23)	−4	−60	16		49.61	0.001
Bi ACC	0	34	10	1583	101.60	0.000
R ACC	2	28	18		80.04	0.000
L ACC (32)	−16	44	8		63.78	0.000
R Cuneus (19)	16	−92	20	432	93.31	0.000
R Precuneus	16	−72	34		37.62	0.014
R Precuneus (7)	12	−64	30		37.61	0.014
R LING	24	−64	−6	399	76.56	0.000
R LING (18)	18	−76	−8		72.35	0.000
R PHG	26	−52	−6		43.00	0.005
R IPL (40)	54	−30	34	735	63.77	0.000
R INS	56	−36	20		56.97	0.000
R IPL	48	−34	26		53.04	0.001
R MCC (24)	6	−14	42	490	62.68	0.000
L MCC (24)	−2	−20	38		58.92	0.000
R MCC	10	−30	48		48.70	0.002
R INS	40	−8	−8		49.67	0.001
R Thalamus/ pulvinar	12	−28	8	47	59.23	0.000
L IFG	−42	8	32	162	55.53	0.000
L FL/subgyral	−38	14	28		38.46	0.012
L IPL (40)	−48	−42	56	206	54.16	0.001

Continued on next page

Table 3.12 – continued from previous page

Region (BA)	x	y	z	K_E	F value	P
L IPL	−40	−40	42		47.74	0.002
L IPL	−48	−40	46		46.83	0.002
L OL/ Cuneus	−14	−88	26	151	53.49	0.001
L Cuneus (19)	−10	−94	20		49.83	0.001
L Cuneus	−22	−96	−4	84	50.91	0.001
L MOG	−34	−94	−2		34.72	0.027
R Precuneus (7)	10	−48	54	145	50.61	0.001
L SPMG	−46	−54	34	120	50.42	0.001
R Angular (39)	−42	−66	30		37.17	0.016
R MTG	52	−62	8	262	50.32	0.001
R MTG	40	−72	16		41.40	0.006
R STG	46	−54	20		40.07	0.009
L ParaC	−16	−36	50	68	44.26	0.004
R INS (13)	38	6	10	22	44.15	0.004
R PUT	30	8	12		37.37	0.015
L SPL	−28	−64	48	29	41.80	0.006
R IOG	28	−94	−8	25	40.27	0.008
L LING (19)	−24	−74	−10	43	40.02	0.009
LFFG	−28	−58	−6		38.35	0.012
L SFG (8)	−8	38	50	30	38.89	0.011
L MedFG	−8	44	44		37.98	0.013

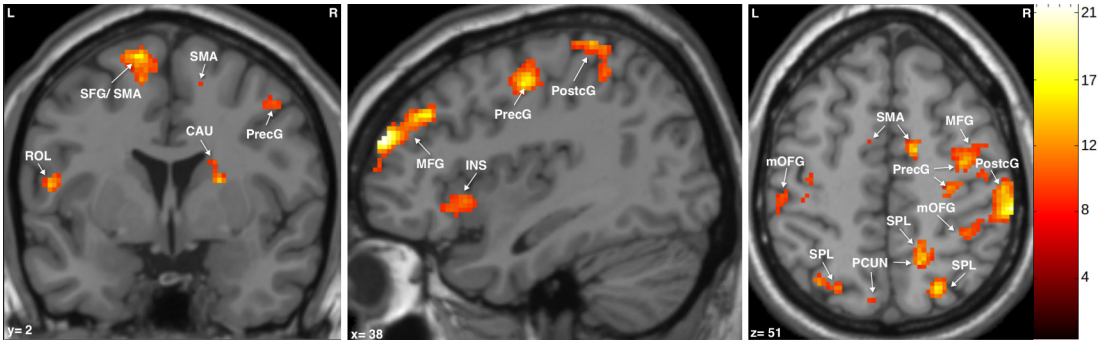
FL = frontal lobe; MFG = middle frontal gyrus, IFG = inferior frontal gyrus; CG = cingulate gyrus; MCC = mid-cingulate cortex; ACC = anterior cingulate cortex; PCC = posterior cingulate cortex;PrecG = precentral gyrus; PostcG = postcentral gyrus; AMYG = amygdala, INS = insula; MTG = middle temporal gyrus; STG = superior temporal gyrus; HC = hippocampus; PHG = parahippocampal gyrus; LING = lingual gyrus; MDN = medial dorsal nucleus; VLN = ventral lateral nucleus.

Peak MNI coordinate region.

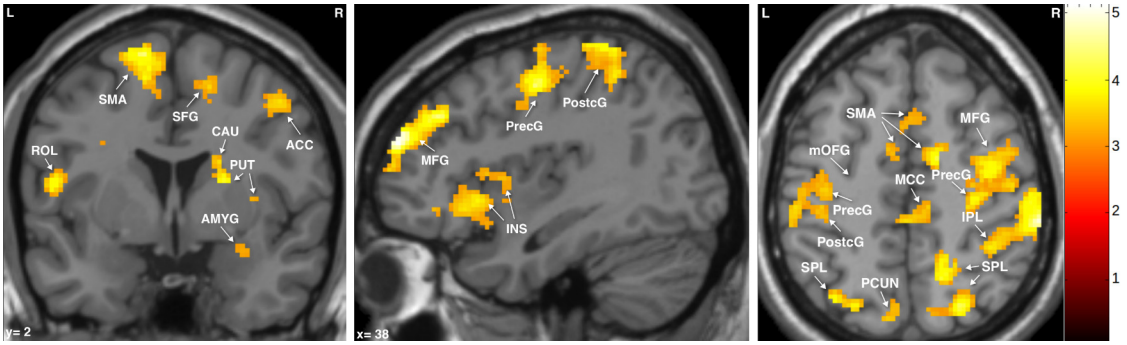
Cluster size in voxels.

[a] No clusters detected.

Next, a whole-brain full-factorial GLM random effects analysis thresholded at $P_{uncorrected} \leq .005$ ($k = 20$), revealed significant main effects of personality on brain response to the "stress versus nonstress" contrast (Figure 3.18**A**, Table 3.13). All personality group activation differences favored the SS group (Figure 3.18**B**. Brain clusters showing significant response change in each personality group in response of the same contrast are displayed in Table 3.14).



(A) Main effect of personality profile



(B) Sensation Seeking Subjects > Anxiety Sensitive Subjects

Figure 3.18 The Effects of Personality Risk Profile on Whole-Brain Activation to Acute Psychosocial Stress Under Placebo. Depicted are the main effects of personality risk profile ***(A)***, and the linear contrast between the personality groups (SSSs > ASSs) ***(B)*** under Stress versus Nonstress. Each panel shows in a coronal (y), sagittal (x) and axial (z) view (in MNI coordinates), activation maps thresholded at $P_{uncorr.} \leq .005$ ($k = 20$), superimposed on the mean structural image of all subjects. The reverse contrast (ASSs > SSSs) yielded no significant results. Color map represents the corresponding t-score. x, y, z = sagittal, coronal and horizontal view in MNI coordinates. L and R correspond to, respectively, the left and right sides of the brain. For values, see Table 3.13. CAU = caudate; IFG = inferior frontal gyrus; INS = insula; IPL = inferior parietal lobule; MCC = mid-cingulate cortex; MFG = middle frontal gyrus; MedFG = medial frontal gyrus; mOFG = medial orbitofrontal gyrus; PCUN = precuneus; SFG = superior frontal gyrus; SPL = superior parietal lobule; SPMG = supramarginal gyrus; PostcG = postcentral gyrus and PrecG = precentral gyrus.

Table 3.13: Effects of personality on whole-brain response to acute psychosocial stress under placebo, at $p \leq .005$, $k = 20$.

Region (BA)	x	y	z	K_E	***F* value**	P
R MFG	36	54	22	455	21.45	0.000
R MFG	34	36	34		18.83	0.000
R MFG (10)	32	46	28		13.60	0.001
R PostcG	58	−32	52	649	20.66	0.000
R IPL (40)	46	−36	60		18.58	0.000
R PostcG (2)	54	−24	52		15.65	0.000
L FL/ subgyral	−32	10	26	141	20.04	0.000
L FL/ subgyral	−40	16	26		16.35	0.000
R MCC (32)	14	24	36	98	19.72	0.000
R MCC (32)	10	18	30		10.53	0.002
R MedFG/ SMA	10	−2	56	117	19.47	0.000
R CG (24)	16	−8	48		16.28	0.000
L MFG (6)	−38	−8	60	151	18.75	0.000
L PrecG (4)	−38	−18	56		13.71	0.001
R Caudate	18	2	22		10.79	0.002
L FL/ SMA	−14	−2	62	361	18.40	0.000
L SFG (6)	−8	4	64		11.46	0.002
L SFG	−14	8	58		11.41	0.002
R SPL (7)	24	−70	54	255	18.38	0.000
R PCUN	14	−56	50		16.43	0.000
R PCUN (7)	20	−66	48		14.27	0.001
R MFG	36	−8	48	374	17.07	0.000
R PrecG	42	−16	50		13.56	0.001
R PrecG	28	−22	52		13.44	0.001
L PCUN	−12	−42	64	61	15.14	0.000
L ParacL (5)	−18	−46	60		10.32	0.003
R PCC (23)	6	−32	26	29	15.07	0.000
L IFG	−60	12	14	110	14.83	0.000
L PrecG	−54	2	12		14.73	0.000
R PostcG	14	−46	66	45	14.57	0.000
R INS (13)	56	−38	20	55	14.54	0.000
L SPL	−34	−66	54	104	14.33	0.001
L SPL (7)	−24	−70	48		13.64	0.001
R IPL	60	−26	24	25	13.73	0.001
R IFG/ INS (47)	36	18	−4		12.86	0.001
R FL/ subgyral	30	8	−14		11.76	0.001
R SFG	26	62	0	64	13.37	0.001
R MFG (10)	26	56	−6		11.83	0.001
R SFG	20	54	4		9.75	0.003
L MedFG	−4	10	48	69	12.85	0.001
R Claustrum	34	4	6	39	12.83	0.001

Continued on next page

Table 3.13 – continued from previous page

Region (BA)	x	y	z	K_E	F value	P
R INS	36	14	8		10.10	0.003
L PostcG (2)	−40	−28	50	64	12.80	0.001
L PostcG	−52	−28	50		10.54	0.002
L PCUN	−10	−76	48	42	11.75	0.001
L ParacL (5)	−2	−32	52	48	11.67	0.002
R ParacL/ MCC	6	−28	50		10.95	0.002
L Cerebellum	−10	−74	−22	24	11.59	0.002
L Cerebellum	−30	−62	−32	20	11.52	0.002
R Cerebellum/ LING	8	−68	−10	26	11.10	0.002
R LING	8	−78	−12		9.94	0.003
Bi Thalamus	0	−14	8	26	10.44	0.003

ASSs = anxiety sensitive subjects; SSSs = sensation-seeking subjects; FL = frontal lobe; MFG = middle frontal gyrus, IFG = inferior frontal gyrus; CG = cingulate gyrus; MCC = mid-cingulate cortex; ACC = anterior cingulate cortex; PCC = posterior cingulate cortex; thalamus PrecG = precentral gyrus; PostcG = postcentral gyrus; AMYG = amygdala, INS = insula; MTG = middle temporal gyrus; STG = superior temporal gyrus; HC = hippocampus; PHG = parahippocampal gyrus; LING = lingual gyrus;

Peak MNI coordinate region.

Cluster size in voxels.

[a] No clusters detected.

Table 3.14: Whole-Brain Response to Acute Psychosocial Stress Under Placebo by Personality Group, at $P_{FWE-corrected} \leq .05, k = 10$

Region (BA)	x	y	z	K_E	T score	P
ASSs: stress > nonstress						
L CG/ PCC	−2	−48	30	528	8.03	0.000
R PCC (23)	4	−46	22		7.45	0.000
L CG (31)	−10	−58	28		6.26	0.005
R Cuneus (18)	18	−90	22	60	7.41	0.000
Bi	0	32	8	149	7.38	0.000
Bi ACC	0	26	18		5.82	0.017
Bi MCC	0	−20	38	44	6.10	0.008
R LING (18)	18	−76	−8	10	5.94	0.012
L IPL (40)	−48	−42	56	263	− 8.19	0.000
L IPL	−48	−40	44		− 6.86	0.001
L PostG (40)	−54	−38	52		− 6.45	0.003
L IFG	−42	6	34	448	− 7.83	0.000
L FL/ subgyral	−38	16	26		− 7.71	0.000
L FL/ subgyral	−32	10	28		− 7.27	0.000

Continued on next page

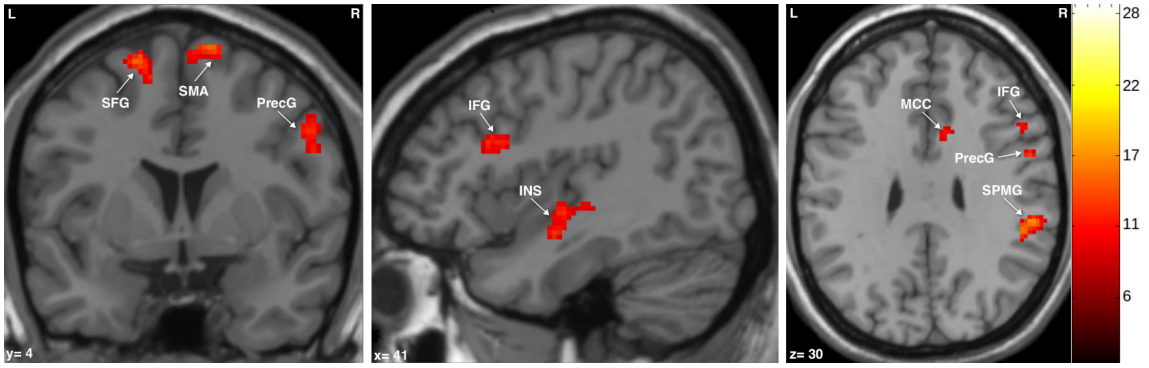
Table 3.14 – continued from previous page

Region (BA)	x	y	z	K_E	T score	P
L Precuneus (7)	−24	−72	50	290	− 7.32	0.000
L SPL	−28	−64	44		− 7.30	0.000
L SPL (7)	−30	−68	54		− 7.03	0.001
R SPL	30	−70	54	150	− 6.89	0.001
R IPL	36	−58	42		− 6.75	0.001
L Cuneus/ MOG	−22	−96	−4	108	− 6.56	0.002
L MOG (18)	−36	−92	−2		− 6.13	0.007
L MOG	−42	−86	−2		− 5.69	0.024
L IFG	−38	34	12	32	− 6.11	0.008
R IOG	34	−92	−8	84	− 6.07	0.008
R IOG	42	−84	−10		− 6.06	0.009
R MOG	26	−98	−2		− 6.06	0.009
L MFG (46)	−46	30	20	19	− 5.91	0.013
L IFG	−52	6	16	11	− 5.79	0.018
SSSs: stress > nonstress						
R ACC (24)	2	34	12	343	7.33	0.000
R FL/ subgyral	2	28	18		6.98	0.001
L PCC	−4	−46	28	162	7.25	0.000
R INS	56	−36	20	353	7.02	0.001
R IPL	60	−26	26		6.52	0.003
R IPL (40)	56	−30	32		6.28	0.005
R Cuneus (19)	16	−92	20	144	6.84	0.001
R Cuneus	18	−86	26		6.60	0.002
R LING/ FFG	24	−66	−8	109	6.71	0.002
R LING (18)	18	−76	−8		6.15	0.007
R MCC (31)	16	−26	44	52	6.22	0.006
R FL/ subgyral/ MCC	10	−30	48		5.99	0.011
R MCC (24)	6	−14	42	45	6.09	0.008
R INS	38	−12	−2	23	6.05	0.009
R Thalamus	14	−30	8	14	6.05	0.009
R MTG	48	−62	8	42	5.93	0.012
R MedFG	14	48	6	18	5.90	0.013
L Precuneus (7)	−8	−62	30	15	5.88	0.014
R Precuneus (7)	10	−48	54	24	5.84	0.016
R ParacL	8	−42	60		5.50	0.038
R INS	34	6	8	12	5.78	0.018

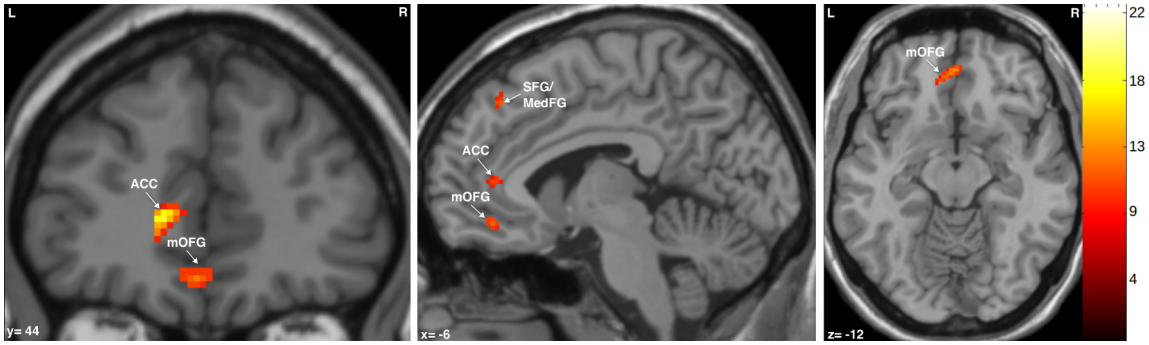
ASSs = anxiety sensitive subjects; SSSs = sensation-seeking subjects; FL = frontal lobe; MFG = middle frontal gyrus, IFG = inferior frontal gyrus; CG = cingulate gyrus; MCC = mid-cingulate cortex; ACC = anterior cingulate cortex; PCC = posterior cingulate cortex; thalamus PrecG = precentral gyrus; PostcG = postcentral gyrus; AMYG = amygdala, INS = insula; MTG = middle temporal gyrus; STG = superior temporal gyrus; HC = hippocampus; PHG = parahippocampal gyrus; LING = lingual gyrus.

Peak MNI coordinate region.
Cluster size in voxels.
[a] No clusters detected.

Examining the main effects of sex, the same whole-brain full-factorial GLM random effects analysis, thresholded at $P_{uncorrected} \leq .005$ ($k = 20$), revealed significances in a number of brain clusters (Figure 3.19**A**, Table 3.15). A personality-by-sex interaction effect was also found demonstrated by brain clusters and was mainly driven by SSMSs (Figure 3.19**B**, Table 3.15).



(A) Main effect of sex.



(B) Personality-by-sex interaction effect.

Figure 3.19 ***A-B***, The effects of sex ***(A)***, and personality-by-sex interaction ***(B)*** on the brain response to acute psychosocial stress under placebo. Activation maps were thresholded at $P_{uncorr.} \leq .005$ ($k = 20$), superimposed on the mean structural image of all subjects. x, y, z = sagittal, coronal and horizontal view in MNI coordinates. L and R correspond to, respectively, the left and right sides of the brain. For values, see Table 3.15. ACC = anterior cingulate cortex; CAU = caudate; IFG = inferior frontal gyrus; INS = insula; MCC = mid-cingulate cortex; MFG = middle frontal gyrus; MedFG = medial frontal gyrus; mOFG = medial orbitofrontal gyrus; PCUN = precuneus; SFG = superior frontal gyrus; SPL = superior parietal lobule; SPMG = supramarginal gyrus; PostcG = postcentral gyrus and PrecG = precentral gyrus.

Table 3.15: The Effects of Sex and Personality-by-Sex Interaction on Whole-Brain Activation to Acute Psychosocial Stress Under Placebo at $p < .005$, $k = 20$.

Region (BA)	x	y	z	K_E	***F* value**	P
Sex						
R PostcG/ SPMG (2)	54	−30	36	311	28.19	0.000
R IPL/ SPMG	50	−36	28		17.89	0.000
R SFG	10	4	72	80	15.00	0.000

Continued on next page

Table 3.15 – continued from previous page

Region (BA)	x	y	z	K_E	F value	P
L INS	−42	−8	16	104	14.98	0.000
L INS (13)	−34	−2	16		12.62	0.001
L MFG	−18	2	66	86	14.85	0.000
L Cerebellum	−36	−52	−30	83	14.19	0.001
L Cerebellum	−44	−56	−32		12.71	0.001
R TL/ subgyral	40	−8	−14	132	13.96	0.001
R INS	40	−12	−6		13.25	0.001
R INS	40	−22	−2		11.51	0.002
R FL/ subgyral	38	20	20	113	13.65	0.001
R FL/ subgyral	42	14	24		12.84	0.001
R INS (13)	34	16	14		10.71	0.002
R PrecG	52	2	30	116	13.53	0.001
R FL/ subgyral	48	18	32		12.83	0.001
R IFG/ PrecG (9)	50	6	38		12.74	0.001
L INS	−36	10	−6	35	13.19	0.001
L Cerebellum	−4	−54	−4	100	12.82	0.001
L Cerebellum	−2	−68	−12		10.50	0.002
R Cerebellum	2	−48	−2		9.71	0.003
L FL/ subgyral	−40	16	26	52	12.77	0.001
L FL/ subgyral	−32	14	24		12.66	0.001
L MFG	−48	16	32		10.71	0.002
Bi midbrain	0	−38	−24	41	12.38	0.001
R Cerebellum	2	−40	−32		10.96	0.002
R MCC	8	14	30	40	12.36	0.001
R LING/ PHG	20	−42	−4	22	11.94	0.001
R STG	44	−46	12	27	11.71	0.002
L INS (13)	−42	12	6	20	11.54	0.002
L FL/ subgyral	−36	12	16		10.63	0.002
L MFG	−28	32	28	32	11.19	0.002
L MFG	−34	34	22		10.29	0.003
L MFG	−34	40	28		9.45	0.004
L INS/ STG (13)	−48	−38	20	40	10.91	0.002
L PL/ subgyral	−38	−36	24		9.90	0.003
Personality-by-Sex						
L MedFG (10)	−16	46	6	206	24.36	0.000
L MedFG/ mOFG	−2	46	−12		14.30	0.001
L MedFG/ mOFG	−10	46	−6		11.64	0.002
L MedFG	−10	36	44	47	16.99	0.000
L SPMG	−52	−48	26	60	16.49	0.000
R ACC	8	42	10	27	12.19	0.001
R MFG	30	56	12	108	11.83	0.001
R SFG	28	60	2		11.82	0.001
R SFG	20	58	12		10.16	0.003

ASSs = anxiety sensitive subjects; SSSs = sensation-seeking subjects; FL = frontal lobe; MFG = middle frontal gyrus, IFG = inferior frontal gyrus; CG = cingulate gyrus; MCC = mid-cingulate cortex; ACC = anterior cingulate cortex; PCC = posterior cingulate cortex; thalamus PrecG = precentral gyrus; PostcG = postcentral gyrus; AMYG = amygdala, INS = insula; MTG = middle temporal gyrus; STG = superior temporal gyrus; HC = hippocampus; PHG = parahippocampal gyrus; LING = lingual gyrus; MDN = medial dorsal nucleus; VLN = ventral lateral nucleus.

Peak MNI coordinate region.

Cluster size in voxels.

[a] No clusters detected.

ROIs analyses. Two-way between-subjects ANOVAs performed for each of our functional ROIs, bilaterally, revealed a significant personality × sex interaction effect on the mOFG activity, bilaterally (L: $F_{(1,38)} = 9.16$; $P = .004$; $\eta_p^2 = .194$; R: $F_{(1,38)} = 7.01$, $P = .012, \eta_p^2 = .156$). Decomposition of this 2-way interaction using post-hoc two-sample t-tests thresholded at a Bonferroni adjusted alpha of $p = .025$, indicated statistically greater activation in SSMSs (L:$M = .80, SD = 1.5$; R: $M = .64, SD = 1.61$) compared with SSFSs (L:$M = -.64, SD = .95$; R: $M = -.64, SD = .95$) and ASMSs (L:$M = -.47, SD = .61$; R: $M = -.47, SD = .61$; Figure 3.20**A**).

A significant effect of personality profile on aINS activity, bilaterally, was also found, though its significance did not withstand correction for multiple comparisons (L: $F_{(1,38)} = 4.24$; $p = 0.046, \eta_p^2 = .100$; R: $F_{(1,38)} = 5.12$, $p = 0.028, \eta_p^2 = .121$; Figure 3.21**A**). Main effect of personality on aINS activity (L: $F_{(1,38)} = 4.24$; $p = 0.046, \eta_p^2 = .100$; R: $F_{(1,38)} = 5.12$, $p = 0.028, \eta_p^2 = .121$), with greater activation being seen in the SS (L:$M = .58, SD = 1.04$; R: $M = .08, SD = .56$) than AS group (L:$M = -.001, SD = .51$; R: $M = .08, SD = 1.30$)

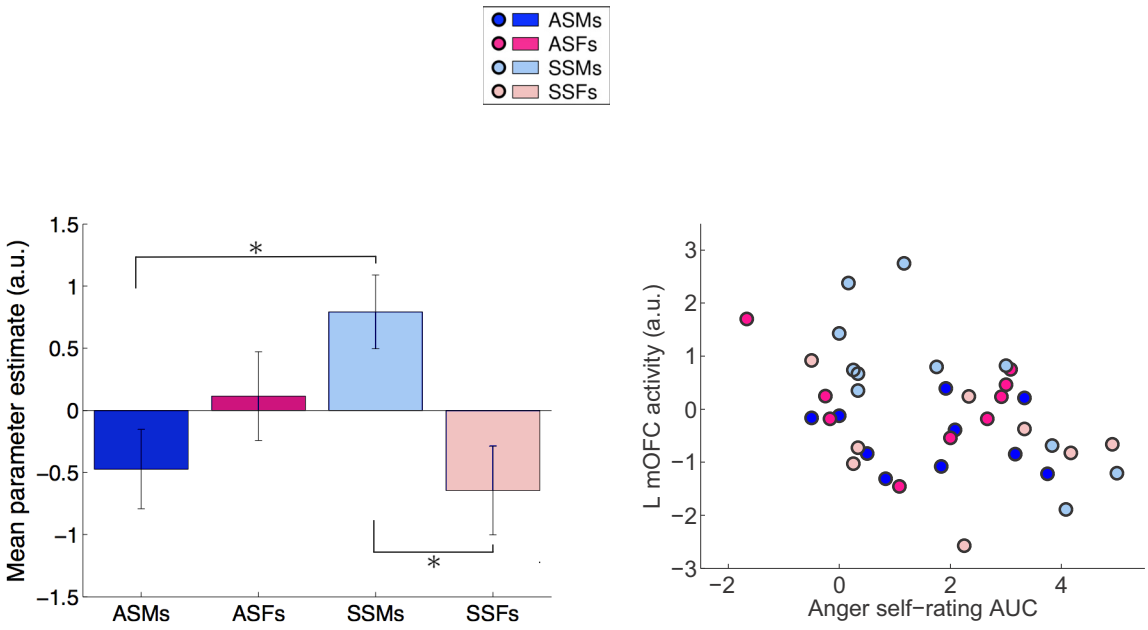
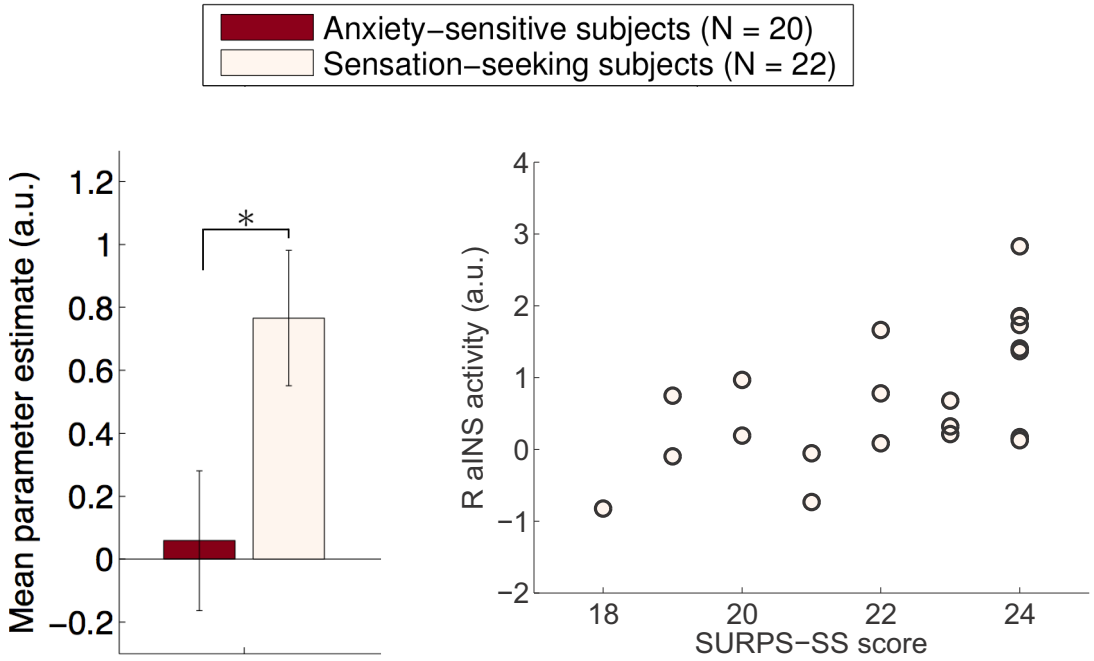


Figure 3.20 Medial Orbitofrontal activation differences and its relation to subjective Anger in the context of acute psychosocial stress under placebo. Depicted in ***(A)*** are the parameter estimates (arbitrary units) in left mOFG activation ($y-axis$) for each of the four subgroups ($x-axes$). The personality $\times$ sex interaction effect on this region's activity was significant. An asterisk (*) denotes a significant difference at Bonferroni adjusted $p \leq .025$. See text for values. Depicted in ***(B)*** is the significant correlation between stress-related increments in self-rated anger ($x-axis$) and parameter estimates (arbitrary units) of mean left mOFG activity ($y-axis$), in the entire sample combined ($r(38) = -.408, p = .011$)



(A) R aINS Activation to Stress by Personality Group.

(B) Association of R aINS activity with sensation-seeking trait.

Figure 3.21 Anterior insular Activation Differences and Its Relationship with Sensation-Seeking Scores In the Context of Acute Psychosocial Stress Under Placebo.. Depicted in ***(A)*** are the parameter estimates (arbitrary units) in right aINS activation ($y-axis$) for the AS and SS groups (dark and light bars, respectively; $x-axes$). * $p < .05$. See text for values. Depicted in ***(B)*** is the significant correlation between right aINS activity ($y-axis$) and SURPS-SS scores ($x-axis$), uniquely in the SS group ($r(20) = .556, p = .007$)

Correlational analyses.

3.3.2 Alcohol Condition

3.3.2.1 Behavioral Results

Using three-way mixed-design ANCOVA to assess for the effects of alcohol and its interaction with personality and sex on performance outcome on the MIST with BAC throughout the MIST assigned as a covariate, a significant condition-by-personality interaction effect on percent correct responses was found: $F_{(1,36)} = 16.62, p = .000, \eta^2_{\mathrm{p}} = .316$ (Table 3.11, Figure 3.22). Paired-sample t-tests indicated this performance outcome was, relative to placebo, significantly better in ASSs ($t_{(18)} = 3.245$, $p_{(2-tailed)}$

= .004) but worse in SSSs ($t_{(21)} = 2.732$, $p_{(2-tailed)} = .012$) under the influence of alcohol, although significance of said change in the SS group did not survive Bonferroni correction for multiple comparisons (Table 3.16, Figure 3.22). Results for incorrect responses and time overshoots were not significant (Table 3.11).

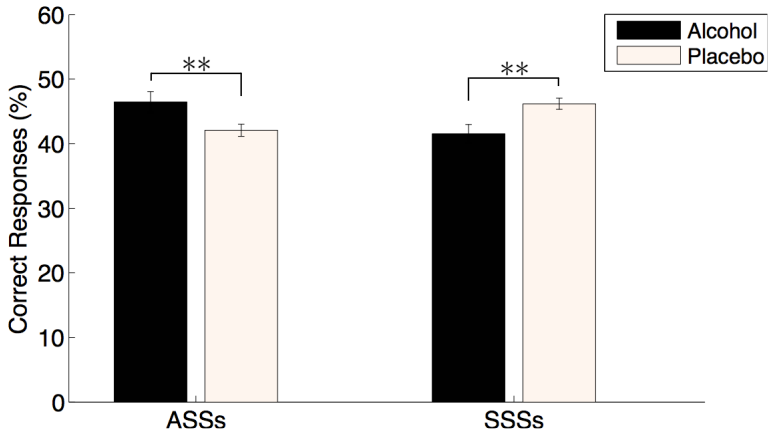


Figure 3.22 Condition Differences in performance outcomes on the MIST by personality group. Covarying for BAC Double artesik signifies significant $^{**}p_{(2-tailed)} < .025$.

Table 3.16 Mean condition differences in performance outcomes (standard error mean) on the MIST by personality group.

Performance Measure	Alcohol	Placebo	Mean Difference[†]
Correct Responses (%)			
ASSs	46.46 (1.62)	42.08 (0.96)	**4.27 (1.32)**
SSSs	41.52 (1.48)	46.18 (0.87)	**−4.36 (1.60)**
Incorrect Responses (%)			
ASSs	24.61 (3.32)	22.76 (2.90)	2.54 (2.42)
SSSs	22.80 (3.03)	17.26 (2.65)	4.83 (3.73)
Time Overshoots (%)			
ASSs	28.91 (3.21)	35.16 (3.27)	−6.82 (2.62)
SSSs	35.66 (2.93)	36.56 (2.98)	−0.47 (3.02)

Abbreviations: ASSs, anxiety sensitive subjects; SSSs, sensation-seeking subjects.
Significant mean differences are printed in bold.

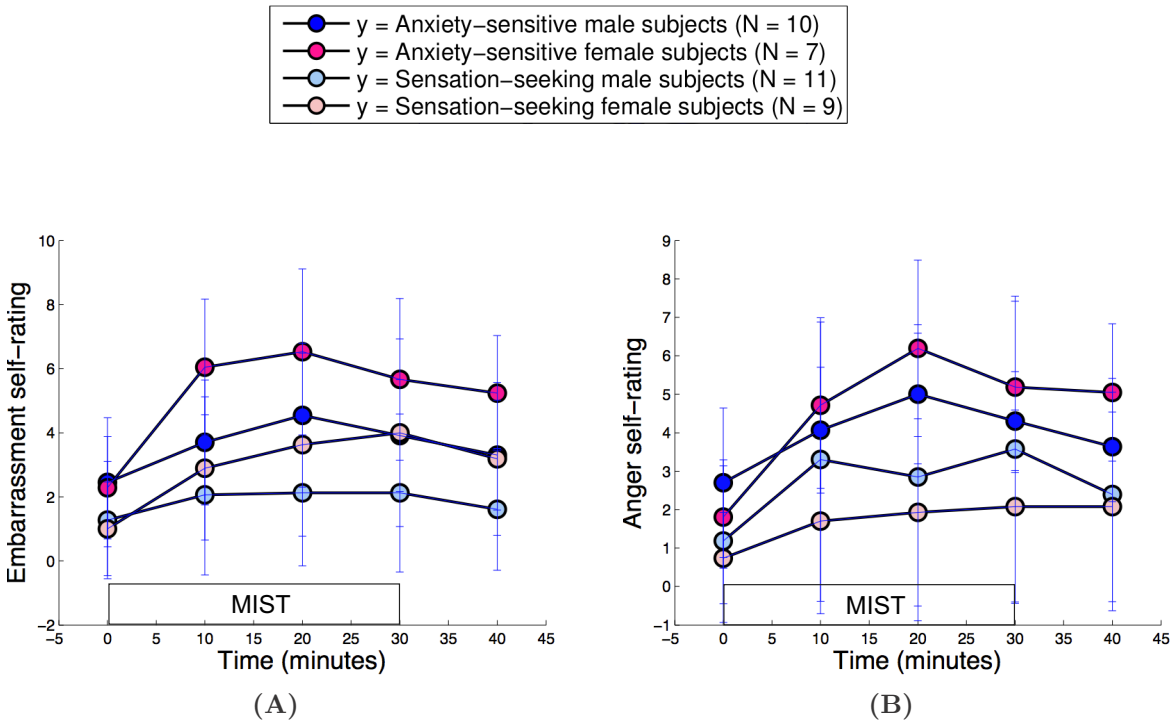
[†] Alcohol > Placebo
[*] $p < 0.025$

3.3.2.2 Subjective Mood Results

Pre-stressor mood self-ratings. Three-way mixed-design ANCOVA indicated no significant effects of condition (alcohol or placebo) or an interaction with either or both personality and sex on pre-stressor self-rating of embarrassment or anger, with pre-stressor BAC being assigned as a covariate.

Stress-reactive change in mood self-ratings. Three-way mixed-design ANCOVA indicated no significant effects of condition (alcohol or placebo) or an interaction with either or both personality and sex on stress-related changes in self-rating of embarrassment (Figure 3.23**A**) or anger (Figure 3.23**B**), with the average of BAC measurements throughout the MIST covaried for.

Assessing the effects of alcohol and its interaction with either and both personality and sex on stress-related changes in embarrassment and anger self-ratings (Figure 3.23), 3 -way mixed-design ANOVAs, covarying for BAC throughout the course of the MIST were conducted. These tests revealed no significant results ($p > .1$).



(A) **(B)**

Figure 3.23 ***A-B***, Change in self-rated embarrassment ***(A)*** and anger ***(B)*** throughout the course of the MIST (at 0 min, +10 min, +20 min, +30 min and +40 min; y-axes) under alcohol in ASM, ASF, SSM and SSF subjects (respectively, dark blue, dark pink, light blue and light pink circles).

3.3.2.3 Endocrine Results

Pre-stressor cortisol. Three-way mixed-design ANCOVA, covarying for pre-stressor BAC and "session time" under each alcohol and placebo conditions, found a significant condition-by-personality-by-sex interaction effect on pre-stressor cortisol levels: $F_{(1,34)} = 6.91$, $p = .013$, $\eta^2_{\mathrm{p}} = .169$. This significance was amplified by additional covariation for early-life parental care and protection: $F_{(1,32)} = 9.71$, $p = .004$, $\eta^2_{\mathrm{p}} = .233$.

Decomposing said three-way interaction, paired-sample t-tests indicated a significant decrease of pre-stressor cortisol levels in SSMSs when alcohol intoxicated relative to sober ($t_{(11)} = 2.89$, $p_{(2-tailed)} = .015$; Table 3.17). This change was nonetheless no longer significant when alpha level was adjusted ($p = .0125$ per test) to correct for multiple comparisons.

Table 3.17 Time- and BAC- adjusted means (standard error of sample mean) of pre-stressor cortisol (nmol/l) as a Function of Personality and Sex in the context of the MIST under alcohol and placebo conditions.

Pre-stressor cortisol (nmol/l)	**Alcohol**	**Placebo**	**Paired t-test**[†]
ASMSs	.88 (.13)	.54 (.09)	1.28
ASFSs	.62 (.14)	.83 (.09)	−1.57
SSMSs	.68 (.12)	.91 (.08)	−2.88[a]
SSFSs	.68 (.13)	.52 (.09)	1.35

MIST, Montreal Imaging Stress Task; BAC, blood alcohol curve; AUC, area under the curve; ASMSs and ASFSs, anxiety sensitive male and female subjects, respectively; SSMSs and SSFSs, sensation-seeking male and female subjects, respectively.

[†] Alcohol > Placebo

[a] $p_{(2-tailed)} \leq .05$

Stress-reactive cortisol. Three-way mixed-design ANCOVA, covarying for BAC throughout the course of the MIST and "session time" under each alcohol and placebo conditions, found significant condition-by-personality-by-sex and condition-by-personality-by-sex interaction effects; respectively, $F_{(1,34)} = 4.57$, $p = .040$, $\eta^2_{\mathrm{p}} = .119$ and $F_{(1,34)} = 7.83$, $p = .008$, $\eta^2_{\mathrm{p}} = .187$ (Figure 3.24). These significance were amplified by additional covariation for early-life parental care and protection: respectively, $F_{(1,32)} = 5.73$, $p = .023$, $\eta^2_{\mathrm{p}} = .152$ and $F_{(1,32)} = 8.18$, $p = .007$, $\eta^2_{\mathrm{p}} = .204$.

Decomposing said two− and three− way interactions, paired-sample t-tests showed that under the influence of alcohol relative to placebo, SSM subjects showed significant increments in cortisol AUC ($t_{(11)} = 2.27$, $p_{(2-tailed)} = .044$), ASM subjects showed significant decrements ($t_{(9)} = 2.28$, $p_{(2-tailed)} = .049$), whereas the female subgroups had no significant change, nor did the same-personality opposite-sex subjects analyzed together. The previously noted significances, however, did not survive Bonferroni correction for multiple comparisons.

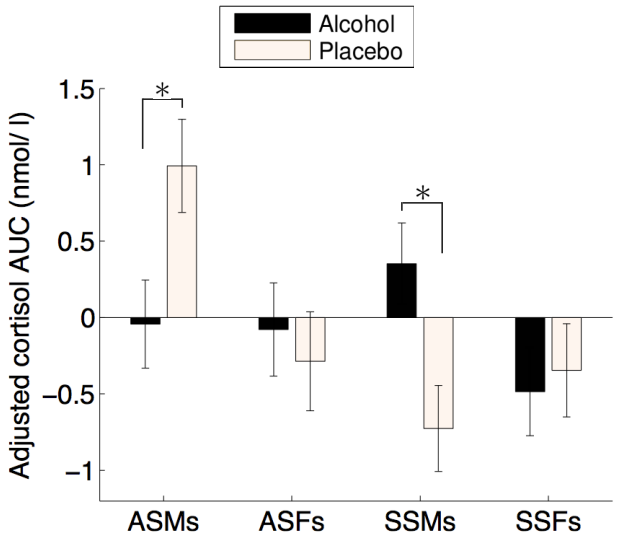


Figure 3.24 Time- and BAC- adjusted means of cortisol AUC ($n/nmol$) levels under alcohol (dark bars) and placebo (light bars) in anxiety sensitive and sensation-seeking male and female subjects (respectively, ASMs, ASFs, SSMSs and SSFs) in the context of the MIST. A significant condition-by-personality-by-sex interaction effect was indicated by three-way mixed-design ANCOVA, covarying for "session time" under each condition and BAC readings obtained throughout the course of the task. * $P_{(2-tailed)} \leq .05$. For values, see Table 3.17. Error bars indicate SEM.

Table 3.18 Time- and BAC- adjusted means (standard error of sample mean) of stress-reactive cortisol (cortisol AUC; nmol/l) as a function of personality and sex in the context of the MIST under alcohol and placebo conditions.

Cortisol AUC (nmol/l)	**Alcohol**	**Placebo**	**Paired t-test**[†]
ASMSs	−0.04 (.29)	0.99 (.31)	−2.27[a]
ASFSs	−0.07 (.31)	-0.28 (.32)	0.39
SSMSs	0.35 (.27)	−0.72 (.28)	2.27
SSFSs	−0.48 (.29)	−0.34 (.31)	−0.24[a]

MIST, Montreal Imaging Stress Task; SE_M, standard error of sample mean; BAC, blood alcohol curve; AUC, area under the curve; ASMSs and ASFs, anxiety sensitive male and female subjects, respectively; SSMSs and SSFs, sensation-seeking male and female subjects, respectively.

[†] Alcohol > Placebo

[a] $p_{(2-tailed)} \leq .05$

3.3.2.4 Neurofunctional Results

Exploratory voxel-wise analyses. Examining the effects of alcohol and its interaction with either or both personality and sex on brain response to acute psychosocial stress, whole-brain analyses, thresholded at $p_{uncorr} < .005$ ($k = 20$) revealed main effects of alcohol as well as condition-by-personality, condition-by-sex and condition-by-personality-by-sex interactions (Table 3.19, Figure 3.25).

Table 3.19 Main effect of alcohol and its interaction with either and both personality and sex on Whole Brain Response to Acute Psychosocial Stress. All significances found at $p_{uncorr} < .005, k = 20$.

Region	x	y	z	K_E	F value	P_{uncorr}
Condition						
L MFG	−42	52	16	23	12.52	0.001
L IFG/ MFG(46)	−46	44	16		12.23	0.001
L SFG	−14	46	34	66	12.25	0.001
L SFG	−8	54	32		11.90	0.001
Condition-by-personality						
R SFG/ mOFG	20	56	−14	34	13.40	0.001
R SFG/ mOFG	28	54	−10		12.47	0.001
L SFG	−30	−8	68	22	11.75	0.001
L PrecG (6)	−26	−14	72		9.87	0.003
Condition-by-sex						
L ACC/ Caudate	−4	16	−6	72	14.25	0.001
L FL/ RecG (11)	−4	26	−2		12.93	0.001
L ACC	−10	24	−10		11.27	0.002
R MFG	40	8	8	44	11.88	0.001
Condition-by-personality-by-sex						
L MedFG/ Rectus (11)	−4	46	−16	1136	26.50	0.000
R ACC	10	32	−8		24.99	0.000
L ACC (10)	−16	50	0		24.64	0.000
R MFG	22	34	−12	195	20.23	0.000
R FL/ subgyral	24	20	−12		13.49	0.001
R IFG (47)	16	30	−18		12.87	0.001
L IFG (45)	−54	18	18	37	12.21	0.001

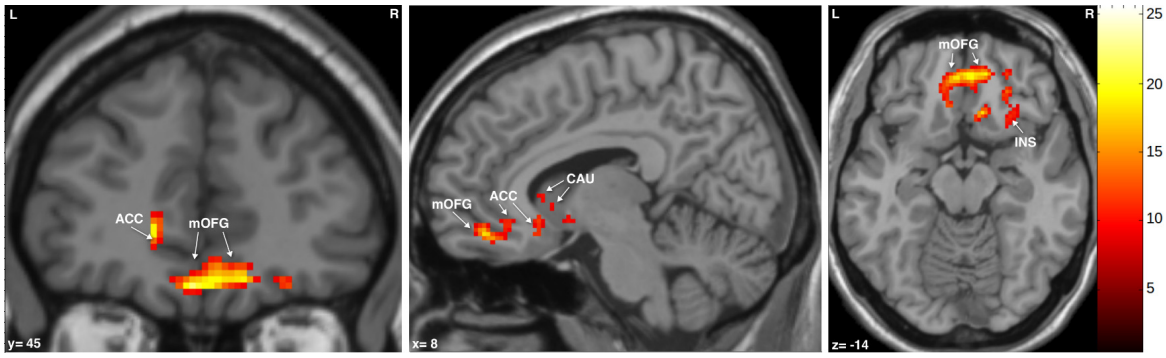


Figure 3.25 Effects of the Interaction of Condition with Personality Risk Profile and Sex on Whole-Brain Response to Acute Psychosocial Stress. A statistical map of the condition-by-personality-by-sex effect was computed by conducting a voxel-wise flexible-factorial GLM random effects analysis of β coefficients. In this model, personality (AS or SS), sex (M or F) and condition (alcohol or placebo) were fixed factors and individual subject was a random factor. Activation maps were thresholded at $P_{uncorr.} \leq .005$, $k = 20$. x, y, z = sagittal, coronal and horizontal view in MNI coordinates. The color map represents the corresponding F value (see Table 3.20). L and R indicate, respectively, the left and right sides of the brain; ACC = anterior cingulate cortex; CAU = caudate; INS = insula; and mOFG = medial orbitofrontal gyrus.

Decomposing the current 3-way interaction, revealed the interaction was mainly driven by the male subgroups, with ASMSs showing increase prefrontal activation under alcohol relative to placebo and SSMSs, decreased activation (Table 3.20).

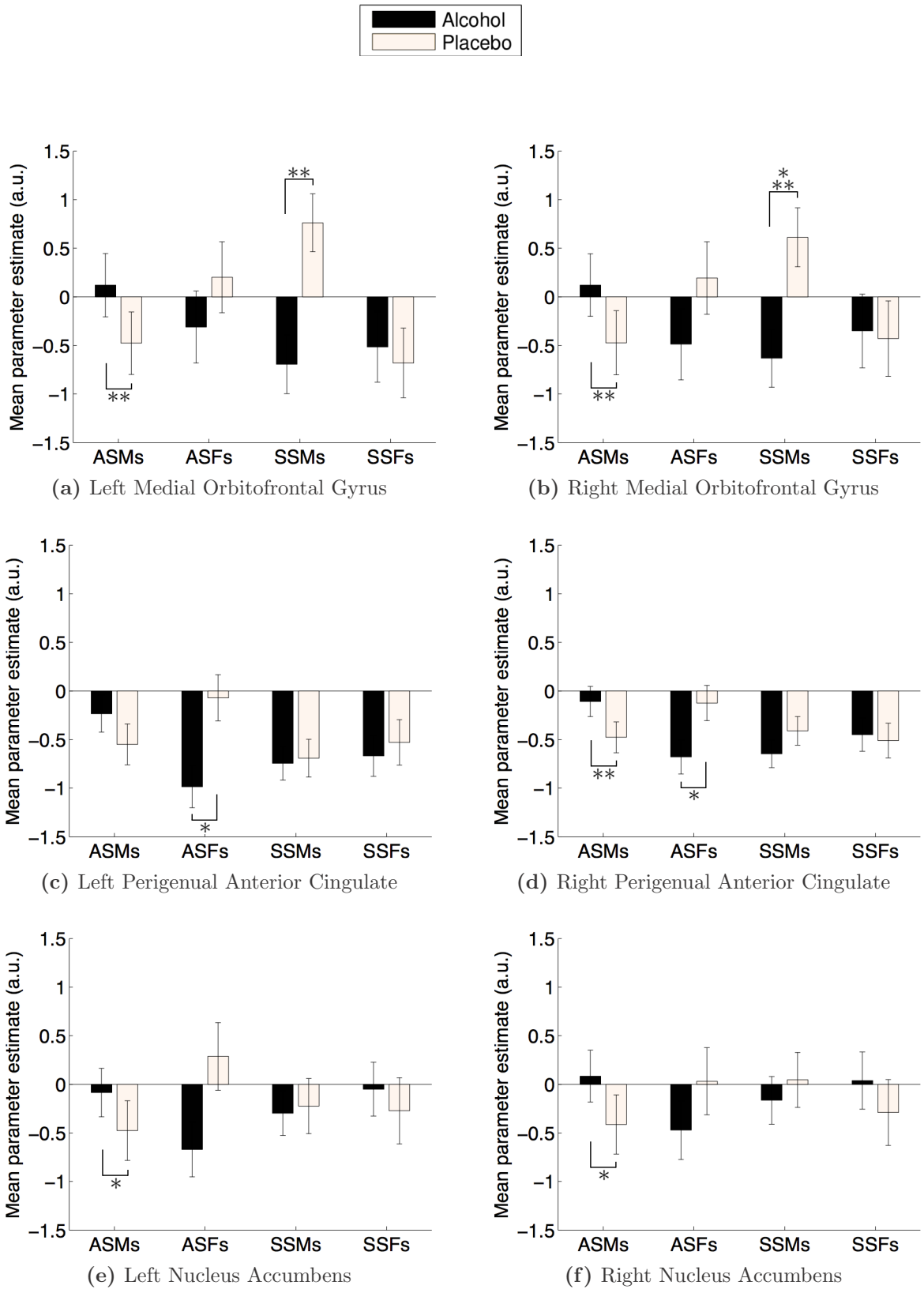
Table 3.20 Decomposition of the Condition-by-Personality-by-Sex Effect on Whole-Brain Activation to Acute Psychosocial Stress at $p_{uncorr} < .005(k = 20)$.

Region	*x*	*y*	*z*	K_E	*t*- value	P_{uncorr}
ASMSs: alcohol > placebo						
L FL/ Rectus	−12	38	−18	48	4.75	0.000
R ACC (32)	8	20	−8	130	4.61	0.000
R MedFG/ Rectus	10	24	−18		3.67	0.000
R MedFG/ mOFG (11)	4	44	−14	35	3.92	0.000
L MFG (46)	−44	38	−18	34	3.14	0.002
ASFSs: alcohol > placebo						
L ACC	−10	20	−10	273	−4.76	0.000
R ACC	8	32	−8		−3.57	0.000
L ACC (32)	−4	26	−10		−3.33	0.001
SSMSs: alcohol > placebo						
L MedFG/ Rectus	−6	44	−16	521	−4.55	0.000
R MedFG/ mOFG	10	48	−14		−4.48	0.000
R MedFG/ mOFG	24	52	−10		−4.24	0.000
R FL/ subgyral	24	20	−12	67	−3.56	0.000
R IFG	26	30	−8		−3.27	0.001
SSFSs: alcohol > placebo						

ROI analyses. Assessing the effects of alcohol and its interaction with either or both personality and sex on mean parameter estimate of spherically defined regions-of-interest activity, 3-way mixed-design ANOVAs, covarying for BAC throughout the course of the MIST revealed a significant condition-by-personality-by-sex interaction effects for the left mOFG ($F_{(1,37)} = 24.12$, $p = .000$ $\eta^2_p = .395$; Figure 3.26**a**), right mOFG ($F_{(1,36)} = 20.04$, $p = .000$, $\eta^2_p = .358$, 3.26**b**), left pgACC ($F_{(1,37)} = 8.53$, $p = .006$ $\eta^2_p = .187$; Figure 3.26**c**), right pgACC ($F_{(1,37)} = 16.82$, $p = .000$ $\eta^2_p = .312$; Figure 3.26**d**), left NAc ($F_{(1,37)} = 9.11$, $p = .005$ $\eta^2_p = .198$; Figure 3.26**e**) and right NAc ($F_{(1,37)} = 9.34$, $p = .004$ $\eta^2_p = .202$; Figure 3.26**f**).

Decomposition of the current 3-way interactions using paired-sample t-tests and an adjusted alpha level of $p = .0125$ per test (.05/4) indicated that intoxicated, relative

to sober, ASMSs activated the mOFG, bilaterally, in response to acute psychosocial stress (L: $t_{(10)} = 4.05$, $p_{(2-tailed)} = .002$; R: $t_{(10)} = 4.034$, $p_{(2-tailed)} = .002$), whereas SSMSs deactivated it (L: $t_{(12)} = 4.96$, $p_{(2-tailed)} = .000$; R: $t_{(12)} = 3.64$, $p_{(2-tailed)} = .003$). Further, relative to placebo, the left pgACC significantly deactivated to acute psychosocial stress in ASFSs ($t_{(8)} = 3.49$, $p_{(2-tailed)} = .008$) under the influence of alcohol, while the R pgACC activated in ASMSs ($t_{(10)} = 2.34$, $p_{(2-tailed)} = .010$). Values are displayed in Table 3.21.



(a) Left Medial Orbitofrontal Gyrus

(b) Right Medial Orbitofrontal Gyrus

(c) Left Perigenual Anterior Cingulate

(d) Right Perigenual Anterior Cingulate

(e) Left Nucleus Accumbens

(f) Right Nucleus Accumbens

Figure 3.26 ***a-f*** Means of parameter estimate activity (y-axes) of the, respectively, left and right mOFG ***(a-b)***, pgACC ***(c-d)***, and NAc ***(e-f)*** under stress versus nonstress conditions in ASM, ASF, SSM and SSF subjects (x-axes) under alcohol (dark bars) and placebo (light bars). Means for alcohol are BAC-adjusted. All of three ROIs, bilaterally, showed significant condition-by-personality-by-sex effects. *, $p \leq .05$, **: $p \leq .0125$ and ***: $p \leq 0.001$.

Table 3.21: The condition differences in mean parameter estimates for ROIs ROIs activation to Acute Psychosocial Stress (standard deviations in parentheses). A negative *t*-value is indicative of greater BOLD activity under the placebo than to alcohol condition.

Region of Interest	Alcohol	Placebo	Paired *t*-tests
ASMSs			
L mOFG	0.12 (0.77)	−0.47 (0.61)	**4.05**[a]
R mOFG	0.12 (0.77)	−0.47 (0.61)	**4.04**[a]
L pgACC	−0.23 (0.57)	−0.55 (0.57)	2.01
R pgACC	−0.11 (0.50)	−0.47 (0.39)	**3.15**[a]
L NAc	−0.09 (0.64)	−0.47 (0.74)	**2.34**[b]
R NAc	0.08 (0.62)	−0.41 (0.75)	**2.60**[b]
ASFSs			
L mOFG	−0.37 (1.05)	0.11 (0.88)	−1.29
R mOFG	−0.53 (0.69)	0.11 (0.87)	−2.14
L pgACC	−1.05 (0.82)	−0.16 (0.99)	**−3.49**[a]
R pgACC	−0.71 (0.57)	−0.20 (0.53)	**−1.35**[b]
L NAc	−0.67 (0.50)	0.13 (1.34)	**−.280**
R NAc	−0.47 (0.76)	−0.09 (1.05)	−2.28
SSMSs			
L mOFG	−0.67 (1.48)	0.79 (1.48)	**−4.96**[a]
R mOFG	−0.62 (1.60)	0.64 (1.61)	**−3.64**[a]
L pgACC	−0.72 (0.69)	−0.66 (0.75)	-0.34
R pgACC	−0.64 (0.57)	−0.38 (0.71)	−1.62
L NAc	−0.30 (1.18)	−0.17 (1.15)	-0.43
R NAc	−0.16 (1.19)	0.09 (1.23)	−0.94
SSFSs			
L mOFG	−0.49 (0.59)	−0.64 (0.95)	0.79
R mOFG	−0.33 (0.38)	−0.39 (0.65)	0.30
L pgACC	−0.64 (0.30)	−0.49 (0.42)	−0.97
R pgACC	−0.44 (0.34)	−0.48 (0.45)	0.34
L NAc	−0.05 (0.57)	−0.21 (0.92)	0.54
R NAc	0.04 (0.63)	−0.24 (0.96)	1.09

ASSs = anxiety sensitive subjects; L = left; R = right; mOFG = medial orbitofrontal gyrus ; pgACC = perigenual anterior cingulate cortex; NAc = nucleus accumbens

Significant differences are printed in bold.

Only the interactions that held their significance after adjusting alpha to correct for multiple comparisons are shown.

[a] $p < .0125$

[b] $p < .025$

[c] $p < .05$

Correlational analyses. Partial correlation analysis controlling for BAC showed an inverse correlation between stress-related increases in subjective anger and embarrassment self-ratings under alcohol and activation of (respectively) the mOFG (L: $r(35) = -.536$, $p_{(2-tailed)} = .001$; y-axis; R: $t(34) = -.546, p = .001$) and left pgACC ($r(35) = -.477$, $p_{(2-tailed)} = .003$; y-axis activation, for the entire sample combined (Figures 3.27**A** and 3.27**B**).

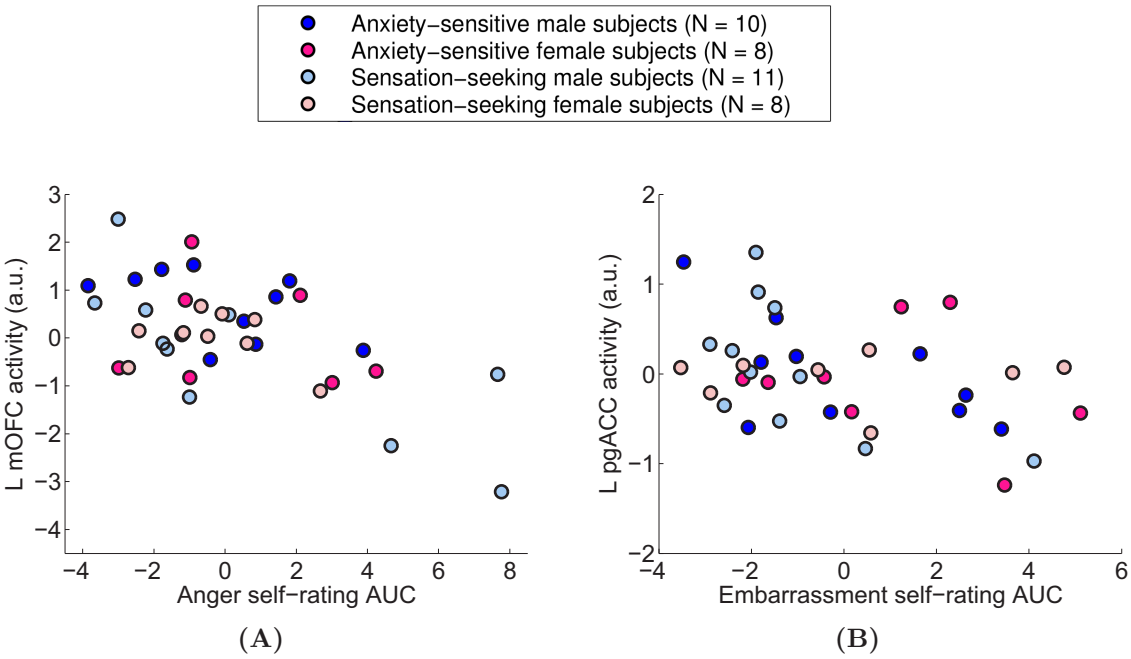


Figure 3.27 Significant inverse linear correlations between stress-related change in subjective mood (x-axes) and ROIs activation to acute psychosocial stress under alcohol (y-axes), for the entire sample combined, with BAC controlled for. Depicted are the associations between anger and left mOFG activity ($r(35) = -.536$, $p_{(2-tailed)} = .001$; y-axis) ***(A)***, and between stress-related change in self-rated embarrassment self-rating (x-axis) and left pgACC activity ($r(35) = -.477$, $p_{(2-tailed)} = .003$; y-axis) ***(B)***. Light blue and pink circles denote respectively ASM and ASF subjects, and darker blue and pink circles, SSM and SSF subjects.

3.3.3 Summary of Results

Under placebo, ASSs had higher ratings of pre-stress embarrassment and anger than SSSs. Throughout the course of the MIST, self-rated embarrassment significantly increased in ASMSs, whereas anger did not in the entire sample combined. A greater

increase in stress-related cortisol secretion was seen in ASSs compared with SSSs, and in ASMSs compared with ASFSs.

Relative to placebo, alcohol improved task performance in the AS group and hindered it in the SS group, decreased cortisol AUCi in the AS group, specifically ASMSs and decreased it in the SS group, especially SSMSs, and increased frontal activation in ASMss and decreased it in SSMSs.

3.4 Follow-up Assessment

Within a time range of 2-3 years, 9 out of out 44 subjects were lost to follow-up. Out of the 35 remaining (18 ASSs; 7 females and 18 SSSs; 7 females) who underwent assessment for mental health and drug use status, 11 had escalated in their alcohol and/ or illicit drug use and thus classified as 'TRAs' (TRAs). These were 8 ASSs (4 females) and 7 SSSs (1 female). Conversely, subjects ($N = 24$) who consistently remained social drinkers and casual drug users up until follow-up assessment classified as 'non-TRAs' (non-TRAs). These were 10 ASSs (4 females) and 11 SSSs (6 females).

The 'TRAs' and 'non-TRAs' of each personality group statistically differed in their MAST scores and drinking frequency at follow-up, and it is notable that at study entry. They did however differ in terms of familial alcoholism (greater ratio of FHP 'TRAs' to 'non-TRAs') and male to female ratio (6 to 1 in the SS group), which required covariation in our subsequent analyses. Furthermore, AS 'TRAs' did report exposure to more adverse, though not necessarily overtly traumatic, environmental events (e.g, abortion, romantic partner dumping, watching parent passed out drunk on regular bases). The temporal associations of said events and escalating use picture, however, were not entirely clear to us. This led us to decide to not incorporate environmental adversity as an additional covariate in our analyses, as a statistical control for said variable could be an overcontrol. 7 AS TRA had developed subclinical or clinical symptoms of an anxiety (versus 3 AS non-TRA), which manifested as either or both

social phobia and panic, and appear to have worsened concurrently with escalating use. 3 AS TRA had developed subclinical or clinical symptoms of an major depression (versus 1 AS non-TRA). The temporal precedence pattern is this case was unclear. One SS TRA had developed depression by follow-up (in remission; versus 1 SS non-TRA) reportedly after making an attempt to quit cocaine after few months of misuse.

Importantly, TRAs were not distinguishable from their same-personality 'non-TRAs' counterparts based on their years of education, reported age at drug use, drinking frequency (MAST), scores on personality measures of AS (ASI and SURPS-AS), SS (SURPS-SS), sensitivity to reward and punishment (SRSPQ), self-esteem (RSE), perceived self-efficacy (CCQ), alcohol expectancy in the domains of tension reduction and social and physical pleasure (AEQ), developmental experiences (i.e, childhood trauma [CTQ] and early-life parental *care* and protection [PBI]), all measured at study entry. These results are displayed in Table 3.22).

Table 3.22: Means, Standard Deviations, and Group Comparisons of Demographic Data and Rating Scale Scores. Demographic characteristics of transitioner and non-transitioner* AS and SS Subjects

	Transitioners	**Non-transitioners**	**Mean Difference** ($p - value$)
ASSs (n (%))	8 (44.4%)	10 (55.6%)	
SSSs (n (%))	5 (29.4%)	12 (70.6%)	
Age ($M \pm SD$)			
ASSs	23.50 ± 1.10	22.83 ± 1.33	ns
SSSs	23.25 ± 2.86	23.28 ± 2.03	ns
Sex Women (n (%))			
ASSs	4 (50.0%)	4 (40.0%)	ns
SSSs	1 (16.7%)	6 (54.5%)	–
Race (n (%))			
Caucasian			
ASSs	8 (100%)	8 (80.0%)	–
SSSs	4 (66.7%)	7 (63.6%)	–
Asian			
ASSs	0	0	–
SSSs	0	2 (18.2%)	–
Other			
ASSs	0	2 (20.0%)	–
SSSs	1	1 (10%)	–

Continued on next page

Table 3.22 – continued from previous page

	Transitioners	**Non-transitioners**	**Mean Difference** ($p - value$)
Years of Education ($M \pm SD$)			
ASSs	14.50 ± 0.76	13.90 ± 0.88	ns
SSSs	14.00 ± 1.26	14.09 ± 1.04	ns
Baseline SURPS Score ($M \pm SD$)			
AS scale			
ASSs	17.38 ± 1.92	16.70 ± 1.57	ns
SSSs	6.17 ± 1.72	7.55 ± 2.02	ns
SS scale			
ASSs	10.63 ± 1.30	10.40 ± 2.01	ns
SSSs	22.67 ± 1.75	22.09 ± 2.34	ns
Baseline SPSRQ-SP ($M \pm SD$)			
ASSs	13.13 ± 5.38	12.90 ± 4.56	ns
SSSs	6.50 ± 2.35	6.73 ± 4.67	ns
Baseline SPSRQ-SR ($M \pm SD$)			
ASSs	11.50 ± 2.33	11.40 ± 3.50	ns
SSSs	16.33 ± 3.20	16.00 ± 2.68	ns
Baseline ASI score ($M \pm SD$)			
ASSs	34.38 ± 6.65	33.60 ± 6.33	ns
SSSs	11.33 ± 5.47	10.82 ± 5.10	ns
Baseline MAST score ($M \pm SD$)			
ASSs	1.20 ± 1.10	0.00 ± 0.00	ns
SSSs	0.33 ± 0.82	0.18 ± 0.60	ns
Follow-up MAST score ($M \pm SD$)			
ASSs	6.25 ± 3.99	0.00 ± 0.00	.003
SSSs	7.33 ± 3.93	0.18 ± 0.60	.006
Alcoholic drinks per week at baseline ($M \pm SD$)			
ASSs	10.50 ± 5.10	6.20 ± 2.39	.031
SSSs	10.67 ± 5.85	11.18 ± 9.21	ns
Alcoholic drinks per week at follow-up ($M \pm SD$)			
ASSs	22.00 ± 5.15	6.00 ± 2.79	.000
SSSs	25.83 ± 10.21	6.91 ± 4.55	.000
Family history of AUDs (n (%))			
Negative			

Continued on next page

Table 3.22 – continued from previous page

	Transitioners	**Non-transitioners**	**Mean Difference** ($p - value$)
ASSs	2 (25.0%)	7 (70.0%)	–
SSSs	3 (50.0%)	6 (54.5%)	–
Mild			
ASSs	1 (12.5%)	2 (20.0%)	–
SSSs	1 (16.%)	2 (18.2%)	–
Positive			
ASSs	5 (62.5%)	0	–
SSSs	2 (33.3%)	3 (27.3%)	–
Multigenerational			
ASSs	0	1 (10.0%)	–
SSSs	0	0	–
Anxiety-disorder or subthreshold			
ASSs	7[a](87.5 %)	3 (30.0 %)	–
SSSs	0	0	–
Major depression (in past 3 y) (n (%))			
ASSs	3 (37.5 %)	1 (10.0 %)	–
SSSs	1[b](16.7 %)	1 (9.1 %)	–
Environmental adversity[†] (in past 3 y) (n (%))			
ASSs	5 (62.5%)	0	–
SSSs	2 (33.3 %)	1 (9.1 %)	–
Drinking age of onset ($M \pm SD$)			
ASSs	15.63 ± 0.92	16.30 ± 2.11	ns
SSSs	15.33 ± 1.21	15.09 ± 1.45	ns
Drug use age of onset ($M \pm SD$)			
ASSs	15.00 ± 1.31	17.43 ± 1.99	.014
SSSs	16.33 ± 0.82	15.89 ± 1.90	ns
Number of illicit drugs ever used ($M \pm SD$)			
ASSs	2.00 ± 1.41	1.43 ± 1.13	ns
SSSs	5.00 ± 6.90	3.56 ± 2.07	ns
PBI($M \pm SD$)			
Maternal Care			
ASSs	23.25 ± 5.20	26.00 ± 6.70	ns
SSSs	27.83 ± 2.56	29.27 ± 2.57	ns
Maternal Overprotection			
ASSs	12.50 ± 6.72	14.22 ± 7.12	ns
SSSs	13.60 ± 7.44	11.22 ± 6.82	ns
Paternal Care			

Continued on next page

Table 3.22 – continued from previous page

	Transitioners	**Non-transitioners**	**Mean Difference** ($p - value$)
ASSs	17.38 ± 7.21	22.40 ± 5.62	ns
SSSs	25.67 ± 3.27	26.27 ± 4.00	ns
Paternal Overprotection			
ASSs	14.60 ± 1.34	9.78 ± 7.21	ns
SSSs	11.00 ± 5.34	9.43 ± 8.12	ns
CTQ Score ($M \pm SD$)			
Phyisical Abuse			
ASSs	5.14 ± 0.38	5.33 ± 1.00	ns
SSSs	5.00 ± 3.24	5.45 ± 0.93	ns
Emotional Abuse			
ASSs	7.86 ± 1.57	7.00 ± 2.50	ns
SSSs	6.20 ± 4.15	6.82 ± 2.04	ns
Sexual Abuse			
ASSs	5.00 ± 0.00	5.00 ± 0.00	ns
SSSs	4.00 ± 2.24	5.00 ± 0.00	ns
Physical Neglect			
ASSs	7.29 ± 2.36	5.56 ± 1.01	ns
SSSs	6.40 ± 3.13	5.64 ± 1.29	ns
Emotional Neglect			
ASSs	8.86 ± 3.34	9.44 ± 4.90	ns
SSSs	11.80 ± 10.21	6.91 ± 2.21	ns
AEQ ($M \pm SD$)			
Careless Unconcern			
ASSs	19.00 ± 2.62	17.00 ± 2.56	ns
SSSs	18.00 ± 1.26	17.82 ± 3.76	ns
Cognitive and Physical Impairment			
ASSs	46.25 ± 4.30	45.50 ± 7.03	ns
SSSs	52.00 ± 11.22	38.45 ± 10.80	.028
Global Positive			
ASSs	20.13 ± 3.23	15.88 ± 5.57	ns
SSSs	14.00 ± 3.03	16.55 ± 6.71	ns
Power and Aggression			
ASSs	25.75 ± 2.92	21.75 ± 3.24	.021
SSSs	23.67 ± 4.59	24.09 ± 5.20	ns
Sexual Enhancement			
ASSs	20.50 ± 4.84	16.25 ± 2.71	.048
SSSs	18.33 ± 2.94	20.45 ± 3.96	ns
Social and Physical Pleasure			
ASSs	25.63 ± 2.88	23.38 ± 3.34	ns
SSSs	24.17 ± 2.79	25.18 ± 3.06	ns
Tension Reduction			
ASSs	22.75 ± 4.06	19.50 ± 2.78	ns

Continued on next page

Table 3.22 – continued from previous page

	Transitioners	**Non-transitioners**	**Mean Difference** ($p - value$)
SSSs	22.00 ± 3.69	22.36 ± 4.95	ns
RSE score ($M \pm SD$)			
ASSs	22.00 ± 4.87	21.25 ± 4.77	ns
SSSs	23.00 ± 3.61	22.18 ± 3.76	ns
CCQ ($M \pm SD$)			
Self-esteem			
ASSs	29.00 ± 6.28	28.25 ± 5.06	ns
SSSs	32.25 ± 1.50	31.09 ± 7.06	ns
Internality			
ASSs	31.13 ± 6.33	31.13 ± 3.27	ns
SSSs	34.25 ± 4.35	33.36 ± 3.41	ns
Perceived control of others			
ASSs	27.88 ± 5.67	28.63 ± 2.77	ns
SSSs	28.00 ± 1.15	26.55 ± 3.72	ns
Chance			
ASSs	23.38 ± 6.41	24.88 ± 4.55	ns
SSSs	19.00 ± 3.83	22.91 ± 2.98	ns

Abbreviations: ASSs = anxiety sensitive subjects; SSSs, sensation-seeking subjects; RSES, Rosenberg Self-Esteem; IQ, Intelligent Quotient; AEQ, Alcohol Expectancy Questionnaire; CTQ, Childhood Trauma Questionnaire; PBI, Parental Bonding Instrument; BAC, blood alcohol curve and AUDs, alcohol use disorders.

[a] symptom worsening (relative to severity at study entry) reportedly preceded escalating use but was further exacerbated after.

[b] Drug-induced.

[†] For the SS 'TRAs', environmental adversity (job loss, dumped by romantic partner) reportedly occurred in the aftermath of and as a direct result of drug misuse.

3.4.1 Face Emotion Processing Task

Assessing whether the BOLD response to negative (versus neutral) faces (assessed seperately and together) in either or both personality group, under either or both testing conditions was prospectively associated with escalation into alcohol and/ or other drug misuse within the subsequent 2-3 years, a univariate analysis were carried out, with the AMYG activation to stress under placebo being the dependent variable, 'transitioning' status and group as fixed factors. Sex and familial alcoholism were specified as covariates. No significant results were found. The same analysis was

carried out for the alcohol condition, also with null results.

Examining the main effects of transitioning (to alcohol and/ or drug misuse within the 3 years following initial fMRI testing) status and its interaction with personality on a spherically defined ROI, namely the amygdala, activity under placebo, ANCOVA testing, covarying for sex and familial alcoholism and using an adjusted alpha level of $p = 0.025$ per test (.05/2) indicated a personality-by-transitioning interaction effect on mean parameter estimates (arbitrary units) of activity within the AMYG, bilaterally, in response to "negatively valent minus neutral face" contrast under placebo (L: $F_{(1,26)} = 7.40$, $p = .011$, $\eta^2_p = .222$ and R: ($F_{(1,26)} = 3.52$, $p = .026$, $\eta^2_p = .176$). Paired sample t-tests showed only condition difference significance for AS TRAs (L: $t(7) = -3.08$, $p_{(2-tailed)} = .018$; R: $t(7) = -3.71$, $p_{(2-tailed)} = .008$; Figures 3.28**a** and 3.28**b**, respectively; L: placebo: $M = -1.46, SD = 2.11$; Alcohol: $M = 1.48, SD = 1.06$ and R: placebo: $M = -1.57, SD = 2.33$; Alcohol: $M = 1.67, SD = 1.20$)

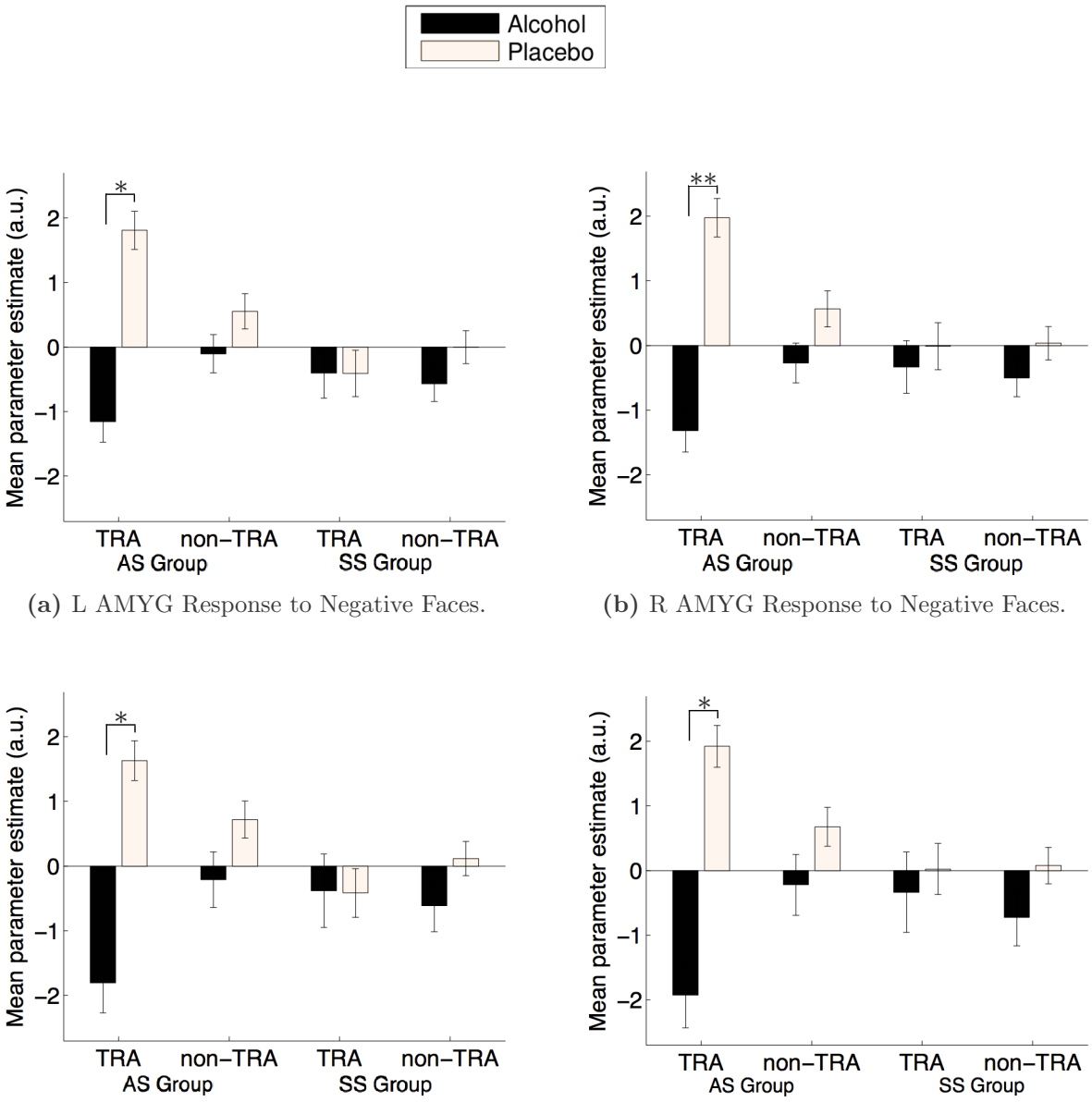
For the "Fearful minus Neutral faces" contrast, there was condition-by-personality-by-transitioning status interaction effect on AMYG activity (L: $F_{(1,26)} = 8.37$, $p = .008$, $\eta^2_p = .243$; R: $F_{(1,26)} = 7.29$, $p = .012$, $\eta^2_p = .219$; Table 3.23; Figures 3.28**c** and 3.28**d**).

For the "Angry minus Neutral faces" contrast, there was condition-by-personality-by-transitioning status interaction effect on AMYG activity (L: $F_{(1,26)} = 5.83$, $p = .023$, $\eta^2_p = .183$; R: $F_{(1,26)} = 4.68$, $p = .040$, $\eta^2_p = .152$). However, the significance of the right AMYG effect did not withstand correction for multiple comparisons (Table 3.23).

For the "Disgusted minus Neutral faces" contrast, there was condition-by-personality-by-transitioning status interaction effect on the left AMYG activity $F_{(1,26)} = 5.07$, $p = .033$, $\eta^2_p = .163$). However, this significance diminished after alpha was adjusted to correct for multiple comparisons (Table 3.23).

For the "Sad minus Neutral faces" contrast, there was condition-by-personality-by-transitioning status interaction effect on the bilateral AMYG activity (L: $F_{(1,26)} = 8.58$, $p = .007$, $\eta^2_p = .248$; R: $F_{(1,26)} = 5.03$, $p = .034$, $\eta^2_p = .162$). However, the significance of the right AMYG effect did not withstand correction for multiple

comparisons (Table 3.23).



(a) L AMYG Response to Negative Faces.

(b) R AMYG Response to Negative Faces.

(c) L AMYG Response to Fearful Faces.

(d) R AMYG Response to Fearful Faces.

Figure 3.28 Prospective Association Between AMYG Activation to Socioaffective Signals of Threatening and Escalating Use ***a-b***, Mean parameter estimates (arbitrary units) of AMYG activity in response to negatively (fearful, angry, disgusted and sad) versus neutral faces ***(a-b)*** and fearful versus neutral faces ***(c-d)*** in anxiety-sensitive (AS) and sensation-seeking (SS) subjects who classified as transitioners (TRA) and non-transitioners (non-TRA) to alcohol and/ or other drug misuse within the 3 years subsequent to initial fMRI testing under alcohol (dark bars) and placebo (light bars) conditions. **, $p_{(2-tailed)} \leq .0125$ (Bonferroni adjusted alpha); *, $p_{(2-tailed)} \leq .02$. Error bars indicate SEM.

Table 3.23: The condition difference in threat-related AMYG activity as a function of Personality Profile and Transitioning Status. A negative t-value is indicative of greater BOLD activity under the placebo than to alcohol condition.

Region of Interest	Alcohol	Placebo	Paired t-tests
Fearful > Neutral: ASSs TRA			
L AMYG	−1.46 (2.11)	1.48 (1.06)	**−3.00**[b]
R AMYG	−1.57 (2.33)	1.67 (1.20)	**−3.18**[b]
Fearful > Neutral: ASSs non-TRA			
L AMYG	−0.51 (0.92)	0.85 (0.83)	**−3.18**[b]
R AMYG	−0.54 (1.01)	0.89 (0.97)	**−2.51**[b]
Fearful > Neutral: SSSs TRA			
L AMYG	−0.48 (1.53)	−0.38 (0.73)	**−.23**[c]
R AMYG	−0.48 (1.64)	0.04 (0.73)	−.81
Fearful > Neutral: SSSs non-TRA			
L AMYG	−0.56 (0.63)	0.10 (0.67)	−2.59
R AMYG	−0.65 (0.67)	0.08 (0.70)	−2.07
Angry > Neutral: ASSs TRA			
L AMYG	−0.94 (1.68)	1.86 (1.67)	**−2.94**[b]
Angry > Neutral: ASSs non-TRA			
L AMYG	−0.27 (0.76)	0.65 (0.47)	**−3.49**[b]
Angry > Neutral: SSSs TRA			
L AMYG	−1.06 (1.27)	−0.56 (0.84)	−1.21
Angry > Neutral: SSSs non-TRA			
L AMYG	−0.50 (0.87)	−0.06 (0.79)	−1.14
Disgusted > Neutral: ASSs TRA			
L AMYG	−0.49 (1.20)	1.59 (1.43)	**−2.76**[c]
Disgusted > Neutral: ASSs non-TRA			
L AMYG	−0.24 (1.12)	0.71 (0.88)	**−1.68**[c]
Disgusted > Neutral: SSSs TRA			
L AMYG	−0.16 (0.85)	−0.06 (0.67)	−.204
Disgusted > Neutral: SSSs non-TRA			
L AMYG	−0.42 (0.70)	0.06 (0.57)	−1.42
Sad > Neutral: ASSs TRA			
L AMYG	−0.86 (1.26)	1.46 (1.50)	**−3.41**[a]
Sad > Neutral: ASSs non-TRA			
L AMYG	−0.21 (1.04)	0.66 (0.58)	**−1.78**[b]
Sad > Neutral: SSSs TRA			
L AMYG	−0.36 (0.51)	−0.73 (0.88)	.81
Sad > Neutral: SSSs non-TRA			
L AMYG	−0.55 (0.64)	0.02 (0.53)	−1.93

Abbreviations: ASSs = anxiety sensitive subjects; SSSs = sensation-seeking subjects; TRA = 'transitioners'; non-TRA = 'non-transitioners'; L = left; R = right; AMYG = amygdala. Significant differences are printed in bold.

Only the interactions that held their significance after adjusting alpha to correct for

multiple comparisons are shown.

[a] $p < .0125$
[b] $p < .025$
[c] $p < .05$

The behavioral, subjective and endocrine measures response profiles in the context of the FEPT did not statistically differ as a function of condition-by-personality-by-transitioning interaction ($p > .1$).

3.4.2 Montreal Imaging Stress Task

A 3-way mixed-design ANOVA, covarying for sex, BAC and family history of AUDs, found a significant condition-by-personality-by-transitioning status was found: bilateral mOFG (L: $F_{(1,27)} = 10.11, p = .004$, $\eta^2_{\mathrm{p}} = .273$ and R: $F_{(1,26)} = 8.27, p = .008$, $\eta^2_{\mathrm{p}} = .235$); Figures 3.29**a** and 3.29**b**, respectively. This 3-way interaction was mainly driven by SS-TRAs (Table 3.24).

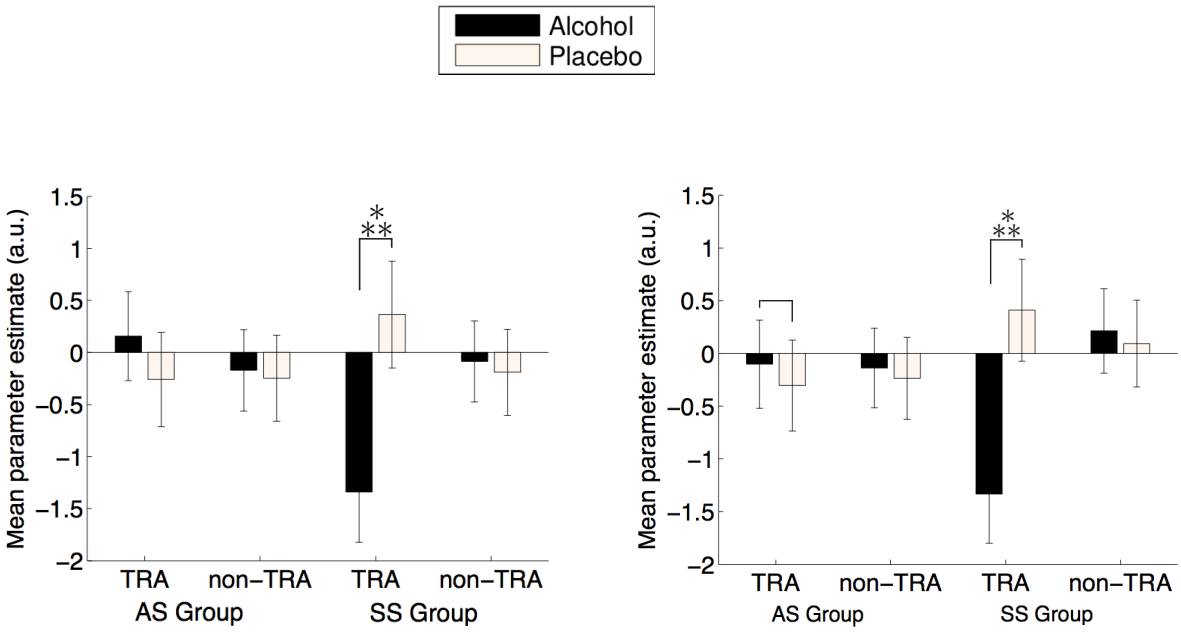


Figure 3.29 Prospective Association Between Medial Orbitofrontal Activation to Acute Psychosocial Stress and Escalating Use. Mean parameter estimates (arbitrary units) of the left ***(a)*** and right ***(b)*** mOFG in response to an acute psychosocial stressor in AS and SS subjects who classified as transitioners (TRA) and non-transitioners (non-TRA) to alcohol and/ or other drug misuse within the 3 years subsequent to initial fMRI testing under alcohol (dark bars) and placebo (light bars) conditions. *, $p_{(2-tailed)} \leq .05$; **, $p_{(2-tailed)} \leq .0125$ (Bonferroni adjusted alpha); ***, $p_{(2-tailed)} \leq .001$. Error bars indicate SEM.

Table 3.24: The condition difference (SD) in mOFG activation to acute psychosocial stress as a function of personality profile and transitioning status. A negative t-value is indicative of greater BOLD activity under the placebo than to alcohol condition.

Region of Interest	Alcohol	Placebo	Paired t-tests
ASSs TRA			
L mOFG	.05 (.17)	−.32 (.80)	1.38
R mOFG	−.18 (.91)	−.32 (.80)	.57
ASSs non-TRA			
L mOFG	−1.7 (.82)	−.32 (.60)	.50
R mOFG	−1.2 (.80)	−3.2 (.60)	.66
SSSs TRA			
L mOFG	−1.21	.45 (1.52)	**−6.80**[a]
R mOFG	−1.20	.46 (1.83)	**−6.67**[a]
SSSs non-TRA			
L mOFG	−.08	−.12	.12

Continued on next page

Table 3.24 – continued from previous page

Region of Interest	Alcohol	Placebo	Paired t-tests
R mOFG	.07 (1.17)	−.01 (1.14)	.48

Abbreviations: ASSs = anxiety sensitive subjects; SSSs = sensation-seeking subjects; TRA = 'transitioners'; non-TRA = 'non-transitioners'; L = left; R = right; mOFG = medial orbitofrontal gyrus.

Significant differences are printed in bold.

Only the interactions that held their significance after adjusting alpha to correct for multiple comparisons are shown.

[a] $p = .001$

The behavioral, subjective and endocrine measures response profiles in the context of the MIST did not statistically differ as a function of condition-by-personality-by-transitioning interaction ($p > .1$).

3.4.3 Summary of Results

There were significant condition-by-personality-by-transitioning interactions on the AMYG activation to threatening faces and mOFG activation to acute psychosocial stress, that were mainly driven by (respectively) AS-TRAs and SS-TRAs.

Chapter 4

Discussion

4.1 Face Emotion Processing Task

Using a well-validated facial emotion-processing paradigm known to tap the function or dysfunction of the limbic circuitry (Hariri et al., 2002; Paulus et al., 2005; Stein et al., 2007b), we demonstrated that (1) ASSs compared with SSSs more strongly activated all of our three functional ROIs, namely AMYG, aINS and vACC, to negatively valent (assessed separately and together), especially fearful versus neutral faces. This was particularly true for the AMYG, which was the only brain region that stringent whole-brain analyses found to demonstrate differential activation cluster(s) as a function of personality profile. Uniquely to the AS group, task-related activation of the bilateral AMYG to fearful vs neutral faces, but not for other affective conditions, bore a dose-dependent association with AS scores (SURPS, and, to a lesser extent, total ASI), such that the the most ASSs showed the greatest magnitude of BOLD signal response. This relationship was not held by other functional ROIs. Also uniquely to the AS group, the magnitude of BOLD response within the AMYG to negatively valent (assessed together) but especially fearful versus neutral faces was inversely associated with pre-task cortisol levels, with "testing time" controlled for; (2) the same pattern of personality group neural activation differences emerged during presentions of surprised (versus neutral) faces, alongside an increased tendency on part of ASSs (relative to SSSs) to misrecognize such faces as harsh (i.e, angry, fearful or disgusted) expressions; (3) SSSs were neurally unresponsive under the aforementioned affective conditions. This reactivity - or lack thereof - occurred in the context of an intact ability to accurately identify face emotion, which was comparable to their AS counterparts'; (4) happy vs neutral faces evoked greater aINS activity in the AS than SS group, although only the left-lateralized differences survived correction for multiple comparisons. No differential activation clusters were found by whole-brain analyses. Relatedly, happiness was the only facial expression to be detected with 100% accuracy in the entire sample, which confirms previous reports (Hess et al., 1997; Gur et al.,

2002; Leppänen and Hietanen, 2004; Horstmann et al., 2006); (5) alcohol substantially blunted the BOLD activations displayed by the AS group under placebo, but caused no brain response change in SSSs. These effects occurred in the context of an increased proclivity for negative emotion misrecognition as neutral in the AS group, and reduced overall face emotion detection accuracy in the entire sample combined, relative to placebo. No statistical effects of sex were detected. The aforementioned results are broadly consistent with our primary *a priori* hypothesis and are unpacked below in chronological order.

ASSs are more reactive to negatively valent or surprised vs neutral faces than SSSs. Stronger engagement of the brain's "defensive survival circuit" (LeDoux, 2015, p. 442), most prominently the AMYG, in the AS group when viewing negatively valent (especially if immediately threatening, e.g, fearful), or surprised versus neutral faces is indicative of a neural bias toward hypervigilance for potential threat. This finding was expected *a priori*, is in line with the function of anxiety (i.e, to promote vigilance towards whatever is perceived potential threat to enhance the capacity to detect and evade potential danger; Robinson et al. 2012; LeDoux 2015), and adds to a wealth of literature that has extended said neural phenomenon from the anxiety-disordered (Rauch et al., 2000; Stein et al., 2002; Phan et al., 2006; Etkin and Wager, 2007; Monk et al., 2008b; Evans et al., 2008; Goldin et al., 2009; Fonzo et al., 2010; Shin and Liberzon, 2010; Killgore et al., 2014; Poletti et al., 2015; Brooks and Stein, 2015; Herrington et al., 2016; van den Bulk et al., 2016; Bandelow et al., 2016; Fredrikson, 2016), to the anxiety-prone (i.e, individuals temperamentally high in anxiety-related traits; Paulus et al. 2003; Bertolino et al. 2005; Cools et al. 2005; Killgore and Yurgelun-Todd 2005; Killgore et al. 2011; Simmons et al. 2006, 2008a; Stein et al. 2007b; Wolfensberger et al. 2008; Baeken et al. 2009; Chan et al. 2009; Pujol et al. 2009; Hyde et al. 2011; Blackford et al. 2012; Ball et al. 2012; Shackman et al. 2013; Van Schuerbeek et al. 2014; Everaerd et al. 2015). This finding also helps

specifically explain the relationship of limbic activation with SA (Ball et al., 2012) and IU (Simmons et al., 2008a), because persons high in either or both of these traits have been found to also score high in AS measures (Watson and Friend, 1969; Asmundson et al., 1994; Orsillo et al., 1994; Ball et al., 1995; Anderson and Hope, 2009; Carleton et al., 2007; Carleton, 2016a,b; Wright et al., 2016; Ursa, 2016; Shihata et al., 2016). The present finding additionally resonates with previous reports suggesting that the link between a behaviorally inhibited temperament and internalizing symptomatology is moderated by altered topography of intrinsic functional connectivity, specifically AMYG−INS connectivity (Hardee et al. 2013; Nicholson et al. 2016b; also see Andreescu et al. 2015; Makovac et al. 2015; Greening and Mitchell 2015; Makovac et al. 2015; Bijsterbosch et al. 2015; Taber-Thomas et al. 2016; Kujawa et al. 2016; Herringa et al. 2016; Gold et al. 2016).

The aINS has a vital role in monitoring changes in internal bodily state or homeostasis (Craig, 2002, 2009, 2011; Paulus and Stein, 2006; Gray et al., 2007; Menon and Uddin, 2010; Nguyen et al., 2016), and consistently activates to pain delivery (correspondingly with decoded intensity; Peyron et al., 1999; Craig et al., 2000; Bantick et al., 2002), its anticipation (Wager et al., 2004; Paulus and Stein, 2006; Simmons et al., 2006; Drabant et al., 2011; Eisenberger, 2015b) and imagined experience (Ploghaus et al., 1999; Carlsson et al., 2006; Ogino et al., 2007), as well as in and situations with an uncertain outcome (Kuhnen and Knutson, 2005; Preuschoff et al., 2008; Singer et al., 2009; Sarinopoulos et al., 2010; Grupe and Nitschke, 2013), especially uncertain threat (Dunsmoor et al. 2007; Somerville et al. 2013; Alvarez et al. 2015; for meta-analyses, see Shackman et al. 2011; Cacioppo et al. 2013; Rotge et al. 2014). Heightened INS activity under aversive affective conditions is especially characteristic of nonclinical persons high in AS (Paulus and Stein 2006; Stein et al. 2007b; Rosso et al. 2010; Domschke et al. 2010; Killgore et al. 2011; Yang et al. 2016; although see Harrison et al. 2015), SA (Ball et al., 2012) and IU (Simmons et al., 2008a; Gorka et al., 2016c), and those with anxious pathologies for which the aforementioned con-

structs specifically dispose, such as GAD (Nitschke et al., 2009), SAD (Stein et al., 2002; Killgore and Yurgelun-Todd, 2005) and PD (Poletti et al., 2015). Heightened activation of this region in our cohort of AS persons might thus be specifically tied to increased attention to, tense arousal by, apprehensions about, and aversive interpretation of the physical arousal related to anxiety elicited by negative versus neutral face presentions and perhaps over-prediction of signalled danger (Nitschke et al. 2006; Paulus and Stein 2006; Stein et al. 2007b; Rosso et al. 2010; Domschke et al. 2010; Craig 2011; Killgore et al. 2011; Simmons et al. 2006, 2008a, 2011; Haase et al. 2016; Kawaguchi et al. 2016; also see Gutiérrez-García and Calvo 2016).

The left-lateralization of the differential activation of the aINS resonates with previous reports finding that (1) left aINS activity during specifically aversive anticipation was greater in highly anxious persons compared with their anxiety-normative peers (as opposed to greater right aINS activation under positive and aversive anticipation conditions; Simmons et al. 2011); (2) increased face fearfulness correlated with to enhanced left INS activity under negatively valent cues in normal persons (Wudarczyk et al., 2016); and (3) left, but not right, aINS activation to emotional faces predicted escalating drinking 5 years later (Schuckit et al., 2016).

The vACC ostensibly contributes to conscious aspects of apprehension or anxiety, such as catastrophizing and worry (Etkin and Wager, 2007; Ball et al., 2012), although it remains unclear via which mechanisms. Its enhanced activity in the AS group may signify hypervigilance towards arousal, or dyscontrol over distress and arousal (see Ball et al. 2012), and is particularly consistent with prior research describing heightened vACC activation to emotional faces in direct association with trait AS (Ball et al. 2012; also see Poletti et al. 2015; Harrison et al. 2015).

As to the AMYG, this region is viewed as the epicenter of the "defensive survival circuit" (LeDoux, 1996; Ledoux, 2002; LeDoux, 2012, 2013, 2014a,b,b, 2015), operating on relatively primal and rigid principles (LeDoux, 1996; Whalen et al., 2004), and being supremely sensitive and precipitously reactive to the most subtle of threat signals,

including the non-consciously processed ones (e.g, subliminally presented fearful faces; Öhman, 2002; Méndez-Bértolo et al., 2016). In fact out of all brain regions, the AMYG is thought to be the most reliable predictor of threat and discriminator between appetitive and aversive stimuli (Ferguson and Bargh 2004; Costafreda et al. 2008; Satpute et al. 2015; Lindquist et al. 2012b, 2016; although see Sabatinelli et al. 2011; Kang et al. 2016), perhaps a signifier of "negativity bias" (see Cunningham et al., 2008; Stillman et al., 2015; Meder et al., 2016)). This could explain why the brain cluster(s) showing differential activation to threatening faces as a function of personality were after employing a the highly conservative FWE-corrected threshold for the whole brain was(were) localized to the AMYG.

The fact that this differential activation was, depending on the specific affective condition, more significant or only significant in the left hemisphere is consistent with previous studies showing that the left- versus right- lateralized AMYG responses to emotionally salient information were generally stronger and more sustained (Sergerie et al. 2008; Paulus et al. 2012; also see Ball et al. 2012).

The finding that said activation difference stood out in response to each of the negatively valent (fearful, angry, disgusted and sad) versus neutral faces could reflect overgeneralized anxiety and a "better safe than sorry" response of sorts (Laufer et al., 2016), a phenomenon that AS and its closely interrelated construct IU are strongly predictive of (Morriss et al., 2016). This finding corroborates a large body of research showing that even though the AMYG is most consistently responsive to signals of fear (Adolphs et al., 1995; Quirk et al., 1995; Collins and Paré, 2000; Whalen et al., 2001; Davis and Whalen, 2001; Zald, 2003; LeDoux, 2003; Wilensky et al., 2006; LeDoux, 2007; Davis et al., 2010; Duvarci and Pare, 2014; Johnson and Casey, 2015; Grant et al., 2015b; Rigoli et al., 2016; Felix-Ortiz et al., 2016; Kim et al., 2016b; Méndez-Bértolo et al., 2016), it also reacts to other negatively valent stimuli (e.g, angry faces Adams et al. 2003; Monk et al. 2006; McCloskey et al. 2016; and sad faces Killgore and Yurgelun-Todd 2004; Almeida et al. 2010; Grant et al. 2011; Touroutoglou et al.

2015; Arnone et al. 2012; Szczepanik et al. 2016; Gaffrey et al. 2016; Lemche et al. 2016; for meta-analyses, see Fusar-Poli et al. 2009; Lindquist et al. 2012b).

Notwithstanding, we would point out that a qualitative comparison between the differentially negative affective conditions did indicate that the strength of personality group difference in AMYG activation (i.e., Z-score value) was slightly more robust during the presentation of fearful than other negative compared with neutral faces. Thus, while the present results clearly refute locationistic accounts whereby the AMYG is basically equated with fear (see Kringelbach and Berridge, 2009; Lindquist et al., 2012b,a), they also align with a body of literature describing greater AMYG activation during the processing of fearful than other emotional faces (Whalen et al., 2001; Gorka et al., 2013), and suggesting that the centrality of the AMYG in processing fear might not be generalizable to other emotions (Marsh 2015; although see Tranel and Damasio 1989; Meadows and Kaplan 1994; Anderson and Phelps 2002; Becker et al. 2012). The story of patients with focal bilateral AMYG damage is a good case in point, as these exhibit deficient recognition of and sensitivity to fear-signaling stimuli (Adolphs et al. 1994, 1999, 2002, 2005; Young et al. 1995; Anderson and Phelps 2001; Sato et al. 2002; Wiest et al. 2006; Scheele et al. 2012; Feinstein et al. 2013; Bach et al. 2015; Dal Monte et al. 2015; Amaral and Adolphs 2016; Khalsa et al. 2016; De Winter et al. 2016; Pishnamazi et al. 2016; Claire et al. 2016; but see Becker et al. 2012), and lack the capacity to experience any sort of subjective fear (Feinstein et al., 2011; Klumpers et al., 2015).

The association between greater task-related AMYG, but not aINS nor vACC, activation and higher AS scores within the AS group in response to aversive, but not happy, versus neutral faces, suggests that this relationship was specific to the AMYG, as opposed to the "defensive survival circuit" more generally, and dependent on the presence of cues clearly predictive of negative outcomes. It could be that the vital role of the AMYG in fear conditioning and threat detection (Adolphs et al., 1995; Davis et al., 2010; Davis and Whalen, 2001; Zald, 2003; Tamietto and

De Gelder, 2010; LeDoux, 2014b; Maren, 2016), especially in social contexts (Haxby et al., 2002) might underlie the dose-dependent relationship between the magnitude of AMYG threat-related activation in AS persons and the extent to which they fear their anxiety-related symptoms (and might thus perceive negative faces to be more intensely threatening). However, considering that we did not systematically disentangle how the specific, yet interrelated, components of the anxiety constructs related to AMYG reactivity to emotional faces, and the only study to date that has, to our knowledge, done that found a unique (left) AMYG-SA association after controlling for AS scores (Ball et al., 2012), we cannot preclude the possibility that our observed AMYG-AS association is not accounted for by SA or some other third variable. It is also notable that the present correlative finding is at odds with previous studies demonstrating an association between the aINS, but not the AMYG, with AS scores during negative face processing (Killgore et al., 2011; Stein et al., 2007b; Poletti et al., 2015). It is plausible that had the anxiety-related physical symptoms been more strongly provoked across all subjects, an association between INS activity and AS scores would have been detected (see Ball et al., 2012). Again, though, in none of those studies were the separate elements of the anxious phenotype systematically disentangled, and the previously discussed Ball study found that it was the SA, not the AS that uniquely associated with aINS activity (Ball et al., 2012). More to the point, recent evidence has directly challenges the popular notion trait AS is predominantly mediated as part of a broader network in which introceptive processes are instantiated (Harrison et al., 2015). Further research will therefore need to sort out these alternative explanations.

Our observation that pre-stress cortisol levels in the AS group dose-dependently attenuated threat-related AMYG activation is in line with the AMYG's well-recognized role as one of the top regulators of the HPAA, and reinforces previous studies suggesting that higher concentration of cortisol (naturally occurring or pharmacologically induced) prior to exposure to negative material could be stress-buffering and fear-reducing, and thus conducive of effective coping (contrarily to stress-evoked elevation

of cortisol secretion, which signifies enhanced stress; Het and Wolf, 2007; Het et al., 2012; Bertsch et al., 2011; Walter et al., 2015; Hoyt et al., 2016). Such outcomes have previously been noted in nonpathological high trait anxiety persons (Putman et al., 2010; van Peer et al., 2010), and ostensibly occur via adaptive regulation of automatic threat-related processing (reviewed in Putman and Roelofs, 2011).

The presence aforementioned differential activation patterns during the presentation of surprised (versus neutral) faces and particularly relevant and revealing. Expressions of surprise are unique in that they can predict either positive or negative outcomes depending on individual factors (Tomkins and McCarter, 1964; Neta et al., 2009; Davis et al., 2016; Neta et al., 2016) and/ or contextual information (Whalen and Phelps, 2009; Neta et al., 2011; Davis et al., 2016), and are thus considered ambiguously valent. Previous studies have found that facial displays of surprise engage the AMYG when they are negatively interpreted (Kim et al., 2003), or presented in a temporally unpredictable fashion (Davis et al., 2016) or after exposure to negatively valent stimuli (Kim et al., 2004). Such outcomes are in the line with the vital role of the AMYG in resolving ambiguity in aversive situations (Madarasz et al., 2016), and the supposition that unpredictability is a potent stressor (Monat et al., 1972; Zakowski, 1995; Greco and Roger, 2001, 2003) that can, in it is own right, stimulate the AMYG (Whalen 1998, 2007; Herry et al. 2007). Hence, the over-engagement of this and other limbic regions in the AS group in response to temporally unpredictable presentions of surprised (versus neutral) faces might suggests the enhanced search for danger in response to unpredictability (Whalen, 2007), a supposition supported by the centrality of the uncertainty element in AS (Carleton et al., 2010). Interpreted this way, our findings are in line with prior demonstrations of heightened elevated of AMYG activation to uncertain threat in dispositionally-negative human and nonhuman primates (Fox et al., 2008; Somerville et al., 2010; Shackman et al., 2016a), and resonates with the predilection of persons high in AS and/ or its closely interrelated constructs, particularly IU for heightened anxiety under conditions with unpredictable outcomes

(Dugas et al., 2001; Kuckertz et al., 2016). The behaviorally evident proclivity of ASSs to misidentify surprised faces as harsh faces echoes prior reports of negatively biased interpretation of ambiguously valent material in social phobics (Gutiérrez-García and Calvo, 2016; Maoz et al., 2016), depressives (Leppänen et al., 2004; Oliveira et al., 2013) and individuals high in UI (Heydayati et al., 2003). This observation may be interpreted as signifying a fundamental problem of the PFC mishandling the calculation of impending danger in the face of ambiguously valent socioaffective signals, perhaps in addition to or instead of a deficit necessarily intrinsic to the AMYG (see Whalen, 2007; Stein et al., 2007b).

SSSs are unresponsive to negatively valent or surprised compared with neutral faces. The finding that not only were SSSs less neurally responsive than ASSs, but they also appeared to be unresponsive altogether confirmed our working hypothesis and accords well with multiple lines of evidence suggesting that (healthy) sensation-seekers generally perceive the world as 'non-threatening' (Franken et al., 1992; Mujica-Parodi et al., 2014; Norbury and Husain, 2015), underestimate physical risk incurred by various activities (e.g, sky-diving; Mujica-Parodi et al., 2014; Zheng et al., 2015), and when challenged and/ or faced with aversive information, are compared with non-SS controls (1) less subjectively anxious or not at all anxious (Blankstein, 1975; Schwarz et al., 1978; Franken et al., 1992; Mujica-Parodi et al., 2014); (2) less physiologically responsive or prone to defensive reactions (e.g, cortisol, affective startle reflex, skin conductance and HR; Schulkin et al., 1994; Herman et al., 2003a; Sorocco et al., 2006; De Pascalis et al., 2007; Mujica-Parodi et al., 2014) ; and (3) neurally hyposensitive or insensitive altogether (Joseph et al. 2009; Santesso and Segalowitz 2009; Zheng et al. 2014; Zheng and Liu 2015; also see Orsini et al. 2015). Our finding additionally echoes previous reports of diminished AMYG activation to threatening faces in cohorts of disinhibited SOA (Glahn et al., 2007), *non-dependent* heavy drinkers who display heightened sensitivity to alcohol-induced stimulation (Gilman

et al., 2012a), individuals with a IED and a past history of AUDs (Coccaro et al., 2016), and those who escalate in drinking via impulsivity (Nikolova and Hariri, 2012; Nikolova et al., 2016).

Recognize the significance of the fact that the neural unresponsiveness of the SS group occurred absent a fundamental problem of misrecognition of socioaffective signals of negative outcomes, which suggests that said neural irregularity most likely originates at the level of appraisal as opposed to detection. Face emotion recognition deficits have been observed in multiple psychiatric populations (e.g, Fairchild et al., 2009; Collin et al., 2013; Hopfer et al., 2013; Morgan and Marshall, 2013; Kim et al., 2011b; Kemmis et al., 2007; Verdejo-García et al., 2007; Bora and Zorlu, 2016), and described in association with maladaptive behaviors and social difficulties (Adolphs, 2003; Blair, 2012; Ersche et al., 2015). Because of that, their presence in our cohort of relatively intelligent and high-functioning university students would have falsified out working hypothesis. Can the SSSs in the present study then be viewed as 'super-regulators'? In support of an affirmative answer is prior research demonstrating fewer self-reported PTSD symptoms and milder psychopathologic severity in general among ex-prisoners of war scoring high versus low in SS measures (Solomon et al. 1995; Neria et al. 2000; also see Clinton et al. 2014), lower SS scores among substance abusers with comorbid PTSD relative to those without (Weiss et al., 2013), and greater tolerance of experienced physiological pain and emotional distress (Bender et al., 2012). However, it is important to point out that inherent hypoarousal by and fearlessness in the face of threat is not consistently adaptive and can in fact, under certain situations, be dangerous and maladaptive.

Stimuli signaling danger in one's surrounding environment are "inherently tied to our powerful self-preservation motives" (Stillman et al., 2015), for they are immediately relevant to our survival. After all, it is survival that life, if nothing else, is about for all living things.

This is why stimuli signaling aversive versus appetitive outcomes (e.g, fearful versus

happy faces), irrespective of context, consistently activate the AMYG across (healthy) individuals (Whalen, 1998; Whalen et al., 1998b; Whalen and Phelps, 2009; Stillman et al., 2015; Phelps et al., 2004; Barrett and Armony, 2009; Sarinopoulos et al., 2010), including infants as young as 6-months old (Leppänen and Nelson, 2012; Erlich et al., 2013; Otte et al., 2015; Graham et al., 2016). This is also why typical trajectory of development involves fast-paced development of the fear systems in the first year of life (Carranza Carnicero et al., 2000; Gartstein and Rothbart, 2003; Gartstein et al., 2010), which explains the threat-related AMYG activation in infant. It is interesting, in this context, that neonatal fear appears to promote important adaptive functions (Ainsworth and Bell, 1970; Hofer, 1994; Kochanska et al., 2002; Belsky et al., 2007; Belsky and Pluess, 2013; Leppänen and Nelson, 2012; Baker et al., 2012; Landers and Sullivan, 2012; Graham et al., 2016) and has in fact been associated with lower levels of externalizing problems later in life (Rothbart and Bates, 2006; Biederman et al., 2001).

Indeed, there are indications in the literature that AMYG underractivity to threat may be associated with diminished responsiveness to hazards and propensity for drug misuse via reduced inhibition and externalizing problems in general (Glahn et al. 2007; Hariri 2009; Carroll et al. 2009; Lovallo 2011; Raine 2013; Manzo et al. 2014; also see Goeders 2003; Koob and Kreek 2007; Evans et al. 2016a).

On these bases, we tentatively theorize that whereas our cohort of SS persons was selected in a way that their AMYG hyporesponsiveness to threatening socioadffective signals may stand for resilience and be functionally useful under conditions extreme stress, this same neural characteristic can under certain circumstances can propel them to engage in maladaptive forms of risky behavior, including but not limited to problematic alcohol and other drug use. Parenthetically, these individuals might stand out as 'super-regulators' (of perceived threat) in some contexts and 'dysregulators' in others.

ASSs are more neurally responsive to happy versus neutral faces than SSSs. In contrast to the massive human research performed to date on negatively valent material, the literature on stimuli that serve as "safety signals" (e.g, happy faces) has been much smaller and decidedly mixed. There are nonetheless indications that socially anxious persons, which individuals high in AS typically are (Watson and Friend, 1969), tend to discount positive social interactions (Wallace and Alden 1997; although see Dedovic et al. 2015), and fear positive (as opposed to only negative) evaluation (Weeks et al. 2008b,a; Weeks and Howell 2012; Weeks et al. 2015; Weeks and Howell 2014; Weeks 2015; Weeks and Zoccola 2015; Barber 2015; Teale Sapach et al. 2015; Dryman et al. 2016; also see Davoudi et al. 2013; Lipton et al. 2014; Howell et al. 2016a; Kocijan and Harris 2016; Torro-Alves et al. 2016; Yap et al. 2016; Reichenberger et al. 2017). On these bases, we had initially very tentatively predicted stronger limbic reactivity during the presentation of happy versus neutral faces would evince in the AS compared with SS group, though not necessarily to the extent seen under negative affective conditions and perhaps not in the AMYG. This prediction was confirmed: functional ROIs analyses found comparatively greater BOLD activation within the spherically defined aINS, bilaterally, although only the significance of left-lateralized differences withstood correction for multiple comparisons. A plausible interpretation of the present finding is that relative to their SS counterparts, ASSs were averse to happy faces, presumably because they can signal, in addition to positive judgment, an invitation to initiate or engage in a social interaction that is placed under attentional spotlight and must be properly navigated if one is to avoid acting in a socially undesirable manner and feeling embarrassed as a result (Ball et al., 2012; Blalock et al., 2016). Enhanced aINS activity might reflect (respectively) the aversive physical arousal sensations and catastrophic appraisals, inducted through the tapping of ASSs' conceptions of social inadequacy, and fear of social scrutiny. This interpretation is reinforced by a recent study in which fear of positive evaluation was directly linked with heightened INS sensitivity (Miedl et al., 2016). It will be important that

future research more carefully scrutinize this fear of positive evaluation phenomenon, if for the fact that it has been uniquely linked to alcohol misuse via DTC motives (Howell et al., 2016a).

The absence of heightened AMYG activity in the AS group under this affective condition is consistent with prior evidence suggesting that defensive responding is not readily instigated by happy faces in non-clinically anxious cohorts (Robinson et al., 2012) and, more broadly, resonates with the "negativity bias" purportedly exemplifying this region (Cunningham et al., 2008; Stillman et al., 2015; Satpute et al., 2015; Lindquist et al., 2016; Meder et al., 2016) and the evolutionary perspective whereby "bad is stronger than good" (Brickman et al., 1978; Pratto and John, 1991; Sheldon et al., 1996; David et al., 1997; Öhman and Mineka, 2001; Sander et al., 2003; Williams et al., 2005; Cunningham et al., 2008; Stillman et al., 2015).

Alcohol blunted threat-related limbic activity, created a positivity bias in interpreting emotional faces, and impaired facial affect recognition in ASSs. As expected *a priori*, whole-brain and functional ROIs analyses found that in the AS group, alcohol intoxication (BAC = 0.08 %) relative to placebo substantially deactivated the "defensive survival circuit" activation during the presentation of negatively valent (assessed separately and together) or surprised versus neutral faces. These condition differences were most pronounced in the AMYG, especially in the left hemisphere, especially in response to faces signalling immediate threat (i.e, fearful and angry) or uncertain threat (i.e, surprised), and did not evince in response to the "happy versus neutral face" contrast. The aforementioned inhibitory effects co-occurred with (behaviorally measured) (1) prolonged facial affect decoding latency; (2) an increased rate of emotional (negatively valent and surprised) faces mislabeled as neutral; (3) and a spike in face emotion, especially negative face emotion detection errors.

Being that the AMYG consistently activates when threat, especially threat signaled

by socioaffective stimuli, is detected and fear learnt (LeDoux, 2000a; Phan et al., 2002; Haxby et al., 2002; Zald, 2003; Pessoa, 2010; Phelps, 2004; LeDoux, 2015), and alcohol completely abolished this activation, our fMRI findings, in general, corroborate the self-medication and tension reduction (Conger, 1956) models of alcohol use, whereby drinking dampens stress and attenuates fear (Levenson, 1980; Sayette et al., 1992; Kushner et al., 1996; Sher et al., 2007; Hefner and Curtin, 2012). In particular, these findings adhere with multiple converging strands of evidence indicating that alcohol might induce anxiolysis via an action on and down-regulation of the threat reactivity of the AMYG (Spanagel et al., 1995; Nie et al., 2004, 2009; Roberto et al., 2003, 2004; Zhu and Lovinger, 2006; Silberman et al., 2008, 2009; Weiner and Valenzuela, 2006; Criswell and Breese, 2005; Kumar et al., 2009; Koob, 2003, 2004; Hyytiä and Koob, 1995; Buck, 1996) and the brain's threat-detection system (see Sripada et al., 2011; Arce et al., 2006; Paulus et al., 2005; Pandey et al., 2006; Allan et al., 1987; McBride, 2002; Möller et al., 1997; Sommer et al., 2001; Criswell and Breese, 2005; Kumar et al., 2009; Weiner and Valenzuela, 2006; Gorka et al., 2013). Very few neuroimaging studies to date have examined the effects of acute alcohol intoxication on the processing of socioaffective signals. Bearing in mind that methodological discrepancies between these studies and ours preclude direct comparability or straightforward extrapolation, these investigations have demonstrated alcohol-induced attenuation of AMYG activation to facial expressions of fear (Gilman et al., 2008, 2012a; Sripada et al., 2011; Gorka et al., 2013) and anger (Sripada et al., 2011; Gorka et al., 2013) but not happiness (Sripada et al., 2011; Padula et al., 2011; Gorka et al., 2013) in community-recruited samples of *non-dependent* young adults. We extend these findings by employing a paradigm that alternated between 7 as opposed to 2 or 3 types of face emotions, and a cohort of selected *a priori* for trait AS to demonstrate that alcohol markedly blunted limbic activation, particularly the left AMYG, to negatively valent, especially if immediately threatening socioaffective signals (i.e, fearful, angry, disgusted and sad versus neutral faces; assessed separately and together), and signals of uncertain threat (i.e., surprised

faces) with no effect on BOLD activation to happy versus neutral faces.

One very notable difference between the aforementioned studies and ours, though, is that while they have in common the finding of alcohol induced attenuation of AMYG activation to threatening faces, the magnitude of this inhibitory effect in our cohort of AS persons was comparatively more pronounced and detectable at a considerably more stringent statistical threshold (FWE-corrected for whole-brain). Considering alongside the observations that (1) subjects in the aforementioned studies were not selected *a priori* for any personality trait (nor were they personality profiled after the fact; Gilman et al., 2008, 2012a; Sripada et al., 2011; Gorka et al., 2013), and (2) the AMYG was comparably unresponsive to socioaffective signals of threat in the our cohort of SS individuals in both testing sessions, the aforementioned piece of information resonates with a body of literature showing that DTC motives are more frequently endorsed by (pathological and nonpathological) those with high scores on measures of AS (Stewart and Zeitlin, 1995; Stewart et al., 2001; Pihl and Peterson, 1995; Kushner et al., 2001; Chandley et al., 2014; Goldstein and Flett, 2009; Novak et al., 2003; Kuntsche et al., 2006; DeMartini and Carey, 2011), SA (Carrigan and Randall, 2003; Thomas et al., 2003; Buckner et al., 2006; Stewart et al., 2006; Ham et al., 2007, 2016; Keough et al., 2016; Mulligan et al., 2016), and IU (Oglesby et al., 2015; Kraemer et al., 2015; Banducci et al., 2016), the notion that these cohorts of individuals, relative to anxiety-normative people, have more to gain by drinking under aversive conditions on account of they have repeatedly been found to overactivate the AMYG in response to socioaffective stimuli signaling threat (Stein et al., 2002, 2007b; Phan et al., 2006; Etkin and Wager, 2007; Shin and Liberzon, 2010) and be particularly susceptible for the anxiolytic and SRD effects of alcohol (Levenson, 1980; Sher, 1987; Stewart and Pihl, 1994; Stewart, 1996; Stewart et al., 1999; Stewart and Kushner, 2001; Conrod et al., 1998; MacDonald et al., 2000a; Brown et al., 2001, 2002, 2009; Zack et al., 2007). This can be (and has been) invoked as an mechanistic explanation for why among all anxiety-disordered, lifetime (and 12-month) prevalence of AUDs is

highest in those with disorders that the aforementioned traits most strongly predict, namely (in descending order of prevalence) SAD, PD and GAD (Lai et al., 2015).

The obvious centrality of the AMYG in alcohol-elicited SRD notwithstanding, our findings and those of others (e.g, Gilman et al., 2008, 2012a; Padula et al., 2011; Gorka et al., 2013) should not be taken to necessarily mean that alcohol most strongly exerts said effects by directly and/ or only acting on the AMYG. Other brain regions that anchor the "defensive survival circuit" and bear direct structural and functional connections with the AMYG such as the INS (Baur et al., 2013; Nicholson et al., 2016b), which our AS group substantially deactivated in response to threatening (vs neutral) faces under alcohol, also appear be important, which resonates with their intimate interconnections with the AMYG and consistently found responsiveness to socioaffetive signals of threat. Specifically the INS, with a vital role in introception (Critchley et al., 2004; Craig, 2003, 2009, 2011; Paulus et al., 2005; Chong et al., 2016), robustly activates to aversion (Peyron et al., 1999; Craig et al., 2000; Bantick et al., 2002) and its anticipation (Wager et al., 2004; Paulus and Stein, 2006; Simmons et al., 2006; Drabant et al., 2011; Eisenberger, 2015b), and its attenuated threat-related activation under alcohol intoxication has, in fact, been previously found to occur absent response change in the AMYG, or any other brain region for that matter (Padula et al., 2011), alluding to anxiolysis solely via disruption of the processes instantiated in this region. It is also entirely conceivable that in the context of our investigation, INS inactivation, with its resultant disruption of anxious anticipation of potential danger, was an indispensable to alcohol's potent negatively reinforcing effects on ASSs, given that it is the physical arousal sensations that emerge during a bout of anxiety that such individuals dread most (Reiss et al., 1986; Reiss, 1991; Peterson and Reiss, 1992), and it is the INS that is often presumed to be at the epicenter of this "fear of fear" (Paulus and Stein, 2006; Stein et al., 2007b; Killgore et al., 2011; Poletti et al., 2015).

According to several theoretical accounts of alcohol use, acute alcohol intoxication attenuates fear and bring an perceived and/ or actual relief from aversive affect (Lev-

enson, 1980; Sayette et al., 1992; Kushner et al., 1996; Sher et al., 2007; Hefner and Curtin, 2012) by impairing recognition accuracy of threatening faces (Borrill et al. 1987; also see Mitchell et al. 2015), and hampering attention to and negative appraisal/ perceived salience of the socio-emotional threat cues (Stevens et al., 2008, 2009; Gilman et al., 2008, 2012a; Gorka et al., 2013). The increased tendency of ASSs to mistake negative faces expressions for neutral under alcohol relative to placebo is compatible with these models and empirical evidence supporting them, or aspects thereof. For example, showed that alcohol has been found to be more robustly anxiolytic when ingested before exposure to, and thus prior to appraisal of, stressors or threat signals than after (Sayette et al., 2001), with indications that this might be especially or specifically true when the aversive stimulus is temporally unpredictable, and the threat it signals, uncertain (Moberg and Curtin, 2009; Hefner and Curtin, 2012).

The neurochemical substrates which acute drinking down-regulates threat-related responding and reduces stress are incompletely understood, but GABAergic neurotransmission is most likely key (Criswell and Breese, 2005; Weiner and Valenzuela, 2006; Kumar et al., 2009; Mitchell et al., 2015). Chief among neural structures in which alcohol exerts pro-GABAergic effects is the amygdaloid complex, specifically the CeA (Nie et al., 2004, 2009; Roberto et al., 2003, 2004; Nie et al., 2004, 2009) and/ or BLA (Zhu and Lovinger 2006; Silberman et al. 2008, 2009; also see Wang et al. 2000; Volkow et al. 2008). Similar effects have also been described in other regions that anchor the brain's defensive survival system, particularly the INS (see Allan et al., 1987; Möller et al., 1997; Wang et al., 2000; Sommer et al., 2001; McBride, 2002; Paulus et al., 2005; Arce et al., 2006; Pandey et al., 2006; Volkow et al., 2008), and are producible by other drugs in humans in similar contexts, such as the benzodiazepine laropzam (Paulus et al., 2005; Arce et al., 2006), heroin (Schmidt et al., 2014), and even oxytocin (Heinrichs et al. 2003; Domes et al. 2007; Mitchell et al. 2015; Koch et al. 2015; Kanat et al. 2015; Gorka et al. 2015; but see Frijling et al. 2015) - all

are pharmacological manipulations that promote GABAergic transmission. (Mitchell et al., 2015). This helps explain the higher rates of nonmedical use and abuse of benzodiazepines among individuals high in AS.

Alternative pathways (e.g, dopaminergic) have nonetheless been proposed (Gilman et al. 2008, 2012a; Sripada et al. 2011; Gorka et al. 2013; also see Tran et al. 2016), which resonates with previous studies implicating the mesolimbic mesotelencephalic dopamine system in anxiety (Talalaenko et al., 1994; de la Mora et al., 2005; Diaz et al., 2011), linking DA levels in the AMYG to threat-related activation in this system (Kienast et al., 2008) and demonstrating the effects of alcohol on several neurotransmitter systems including, but not limited to, DA (Nutt and Peters, 1994; Chastain, 2006).

Alcohol caused no change in brain response to emotional faces in SSSs. In a jarring contrast to their AS counterparts, SSSs showed an increase in face emotion decoding errors but no statistical changes in brain activation to negatively valence surprised (vs neutral) faces under alcohol relative to placebo. This fMRI finding confirmed our working hypothesis.

While it is well-established that sensation-seekers do not primarily drink to dampen stress *per se* as these individuals are generally hyposensitive and underresponsive to stressors, no prior neuroimaging studies have, to our knowledge, examined how acute alcohol intoxication influenced emotional processing in non-pathological individuals selected *a priori* for SS trait. Doing just that, we here demonstrate that SS were as neurally unresponsive to emotional versus neutral faces under when alcohol intoxicated as they were when sober, perhaps suggesting that when alcohol was ingested, there was nothing for it in the brain function to alter, as far as brain reactivity in the aforementioned context goes.

The pattern of the current fMRI findings closely resembles that found in the previously cited fMRI study by Gilman et al. (2012a). These investigators examined the

effects of intravenously administered alcohol (BAC = 0.08 g%) versus saline (placebo) on fearful and neutral face processing in two nonpathological groups of, respectively, SDs and HDs (referred to by the authors as "low-risk" and "high-risk") and found that threat-related AMYG activation was present in SDs under placebo and dampened by alcohol, but conspicuously absent in HDs in both testing sessions (Gilman et al., 2012a). Though no personality assessments were administered in that study and its Achilles heel being in how risk status was determined must be kept in mind, the "high-risk" group notably displayed heightened sensitivity to alcohol-induced stimulation relative to the "low-risk" group (Gilman et al., 2012a), and we know that this characteristic is typically displayed in cohorts of externalizing, including SS, individuals (Peterson et al., 1996; Assaad et al., 2003; Dawe et al., 2004; Assaad et al., 2006). In this way, our findings corroborate and extend those of the Gilman study (Gilman et al., 2012a). The aforementioned absence of alcohol effects helps explain why it is very unlikely for extroverts such as sensation-seekers to escalate into AUDs/ SUDs through the internalizing pathway.

4.2 Montreal Imaging stress Task

Using an acute psychosocial stress paradigm MIST (Dedovic et al., 2005) previously demonstrated to effectively induce a sense of helplessness and and elicit a moderate increase in reactive cortisol production, we demonstrated that under the placebo condition (1) there was a main effect of personality on task performance, with a better performance outcome (i.e, indexed by higher percent correct responses to math problems) was displayed by the SS than AS group; (2) there was a main effect of personality on pre-stress subjective stress, with higher levels embarrassment and anger being reported by the AS groups; (3) throughout the course of the stressor, embarrassment self-ratings increased as a function of time-by-personality-by-sex interaction that was mainly driven by ASMSs, whereas anger self-ratings showed a main effect of time,

increasing in the entire sample independent of personality and sex; (4) cortisol AUCi showed main personality and personality-by-sex interaction effects, being greater in the AS than SS group, and in the ASM than ASF subgroup; (5) cortisol AUCi showed was uniquely associated with a dose-dependent increase in embarrassment self-ratings in the entire sample, combined; and, finally, (6) exploratory whole-brain of the response to "experimental/stress versus control/ nonstress" contrast revealed the following: (a) substantial main effects of stress; (b) pronounced and extensive personality effects; (c) revealed main effects of stress, personality, sex and an interaction on BOLD activation to the "experimental/stress versus control/ nonstress" contrast, some more substantial than others. Functional ROIs revealed a main personality effect on aINS and personality-by-group interaction effect that was mainly driven by mOFG Of particular interest to us were the personality group differences, which were both pronounced and extensive, all favored the SS group, and collectively suggested that compared with their AS counterparts, SSSs were more energetically aroused but less intensely threatened and better able at distancing themselves from the aversiveness of the situation so as to focus on the task at hand; (7) functional ROIs revealed a personality-by-group interaction effect on the mOFG response to response to "experimental/stress versus control/ nonstress" contrast that was mainly driven by SSMs. This activation correlated negatively with the stress-induced increments in subjective anger, in the entire sample combined.

The aforementioned findings generally confirmed our initial predictions, though the absence of differential hippocampal deactivation correspondingly with inter-individual variation in cortisol AUCi was not necessarily expected.

As to the alcohol condition, we found that (1) there was a condition-by-personality interaction effect on task performance, such that when intoxicated versus sober, ASSs performed better, whereas SSSs performed worse; (2) pre-stress and stress-reactive mood (embarrassment and anger) self-ratings[1] did not statistically differ as a func-

[1]Recognize, however, that these null findings are likely attributable to the subjective mood data

tion of condition or an interaction of condition with either or both personality and sex; (2) controlling for BAC and "session time", cortisol AUCi showed a condition-by-personality-by-sex interaction effect, decreasing in ASMSs and increased in SSMSs when alcohol intoxicated relative to sober. Notably, the condition-by-personality interaction effect on cortisol AUC trended towards significance ($p \leq .08$; prior to correcting for multiple comparisons), decreasing and increasing in (respectively) ASSs and SSSs under alcohol relative to placebo (these changes were not statistically significant). Psychoendocrine covariance was conspicuously absent, which confirms previous reports indicating a dissociation between alcohol's effects on the subjective and physiological stress systems (e.g, Lewis and Vogeltanz-Holm, 2002; de Wit et al., 2003; Söderpalm and Wit, 2002); (3) exploratory whole-brain found, among others, (a) condition-by-personality interaction effects on the frontal cortex (e.g, IFG, MFG and MedFG; ROIs: mOFG) under alcohol relative to placebo, ASMSs activated the whereas ASFSs deactivated the (left) MedFG and (right) ACC and SSMSs deactivated the (left) MedFG while SSFSs activated the (left) ACC; and (b) condition-by-personality-by-sex interaction effects on the frontal and anterior cingulate cortices (ROIs: mOFG and pgACC and NAc); (4) functional ROIs revealed (a) a condition-by-personality interaction effect on BOLD activation within the left mOFG, although we should note that the former effect did not survive after adjusting alpha to correct for multiple comparisons; and (b) a condition-by-sex effect on (bilateral) pgACC activity, although the right did not withstand correction for multiple comparisons Condition-by-personality-by-sex interaction effects on the (bilateral) mOFG, pgACC and NAc, with all of these activating more strongly in intoxicated versus sober and the mOFG deactivating in SSMSs under intoxication. pgACC deactivated in ASFs, R pgACC act in ASMs; (5) controlling for BAC, mOFG activation bilaterally but especially in the left hemisphere correlated inversely with (a) stress-related increments in anger self-ratings; (b) cor-

on two testing occasion being missing for 25% of our sample. Because of that, they are not interpreted here as being necessarily suggestive of an absent effect of alcohol on subjective mood.

tisol AUCi; and (c) percent rate of incorrect responses to math problems. Among all our regions of interest, these covariation patterns were unique to the mOFG; and (6) controlling for BAC, pgACC activation negatively correlated with stress-related increments embarrassment self-ratings in the entire sample combined, although this association did not hold its significance after controlling for other state emotions, suggesting the association was with generally negative affect as opposed to specifically embarrassment.

Most of the aforementioned findings with respect to the alcohol condition were expected *a priori*, others not necessarily so. The general pattern of these findings nevertheless appears to point to alcohol-induced anxiolysis and stimulation in (respectively) the AS and SS group, particularly their male members, and are thus consistent with the self-medication and disinhibition pathways for AUDs (Victorio-Estrada et al., 1996; Verheul et al., 1999; Colder and O'Connor, 2002).

These results are unpacked below, in chronological order.

ASSs experienced greater anxious apprehension than SSSs. Our demonstration that ASSs compared with SSSs self-reported experiencing greater embarrassment and anger just before the start of the MIST confirmed our initial hypothesis of heightened anxious apprehension[2] in the AS group as the challenge drew closer. This finding augments a body of literature indicating that socially anxious and generally dispositionally negative persons (1) are more prone to experiencing embarrassment, guilt, anger, self-criticism insecurity, on regular bases (Kocovski and Endler, 2000; Caspi et al., 2005; Clark and Watson, 2008; Lahey, 2009; Barlow et al., 2014; Shackmana et al., ress; Versella et al., 2016), in addition to a lack of positive affect and pleasant experiences, especially on days when failure to manage and quell social anxiousness occurs, relative to controls (Kashdan and Steger, 2006). Having occurred in

[2]Anxious apprehension during the anticipation of threat in an aversive emotional state that alters behavior depending on the perceived intensity of said threat (Mogg and Bradley, 1998; Gray and McNaughton, 2000).

the context of a comparatively worse performance outcome compared with SS group, it is possible that greater anticipatory anxiety impinged on ASSs' regulatory processes, given the well-documented disruptive effects that aversive affect can have on cognitive performance quality by limiting the availability of attentional resources that could or would otherwise be allocated to serve goal-directed behavior (Bertsch et al. 2011; Plessow et al. 2012; Sänger et al. 2014; Dambacher and Hübner 2015; Qi et al. 2016; also see Easterbrook 1959; Kowalski-Trakofler et al. 2003; Dambacher and Hübner 2015). This interpretation is supported by prior research noting greater anticipatory anxiety to a public speech task in highly (trait) anxious persons (Daly et al., 1989; Addison et al., 2004; Lorberbaum et al., 2004), and social phobics (Morrison et al., 2016) relative to matched controls, which hampered public speech performance quality by focusing attention on the perceived aversiveness of the situation during preparation (for similar results, see Butler and Mathews 1987; Cain et al. 2011; Laposa and Rector 2016; Yoon and Weierich 2016). It seems as though once the attention of such persons has been directed to it to the social threat, a difficulty disengaging from and directing attention away from it is encountered (Morrison et al., 2016; Liang et al., 2017).

These findings plus ours and similar others within the literature converges on the claim that anxiety-prone persons are worse at deploying cognitive regulatory strategies under aversive conditions - that is, they less effectively exert top-down control on bottom-up emotional processes than their anxiety-normative peers (Behnke and Sawyer, 2000).

Either our ASSs inflated the probability of failure outcome as performance social evaluation draws closer, knowing that failing to perform at par would result in receiving negative psychosocial feedback (see Motley, 1990), or they became highly worried about and increasingly preoccupied with being socially scrutinized in general. Extant evidence suggests the plausibility of both scenarios: socially anxious persons, which individuals high in AS typically are (Watson and Friend, 1969), fear being negatively evaluated by others (Watson and Friend, 1969; Rapee and Heimberg, 1997; Stein

et al., 1999), making a bad impression, or acting in a way that might be embarrassing (Antony and Swinson, 2000). They tend to over-predict catastrophic outcomes that would make them subject to public humiliation, as per the availability heuristic of Kahneman et al. (1982) (also see Chung et al., 2016; Müller-Pinzler et al., 2016a). At the same time, they also tend to discount positive social interactions (Wallace and Alden 1997; although see Dedovic et al. 2015), and fear positive evaluation (Weeks et al. 2008b,a; Weeks and Howell 2012, 2014; Weeks 2015; Weeks and Zoccola 2015; Weeks et al. 2015; Barber 2015; Teale Sapach et al. 2015; Dryman et al. 2016; also see Davoudi et al. 2013; Lipton et al. 2014; Howell et al. 2016a; Kocijan and Harris 2016; Torro-Alves et al. 2016; Yap et al. 2016; Reichenberger et al. 2017), presumably because the latter can signal invitation to initiate or engage in a social interaction that is placed under attentional spotlight and must be properly navigated if one is to avoid acting in a socially undesirable manner and feeling embarrassed as a result (Ball et al., 2012; Blalock et al., 2016). In sum, greater anxious apprehension was subjectively experienced by the AS than SS group, suggesting the former perceived the impending social evaluative performance challenge as highly threatening.

Stress elicited a significant increase in subjective embarrassment in ASMSs. Our finding of a time-by-personality-by-sex interaction effect on embarrassment self-ratings, with significant increments being seen in ASMSs, confirmed our initial prediction that the combination of AS personality profile and male sex would confer the greatest susceptibility to the self-conscious emotional experience in the context of the MIST.

Prior research has shown that relative to anxiety-normative individuals, those high in the trait exhibit greater attentional shifts to their evaluative audience in public (as opposed to private) contexts (Müller-Pinzler et al. 2015; also see Liang et al. 2017), ruminate more frequently (Mellings and Alden, 2000; Rachman et al., 2000; Laposa and Rector, 2016), display negatively biased appraisals in contexts of subjec-

tive social evaluative threat (Kashdan and Roberts, 2006; Moscovitch, 2009; Shimizu et al., 2011; Lehman et al., 2015) and high demand stressors (Zunhammer et al., 2013; O'Brien et al., 2008), fear and self-blame for increases in negative evaluative feedback (Bautista and Hope, 2015; Watson and Friend, 1969; Rapee and Heimberg, 1997; Stein et al., 1999), and are more likely to experience heightened anxiety, particularly embarrassment and shame under similar situations on account of all of the above (Taylor 1995a,b; Antony and Swinson 2000; Kashdan and Steger 2006; Rohleder et al. 2007; Shimizu et al. 2011; Crisan et al. 2016; Kneeland et al. 2016; Sadikaj et al. 2015; Leary 2015; reviewed in Lehman et al. 2015). Along the same lines, one study has found that a speech stressor amplified subjective anxiety only in subjects who endorsed DTC motives (Field and Quigley, 2009). It has additionally been established that men are more reactive than women to performance-based social stressors (e.g, Stroud et al., 2002; Kudielka and Kirschbaum, 2005), with some indications that this sex variability might be specific to (nonpathological) anxiety-prone cohorts (Takai et al., 2007; Hartman et al., 2013), and could be dependent on the presence of a panel of female judges (Duchesne et al. 2012; also see Allen et al. 2014). Our subjective results reinforce the picture emerging from the aforementioned information, which suggests that the most pronounced stress response in a cognitively demanding situation involving a psychosocial evaluative pressure component will likely be exhibited by a highly anxious male who is exposed to female confederates.

Stress elicited a significant increase in subjective anger in the entire sample, independent of personality and sex. Our finding of stress-induced increments of anger self-ratings as a function main effect of time was at odds with our initial hypothesis that, based on the hypoactive and hyperactive BAS in (respectively) AS and SS persons, stress-induced increase in subjective anger would only be significant in SSSs. We should, however, point out that this hypothesis was based on the presumption that anger is associated with approach activation, which we now know to

commonly or often, but not always, be true. In detail, the anger construct reflects a multidimensional phenomenon that varies in experience and expression (Funkenstein et al., 1954; Spielberger et al., 1982; Averill, 1983), and can be conceptualized in terms of "anger-out" and "anger-in" (i.e, anger inwards outwards and inwards, respectively; Corr 2002; Smits and Kuppens 2005; Cooper et al. 2008; Guo et al. 2015; Yun et al. 2016; Eisenlohr-Moul et al. 2016; Versella et al. 2016; Russell et al. 2016; Bongard et al. 2016; Eisenlohr-Moul et al. 2016; Kidwell et al. 2016; Akutsu et al. 2016; Lee and Bierman 2016; Jasinski et al. 2016). "Anger-out", is approach-oriented and primarily associated with up-regulation of antagonism by disinhibition. Contrarily, "anger-in" is inhibition-oriented associated with behavioral inhibition and implies regulation by suppression (Smits et al., 2004; Smits and Kuppens, 2005), frequently manifesting itself when engaging in self-loathing and -blame for performance deficiencies. It is interesting in this context that some studies have found anger (assessed as a uniatry construct) to decrease cortisol secretion (e.g, Matheson and Anisman, 2009; Herrero et al., 2010; Kazén et al., 2012), while others have noted the opposite effect (e.g, Moons et al., 2010). Considered in this framework, it is plausible that our observed increase in subjective anger in the entire sample was directed inwards in the AS group, and outwards, the SS group. Though highly speculative in its nature, as the POMS treats anger as a unitary construct, this supposition is supported by careful observation of our subjects' behavior throughout the course of the MIST and thereafter that was documented by a trained doctoral student of Clinical Psychology. This supposition is also consistent with AS individuals being highly susceptible to punishment and experientially avoidant, and the opposite of just that being true of SS persons (for more information, see 4.1; Depue and Collins 1999; Lang et al. 2005; Bardo et al. 1996; Lissek et al. 2005; Roberti 2004; Joseph et al. 2009), and resonates with a recent characterization of anger profile typified by a predilection for the suppression of anger expression in social phobics (Versella et al., 2016).

Cortisol AUCi was greater in ASSs than SSSs and greatest in ASMSs. As expected *a priori*, we found that controlling for "session time", cortisol AUCi differed as a function of personality and personality-by-sex interactions, being higher in the AS compared with SS group, and in the ASM compared with the ASF and SSM subgroups. The SS sexes were comparably unresponsive (i.e, mean AUC below 0). The significance of these effects survived additional covariation for the potentially confounding effects of early-life parental care and protection, and in fact increased as a result. This remained the case after further covarying for self-esteem and perceived self-efficacy scores, although it is notable that the current 3-way interaction did not hold its significance when pre-stress cortisol values[3] were controlled for. In general, our findings are in agreement with prior research demonstrating cortisol hyper-responsiveness to acute stress in persons bearing characteristics that amplify sensitivity to social evaluation and public mistakes (e.g, low social-competence: Schmidt et al. 1999; behavioral shame-proneness: Tops et al. 2006; Lupis et al. 2016; low self-esteem: Seeman et al. 1995; Kirschbaum et al. 1995b; Pruessner et al. 1999b; Ford and Collins 2010; depressive tendencies: Kirschbaum et al. 1995b; Powers et al. 2016; dysphoria: Hankin et al. 2010; social phobia: Van West et al. 2008; Roelofs et al. 2009; and clinical anxiety in general Powers et al. 2016), and hypo-responsiveness in individuals with disinhibitory traits (Hartman et al. 2013; Evans et al. 2016a; SS: Zuckerman 1994; Netter et al. 1996; Wang et al. 1997; Rosenblitt et al. 2001; impulsivity: Moss et al. 1995; Dawes et al. 1999; Hardie et al. 2002; antisociality: Vanyukov et al. 1993; Sorocco et al. 2006; and psychopathy: O'Leary et al. 2007). Particularly, our findings corroborate those of a recent study by Hartman et al. (2013), which found that self-reported internalizing and externalizing symptomatology in teens were associated with (respectively) heightened and blunted cortisol AUCi in the context of the TSST, with the association between

[3]Pre-stress cortisol levels differed as a function of personality-by-sex interaction, being higher in ASFSs and SSMSs compared with their same-personality opposite-sex counterparts. The source of these variation is therefore unclear, but values were not statistically differ from those indicated by the two cortisol readings obtained prior.

enhanced endocrine responsiveness and the internalizing phenotype being significant for boys but not girls. Thus, it seems as though stronger endocrine stress reactivity in the male sex might depend on the presence of an internalizing personality profile and/ or the absence of an externalizing one. This point is reaffirmed by two other studies indicating, respectively, that men were more physiologically responsive to experimentally induced stress only if the sexes being compared were high in trait anxiety profile (Takai et al., 2007), and low in trait psychopathy (O'Leary et al., 2007). Such outcomes might additionally explain why the aforementioned pattern of sex difference has been noted in some studies of acute social stress (e.g, Taylor et al., 2000; Stroud et al., 2002; Kudielka and Kirschbaum, 2005; Kumar et al., 2014) but not others (e.g, Kogler et al., 2015a, 2016). It is of note, in this context, that our panel of female judges might have contributed, to some extent, to the endocrine results pattern observed, as Duchesne et al. (2012) have documented greater physiological reactivity to a public speech task in men than women when subjects were exposed to a panel of female judges.

The diminishing of our observed sex difference after controlling for pre-stressor cortisol levels is interesting, and generally consistent with the notion that higher cortisol concentration prior to exposure to negative material (naturally occurring or pharmacologically induced) could buffer stress and reduce fear by precluding, at least partially, the ability of the stressor to recruit the HPAA (Het and Wolf 2007; Het et al. 2012; van Peer et al. 2010; Bertsch et al. 2011; Walter et al. 2015; Hoyt et al. 2016; reviewed in Putman and Roelofs 2011). Whether the apparent saturation of HPAA at pre-stress in ASFSs is situational, trait-like, or some combination of both is unclear. It could be that their anticipatory anxiety fully, or almost fully, primed their anxiety circuits prior to being confronted with the stressor (see Behnke and Sawyer, 2001; Takahashi et al., 2005; Ulrich-Lai and Herman, 2009), though statistical difference between pre-stress cortisol value and those obtained prior to it were absent in this subgroup (and the three others) and might be seen as arguing against this. Conversely, said endocrine

characteristic might be trait-like, in which case it could be dependent on or independent from the female sex. Future research will be needed to sort out these and other alternative explanations.

A large body of extant evidence from humans and animals suggests that stress-evoked HPAA activation is ostensibly recruited by a more circumscribed and specific (as opposed to general) set of negative events/ conditions (Weiner, 1992, p. 243) as opposed to any and all stressors (e.g., Selye 1956; for a meta-analysis, see Dickerson and Kemeny 2004), with a number of situational components being required for the physiological stress response to be mounted: (1) a threat of negative social evaluation (as opposed to mere social presence; Dickerson et al. 2008); (2) a threat to central goals, primarily the physical and/ or social-self integrity be posed (Lazarus and Folkman, 1984; Dienstbier, 1989; Blascovich and Tomaka, 1996; Carver and Scheier, 1999; Lazarus, 1999; Gruenewald et al., 2004; Gaab et al., 2005; Lazarus, 2006; Koolhaas et al., 2011; Buchanan and Preston, 2014); and (3) a context of forced failure created (i.e, uncontrollablity; Hanson et al. 1976; Davis et al. 1977; Dess et al. 1983; Swenson and Vogel 1983; Breier 1989; Henry and Grim 1990; Sapolsky 1993; Croes et al. 1993; Peters et al. 1998; for a meta-analysis, see Dickerson and Kemeny 2004). Simple arousal and motivated performance situations are considered to be insufficient to recruit the HPAA (Lundberg and Frankenhaeuser, 1980; Lovallo et al., 1985; Dienstbier, 1989; Blascovich and Tomaka, 1996; Dickerson et al., 2004b), and the perception of the stressor as being primarily challenging as opposed to threatening has been linked to more "resilient" endocrine profiles (Lazarus and Folkman, 1984; Epel et al., 1998; Buchanan and Preston, 2014).

Understood within this framework, our endocrine findings might reflect the effectiveness of the MIST procedure in inducing a sense of helplessness, uncontrollability, and threat to social value or status in the AS group, and more so its male than female members, but not the SS group. It indeed appears to be the case that in a jarring contrast to their tensely aroused and intensely threatened AS counterparts who self-

blamed for their inferior performance, SSSs viewed the task as a motivationally salient and energetically arousing challenge that was not threatening or stressful enough to erode their sense of competence, self-worth and mastery. In the aftermath of this, they might have pursued their central goal (i.e, performing at par") harder and when they failed, attributed the Perhaps this is why they performed better than ASSs, and when they failed, attribute their "below average" performance to no fault of their own. To the extent that this is true, it could explain why the SSSs performed comparatively better on the task, as a recent meta-analysis has confirmed the ability of stress to acutely hinder executive functions through cortisol and other pathways (Shields et al., 2016).

Such outcomes can be viewed through the lens of the optimal arousal theory, which asserts that there exists an optimal level of arousal at which performance is maximized and is related to the inverted-U curve between arousal and performance Hebb 1955; also see Sapolsky 2015). Different arousal level leads people to seek or avoid stimulation to maintain optimal arousal (Eysenck, 1976), the threshold for the latter unusually high in extroverts (e.g, sensation-seekers; Lubin and Zuckerman 1969; Eysenck 1967; Zaleski 1984; Zuckerman 1971, 1979, 1984, 1994, 2016; Trofimova and Robbins 2016), and particularly low in introverts (e.g, AS persons; reviewed in Olsen et al. 2016). It is henceforth conceivable that the absolute levels of stimulation induced by the forced failure and inescapable social devaluation situation that the MIST is designed to create were comparable in the two personality groups, but led them to experience different aspects of the U-curve, hence the differential activation - and lack thereof - of the HPAA (Dickerson and Kemeny, 2004).

Most parsimoniously the general pattern of our results is consistent with two alternative endocrine pathways for AUDs development (see Majewska, 2002; Sher et al., 2005; Evans et al., 2016a): hyperarousal, characterized by an inherently exaggerated sensitivity and heightened physiological reactivity to stressors (and their anticipation) and predominantly seen in populations high in (nonclinical and (sub)clinical) anxiety

(Roelofs et al., 2009; Elzinga et al., 2010), and hypoarousal, which is fundamentally disinhibitory, can be seen somewhat the diametric opposite of the first one (Evans et al., 2016a) and is predominantly exemplified by externalizing individuals (e.g, Van Goozen et al. 1998; Snoek et al. 2004; Sorocco et al. 2006; Couture et al. 2008; Fairchild et al. 2008; Hastings et al. 2009; Vries-Bouw et al. 2011; van Leeuwen et al. 2011; Evans et al. 2012, 2013; Hartman et al. 2013; Sorocco et al. 2015; Bibbey et al. 2016; Evans et al. 2016a; also see Errico et al. 1993; Moss et al. 1995; Bernardy et al. 1996; Lovallo et al. 2000; Hardie et al. 2002; Gerra et al. 2003; Dai et al. 2007; Sinha et al. 2009; Prince van Leeuwen et al. 2014), including sensation-seekers (Netter et al., 1996; Wang et al., 1997; Rosenblitt et al., 2001; Mazur, 1995).

Notwithstanding, whether the physiological phenotypes characterized here are potentially pathogenic (i.e, present a preexisting element of vulnerability) is a question for future research and one we are unable to definitively answer. To say nothing of the fact that the current study did not include a third low-risk group, the literature remains highly ambiguous with respect to where to situate a given endocrine response on the scales of *normalcy* and adaptiveness. We know, for example, that a *normal* HPA-axis response to acute social stress is characterized by a quick increase of stress hormones (e.g, cortisol) followed by rapid recovery (i.e, an efficient return to pre-stress levels upon termination of the stressful challenge De Kloet 2004; Dai et al. 2007), but how much of an increase is too much remains unresolved (and likely varies across stress modalities). We also know that physiological unresponsiveness in the presence of a subjective stress response ('biological disengagement'[4]) is maladaptive, but whether

[4]However, such findings has typically been obtained in studies of pathologically anxious individuals, especially social phobics (Crisan et al., 2016) or depressives, so as to protect against unmanageable intense emotional arousal by reducing cortisol mobilization and attention allocation (Ginty, 2013; Tops et al., 2006, 2008). This phenomenon, purportedly meant to protect against unmanageable intense emotional arousal by reducing cortisol mobilization and attention allocation (Ginty, 2013; Tops et al., 2006, 2008), appears to develop in the aftermath of allostatic load, which tends to ensue when the HPAA is challenged/ overactivated too much and/ or too often (McEwen and Stellar, 1993; McEwen, 1998a, 2015; Crisan et al., 2016), and is associated with a host of with its possible pathogphysiolologic and psychopathologic consequences (Kaplan et al., 1982; Dienstbier, 1989; Sapolsky, 1993; McEwen, 1998a; Griep et al., 1998; Heim et al., 1998; Pruessner et al., 1999a; Gold and Chrousos, 2002; Susman, 2006; Gur et al., 2004; Cicchetti, 2002; Phillips et al., 2011; Jones et al.,

the lack of reactivity of the both the physiological and psychological stress systems, which was the case for our SSSs, stands for resilience (and if so, against what) is unclear.

Cortisol AUCi was associated with a dose-dependent increase in stress-related embarrassment self-ratings. Our finding that cortisol AUCi strongly correlated with a dose-dependent increase in stress-related embarrassment self-ratings in the entire sample combined (controlling for "session time") was expected *a priori*, is a replication of previous findings (Lewis and Ramsay 2002; Gruenewald et al. 2004; Weitzman et al. 2004; Mills et al. 2008; Dickerson et al. 2008; see also Lewis and Ramsay 2002; Gruenewald et al. 2004; Dickerson et al. 2004a; Sznycer et al. 2016; reviewed in Kahle and Hastings 2015; Leary 2015) and suggests that the mounting of a physiological stress response piggybacked on the subjective experience of embarrassment, the fact that correlation does not mean causation notwithstanding. More generally this high psychoendocrine covariance is congruent with theoretical assumptions that psychological and endocrine responses to stressors (and their anticipation; Gaab et al., 2005) represent indicators of the same construct (see Gaab et al., 2005; Schlotz et al., 2008; Kudielka et al., 2009; Balodis et al., 2010). Embarrassment being an avoidance-oriented emotion, our finding also reinforces human and animal studies linking heightened stress-related HPAA activity to socially avoidant and inhibitory behavior (e.g. freezing reactions; in humans: Van Honk et al. 1998, 2000; Roelofs et al. 2005, 2007, 2009; in animals: Sapolsky 1990; Núñez et al. 1996; Kalin et al. 1998; Cavigelli et al. 2007; Feng et al. 2016).

The observation that this relationship was maintained after controlling for the self-ratings of other mood states, namely anger, confidence, cheerfulness, relaxation and efficiency, reinforces the supposition that the experience of self-conscious emotions (e.g, embarrassment) may be vital in instigating cortisol response in the context of social

2012; Voellmin et al., 2015).

evaluative threat (Dickerson et al. 2004b,a; Dickerson and Kemeny 2004; Gruenewald et al. 2004; also see Weitzman et al. 2004; Lewis and Ramsay 2002; Lehman et al. 2015; but see Bosch et al. 2009). More broadly, this observation reaffirms the idea of specific biological fingerprints of distinct emotional states (see Adam et al., 2006; Matheson and Anisman, 2009; Herrero et al., 2010; Moons et al., 2010; Kazén et al., 2012), which is compatible with the functional account of emotions (Keltner and Gross, 1999; Kemeny and Schedlowski, 2007; Kemeny and Shestyuk, 2008; Moons et al., 2010), in that the increase in stress reactive cortisol production is inducible by only some, as opposed to any and all, aversive emotions (see Buchanan et al. 1999; Hellhammer and Schubert 2012; Weitzman et al. 2004; Lewis and Ramsay 2002; Dickerson et al. 2004b; for a meta-analysis, see Dickerson and Kemeny 2004). It is notable, in this context, that cortisol AUCi was not statistically related to absolute levels of self-reported affect throughout the course of the task, indicating that the increase in stress reactive cortisol production piggybacked on the mood change brought about by the stressor.

It is noteworthy that a dissociation between subjective and physiological responses to stress has been a frequently documented finding (e.g, Al'Absi et al., 1997; Buchanan et al., 1999; Cohen et al., 2000; Alpers et al., 2003; Oswald et al., 2004; Back et al., 2005; Abelson et al., 2005; Sinha et al., 2009; Sher et al., 2007), initially culminating in the claim that because the psychological and physiological stress systems have different dynamics and are imperfectly coupled (see Behnke and Sawyer, 1999; Addison et al., 2004; Hellhammer et al., 2009), the responses of one are uninformative and about the other's (Sher et al. 2007; Back et al. 2005; Sinha et al. 2009; also see Clevenger et al. 1967; Behnke and Carlile 1971; Carlile et al. 1977; Behnke and Beatty 1981a,b). However more recent evidence has suggested that the coupling of the psychoendocrine stress responses may be closer than previously thought (Schlotz et al., 2008; Balodis et al., 2010). It has additionally been argued that the inconsistency within the literature on this topic might be explainable by inter-study heterogeneity in terms of the construct validity of the self-report measures employed to quantify subjective stress

(Balodis et al., 2010), and perhaps compounded by a temporal lag between subjective and endocrine stress measurements (e.g, cortisol measured during the course of stressor whereas subjective stress, before and after; (Schlotz et al., 2008; Balodis et al., 2010; Hellhammer and Schubert, 2012). The study of Balodis et al. (2010) is a case in point. These authors administered the POMS (McNair, 1971) and obtained salivary cortisol readings at multiple time points during the course of the TSST, subsequently revealing high psychoendocrine covariance (Balodis et al., 2010). Our findings reinforce this latter study and recapitulate the previously mentioned points.

Acute psychosocial stress had substantial effects on brain activation in the entire sample. Conservative exploratory whole-brain analyses of the main effect of stress, i.e. "stress versus nonstress" contrast, yielded pronounced and extensive activations in a network of regions that have been systematically associated with various social cognitive functions, such as self-referential activity and self-reflective processing (e.g, precuneus and PCC; Northoff and Bermpohl, 2004; Blanke and Arzy, 2005; Northoff et al., 2006; Decety and Lamm, 2007; Ngô, 2012; Cabanis et al., 2013; Herold et al., 2015; Hu et al., 2016), aversion and its anticipation and evaluation (e.g, INS; Fiddick, 2011; Grupe et al., 2012; Lee et al., 2014; Alvarez et al., 2015; Palermo et al., 2015; Smith et al., 2016b; Levine, 2016; Zhuo, 2016; Miedl et al., 2016), introception and subjective awareness of emotionally potent stimuli (e.g, INS; Craig, 2003; Critchley et al., 2004; Lou et al., 2004; Craig, 2009; Terasawa et al., 2012; Grupe and Nitschke, 2013; Haase et al., 2016; Nguyen et al., 2016; Müller-Pinzler et al., 2016a), perspective-taking (e.g, IPL; Ruby and Decety, 2003), mentalizing and theory of mind (Allison et al., 2000; Pelphrey et al., 2003; Saxe and Wexler, 2005; Saxe, 2006; Lawrence et al., 2006; Amodio and Frith, 2006; Vuilleumier and Pourtois, 2007; Wyk et al., 2009; Iacoboni, 2009; Nolte et al., 2012; Denny et al., 2012; Takahashi et al., 2015; Mizuguchi et al., 2016; Lavoie et al., 2016), social inferences (Ciaramidaro et al., 2007; Decety and Grezes, 2006; Frith and Frith, 2010), processing of social

exclusion (Eisenberger et al., 2003; MacDonald and Leary, 2005; Eisenberger, 2012a; Cacioppo et al., 2013; Rotge et al., 2014; Woo et al., 2014; Eisenberger, 2015b,a; Müller-Pinzler et al., 2016a; Cacioppo and Cacioppo, 2016; Chester and Riva, 2016) and attentional re-orienting (Decety and Lamm, 2007; Cacioppo et al., 2009; Japee et al., 2015; Igelström et al., 2016). These included the insular and (posterior and mid-anterior) cingulate cortices, the (medial and superior) frontal and (middle and superior) temporal gyri, IPL, precuneus and the thalamus. Significant deactivation of the pgACC, a purported important mediator of the subjective threat experience (Holz et al., 2016).

Given that subjects were told they would be performing the MIST in the presence of an evaluative audience, which included but was not limited to the confederates that provided performance feedback, and considering that negative evaluation was based on a below "average" performance outcome, and subjects could see - throughout the entire course of the task - how far behind the "average" user's performance theirs trailed, the engagement of the aforementioned neural loci in said context accords well with their respective functions. Furthermore, the diversity of the aforementioned functions is congruent with the inherent complexity of and numerous processes involved in the psychological responding to acute psychosocial stress (see Eisenberger, 2015a); from the social cognitive processing which allows one to recognize that he or she has been negatively valuated by others, to the affective reactivity in this sort of situations; and from making social cognitive attributions of why social devaluation of one has occurred to one might have been socially rejected or excluded, to the modulation of control over behavioral and emotional reactions, different brain systems will likely to be recruited by each of these processes and to different extents as across different tasks or contexts (see Eisenberger, 2015a). The aforementioned activation patterns broadly resemble and overlap with those previously characterized in nonclinical cohorts in the context of the MIST (Lederbogen et al., 2011; Soliman et al., 2011; Dedovic et al., 2013, 2014; Eckstein et al., 2014; Kogler et al., 2015a) or comparable forms of stress

paradigms (Wang et al. 2007a; Drabant et al. 2011; Lee et al. 2014; Müller-Pinzler et al. 2015; Tang et al. 2016; Rudolph et al. 2016; Miedl et al. 2016; for a meta-analysis, see Stevens and Hamann 2012). as well as during provocation-based experimental manipulations designed to elicit specifically anger[5] (Damasio et al., 2000; Kimbrell et al., 1999; Grecucci and Sanfey, 2013), the latter which was a particularly strong emotional correlate of stress in our entire sample combined.

In particular, the INS is thought to be primarily involved in the introceptive awareness of emotionally laden experiences (for more details, see section 1.10.1; Stoleru et al. 1999; Simmons et al. 2005; Joseph et al. 2009). It is the core component of the "salience network", which additionally also encompasses the MCC (also known as dACC) and thalamus and activates - typically in a dose-dependent manner - to provocation-induced angry rumination (Kimbrell et al. 1999; Damasio et al. 2000; for a review, see Gilam and Hendler 2015), and to aversion and its anticipation. This activation co-occurs with "deactivation" within the pgACC via reciprocal inhibition with the MCC (Shulman et al., 1997; Drevets and Raichle, 1998; Whalen et al., 1998a; Bantick et al., 2002), presumably signifying stress-induced disruption of its regulatory function (Büchel et al. 1999; Rainville et al. 1999; Peyron et al. 1999; Ploghaus et al. 2001; Bush et al. 2002; Petrovic and Ingvar 2002; Petrovic et al. 2002; Bishop et al. 2004; Wager et al. 2004; Valet et al. 2004; Eldreth et al. 2004; Shiba et al. 2016; for more information on the pgACC, see section 1.10.2). We therefore interpret the deactivation of this system alongside enhanced salience network activity in the context of this activation as an being an indication of the motivational value of the MIST and the potency of this procedure in being emotionally potent enough to focus subjects' attention on the stressfulness of the situation.

The PCC and precuneus, on the other hand, are key nodes of the so-called default-

[5]Such studies have typically induced anger by exposing subjects to the experimenter's criticism as they lay in the MRI scanner, completely passive and unable to react (Denson et al., 2009), giving the subject an unfair offer in a money bargaining context (Feng et al., 2015) or exposing them to autobiographical memories of angry experiences (reviewed in Gilam and Hendler 2015).

mode network (DMN; Buckner et al., 2008; Fransson and Marrelec, 2008; Andrews-Hanna, 2012; Amft et al., 2015), which consistently de-activates during attention-demanding, externally-oriented, non-self-referential, goal-directed cognitive tasks (Shulman et al., 1997; Mazoyer et al., 2001; Raichle et al., 2001; Gusnard and Raichle, 2001; Greicius et al., 2003; Gusnard, 2005) and robustly activates while engaging in task-independent mind-wandering and internal mentation as well as during tasks involving social, affective and introspective processes (Damasio 1999; Maddock et al. 2001; Kelley et al. 2002; Kjaer et al. 2002; Kircher et al. 2002; Maddock et al. 2003; Northoff and Bermpohl 2004; Northoff et al. 2006; McKiernan et al. 2006; Smallwood and Schooler 2006; Mitchell et al. 2006; Mason et al. 2007; Szpunar et al. 2007; Addis et al. 2007; Schilbach et al. 2008; Christoff et al. 2009; Han and Northoff 2009; Legrand and Ruby 2009; van der Meer et al. 2010; Zhang and Raichle 2010; Jang et al. 2011; Schooler et al. 2011; Brewer et al. 2013; Herold et al. 2015; Schurz et al. 2015; for a comprehensive recent review, see Raichle 2015). The activation of this network here might thus reflect instantiation of these processes, although it is notable that both the PCC and precuneus are complex and multifaceted regions with widespread anatomical connections (Kobayashi and Amaral, 2003; Parvizi et al., 2006; Vogt et al., 2006; Kobayashi and Amaral, 2007; Hagmann et al., 2008; Saleem et al., 2008; Margulies et al., 2009; Leech and Sharp, 2014; Parvizi et al., 2006) and broad functional repertoires (Selemon and Goldman-Rakic, 1988; Tulving et al., 1994; Kapur et al., 1995; Culham et al., 1998; Nyberg, 1999; Nagahama et al., 1999; Lundstrom et al., 2003; Grefkes et al., 2004; Lou et al., 2004; Naghavi and Nyberg, 2005; Cavanna and Trimble, 2006; Gilbert et al., 2007; Cabanis et al., 2013; Müller-Pinzler et al., 2015; Mäki-Marttunen et al., 2016; Margulies et al., 2009; Vincent et al., 2008; Leech et al., 2011; Leech and Sharp, 2014; Heilbronner and Platt, 2013; Heilbronner et al., 2011; Pearson et al., 2011; Cohen et al., 2016a; Spreng et al., 2010; Leech et al., 2012; Heilbronner and Platt, 2013; Pearson et al., 2011; Cohen et al., 2016a), raising the possibility that their activation could, to some extent, reflect engagement of other cognitive processes, the exact na-

ture of which we cannot infer. It is notable that while some of the previous studies of healthy individuals have noted increased DMN activation in the context of the MIST (Lederbogen et al., 2011; Dedovic et al., 2013, 2014; Eckstein et al., 2014), other have found deactivation (e.g, Pruessner et al., 2008; Dagher et al., 2009; Soliman et al., 2011; Dedovic et al., 2009b; Khalili-Mahani et al., 2010; Grimm et al., 2014; Albert et al., 2015). This discrepancy within the literature might be explainable by a inter-study variations in terms of specific task features, such as the failure rate enforced (e.g, 60–75% as opposed to 40-60%: Lederbogen et al. 2011; and difficulty gradient of math problems: Dedovic et al. 2013, 2014). However, given that the previously cited studies in which DMN activation was found employed variants of the MIST that were intended to be more stressful than its original version used here (Lederbogen et al., 2011; Dedovic et al., 2013, 2014), it is not inconceivable that the activation of said network in our sample signifies, at least in part, failure to deactivate - that is, relative inefficiency of resource allocation between functionally competitive large-scale neurocognitive systems (see Pomarol-Clotet et al., 2008).

Last but not least, the middle and superior temporal gyri tend to preferentially activate to emotionally potent material (Narumoto et al., 2001; Stevens and Hamann, 2012) and during socioaffective processing (Morris et al., 1998; Kohn et al., 2014; Wager et al., 2003; Müller et al., 2012), although their functions are not necessarily specifically stress-related (Buckner et al. 2008; Ellison et al. 2004; Karnath et al. 2001; Stevens and Hamann 2012; also see Völlm et al. 2006). The activation of either or both gyri to aversion has been observed in normal persons across various stress modalities (Wang et al., 2005a; Goldin et al., 2008), including the MIST (Kogler et al., 2015a; Eckstein et al., 2014; Dagher et al., 2009; Pruessner et al., 2008; Wang et al., 2005a; Dedovic et al., 2013, 2014; Kogler et al., 2015a; Chung et al., 2016), presumably indicating heightened threat reactivity (Warren et al., 2013) and anxious apprehension (Warren et al. 2013; Kogler et al. 2015a; also see Wang et al. 2005a) that could hinder inhibitory functions and cognitive regulation upon stress elicitation (Warren et al., 2013). This

is probably what the activation of these regions observed here reflects as well.

Considering the aforementioned information, in combination with our subjective data indicating that the MIST was a generally upsetting and anger-inducing experience for the entire sample, we postulate that the present fMRI results collectively connote the emotional salience and motivational value of the stress element involved in said procedure and its effectiveness in jeopardizing subjects' sense of relational value and need for belonging enough to focus their attention on the unpleasantness of the situation.

SSSs showed more pronounced and extensive brain activation in response to acute psychosocial stress compared with ASSs. We had predicted, *a priori*, that in the context of acute psychosocial stress ("stress minus nonstress" contrast), the SS compared with AS group would more strongly engage brain regions subserving arousal, motivation processing and cognitive regulation. This prediction was confirmed: explanatory whole-brain analyses found that numerous brain clusters throughout the brain demonstrated a main effect of personality. These were localized to, among others, functional elements of the salience network (e.g, insula, MCC and thalamus), striatal network (i.e, caudate), dorsal attention network (e.g, SPL, dlPFC [MFG] and vlPFC [IFG]) and DMN (e.g, precuneus and PCC), and all favored the SS group. Along the same lines, functional ROIs analyses revealed greater bilateral aINS activity in SSSs compared ASSs, though these differences did not withstand correction for multiple comparisons. Uniquely to the SS group, greater (right) aINS activation magnitude corresponded to (1) higher traits SS (SURPS) and internal locus on control scores; and (2) less pronounced stress-related decrements in subjective confidence and increments embarrassment. This was in contrast to the AS group, in which aINS activity positively correlated with trait sensitivity to punishment scores and stress-elicited increases in subjective embarrassment and tension.

These findings come against a broader background of neuroimaging research doc-

umenting hyperlinks between BOLD activation within components of the aforementioned intrinsic networks under conditions of emotional challenge and internalizing and externalizing trait-based phenotypes. This literature generally suggests that BIS- and BAS- personality traits, e.g, (respectively) neuroticism and sensation-seeking, negatively and positively correlate with insular (Reuter et al., 2004; Leland et al., 2006; Iaria et al., 2008; Straube et al., 2010; Barrós-Loscertales et al., 2010; Coen et al., 2011; Kret et al., 2011; Brühl et al., 2011), thalamic (Leland et al., 2006; Straube et al., 2010; Coen et al., 2011; Brühl et al., 2011), dorsal striatal (Leland et al., 2006; Kumari et al., 2007), posterior cingulate (Kumari et al., 2007; Coen et al., 2011) parietal lobe (Leland et al., 2006; Hooker et al., 2008; Suslow et al., 2010; Brühl et al., 2011; Coen et al., 2011) and prefrontal (Canli et al., 2001; Williams et al., 2006a; Bishop et al., 2007; Hooker et al., 2008; Barrós-Loscertales et al., 2010; Kret et al., 2011; Coen et al., 2011; Lawson et al., 2012) activation to aversion and its anticipation, and to stimuli of an unknown valence and their anticipation (reviewed in Kennis et al., 2013). Such outcomes are in keeping with the longstanding idea of inter-individual variations in cognitive and affective processing as a function of the introversion-extroversion spectrum purportedly correspond to different neurofunctional features (see Peña-Gómez et al., 2011).

As detailed in the previous section, the INS, particularly the aINS, instantiates introceptive processes and together with the MCC and thalamus, encompass the 'salience network' (Seeley et al., 2007), which subserves vigilance, attention orientation and processing of emotionally potent material (e.g., Van Marle et al., 2010). Heightened activity of this network in SSSs correspondingly with increased SS scores and less pronounced negative affect, could reflect enhanced motivational value of and energetic arousal by the social evaluative pressure component of the MIST, without feeling 'stressed' in the aversive sense of the term (recognize that the 'salience network' captures motivational meaning, not directionality of valence). Our interpretation finds support in an fMRI study by Joseph et al. (2009), which found healthy young adult

sensation-seekers to display selectively stronger INS activation to high-arousal pictorial stimuli imbued within a social context than low-SS matched controls. This effect was particularly pronounced in the right aINS, occurred irrespective of emotional content and was primarily predicted by trait SS scores (Joseph et al., 2009). It thus seems as though sensation-seekers' predilection for intense arousal obviate the emotional content, leading them to focus more on the former at the detriment of the latter (Feldman, 1995; Joseph et al., 2009). Indeed, when given the opportunity to self-administer some sort of intense and unusual, but not painful, electrical stimulation, healthy SS persons have been noted to find such stimulation to be behaviorally invigorating and intrinsically rewarding (produced a subjective "high" and elevated "liking" ratings), and to seek to self-administer it at greater intensities, even at the cost of monetary sacrifice, contrarily to non-SS subjects who displayed aversion and an avoidance response (Norbury et al., 2015). It is interesting that in the latter study, said "behavioral sensation-seeking" index was diminished by antagonism at D2 receptors (Norbury et al., 2015), the same receptors of which binding in specifically the right insular cortex has previously been directly linked to human novelty-seeking (Suhara et al., 2001).

Stronger activation of the mediodorsal striatum (i.e, caudate), along with the precentral gyrus, in SSSs is suggestive of enhanced motor preparation (e.g, "fight"), if unconsciously or automatically considering that subjects laid still in the scanner and were asked not to move (White, 2009; Drabant et al., 2011). This explanation is in line with the functions covered by the caudate (White, 2009), and has been previously offered by Drabant et al. (2011), who documented the same fMRI finding in the context of a shock pain anticipation paradigm (also see Yu, 2016; Lighthall et al., 2012). This explanation is also consistent with with reports of increased approach-like speeding behavior in the face of intense sensory stimulation (Smith et al., 1990; Zuckerman, 2005; Norbury et al., 2015) and weaker avoidance response to stressors (Roberti, 2004; Lissek et al., 2005) in healthy sensation seekers relative to non-SS individuals. Such

outcomes appear to be underpinned by an overall greater DAergic tone, particularly in striatal areas (e.g, Zuckerman, 1985; Riccardi et al., 2006; Gjedde et al., 2010; Derringer et al., 2010; O'Sullivan et al., 2011; Carrasco et al., 1999; Verdejo-García et al., 2013; Ratsma et al., 2001; Eisenberg et al., 2007; Laakso et al., 2005; Cools et al., 2008; Norbury and Husain, 2015), as the striatal dopaminergic system is thought to crucially contribute to the vigor of approach behavior and generally heightened sensitivity of the BAS in this population (Zuckerman, 1990; Norbury et al., 2015).

Heightened activity of the superior parietal lobule (SPL, BA 7), dlPFC (MFG) and vlPFC (IFG) in the SS relative to the AS group suggests the invoking of some form of externally induced top-down inhibitory control to regulate bottom–up emotional processes. These regions are thought to anchor the 'dorsal attention network' of brain function (Spreng et al., 2013; Petrican et al., 2015), which reliably activates to externally-focused attention (Corbetta and Shulman, 2002; Fox et al., 2005; Toro et al., 2008; Petrican et al., 2015). The SPL is particularly involved in, among other functions, sustained visuospatial attention for nonemotional material (Pardo et al., 1991; Fink et al., 2000, 2001; Posner and Raichle, 1994; Shibata and Ioannides, 2001; Szczepanski et al., 2010; Paquette et al., 2003; Wu et al., 2016b). Its enhanced activity here could thus reflect vigilance devoid of emotion.

The ventral and lateral prefrontal cortices (respectively vPFC and lPFC) cover a wide range of executive functions (Sakai et al., 2002; Ochsner and Gross, 2005; Ochsner et al., 2012; Morawetz et al., 2016; Robbins, 2016; Rodrigo et al., 2014) and through their connections to subcortical nuclei that boost negative emotions (e.g. AMYG), they foster inhibition across an array of control-related processes (Menon et al., 2001; Rubia et al., 2001; Beauregard et al., 2001; Lieberman et al., 2006; Dagher et al., 1999; Christoff et al., 2003; Dillon and Pizzagalli, 2007; Chiu et al., 2008; Rolls et al., 2008; Ochsner et al., 2004; Davidson et al., 2000, 2007; Sotres-Bayon and Quirk, 2010; Agustín-Pavón et al., 2012; Gross, 1998; Wager et al., 2008; Heatherton and Wagner, 2011; Lindquist et al., 2012b; Sylvester et al., 2012; Viviani, 2013; Chester et al., 2016;

Morawetz et al., 2016). This is especially true of the lateral, particularly dorsolateral, prefrontal region (dlPFC; Amting et al. 2010; Bunge et al. 2001; Rodrigo et al. 2014), which is considered a core hub of the circuitry subserving cognitive regulation of negative affect (Ochsner and Gross, 2005; Ochsner et al., 2009, 2012; Peña-Gómez et al., 2011; Morawetz et al., 2015; Emmert et al., 2016), such as reappraisal (Ochsner et al., 2002, 2012; Sang and Hamann, 2007; Kim and Hamann, 2007; McRae et al., 2010; Kim and Hamann, 2012; Ray and Zald, 2012; Buhle et al., 2014; Kogler et al., 2015a; Morawetz et al., 2015) and distraction (Ochsner et al., 2002, 2004; Kalisch et al., 2006; Kim and Hamann, 2007; Blair et al., 2007), and those can be recruited consciously or automatically in the absence of explicit instruction (see Wang et al., 2007a; Mak et al., 2009; Drabant et al., 2009, 2011; Lee et al., 2014). Indeed, previous studies have shown that enhanced lPFC activity (1) correlated with lower intensity of perceived social pain during social exclusion in a virtual ball toss game (i.e, cyberball software; Eisenberger et al., 2003); (2) coincided with reduced subjective distress while observing a video of oneself (vs others) performing TSST (Lee et al., 2014); (3) decreased limbic activity in an emotional Go/no-Go task (Berkman et al., 2009); (4) co-occurred with more 'neutral' ratings of negatively valent material (Peña-Gómez et al., 2011); (5) promoted adequate performance in the presence of competing stimuli (MacDonald et al., 2000b; Bunge et al., 2001); and (6) was associated with proper suppression of the urge to aggress towards others after being subjected to their negative social feedback (Casey et al., 2011b). Such outcomes can be understood within a framework in which inhibition (of negative affect) fails when regulatory processes stop, on account of a bidirectional relation between brain systems that contribute to goal-relevant behavior and those that promote emotional responding. (Gomez et al. 2007; Blair et al. 2007; Ullsperger et al. 2010; Peña-Gómez et al. 2011; although see Chester et al. 2016 for a different perspective).

Hence, and as the dlPFC was included in the cluster showing the most profound main personality effect in the current study, a plausible interpretation of the current

finding may be that these individuals were better at distancing themselves from the aversiveness of the situation, ostensibly by automatically re-appraising it and/ or redirecting attentional processes so as to keep unwanted information "out of mind" (see Wager et al., 2004). In the aftermath of this, more "neural resources" that deal with the more 'cognitive' aspects (e.g, goal-directed or attentional networks) of the negative situation became available for allocation. Hence the better performance quality and more resilient subjective and endocrine response profiles that evinced in SSSs relative to their AS counterparts, whose regulatory processes appear to have been hijacked by and most of their attentional resources summonsed to dealing with the aversiveness of and psychologically intense sense of threat induced by the cognitively demanding situation (see Phelps, 2006).

If true, this could help explain the propensity of AS (and generally neurotic) individuals for developing anxious (and depressive) psychopathologies and the resilience of SS to them, as reappraisal compared with avoidance/ suppression of negative affect has been linked to more adaptive emotion responding patterns, lower risk of clinical emotional dysregulation, higher social functioning, better mental health status and higher life satisfaction relative to (John and Gross 2004; Kim et al. 2016a; also see Hankin et al. 2005; Marganska et al. 2013; von dem Hagen et al. 2013).

A compromised 'line of defense' in cognitive control areas in contexts of negative emotional processing on part of (nonpathological) anxiety-prone individuals is a usual finding in the literature (Drabant et al., 2011; Sussman et al., 2016; Kim et al., 2016a). For example, neurotic individuals underactivate, whereas extroverts activate, the lPFC during a social exclusion (odd-ball) paradigm (Eisenberger et al., 2005), and while engaging in inhibition tasks (Sosic-Vasic et al. 2012; Rodrigo et al. 2016; reviewed in Kennis et al. 2013). Attenuated prefrontal and orbitofrontal activity is shown by individuals high in anxiety, or dimensions thereof (e.g, SA) during symptom provocation (Wik et al. 1993; Johanson et al. 1998; Van Ameringen et al. 1998; Fredrikson et al. 1995, 1993; Bremner et al. 1999; although see Reiman 1997; Shin

et al. 1997). Further, when the intensity of anticipated threat (i.e. electrical shock) goes from moderate to strong, those high in neuroticism (relative to those who are not) have been found to deactivate the middle and inferior frontal gyri, perhaos alluding to suppression (Drabant et al., 2011). In a similar fashion, highly compared with lowly neurotic (nonclinical) persons also deactivate (BA 46 - containing part of Middle FG and IFG) when anticipating threat (i.e. electrical shock) of strong relative to moderate intensity (Drabant et al., 2011). These findings, and ours, represent an extension of a clinical literature documenting said phenomenon in cohorts with pathological emotional dysregulation including social phobia (Kamphausen et al., 2013; Heeren et al., 2016; Hwang et al., 2016; Perez et al., 2016), and dovetail nicely with functional connectivity studies indicating attenuated functional connectivity in neural networks subserving in cognitive and affective control in across nonclinically neurotic persons (Gao et al., 2013; Servaas et al., 2015; Rodrigo et al., 2016), in contrast to stronger functional connectivity in similar brain networks across extroverts (Haas et al., 2007; Adelstein et al., 2011; Gao et al., 2013). It is interesting, in this context, that disrupted structural integrity of the WM tracts interconnecting the lPFC with emotional hub networks (AMYG) has recently been been reported in (nonpathologically) neurotic individuals (Xu and Potenza, 2012), perhaps alluding to a fundamentally and at least partly "hard-wired" problem of a problem emotional dysregulation, considering that the WM microstructure is 96% genetic (Jansen et al., 2015). It is also notable that that in the above discussed study by Drabant et al. (2011), neurotic subjects did, in fact, increase their prefrontal (BA 46) activation from "safe" to "medium" threat trials, and only from "medium" to "strong" trials did they come to prefrontally deactivate. These researchers consequently postulated that at a sufficiently high threshold threat level, neurotic persons seem to go from being frightened to panic stricken, which leads them to shut down and switch their avoidance system "on". Hence, and as our cohort of AS individuals showed deactivation in prefrontal areas including the dlPFC, it could very well be that the threat intensity posed by the MIST to these subjects

has passed the threshold to which the Drabant study referred (Drabant et al. 2011; also see Straube et al. 2009a). Though speculative in its nature, this proposition is in line with the avoidance coping style that exemplifies AS individuals, and adheres to an abundant evidence for the proclivity of neurotic people to resort to avoidance (McCrae and Costa, 1986; Bolger, 1990; Parkes, 1986) and/or suppression (Canli et al., 2001; Drabant et al., 2011) as coping mechanisms in the face of intense subjective distress.

Finally, the greater activity exhibited under stress by the SS compared with AS group in the precuneus, PCC and IPL, all of which cover complex social functions required for successful social interactions (Amodio and Frith, 2006; Carter and Huettel, 2013; Cavanna and Trimble, 2006) and have been ascribed to the intrinsic DMN (detailed in section 4.2; Gusnard and Raichle 2001; D'Argembeau et al. 2005; Christoff et al. 2009; Mason et al. 2007; Raichle et al. 2001; Simpson et al. 2001; McKiernan et al. 2006; Brewer et al. 2013; Raichle 2015), might suggest that SSSs more strongly engaged in mentalizing, perhaps by means of self-referential processing and self-reflective judgement (see Gallese and Goldman, 1998; Keysers and Gazzola, 2007; Meltzoff et al., 2010; Herold et al., 2015). That is, they were more preoccupied with trying to understand or predict the mental state of the confederates as it related to them (see Muscatell et al., 2012, 2016) and potentially more aware of the negative evaluative feedback administered in this stress paradigm (see Eckstein et al., 2014). Considered in the context of the comparatively greater prefrontal activation shown by SSSs (above), we propose a scenario whereby the DMN acted alongside of frontoparietal networks to promote effective cognitive regulation of negative affect, suspectedly by culminating in a self-serving bias of sorts (e.g., "I am not to blame for my trailing performance"). Though this theory should be directly tested in future research, it is congruent with a recent report finding that some functional nodes within the DMN, more specifically the recently characterized 'social-DMN' (e.g, precuneus, see Schilbach et al., 2012) co-activated with the dlPFC and vlPFC during social cognitive regulation of negative affect, with a correspondingly increased regulatory success (Xie et al., 2016). Also in

support of this proposition is evidence indicating that co-activation of the DMN with frontoparietal networks while engaging in goal-oriented tasks might promote flexible allocation of cognitive processes under cognitively challenging conditions in the service of adequate task performance (Pearson et al., 2009, 2011; Heilbronner et al., 2011; Heilbronner and Platt, 2013; Leech et al., 2012; Cohen et al., 2016a).

In sum, SS compared with AS subjects more strongly engaged regions involved in arousal, reinforcement, motivation processing, externalized attention and internal mentation in the context of an acute psychosocial stressor, suggesting they were comparatively more energetically aroused and motivationally engaged in, yet still less intensely threatened by the MIST procedure.

MSs activated more brain regions and more strongly the same brain regions than FSs. Numerous brain clusters and one spherical ROI demonstrated differential activity as a function of main effect of sex, with all such differences favoring males. Clusters showing sex effects were distributed throughout the brain and located in the midbrain, cerebellum, lingual gyrus, insular and midcingulate cortices, parietal regions (postcentral and supramarginal gyri), temporal areas (e.g, STG) and frontocortical regions (e.g, precentral gyrus, MFG, IFG and SFG). Spherical ROIs activating differently between the sexes were the aINS and pgACC. Analyzing the association of aINS activity with stress-related mood self-ratings, no significances were found when the male subgroups were analyzed together. When analyzed separately, however, aINS activation was found to correlate positively (vs negatively) with a dose-dependent increase in subject embarrassment in ASMSs (vs SSMs). This departure from orthogonality resonates with the dichotomy of the behavioral, subjective and endocrine response profiles exhibited by ASMSs and SSMSs and in combination with the sex activation differences in other neural loci, reflect more intensely arousal and greater motivational involvement in the MIST as a function of the male sex without without necessarily capturing emotional content (see Li et al., 2006; Salamone, 1994;

Bromberg-Martin et al., 2010). Thus, while previous studies have shown that aINS activity corresponded to shame, embarrassment or guilt emotions (recently reviewed in Bastin et al. 2016), ours suggest that the picture shifts in the case of sensation-seekers, which again reaffirms the notion that shared neural activations do not necessary map onto shared psychological experiences and is in keeping with the general idea of valence-general responsivity as a feature of large-scale brain activity (Guillory and Bujarski 2014; Chikazoe et al. 2014; Lindquist et al. 2016; although see Kragel and LaBar 2016).

We know of only one other study to date that has assessed sex differences in neural responding in the context of the MIST in healthy young adults (Kogler et al., 2015a). That study found (1) enhanced AMYG activity in women but not men; (2) stronger STG activity in women compared with men; and (3) stronger putamen activity in men compared with women (Kogler et al., 2015a). The investigators suggested that women were more emotionally involved in the task, whereas men were more motivationally engaged (Kogler et al. 2015a; also see Taylor et al. 2000; Stroud et al. 2002; Kumar et al. 2014; Kogler et al. 2016). Bearing in mind that important methodological discrepancies between the Kogler et al. (2015a) study and ours abound and thus direct comparability of findings is not possible, we provide replication for the finding of a greater putamen activation in men compared with women subjects. Thus, and as putamen activity is known to promote motivation processing ("fight-or-flight"), we propose that our male subjects were, similarly to those in the Kogler et al. (2015a) study, more motivationally engaged than their female counterparts. This interpretation is in line with the functions of the other regions that more strongly activated as a function of the male sex, and it is notable that this list of regions overlaps with that provided by the comprehensive meta-analysis of Stevens and Hamann (2012), which too, included the precentral gyrus, IFG, INS, STG, putamen, lingual gyrus (although note that most studies included in that meta-analysis involved the use of aversive face or other negative pictorial stimuli, which are ecologically valid but differ from the

MIST in both form and affect, and have distinct neural correlates because of that (see e.g, Pruessner et al., 2008; Dedovic et al., 2013).

It is notable that a pattern of sex differences in regional brain activation in socially stressful and/ or cognitively demanding situations, whereby all differential activations favor the male sex is not an unusual finding in the literature. Lee et al. (2014) administered the TSST to a sample of healthy adults and subsequently MRI scanned them as they watched video clips of themselves (versus a same-sex apparently non-stressed other) performing said task, and noted lower self-reported stress scores concurrent with strongly activated neural structures subserving cognitive control (e.g, IFG) and regions implicated in introceptive awareness (e.g, INS) in men compared with women, with no activation differences that favored female subjects. In a similar vein, Li et al. (2006) used an inhibitory control paradigm (Stop Signal Response Task) and observed stronger recruitment of the cortical and subcortical brain areas, including the medial frontal and cingulate cortices, thalamus and parahippocampal gyrus in male than female subjects, in the absence of sex differences in task performance. In this study, too, no brain regions activating more strongly in female in than male subjects (Li et al., 2006). In sum, the motivational value of our acute psychosocial stressor was greater for male compared with female subjects, irrespective of personality profile.

SSMSs activated more emotion regulatory and default brain regions brain than other subgroups. Exploratory whole-brain analyses and functional ROIs analyses found personality-by-sex interaction effects on the "stress minus nonstress" contrast in (respectively) a number of brain clusters (localized to the ACC, SFG, MFG and IPL) and one ROIs, namely the mOFG. Differential activations in the aforementioned neural loci all favored SSMSs over their same-sex opposite-personality and opposite-sex same-personality counterparts, suggesting that the current 2-way interaction was mainly driven by the SSM subgroup. Considering these differences in the context of SSMS' task performance, which was better than ASMSs' and compara-

ble to SSFs', and their subjective and endocrine stress response profiles, which were more 'resilient' than ASMSs' and (statistically) the same as SSFSs', we interpret our present fMRI findings as suggesting that SSS were were better at exerting top-down regulation of bottom-up emotional processes than ASSs, but had to more strongly engage more self-referential processes and cognitive regulatory functions than SSFSs in order to perform comparably on the task, perhaps because the stress component of the MIST held more salience to them and made it more difficult to suppress their initial bias to preferentially attend to the anger-inducing characteristics of the situation (recall that mOFG activation was inversely associated with a dose-dependent increase in subjective anger in the entire sample combined).

Whether this exertion of greater effortful control to prevent their subjective anger experience from becoming more pronounced and maintain focus on the central goal of achieving "at par" is 'excessive', which would connote a defective cognitive control neurocircuitry, is not entirely clear, and it is interesting that SSFSs substantially deactivated the mOFG while still managing to perform comparably to SSMSs. We would point out, though, that this pattern of fMRI response differences is immediately reminiscent of a recent study by Smith et al. (2014), in which cocaine addicts and regular recreational users (8 years) respectively activated and de-activated the OFG in an emotionally challenging context (cocaine-related cues), with only the dependent users being preferentially attentive to cocaine cues[6] (Smith et al., 2014). The authors went to suggest that decreased OFC activity in the recreationally using group possibly indicated that they did not perceive drug-related cues to be as salient as did their dependent counterparts, and hence their apparently less prevalent need to exert much neural effort so as to disengage from the distracting drug stimuli (Smith et al., 2014).

As such, we postulate that the fMRI response differences between the SS sexes allude to resilience on part of SSFSs against this form of stress manipulations, though

[6]attentional bias to drug-related cues has been linked to increased motivation to obtain the substance, as well as heightened emotional salience for these cues (Goldstein and Volkow, 2002; Field and Cox, 2008; Smith et al., 2014).

the generalizablity of this resiliency to other stressful situations that are not known to evoke stronger reactivity in the male sex remains to be determined. Note that the prospective association of mOFG activation in the context of the MIST and escalating drinking was addressed in part 2 of our study and is discussed in section 4.3.

No differential hippocampal activation was detected. While we are unable to definitively explain the absence of significant results with respect to the HC, especially in ASMSs who demonstrated the most pronounced stress responsiveness among all subjects. Deactivation of this region, typically in association with dose-dependent AUCi, has been a recurring theme across most studies incorporating the MIST (e.g, Soliman et al. 2011; Lederbogen et al. 2011; Dedovic et al. 2009b,a; Pruessner et al. 2008; Khalili-Mahani et al. 2010; Grimm et al. 2014; Dagher et al. 2009; Albert et al. 2015; but see for exceptions Dedovic et al. 2013, 2014), and it has been argued that this response *per se* reflects a specific type of stress response (for more information, see section 1.10.2). Bearing in mind that methodological discrepancies between the aforementioned studies and ours in terms of, among other variables, personality composition and sex-bias of ascertained sample), preclude direct comparability, it might be speculated that while the MIST procedure was designed to instigate a specific type of stress (i.e, subjective social evaluative threat), in certain individuals (e.g, AS persons) it might (alternatively or additionally) instigate another that on a neural level is not identically processed. It could alternatively be speculated that the same type of stress is differentially processed in some individuals, AS persons being among them, with the governing neuronal substrates not including the HC. A third possible scenario is that the stress induced by the MIST in ASMSs was too mild and its induced increase in cortisol secretion not significant enough for hippocampal deactivation to occur. If true, the hippocampal activation which trended towards significance in this subgroup could connote increased modulation of the HPAA to a relatively mild social stress, thus indirectly confirming the regulatory function of the HC. (see Dedovic et al., 2013,

2014). While the observable behaviors of ASSs, especially ASMSs pointed to fairly high levels of anxiety and thus suggest that this scenario is perhaps unlikely, absent inclusion of a group that is both AS- and SS- normative precludes our ability to rule it out. Future research will need to sort out these and other alternative explanations by systematically disentangling the aforementioned elements of the stressful situation while also accounting for personality composition on internalizing and externalizing dispositions and specific aspects thereof.

Alcohol decreased cortisol AUCi and increased activation of reward-related and emotion regulatory brain regions in ASSs, specifically ASMSs. Our finding that in ASSs, specifically ASMSs, alcohol attenuated endocrine stress reactivity, and enhanced the activation of the NAc, pgACC and mOFC to social stress relative to placebo is generally consistent with our primary *a priori* hypothesis that to the extent that ASSs are reactive to and tensely aroused by acute social stress under placebo, alcohol would bring them relief from their stress and negative affect.

The decrease in HPAA activation to stress as a function of intoxication presumably signifies our predicted SRD effects, the dissociation between the subjective and physiological stress systems under alcohol notwithstanding. Prior research has found that among FHP individuals, it was those who were high cortisol responders to acute stress (when sober) that drank most (Brkic et al., 2015), and it was those same individuals that were also most sensitive to alcohol's sedative properties (Brkic et al. 2016; also see Taylor et al. 1990; Croissant and Olbrich 2004; Hefner et al. 2013). These findings plus ours, allude to negative reinforcement of drinking behavior via inhibition of stress reactive cortisol production in individuals who are most physiologically reactive to acute stress when sober, those being apparently high in internalizing traits and, by virtue, highly susceptible to alcohol's sedative properties. A similar results pattern has emerged from studies of other anxiolytic drugs, such as heroin (Walter et al., 2013; Gerber et al., 2012; Schmidt et al., 2014) and oxytocin (Heinrichs et al. 2003; Domes

et al. 2007; Mitchell et al. 2015; Koch et al. 2015; Kanat et al. 2015; also see Miller et al. 2015), and generally culminated in similar claims.

The mOFG and pgACC are, as detailed in sections 1.10.2 and 1.10.2 respectively, both target regions for cortisol (Pruessner et al., 2010) and are key modulators of limbic, especially AMYG responsiveness, particularly under conditions of stress and negative affect (Diorio et al., 1993; M.L. et al., 2003; Pezawas et al., 2005; Eippert et al., 2007; Pessoa, 2008; Canterberry and Gillath, 2013). Enhanced pgACC activity consistently coincides with attenuated intensity and unpleasantness of perceived pain, social or physical (Bush et al., 2002; Bantick et al., 2002; Büchel et al., 1999; Petrovic et al., 2002; Peyron et al., 1999; Ploghaus et al., 2001; Rainville et al., 1999; Valet et al., 2004; Wager et al., 2004), which resonates with our observed inverse association between this region's activation and stress-induced increase in self-reported negative affect under alcohol, particularly embarrassment. The mOFG also activates in a dose-dependent association with perceived pain (e.g, Valet et al., 2004), though it appears to play a particularly prominent role in provocation-based and/ or anger-infused situations, often correspondingly with emotion regulatory success. Such is consistent with the unique inverse association noted here between the mOFG activation and stress-induced increase in self-reported anger under alcohol. The NAc, on the other hand, most consistently activates to rewards and their cues (Knutson et al., 2001; Reynolds and Berridge, 2002; Schultz, 2004; Ernst et al., 2004; May et al., 2004; Kelley, 2004; Ernst et al., 2005; Monk et al., 2008b; Alvarez, 2016; Collins et al., 2016; Hikida et al., 2016; Braams et al., 2016), and its stimulation is known to attenuate state anxiety (Sturm et al., 2003; Bewernick et al., 2010; Denys et al., 2010) and depressed affect (Bewernick et al., 2010). Resultant euphoria ("high") (Brunelle et al., 2004) has also been frequently described, although typically in externalizing individuals, who consequently go on to show an acute increase in risk-taking behavior (Gilman et al., 2012b). Based on the aforementioned regions' respective functions and association patterns with mood in the context of our investigation, their enhanced activity

in our cohort of AS young men under alcohol intoxication relative to placebo may be interpreted as reflecting, as does their decrease cortisol AUCi, the SRD effects of alcohol. Considered in the context of their improved task performance when intoxicated relative to sober, a finding that was not necessarily expected, it is plausible that in the aftermath of alcohol's SRD effects, dissipation of bottom-up emotional responses left available for "grabbing" by the task itself as opposed to the social threat it poses, hence the improved performance quality. (Fairbairn and Sayette, 2014, see).

This interpretation is speculative in its nature, and might perhaps, at first glance, appear to be counter-intuitive on account of the well-recognized acutely disruptive effects of alcohol on prefrontal functioning (Yuille and Tollestrup 1990; Lyvers and Maltzman 1991; Peterson et al. 1990; Holloway 1995; Chermack and Giancola 1997; Mulvihill et al. 1997; Eckardt et al. 1998; Finn et al. 1999; Easdon and Vogel-Sprott 2000; Dysart et al. 2002; Weissenborn and Duka 2003; Schreckenberger et al. 2004; Calhoun et al. 2004; Benton et al. 2006; Schweizer et al. 2006; Mintzer 2007; Guillot et al. 2010; Schreiber Compo et al. 2011; Heinz et al. 2011; Oorsouw and Merckelbach 2012; Hagsand et al. 2013; Harvey et al. 2013; Gorka et al. 2013; Colloff and Flowe 2016; recently reviewed in Weafer and Fillmore 2016). It however aligns well with a previous neuroimaging report of potentially desirable effects of acute alcohol intoxication, at least temporarily, for certain individuals, because it decreases anxiety without hindering cognitive performance (Trim et al., 2010), and resonates with findings suggesting that in some instances, alcohol can have no effects, or even beneficial effects on cognitive functions such as (see Mintzer and Griffiths, 2001; Colflesh and Wiley, 2013).

Interpreted this way, the present fMRI and endocrine findings, corroborate the self-medication and tension-reduction models of alcohol use (Conger, 1956) and the negative affect regulation pathway for AUDs development.

Alcohol increased cortisol AUCi and deactivated emotion regulatory brain regions in SSSs, especially SSMSs. Our finding that in SSSs, especially SSMSs, alcohol stimulated the HPAA activation and deactivated the mOFG to acute social stress relative to placebo is consistent with our initial prediction that the MIST procedure motivationally engages and holds salience to SSSs when sober, alcohol would disinhibit their prefrontal functioning and up their physiological arousal level. The increase in HPAA to stress as a function of intoxication purportedly confirms exactly that. Though the effects of alcohol on the HPAA remain poorly characterized, if repeatedly documented Croissant and Olbrich 2004; Cobb and Thiel 1982; Elias et al. 1982; Rivier et al. 1984; Merry and Marks 1969; Dai et al. 2007; Välimäki et al. 1984; Magrys et al. 2013; Brkic et al. 2015, and we are unaware of any previous studies that have examined the effect of alcohol intoxication on the endocrine responding of sensation-seekers or externalizing persons in general to acute stress, the general pattern of the current endocrine finding lends support to the sensation-seeking hypothesis, which predicts that inherent hypoarousal leads to the deliberate seeking-out of substances of abuse in order to increase arousal (see Goeders, 2003; Koob and Kreek, 2007; Evans et al., 2016a). This finding additionally resonates with previous alcohol challenge studies finding that pre-stressor alcohol administration attenuated physiological responsiveness to stress in FHN but not FHP individuals (Dai et al., 2002b, 2005, 2007), FHP persons known to frequently score high on measures of disinhibitory traits including SS (see e.g, Peterson et al., 1996; Assaad et al., 2003). Unresolved, though, is whether this stimulatory effect on HPAA activation corresponded to enhanced sensations of stress in the aversive sense of the term. The absence of an association between cortisol AUCi and self-related negative mood ratings under the alcohol condition could be seen as arguing against an answer in the affirmative. Furthermore, there are indications in the human and animal literatures that for certain subjects, stimulation of the stress systems along with resultant increase in glucocorticoid secretion could suggest that alcohol acted as an energizer and euphoriant (see Piazza

et al. 1993; Deroche et al. 1993; Fahlke et al. 1994a,b, 1995, 1996; Fahlke and Hansen 1999; Lamblin and De Witte 1996; for reviews, see Miczek et al. 2008; Sinha 2008; Cleck and Blendy 2008; Uhart and Wand 2009; Melis et al. 2009; Becker et al. 2011). At the same time, a scenario whereby intoxication in the context of the MIST did cause SSSs to feel more stressed, perhaps via frontal disinhibition, is not inconceivable and, if indeed true, could buffer SS persons from resorting to alcohol under stressful situations and thus explain why it is very unlikely that these individuals escalate in drinking through the negative affect regulation pathway. This would also help explain why it is that some studies of normal individuals have found alcohol to produce, as opposed to reduce, anxiety (e.g, Cappell, 1987; Pohorecky, 1991), and stress to predict voluntary alcohol consumption only in certain (e.g, highly anxious) individuals (e.g, Magrys and Olmstead, 2015).

The mOFG deactivation that evinced in this group as a function of intoxication is consistent with our aforementioned postulations, as does our anecdotal observation that under the influence of alcohol, sensation-seekers (but not ASSs), especially males became noticeably more hostile and antagonistic towards the confederates, relative to placebo (see Coccaro et al., 2009; Böhnke et al., 2010b; Bertsch et al., 2011).

Considering this change in fMRI response alongside the worsened performance quality and increased cortisol AUC, and then juxtaposing those to the enhanced mOFG activity, improved performance and decreased cortisol AUC that evinced in ASMSs under alcohol relative to placebo, we are tempted to conclude that it was these diametrically opposing response changes in mOFG activity largely contributed to the aforementioned paradoxical patterns of change in task performance and endocrine responding, although we cannot definitively prove causation. Through its deactivation of the mOFG, bilaterally, alcohol might have led the higher-order cognitive faculties of SSMSs to lay dormant, thus hindering their capacity to regulate emotion and to inhibit automatic and inappropriate behaviors and properly contain their heightened level of state arousal in order to maintain goal-focused behavior in a cognitively

demanding situations involving the pressure of time and negative psychosocial evaluation. That, perhaps in combination with an unsettling sense of uncontrollability and alcohol-induced propensity for hostile attribution biases might could have led them to feel angry and stressed (see Luna et al., 2004; Luijten et al., 2014). Poorer performance and greater endocrine responsiveness (relative to placebo) might have occurred in the aftermath of this. While speculative in its nature, and other readings of our findings are certainly possible, this proposition is supported by our observation that in the entire sample, combined, deactivation of the mOFG to acute social stress was associated with a dose-dependent increase in (1) stress-related anger self-ratings; (2) the rate of incorrect responses to math problems; and (3) cortisol AUCi, the correlative nature of these associations notwithstanding. This explanation also fits nicely within a literature suggesting that stress-induced anger in the context of the MIST dose-dependently can impair performance in healthy adults (Kazén et al. 2012; also see Nater et al. 2007; Okon-Singer et al. 2016), provoke aggression in healthy individuals positively correlates with reactive cortisol production (Gerra et al. 2007; Böhnke et al. 2010b; also see Böhnke et al. 2010a); (2) the OFC may be more responsive to stimuli signaling anger than other emotions (Murphy et al., 2003); (3) alcohol might more robustly effect the response of the OFC to signals of anger relative to other emotions (Gorka et al., 2013); and (4) that in externalizing individuals, alcohol primarily acts by targeting and disrupting higher-order frontocortical functions and impairing top–down, strategic processing, thereby producing disinhibition (de Wit et al., 2000; Marczinski et al., 2005; Marinkovic et al., 2012) and hampering goal-directed action (Marinkovic et al., 2012).

Being that the vital role of mOFG in down-regulating reactive aggression has been recognized for decades (Ohira et al. 2006; Muehlberger 1957; McDonald 1991; Anderson et al. 1999; Blair et al. 1999; Davidson et al. 2000; Rule et al. 2002; Izquierdo et al. 2005; Coccaro et al. 2007; Marsh et al. 2008; Jones et al. 2009; Fabiansson et al. 2012; Márquez et al. 2013; Attwood and Munafò 2014,?; Gilam and Hendler 2015;

Shiba et al. 2016; Sierra et al. 2016), our findings of the opposite patterns of alcohol-induced change in mOFG response to stress in the personality groups suggest that the susceptibility of this regulatory region to the acute effects of alcohol might be limited to a specific subset of individuals, those including sensation-seekers, especially male sensation-seekers. This premise is highly consistent with extensive evidence for the unique susceptibility of individuals bearing a certain risk profile to alcohol-heightened aggression, (LeMarquand et al. 1999; Pihl and Sutton 2009; Heinz et al. 2011; also see Perna et al. 2016), with the list of risk factors including high trait SS scores (Cheong and Nagoshi, 1999; Jonah et al., 2001; Heinrichs et al., 2003; Pihl and Sutton, 2009), male sex (Giancola and Zeichner, 1995; Pihl and Sutton, 2009; Giancola et al., 2009; Wiley, 2014), older adolescence and young adulthood age (Pihl and Sutton, 2009), enhancement drinking motives (Assaad et al., 2006; Pihl and Sutton, 2009; Mihic et al., 2009), with situational features, such as provocation (Giancola et al., 2002; Taylor et al., 1979), threat (Taylor et al., 1976; Gallagher et al., 2014) and social pressure (Taylor and Sears, 1988; Pihl and Sutton, 2009) likely interacting with all of the above to instigate or exacerbate alcohol-related aggression (Pihl and Sutton, 2009; Heinz et al., 2011).

This behavioral tendency has been interestingly noted by numerous research groups under nondrug conditions in pathologically aggressive populations (e.g, intermittent explosive-, conduct- and antisocial personality- disordered individuals; Matthews and Norris, 2002; Helfritz-Sinville and Stanford, 2014, 2015; McCloskey et al., 2016), alongside (particularly medial) orbitofrontal hypothactivity during the processing of effectively salient negative stimuli/ in contexts of acute emotional challenges (e.g, Herpertz et al., 2001; Donegan et al., 2003; Dougherty et al., 2004; Schmahl et al., 2004; Blair, 2008; Schulze et al., 2011; Huang et al., 2014; Herpers et al., 2014), among other irregularities in this region (Davidson et al., 2000; Pol et al., 2001; Blair, 2003b; van Elst et al., 2003; Coccaro et al., 2007; Passamonti et al., 2012). Thus, blunted OFC activation in SSMSs may contribute to many of the well-known dysregulated emotional

and behavioral consequences of alcohol use including increased risk-taking (Morris and Albery, 2001; Burian et al., 2002), aggression (Hull and Bond, 1986; Bushman and Cooper, 1990; Ito et al., 1996; Chermack and Giancola, 1997; Parrott and Giancola, 2004; Heinz et al., 2011; Gan et al., 2015). and impaired inhibitory control (de Wit et al., 2000; Marczinski et al., 2005; Euser and Franken, 2012), angry driving, sexual risk-taking (Halpern-Felsher et al., 1996; George and Stoner, 2000), driving while drunk and the risk of automobile accidents (Koelega, 1995), all of which outcomes that we know are more prone to manifest themselves in SS under alcohol than those who score low in this trait and the broader externalizing construct.

Left unresolved in the present study is whether SSSs, particularly SSMSs, recruited the mOFG and other prefrontal regions to excess when sober, resulting in alcohol intoxication functioning as a *de facto* 'downer' for an overworked/ fatigued prefrontal functioning system that is is challenged too frequently or too heavily. As is the case with just about everything, more prefrontal activity is not always better and can sometimes be bad, if still temporarily adaptive ("too much of anything will eventually suppress something"; Chester et al., 2016).

Finally, our finding of no alcohol-produced change in accumbal activation in either of the SS subgroups was not surprising. Even though findings of studies examining altered activation within the NAc in high risk persons (e.g, FHP, high trait SS scores) have reported inconsistent and frequently contradictory finding (for more details, see section 1.9.1.2), the picture emerging from the literature seems to suggest that comparatively weaker NAc activity to reward (e.g, monetary) and/ or its anticipation in high-risk persons might reflect a resilience mechanism (e.g, no personal history of alcohol misuse; Andrews et al. 2011; Yau et al. 2012), as the opposite phenotype (enhanced NAc activity) might specifically mark problem drinker FHP individuals (Yau et al., 2012), and has been described in association with a dose-dependent increase in externalizing symptom severity and lifetime drinking (Yau et al. 2012; also see Lopez et al. 2014; Cservenka 2016), a propensity for self-dyscontrol (Lopez et al., 2014) and sub-

sequent escalating drinking (Dager et al., 2014). Based on this and the fact that our subjects were high-functioning and relatively intelligent university students, increased NAc activation by alcohol would have falsified our working hypothesis.

Summary. The MIST procedure (Dedovic et al., 2005) was upsetting to and increased subjective anger in the entire sample. However, it only elicited an increase in stress reactive cortisol production in ASSs, and effect that was mainly driven by ASMSs and apparently piggyback on the amplified subjective experience of embarrassment. Neural activation patterns in response to the "stress versus nonstress" contrast indicated that SS compared with AS subjects were more energetically aroused and motivationally engaged, and less emotionally involved and subjectively threatened, which appears to have contributed to their comparatively better task performance outcome. The motivational values of the task was greater to male than female subjects, irrespective of personality profile. Further, SSMSs more strongly engaged regulatory processes than SSFSs, likely a result of the greater salience held by said task to them.

Alcohol challenge altered the endocrine and neural responses to stress in both personality groups. These effects were more significant or only significant in the male subjects and diametrically opposing: alcohol relative to placebo dampened HPAA activation of ASSs, specifically ASMSs, to stress while enhancing the activity of cognitive regulatory brain brain regions and their performance on the task. The opposite of exactly that was the case for SSSs, especially SSMSs. Such outcomes are likely indicative of the alcohol-induced calming and stress-dampening effects on the AS group, and energizing and stimulating, and maybe stress-promoting effects on the SS group.

The pattern of the aforementioned findings is consistent with the two alternative pathways for AUDs development, namely negative affect dysregulation and disinhibition (Victorio-Estrada et al., 1996; Verheul et al., 1999; Colder and O'Connor, 2002; Sher et al., 2005; Stewart and Pihl, 1994; Stewart et al., 1999; Stewart and Kushner, 2001; Conrod et al., 1998; MacDonald et al., 2000a; Hussong et al., 2011; Zucker et al.,

2011).

The starkly different effects of alcohol on stress reactivity as a function of personality profile, and the dependency of the extent of those effect on sex, help explain the inconsistencies and even contradictions within the literature on the acute effects of alcohol intoxication on anxiety/ stress (see Cappell and Herman, 1972; Cappell, 1987; Hodoson et al., 1979; Pohorecky, 1991; Sayette, 1999; Thomas et al., 2012; Levenson, 1980; Borrill et al., 1987; Sayette et al., 1992; Cooper et al., 1995; Khantzian, 1997; Kushner et al., 1996; Baker et al., 2004; Sher et al., 2007; Stevens et al., 2008, 2009; Moberg and Curtin, 2009; Hefner and Curtin, 2012; Hefner et al., 2016) and on risk taking behavior (see Teger et al., 1969; Dougherty et al., 1999; Lane et al., 2004; George et al., 2005; Gilman et al., 2012b; Meier et al., 1996; Richards et al., 1999; Breslin et al., 1999; Ortner et al., 2003; Dougherty et al., 2008). Future studies incorporating the MIST or comparable forms of stress paradigms are thus strongly encouraged to personality profile their subjects *a priori* and be sufficiently powered to detect possible interactions with sex.

Though not necessarily generalizable to other forms of stress, the aforementioned findings may serve as a significant initial step in the elucidation of the neurobiological substrates governing the contrasting risk trajectories of AUDs in AS and SS persons and more generally, persons who drink to sedate and self-medicate, and those who do so to excite and stimulate.

4.3 Follow-up Assessment

The current work examined whether the neural response to differentially aversive material as a function of personality profile predicted follow-up drug-use patterns among university students, and, if so, whether or not this predictive power was above and beyond other measured risk factors. Subjects performed the FEPT and MIST in the MRI scanner at age 18-20, when they were all social drinkers and up until then,

psychopathology-free ('baseline'). A follow-up assessment of mental health and drug use status was performed 2-3 years later, thus capturing the time window of greater propensity for alcohol misuse (Fillmore et al., 1991; Naimi et al., 2003; Hasin et al., 2007; Abuse, 2012; Organization, 2012; Merikangas and McClair, 2012; Sathe et al., 2013; Paksarian et al., 2016) and co-occurring psychopathologies (e.g, anxiety disorders; de Lijster et al., 2016). Accordingly, each personality group further subdivided into two subgroups: 'TRAs' (those who came to misuse either or both alcohol and illicit drugs) or 'non-TRAs' (those who consistently remained social drinkers and casual illicit drug users).

We had initially hypothesized, based on previous findings (Paulus and Stein, 2006; Stein et al., 2007b; Killgore et al., 2011; Smith et al., 2014; Hardee et al., 2014) that AS 'TRAs' compared with 'non-TRAs' would be those whose AMYG and aINS are most pronouncedly reactive to presentions of aversive, especially immediately threatening (fearful) versus neutral faces under placebo and most substantially deactivated by alcohol, relative to placebo. We also predicted, albeit tentatively, that SS 'TRAs' compared with 'non-TRAs' would be those whose mOFG shows the strongest activation to acute psychosocial stress (MIST) under placebo and deactivation by alcohol, relative to placebo. Lastly, we predicted that the predictive power of said neural phenotypes would be above and beyond other measured risk factors and response profiles.

The findings of our functional ROIs analyses, all covarying for familial AUDs and sex, partially confirmed the aforementioned predictions: there was a condition $\times$ personality risk profile $\times$ drug use status interaction effect on the activation of the AMYG and mOFG in the context of, respectively, the FEPT ("aversive versus neural face" contrast) and MIST ("stress versus nonstress" contrast), whereas results for the aINS were insignificant. The 3-way interaction effect on the AMYG was mainly driven by the AS 'TRAs', whose bilateral AMYG activation to threatening (versus neutral) faces was most pronounced under placebo and most substantially dampened by alcohol, relative to placebo, thus creating a starkly sharp contrast between their AMYG

response in the alcohol and placebo sessions. AMYG BOLD response contrasts between the two testing sessions in both SS subgroups. The 3-way interaction effect on the mOFG activity, on the hand, was mainly driven by the SS 'TRAs'. These subjects substantially activated in the mOFG to acute social stress when sober and deactivated it when alcohol intoxicated, contrarily to SS 'non-TRAs', who comparably deactivated the mOFG in the two testing sessions.The mOFG BOLD response contrasts with placebo compared to alcohol were diminished in ASSs regardless of drug use status at follow-up.

Our prediction that that neural responsiveness to the anxiety-evoking tasks prospectively predicted escalating use above and beyond other measured risk factors and response profiles was also confirmed: 'TRAs' were (statistically) indistinguishable from their same-personality 'non-transitioner' counterparts based on their self-reported age at drinking and illicit drug use onset, alcohol and other drug use habits at study entry, scores on personality measures of traits SS, AS, sensitivity to reward and punishment, self-esteem and perceived self-efficacy, or developmental experiences (i.e, childhood trauma and early-life parental bonding). Further, none of the behavioral, subjective and endocrine responses in the context of either the FEPT or the MIST showed significant personality risk profile $\times$ drug use status or condition $\times$ personality risk profile $\times$ drug use status interaction effects. =

The current fMRI results are preliminary and must be considered very tentative pending replication. With that in mind, they resonate with the extensively debated roles of the AMYG and OFG dysfunction and dysmorphology in the context of alcohol and illicit drug abuse (AMYG: Wrase et al. 2008; Zhang et al. 2013; Dager et al. 2015; Hill et al. 2001, 2010, 2013; Benegal et al. 2007; Dager et al. 2015; OFC: Ersche et al. 2013a; Smith et al. 2014; for a review, see Fishbein et al. 2016b; detailed in sections 1.9.2.2 and 1.9.2.2, respectively). More specifically, these results additionally augment a growing, if still small, body of literature demonstrating prospective associations between neurofunctional alterations during cognitive and/ or emotionally chal-

lenging paradigms and escalating drinking, absent observable behavioral differences (Norman et al. 2011; Squeglia et al. 2012b; Mahmood et al. 2013; Cservenka et al. 2013; Wetherill et al. 2013b,a; Heitzeg et al. 2014a,b; Whelan et al. 2014; Dager et al. 2014; Ramage et al. 2015; reviewed in Heitzeg et al. 2015; Cservenka 2016; Squeglia et al. 2016). In particular, our results corroborate the Nikolova studies, in which two distinct neurofunctional risk profiles for alcohol misuse were delineated in university undergraduates during emotional face processing, one in which reduced threat-related AMYG (and relatively enhanced reward-related VS activity) predicted escalating use via impulsivity, and another where heightened AMYG (and diminished reward-related VS activity) predicted the clinical outcome via anxious/ depressive symptomatology (Nikolova and Hariri, 2012; Nikolova et al., 2016). These findings plus ours recapitulate the existence of two alternative risk pathways for escalation intro AUDs: negative affect dysregulation and behavioral disinhibition.

As detailed in previous sections, the AMYG is known as the epicenter of the "defensive survival circuit" (LeDoux, 1996; Ledoux, 2002; LeDoux, 2012, 2013, 2014a,b,b, 2015). It causally promotes aversive affect (Shackman et al., 2016a), and its hyperactivation to signals of threat connoting hypervigilance and difficulty disengaging from aversive stimuli, prospectively predicts of the development of internalizing symptoms (Swartz et al., 2015), and has been a ubiquitous findings in the human neuroimaging literature on clinical (Stein et al., 2002; Wright et al., 2003; Straube et al., 2004; Schienle et al., 2005b; Armony et al., 2005; Sakai et al., 2005; Phan et al., 2006; Straube et al., 2007b; Rauch et al., 2000; Whalen et al., 2008; Blair et al., 2008; Evans et al., 2008; Shah and Angstadt, 2009; Klucken et al., 2009; Kleinhans et al., 2010; Freitas-Ferrari et al., 2010; Fonzo et al., 2010, 2015; Ottaviani et al., 2012; Fredrikson and Faria, 2012; Demenescu et al., 2013; Fouche et al., 2013; Via et al., 2014; Brühl et al., 2014; Binelli et al., 2014; Mahabir et al., 2015; Poletti et al., 2015; Blair et al., 2016; Charpentier et al., 2016; Rabellino et al., 2016; Weidt et al., 2016; Nikolova et al., 2016) and subclinical (Etkin et al., 2004; Bertolino et al., 2005; Phan et al.,

2006; Rauch et al., 2000; Stein et al., 2007b; Haas et al., 2007; Paulus, 2008; Killgore and Yurgelun-Todd, 2005; Killgore et al., 2011; Barrett and Armony, 2009; Ball et al., 2012; Shackman et al., 2013) anxiety (reviewed in Etkin and Wager 2007; Brooks and Stein 2015; Taylor and Whalen 2015; Britton and Rauch 2008; Shin and Liberzon 2010; Holzschneider and Mulert 2011; Blackford and Pine 2012; Paulus 2008; Schienle et al. 2010; Mochcovitch et al. 2014; Brühl et al. 2014; Stern and Taylor 2014; Bas-Hoogendam et al. 2016; Habecker et al. 2016; Ducharme et al. 2016; Hendler and Admon 2016; for more information, see sections 1.10.1).

Multiple strands of evidence have converged on the claim that it is precisely by dampening the threat-related activation of this region and/ or the regions heavily interconnected with it (e.g, aINS) that alcohol exerts its anxiolytic and SRD effects in humans (Gilman et al., 2008, 2012a; Sripada et al., 2011; Padula et al., 2011; Gorka et al., 2013) and animals (Allan et al., 1987; Möller et al., 1997; Spanagel et al., 1995; Hyytiä and Koob, 1995; Buck, 1996; Sommer et al., 2001; McBride, 2002; Koob, 2004; Nie et al., 2004, 2009; Roberto et al., 2003, 2004; Criswell and Breese, 2005; Paulus et al., 2005; Pandey et al., 2006; Arce et al., 2006; Zhu and Lovinger, 2006; Weiner and Valenzuela, 2006; Silberman et al., 2008, 2009; Kumar et al., 2009).

Our observation that the most pronounced threat-related AMYG activation under placebo and deactivation by alcohol relative to placebo evinced in AS 'TRAs', reinforce prior studies suggesting that it is in people who are victims of fear (e.g, high in AS, IU and SA) where alcohol's negatively reinforcing effects are most pronounced, and it is these particularly pronounced of effects, suggestive of having more to gain by procuring alcohol under stress, that predict escalating drinking in these individuals (Levenson, 1980; Sher, 1987; Stewart and Pihl, 1994; Stewart and Zeitlin, 1995; Stewart, 1996; Stewart et al., 1997b, 1999; Stewart and Kushner, 2001; Stewart et al., 2002; Cooper et al., 1995; Conrod et al., 1998; Maisto et al., 1999; MacDonald et al., 2000a; Schroder and Perrine, 2007; Hefner et al., 2013). It is of note, in this context, that numerous neuroimaging studies of patients with anxious (or depressive) psychopathologies have

shown symptom improvement post-CBT (cognitive behavioral treatment) to be inversely associated with pre-CBT threat-related AMYG activation (e.g, McClure et al. 2007; Bryant et al. 2008; Szczepanik et al. 2016; also see (Whitfield-Gabrieli et al., 2015; Kujawa et al., 2015); for reviews, see Shin et al. 2013; Brooks and Stein 2015; Mason et al. 2016; Lueken and Hahn 2016; Lueken et al. 2016). The same association has been documented in anxiety-disordered patients who underwent selective serotonin reuptake inhibitor treatment (Bunford et al. 2016; also see Gingnell et al. 2016). Relatedly, more than 85% and 35% of our cohort of AS 'TRAs' had developed subthreshold symptoms of or a fully-blown anxiety disorder and major depression(versus 30% and 10% of AS 'non-TRAs') at follow-up (see Nikolova et al. 2016, for a similar observation).

That the predictive power of the AMYG was not applicable to the aINS was not entirely unexpected, though it did falsify our working hypothesis. Extensive evidence has implicated the aINS, which instantiates introceptive processes (Critchley et al., 2002, 2004; Craig, 2002, 2009; Gray et al., 2007), in the motivation to use and misuse substances of abuse (particularly in contexts that tap the BAS or BIS; Naqvi et al., 2007; Naqvi and Bechara, 2009, 2010; Verdejo-Garcia et al., 2012; Paulus and Stewart, 2014; Belin-Rauscent et al., 2016), and threat-related aINS hyperactivity been a recurring theme across neuroimaging investigations of the anxiety-disordered (Etkin and Wager, 2007; Poletti et al., 2015) and anxiety-prone (Stein et al., 2007b; Simmons et al., 2008b; Killgore et al., 2011; Ball et al., 2012). Several research groups have additionally gone to suggest the that aINS is particularly pertinent to the AS phenotype (Paulus and Stein 2006; Stein et al. 2007b; Killgore and Yurgelun-Todd 2001; Poletti et al. 2015; although see Ball et al. 2012; Harrison et al. 2015). Notwithstanding the previously mentioned information, and considering that AS scores in our cohorts of AS individuals bore a dose-dependent association with the BOLD activation of the threat-related AMYG, but not the aINS (nor the vACC, for that matter) under placebo, it is entirely conceivable that out of the regions that anchor the "defensive survival circuit"

(LeDoux, 2015, p. 44), only the AMYG is powerful enough to capture those otherwise undetectable subtle inter-individual differences in threat sensitivity that ultimately "pull the trigger" on certain AS persons. The substantiated notion that the AMYG more reliably predicts threat and discriminates between appetitive and aversive stimuli than any other brain region (Ferguson and Bargh 2004; Costafreda et al. 2008; Satpute et al. 2015; Lindquist et al. 2012b, 2016; although see Sabatinelli et al. 2011; Kang et al. 2016), which hints at "negativity bias" (see Cunningham et al., 2008; Stillman et al., 2015; Meder et al., 2016), makes this scenario particularly appealing. We are aware of the recent fMRI work of Schuckit et al. (2016), demonstrating a prospective association between the greater aINS activation to emotional faces and escalating drinking 5-years later in young adults. Such finding might, at first glance, appear at odds with our null result, but it is important to note that subjects in that study were not personality profiled, *a priori* or *a posteriori*, and in fact, those who displayed the overactive aINS phenotype were also hyposensitive to alcohol's sedative properties and, therefore most likely externalizing individuals (Schuckit et al., 2016; Quinn and Fromme, 2016). Understood in this context, the predictive power ascribed to the aINS in the Schuckit study is consistent with the documented effects of this region on 'downstream' structures such as NAc and striatum (Cho et al., 2013b; Goldstein et al., 2009), those being consistently responsive to reward cues (Kirsch et al., 2003; O'Doherty et al., 2004; Phelps and LeDoux, 2005; Balleine et al., 2007; Valentin and O'Doherty, 2009; Delgado et al., 2011; Lewis et al., 2014), and differentially so in those with a precursive externalizing risk profile (Andrews et al. 2011; Yau et al. 2012; Oberlin et al. 2013; reviewed in Heitzeg et al. 2015; Cservenka 2016).

Switching gears to the mOFG, of which activation in the context of a performance-based acute psychosocial stressor predicted escalating drug use, this region, as detailed in section 1.10.2, participates in negative affect down-regulation (through its dense inhibitory projections to the AMYG), and is particularly critical in the suppression of outward expression of affective dyscontrol (e.g, reactive aggression; Blair 2001; Coccaro

et al. 2007; Goldstein and Volkow 2011; Motzkin et al. 2015; Amodeo et al. 2016; Angus et al. 2016). Failures in this system (e.g, hypoactivity) in anger-infused situations (e.g, presentions of angry faces) has been a recurring them across studies of pathologically aggressive populations (e.g, individuals with intermittent explosive disorder) - that is, populations bearing the externalizing pathway for disordered drinking (e.g, Pol et al. 2001; Blair 2003b; van Elst et al. 2003; Herpertz et al. 2001; Donegan et al. 2003; Dougherty et al. 2004; Schmahl et al. 2004; Blair 2008; Schulze et al. 2011; Huang et al. 2014; Herpers et al. 2014; reviewed in Davidson et al. 2000). Interestingly it is externalizing individuals who are particularly prone to displaying heightened aggression in the context of experimentally-induced psychosocial stress (Twenge et al., 2001; Leary et al., 2006; DeWall and Bushman, 2011; Chester et al., 2013; Riva et al., 2014; Chester and DeWall, 2015; Achterberg et al., 2016), when alcohol-challenged (especially if then provoked), as they appear to be highly susceptible alcohol-induced frontal disinhibition and consequent taxation of self-control resources (Conrod et al., 1998) resonates with other reports of alcohol-induced frontal disinhibition.

Hence, and as an inverse mOFG-anger association was observed in the present study in both testing sessions, we tentatively theorize that the mOFG activity under performance-based emotionally "heated" conditions may provide a unique mechanism to single out the most vulnerable individuals in a group of otherwise behaviorally homogeneous sensation-seekers. In detail, it seems as though the more 'vulnerable' SS individuals are required to allocate more cognitive "neural resources" to evade improper enactment of approach behavior in the service of persistent goal-focused behavior, relative to those who are more resilient. From the perspective of typical brain development, as the cognitive control neurocircuitry matures (e.g, become functionally specialized and its anatomical interconnections more refined, efficient and optimized; Giedd 2004; Rubia et al. 2006; Luna et al. 2010; Lebel and Beaulieu 2011; Lebel et al. 2012a; Jacobus and Tapert 2013; Dubois et al. 2014; Giedd and Denker 2015), its components (e.g, middle frontal gyrus) come to decreases their activation during suc-

cessful response inhibition (Hardee et al., 2014). Based on this, a neurofunctional irregularity of the sort displayed by our cohort of SS 'TRAs' might signifies a perturbed development of said neurocircuitry and a resultant compensatory mechanisms whereby suppressing inappropriate automatic response instigated in cognitively demanding situations necessitate the overworking of the brain's regulatory systems (e.g, Hardee et al. 2014; reviewed in Heitzeg et al. 2015; Cservenka 2016). Indeed, the same or similar pattern of aberration has been previously documented in unnecessarily drug-using OOA in effortful contexts (e.g, Go/no-Go task) despite comparable task performance to matched low-risk controls (e.g, Heitzeg et al. 2010; Silveri et al. 2011; DeVito et al. 2013; Acheson et al. 2014; Hardee et al. 2014), with extant indications of specificity of said deficit to OOA who classify as 'vulnerable' as opposed to resilient (e.g, Heitzeg et al. 2010; reviewed in Heitzeg et al. 2015; Cservenka 2016; for more details, see section 1.9.1.1). Overtime, repeated aggravation of the brain's impulse control networks could cause them to become 'fatigued', and in the aftermath of that, a host of psychopathologies not the last of which is disordered drug use might come to manifest ("too much of anything will eventually suppress something"; see Bocanegra and Hommel, 2014; Chester and DeWall, 2014; Chester et al., 2016). More to the point, Smith et al. (2014) found that in response to drug-related cues (1) cocaine-abusing young adults showed enhanced attentional bias[7] (words), whereas healthy non-using controls did not, nor did regular recreational cocaine users (8 years); and (2) relative to both the disordered users and healthy controls, recreational users substantially deactivated the OFC. Contrarily, the disordered users activated it. These findings were interpreted by the authors as reflecting a resiliency mechanism on part of the recreational users using group that ostensibly underpins the intrinsic difference between their stimulant-taking habits and the the disordered users' (Smith et al., 2014).

Left unresolved in the current study, however, is what accounts for the seemingly

[7]Substance-related attentional bias has been related to enhanced motivation to procure the drug, and promoted affective salience for these cues (Goldstein and Volkow, 2002; Field and Cox, 2008; Smith et al., 2014).

excessive mOFG activation exhibited by the SS 'TRAs' under placebo. In the previously discussed study by Smith et al. (2014), both the recreational and disordered stimulant user groups were high on SS, but only the latter was highly impulsive as well (Smith et al., 2014). As assessed using the SURPS, our entire sample was, at study entry, non-impulsive (high impulsivity scores was an exclusion criterion). Furthermore, in the previously cited Heitzeg study, the 'vulnerable' FHP persons who exhibited said neural risk profile had a personal history of alcohol misuse (Heitzeg et al., 2010). Relatedly, self-rated cocaine craving has been linked to increased OFC activation to drug-related cues in dependent users (Bendriem et al., 1991; Grant et al., 1996; Wang et al., 1999; London et al., 2000; Smith et al., 2014). To our knowledge, all of our subjects were, as self-reported at time of initial testing, social drinkers who never before problematically used alcohol or other drugs. Barring misreporting or underreporting of impulsivity or prior experience with drugs, we are unable to identify the source of the substantial mOFG activation that was displayed by SS 'TRAs' and prospectively predicted escalating use. One possibility is that this irregularity predated their exposure to drugs (i.e, genetic) and stemmed from some unforeseen variable (or a combination of variables) that we did not assess for, and that meaningfully differed between these individuals and their SS counterparts who consistently remained casual users. Another possibility is that the trajectory of brain development in some of our SSSs was stunted by some sort of exogenous insult(s) that ultimately led them, to escalate in drinking. Risky drug use, if still non-abusive in its nature, would be an exemplar. The pattern and type of drug-use during teen years might have differed between our SS subgroups in a way that our questionnaires failed to capture, and these variations could have still been within the norm. Alternatively both groups could have had comparable experiences with drugs at the time, but were differentially affected by them, perhaps for reasons that have to do with genetic make-up and could very well be sex-specific (recall that our SS 'transitioner' males outnumbered females six to one, and the male sex is, in its own right, a risk factor for alcohol-induced

aggression; Pihl and Sutton 2009). Future research will need to sort these and other alternative explanations. Additional studies that follows these cohorts for extended period of time will also be important to clarify whether SSFs might be more 'resilient' to AUDs than SSMs who score comparably on trait SS measures, or whether their risk trajectory is more protracted such that they tend to develop the condition at a relatively older age, for reasons dependent on or independent from sex. Notably, SSFs remain an understudied population, in the neuroimaging and non-neuroimaging literatures alike.

The juxtaposition of our prospective findings with respect to the AMYG and mOFG is both interesting and revealing, if for the fact that these two emotion-subserving regions differ in terms of typical developmental trajectory and phylogenetic status, and their dysfunction was captured using aversive tasks that distinctly differed in both form and affect. To elaborate, the AMYG constitutes a phylogenetically archaic danger-recognition system that is evolutionarily older any other (LeDoux 1998b, 2015; Tillfors et al. 2001; Waraczynski 2016; Méndez-Bértolo et al. 2016; also see Madarasz et al. 2016), and of which the development in the typically developing brain predominate others', largely completing during the first year of life (Sowell et al., 2003; Gogtay et al., 2004; Ernst et al., 2005; Galvan et al., 2006; Hare et al., 2008; Powers and Casey, 2015). It is the dysfunction of this system that predicted escalation in AS, and it is the FEPT that captured this dysfunction. By comparison, the OFG is a younger system (though still much older than the rest of the PFC; Tillfors et al. 2001; Kringelbach and Rolls 2004). Its typical developmental trajectory is most dramatic in adolescence and is, relative to the AMYG, protracted (Chambers et al., 2003; Gogtay et al., 2004; Toga et al., 2006; Hare et al., 2008; Casey et al., 2008; Luna et al., 2010; Koob and Volkow, 2010; Stiles and Jernigan, 2010; Sturman and Moghaddam, 2011; Mills et al., 2014; Dean et al., 2015). It is the aberrant functioning of the OFG that predicted escalation in SSSs and it is the MIST that successfully captured this irregularity. From the standpoint of neurodevelopmental pathology, the

discussion here is really of two distinct personality groups that share their arrested neurodevelopment, with the differences being in the how and when.

It is important to point out that the portion of the variance in predicting their alcohol-related 'career' in the current study was modest (similar to other prospective studies; e.g, Schuckit et al. 2016), meaning neither of these neural phenotypes could have been both requisite and sufficient to "pull the trigger". Such outcomes reinforces prior research illustrating the relevance of a constellation of genetic and non-genetic (e.g, environmental) factors in the genesis of problem alcohol use (Schuckit, 2014). Also, recognize that our study design prohibits making causal inferences (see Moffitt, 2005; Jaffee et al., 2012; Young, 2016; Pingault et al., 2016). The possibility that the prospective associations we identified might be reverse, bidirectional or accounted for by some unknown "third" variable (e.g, environmental stress) was not systematically addressed here and thus cannot be precluded (see Moffitt 2005; Jaffee et al. 2012). That is to say, we cannot definitively attest as to whether the prospective associations demonstrated here are causal, or like AUD itself, consequential to the true case and so at best, what we offer is a warm gun but non-smoking, so to speak.

Based on the above, the AMYG and mOFC hyperactivation to certain types of aversive stimuli under nondrug conditions, in combination with their hypoactivation to such stimuli under alcohol, might be very tentatively regarded as endophenotypic markers that could transcend conventionally defined diagnoses.

4.4 Strengths and Limitations

Perhaps the most important strength of the work presented herein is the use of a personality profiled sample of at-risk young adults who, up until and including time of initial testing, were psychopathology-free and never before drank heavily or excessively on regular bases. This precluded possible contamination of our results by aftermath of syndromal psychiatric manifestations. Additionally, the inclusion of a prospective

analyses bypasses the caveats inherent to cross-sectional data.

Other strengths are notable, as follows: (1) inclusion of a repeated-measure, double-blind, counter-balanced, placebo-controlled design, which allowed that subjects serve as their own controls; (2) use of a well-characterized anxiety-evoking tasks; (3) administration of multiple measures of stress to characterize different parameters of the stress response as well as with ensuring an appropriate timeframe of measurement. (4)being sufficiently powered to detect main effects of and possible interactions with sex; (5) assessing for a number of possible confounders and covarying for them when needed; (6) obtaining BAC reading throughout the MRI scanning sessions, instead of estimating BAC levels (as has been done in other fMRI studies, e.g, Padula et al. 2011); (7) using a metric of brain function (fMRI 3T) characterized by relatively high spatial and temporal resolution; and (8) collecting subjective measures of mood and obtaining salivary cortisol readings throughout the course of MRI sessions.

Notwithstanding, our findings must be interpreted in light of potential confounds and considered in the context of several limitations. First and foremost, despite being sufficiently powered to detect significant between- and within- subject differences, this study had a propensity for, respectively, both Type I and II errors (false positives and negative; Yarkoni 2009), given the lack of statistical power that might be necessary to allow detection of small to medium effects and is attainable using a lager sample size. The use of relatively small sample sizes is, however, particularly common in personality neuroscience given the great costs associated with individual subject sessions in fMRI research (DeYoung, 2010), and does not preclude the instrumentality of generated finding for helping move the field forward. Relatedly, due to fMRI-related costs, the inclusion of a third, low-risk group was not possible, and the two personality groups thus served as controls for each other (under placebo). Conceptually, however, this should not be problematic as subjects high in AS were low in SS and vice versa.

Second, this study lacked random population sampling, predominantly using a cohort of high functioning and relatively intelligent university students.

Third, potential confounds might have risen due to the likely complex vasodilatory effects of alcohol administration on the BOLD signaling response (see Volkow et al. 1988; Ogawa et al. 1990; Luchtmann et al. 2010; Sripada et al. 2011).

Fourth, while we attempted to the best of our ability to mask the placebo drinks, it is conceivable that some subjects saw through the placebo manipulation and were able to tell the difference between the two testing sessions. If true, such recognition could have influenced our findings in some meaningful yet unforeseen way. In retrospect, we would have done well to employ a subjective measure assessing perceived intoxication, as to get an indication of how effective (or ineffective) our placebo manipulation was. Fourth, the size of our groups was too small to allow that fMRI scans be analyzed with the ordering of alcohol/ placebo administration as a third between subjects factor. However, we were careful to equally match the groups with regard to the number of subjects administered placebo on the first versus the second day, making it unlikely, in our opinion, that ordering significantly impacted our results.

Fifth, for roughly 80% of subjects, the two fMRI scanning sessions were roughly two weeks apart. For the remainder 20%, practical and/ or technical issues led to the testing days being separated by as little as two days and as long as three weeks. We could not include the length of said period as an additional between subjects factor on account of our small sample size and have no way of knowing whether, how and to what extent this variable influenced our findings. A related concern is that we cannot discount the possibility that something transpired between the two testing occasions of some subjects to meaningfully affect how they responded to our experimental manipulations on the second day. We did, however, explicitly ask this question to subjects after debriefing them; one subject reported having become almost certain that the MIST was designed to induce uncontrollable failure (by searching online), but also added that having this knowledge did not make this paradigm any less stressful. True or not, exclusion of that subject left our results unaltered. Fifth, it is impossible to determine whether and to what extent the administration of the

FEPT immediately prior to the MIST might have primed some of all subjects to respond differently that they would have otherwise had. Sixth, a relatively liberal threshold was employed in our whole-brain analyses of imaging results for the MIST ($P = .005, k = 10$). Plus As well, relative to our sample size, a large number of analyses was performed, and interpretive caution with respect to our correlational results is thus warranted. With that said, in analyzing our MIST fMRI data we chose to prioritize avoiding false negatives, even if at the risk of the cost of increasing risk of false positives. This decision was driven by the relative lack of prior fMRI studies incorporating the MIST, and absence of any such studies using cohorts of AS or SS persons, combined with the fact that when meta-analyses (on which focus should be placed for establishing scientific truth Lieberman and Cunningham 2009) are performed, Type I errors results wont replicate and therefore self-erase, whereas unreported false negatives will remain obscure and can never drive attempts at replications or extensions. (Lieberman and Cunningham, 2009).

Sixth, although steps were taken to minimize the possible influence of the menstrual cycle phase (by testing at day 14 and then again one week later), this factor was uncontrolled for and could have, therefore, influenced our results. We know that menstrual phase can impact neural activity and stress reactivity to emotional challenge (e.g, viewing of affective stimuli Amin et al., 2006; Andreano and Cahill, 2010; Ossewaarde et al., 2010; Protopopescu et al., 2005; Kirschbaum et al., 1999; Kajantie and Phillips, 2006; Nillni et al., 2011; Chung et al., 2016). Some have also suggested subtle effects on alcohol response (e.g, Evans and Levin, 2011), although critical reviews and careful scrutiny of the literature on this topic suggested it lacked methodological rigor (Carroll et al., 2015), and that the effect of ovarian hormones on reactivity to substances of abuse appeared to be either modest or altogether absent (reviewed in Terner and De Wit, 2006). Either way, to control for this factor would have meant that the scanning sessions of female subjects would have had to be a month part, which would have in turn necessitated that the same goes for male subjects so as to maintain homo-

geneity in this respect (to control for length of period separating scanning sessions). Doing so was not feasible, for practical reasons, and on account our prior experience of too frequently losing subjects after more than 2-3 weeks of initial testing. Our results with respect to the fMRI response of female subjects can be viewed as representing the averaged patterns of BOLD signaling across the menstrual cycle (see Wang et al. 2007a).

Seventh, the mood questionnaire used here (POMS) is obviously limited by its self-report nature as as with any subjective measure, misreporting is possible. The POMS is also limited in scope, such that it does not tap the subjective emotional experience in its entirety such that does not assess some of the emotions that are commonly elicited by acute psychosocial stressors (e.g, determination, inferiority or frustration, fear, alertness, anxiousness and nervousness), and additionally fails to capture the differential experience and expression of anger (e.g, "anger-in" vs "anger-out"; see Gilam and Hendler 2015).

Ninth, our prospective study was insufficiently powered to detect higher-order interactions with sex, included a number of caveats, among those is the small number of subjects that was was restricted to the three-year study period and did not include more objective assessment measures.

All the above potentially limit the generalizability of our findings and necessitates their replication in larger samples selected for the same personality profiles investigated here but in a more random fashion from the general community.

4.5 Summary and Perspective

The work presented in this thesis examined (1) how otherwise healthy young adults who are at-risk of AUDs respond to differentially aversive material, on the subjective, endocrine and neural levels, and how these responses differ by personality risk profile (AS versus SS), sex and acute alcohol intoxication; and (2) whether the neural response

to negatively valent stimuli as a function of personality risk profile predicted escalating alcohol and/ or illicit drug use 2-3 years later, and, if so, whether or not this predictive power was above and beyond other measured risk factors and response profiles.

Subjects performed a FEPT and a psychosocial evaluative stress task in the MRI scanner on two separate occasions, when sober and moderately intoxicated. 2-3 years later they were contacted and their mental health and drug use status assessed. Most of our findings were expected *a priori*, some not, but virtually all converged on the claim that different at-risk individuals respond differentially to stressors, and to alcohol by stressor, and these differences predict how later changes in drinking and illicit substance use habits.

Using the FEPT ("threatening versus neutral face" contrast), we demonstrated the importance of the "defensive threat circuitry" in the aetiology and manifestation of the AS phenotype. This circuitry showed robust stimulation in the AS group, but no response change in the SS group. We then presented evidence of substantial alcohol-elicited deactivation of said circuitry, especially the AMYG, in ASSs. This was contrarily to the case of SSSs, who remained as unresponsive to negative socioaffective signals when intoxicated as when sober.

Using the MIST ("stress versus nonstress" contrast), a set of behavioral, subjective, endocrine and neural findings stood out and painted a picture in which the threat posed by this social stress task to the social self integrity caused ASSs to become frightened, if not panic stricken but was not potent enough to do the same in SSSs, who ostensibly perceived this procedure as a challenge as opposed to a threat and had a considerably stronger 'line of defense' in higher-order brain structures than their AS counterparts. Evidence that this task was more motivationally relevant to male than female subjects was also provided. We then showed that alcohol exerted diametrically opposing effects on the behavioral, endocrine, and neural response profiles of the personality groups, especially their male members. The patterns of these effects seemed to indicate that relative to placebo, alcohol buffered the stress sensations associated with the MIST in

ASSs, and promoted them in SSSs.

That was part one: AS and SS the neurofunctionally distinct risk phenotypes for AUDs. Part two: AMYG and mOFG the distinct neural predictors of drug misuse in said at-risk phenotypes.

Re-assessing subjects' drug use status 2-3 years after initial testing, two neural predictors of escalating alcohol and/ or illicit drug use were identified. These differed by personality group, and were captured by different tasks: AS 'TRAs' were those who showed the strongest AMYG activation to presentions of negative versus neutral faces under placebo, and deactivation under alcohol relative to placebo. SS 'TRAs', on the other hand, were those who showed the strongest mOFG activation to acute psychosocial evaluative stress (MIST) under placebo and deactivation under alcohol relative to placebo. We also showed that the predictive power of said neural phenotypes was above and beyond other measured risk factors. These results suggested that the two aforementioned tasks captured the dysfunction of systems of different phylogenetic ages and typical developmental trajectories in different at-risk individuals.

Whether our findings will withstand the test of time remains to be seen, and we are aware that some of our proposed interpretations were speculative in their nature, could be subject to debate and might, in the future, be proven wrong. What is strikingly clear and indisputable, nonetheless, is the jarring contrast between our cohorts of AS and SS individuals in terms of (1) how they responded to different stressors, and to alcohol by stressor, on the behavioral, subjective, endocrine and neural levels; and (2) what fMRI responses to which stressor prospectively predicted escalating use. And what this sharp discrepancy suggests, and cements, is rather self-evident and elemental: AUDs are heterogeneous and neurodevelopmental. Heterogeneous in that the pathways leading up to and causing them are divergent, and neurodevelopmental in that their neural signifiers, connoting early brain development gone awry, predate the overtly behavioral.

By demonstrating the ability of MRI to help detect neurophenotypic features that

single out the most vulnerable individuals from groups of otherwise homogeneous AS and SS persons, the current work essentially establishes the utility of neuroimaging tools above and beyond other available and perhaps less costly techniques (see Berkman and Falk 2013; Berkman 2015). The next logical step would be to search for alternative methods (e.g, neuropsychological tasks) that are significantly cheaper to administer, yet rigorously capture the neurophenotypic irregularities detected by fMRI (see Schuckit et al., 2016; Fishbein et al., 2016b; Nikolova et al., 2016).

The explanatory power of uncovering neurophenotypic alterations that pave the path to, but precede the occurrence of, alcohol abuse and even use itself cannot be overstated. If the field of medicine is any indication, reversing the pathologic trajectory in late phases, which symptoms of disordered drinking are, is an exceedingly challenging undertaking (see Wang et al. 2005b, 2007b; Kalivas and O'Brien 2008; Insel and Wang 2010; Shoham and Insel 2011; Chiamulera and Cibin 2014). The delineation of early-occurring neural markers that rigorously and specifically predict AUDs years before behavioral symptoms have occurred should allow that interventions move from being ameliorative or rehabilitative to preemptive or preventive (see Insel and Wang, 2010; Insel, 2010), as early targeted interventions leverage on the extraordinary plasticity of the brain during "critical periods" of development. By altering the neurodevelopmental trajectory, and potentially enduringly, such interventions can buffer against alcoholism and the host of psychopathologies that frequently co-occur with it (e.g, anxiety disorders; Fishbein et al. 2016b). Early interventions aimed at improving the development of executive control networks and down-regulation of limbic responsiveness are a perfect example (Diamond, 2006; Diamond and Lee, 2011; Diamond, 2012, 2013, 2016; Diamond and Ling, 2016; Fishbein et al., 2016a,b; Cabrera et al., 2016).

It is particularly interesting, in this context, that from the differential-susceptibility perspective, genes associated with psychiatric disorders are not so much vulnerability genes as they are plasticity genes, in the sense that they render one sort of like a sponge

that will be super absorbent of and affected by the gamut of environmental conditions, be they negative or positive, in a "better and for worse" fashion (Belsky et al., 2009; Belsky and Pluess, 2009; Ellis et al., 2011; Homberg and Lesch, 2011; Bakermans-Kranenburg and Van IJzendoorn, 2015). Said differently, place highly susceptible children or adolescents under negative conditions (e.g, parental maltreatment), they will be more adversely affected than their lowly susceptible peers. Place them under positive conditions (e.g, nurturance), or just conditions that are devoid of adversity, and they will benefit comparatively more. It really is a window of opportunity as much as it is a window of vulnerability.

In the case of specifically AS individuals, in whom the neural vulnerability heavily features (hyperactivity of) the AMYG, a brain system that dramatically develops in the first year of life and before any other (Sowell et al., 2003; Gogtay et al., 2004; Ernst et al., 2005; Galvan et al., 2006; Hare et al., 2008; Powers and Casey, 2015), environmental interventions could prove especially useful if implemented in early childhood and geared towards optimizing parental-child (especially maternal-child) care and bonding, so as to prevent mothering from going awry (see Curley and Champagne, 2016). This proposition is based on the increasingly recognized capacity of childhood maltreatment in all of its forms including neglect to disrupt emotional regulation (Shin et al., 2015; Heleniak et al., 2016; Fonzo et al., 2016b), and irreparably scar the limbic system (Dannlowski et al., 2012, 2013; Whittle et al., 2013; Blanco et al., 2015; Teicher et al., 2012, 2014, 2016; Teicher and Samson, 2016; Morey et al., 2016; Fonzo et al., 2016a), and contribute to specifically alcohol abuse (Enoch, 2011; Oshri et al., 2016) although we do not purport to know for a fact that this association is necessarily causal (note the lower level of maternal care in our cohort of AS compared with SS persons). Conversely, considering that the risk profile exemplifying sensation-seekers appears to prominently feature, among potentially other PFC regions, the mOFG, and being that the typical developmental trajectory of the latter systems is most dramatic during adolescence (Chambers et al., 2003; Gogtay et al., 2004; Toga et al., 2006; Hare

et al., 2008; Casey et al., 2008; Luna et al., 2010; Koob and Volkow, 2010; Stiles and Jernigan, 2010; Sturman and Moghaddam, 2011; Mills et al., 2014; Dean et al., 2015), interventions for this subset of individuals might do particularly well to help them avoid risk-taking behaviors that could irreversibly stunt their prefrontal development during this sensitive time window. Helping them find healthy and socially acceptable outlets for thrill-seeking tendencies, adventure and/ or competitive sports being a good example, is one of the various ways of achieving that (see Farley, 1981; Norbury and Husain, 2015). Working with the parents to promote monitoring behavior of their teen offspring risk involvement might also be of value, as parental SS propensities (recall that SS is largely genetic) have been found to correlate negatively and positively with (respectively) parental monitoring and peer effect on risky-taking (Wang et al., 2016).

Furthermore, patients high in SS would particularly benefit from help to formulate clear personal goals. This supposition is based on our (anecdotal) observation and others' (e.g, Ersche et al. 2013a) that the more resilient sensation-seekers tend to report having clearly defined personal goals, which they are passionate about and prioritize over the pleasure derived from their drug-using activities (interestingly in the Ersche study the 'resilient' and 'vulnerable' sensation-seekers primarily differed in their OFC morphology; Ersche et al. 2013a).

All of the above methods of intervention can take place in the context of motivation-matched and personality-specific interventions, of which effectiveness in reducing drug misuse and co-occurring psychopathologies in AS and SS adolescents has been established (Conrod et al. 2008, 2010, 2013; O'Leary-Barrett et al. 2013; reviewed in Conrod and Nikolaou 2016; O'Leary-Barrett and Conrod 2016).

Notwithstanding the fact that the earlier the intervention the better the outcome, high-risk young adults whose susceptibility for AUDs has not been attended to (or attended to but improperly treated) in the past are not doomed. Though the relatively considerable waxing of psychopathologic symptoms at this developmental stage can indeed make helping such individuals an uphill battle (Sapolsky, 2015), we now know

that the adult brain is much more malleable that previously thought (see Rubin, 2009). Indeed, the ability of successful[8] psychotherapeutic interventions to dampen threat-related activation of the "defensive survival circuitry", particularly the AMYG has been repeatedly documented, though a clear overrepresentation of anxiety-disordered patients in this literature in notable (recently reviewed in Brooks and Stein 2015; Mason et al. 2016; Lueken and Hahn 2016; Lueken et al. 2016). Such interventions come under different names (e.g, CBT, dialectical behavior therapy, mindfulness and motivational interviewing [MI]) and differ in their general approach, but are essentially the same in what they are set to achieve, and that is an improved capacity to self-regulate, e.g, cognitively down-regulate negative affect in emotionally "heated" or phobic situations (McRae, 2016). Reappraising such situations is one way of doing that (using CBT or other differently named approaches; see Arnsten et al. 2015; Arnsten 2015; Cohen et al. 2016b; Zilverstand et al. 2016b,a; Cabrera et al. 2016; Wiers and Wiers 2016; Fernandez et al. 2016; Etkin et al. 2016; Li 2016; Warnock-Parkes et al. 2016). Distracting attention away from perceived aversiveness by engaging oneself in cognitively demanding tasks is another (e.g, Bantick et al. 2002; Valet et al. 2004; Kanske et al. 2010; McRae et al. 2010; Simon et al. 2014; Han et al. 2016; Hermann et al. 2016).

Being that almost all of our subjects were high-functioning and relatively intelligent university students, they are most likely to be considerably receptive and responsive to interventions that center on MI[9], which has proven to be particularly effective in treating anxiety (Barrera et al., 2016) and substance use problems (see Miller 1983, 1996; Amrhein et al. 2003; Miller et al. 2004; Miller and Rose 2009; Miller and Rollnick 2013a,b; Miller and Rose 2015; Arkowitz et al. 2015; Hettema et al. 2005; Ehret et al. 2015; Polcin et al. 2015; Houck and Moyers 2015; Randall and McNeil 2016; Madson et al. 2016a,b; Apodaca et al. 2016; Dean et al. 2016; Wagner et al. 2016; Dickerson

[8] A treatment is generally considered to be successful if it results in => 50% symptom reduction

[9] MI is "a person-centered counseling style for addressing ambivalence about change and has had widespread evidence of efficacy, particularly in treating addictions (Miller and Rollnick, 2013b)".

et al. 2016; Kahler et al. 2016; Dupree et al. 2016; Westra et al. 2016; Balán et al. 2016; for reviews, see Rubak et al. 2005; Lundahl and Burke 2009; Apodaca and Longabaugh 2009; Hettema and Hendricks 2010; Lundahl et al. 2013; VanBuskirk and Wetherell 2014; Kohler and Hofmann 2015; Mun et al. 2015; Platt et al. 2016a; Palacio et al. 2016; Li et al. 2016b; for meta-analysis, see Burke et al. 2004; Rubak et al. 2005; Vasilaki et al. 2006; Lundahl et al. 2010, 2013; Heckman et al. 2010; Jensen et al. 2011; Magill et al. 2014; VanBuskirk and Wetherell 2014; Romano and Peters 2015; Yakovenko et al. 2015; Kohler and Hofmann 2015; Huh et al. 2015; Tanner-Smith et al. 2015; Palacio et al. 2016; Li et al. 2016b). The efficacy of CBT in reducing threat-related experiential avoidance has also been established (Espejo et al., 2016), as has been that of mindfulness in attenuating AS levels (Alimehdi et al., 2016). Inclusion of psychoeducation (e.g, about the bidirectional competition between the brain's emotional responding and cognitive control systems Gomez et al. 2007; Blair et al. 2007; Ullsperger et al. 2010) as an adjuncts might also prove to be valuable, on account of the recently documented beneficial effects of neurofeedback[10] (Keynan et al., 2016; George, 2016; Nicholson et al., 2016a; Paret et al., 2016b,a; Marxen et al., 2016; Emmert et al., 2016; Radua et al., 2016; Nicholson et al., 2016a).

It is notable that the most commonly used approach to ameliorate clinical and subclinical symptoms of anxiety (or depression) has been through prescription of anti-anxiety medications (or anti-depressants; Gosselin et al. 2006), with benzodiazepines being the most widely prescribed of all psychotropic drugs (Barker et al., 2004). To say nothing of the fact that benzodiazepines (and similar anti-anxiety prescription medications) produce dependence (Miller, 1995; Ashton, 2005; Arria and Compton, 2016) and have various side effects (Rickels et al., 1990; Ashton, 2001), prescribing them to individuals high on AS or its closely interrelated constructs, will likely prove to be inappropriate or iatrogenic and alas such has been the historical case (see Ashton

[10]Neurofeedback refers to a type of learning which involves the use of real-time neural activity as feedback (Shackman et al., 2011).

2005; Kroll et al. 2016).

Benzodiazepine abuse is highly prevalent among psychiatric patients with co-morbid AUDs and/ or SUDs (Brunette et al., 2003; Cook et al., 2016) and has, in fact, been directly linked to trait AS in opioid abusing adults via coping motives (McHugh et al., 2016).

And why wouldn't said population abuse their anti-anxiety medications? Like alcohol, benzodiazepines induce their anxiolytic effects by targeting primarily the AMYG (Pesold and Treit, 1995), which is rich in benzodiazepines receptors (Niehoff and Kuhar, 1983; Niehoff and Whitehouse, 1983). Like alcohol, benzodiazepines are particularly negatively reinforcing to those who drink "to forget". And like alcohol, benzodiazepines are substances of abuse either on their own or in conjunction with addictive others (Lader, 2014). The take home point being, it is important that physicians pause before prescribing those drugs (and that clinical psychologists do the same before recommending them), especially to patients who endorse DTC motives and/ or have a predilection for drinking their troubles away. The same level of caution should be taken when the patient is drug-naïve but is a victim of fear (i.e, high in AS, SA, IU or all of the above) and thus, in all likelihood, highly susceptible to the SRD effect of anxiolytics. For all we know, introducing such persons to benzodiazepines might simultaneously fail to treat their anxiety (or depression) and successfully open a door that could have otherwise remained closed to disordered alcohol and other drug use. Besides, individual studies have consistently shown and meta-analyses repeatedly confirmed that the effectiveness of anti-anxiety prescription medications (and antidepressants) is comparable (Gould et al., 1997; Mitte, 2005; Bandelow et al., 2007; Gonçalves and Byrne, 2012; Cuijpers et al., 2016; Scaini et al., 2016; Jazaieri et al., 2016) or inferior (Butler et al. 2006; Öst et al. 2016; also see Fedoroff and Taylor 2001; Otto et al. 2004; Manzoni et al. 2008; Mayo-Wilson et al. 2014; but see Bandelow et al. 2015) to behavioral interventions (i.e, CBT and mindfulness; Lipka et al. 2014; Wiers and Wiers 2016; Straube 2016; Yuan et al. 2016), and both approaches exert the same

or similar effects on the same neural loci (e.g, attenuating AMYG activity; Pesold and Treit 1995; Kircher et al. 2013; Lueken et al. 2013; Månsson et al. 2013; Klumpp et al. 2013a; Straube et al. 2014; Strawn et al. 2016; Soravia et al. 2016). That is to say, nonpaharmacological alternatives to anxiolytic medications exist, are safer and at the very least comparably effective, and should be seriously considered on account of all of the above (recently reviewed in Platt et al. 2016b).

Our findings should surprise no one. It has been long known that people with different personality profiles drink for different reasons, and if they escalate in their alcohol use, they do so through different pathways (see Jellinek, 1960; Jester et al., 2015; Burns et al., 2016; Zucker et al., 2016). It has additionally been empirically substantiated for at least two decades now that, retrospectively and prospectively, kindergartners with a pre-existing vulnerability to AUDs/ SUDs stand out in a crowd, and those are typified by marked aggressivity, insensitivity, and hyperactivity, or are - paradoxically - particularly timid with unfamiliarity and shrink from novelty (i.e, temperamental disinhibition versus inhibition, respectively; Caspi and Silva 1995; Caspi et al. 1996; also see Schwartz et al. 1999, 2003; Isler et al. 2016; Prokasky et al. 2016). All are sobering reminders that AUDs are deeply rooted in very early development. Except that this reality has been largely, and at least implicitly ignored, and appears to have become virtually invisible, despite being so obvious, or perhaps because of that. Consider neuroimaging studies of alcoholism. Those have often ascertained their samples by relying exclusively, or almost exclusively, on the DSM classification system, which treats AUD as a homogeneous disorder with neatly delineated boundaries, thus obscuring its biological reality. The same conceptual conundrum has also been a frequent guest to studies of non-disordered individuals, where the goal is to etiologically understand precursive risk, yet risk status is determined based on drinking frequency, such that heavy drinkers qualify as "high-risk" and social-drinkers "low-risk", irrespective of personality traits (e.g, Gilman et al. 2012a). Result? a body of information that continues to balloon as the treatment state remains a constant. Orwell was right.

"To see what is in front of one's nose needs a constant struggle" (Orwell, 1968). He was also right to emphasize the power of the Doublethink: the act of simultaneously holding two beliefs that cancel out. Today we call this cognitive dissonance. It is our hope that by reaffirming the heterogeneous pathways for and neurodevelopmental origins of AUDs using fMRI, a technology that, justifiably or not, has come to hold such a 'privileged' status in the field, that the aforementioned information become information of a different order, and that future studies are inclined to address the question of who the affected or vulnerable individual under study is, as opposed to merely what psychopathology he or she has or is at-risk of.

References

Abbey, A., Zawacki, T., Buck, P. O., Clinton, A. M., and McAuslan, P. (2004). Sexual assault and alcohol consumption: What do we know about their relationship and what types of research are still needed? *Aggression and violent behavior*, 9(3):271–303.

Abelson, J., Liberzon, I., Young, E., and Khan, S. (2005). Cognitive modulation of the endocrine stress response to a pharmacological challenge in normal and panic disorder subjects. *Archives of General Psychiatry*, 62(6):668–675.

Abiri, D., Douglas, C. E., Calakos, K. C., Barbayannis, G., Roberts, A., and Bauer, E. P. (2014). Fear extinction learning can be impaired or enhanced by modulation of the crf system in the basolateral nucleus of the amygdala. *Behavioural brain research*, 271:234–239.

Abracen, J. and Looman, J. (2016). Alcohol abuse, drug abuse, and sexual offending. *Treatment of High-Risk Sexual Offenders: An Integrated Approach*, pages 154–162.

Abuse, S. (2012). *Results from the 2010 National Survey on Drug Use and Health: MentalHealth Findings*.

Acheson, A., Franklin, C., Cohoon, A. J., Glahn, D. C., Fox, P. T., and Lovallo, W. R. (2014). Anomalous temporoparietal activity in individuals with a family history of alcoholism: studies from the oklahoma family health patterns project. *Alcoholism: Clinical and Experimental Research*, 38(6):1639–1645.

Acheson, A., Lake, S. L., Bray, B. C., Liang, Y., Mathias, C. W., Ryan, S. R., Charles, N. E., and Dougherty, D. M. (2016). Early adolescent trajectories of impulsiveness and sensation seeking in children of fathers with histories of alcohol and other substance use disorders. *Alcoholism: Clinical and Experimental Research*.

Achterberg, M., van Duijvenvoorde, A. C., Bakermans-Kranenburg, M. J., and Crone, E. A. (2016). Control your anger! the neural basis of aggression regulation in response to negative social feedback. *Social Cognitive and Affective Neuroscience*, page nsv154.

Adam, E. K., Hawkley, L. C., Kudielka, B. M., and Cacioppo, J. T. (2006). Day-to-day dynamics of experience–cortisol associations in a population-based sample of older adults. *Proceedings of the National Academy of Sciences*, 103(45):17058–17063.

Adams, C., Tull, M., and Gratz, K. (2012). The role of emotional nonacceptance in the relation between depression and recent cigarette smoking. *American Journal on Addictions*, 21(4):293–301.

Adams, R. B., Gordon, H. L., Baird, A. A., Ambady, N., and Kleck, R. E. (2003). Effects of gaze on amygdala sensitivity to anger and fear faces. *Science*, 300(5625):1536–1536.

Addis, D., Wong, A., and Schacter, D. (2007). Remembering the past and imagining the future: Common and distinct neural substrates during event construction and elaboration. *Neuropsychologia*, 45(7):1363–1377.

Addison, P., Ayala, J., Hunter, M., Behnke, R. R., and Sawyer, C. R. (2004). Body sensations of higher and lower anxiety sensitive speakers anticipating a public presentation. *Communication Research Reports*, 21(3):284–290.

Addolorato, G., Abenavoli, L., Leggio, L., and Gasbarrini, G. (2005a). How many cravings? pharmacological aspects of craving treatment in alcohol addiction: a review. *Neuropsychobiology*, 51(2):59–66.

Addolorato, G., Leggio, L., Abenavoli, L., Gasbarrini, G., Group, A. T. S., et al. (2005b). Neurobiochemical and clinical aspects of craving in alcohol addiction: a review. *Addictive behaviors*, 30(6):1209–1224.

Adelstein, J., Shehzad, Z., Mennes, M., DeYoung, C., Zuo, X.-N., Kelly, C., Margulies, D., Bloomfield, A., Gray, J., Castellanos, F., and Milham, M. (2011). Personality is reflected in the brain's intrinsic functional architecture. *PLoS ONE*, 6(11).

Adolphs, R. (2002). Neural systems for recognizing emotion. *Current opinion in neurobiology*, 12(2):169–177.

Adolphs, R. (2003). Cognitive neuroscience of human social behaviour. *Nature Reviews Neuroscience*, 4(3):165–178.

Adolphs, R. (2008). Fear, faces, and the human amygdala. *Current opinion in neurobiology*, 18(2):166–172.

Adolphs, R. (2013). The biology of fear. *Current Biology*, 23(2):R79–R93.

Adolphs, R., Baron-Cohen, S., and Tranel, D. (2002). Impaired recognition of social emotions following amygdala damage. *Journal of cognitive neuroscience*, 14(8):1264–1274.

Adolphs, R., Gosselin, F., Buchanan, T., Tranel, D., Schyns, P., and Damasio, A. (2005). A mechanism for impaired fear recognition after amygdala damage. *Nature*, 433(7021):68–72.

Adolphs, R., Russell, J. A., and Tranel, D. (1999). A role for the human amygdala in recognizing emotional arousal from unpleasant stimuli. *Psychological Science*, 10(2):167–171.

Adolphs, R., Tranel, D., Damasio, H., and Damasio, A. (1994). Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature*, 372(6507):669–672.

Adolphs, R., Tranel, D., Damasio, H., and Damasio, A. R. (1995). Fear and the human amygdala. *The Journal of neuroscience*, 15(9):5879–5891.

Afifi, T. O., Henriksen, C. A., Asmundson, G. J., and Sareen, J. (2012). Victimization and perpetration of intimate partner violence and substance use disorders in a nationally representative sample. *The Journal of nervous and mental disease*, 200(8):684–691.

Agnew-Blais, J. and Danese, A. (2016). Childhood maltreatment and unfavourable clinical outcomes in bipolar disorder: a systematic review and meta-analysis. *The Lancet Psychiatry*, 3(4):342–349.

Agustín-Pavón, C., Braesicke, K., Shiba, Y., Santangelo, A. M., Mikheenko, Y., Cockroft, G., Asma, F., Clarke, H., Man, M.-S., and Roberts, A. C. (2012). Lesions of ventrolateral prefrontal or anterior orbitofrontal cortex in primates heighten negative emotion. *Biological psychiatry*, 72(4):266–272.

Ahn, K., Gotay, N., Andersen, T., Anvari, A., Gochman, P., Lee, Y., Sanders, S., Guha, S., Darvasi, A., Glessner, J., et al. (2014). High rate of disease-related copy number variations in childhood onset schizophrenia. *Molecular psychiatry*, 19(5).

Ainsworth, M. D. S. and Bell, S. M. (1970). Attachment, exploration, and separation: Illustrated by the behavior of one-year-olds in a strange situation. *Child development*, pages 49–67.

Akdeniz, C., Tost, H., Streit, F., Haddad, L., Wüst, S., Schäfer, A., Schneider, M., Rietschel, M., Kirsch, P., and Meyer-Lindenberg, A. (2014). Neuroimaging evidence for a role of neural social stress processing in ethnic minority–associated environmental risk. *JAMA psychiatry*, 71(6):672–680.

Akutsu, S., Yamaguchi, A., Kim, M.-S., and Oshio, A. (2016). Self-construals, anger regulation, and life satisfaction in the united states and japan. *Frontiers in Psychology*, 7:768.

Al'Absi, M., Bongard, S., Buchanan, T., Pincomb, G. A., Licinio, J., and Lovallo, W. R. (1997). Cardiovascular and neuroendocrine adjustment to public speaking and mental arithmetic stressors. *Psychophysiology*, 34(3):266–275.

Albert, K., Pruessner, J., and Newhouse, P. (2015). Estradiol levels modulate brain activity and negative responses to psychosocial stress across the menstrual cycle. *Psychoneuroendocrinology*, 59:14–24.

Alia-Klein, N., Parvaz, M. A., Woicik, P. A., Konova, A. B., Maloney, T., Shumay, E., Wang, R., Telang, F., Biegon, A., Wang, G.-J., et al. (2011). Gene× disease interaction on orbitofrontal gray matter in cocaine addiction. *Archives of general psychiatry*, 68(3):283–294.

Alimehdi, M., Ehteshamzadeh, P., Naderi, F., Eftekharsaadi, Z., and Pasha, R. (2016). The effectiveness of mindfulness-based stress reduction on intolerance of uncertainty and anxiety sensitivity among individuals with generalized anxiety disorder. *Asian Social Science*, 12(4):179.

Allan, A., Huidobro-Toro, J., Bleck, V., and Harris, R. (1987). Alcohol and the gaba receptor-chloride channel complex of brain. *Alcohol and alcoholism (Oxford, Oxfordshire). Supplement*, 1:643.

Allan, C. A. (1995). Alcohol problems and anxiety disorders—a critical review. *Alcohol and Alcoholism*, 30(2):145–151.

Allan, N. P., Albanese, B. J., Norr, A. M., Zvolensky, M. J., and Schmidt, N. B. (2014). Effects of anxiety sensitivity on alcohol problems: evaluating chained mediation through generalized anxiety, depression and drinking motives. *Addiction*.

Allan, N. P., Macatee, R. J., Norr, A. M., Raines, A. M., and Schmidt, N. B. (2015). Relations between common and specific factors of anxiety sensitivity and distress tolerance and fear, distress, and alcohol and substance use disorders. *Journal of anxiety disorders*, 33:81–89.

Allen, A. P., Kennedy, P. J., Cryan, J. F., Dinan, T. G., and Clarke, G. (2014). Biological and psychological markers of stress in humans: Focus on the trier social stress test. *Neuroscience & Biobehavioral Reviews*, 38:94–124.

Allison, T., Puce, A., and McCarthy, G. (2000). Social perception from visual cues: Role of the sts region. *Trends in Cognitive Sciences*, 4(7):267–278.

Almasy, L. and Blangero, J. (2001). Endophenotypes as quantitative risk factors for psychiatric disease: rationale and study design. *American journal of medical genetics*, 105(1):42–44.

Almeida, J. R., Versace, A., Hassel, S., Kupfer, D. J., and Phillips, M. L. (2010). Elevated amygdala activity to sad facial expressions: a state marker of bipolar but not unipolar depression. *Biological psychiatry*, 67(5):414–421.

Alonso, J., Angermeyer, M. C., Bernert, S., Bruffaerts, R., Brugha, T., Bryson, H., Girolamo, G. d., Graaf, R. d., Demyttenaere, K., Gasquet, I., et al. (2004). Use of mental health services in europe: results from the european study of the epidemiology of mental disorders (esemed) project. *Acta Psychiatrica Scandinavica*, 109(s420):47–54.

Alpers, G., Abelson, J., Wilhelm, F., and Roth, W. (2003). Salivary cortisol response during exposure treatment in driving phobics. *Psychosomatic Medicine*, 65(4):679–687.

Alterman, A. I. (1988). Patterns of familial alcoholism, alcoholism severity, and psychopathology. *The Journal of nervous and mental disease*, 176(3):167–175.

Aluja, A., Garcia, O., and Garcia, L. F. (2003). Relationships among extraversion, openness to experience, and sensation seeking. *Personality and Individual Differences*, 35(3):671–680.

Alvarez, R., Kirlic, N., Misaki, M., Bodurka, J., Rhudy, J., Paulus, M., and Drevets, W. (2015). Increased anterior insula activity in anxious individuals is linked to diminished perceived control. *Translational psychiatry*, 5(6):e591.

Alvarez, V. A. (2016). Clues on the coding of reward cues by the nucleus accumbens. *Proceedings of the National Academy of Sciences*, page 201601162.

Amaral, D. and Price, J. (1984). Amygdalo-cortical projections in the monkey (macaca fascicularis). *Journal of Comparative Neurology*, 230(4):465–496.

Amaral, D. G. (2002). The primate amygdala and the neurobiology of social behavior: implications for understanding social anxiety. *Biological psychiatry*, 51(1):11–17.

Amaral, D. G. and Adolphs, R. (2016). *Living without an amygdala*. Guilford Publications.

Amaral, D. G., Price, J. L., Pitkanen, A., and Carmichael, S. T. (1992). Anatomical organization of the primate amygdaloid complex. *The amygdala: Neurobiological aspects of emotion, memory, and mental dysfunction*, 1992166.

Amft, M., Bzdok, D., Laird, A. R., Fox, P. T., Schilbach, L., and Eickhoff, S. B. (2015). Definition and characterization of an extended social-affective default network. *Brain Structure and Function*, 220(2):1031–1049.

Amin, Z., Epperson, C., Constable, R., and Canli, T. (2006). Effects of estrogen variation on neural correlates of emotional response inhibition. *NeuroImage*, 32(1):457–464.

Amlerova, J., Cavanna, A. E., Bradac, O., Javurkova, A., Raudenska, J., and Marusic, P. (2014). Emotion recognition and social cognition in temporal lobe epilepsy and the effect of epilepsy surgery. *Epilepsy & Behavior*, 36:86–89.

Amodeo, L., McMurray, M., and Roitman, J. (2016). Orbitofrontal cortex reflects changes in response–outcome contingencies during probabilistic reversal learning. *Neuroscience*.

Amodio, D. and Frith, C. (2006). Meeting of minds: The medial frontal cortex and social cognition. *Nature Reviews Neuroscience*, 7(4):268–277.

Amrhein, P. C., Miller, W. R., Yahne, C. E., Palmer, M., and Fulcher, L. (2003). Client commitment language during motivational interviewing predicts drug use outcomes. *Journal of consulting and clinical psychology*, 71(5):862.

Amting, J., Greening, S., and Mitchell, D. (2010). Multiple mechanisms of consciousness: The neural correlates of emotional awareness. *Journal of Neuroscience*, 30(30):10039–10047.

Anderson, A., Christoff, K., Panitz, D., De Rosa, E., and Gabrieli, J. (2003). Neural correlates of the automatic processing of threat facial signals. *Journal of Neuroscience*, 23(13):5627–5633.

Anderson, A. K. and Phelps, E. A. (2001). Lesions of the human amygdala impair enhanced perception of emotionally salient events. *Nature*, 411(6835):305–309.

Anderson, A. K. and Phelps, E. A. (2002). Is the human amygdala critical for the subjective experience of emotion? evidence of intact dispositional affect in patients with amygdala lesions. *Journal of cognitive neuroscience*, 14(5):709–720.

Anderson, E. R. and Hope, D. A. (2009). The relationship among social phobia, objective and perceived physiological reactivity, and anxiety sensitivity in an adolescent population. *Journal of anxiety disorders*, 23(1):18–26.

Anderson, S. W., Bechara, A., Damasio, H., Tranel, D., and Damasio, A. R. (1999). Impairment of social and moral behavior related to early damage in human prefrontal cortex. *Nature neuroscience*, 2(11):1032–1037.

Andreano, J. and Cahill, L. (2010). Menstrual cycle modulation of medial temporal activity evoked by negative emotion. *NeuroImage*, 53(4):1286–1293.

Andreescu, C., Mennin, D., Tudorascu, D., Sheu, L. K., Walker, S., Banihashemi, L., and Aizenstein, H. (2015). The many faces of anxiety-neurobiological correlates of anxiety phenotypes. *Psychiatry Research: Neuroimaging*, 234(1):96–105.

Andrews, J., Wadiwalla, M., Juster, R. P., Lord, C., Lupien, S. J., and Pruessner, J. C. (2007). Effects of manipulating the amount of social-evaluative threat on the cortisol stress response in young healthy men. *Behavioral neuroscience*, 121(5):871.

Andrews, M. M., Meda, S. A., Thomas, A. D., Potenza, M. N., Krystal, J. H., Worhunsky, P., Stevens, M. C., O'Malley, S., Book, G. A., Reynolds, B., et al. (2011). Individuals family history positive for alcoholism show functional magnetic resonance imaging differences in reward sensitivity that are related to impulsivity factors. *Biological psychiatry*, 69(7):675–683.

Andrews-Hanna, J. R. (2012). The brain's default network and its adaptive role in internal mentation. *The Neuroscientist*, 18(3):251–270.

Angrilli, A., Bianchin, M., Radaelli, S., Bertagnoni, G., and Pertile, M. (2008). Reduced startle reflex and aversive noise perception in patients with orbitofrontal cortex lesions. *Neuropsychologia*, 46(4):1179–1184.

Angus, D. J., Schutter, D. J., Terburg, D., van Honk, J., and Harmon-Jones, E. (2016). A review of social neuroscience research on anger and aggression. *Social Neuroscience: Biological Approaches to Social Psychology*, page 223.

Anker, J., Kushner, M., Thuras, P., Menk, J., and Unruh, A. (2016). Drinking to cope with negative emotions moderates alcohol use disorder treatment response in patients with co-occurring anxiety disorder. *Drug and alcohol dependence*, 159:93–100.

Ansell, E. B., Rando, K., Tuit, K., Guarnaccia, J., and Sinha, R. (2012). Cumulative adversity and smaller gray matter volume in medial prefrontal, anterior cingulate, and insula regions. *Biological psychiatry*, 72(1):57–64.

Anton, R. F., O'Malley, S. S., Ciraulo, D. A., Cisler, R. A., Couper, D., Donovan, D. M., Gastfriend, D. R., Hosking, J. D., Johnson, B. A., LoCastro, J. S., et al. (2006). Combined pharmacotherapies and behavioral interventions for alcohol dependence: the combine study: a randomized controlled trial. *Jama*, 295(17):2003–2017.

Antony, M. M. and Swinson, R. P. (2000). *Phobic disorders and panic in adults: A guide to assessment and treatment.* American Psychological Association.

APA (2013). *Diagnostic and statistical manual of mental disorders, Fifth Edition (DSM-5)*. Washington, DC: American Psychiatric Association.

Apodaca, T. R., Jackson, K. M., Borsari, B., Magill, M., Longabaugh, R., Mastroleo, N. R., and Barnett, N. P. (2016). Which individual therapist behaviors elicit client change talk and sustain talk in motivational interviewing? *Journal of substance abuse treatment*, 61:60–65.

Apodaca, T. R. and Longabaugh, R. (2009). Mechanisms of change in motivational interviewing: a review and preliminary evaluation of the evidence. *Addiction*, 104(5):705–715.

Arce, E., Miller, D., Feinstein, J., Stein, M., and Paulus, M. (2006). Lorazepam dose-dependently decreases risk-taking related activation in limbic areas. *Psychopharmacology*, 189(1):105–116.

Arkowitz, H., Miller, W. R., and Rollnick, S. (2015). *Motivational interviewing in the treatment of psychological problems*. Guilford Publications.

Armony, J. and LeDoux, J. (1997). How the brain processes emotional information. *Annals of the New York Academy of Sciences*, 821:259–270.

Armony, J. L., Corbo, V., Clément, M.-H., and Brunet, A. (2005). Amygdala response in patients with acute ptsd to masked and unmasked emotional facial expressions. *American Journal of Psychiatry*, 162(10):1961–1963.

Arnett, J. (1994). Sensation seeking: A new conceptualization and a new scale. *Personality and Individual Differences*, 16(2):289–296.

Arnone, D., McKie, S., Elliott, R., Thomas, E. J., Downey, D., Juhasz, G., Williams, S. R., Deakin, J. W., and Anderson, I. M. (2012). Increased amygdala responses to sad but not fearful faces in major depression: relation to mood state and pharmacological treatment. *American Journal of Psychiatry*, 169(8):841–850.

Arnsten, A. F. (2015). Stress weakens prefrontal networks: molecular insults to higher cognition. *Nature neuroscience*, 18(10):1376–1385.

Arnsten, A. F., Raskind, M. A., Taylor, F. B., and Connor, D. F. (2015). The effects of stress exposure on prefrontal cortex: Translating basic research into successful treatments for post-traumatic stress disorder. *Neurobiology of stress*, 1:89–99.

Aronson, H. and Gilbert, A. (1963). Preadolescent sons of male alcoholics: An experimental study of personality patterning. *Archives of General Psychiatry*, 8(3):235–241.

Aronson, M., Kyllerman, M., Sabel, K.-G., Sandin, B., and Olegård, R. (1985). Children of alcoholic mothers: Developmental, perceptual and behavioural characteristics as compared to matched controls. *Acta Paediatrica*, 74(1):27–35.

Aronsson, M., Fuxe, K., Dong, Y., Agnati, L., Okret, S., and Gustafsson, J.-A. (1988). Localization of glucocorticoid receptor mrna in the male rat brain by in situ hybridization. *Proceedings of the National Academy of Sciences of the United States of America*, 85(23):9331–9335.

Arria, A. M. and Compton, W. M. (2016). Complexities in understanding and addressing the serious public health issues related to the nonmedical use of prescription drugs. *Addictive Behaviors*.

Arriza, J., Simerly, R., Swanson, L., and Evans, R. (1988). The neuronal mineralocorticoid eeceptor as a mediator of glucocorticoid response. *Neuron*, 1(9):887–900.

Arsalidou, M., Pascual-Leone, J., Johnson, J., Morris, D., and Taylor, M. J. (2013). A balancing act of the brain: Activations and deactivations driven by cognitive load. *Brain and behavior*, 3(3):273–285.

Arseneault, L., Cannon, M., Fisher, H. L., Polanczyk, G., Moffitt, T. E., and Caspi, A. (2011). Childhood trauma and children's emerging psychotic symptoms: a genetically sensitive longitudinal cohort study. *American Journal of Psychiatry*, 168(1):65–72.

Arseneault, L., Moffitt, T., Caspi, A., Taylor, P., and Silva, P. (2000). Mental disorders and violence in a total birth cohort: Results from the dunedin study. *Archives of General Psychiatry*, 57(10):979–986.

Ashenhurst, J. R., Harden, K. P., Corbin, W. R., and Fromme, K. (2016). Alcohol-related genes show an enrichment of associations with a persistent externalizing factor. 125(7):933–945.

Ashton, C. (2001). Benzodiazepines: How they work and how to withdraw. the ashton manual, aug. 2002.

Ashton, H. (2005). The diagnosis and management of benzodiazepine dependence. *Current opinion in Psychiatry*, 18(3):249–255.

Asmundson, G. J., Norton, G. R., Wilson, K. G., and Sandler, L. S. (1994). Subjective symptoms and cardiac reactivity to brief hyperventilation in individuals with high anxiety sensitivity. *Behaviour Research and Therapy*, 32(2):237–241.

Assaad, J.-M., Pihl, R. O., Séguin, J. R., Nagin, D., Vitaro, F., Carbonneau, R., and Tremblay, R. E. (2003). Aggressiveness, family history of alcoholism, and the heart rate response to alcohol intoxication. *Experimental and Clinical Psychopharmacology*, 11(2):158.

Assaad, J.-M., Pihl, R. O., Séguin, J. R., Nagin, D., Vitaro, F., and Tremblay, R. E. (2006). Heart rate response to alcohol and intoxicated aggressive behavior. *Alcoholism: Clinical and Experimental Research*, 30(5):774–782.

Asthana, H. S. and Mandal, M. K. (1998). Hemifacial asymmetry in emotion expressions. *Behavior modification*, 22(2):177–183.

Attwood, A. S. and Munafò, M. R. (2014). Effects of acute alcohol consumption and processing of emotion in faces: Implications for understanding alcohol-related aggression. *Journal of Psychopharmacology*, 28(8):719–732.

Augustine, J. R. (1996). Circuitry and functional aspects of the insular lobe in primates including humans. *Brain research reviews*, 22(3):229–244.

Austin, G. A. (1985). Alcohol in western society from antiquity to 1800: A chronological history.

Averill, J. R. (1983). Studies on anger and aggression: Implications for theories of emotion. *American psychologist*, 38(11):1145.

Babor, T. F. (1996). The classification of alcoholics: Typology theories from the 19th century to the present. *Alcohol Research and Health*, 20(1):6.

Babor, T. F. and Caetano, R. (2006). Subtypes of substance dependence and abuse: implications for diagnostic classification and empirical research. *Addiction*, 101(s1):104–110.

Babor, T. F., Dolinsky, Z. S., Meyer, R. E., Hesselbrock, M., Hofmann, M., and Tennen, H. (1992). Types of alcoholics: concurrent and predictive validity of some common classification schemes. *British journal of addiction*, 87(10):1415–1431.

Bach, D. R., Hurlemann, R., and Dolan, R. J. (2015). Impaired threat prioritisation after selective bilateral amygdala lesions. *cortex*, 63:206–213.

Bachman, J. G. and O'Malley, P. M. (1977). Self-esteem in young men: A longitudinal analysis of the impact of educational and occupational attainment. *Journal of personality and social psychology*, 35(6):365.

Back, S., Brady, K., Jackson, J., Salstrom, S., and Zinzow, H. (2005). Gender differences in stress reactivity among cocaine-dependent individuals. *Psychopharmacology*, 180(1):169–176.

Back, S. E., Waldrop, A. E., Saladin, M. E., Yeatts, S. D., Simpson, A., McRae, A. L., Upadhyaya, H. P., Sisson, R. C., Spratt, E. G., Allen, J., et al. (2008). Effects of gender and cigarette smoking on reactivity to psychological and pharmacological stress provocation. *Psychoneuroendocrinology*, 33(5):560–568.

Baddam, S., Laws, H., Crawford, J. L., Wu, J., Bolling, D. Z., Mayes, L. C., and Crowley, M. J. (2016). What they bring: baseline psychological distress differentially predicts neural response in social exclusion by children's friends and strangers in best friend dyads. *Social Cognitive and Affective Neuroscience*, page nsw083.

Baeken, C., De Raedt, R., Ramsey, N., Van Schuerbeek, P., Hermes, D., Bossuyt, A., Leyman, L., Vanderhasselt, M.-A., De Mey, J., and Luypaert, R. (2009). Amygdala responses to positively and negatively valenced baby faces in healthy female volunteers: influences of individual differences in harm avoidance. *Brain research*, 1296:94–103.

Bagge, C. L., Lee, H.-J., Schumacher, J. A., Gratz, K. L., Krull, J. L., and Holloman Jr, G. (2013). Alcohol as an acute risk factor for recent suicide attempts: a case-crossover analysis. *Journal of studies on alcohol and drugs*, 74(4):552–558.

Baglama, B. (2016). Evaluating the usefulness of dsm in diagnosing mental health problems: A review of the literature. *Global Journal of Psychology Research*, 6(1):46–51.

Baker, E., Baibazarova, E., Ktistaki, G., Shelton, K. H., and Van Goozen, S. H. (2012). Development of fear and guilt in young children: Stability over time and relations with psychopathology. *Development and Psychopathology*, 24(03):833–845.

Baker, S. T., Yuecel, M., Fornito, A., Allen, N. B., and Lubman, D. I. (2013). A systematic review of diffusion weighted mri studies of white matter microstructure in adolescent substance users. *Neuroscience & Biobehavioral Reviews*, 37(8):1713–1723.

Baker, T. B., Piper, M. E., McCarthy, D. E., Majeskie, M. R., and Fiore, M. C. (2004). Addiction motivation reformulated: an affective processing model of negative reinforcement. *Psychological review*, 111(1):33.

Bakermans-Kranenburg, M. J. and Van IJzendoorn, M. H. (2015). The hidden efficacy of interventions: Gene× environment experiments from a differential susceptibility perspective. *Annual Review of Psychology*, 66:381–409.

Bakhshaie, J., Kauffman, B. Y., Viana, A. G., Garza, M., Ochoa-Perez, M., Lemaire, C., Bogiaizian, D., Robles, Z., and Zvolensky, M. J. (2016). Synergistic effects of pain intensity and experiential avoidance in relation to anxiety symptoms and disorders among economically disadvantaged latinos in a community-based primary care setting. *Journal of Anxiety Disorders*.

Balakrishnan, R., Allender, S., Scarborough, P., Webster, P., and Rayner, M. (2009). The burden of alcohol-related ill health in the united kingdom. *Journal of public health*, page fdp051.

Balán, I. C., Lejuez, C., Hoffer, M., and Blanco, C. (2016). Integrating motivational interviewing and brief behavioral activation therapy: Theoretical and practical considerations. *Cognitive and Behavioral Practice*, 23(2):205–220.

Ball, S. G., Otto, M. W., Pollack, M. H., Uccello, R., and Rosenbaum, J. F. (1995). Differentiating social phobia and panic disorder: A test of core beliefs. *Cognitive Therapy and Research*, 19(4):473–482.

Ball, T. M., Sullivan, S., Flagan, T., Hitchcock, C. A., Simmons, A., Paulus, M. P., and Stein, M. B. (2012). Selective effects of social anxiety, anxiety sensitivity, and negative affectivity on the neural bases of emotional face processing. *Neuroimage*, 59(2):1879–1887.

Balleine, B. W., Delgado, M. R., and Hikosaka, O. (2007). The role of the dorsal striatum in reward and decision-making. *The Journal of Neuroscience*, 27(31):8161–8165.

Balodis, I. M., Wynne-Edwards, K. E., and Olmstead, M. C. (2010). The other side of the curve: examining the relationship between pre-stressor physiological responses and stress reactivity. *Psychoneuroendocrinology*, 35(9):1363–1373.

Bandelow, B., Baldwin, D., Abelli, M., Altamura, C., Dell'Osso, B., Domschke, K., Fineberg, N. A., Grünblatt, E., Jarema, M., Maron, E., et al. (2016). Biological markers for anxiety disorders, ocd and ptsd–a consensus statement. part i: Neuroimaging and genetics. *The World Journal of Biological Psychiatry*, 17(5):321–365.

Bandelow, B., Reitt, M., Röver, C., Michaelis, S., Görlich, Y., and Wedekind, D. (2015). Efficacy of treatments for anxiety disorders: a meta-analysis. *International clinical psychopharmacology*, 30(4):183–192.

Bandelow, B., Seidler-Brandler, U., Becker, A., Wedekind, D., and Rüther, E. (2007). Meta-analysis of randomized controlled comparisons of psychopharmacological and psychological treatments for anxiety disorders. *The World Journal of Biological Psychiatry*, 8(3):175–187.

Banducci, A. N., Bujarski, S. J., Bonn-Miller, M. O., Patel, A., and Connolly, K. M. (2016). The impact of intolerance of emotional distress and uncertainty on veterans with co-occurring ptsd and substance use disorders. *Journal of anxiety disorders*.

Banes, K. E., Stephens, R. S., Blevins, C. E., Walker, D. D., and Roffman, R. A. (2014). Changing motives for use: Outcomes from a cognitive-behavioral intervention for marijuana-dependent adults. *Drug and alcohol dependence*, 139:41–46.

Bantick, S. J., Wise, R. G., Ploghaus, A., Clare, S., Smith, S. M., and Tracey, I. (2002). Imaging how attention modulates pain in humans using functional mri. *Brain*, 125(2):310–319.

Bantin, T., Stevens, S., Gerlach, A. L., and Hermann, C. (2016). What does the facial dot-probe task tell us about attentional processes in social anxiety? a systematic review. *Journal of behavior therapy and experimental psychiatry*, 50:40–51.

Baratta, M. V., Pomrenze, M. B., Nakamura, S., Dolzani, S. D., and Cooper, D. C. (2015). Control over stress accelerates extinction of drug seeking via prefrontal cortical activation. *Neurobiology of stress*, 2:20–27.

Barbas, H. (2007). Flow of information for emotions through temporal and orbitofrontal pathways. *Journal of Anatomy*, 211(2):237–249.

Barbas, H., Zikopoulos, B., and Timbie, C. (2011). Sensory pathways and emotional context for action in primate prefrontal cortex. *Biological Psychiatry*, 69(12):1133–1139.

Barber, K. (2015). Measuring, understanding, and evoking fear of positive evaluation in social anxiety.

Bardo, M. T., Donohew, R., and Harrington, N. G. (1996). Psychobiology of novelty seeking and drug seeking behavior. *Behavioural brain research*, 77(1):23–43.

Barker, M. J., Greenwood, K. M., Jackson, M., and Crowe, S. F. (2004). Cognitive effects of long-term benzodiazepine use. *CNS drugs*, 18(1):37–48.

Barlow, D. H. (2002). *Anxiety and its disorders*. Guilford Press New York.

Barlow, D. H., Allen, L. B., and Choate, M. L. (2004). Toward a unified treatment for emotional disorders. *Behavior Therapy*, 35(2):205–230.

Barlow, D. H., Sauer-Zavala, S., Carl, J. R., Bullis, J. R., and Ellard, K. K. (2014). The nature, diagnosis, and treatment of neuroticism back to the future. *Clinical Psychological Science*, 2(3):344–365.

Barrera, T. L., Smith, A. H., and Norton, P. J. (2016). Motivational interviewing as an adjunct to cognitive behavioral therapy for anxiety. *Journal of clinical psychology*, 72(1):5–14.

Barrett, J. and Armony, J. (2009). Influence of trait anxiety on brain activity during the acquisition and extinction of aversive conditioning. *Psychological medicine*, 39(02):255–265.

Barrós-Loscertales, A., Ventura-Campos, N., Sanjuán-Tomás, A., Belloch, V., Parcet, M.-A., and Ávila, C. (2010). Behavioral activation system modulation on brain activation during appetitive and aversive stimulus processing. *Social cognitive and affective neuroscience*, page nsq012.

Barsky, P. and Gaysina, D. (2016). Gene-environment interplay and individual differences in psychological traits. In *Behavioural Genetics for Education*, pages 24–41. Springer.

Barton, A. S., Zakreski, E., and Pruessner, J. (2016). The effects of early life adversity on responses to the montreal imaging stress task. *Psychoneuroendocrinology*, 71:67.

Bas-Hoogendam, J. M., Blackford, J. U., Brühl, A. B., Blair, K. S., van der Wee, N. J., and Westenberg, P. M. (2016). Neurobiological candidate endophenotypes of social anxiety disorder. *Neuroscience & Biobehavioral Reviews*.

Bastin, C., Harrison, B. J., Davey, C., Moll, J., and Whittle, S. (2016). Feelings of shame, embarrassment and guilt and their neural correlates: A systematic review. *Neuroscience & Biobehavioral Reviews*.

Battista, S., Stewart, S., Fulton, H., Steeves, D., Darredeau, C., and Gavric, D. (2008). A further investigation of the relations of anxiety sensitivity to smoking motives. *Addictive Behaviors*, 33(11):1402–1408.

Battista, S. R., Stewart, S. H., and Ham, L. S. (2010). A critical review of laboratory-based studies examining the relationships of social anxiety and alcohol intake. *Current Drug Abuse Reviews*, 3(1):3–22.

Baum-Baicker, C. (1985). The psychological benefits of moderate alcohol consumption: a review of the literature. *Drug and alcohol dependence*, 15(4):305–322.

Baumeister, R., Twenge, J., and Nuss, C. (2002). Effects of social exclusion on cognitive processes: Anticipated aloneness reduces intelligent thought. *Journal of Personality and Social Psychology*, 83(4):817–827.

Baumeister, R. F., Brewer, L. E., Tice, D. M., and Twenge, J. M. (2007). Thwarting the need to belong: Understanding the interpersonal and inner effects of social exclusion. *Social and Personality Psychology Compass*, 1(1):506–520.

Baumeister, R. F. and Leary, M. R. (1995). The need to belong: desire for interpersonal attachments as a fundamental human motivation. *Psychological bulletin*, 117(3):497.

Baur, V., Hänggi, J., Langer, N., and Jäncke, L. (2013). Resting-state functional and structural connectivity within an insula–amygdala route specifically index state and trait anxiety. *Biological psychiatry*, 73(1):85–92.

Bautista, C. L. and Hope, D. A. (2015). Fear of negative evaluation, social anxiety and response to positive and negative online social cues. *Cognitive Therapy and Research*, 39(5):658–668.

Bava, S., Jacobus, J., Thayer, R., and Tapert, S. (2013a). Longitudinal changes in white matter integrity among adolescent substance users. *Alcoholism: Clinical and Experimental Research*, 37(SUPPL.1):E181–E189.

Bava, S., Jacobus, J., Thayer, R. E., and Tapert, S. F. (2013b). Longitudinal changes in white matter integrity among adolescent substance users. *Alcoholism: clinical and experimental research*, 37(s1):E181–E189.

Bava, S., Thayer, R., Jacobus, J., Ward, M., Jernigan, T. L., and Tapert, S. F. (2010). Longitudinal characterization of white matter maturation during adolescence. *Brain research*, 1327:38–46.

Baxter, A., Scott, K., Vos, T., and Whiteford, H. (2013). Global prevalence of anxiety disorders: a systematic review and meta-regression. *Psychological Medicine*, 43(05):897–910.

Bazinet, A. D., Squeglia, L., Riley, E., and Tapert, S. F. (2016). Effects of drug exposure on development. In *The Oxford Handbook of Substance Use and Substance Use Disorders, Volume 2*.

Beauregard, M., Levesque, J., and Bourgouin, P. (2001). Neural correlates of conscious self-regulation of emotion. *The Journal of neuroscience*, 21(18):RC165–RC165.

Bechara, A., Damasio, A., Damasio, H., and Anderson, S. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition*, 50(1-3):7–15.

Bechara, A., Damasio, H., and Damasio, A. R. (2000). Emotion, decision making and the orbitofrontal cortex. *Cerebral cortex*, 10(3):295–307.

Beck, A., Schlagenhauf, F., Wüstenberg, T., Hein, J., Kienast, T., Kahnt, T., Schmack, K., Hägele, C., Knutson, B., Heinz, A., et al. (2009a). Ventral striatal activation during reward anticipation correlates with impulsivity in alcoholics. *Biological psychiatry*, 66(8):734–742.

Beck, I., Smits, D. J., Claes, L., Vandereycken, W., and Bijttebier, P. (2009b). Psychometric evaluation of the behavioral inhibition/behavioral activation system scales and the sensitivity to punishment and sensitivity to reward questionnaire in a sample of eating disordered patients. *Personality and Individual Differences*, 47(5):407–412.

Becker, B., Mihov, Y., Scheele, D., Kendrick, K. M., Feinstein, J. S., Matusch, A., Aydin, M., Reich, H., Urbach, H., Oros-Peusquens, A.-M., et al. (2012). Fear processing and social networking in the absence of a functional amygdala. *Biological psychiatry*, 72(1):70–77.

Becker, B., Wagner, D., Koester, P., Tittgemeyer, M., Mercer-Chalmers-Bender, K., Hurlemann, R., Zhang, J., Gouzoulis-Mayfrank, E., Kendrick, K. M., and Daumann, J. (2015). Smaller amygdala and medial prefrontal cortex predict escalating stimulant use. *Brain*, page awv113.

Becker, H. C., Lopez, M. F., and Doremus-Fitzwater, T. L. (2011). Effects of stress on alcohol drinking: a review of animal studies. *Psychopharmacology*, 218(1):131–156.

Beckmann, J., Marusich, J., Gipson, C., and Bardo, M. (2011). Novelty seeking, incentive salience and acquisition of cocaine self-administration in the rat. *Behavioural Brain Research*, 216(1):159–165.

Beer, J., John, O., Scabini, D., and Knight, R. (2006). Orbitofrontal cortex and social behavior: Integrating self-monitoring and emotion-cognition interactions. *Journal of Cognitive Neuroscience*, 18(6):871–879.

Beesdo, K., Lau, J. Y., Guyer, A. E., McClure-Tone, E. B., Monk, C. S., Nelson, E. E., Fromm, S. J., Goldwin, M. A., Wittchen, H.-U., Leibenluft, E., et al. (2009). Common and distinct amygdala-function perturbations in depressed vs anxious adolescents. *Archives of general psychiatry*, 66(3):275–285.

Begemann, M. J., Heringa, S. M., and Sommer, I. E. (2016). Childhood trauma as a neglected factor in psychotic experiences and cognitive functioning. *JAMA psychiatry*.

Behnke, R. R. and Beatty, M. J. (1981a). A cognitive-physiological model of speech anxiety. *Communications Monographs*, 48(2):158–163.

Behnke, R. R. and Beatty, M. J. (1981b). A comparison of anticipatory and performance anxiety in public speaking. *Texas Speech Communication Journal*, 1:3–6.

Behnke, R. R. and Carlile, L. W. (1971). Heart rate as an index of speech anxiety. *Speech Monographs*.

Behnke, R. R. and Sawyer, C. R. (1999). Milestones of anticipatory public speaking anxiety. *Communication Education*, 48(2):165–172.

Behnke, R. R. and Sawyer, C. R. (2000). Anticipatory anxiety patterns for male and female public speakers. *Communication Education*, 49(2):187–195.

Behnke, R. R. and Sawyer, C. R. (2001). Public speaking arousal as a function of anticipatory activation and autonomic reactivity. *Communication Reports*, 14(2):73–85.

Bekker, M. H. and van Mens-Verhulst, J. (2007). Anxiety disorders: sex differences in prevalence, degree, and background, but gender-neutral treatment. *Gender Medicine*, 4:S178–S193.

Belin, D., Belin-Rauscent, A., Everitt, B. J., and Dalley, J. W. (2016). In search of predictive endophenotypes in addiction: insights from preclinical research. *Genes, Brain and Behavior*, 15(1):74–88.

Belin, D., Berson, N., Balado, E., Piazza, P., and Deroche-Gamonet, V. (2011). High-novelty-preference rats are predisposed to compulsive cocaine self-administration. *Neuropsychopharmacology*, 36(3):569–579.

Belin, D., Mar, A., Dalley, J., Robbins, T., and Everitt, B. (2008). High impulsivity predicts the switch to compulsive cocaine-taking. *Science*, 320(5881):1352–1355.

Belin-Rauscent, A., Daniel, M., Puaud, M., Jupp, B., Sawiak, S., Howett, D., McKenzie, C., Caprioli, D., Besson, M., Robbins, T., et al. (2016). From impulses to maladaptive actions: the insula is a neurobiological gate for the development of compulsive behavior. *Molecular Psychiatry*, 21(4):491–499.

Bellis, M. D., Narasimhan, A., Thatcher, D. L., Keshavan, M. S., Soloff, P., and Clark, D. B. (2005). Prefrontal cortex, thalamus, and cerebellar volumes in adolescents and young adults with adolescent-onset alcohol use disorders and comorbid mental disorders. *Alcoholism: Clinical and Experimental Research*, 29(9):1590–1600.

Belsky, J., Bakermans-Kranenburg, M. J., and Van IJzendoorn, M. H. (2007). For better and for worse differential susceptibility to environmental influences. *Current Directions in Psychological Science*, 16(6):300–304.

Belsky, J., Jonassaint, C., Pluess, M., Stanton, M., Brummett, B., and Williams, R. (2009). Vulnerability genes or plasticity genes&quest. *Molecular psychiatry*, 14(8):746–754.

Belsky, J. and Pluess, M. (2009). Beyond diathesis stress: differential susceptibility to environmental influences. *Psychological bulletin*, 135(6):885.

Belsky, J. and Pluess, M. (2013). Beyond risk, resilience, and dysregulation: Phenotypic plasticity and human development. *Development and Psychopathology*, 25(4pt2):1243.

Benarroch, E. E. (1997). *Central autonomic network: functional organization and clinical correlations*. Futura Publishing Company.

Bendall, S., Jackson, H. J., Hulbert, C. A., and McGorry, P. D. (2008). Childhood trauma and psychotic disorders: a systematic, critical review of the evidence. *Schizophrenia bulletin*, 34(3):568–579.

Bender, T. W., Anestis, M. D., Anestis, J. C., Gordon, K. H., and Joiner, T. E. (2012). Affective and behavioral paths toward the acquired capacity for suicide. *Journal of Social and Clinical Psychology*, 31(1):81.

Bendriem, B., Alpert, R., and Hoff, A. (1991). Changes in brain glucose metabolism in cocaine dependence and withdrawal. *Am. J. Psychiatry*, 148(5):621626.

Benegal, V., Antony, G., Venkatasubramanian, G., and Jayakumar, P. N. (2007). Imaging study: gray matter volume abnormalities and externalizing symptoms in subjects at high risk for alcohol dependence. *Addiction biology*, 12(1):122–132.

Benjamin, J., Ebstein, R. P., and Belmaker, R. H. (2001). Genes for human personality traits:"endophenotypes" of psychiatric disorders? *The World Journal of Biological Psychiatry*, 2(2):54–57.

Benton, T. R., Ross, D. F., Bradshaw, E., Thomas, W. N., and Bradshaw, G. S. (2006). Eyewitness memory is still not common sense: Comparing jurors, judges and law enforcement to eyewitness experts. *Applied Cognitive Psychology*, 20(1):115–129.

Bentz, D., Michael, T., Wilhelm, F. H., Hartmann, F. R., Kunz, S., von Rohr, I. R. R., and Dominique, J.-F. (2013). Influence of stress on fear memory processes in an aversive differential conditioning paradigm in humans. *Psychoneuroendocrinology*, 38(7):1186–1197.

Berkman, E., Burklund, L., and Lieberman, M. (2009). Inhibitory spillover: Intentional motor inhibition produces incidental limbic inhibition via right inferior frontal cortex. *NeuroImage*, 47(2):705–712.

Berkman, E. T. (2015). Functional neural predictors of addiction outcomes. *The Wiley Handbook on the Cognitive Neuroscience of Addiction*, pages 503–526.

Berkman, E. T. and Falk, E. B. (2013). Beyond brain mapping using neural measures to predict real-world outcomes. *Current Directions in Psychological Science*, 22(1):45–50.

Berkowitz, L. (2000). *Causes and consequences of feelings*. Cambridge University Press.

Bernardy, N. C., King, A. C., Parsons, O. A., and Lovallo, W. R. (1996). Altered cortisol response in sober alcoholics: an examination of contributing factors. *Alcohol*, 13(5):493–498.

Berns, G. S., Moore, S., and Capra, C. M. (2009). Adolescent engagement in dangerous behaviors is associated with increased white matter maturity of frontal cortex. *PloS one*, 4(8):e6773.

Bernstein, A., Zvolensky, M. J., Stewart, S. H., Comeau, M. N., and Leen-Feldner, E. W. (2006). Anxiety sensitivity taxonicity across gender among youth. *Behaviour Research and Therapy*, 44(5):679–698.

Bernstein, D. P., Stein, J. A., Newcomb, M. D., Walker, E., Pogge, D., Ahluvalia, T., Stokes, J., Handelsman, L., Medrano, M., Desmond, D., et al. (2003). Development and validation of a brief screening version of the childhood trauma questionnaire. *Child abuse & neglect*, 27(2):169–190.

Bertolino, A., Arciero, G., Rubino, V., Latorre, V., De Candia, M., Mazzola, V., Blasi, G., Caforio, G., Hariri, A., Kolachana, B., Nardini, M., Weinberger, D., and Scarabino, T. (2005). Variation of human amygdala response during threatening stimuli as a function of 5httlpr genotype and personality style. *Biological Psychiatry*, 57(12):1517–1525.

Bertsch, K., Böhnke, R., Kruk, M. R., Richter, S., and Naumann, E. (2011). Exogenous cortisol facilitates responses to social threat under high provocation. *Hormones and behavior*, 59(4):428–434.

Betancourt, T. S., McBain, R., Newnham, E. A., and Brennan, R. T. (2013). Trajectories of internalizing problems in war-affected sierra leonean youth: Examining conflict and postconflict factors. *Child development*, 84(2):455–470.

Bettencourt, B. and Miller, N. (1996). Gender differences in aggression as a function of provocation: a meta-analysis. *Psychological bulletin*, 119(3):422.

Bewernick, B. H., Hurlemann, R., Matusch, A., Kayser, S., Grubert, C., Hadrysiewicz, B., Axmacher, N., Lemke, M., Cooper-Mahkorn, D., Cohen, M. X., et al. (2010). Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. *Biological psychiatry*, 67(2):110–116.

Beyeler, A., Namburi, P., Glober, G. F., Simonnet, C., Calhoon, G. G., Conyers, G. F., Luck, R., Wildes, C. P., and Tye, K. M. (2016). Divergent routing of positive and negative information from the amygdala during memory retrieval. *Neuron*, 90(2):348–361.

Beyer, F., Münte, T. F., Göttlich, M., and Krämer, U. M. (2015). Orbitofrontal cortex reactivity to angry facial expression in a social interaction correlates with aggressive behavior. *Cerebral Cortex*, 25(9):3057–3063.

Bibbey, A., Ginty, A. T., Brindle, R. C., Phillips, A. C., and Carroll, D. (2016). Blunted cardiac stress reactors exhibit relatively high levels of behavioural impulsivity. *Physiology & Behavior*, 159:40–44.

Biederman, J., Hirshfeld-Becker, D. R., Rosenbaum, J. F., Hérot, C., Friedman, D., Snidman, N., Kagan, J., and Faraone, S. V. (2001). Further evidence of association between behavioral inhibition and social anxiety in children. *American journal of Psychiatry*, 158(10):1673–1679.

Bierut, L., Goate, A., Breslau, N., Johnson, E., Bertelsen, S., Fox, L., Agrawal, A., Bucholz, K., Grucza, R., Hesselbrock, V., Kramer, J., Kuperman, S., Nurnberger, J., Porjesz, B., Saccone, N., Schuckit, M., Tischfield, J., Wang, J., Foroud, T., Rice, J., and Edenberg, H. (2012). Adh1b is associated with alcohol dependence and alcohol consumption in populations of european and african ancestry. *Molecular Psychiatry*, 17(4):445–450.

Bijleveld, C., Hill, J., and Hendriks, J. (2016). Sexual abuse within the family: The intergenerational transmission of victimhood and offending. In *Women and Children as Victims and Offenders: Background, Prevention, Reintegration*, pages 905–921. Springer.

Bijsterbosch, J., Smith, S., and Bishop, S. J. (2015). Functional connectivity under anticipation of shock: Correlates of trait anxious affect versus induced anxiety. *Journal of cognitive neuroscience*.

Binelli, C., Subirà, S., Batalla, A., Muñiz, A., Sugranyés, G., Crippa, J., Farré, M., Pérez-Jurado, L., and Martín-Santos, R. (2014). Common and distinct neural correlates of facial emotion processing in social anxiety disorder and williams syndrome: A systematic review and voxel-based meta-analysis of functional resonance imaging studies. *Neuropsychologia*, 64:205–217.

Birley, A., James, M., Dickson, P., Montgomery, G., Heath, A., Martin, N., and Whitfield, J. (2009). Adh single nucleotide polymorphism associations with alcohol metabolism in vivo. *Human Molecular Genetics*, 18(8):1533–1542.

Bishop, S., Duncan, J., Brett, M., and Lawrence, A. D. (2004). Prefrontal cortical function and anxiety: controlling attention to threat-related stimuli. *Nature neuroscience*, 7(2):184–188.

Bishop, S. J., Jenkins, R., and Lawrence, A. D. (2007). Neural processing of fearful faces: effects of anxiety are gated by perceptual capacity limitations. *Cerebral cortex*, 17(7):1595–1603.

Bjork, J. M. and Gilman, J. M. (2014). The effects of acute alcohol administration on the human brain: Insights from neuroimaging. *Neuropharmacology*, 84:101–110.

Bjork, J. M., Knutson, B., and Hommer, D. W. (2008). Incentive-elicited striatal activation in adolescent children of alcoholics. *Addiction*, 103(8):1308–1319.

Blackford, J. U., Allen, A. H., Cowan, R. L., and Avery, S. N. (2012). Amygdala and hippocampus fail to habituate to faces in individuals with an inhibited temperament. *Social cognitive and affective neuroscience*, page nsr078.

Blackford, J. U. and Pine, D. S. (2012). Neural substrates of childhood anxiety disorders a review of neuroimaging findings. *Child and adolescent psychiatric clinics of North America*, 21(3):501.

Blair, K., Otero, M., Teng, C., Geraci, M., Lewis, E., Hollon, N., Blair, R., Ernst, M., Grillon, C., and Pine, D. (2016). Learning from other people's fear: amygdala-based social reference learning in social anxiety disorder. *Psychological medicine*, page 1.

Blair, K., Shaywitz, J., Smith, B. W., Rhodes, R., Geraci, M., Jones, M., McCaffrey, D., Vythilingam, M., Finger, E., Mondillo, K., et al. (2008). Response to emotional expressions in generalized social phobia and generalized anxiety disorder: evidence for separate disorders. *American Journal of Psychiatry*.

Blair, K., Smith, B., Mitchell, D., Morton, J., Vythilingam, M., Pessoa, L., Fridberg, D., Zametkin, A., Nelson, E., Drevets, W., et al. (2007). Modulation of emotion by cognition and cognition by emotion. *Neuroimage*, 35(1):430–440.

Blair, R. (2003a). Facial expressions, their communicatory functions and neuro–cognitive substrates. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 358(1431):561–572.

Blair, R. (2003b). Neurobiological basis of psychopathy. *British Journal of Psychiatry*, 182(JAN.):5–7.

Blair, R. (2008). The amygdala and ventromedial prefrontal cortex: functional contributions and dysfunction in psychopathy. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*, 363(1503):2557–2565.

Blair, R. (2012). Considering anger from a cognitive neuroscience perspective. *Wiley Interdisciplinary Reviews: Cognitive Science*, 3(1):65–74.

Blair, R., Morris, J. S., Frith, C. D., Perrett, D. I., and Dolan, R. J. (1999). Dissociable neural responses to facial expressions of sadness and anger. *Brain*, 122(5):883–893.

Blair, R. J. R. (2001). Neurocognitive models of aggression, the antisocial personality disorders, and psychopathy. *Journal of Neurology, Neurosurgery & Psychiatry*, 71(6):727–731.

Blalock, D. V., Kashdan, T. B., and Farmer, A. S. (2016). Trait and daily emotion regulation in social anxiety disorder. *Cognitive Therapy and Research*, 40(3):416–425.

Blanchard, M. M., Mendelsohn, D., and Stamp, J. A. (2009). The hr/lr model: further evidence as an animal model of sensation seeking. *Neuroscience & Biobehavioral Reviews*, 33(7):1145–1154.

Blanchard, R. J., Magee, L., Veniegas, R., and Blanchard, D. C. (1993). Alcohol and anxiety: ethopharmacological approaches. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 17(2):171–182.

Blanco, C., Rubio, J. M., Wall, M., Secades-Villa, R., Beesdo-Baum, K., and Wang, S. (2014). The latent structure and comorbidity patterns of generalized anxiety disorder and major depressive disorder: a national study. *Depression and anxiety*, 31(3):214–222.

Blanco, L., Nydegger, L. A., Camarillo, G., Trinidad, D. R., Schramm, E., and Ames, S. L. (2015). Neurological changes in brain structure and functions among individuals with a history of childhood sexual abuse: a review. *Neuroscience & Biobehavioral Reviews*, 57:63–69.

Blanke, O. and Arzy, S. (2005). The out-of-body experience: disturbed self-processing at the temporo-parietal junction. *The Neuroscientist*, 11(1):16–24.

Blankstein, K. R. (1975). The sensation seeker and anxiety reactivity: Relationships between the sensation-seeking scales and the activity preferences questionnaire. *Journal of clinical psychology*, 31(4):677–681.

Blascovich, J. and Tomaka, J. (1996). The biopsychosocial model of arousal regulation. *Advances in experimental social psychology*, 28:1–52.

Blevins, C. E., Abrantes, A. M., and Stephens, R. S. (2016a). Motivational pathways from antecedents of alcohol use to consequences: a structural model of using alcohol to cope with negative affect. *The American journal of drug and alcohol abuse*, pages 1–9.

Blevins, C. E., Banes, K. E., Stephens, R. S., Walker, D. D., and Roffman, R. A. (2016b). Change in motives among frequent cannabis-using adolescents: Predicting treatment outcomes. *Drug and alcohol dependence*.

Blevins, C. E. and Stephens, R. S. (2016). The impact of motives-related feedback on drinking to cope among college students. *Addictive behaviors*, 58:68–73.

Bocanegra, B. R. and Hommel, B. (2014). When cognitive control is not adaptive. *Psychological science*, 25(6):1249–1255.

Boden, J. M., Fergusson, D. M., and Horwood, L. J. (2012). Alcohol misuse and violent behavior: Findings from a 30-year longitudinal study. *Drug and alcohol dependence*, 122(1):135–141.

Boelema, S. R., Harakeh, Z., Van Zandvoort, M. J., Reijneveld, S. A., Verhulst, F. C., Ormel, J., and Vollebergh, W. A. (2016). Executive functioning before and after onset of alcohol use disorder in adolescence. a trails study. *Journal of psychiatric research*, 78:78–85.

Boelen, P. A. and Reijntjes, A. (2009). Intolerance of uncertainty and social anxiety. *Journal of anxiety disorders*, 23(1):130–135.

Boelen, P. A., Reijntjes, A., and Smid, G. E. (2016). Concurrent and prospective associations of intolerance of uncertainty with symptoms of prolonged grief, posttraumatic stress, and depression after bereavement. *Journal of anxiety disorders*.

Boelen, P. A., Vrinssen, I., and van Tulder, F. (2010). Intolerance of uncertainty in adolescents: Correlations with worry, social anxiety, and depression. *The Journal of nervous and mental disease*, 198(3):194–200.

Bogenschutz, M. P., Scott Tonigan, J., and Pettinati, H. M. (2009). Effects of alcoholism typology on response to naltrexone in the combine study. *Alcoholism: Clinical and Experimental Research*, 33(1):10–18.

Bohlken, M. M., Mandl, R. C., Brouwer, R. M., den Heuvel, M. P., Hedman, A. M., Kahn, R. S., Pol, H., and Hilleke, E. (2014). Heritability of structural brain network topology: a dti study of 156 twins. *Human brain mapping*, 35(10):5295–5305.

Böhnke, R., Bertsch, K., Kruk, M. R., and Naumann, E. (2010a). The relationship between basal and acute hpa axis activity and aggressive behavior in adults. *Journal of Neural Transmission*, 117(5):629–637.

Böhnke, R., Bertsch, K., Kruk, M. R., Richter, S., and Naumann, E. (2010b). Exogenous cortisol enhances aggressive behavior in females, but not in males. *Psychoneuroendocrinology*, 35(7):1034–1044.

Boileau, I., Assaad, J.-M., Pihl, R., Benkelfat, C., Leyton, M., Diksic, M., Tremblay, R., and Dagher, A. (2003). Alcohol promotes dopamine release in the human nucleus accumbens. *Synapse*, 49(4):226–231.

Boileau, I., Dagher, A., Leyton, M., Welfeld, K., Booij, L., Diksic, M., and Benkelfat, C. (2007). Conditioned dopamine release in humans: a positron emission tomography [11c] raclopride study with amphetamine. *The Journal of neuroscience*, 27(15):3998–4003.

Bolger, N. (1990). Coping as a personality process: a prospective study. *Journal of personality and social psychology*, 59(3):525.

Bolton, J., Cox, B., Clara, I., and Sareen, J. (2006). Use of alcohol and drugs to self-medicate anxiety disorders in a nationally representative sample. *The Journal of nervous and mental disease*, 194(11):818–825.

Bongard, S., Olson, L., Nakajima, M., and al'Absi, M. (2016). Anger expression style predicts the domain of the first smoking relapse after a quit attempt. *Substance Use & Misuse*, 51(13):1810–1814.

Bonne, O., Vythilingam, M., Inagaki, M., Wood, S., Neumeister, A., Nugent, A. C., Snow, J., Luckenbaugh, D. A., Bain, E. E., Drevets, W. C., et al. (2008). Reduced posterior hippocampal volume in posttraumatic stress disorder. *The Journal of clinical psychiatry*, 69(7):1087.

Bora, E. and Zorlu, N. (2016). Social cognition in alcohol use disorder: A meta-analysis. *Addiction*.

Borges, G. and Loera, C. R. (2010). Alcohol and drug use in suicidal behaviour. *Current Opinion in Psychiatry*, 23(3):195–204.

Borges, G., Ye, Y., Bond, J., Cherpitel, C. J., Cremonte, M., Moskalewicz, J., Swiatkiewicz, G., and Rubio-Stipec, M. (2010). The dimensionality of alcohol use disorders and alcohol consumption in a cross-national perspective. *Addiction*, 105(2):240–254.

Born, J., Ditschuneit, I., Schreiber, M., Dodt, C., and Fehm, H. L. (1995). Effects of age and gender on pituitary-adrenocortical responsiveness in humans. *European Journal of Endocrinology*, 132(6):705–711.

Borrill, J. A., Rosen, B. K., and Summerfield, A. B. (1987). The influence of alcohol on judgement of facial expressions of emotion. *British Journal of Medical Psychology*, 60(1):71–77.

Bosch, J. A., de Geus, E. J., Carroll, D., Goedhart, A. D., Anane, L. A., van Zanten, J. J. V., Helmerhorst, E. J., and Edwards, K. M. (2009). A general enhancement of autonomic and cortisol responses during social evaluative threat. *Psychosomatic medicine*, 71(8):877.

Boschloo, L., Vogelzangs, N., Smit, J. H., van den Brink, W., Veltman, D. J., Beekman, A. T., and Penninx, B. W. (2011). Comorbidity and risk indicators for alcohol use disorders among persons with anxiety and/or depressive disorders: findings from the netherlands study of depression and anxiety (nesda). *Journal of affective disorders*, 131(1):233–242.

Bosquet Enlow, M., Englund, M. M., and Egeland, B. (2016). Maternal childhood maltreatment history and child mental health: Mechanisms in intergenerational effects. *Journal of Clinical Child & Adolescent Psychology*, pages 1–16.

Bouchery, E. E., Harwood, H. J., Sacks, J. J., Simon, C. J., and Brewer, R. D. (2011). Economic costs of excessive alcohol consumption in the us, 2006. *American journal of preventive medicine*, 41(5):516–524.

Bouton, M. E. (2007). *Learning and behavior: A contemporary synthesis*. Sinauer Associates.

Bowers, M. E. and Yehuda, R. (2016). Intergenerational transmission of stress in humans. *Neuropsychopharmacology*, 41(1):232–244.

Bowlby, J. (1969). Attachment, vol. 1 of attachment and loss.

Bowman, K. M. and Jellinek, E. M. (1941). Alcohol addiction and its treatment. *Quarterly Journal of Studies on Alcohol*, 2(1):98–176.

Boyle, M. P., Brewer, J. A., Funatsu, M., Wozniak, D. F., Tsien, J. Z., Izumi, Y., and Muglia, L. J. (2005). Acquired deficit of forebrain glucocorticoid receptor produces depression-like changes in adrenal axis regulation and behavior. *Proceedings of the National Academy of Sciences of the United States of America*, 102(2):473–478.

Braams, B. R., Peper, J. S., van der Heide, D., Peters, S., and Crone, E. A. (2016). Nucleus accumbens response to rewards and testosterone levels are related to alcohol use in adolescents and young adults. *Developmental cognitive neuroscience*, 17:83–93.

Bradbury, M., Strack, A., and Dallman, M. (1993). Lesions of the hippocampal efferent pathway (fimbria-fornix) do not alter sensitivity of adrenocorticotropin to feedback inhibition by corticosterone in rats. *Neuroendocrinology*, 58(4):396–407.

Bradford, D. E., Shapiro, B. L., and Curtin, J. J. (2013). How bad could it be? alcohol dampens stress responses to threat of uncertain intensity. *Psychological science*, 24(12):2541–2549.

Brady, J. P., Foulks, E. F., Childress, A. R., and Pertschuk, M. (1982). The michigan alcoholism screening test as a survey instrument. *Journal of Operational Psychiatry*.

Branas, C. C., Richmond, T. S., Ten Have, T. R., and Wiebe, D. J. (2011). Acute alcohol consumption, alcohol outlets, and gun suicide. *Substance use & misuse*, 46(13):1592–1603.

Brandon, T. (1994). Negative affect as motivation to smoke. *Current Directions in Psychological Science*, 3(2):33–37.

Brandon, T. H., Vidrine, J. I., and Litvin, E. B. (2007). Relapse and relapse prevention. *Annu. Rev. Clin. Psychol.*, 3:257–284.

Brandt, C. P., Gonzalez, A., Grover, K. W., and Zvolensky, M. J. (2013). The relation between emotional dysregulation and anxiety and depressive symptoms, pain-related anxiety, and hiv-symptom distress among adults with hiv/aids. *Journal of Psychopathology and Behavioral Assessment*, 35(2):197–204.

Bray, G. A. (1979). Obesity in america (dhew publication no. nih 79–359). *(U.S. Department of Health, Education, and Welfare, Publication (NIH))*.

Breier, A. (1989). Experimental approaches to human stress research: Assessment of neurobiological mechanisms of stress in volunteers and psychiatric patients. *Biological Psychiatry*, 26(5):438–462.

Bremner, J., Staib, L., Kaloupek, D., Southwick, S., Soufer, R., and Charney, D. (1999). Neural correlates of exposure to traumatic pictures and sound in vietnam combat veterans with and without posttraumatic stress disorder: A positron emission tomography study. *Biological Psychiatry*, 45(7):806–816.

Bremner, J. D., Vythilingam, M., Vermetten, E., Adil, J., Khan, S., Nazeer, A., Afzal, N., McGlashan, T., Elzinga, B., Anderson, G. M., et al. (2003). Cortisol response to a cognitive stress challenge in posttraumatic stress disorder (ptsd) related to childhood abuse. *Psychoneuroendocrinology*, 28(6):733–750.

Breslau, N. and Klein, D. F. (1999). Smoking and panic attacks: an epidemiologic investigation. *Archives of general psychiatry*, 56(12):1141–1147.

Breslin, F. C., Sobell, M. B., Cappell, H., Vakili, S., and Poulos, C. X. (1999). The effects of alcohol, gender, and sensation seeking on the gambling choices of social drinkers. *Psychology of Addictive Behaviors*, 13(3):243.

Brett, M., Anton, J.-L., Valabregue, R., and Poline, J.-B. (2002). Region of interest analysis using the marsbar toolbox for spm 99. *Neuroimage*, 16(2):S497.

Brewer, J. A., Garrison, K. A., and Whitfield-Gabrieli, S. (2013). What about the 'self'is processed in the posterior cingulate cortex? *Frontiers in Human Neuroscience*, 7.

Brickman, P., Coates, D., and Janoff-Bulman, R. (1978). Lottery winners and accident victims: Is happiness relative? *Journal of Personality and Social Psychology*, 36(8):917–927.

Brière, F. N., Rohde, P., Seeley, J. R., Klein, D., and Lewinsohn, P. M. (2014). Comorbidity between major depression and alcohol use disorder from adolescence to adulthood. *Comprehensive psychiatry*, 55(3):526–533.

Britton, J. C. and Rauch, S. L. (2008). Neuroanatomy and neuroimaging of anxiety disorders. *Oxford Handbook of Anxiety and Related Disorders. Oxford University Press: USA*, page 97.

Brkic, S., Söderpalm, B., and Gordh, A. S. (2015). A family history of type 1 alcoholism differentiates alcohol consumption in high cortisol responders to stress. *Pharmacology Biochemistry and Behavior*, 130:59–66.

Brkic, S., Söderpalm, B., and Gordh, A. S. (2016). High cortisol responders to stress show increased sedation to alcohol compared to low cortisol responders: An alcohol dose–response study. *Pharmacology Biochemistry and Behavior*, 143:65–72.

Bromberg-Martin, E. S., Matsumoto, M., and Hikosaka, O. (2010). Dopamine in motivational control: rewarding, aversive, and alerting. *Neuron*, 68(5):815–834.

Brooks, S. J. and Stein, D. J. (2015). A systematic review of the neural bases of psychotherapy for anxiety and related disorders. *Dialogues in clinical neuroscience*, 17(3):261.

Brooks, S. J. and Stein, D. J. (2016). Brain volumes in adolescents with alcohol use disorder. *Neuropathology of Drug Addictions and Substance Misuse*, 1:587–599.

Brown, R., Lejuez, C., Kahler, C., and Strong, D. (2002). Distress tolerance and duration of past smoking cessation attempts. *Journal of Abnormal Psychology*, 111(1):180–185.

Brown, R., Lejuez, C., Strong, D., Kahler, C., Zvolensky, M., Carpenter, L., Niaura, R., and Price, L. (2009). A prospective examination of distress tolerance and early smoking lapse in adult self-quitters. *Nicotine and Tobacco Research*, 11(5):493–502.

Brown, R. A., Kahler, C. W., Zvolensky, M. J., Lejuez, C., and Ramsey, S. E. (2001). Anxiety sensitivity: Relationship to negative affect smoking and smoking cessation in smokers with past major depressive disorder. *Addictive behaviors*, 26(6):887–899.

Brown, S. A., Goldman, M. S., Inn, A., and Anderson, L. R. (1980). Expectations of reinforcement from alcohol: Their domain and relation to drinking patterns. *Journal of consulting and Clinical Psychology*, 48(4):419.

Brown, S. A., McGue, M., Maggs, J., Schulenberg, J., Hingson, R., Swartzwelder, S., Martin, C., Chung, T., Tapert, S. F., Sher, K., et al. (2008). A developmental perspective on alcohol and youths 16 to 20 years of age. *Pediatrics*, 121(Supplement 4):S290–S310.

Bruce, K. R., Shestowsky, J. S., Mayerovitch, J. I., and Pihl, R. (1999). Motivational effects of alcohol on memory consolidation and heart rate in social drinkers. *Alcoholism: Clinical and experimental research*, 23(4):693–701.

Bruce, V. and Young, A. (1986). Understanding face recognition. *British journal of psychology*, 77(3):305–327.

Brühl, A. B., Delsignore, A., Komossa, K., and Weidt, S. (2014). Neuroimaging in social anxiety disorder—a meta-analytic review resulting in a new neurofunctional model. *Neuroscience & Biobehavioral Reviews*, 47:260–280.

Brühl, A. B., Viebke, M.-C., Baumgartner, T., Kaffenberger, T., and Herwig, U. (2011). Neural correlates of personality dimensions and affective measures during the anticipation of emotional stimuli. *Brain imaging and behavior*, 5(2):86–96.

Brunelle, C., Assaad, J.-M., Barrett, S. P., Ávila, C., Conrod, P. J., Tremblay, R. E., and Pihl, R. O. (2004). Heightened heart rate response to alcohol intoxication is associated with a reward-seeking personality profile. *Alcoholism: Clinical and Experimental Research*, 28(3):394–401.

Brunelle, C., Barrett, S., and Pihl, R. (2005). Alcohol-induced stimulant effects are associated with a heightened cardiac response to alcohol intoxication. 29(5):153.

Brunelle, C., Barrett, S. P., and Pihl, R. O. (2007). Relationship between the cardiac response to acute intoxication and alcohol-induced subjective effects throughout the blood alcohol concentration curve. *Human Psychopharmacology: Clinical and Experimental*, 22(7):437–443.

Brunette, M. F., Noordsy, D. L., Xie, H., and Drake, R. E. (2003). Benzodiazepine use and abuse among patients with severe mental illness and co-occurring substance use disorders. *Psychiatric Services*.

Bryant, R., Felmingham, K., Kemp, A., Das, P., Hughes, G., Peduto, A., and Williams, L. (2008). Amygdala and ventral anterior cingulate activation predicts treatment response to cognitive behaviour therapy for post-traumatic stress disorder. *Psychological medicine*, 38(04):555–561.

Buchanan, T., Al'Absi, M., and Lovallo, W. (1999). Cortisol fluctuates with increases and decreases in negative affect. *Psychoneuroendocrinology*, 24(2):227–241.

Buchanan, T. W. and Preston, S. D. (2014). Stress leads to prosocial action in immediate need situations. *Frontiers in behavioral neuroscience*, 8.

Büchel, C., Dolan, R. J., Armony, J. L., and Friston, K. J. (1999). Amygdala–hippocampal involvement in human aversive trace conditioning revealed through event-related functional magnetic resonance imaging. *The Journal of Neuroscience*, 19(24):10869–10876.

Bucholz, K. K., Heath, A. C., Reich, T., Hesselbrock, V. M., Krarner, J. R., Nurnberger, J. I., and Schuckit, M. A. (1996). Can we subtype alcoholism? a latent class analysis of data from relatives of alcoholics in a multicenter family study of alcoholism. *Alcoholism: Clinical and Experimental Research*, 20(8):1462–1471.

Buck, K. J. (1996). Molecular genetic analysis of the role of gabaergic systems in the behavioral and cellular actions of alcohol. *Behavior genetics*, 26(3):313–323.

Buckingham, J., Moss, A., Gyure, K., Ralph, N., Hindocha, C., Lawn, W., Curran, H. V., and Freeman, T. P. (2016). A moderate dose of alcohol does not influence experience of social ostracism in hazardous drinkers. *Frontiers in psychology*, 7.

Buckner, J. D., Eggleston, A. M., and Schmidt, N. B. (2006). Social anxiety and problematic alcohol consumption: The mediating role of drinking motives and situations. *Behavior therapy*, 37(4):381–391.

Buckner, J. D., Heimberg, R. G., Ecker, A. H., and Vinci, C. (2013). A biopsychosocial model of social anxiety and substance use. *Depression and Anxiety*, 30(3):276–284.

Buckner, R., Andrews-Hanna, J., and Schacter, D. (2008). The brain's default network: Anatomy, function, and relevance to disease. *Annals of the New York Academy of Sciences*, 1124:1–38.

Buhle, J. T., Silvers, J. A., Wager, T. D., Lopez, R., Onyemekwu, C., Kober, H., Weber, J., and Ochsner, K. N. (2014). Cognitive reappraisal of emotion: a meta-analysis of human neuroimaging studies. *Cerebral Cortex*, 24(11):2981–2990.

Buhr, K. and Dugas, M. J. (2009). The role of fear of anxiety and intolerance of uncertainty in worry: An experimental manipulation. *Behaviour Research and Therapy*, 47(3):215–223.

Buizer-Voskamp, J. E., Muntjewerff, J.-W., Risk, G., Strengman, E., Sabatti, C., Stefansson, H., Vorstman, J. A., Ophoff, R. A., et al. (2011). Genome-wide analysis shows increased frequency of copy number variation deletions in dutch schizophrenia patients. *Biological psychiatry*, 70(7):655–662.

Bujarski, S. and Ray, L. A. (2016). Experimental psychopathology paradigms for alcohol use disorders: Applications for translational research. *Behaviour research and therapy*.

Bunford, N., Kujawa, A., Fitzgerald, K. D., Swain, J. E., Hanna, G. L., Koschmann, E., Simpson, D., Connolly, S., Monk, C. S., and Phan, K. L. (2016). Neural reactivity to angry faces predicts treatment response in pediatric anxiety. *Journal of abnormal child psychology*, pages 1–11.

Bunge, S. A., Ochsner, K. N., Desmond, J. E., Glover, G. H., and Gabrieli, J. D. (2001). Prefrontal regions involved in keeping information in and out of mind. *Brain*, 124(10):2074–2086.

Bunzeck, N. and Düzel, E. (2006). Absolute coding of stimulus novelty in the human substantia nigra/vta. *Neuron*, 51(3):369–379.

Burcu, M., Zito, J. M., Metcalfe, L., Underwood, H., and Safer, D. J. (2016). Trends in stimulant medication use in commercially insured youths and adults, 2010-2014. *JAMA psychiatry*.

Burian, S. E., Liguori, A., and Robinson, J. H. (2002). Effects of alcohol on risk-taking during simulated driving. *Human Psychopharmacology: Clinical and Experimental*, 17(3):141–150.

Burke, B. L., Dunn, C. W., Atkins, D. C., and Phelps, J. S. (2004). The emerging evidence base for motivational interviewing: A meta-analytic and qualitative inquiry. *Journal of Cognitive Psychotherapy*, 18(4):309–322.

Burns, A. R., Hussong, A. M., Solis, J. M., Curran, P. J., McGinley, J. S., Bauer, D. J., Chassin, L., and Zucker, R. A. (2016). Examining cohort effects in developmental trajectories of substance use. *International Journal of Behavioral Development*, page 0165025416651734.

Bush, G., Luu, P., and Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends in cognitive sciences*, 4(6):215–222.

Bush, G., Vogt, B., Holmes, J., Dale, A., Greve, D., Jenike, M., and Rosen, B. (2002). Dorsal anterior cingulate cortex: A role in reward-based decision making. *Proceedings of the National Academy of Sciences of the United States of America*, 99(1):523–528.

Bushman, B. and Cooper, H. (1990). Effects of alcohol on human aggression: An integrative research review. *Psychological Bulletin*, 107(3):341–354.

Butler, A. C., Chapman, J. E., Forman, E. M., and Beck, A. T. (2006). The empirical status of cognitive-behavioral therapy: a review of meta-analyses. *Clinical psychology review*, 26(1):17–31.

Butler, G. and Mathews, A. (1987). Anticipatory anxiety and risk perception. *Cognitive Therapy and Research*, 11(5):551–565.

Butler, T., Pan, H., Epstein, J., Protopopescu, X., Tuescher, O., Goldstein, M., Cloitre, M., Yang, Y., Phelps, E., Gorman, J., Ledoux, J., Stern, E., and Silbersweig, D. (2005). Fear-related activity in subgenual anterior cingulate differs between men and women. *NeuroReport*, 16(11):1233–1236.

Cabanis, M., Pyka, M., Mehl, S., Müller, B. W., Loos-Jankowiak, S., Winterer, G., Wölwer, W., Musso, F., Klingberg, S., Rapp, A. M., et al. (2013). The precuneus and the insula in self-attributional processes. *Cognitive, Affective, & Behavioral Neuroscience*, 13(2):330–345.

Cabrera, E. A., Wiers, C. E., Lindgren, E., Miller, G., Volkow, N. D., and Wang, G.-J. (2016). Neuroimaging the effectiveness of substance use disorder treatments. *Journal of Neuroimmune Pharmacology*, pages 1–26.

Cacioppo, J. T., Cacioppo, S., Capitanio, J. P., and Cole, S. W. (2015a). The neuroendocrinology of social isolation. *Annual review of psychology*, 66:733–767.

Cacioppo, J. T., Cacioppo, S., Cole, S. W., Capitanio, J. P., Goossens, L., and Boomsma, D. I. (2015b). Loneliness across phylogeny and a call for comparative studies and animal models. *Perspectives on Psychological Science*, 10(2):202–212.

Cacioppo, J. T., Hawkley, L. C., Norman, G. J., and Berntson, G. G. (2011). Social isolation. *Annals of the New York Academy of Sciences*, 1231(1):17–22.

Cacioppo, J. T., Norris, C. J., Decety, J., Monteleone, G., and Nusbaum, H. (2009). In the eye of the beholder: individual differences in perceived social isolation predict regional brain activation to social stimuli. *Journal of cognitive neuroscience*, 21(1):83–92.

Cacioppo, S. and Cacioppo, J. T. (2016). Research in social neuroscience: How perceived social isolation, ostracism, and romantic rejection affect our brain. In *Social Exclusion*, pages 73–88. Springer.

Cacioppo, S., Frum, C., Asp, E., Weiss, R. M., Lewis, J. W., and Cacioppo, J. T. (2013). A quantitative meta-analysis of functional imaging studies of social rejection. *Scientific reports*, 3.

Cain, M. S., Dunsmoor, J. E., LaBar, K. S., and Mitroff, S. R. (2011). Anticipatory anxiety hinders detection of a second target in dual-target search. *Psychological Science*, 22(7):866–871.

Calboli, F. C., Tozzi, F., Galwey, N. W., Antoniades, A., Mooser, V., Preisig, M., Vollenweider, P., Waterworth, D., Waeber, G., Johnson, M. R., et al. (2010). A genome-wide association study of neuroticism in a population-based sample. *PloS one*, 5(7):e11504.

Calhoun, V. D., Altschul, D., McGinty, V., Shih, R., Scott, D., Sears, E., and Pearlson, G. D. (2004). Alcohol intoxication effects on visual perception: an fmri study. *Human brain mapping*, 21(1):15–26.

Canli, T., Zhao, Z., Desmond, J. E., Kang, E., Gross, J., and Gabrieli, J. D. (2001). An fmri study of personality influences on brain reactivity to emotional stimuli. *Behavioral neuroscience*, 115(1):33.

Cannon, T. D. and Keller, M. C. (2006). Endophenotypes in the genetic analyses of mental disorders. *Annu. Rev. Clin. Psychol.*, 2:267–290.

Cannon, W. (1932). The wisdom of the body (2nd ed). *The American Journal of the Medical Sciences*, 184(6):864.

Canterberry, M. and Gillath, O. (2013). Neural evidence for a multifaceted model of attachment security. *International Journal of Psychophysiology*, 88(3):232–240.

Cappell, H. (1987). Alcohol and tension reduction: What's new? *Stress and addiction*.

Cappell, H. and Herman, C. P. (1972). Alcohol and tension reduction: A review. *Quarterly journal of studies on alcohol*.

Cardno, A. G. and Gottesman, I. I. (2000). Twin studies of schizophrenia: from bow-and-arrow concordances to star wars mx and functional genomics. *American journal of medical genetics*, 97(1):12–17.

Carey, K. B. and Correia, C. J. (1997). Drinking motives predict alcohol-related problems in college students. *Journal of studies on alcohol*, 58(1):100–105.

Cargiulo, T. (2007). Understanding the health impact of alcohol dependence. *American journal of health-system pharmacy*, 64.

Carhart-Harris, R. L. and Nutt, D. (2010). User perceptions of the benefits and harms of hallucinogenic drug use: A web-based questionnaire study. *Journal of Substance Use*, 15(4):283–300.

Carleton, R. N. (2016a). Fear of the unknown: One fear to rule them all? *Journal of anxiety disorders*.

Carleton, R. N. (2016b). Into the unknown: A review and synthesis of contemporary models involving uncertainty. *Journal of anxiety disorders*, 39:30–43.

Carleton, R. N., Collimore, K. C., and Asmundson, G. J. (2010). "it's not just the judgements—it's that i don't know": Intolerance of uncertainty as a predictor of social anxiety. *Journal of Anxiety Disorders*, 24(2):189–195.

Carleton, R. N., Duranceau, S., Freeston, M. H., Boelen, P. A., McCabe, R. E., and Antony, M. M. (2014). "but it might be a heart attack": Intolerance of uncertainty and panic disorder symptoms. *Journal of anxiety disorders*, 28(5):463–470.

Carleton, R. N., Fetzner, M. G., Hackl, J. L., and McEvoy, P. (2013). Intolerance of uncertainty as a contributor to fear and avoidance symptoms of panic attacks. *Cognitive behaviour therapy*, 42(4):328–341.

Carleton, R. N., Sharpe, D., and Asmundson, G. J. (2007). Anxiety sensitivity and intolerance of uncertainty: Requisites of the fundamental fears? *Behaviour Research and Therapy*, 45(10):2307–2316.

Carlile, L. W., Behnke, R. R., and Kitchens, J. T. (1977). A psychological pattern of anxiety in public speaking. *Communication Quarterly*, 25(4):44–46.

Carlsen, J. (1988). Immunocytochemical localization of glutamate decarboxylase in the rat basolateral amygdaloid nucleus, with special reference to gabaergic innervation of amygdalostriatal projection neurons. *Journal of Comparative Neurology*, 273(4):513–526.

Carlson, M. and Earls, F. (1997). Psychological and neuroendocrinological sequelae of early social deprivation in institutionalized children in romania. *Annals of the New York Academy of Sciences*, 807:419–428.

Carlson, S., Iacono, W., and McGue, M. (2002). P300 amplitude in adolescent twins discordant and concordant for alcohol use disorders. *Biological Psychology*, 61(1-2):203–227.

Carlsson, K., Andersson, J., Petrovic, P., Petersson, K. M., Öhman, A., and Ingvar, M. (2006). Predictability modulates the affective and sensory-discriminative neural processing of pain. *Neuroimage*, 32(4):1804–1814.

Carmen Arenas, M., A Aguilar, M., Montagud-Romero, S., Mateos-García, A., I Navarro-Francés, C., Miñarro, J., and Rodríguez-Arias, M. (2016). Influence of the novelty-seeking endophenotype on the rewarding effects of psychostimulant drugs in animal models. *Current neuropharmacology*, 14(1):87–100.

Carmichael, S. and Price, J. (1995). Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys. *Journal of Comparative Neurology*, 363(4):615–641.

Carpenter, K. M. and Hasin, D. S. (1999). Drinking to cope with negative affect and dsm-iv alcohol use disorders: a test of three alternative explanations. *Journal of studies on alcohol*, 60(5):694–704.

Carranza Carnicero, J. A., Pérez-López, J., Del Carmen, G. S., Martínez-Fuentes, M. T., et al. (2000). A longitudinal study of temperament in infancy: Stability and convergence of measures. *European Journal of Personality*, 14(1):21–37.

Carrasco, J., Saiz-Ruiz, J., Diaz-Marsa, M., Cesar, J., and Lopez-Ibor, J. (1999). Low platelet monoamine oxidase activity in sensation-seeking bullfighters. *CNS Spectrums*, 4(12):21–24.

Carrigan, M. H. and Randall, C. L. (2003). Self-medication in social phobia: A review of the alcohol literature. *Addictive behaviors*, 28(2):269–284.

Carrington, R. (1959). *Elephants*. New York: Basic Books.

Carroll, D., Lovallo, W. R., and Phillips, A. C. (2009). Are large physiological reactions to acute psychological stress always bad for health? *Social and Personality Psychology Compass*, 3(5):725–743.

Carroll, H. A., Lustyk, M. K. B., and Larimer, M. E. (2015). The relationship between alcohol consumption and menstrual cycle: a review of the literature. *Archives of women's mental health*, 18(6):773–781.

Carter, C., Braver, T., Barch, D., Botvinick, M., Noll, D., and Cohen, J. (1998). Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science*, 280(5364):747–749.

Carter, R. M. and Huettel, S. A. (2013). A nexus model of the temporal–parietal junction. *Trends in cognitive sciences*, 17(7):328–336.

Carver, C. and Scheier, M. (1999). Stress, coping, and self-regulatory processes. *Handbook of Personality: Theory and Research*, pages 553–575.

Carver, C. S. and White, T. L. (1994). Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: the bis/bas scales. *Journal of personality and social psychology*, 67(2):319.

Case, A. and Deaton, A. (2015). Rising morbidity and mortality in midlife among white non-hispanic americans in the 21st century. *Proceedings of the National Academy of Sciences*, 112(49):15078–15083.

Caseras, X., Avila, C., and Torrubia, R. (2003). The measurement of individual differences in behavioural inhibition and behavioural activation systems: a comparison of personality scales. *Personality and individual differences*, 34(6):999–1013.

Caseras, X., Murphy, K., Mataix-Cols, D., López-Solà, M., Soriano-Mas, C., Ortriz, H., Pujol, J., and Torrubia, R. (2013). Anatomical and functional overlap within the insula and anterior cingulate cortex during interoception and phobic symptom provocation. *Human Brain Mapping*, 34(5):1220–1229.

Casey, B., Ruberry, E. J., Libby, V., Glatt, C. E., Hare, T., Soliman, F., Duhoux, S., Frielingsdorf, H., and Tottenham, N. (2011a). Transitional and translational studies of risk for anxiety. *Depression and anxiety*, 28(1):18–28.

Casey, B., Somerville, L. H., Gotlib, I. H., Ayduk, O., Franklin, N. T., Askren, M. K., Jonides, J., Berman, M. G., Wilson, N. L., Teslovich, T., et al. (2011b). Behavioral and neural correlates of delay of gratification 40 years later. *Proceedings of the National Academy of Sciences*, 108(36):14998–15003.

Casey, B. J., Jones, R. M., and Hare, T. A. (2008). The adolescent brain. *Annals of the New York Academy of Sciences*, 1124(1):111–126.

Casey, K. (1999). Forebrain mechanisms of nociception and pain: Analysis through imaging. *Proceedings of the National Academy of Sciences of the United States of America*, 96(14):7668–7674.

Casey, K. F., Benkelfat, C., Cherkasova, M. V., Baker, G. B., Dagher, A., and Leyton, M. (2014). Reduced dopamine response to amphetamine in subjects at ultra-high risk for addiction. *Biological psychiatry*, 76(1):23–30.

Casey, M., Adamson, G., Shevlin, M., and McKinney, A. (2012). The role of craving in auds: dimensionality and differential functioning in the dsm-5. *Drug and alcohol dependence*, 125(1):75–80.

Caspi, A., Moffitt, T. E., Newman, D. L., and Silva, P. A. (1996). Behavioral observations at age 3 years predict adult psychiatric disorders: Longitudinal evidence from a birth cohort. *Archives of general psychiatry*, 53(11):1033–1039.

Caspi, A., Roberts, B. W., and Shiner, R. L. (2005). Personality development: stability and change. *Review of Psychology*, 56:453–484.

Caspi, A. and Silva, P. A. (1995). Temperamental qualities at age three predict personality traits in young adulthood: Longitudinal evidence from a birth cohort. *Child development*, pages 486–498.

Castellanos, F. X. and Tannock, R. (2002). Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. *Nature Reviews Neuroscience*, 3(8).

Castellanos-Ryan, N. and Conrod, P. (2012). Personality and substance misuse: evidence for a four-factor model of vulnerability. In *Drug Abuse and Addiction in Medical Illness*, pages 47–62. Springer.

Castellanos-Ryan, N., O'Leary-Barrett, M., Sully, L., and Conrod, P. (2013). Sensitivity and specificity of a brief personality screening instrument in predicting future substance use, emotional, and behavioral problems: 18-month predictive validity of the substance use risk profile scale. *Alcoholism: Clinical and Experimental Research*, 37(s1):E281–E290.

Castle, I.-J. P., Dong, C., Haughwout, S. P., and White, A. M. (2016). Emergency department visits for adverse drug reactions involving alcohol: United states, 2005 to 2011. *Alcoholism: Clinical and Experimental Research*.

Cattell, R. B. (1940). Sentiment or attitude? the core of a terminology problem in personality research. *Journal of Personality*, 9(1):6–17.

Cavada, C., Tejedor, J., Cruz-Rizzolo, R. J., Reinoso-Suárez, F., et al. (2000). The anatomical connections of the macaque monkey orbitofrontal cortex. a review. *Cerebral Cortex*, 10(3):220–242.

Cavanna, A. E. and Trimble, M. R. (2006). The precuneus: a review of its functional anatomy and behavioural correlates. *Brain*, 129(3):564–583.

Cavigelli, S. A., Stine, M. M., Kovacsics, C., Jefferson, A., Diep, M. N., and Barrett, C. E. (2007). Behavioral inhibition and glucocorticoid dynamics in a rodent model. *Physiology & behavior*, 92(5):897–905.

Chambers, R. A., Taylor, J. R., and Potenza, M. N. (2003). Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. *American Journal of Psychiatry*.

Chan, S. W., Norbury, R., Goodwin, G. M., and Harmer, C. J. (2009). Risk for depression and neural responses to fearful facial expressions of emotion. *The British Journal of Psychiatry*, 194(2):139–145.

Chandley, R. B., Luebbe, A. M., Messman-Moore, T. L., and Ward, R. M. (2014). Anxiety sensitivity, coping motives, emotion dysregulation, and alcohol-related outcomes in college women: a moderated-mediation model. *Journal of studies on alcohol and drugs*, 75(1):83–92.

Chang, D.-J. and Debiec, J. (2016). Neural correlates of the mother-to-infant social transmission of fear. *Journal of neuroscience research*, 94(6):526–534.

Chang, L. J., Yarkoni, T., Khaw, M. W., and Sanfey, A. G. (2012). Decoding the role of the insula in human cognition: functional parcellation and large-scale reverse inference. *Cerebral Cortex*, page bhs065.

Chapman, C., Slade, T., Hunt, C., and Teesson, M. (2015). Delay to first treatment contact for alcohol use disorder. *Drug and alcohol dependence*, 147:116–121.

Charach, A., Yeung, E., Climans, T., and Lillie, E. (2011). Childhood attention-deficit/hyperactivity disorder and future substance use disorders: comparative meta-analyses. *Journal of the American Academy of Child & Adolescent Psychiatry*, 50(1):9–21.

Charness, M. E., Riley, E. P., and Sowell, E. R. (2016). Drinking during pregnancy and the developing brain: Is any amount safe? *Trends in cognitive sciences*, 20(2):80–82.

Charpentier, C. J., Hindocha, C., Roiser, J. P., and Robinson, O. J. (2016). Anxiety promotes memory for mood-congruent faces but does not alter loss aversion. *Scientific reports*, 6.

Chastain, G. (2006). Alcohol, neurotransmitter systems, and behavior. *The Journal of general psychology*, 133(4):329–335.

Chavarria, J., Allan, N. P., Boffa, J. W., Albanese, B. J., Schmidt, N. B., and Zvolensky, M. J. (2015). Decomposing the relationship between anxiety sensitivity and alcohol use. *Journal of studies on alcohol and drugs*, 76(6):957–961.

Cheetham, A., Allen, N., Whittle, S., Simmons, J., Yücel, M., and Lubman, D. (2012). Orbitofrontal volumes in early adolescence predict initiation of cannabis use: A 4-year longitudinal and prospective study. *Biological Psychiatry*, 71(8):684–692.

Cheetham, A., Allen, N. B., Whittle, S., Simmons, J., Yücel, M., and Lubman, D. I. (2014). Volumetric differences in the anterior cingulate cortex prospectively predict alcohol-related problems in adolescence. *Psychopharmacology*, 231(8):1731–1742.

Chen, E., Turiano, N. A., Mroczek, D. K., and Miller, G. E. (2016). Association of reports of childhood abuse and all-cause mortality rates in women. *JAMA psychiatry*.

Cheong, J. and Nagoshi, C. (1999). Effects of sensation seeking, instruction set, and alcohol/placebo administration on aggressive behavior. *Alcohol*, 17(1):81–86.

Chermack, S. T. and Giancola, P. R. (1997). The relation between alcohol and aggression: An integrated biopsychosocial conceptualization. *Clinical psychology review*, 17(6):621–649.

Cherpitel, C. J. (2009). *Alcohol and injuries: emergency department studies in an international perspective*. World Health Organization.

Chester, D. and Riva, P. (2016). Brain mechanisms to regulate negative reactions to social exclusion. In *Social Exclusion*, pages 251–273. Springer.

Chester, D. S. and DeWall, C. N. (2014). Prefrontal recruitment during social rejection predicts greater subsequent self-regulatory imbalance and impairment: neural and longitudinal evidence. *NeuroImage*, 101:485–493.

Chester, D. S. and DeWall, C. N. (2015). The pleasure of revenge: retaliatory aggression arises from a neural imbalance toward reward. *Social cognitive and affective neuroscience*, page nsv082.

Chester, D. S., Eisenberger, N. I., Pond, R. S., Richman, S. B., Bushman, B. J., and DeWall, C. N. (2013). The interactive effect of social pain and executive functioning on aggression: an fmri experiment. *Social cognitive and affective neuroscience*, page nst038.

Chester, D. S., Lynam, D. R., Milich, R., Powell, D. K., Andersen, A. H., and DeWall, C. N. (2016). How do negative emotions impair self-control? a neural model of negative urgency. *NeuroImage*, 132:43–50.

Chiamulera, C. and Cibin, M. (2014). Drinking reduction and reversibility of neuroadaptation in alcoholism. *Journal of Psychopharmacology*, 28(8):810–812.

Chiappetta, V., García-Rodríguez, O., Jin, C. J., Secades-Villa, R., and Blanco, C. (2014). Predictors of quit attempts and successful quit attempts among individuals with alcohol use disorders in a nationally representative sample. *Drug and Alcohol Dependence*.

Chikazoe, J., Lee, D. H., Kriegeskorte, N., and Anderson, A. K. (2014). Population coding of affect across stimuli, modalities and individuals. *Nature neuroscience*, 17(8):1114–1122.

Chikritzhs, T., Stockwell, T., Naimi, T., Andreasson, S., Dangardt, F., and Liang, W. (2015). Has the leaning tower of presumed health benefits from 'moderate'alcohol use finally collapsed? *Addiction*, 110(5):726–727.

Childs, E., Dlugos, A., and De Wit, H. (2010). Cardiovascular, hormonal, and emotional responses to the tsst in relation to sex and menstrual cycle phase. *Psychophysiology*, 47(3):550–559.

Chiu, P., Holmes, A., and Pizzagalli, D. (2008). Dissociable recruitment of rostral anterior cingulate and inferior frontal cortex in emotional response inhibition. *NeuroImage*, 42(2):988–997.

Cho, Y., Ernst, M., and Fudge, J. (2013a). Cortico-amygdala-striatal circuits are organized as hierarchical subsystems through the primate amygdala. *Journal of Neuroscience*, 33(35):14017–14030.

Cho, Y. T., Fromm, S., Guyer, A. E., Detloff, A., Pine, D. S., Fudge, J. L., and Ernst, M. (2013b). Nucleus accumbens, thalamus and insula connectivity during incentive anticipation in typical adults and adolescents. *Neuroimage*, 66:508–521.

Choi, K., Vickers, K., and Tassone, A. (2014). Trait emotional intelligence, anxiety sensitivity, and experiential avoidance in stress reactivity and their improvement through psychological methods. *Europe's Journal of Psychology*, 10(2):376–404.

Chong, J. S. X., Ng, G. J. P., Lee, S. C., and Zhou, J. (2016). Salience network connectivity in the insula is associated with individual differences in interoceptive accuracy. *Brain Structure and Function*, pages 1–10.

Chou, S. P. (1994). Sex differences in morbidity among respondents classified as alcohol abusers and/or dependent: results of a national survey. *Addiction*, 89(1):87–93.

Christoff, K., Gordon, A. M., Smallwood, J., Smith, R., and Schooler, J. W. (2009). Experience sampling during fmri reveals default network and executive system contributions to mind wandering. *Proceedings of the National Academy of Sciences*, 106(21):8719–8724.

Christoff, K., Ream, J. M., Geddes, L., and Gabrieli, J. D. (2003). Evaluating self-generated information: anterior prefrontal contributions to human cognition. *Behavioral neuroscience*, 117(6):1161.

Christoffel, D. J., Golden, S. A., Walsh, J. J., Guise, K. G., Heshmati, M., Friedman, A. K., Dey, A., Smith, M., Rebusi, N., Pfau, M., et al. (2015). Excitatory transmission at thalamo-striatal synapses mediates susceptibility to social stress. *Nature neuroscience*, 18(7):962–964.

Christopoulos, G. I., Tobler, P. N., Bossaerts, P., Dolan, R. J., and Schultz, W. (2009). Neural correlates of value, risk, and risk aversion contributing to decision making under risk. *The Journal of Neuroscience*, 29(40):12574–12583.

Chung, K. C., Peisen, F., Kogler, L., Radke, S., Turetsky, B., Freiherr, J., and Derntl, B. (2016). The influence of menstrual cycle and androstadienone on female stress reactions: an fmri study. *Frontiers in human neuroscience*, 10.

Chung, T. and Clark, D. B. (2014). Insula white matter volume linked to binge drinking frequency through enhancement motives in treated adolescents. *Alcoholism: Clinical and Experimental Research*, 38(7):1932–1940.

Ciaramidaro, A., Adenzato, M., Enrici, I., Erk, S., Pia, L., Bara, B. G., and Walter, H. (2007). The intentional network: how the brain reads varieties of intentions. *Neuropsychologia*, 45(13):3105–3113.

Cicchetti, D. (2002). The impact of social experience on neurobiological systems: Illustration from a constructivist view of child maltreatment. *Cognitive development*, 17(3):1407–1428.

Claire, M.-D., Sophie, D., Claudia, P., Philippe, M., and Eliane, R.-P. (2016). Verbal emotional memory in a case with left amygdala damage. *Neurocase*, 22(1):45–54.

Clark, C. P., Brown, G. G., Eyler, L. T., Drummond, S. P., Braun, D. R., and Tapert, S. F. (2007). Decreased perfusion in young alcohol-dependent women as compared with age-matched controls. *The American journal of drug and alcohol abuse*, 33(1):13–19.

Clark, D. A. and Beck, A. T. (2010). Cognitive theory and therapy of anxiety and depression: convergence with neurobiological findings. *Trends in cognitive sciences*, 14(9):418–424.

Clark, D. M. (1986). A cognitive approach to panic. *Behaviour research and therapy*, 24(4):461–470.

Clark, L. and Watson, D. (2008). Temperament: An organizing paradigm for trait psychology. handbook of personality: Theory and research . edited by: John op, robins rw, pervin la.

Clarke, T.-K., Smith, A. H., Gelernter, J., Kranzler, H. R., Farrer, L. A., Hall, L. S., Fernandez-Pujals, A. M., MacIntyre, D. J., Smith, B. H., Hocking, L. J., et al. (2015). Polygenic risk for alcohol dependence associates with alcohol consumption, cognitive function and social deprivation in a population-based cohort. *Addiction biology*.

Clauss, J. A. and Blackford, J. U. (2012). Behavioral inhibition and risk for developing social anxiety disorder: a meta-analytic study. *Journal of the American Academy of Child & Adolescent Psychiatry*, 51(10):1066–1075.

Cleck, J. N. and Blendy, J. A. (2008). Making a bad thing worse: adverse effects of stress on drug addiction. *The Journal of clinical investigation*, 118(2):454–461.

Cleckley, H. (1982). The mask of sanity (rev. ed.). *Saint Louis, MO: CV Mosby Co*.

Clevenger, T., Motley, M., and Carlile, L. (1967). Changes in heart rate during classroom public speaking. *Unpublished research report, University of Texas at Austin*.

Clinton, S. M., Watson, S. J., and Akil, H. (2014). High novelty-seeking rats are resilient to negative physiological effects of the early life stress. *Stress*, 17(1):97–107.

Cloninger, C. (1987a). Neurogenetic adaptive mechanisms in alcoholism. *Science*, 236(4800):410–416.

Cloninger, C. (1987b). A systematic method for clinical description and classification of personality variants: A proposal. *Archives of General Psychiatry*, 44(6):573–588.

Cloninger, C., Bohman, M., and Sigvardsson, S. (1981). Inheritance of alcohol abuse. cross-fostering analysis of adopted men. *Archives of General Psychiatry*, 38(8):861–868.

Cloninger, C. R., Sigvardsson, S., and Bohman, M. (1988). Childhood personality predicts alcohol abuse in young adults. *Alcoholism: clinical and experimental research*, 12(4):494–505.

Cobb, C. F. and Thiel, D. H. V. (1982). Mechanism of ethanol-induced adrenal stimulation. *Alcoholism: Clinical and Experimental Research*, 6(2):202–206.

Coccaro, E. F., Keedy, S. K., Gorka, S. M., King, A. C., Fanning, J. R., Lee, R. J., and Phan, K. L. (2016). Differential fmri bold responses in amygdala in intermittent explosive disorder as a function of past alcohol use disorder. *Psychiatry Research: Neuroimaging*, 257:5–10.

Coccaro, E. F., McCloskey, M. S., Fitzgerald, D. A., and Phan, K. L. (2007). Amygdala and orbitofrontal reactivity to social threat in individuals with impulsive aggression. *Biological psychiatry*, 62(2):168–178.

Coccaro, E. F., Noblett, K. L., and McCloskey, M. S. (2009). Attributional and emotional responses to socially ambiguous cues: Validation of a new assessment of social/emotional information processing in healthy adults and impulsive aggressive patients. *Journal of Psychiatric Research*, 43(10):915–925.

Coen, S. J., Kano, M., Farmer, A. D., Kumari, V., Giampietro, V., Brammer, M., Williams, S. C., and Aziz, Q. (2011). Neuroticism influences brain activity during the experience of visceral pain. *Gastroenterology*, 141(3):909–917.

Cohen, A. O., Dellarco, D. V., Breiner, K., Helion, C., Heller, A. S., Rahdar, A., Pedersen, G., Chein, J., Dyke, J. P., Galvan, A., et al. (2016a). The impact of emotional states on cognitive control circuitry and function. *Journal of cognitive neuroscience*.

Cohen, N., Margulies, D., Ashkenazi, S., Schaefer, A., Taubert, M., Henik, A., Villringer, A., and Okon-Singer, H. (2016b). Using executive control training to suppress amygdala reactivity to aversive information. *NeuroImage*, 125:1022–1031.

Cohen, S., Hamrick, N., Rodriguez, M., Feldman, P., Rabin, B., and Manuck, S. (2000). The stability of and intercorrelations among cardiovascular, immune, endocrine, and psychological reactivity. *Annals of Behavioral Medicine*, 22(3):171–179.

Cohn, M. D., Viding, E., McCrory, E., Pape, L., van den Brink, W., Doreleijers, T. A., Veltman, D. J., and Popma, A. (2016). Regional grey matter volume and concentration in at-risk adolescents: Untangling associations with callous-unemotional traits and conduct disorder symptoms. *Psychiatry Research: Neuroimaging*, 254:180–187.

Coid, J., Yang, M., Roberts, A., Ullrich, S., Moran, P., Bebbington, P., Brugha, T., Jenkins, R., Farrell, M., Lewis, G., et al. (2006). Violence and psychiatric morbidity in the national household population of britain: public health implications. *The British Journal of Psychiatry*, 189(1):12–19.

Colder, C. R. and O'Connor, R. (2002). Attention bias and disinhibited behavior as predictors of alcohol use and enhancement reasons for drinking. *Psychology of Addictive Behaviors*, 16(4):325.

Colflesh, G. J. and Wiley, J. (2013). Drunk, but not blind: The effects of alcohol intoxication on change blindness. *Consciousness and cognition*, 22(1):231–236.

Collado, A., Felton, J. W., MacPherson, L., and Lejuez, C. (2014). Longitudinal trajectories of sensation seeking, risk taking propensity, and impulsivity across early to middle adolescence. *Addictive behaviors*, 39(11):1580–1588.

Collin, L., Bindra, J., Raju, M., Gillberg, C., and Minnis, H. (2013). Facial emotion recognition in child psychiatry: a systematic review. *Research in developmental disabilities*, 34(5):1505–1520.

Collins, A. L., Aitken, T. J., Greenfield, V. Y., Ostlund, S. B., and Wassum, K. M. (2016). Nucleus accumbens acetylcholine receptors modulate dopamine and motivation. *Neuropsychopharmacology*.

Collins, D. R. and Paré, D. (2000). Differential fear conditioning induces reciprocal changes in the sensory responses of lateral amygdala neurons to the cs+ and cs-. *Learning & Memory*, 7(2):97–103.

Collins, J. and Messerschmidt, P. (1993). Epidemiology of alcohol-related violence. *Alcohol Health and Research World*, 17(2):93–100.

Collins, P. Y., Patel, V., Joestl, S. S., March, D., Insel, T. R., Daar, A. S., Bordin, I. A., Costello, E. J., Durkin, M., Fairburn, C., et al. (2011). Grand challenges in global mental health. *Nature*, 475(7354):27–30.

Colloff, M. F. and Flowe, H. D. (2016). The effects of acute alcohol intoxication on the cognitive mechanisms underlying false facial recognition. *Psychopharmacology*, pages 1–11.

Conger, J. (1956). Alcoholism: theory, problem and challenge. ii. reinforcement theory and the dynamics of alcoholism. *Quarterly journal of studies on alcohol*, 17(2):296–305.

Conner, K. R., Cox, C., Duberstein, P. R., Tian, L., Nisbet, P. A., and Conwell, Y. (2001). Violence, alcohol, and completed suicide: a case-control study. *American Journal of Psychiatry*, 158(10):1701–1705.

Conner, K. R., Pinquart, M., and Gamble, S. A. (2009). Meta-analysis of depression and substance use among individuals with alcohol use disorders. *Journal of substance abuse treatment*, 37(2):127–137.

Conrod, P. and Nikolaou, K. (2016). Annual research review: On the developmental neuropsychology of substance use disorders. *Journal of Child Psychology and Psychiatry*, 57(3):371–394.

Conrod, P., Petersen, J., and Pihl, R. (1997a). Disinhibited personality and sensitivity to alcohol reinforcement: Independent correlates of drinking behavior in sons of alcoholics. *Alcoholism: Clinical and Experimental Research*, 21(7):1320–1332.

Conrod, P., Peterson, J., and Pihl, R. (2001). Reliability and validity of alcohol-induced heart rate increase as a measure of sensitivity to the stimulant properties of alcohol. *Psychopharmacology*, 157(1):20–30.

Conrod, P. J., Castellanos, N., and Mackie, C. (2008). Personality-targeted interventions delay the growth of adolescent drinking and binge drinking. *Journal of Child Psychology and Psychiatry*, 49(2):181–190.

Conrod, P. J., Castellanos-Ryan, N., and Mackie, C. (2011). Long-term effects of a personality-targeted intervention to reduce alcohol use in adolescents. *Journal of consulting and clinical psychology*, 79(3):296.

Conrod, P. J., Castellanos-Ryan, N., and Strang, J. (2010). Brief, personality-targeted coping skills interventions and survival as a non–drug user over a 2-year period during adolescence. *Archives of General Psychiatry*, 67(1):85–93.

Conrod, P. J., O'Leary-Barrett, M., Newton, N., Topper, L., Castellanos-Ryan, N., Mackie, C., and Girard, A. (2013). Effectiveness of a selective, personality-targeted prevention program for adolescent alcohol use and misuse: A cluster randomized controlled trial. *JAMA psychiatry*, 70(3):334–342.

Conrod, P. J., Peterson, J. B., Pihl, R. O., and Mankowski, S. (1997b). Biphasic effects of alcohol on heart rate are influenced by alcoholic family history and rate of alcohol ingestion. *Alcoholism: Clinical and Experimental Research*, 21(1):140–149.

Conrod, P. J., Pihl, R. O., Stewart, S. H., and Dongier, M. (2000a). Validation of a system of classifying female substance abusers on the basis of personality and motivational risk factors for substance abuse. *Psychology of Addictive Behaviors*, 14(3):243.

Conrod, P. J., Pihl, R. O., and Vassileva, J. (1998). Differential sensitivity to alcohol reinforcement in groups of men at risk for distinct alcoholism subtypes. *Alcoholism: Clinical and Experimental Research*, 22(3):585–597.

Conrod, P. J., Stewart, S. H., Comeau, N., and Maclean, A. M. (2006). Efficacy of cognitive–behavioral interventions targeting personality risk factors for youth alcohol misuse. *Journal of Clinical Child and Adolescent Psychology*, 35(4):550–563.

Conrod, P. J., Stewart, S. H., Pihl, R. O., Cote, S., Fontaine, V., and Dongier, M. (2000b). Efficacy of brief coping skills interventions that match different personality profiles of female substance abusers. *Psychology of Addictive Behaviors*, 14(3):231.

Conway, K. P., Compton, W., Stinson, F. S., and Grant, B. F. (2006). Lifetime comorbidity of dsm-iv mood and anxiety disorders and specific drug use disorders: results from the national epidemiologic survey on alcohol and related conditions. *The Journal of clinical psychiatry*, 67(2):247–258.

Conway, K. P., Swendsen, J., Husky, M. M., He, J.-P., and Merikangas, K. R. (2016). Association of lifetime mental disorders and subsequent alcohol and illicit drug use: results from the national comorbidity survey–adolescent supplement. *Journal of the American Academy of Child & Adolescent Psychiatry*, 55(4):280–288.

Cook, B., Chavez, L., Carmona, R., and Alegria, M. (2016). Assessing comorbidities and service use among patients with benzodiazepine abuse. *European Psychiatry*, 33:S295.

Cools, R., Calder, A. J., Lawrence, A. D., Clark, L., Bullmore, E., and Robbins, T. W. (2005). Individual differences in threat sensitivity predict serotonergic modulation of amygdala response to fearful faces. *Psychopharmacology*, 180(4):670–679.

Cools, R., Gibbs, S. E., Miyakawa, A., Jagust, W., and D'Esposito, M. (2008). Working memory capacity predicts dopamine synthesis capacity in the human striatum. *The Journal of Neuroscience*, 28(5):1208–1212.

Cooper, A., Gomez, R., and Buck, E. (2008). The relationships between the bis and bas, anger and responses to anger. *Personality and Individual Differences*, 44(2):403–413.

Cooper, L. D. and Balsis, S. (2009). When less is more: how fewer diagnostic criteria can indicate greater severity. *Psychological assessment*, 21(3):285.

Cooper, M. (1994). Motivations for alcohol use among adolescents: Development and validation of a four-factor model. *Psychological Assessment*, 6(2):117–128.

Cooper, M., Russell, M., Skinner, J., and Windle, M. (1992a). Development and validation of a three-dimensional measure of drinking motives. *Psychological Assessment*, 4(2):123–132.

Cooper, M. L., Frone, M. R., Russell, M., and Mudar, P. (1995). Drinking to regulate positive and negative emotions: a motivational model of alcohol use. *Journal of personality and social psychology*, 69(5):990.

Cooper, M. L., Kuntsche, E., Levitt, A., Barber, L. L., Wolf, S., and Sher, K. (2016). Motivational models of substance use: A review of theory and research on motives for using alcohol, marijuana, and tobacco. *The Oxford Handbook of Substance Use and Substance Use Disorders: Two-Volume Set*, page 375.

Cooper, M. L., Russell, M., and George, W. H. (1988). Coping, expectancies, and alcohol abuse: a test of social learning formulations. *Journal of abnormal psychology*, 97(2):218.

Cooper, M. L., Russell, M., Skinner, J. B., Frone, M. R., and Mudar, P. (1992b). Stress and alcohol use: moderating effects of gender, coping, and alcohol expectancies. *Journal of abnormal psychology*, 101(1):139.

Cope, L., Ermer, E., Gaudet, L., Steele, V., Eckhardt, A., Arbabshirani, M., Caldwell, M., Calhoun, V. D., and Kiehl, K. (2014). Abnormal brain structure in youth who commit homicide. *NeuroImage: Clinical*, 4:800–807.

Corbetta, M. and Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature reviews neuroscience*, 3(3):201–215.

Cornelisse, S., van Stegeren, A. H., and Joëls, M. (2011). Implications of psychosocial stress on memory formation in a typical male versus female student sample. *Psychoneuroendocrinology*, 36(4):569–578.

Corr, P. (2002). J.a. gray's reinforcement sensitivity theory and frustrative nonreward: A theoretical note on expectancies in reactions to rewarding stimuli. *Personality and Individual Differences*, 32(7):1247–1253.

Corr, P. J. (2008). Reinforcement sensitivity theory (rst): Introduction. *The Reinforcement Sensitivity Theory of personality*, pages 1–43.

Correas, A., Cuesta, P., López-Caneda, E., Holguín, S. R., García-Moreno, L., Pineda-Pardo, J., Cadaveira, F., and Maestú, F. (2016). Functional and structural brain connectivity of young binge drinkers: a follow-up study. *Scientific Reports*, 6.

Costa, P. T. and MacCrae, R. R. (1992). *Revised NEO personality inventory (NEO PI-R) and NEO five-factor inventory (NEO FFI): Professional manual*. Psychological Assessment Resources.

Costafreda, S. G., Brammer, M. J., David, A. S., and Fu, C. H. (2008). Predictors of amygdala activation during the processing of emotional stimuli: a meta-analysis of 385 pet and fmri studies. *Brain research reviews*, 58(1):57–70.

Couture, S., Brown, T. G., Ouimet, M. C., Gianoulakis, C., Tremblay, J., and Carbonneau, R. (2008). Hypothalamic-pituitary-adrenal axis response to stress in male dui recidivists. *Accident Analysis & Prevention*, 40(1):246–253.

Cox, B., Enns, M., Walker, J., Kjernisted, K., and Pidlubny, S. (2001). Psychological vulnerabilities in patients with major depression vs panic disorder. *Behaviour Research and Therapy*, 39(5):567–573.

Cox, B., Parker, J., and Swinson, R. (1996). Anxiety sensitivity: Confirmatory evidence for a multidimensional construct. *Behaviour Research and Therapy*, 34(7):591–598.

Cox, S. M., Benkelfat, C., Dagher, A., Delaney, J. S., Durand, F., McKenzie, S. A., Kolivakis, T., Casey, K. F., and Leyton, M. (2009). Striatal dopamine responses to intranasal cocaine self-administration in humans. *Biological psychiatry*, 65(10):846–850.

Cox, W. M. and Klinger, E. (1988). A motivational model of alcohol use. *Journal of abnormal psychology*, 97(2):168.

Craig, A. (2002). How do you feel? interoception: The sense of the physiological condition of the body. *Nature Reviews Neuroscience*, 3(8):655–666.

Craig, A. (2003). Interoception: the sense of the physiological condition of the body. *Current opinion in neurobiology*, 13(4):500–505.

Craig, A. (2011). Significance of the insula for the evolution of human awareness of feelings from the body. *Annals of the New York Academy of Sciences*, 1225:72–82.

Craig, A. D. (2009). How do you feel - now? the anterior insula and human awareness. *Nature Reviews Neuroscience*.

Craig, A. D., Chen, K., Bandy, D., and Reiman, E. M. (2000). Thermosensory activation of insular cortex. *Nature neuroscience*, 3(2):184–190.

Crandal, R. (1973). The measurement of self-esteem and related constructs, pp. 80-82 in jp robinson and pr shaver (eds), measures of social psychological attitudes. revised edition. *Ann Arbor: ISR*.

Crawford, A., Pentz, M., Chou, C.-P., Li, C., and Dwyer, J. (2003). Parallel developmental trajectories of sensation seeking and regular substance use in adolescents. *Psychology of Addictive Behaviors*, 17(3):179–192.

Crick, N. R. and Zahn-Waxler, C. (2003). The development of psychopathology in females and males: Current progress and future challenges. *Development and psychopathology*, 15(3):719–742.

Crisan, L. G., Vulturar, R., Miclea, M., and Miu, A. C. (2016). Reactivity to social stress in subclinical social anxiety: Emotional experience, cognitive appraisals, behavior and physiology. *Frontiers in Psychiatry*, 7:5.

Criswell, H. and Breese, G. (2005). A conceptualization of integrated actions of ethanol contributing to its gabamimetic profile: A commentary. *Neuropsychopharmacology*, 30(8):1407–1425.

Critchley, H., Corfield, D., Chandler, M., Mathias, C., and Dolan, R. (2000). Cerebral correlates of autonomic cardiovascular arousal: A functional neuroimaging investigation in humans. *Journal of Physiology*, 523(1):259–270.

Critchley, H., Wiens, S., Rotshtein, P., Öhman, A., and Dolan, R. (2004). Neural systems supporting interoceptive awareness. *Nature Neuroscience*, 7(2):189–195.

Critchley, H. D., Mathias, C. J., and Dolan, R. J. (2002). Fear conditioning in humans: the influence of awareness and autonomic arousal on functional neuroanatomy. *Neuron*, 33(4):653–663.

Croes, S., Merz, P., and Netter, P. (1993). Cortisol reaction in success and failure condition in endogenous depressed patients and controls. *Psychoneuroendocrinology*, 18(1):23–35.

Croissant, B. and Olbrich, R. (2004). Stress response dampening indexed by cortisol in subjects at risk for alcoholism. *Journal of studies on alcohol*, 65(6):701–707.

Crum, R., La Flair, L., Storr, C., Green, K., Stuart, E., Alvanzo, A., Lazareck, S., Bolton, J., Robinson, J., Sareen, J., and Mojtabai, R. (2013a). Reports of drinking to self-medicate anxiety symptoms: Longitudinal assessment for subgroups of individuals with alcohol dependence. *Depression and Anxiety*, 30(2):174–183.

Crum, R. M., Mojtabai, R., Lazareck, S., Bolton, J. M., Robinson, J., Sareen, J., Green, K. M., Stuart, E. A., La Flair, L., Alvanzo, A. A., et al. (2013b). A prospective assessment of reports of drinking to self-medicate mood symptoms with the incidence and persistence of alcohol dependence. *JAMA psychiatry*, 70(7):718–726.

Cservenka, A. (2016). Neurobiological phenotypes associated with a family history of alcoholism. *Drug and alcohol dependence*, 158:8–21.

Cservenka, A., Casimo, K., Fair, D. A., and Nagel, B. J. (2014a). Resting state functional connectivity of the nucleus accumbens in youth with a family history of alcoholism. *Psychiatry Research: Neuroimaging*, 221(3):210–219.

Cservenka, A., Fair, D. A., and Nagel, B. J. (2014b). Emotional processing and brain activity in youth at high risk for alcoholism. *Alcoholism: Clinical and Experimental Research*, 38(7):1912–1923.

Cservenka, A., Gillespie, A. J., Michael, P. G., and Nagel, B. J. (2015). Family history density of alcoholism relates to left nucleus accumbens volume in adolescent girls. *Journal of studies on alcohol and drugs*, 76(1):47–56.

Cservenka, A., Herting, M., and Nagel, B. (2012). Atypical frontal lobe activity during verbal working memory in youth with a family history of alcoholism. *Drug and Alcohol Dependence*, 123(1-3):98–104.

Cservenka, A., Herting, M. M., Seghete, K. L. M., Hudson, K. A., and Nagel, B. (2013). High and low sensation seeking adolescents show distinct patterns of brain activity during reward processing. *NeuroImage*, 66:184–193.

Cservenka, A. and Nagel, B. J. (2012). Risky decision-making: An fmri study of youth at high risk for alcoholism. *Alcoholism: Clinical and Experimental Research*, 36(4):604–615.

Cservenka, A. and Nagel, B. J. (2016). Neuroscience of alcohol for addiction medicine: Neurobiological targets for prevention and intervention in adolescents. *Progress in brain research*, 223:215–235.

Cuijpers, P., Gentili, C., Banos, R. M., Garcia-Campayo, J., Botella, C., and Cristea, I. A. (2016). Relative effects of cognitive and behavioral therapies on generalized anxiety disorder, social anxiety disorder and panic disorder: A meta-analysis. *Journal of Anxiety Disorders*, 43:79–89.

Culham, J. C., Brandt, S. A., Cavanagh, P., Kanwisher, N. G., Dale, A. M., and Tootell, R. B. (1998). Cortical fmri activation produced by attentive tracking of moving targets. *Journal of neurophysiology*, 80(5):2657–2670.

Culig, L. and Belzung, C. (2016). Acute stress and anxiety. *Adult Neurogenesis in the Hippocampus: Health, Psychopathology, and Brain Disease*, pages 209–2015.

Cunningham, W., Van Bavel, J., and Johnsen, I. (2008). Affective flexibility: Evaluative processing goals shape amygdala activity: Research article. *Psychological Science*, 19(2):152–160.

Curley, J. P. and Champagne, F. A. (2016). Influence of maternal care on the developing brain: Mechanisms, temporal dynamics and sensitive periods. *Frontiers in neuroendocrinology*, 40:52–66.

Curtin, J. J. and Lang, A. R. (2007). Alcohol and emotion: Insights and directives from affective science. *Emotion and psychopathology: Bridging affective and clinical science*, pages 191–213.

Curtin, J. J., Patrick, C. J., Lang, A. R., Cacioppo, J. T., and Birbaumer, N. (2001). Alcohol affects emotion through cognition. *Psychological Science*, 12(6):527–531.

Cyders, M. A., Dzemidzic, M., Eiler, W. J., and Kareken, D. A. (2016a). An fmri study of responses to sexual stimuli as a function of gender and sensation seeking: A preliminary analysis. *The Journal of Sex Research*, pages 1–7.

Cyders, M. A., VanderVeen, J. D., Plawecki, M., Millward, J. B., Hays, J., Kareken, D. A., and O'Connor, S. (2016b). Gender-specific effects of mood on alcohol-seeking behaviors: Preliminary findings using intravenous alcohol self-administration. *Alcoholism: Clinical and Experimental Research*, 40(2):393–400.

Czisch, M., Wehrle, R., Kaufmann, C., Wetter, T. C., Holsboer, F., Pollmächer, T., and Auer, D. P. (2004). Functional mri during sleep: Bold signal decreases and their electrophysiological correlates. *European Journal of Neuroscience*, 20(2):566–574.

Dager, A. D., Anderson, B. M., Rosen, R., Khadka, S., Sawyer, B., Jiantonio-Kelly, R. E., Austad, C. S., Raskin, S. A., Tennen, H., Wood, R. M., et al. (2014). Functional magnetic resonance imaging (fmri) response to alcohol pictures predicts subsequent transition to heavy drinking in college students. *Addiction*, 109(4):585–595.

Dager, A. D., McKay, D. R., Kent, J. W., Curran, J. E., Knowles, E., Sprooten, E., Göring, H. H., Dyer, T. D., Pearlson, G. D., Olvera, R. L., et al. (2015). Shared genetic factors influence amygdala volumes and risk for alcoholism. *Neuropsychopharmacology*, 40(2):412–420.

Dagher, A., Owen, A. M., Boecker, H., and Brooks, D. J. (1999). Mapping the network for planning: a correlational pet activation study with the tower of london task. *Brain*, 122(10):1973–1987.

Dagher, A., Tannenbaum, B., Hayashi, T., Pruessner, J. C., and McBride, D. (2009). An acute psychosocial stress enhances the neural response to smoking cues. *Brain research*, 1293:40–48.

Dahlen, E. R., Martin, R. C., Ragan, K., and Kuhlman, M. M. (2005). Driving anger, sensation seeking, impulsiveness, and boredom proneness in the prediction of unsafe driving. *Accident Analysis & Prevention*, 37(2):341–348.

Dai, X., Thavundayil, J., and Gianoulakis, C. (2002a). Response of the hypothalamic-pituitary-adrenal axis to stress in the absence and presence of ethanol in subjects at high and low risk of alcoholism. *Neuropsychopharmacology*, 27(3):442–452.

Dai, X., Thavundayil, J., and Gianoulakis, C. (2002b). Response of the hypothalamic-pituitary-adrenal axis to stress in the absence and presence of ethanol in subjects at high and low risk of alcoholism. *Neuropsychopharmacology*, 27(3):442–452.

Dai, X., Thavundayil, J., and Gianoulakis, C. (2005). Differences in the peripheral levels of β-endorphin in response to alcohol and stress as a function of alcohol dependence and family history of alcoholism. *Alcoholism: Clinical and Experimental Research*, 29(11):1965–1975.

Dai, X., Thavundayil, J., Santella, S., and Gianoulakis, C. (2007). Response of the hpa-axis to alcohol and stress as a function of alcohol dependence and family history of alcoholism. *Psychoneuroendocrinology*, 32(3):293–305.

Dal Monte, O., Costa, V. D., Noble, P. L., Murray, E. A., and Averbeck, B. B. (2015). Amygdala lesions in rhesus macaques decrease attention to threat. *Nature communications*, 6.

Dalley, J. W., Everitt, B. J., and Robbins, T. W. (2011). Impulsivity, compulsivity, and top-down cognitive control. *Neuron*, 69(4):680–694.

Dalton, G. L., Wang, N. Y., Phillips, A. G., and Floresco, S. B. (2016). Multifaceted contributions by different regions of the orbitofrontal and medial prefrontal cortex to probabilistic reversal learning. *The Journal of Neuroscience*, 36(6):1996–2006.

Daly, J. A., Vangelisti, A. L., Neel, H. L., and Cavanaugh, P. D. (1989). Pre-performance concerns associated with public speaking anxiety. *Communication Quarterly*, 37(1):39–53.

Damasio, A. R. (1999). *The feeling of what happens: Body and emotion in the making of consciousness*. Houghton Mifflin Harcourt.

Damasio, A. R., Grabowski, T. J., Bechara, A., Damasio, H., Ponto, L. L., Parvizi, J., and Hichwa, R. D. (2000). Subcortical and cortical brain activity during the feeling of self-generated emotions. *Nature neuroscience*, 3(10):1049–1056.

Dambacher, M. and Hübner, R. (2015). Time pressure affects the efficiency of perceptual processing in decisions under conflict. *Psychological research*, 79(1):83–94.

Damsa, C., Kosel, M., and Moussally, J. (2009). Current status of brain imaging in anxiety disorders. *Current Opinion in Psychiatry*, 22(1):96–110.

Dannlowski, U., Kugel, H., Huber, F., Stuhrmann, A., Redlich, R., Grotegerd, D., Dohm, K., Sehlmeyer, C., Konrad, C., Baune, B. T., et al. (2013). Childhood maltreatment is associated with an automatic negative emotion processing bias in the amygdala. *Human brain mapping*, 34(11):2899–2909.

Dannlowski, U., Stuhrmann, A., Beutelmann, V., Zwanzger, P., Lenzen, T., Grotegerd, D., Domschke, K., Hohoff, C., Ohrmann, P., Bauer, J., et al. (2012). Limbic scars: long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. *Biological psychiatry*, 71(4):286–293.

D'Argembeau, A., Collette, F., Van der Linden, M., Laureys, S., Del Fiore, G., Degueldre, C., Luxen, A., and Salmon, E. (2005). Self-referential reflective activity and its relationship with rest: a pet study. *Neuroimage*, 25(2):616–624.

Darke, S. (2010). The toxicology of homicide offenders and victims: a review. *Drug and alcohol review*, 29(2):202–215.

Darwin, C. (1872). Expression of the emotions. *Man and Animals*.

Darwin, C. (1965). *The expression of the emotions in man and animals*, volume 526. University of Chicago press.

David, J., Green, P., Martin, R., and Suls, J. (1997). Differential roles of neuroticism, extraversion, and event desirability for mood in daily life: An integrative model of top-down and bottom-up influences. *Journal of Personality and Social Psychology*, 73(1):149–159.

Davidson, R., Fox, A., and Kalin, N. (2007). Neural bases of emotion regulation in nonhuman primates and humans. *Handbook of Emotion Regulation*, pages 47–68.

Davidson, R. J. (2002). Anxiety and affective style: role of prefrontal cortex and amygdala. *Biological psychiatry*, 51(1):68–80.

Davidson, R. J., Putnam, K. M., and Larson, C. L. (2000). Dysfunction in the neural circuitry of emotion regulation–a possible prelude to violence. *science*, 289(5479):591–594.

Davis, F. C., Neta, M., Kim, M. J., Moran, J. M., and Whalen, P. J. (2016). Interpreting ambiguous social cues in unpredictable contexts. *Social cognitive and affective neuroscience*, page nsw003.

Davis, H., Porter, J. W., Livingstone, J., Herrmann, T., MacFadden, L., and Levine, S. (1977). Pituitary-adrenal activity and leverpress shock escape behavior. *Physiological Psychology*, 5(3):280–284.

Davis, K. (2000a). The neural circuitry of pain as explored with functional mri. *Neurological Research*, 22(3):313–317.

Davis, M. (2000b). The role of the amygdala in conditioned and unconditioned fear and anxiety. *The Amygdala: A Functional Analysis*, pages 213–287.

Davis, M., Walker, D. L., Miles, L., and Grillon, C. (2010). Phasic vs sustained fear in rats and humans: role of the extended amygdala in fear vs anxiety. *Neuropsychopharmacology*, 35(1):105–135.

Davis, M. and Whalen, P. (2001). The amygdala: Vigilance and emotion. *Molecular Psychiatry*, 6(1):13–34.

Davoudi, I., Salahian, A., and Veisy, F. (2013). Fear of positive evaluation and social anxiety. *Journal of Mazandaran University of Medical Sciences (JMUMS)*, 96(22):80–8.

Dawe, S., Gullo, M. J., and Loxton, N. J. (2004). Reward drive and rash impulsiveness as dimensions of impulsivity: implications for substance misuse. *Addictive behaviors*, 29(7):1389–1405.

Dawes, M. A., Dorn, L. D., Moss, H. B., Yao, J. K., Kirisci, L., Ammerman, R. T., and Tarter, R. E. (1999). Hormonal and behavioral homeostasis in boys at risk for substance abuse. *Drug and alcohol dependence*, 55(1):165–176.

Dawson, D. A., Goldstein, R. B., and Grant, B. F. (2007). Rates and correlates of relapse among individuals in remission from dsm-iv alcohol dependence: A 3-year follow-up. *Alcoholism: Clinical and Experimental Research*, 31(12):2036–2045.

Dawson, D. A., Goldstein, R. B., Ruan, W. J., and Grant, B. F. (2012). Correlates of recovery from alcohol dependence: A prospective study over a 3-year follow-up interval. *Alcoholism: Clinical and Experimental Research*, 36(7):1268–1277.

Dawson, D. A., Li, T.-K., Chou, S. P., and Grant, B. F. (2009). Transitions in and out of alcohol use disorders: Their associations with conditional changes in quality of life over a 3-year follow-up interval†. *Alcohol and Alcoholism*, 44(1):84–92.

Dawson, D. A., Saha, T. D., and Grant, B. F. (2010). A multidimensional assessment of the validity and utility of alcohol use disorder severity as determined by item response theory models. *Drug and alcohol dependence*, 107(1):31–38.

De Bellis, M. D., Clark, D. B., Beers, S. R., Soloff, P. H., Boring, A. M., Hall, J., Kersh, A., and Keshavan, M. S. (2000). Hippocampal volume in adolescent-onset alcohol use disorders. *American Journal of Psychiatry*, 157(5):737–744.

De Francesco, P. N., Valdivia, S., Cabral, A., Reynaldo, M., Raingo, J., Sakata, I., Osborne-Lawrence, S., Zigman, J. M., and Perelló, M. (2015). Neuroanatomical and functional characterization of crf neurons of the amygdala using a novel transgenic mouse model. *Neuroscience*.

De Kloet, E. (2004). Hormones and the stressed brain. *Annals of the New York Academy of Sciences*, 1018:1–15.

de Kloet, E. R., Oitzl, M. S., and Joëls, M. (1999). Stress and cognition: are corticosteroids good or bad guys? *Trends in neurosciences*, 22(10):422–426.

de la Mora, M. P., Cárdenas-Cachón, L., Vázquez-García, M., Crespo-Ramírez, M., Jacobsen, K., Höistad, M., Agnati, L., and Fuxe, K. (2005). Anxiolytic effects of intra-amygdaloid injection of the d1 antagonist sch23390 in the rat. *Neuroscience letters*, 377(2):101–105.

de Lijster, J. M., Dierckx, B., Utens, E. M., Verhulst, F. C., Zieldorff, C., Dieleman, G. C., and Legerstee, J. S. (2016). The age of onset of anxiety disorders a meta-analysis. *The Canadian Journal of Psychiatry*, page 0706743716640757.

de Looze, M., Raaijmakers, Q., Ter Bogt, T., Bendtsen, P., Farhat, T., Ferreira, M., Godeau, E., Kuntsche, E., Molcho, M., Pförtner, T.-K., et al. (2015). Decreases in adolescent weekly alcohol use in europe and north america: evidence from 28 countries from 2002 to 2010. *European journal of public health*, 25(suppl 2):69–72.

De Moor, M. H., Costa, P. T., Terracciano, A., Krueger, R. F., De Geus, E. J., Toshiko, T., Penninx, B. W., Esko, T., Madden, P. A., Derringer, J., et al. (2012). Meta-analysis of genome-wide association studies for personality. *Molecular psychiatry*, 17(3):337–349.

De Pascalis, V., Valerio, E., Santoro, M., and Cacace, I. (2007). Neuroticism-anxiety, impulsive-sensation seeking and autonomic responses to somatosensory stimuli. *International Journal of Psychophysiology*, 63(1):16–24.

De Winter, F.-L., Van den Stock, J., de Gelder, B., Peeters, R., Jastorff, J., Sunaert, S., Vanduffel, W., Vandenberghe, R., and Vandenbulcke, M. (2016). Amygdala atrophy affects emotion-related activity in face-responsive regions in frontotemporal degeneration. *Cortex*.

de Wit, H., Crean, J., and Richards, J. B. (2000). Effects of d-amphetamine and ethanol on a measure of behavioral inhibition in humans. *Behavioral neuroscience*, 114(4):830.

de Wit, H., Söderpalm, A. H., Nikolayev, L., and Young, E. (2003). Effects of acute social stress on alcohol consumption in healthy subjects. *Alcoholism: Clinical and Experimental Research*, 27(8):1270–1277.

Dean, D. C., O'Muircheartaigh, J., Dirks, H., Waskiewicz, N., Lehman, K., Walker, L., Piryatinsky, I., and Deoni, S. C. (2015). Estimating the age of healthy infants from quantitative myelin water fraction maps. *Human brain mapping*, 36(4):1233–1244.

Dean, S., Britt, E., Bell, E., Stanley, J., and Collings, S. (2016). Motivational interviewing to enhance adolescent mental health treatment engagement: a randomized clinical trial. *Psychological medicine*, 46(09):1961–1969.

Decety, J. and Grezes, J. (2006). The power of simulation: imagining one's own and other's behavior. *Brain research*, 1079(1):4–14.

Decety, J. and Lamm, C. (2007). The role of the right temporoparietal junction in social interaction: how low-level computational processes contribute to meta-cognition. *The Neuroscientist*.

Dedovic, K., Duchesne, A., Andrews, J., Engert, V., and Pruessner, J. C. (2009a). The brain and the stress axis: the neural correlates of cortisol regulation in response to stress. *Neuroimage*, 47(3):864–871.

Dedovic, K., Duchesne, A., Engert, V., Lue, S. D., Andrews, J., Efanov, S. I., Beaudry, T., and Pruessner, J. C. (2013). Psychological, endocrine and neural responses to social evaluation in subclinical depression. *Social cognitive and affective neuroscience*, page nst151.

Dedovic, K., Duchesne, A., Engert, V., Lue, S. D., Andrews, J., Efanov, S. I., Beaudry, T., and Pruessner, J. C. (2014). Psychological, endocrine and neural responses to social evaluation in subclinical depression. *Social cognitive and affective neuroscience*, 9(10):1632–1644.

Dedovic, K., Giebl, S., Duchesne, A., Lue, S. D., Andrews, J., Efanov, S., Engert, V., Beaudry, T., Baldwin, M. W., and Pruessner, J. C. (2015). Psychological, endocrine, and neural correlates of attentional bias in subclinical depression. *Anxiety, Stress, & Coping*, pages 1–18.

Dedovic, K., Renwick, R., Mahani, N. K., Engert, V., Lupien, S. J., and Pruessner, J. C. (2005). The montreal imaging stress task: using functional imaging to investigate the effects of perceiving and processing psychosocial stress in the human brain. *Journal of Psychiatry and Neuroscience*, 30(5):319.

Dedovic, K., Rexroth, M., Wolff, E., Duchesne, A., Scherling, C., Beaudry, T., Lue, S. D., Lord, C., Engert, V., and Pruessner, J. C. (2009b). Neural correlates of processing stressful information: an event-related fmri study. *Brain research*, 1293:49–60.

Deen, B., Pitskel, N. B., and Pelphrey, K. A. (2011). Three systems of insular functional connectivity identified with cluster analysis. *Cerebral Cortex*, 21(7):1498–1506.

Del Boca, F. K. and Hesselbrock, M. N. (1996). Gender and alcoholic subtypes. *Alcohol Research and Health*, 20(1):56.

Del Giudice, M., Ellis, B., and Shirtcliff, E. (2011). The adaptive calibration model of stress responsivity. *Neuroscience and Biobehavioral Reviews*, 35(7):1562–1592.

Delgado, M. R., Jou, R. L., and Phelps, E. A. (2011). Neural systems underlying aversive conditioning in humans with primary and secondary reinforcers. *Frontiers in Neuroscience*, 5(MAY).

Delker, E., Brown, Q., and Hasin, D. S. (2016). Alcohol consumption in demographic subpopulations: an epidemiologic overview. *Alcohol research: current reviews*, 38(1):7.

DeMartini, K. and Carey, K. (2011). The role of anxiety sensitivity and drinking motives in predicting alcohol use: A critical review. *Clinical Psychology Review*, 31(1):169–177.

Demenescu, L., Kortekaas, R., Cremers, H., Renken, R., van Tol, M., van der Wee, N., Veltman, D., den Boer, J., Roelofs, K., and Aleman, A. (2013). Amygdala activation and its functional connectivity during perception of emotional faces in social phobia and panic disorder. *Journal of psychiatric research*, 47(8):1024–1031.

Demyttenaere, K., Bruffaerts, R., Posada-Villa, J., Gasquet, I., Kovess, V., Lepine, J., Angermeyer, M., Bernert, S., De Girolamo, G., Morosini, P., et al. (2004). Prevalence, severity, and unmet need for treatment of mental disorders in the world health organization world mental health surveys. *Jama*, 291(21):2581–2590.

Denny, B. T., Kober, H., Wager, T. D., and Ochsner, K. N. (2012). A meta-analysis of functional neuroimaging studies of self-and other judgments reveals a spatial gradient for mentalizing in medial prefrontal cortex. *Journal of cognitive Neuroscience*, 24(8):1742–1752.

Denny, C. H., Hungerford, D. W., McKnight-Eily, L. R., Green, P. P., Dang, E. P., Cannon, M. J., Cheal, N. E., and Sniezek, J. E. (2016). Self-reported prevalence

of alcohol screening among us adults. *American journal of preventive medicine*, 50(3):380–383.

Denson, T. F., Pedersen, W. C., Ronquillo, J., and Nandy, A. S. (2009). The angry brain: Neural correlates of anger, angry rumination, and aggressive personality. *Journal of Cognitive Neuroscience*, 21(4):734–744.

Denys, D., Mantione, M., Figee, M., van den Munckhof, P., Koerselman, F., Westenberg, H., Bosch, A., and Schuurman, R. (2010). Deep brain stimulation of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder. *Archives of general psychiatry*, 67(10):1061–1068.

Depue, R. A. and Collins, P. F. (1999). Neurobiology of the structure of personality: Dopamine, facilitation of incentive motivation, and extraversion. *Behavioral and Brain Sciences*, 22(03):491–517.

Derbyshire, S. W., Jones, A. K., Gyulai, F., Clark, S., Townsend, D., and Firestone, L. L. (1997). Pain processing during three levels of noxious stimulation produces differential patterns of central activity. *Pain*, 73(3):431–445.

Derdikman, D. and Moser, E. I. (2010). A manifold of spatial maps in the brain. *Trends in cognitive sciences*, 14(12):561–569.

Deroche, V., Piazza, P. V., Le Moal, M., and Simon, H. (1993). Individual differences in the psychomotor effects of morphine are predicted by reactivity to novelty and influenced by corticosterone secretion. *Brain research*, 623(2):341–344.

DeRosse, P., Nitzburg, G. C., Kompancaril, B., and Malhotra, A. K. (2014). The relation between childhood maltreatment and psychosis in patients with schizophrenia and non-psychiatric controls. *Schizophrenia research*, 155(1):66–71.

Derringer, J., Krueger, R. F., Dick, D. M., Saccone, S., Grucza, R. A., Agrawal, A., Lin, P., Almasy, L., Edenberg, H. J., Foroud, T., et al. (2010). Predicting sensation seeking from dopamine genes a candidate-system approach. *Psychological Science*, 21(9):1282–1290.

Dess, N. K., Linwick, D., Patterson, J., Overmier, J. B., and Levine, S. (1983). Immediate and proactive effects of controllability and predictability on plasma cortisol responses to shocks in dogs. *Behavioral Neuroscience*, 97(6):1005.

DeTurck, K. and Vogel, W. (1982). Effects of acute ethanol on plasma and brain catecholamine levels in stressed and unstressed rats: Evidence for an ethanol-stress interaction. *Journal of Pharmacology and Experimental Therapeutics*, 223(2):348–354.

Devinsky, O., Morrell, M. J., Vogt, B. A., et al. (1995). Contributions of anterior cingulate cortex to behaviour. *Brain*, 118(1):279–306.

DeVito, E. E., Meda, S. A., Jiantonio, R., Potenza, M. N., Krystal, J. H., and Pearlson, G. D. (2013). Neural correlates of impulsivity in healthy males and females with family histories of alcoholism. *Neuropsychopharmacology*, 38(10):1854–1863.

DeWall, C. and Baumeister, R. (2006). Alone but feeling no pain: Effects of social exclusion on physical pain tolerance and pain threshold, affective forecasting, and interpersonal empathy. *Journal of Personality and Social Psychology*, 91(1):1–15.

DeWall, C. N. and Bushman, B. J. (2011). Social acceptance and rejection the sweet and the bitter. *Current Directions in Psychological Science*, 20(4):256–260.

DeYoung, C. (2010). Personality neuroscience and the biology of traits. *Social and Personality Psychology Compass*, 4(12):1165–1180.

Diamond, A. (2006). The early development of executive functions. *Lifespan cognition: Mechanisms of change*, pages 70–95.

Diamond, A. (2012). Activities and programs that improve children's executive functions. *Current directions in psychological science*, 21(5):335–341.

Diamond, A. (2013). Executive functions. *Annual review of psychology*, 64:135.

Diamond, A. (2016). Why improving and assessing executive functions early in life is critical. *Executive function in preschool age children: Integrating measurement, neurodevelopment and translational research. Washington, DC: American Psychological Association.*

Diamond, A. and Lee, K. (2011). Interventions shown to aid executive function development in children 4 to 12 years old. *Science*, 333(6045):959–964.

Diamond, A. and Ling, D. S. (2016). Conclusions about interventions, programs, and approaches for improving executive functions that appear justified and those that, despite much hype, do not. *Developmental cognitive neuroscience*, 18:34–48.

Diaz, M. R., Chappell, A. M., Christian, D. T., Anderson, N. J., and McCool, B. A. (2011). Dopamine d3-like receptors modulate anxiety-like behavior and regulate gabaergic transmission in the rat lateral/basolateral amygdala. *Neuropsychopharmacology*, 36(5):1090–1103.

Dick, D. M. (2011). Developmental changes in genetic influences on alcohol use and dependence. *Child Development Perspectives*, 5(4):223–230.

Dick, D. M., Prescott, C., and McGue, M. (2009). The genetics of substance use and substance use disorders. In *Handbook of behavior genetics*, pages 433–453. Springer.

Dick, D. M., Riley, B., and Kendler, K. S. (2010). Nature and nurture in neuropsychiatric genetics: where do we stand. *Dialogues Clin Neurosci*, 12(1):7–23.

Dickerson, D. L., Brown, R. A., Johnson, C. L., Schweigman, K., and D'Amico, E. J. (2016). Integrating motivational interviewing and traditional practices to address alcohol and drug use among urban american indian/alaska native youth. *Journal of substance abuse treatment*, 65:26–35.

Dickerson, S. S., Gruenewald, T. L., and Kemeny, M. E. (2004a). When the social self is threatened: Shame, physiology, and health. *Journal of personality*, 72(6):1191–1216.

Dickerson, S. S. and Kemeny, M. E. (2004). Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. *Psychological bulletin*, 130(3):355.

Dickerson, S. S., Kemeny, M. E., Aziz, N., Kim, K. H., and Fahey, J. L. (2004b). Immunological effects of induced shame and guilt. *Psychosomatic Medicine*, 66(1):124–131.

Dickerson, S. S., Mycek, P. J., and Zaldivar, F. (2008). Negative social evaluation, but not mere social presence, elicits cortisol responses to a laboratory stressor task. *Health Psychology*, 27(1):116.

Diener, S. J., Nees, F., Wessa, M., Wirtz, G., Frommberger, U., Penga, T., Ruttorf, M., Ruf, M., Schmahl, C., and Flor, H. (2016). Reduced amygdala responsivity during conditioning to trauma-related stimuli in posttraumatic stress disorder. *Psychophysiology*, 53(10):1460–1471.

Dienstbier, R. A. (1989). Arousal and physiological toughness: implications for mental and physical health. *Psychological review*, 96(1):84.

Dillon, D. and Pizzagalli, D. (2007). Inhibition of action, thought, and emotion: A selective neurobiological review. *Applied and Preventive Psychology*, 12(3):99–114.

Dills, A. K. and Miron, J. A. (2004). Alcohol prohibition and cirrhosis. *American Law and Economics Review*, 6(2):285–318.

Diorio, D., Viau, V., and Meaney, M. (1993). The role of the medial prefrontal cortex (cingulate gyrus) in the regulation of hypothalamic-pituitary-adrenal responses to stress. *Journal of Neuroscience*, 13(9):3839–3847.

Doblin, R. (1991). Pahnke's" good friday experiment": A long-term follow-up and methodological critique. *The Journal of Transpersonal Psychology*, 23(1):1.

Dom, G., Sabbe, B., Hulstijn, W., and Van Den Brink, W. (2005). Substance use disorders and the orbitofrontal cortex. *The British Journal of Psychiatry*, 187(3):209–220.

Domes, G., Heinrichs, M., Gläscher, J., Büchel, C., Braus, D. F., and Herpertz, S. C. (2007). Oxytocin attenuates amygdala responses to emotional faces regardless of valence. *Biological psychiatry*, 62(10):1187–1190.

Domschke, K., Stevens, S., Pfleiderer, B., and Gerlach, A. L. (2010). Interoceptive sensitivity in anxiety and anxiety disorders: an overview and integration of neurobiological findings. *Clinical psychology review*, 30(1):1–11.

Donald, K. A., Fouche, J., Roos, A., Koen, N., Howells, F. M., Riley, E. P., Woods, R. P., Zar, H. J., Narr, K. L., and Stein, D. J. (2016). Alcohol exposure in utero is associated with decreased gray matter volume in neonates. *Metabolic brain disease*, 31(1):81–91.

Donchin, E. and Coles, M. G. (1988). Is the p300 component a manifestation of context updating? *Behavioral and brain sciences*, 11(03):357–374.

Donegan, N., Sanislow, C., Blumberg, H., Fulbright, R., Lacadie, C., Skudlarski, P., Gore, J., Olson, I., McGlashan, T., and Wexler, B. (2003). Amygdala hyperreactivity in borderline personality disorder: Implications for emotional dysregulation. *Biological Psychiatry*, 54(11):1284–1293.

Donohew, L., Zimmerman, R., Cupp, P. S., Novak, S., Colon, S., and Abell, R. (2000). Sensation seeking, impulsive decision-making, and risky sex: Implications for risk-taking and design of interventions. *Personality and individual differences*, 28(6):1079–1091.

Donovan, J. E., Leech, S. L., Zucker, R. A., Loveland-Cherry, C. J., Jester, J. M., Fitzgerald, H. E., Puttler, L. I., Wong, M. M., and Looman, W. S. (2004). Really underage drinkers: Alcohol use among elementary students. *Alcoholism: Clinical and Experimental Research*, 28(2):341–349.

Doty, T. J., Japee, S., Ingvar, M., and Ungerleider, L. G. (2013). Fearful face detection sensitivity in healthy adults correlates with anxiety-related traits. *Emotion*, 13(2):183.

Dougherty, D., Rauch, S., Deckersbach, T., Marci, C., Loh, R., Shin, L., Alpert, N., Fischman, A., and Fava, M. (2004). Ventromedial prefrontal cortex and amygdala dysfunction during an anger induction positron emission tomography study in patients with major depressive disorder with anger attacks. *Archives of General Psychiatry*, 61(8):795–804.

Dougherty, D. M., Marsh-Richard, D. M., Hatzis, E. S., Nouvion, S. O., and Mathias, C. W. (2008). A test of alcohol dose effects on multiple behavioral measures of impulsivity. *Drug and alcohol dependence*, 96(1):111–120.

Dougherty, D. M., Moeller, F. G., Steinberg, J. L., Marsh, D. M., Hines, S. E., and Bjork, J. M. (1999). Alcohol increases commission error rates for a continuous performance test. *Alcoholism: Clinical and Experimental Research*, 23(8):1342–1351.

Drabant, E. M., Kuo, J. R., Ramel, W., Blechert, J., Edge, M. D., Cooper, J. R., Goldin, P. R., Hariri, A. R., and Gross, J. J. (2011). Experiential, autonomic, and neural responses during threat anticipation vary as a function of threat intensity and neuroticism. *Neuroimage*, 55(1):401–410.

Drabant, E. M., McRae, K., Manuck, S. B., Hariri, A. R., and Gross, J. J. (2009). Individual differences in typical reappraisal use predict amygdala and prefrontal responses. *Biological psychiatry*, 65(5):367–373.

Dressendörfer, R., Kirschbaum, C., Rohde, W., Stahl, F., and Strasburger, C. (1992). Synthesis of a cortisol-biotin conjugate and evaluation as a tracer in an immunoassay for salivary cortisol measurement. *The Journal of steroid biochemistry and molecular biology*, 43(7):683–692.

Drevets, W. C. and Raichle, M. E. (1998). Reciprocal suppression of regional cerebral blood flow during emotional versus higher cognitive processes: Implications for interactions between emotion and cognition. *Cognition and emotion*, 12(3):353–385.

Drevets, W. C. and Savitz, J. (2008). The subgenual anterior cingulate cortex in mood disorders. *CNS Spectrums: The International Journal of Neuropsychiatric Medicine*, 13(8).

Drummond, C., Gual, A., Goos, C., Godfrey, C., Deluca, P., Von Der Goltz, C., Gmel, G., Scafato, E., Wolstenholme, A., Mann, K., et al. (2011). Identifying the gap between need and intervention for alcohol use disorders in europe. *Addiction*, 106(s1):31–36.

Drummond, W. (1875). *The Large Game and Natural History of South and South-East Africa*. Edinburgh: Edmonston & Douglas.

Dryman, M. T., Gardner, S., Weeks, J. W., and Heimberg, R. G. (2016). Social anxiety disorder and quality of life: How fears of negative and positive evaluation relate to specific domains of life satisfaction. *Journal of anxiety disorders*, 38:1–8.

DuBois, D., Ameis, S. H., Lai, M.-C., Casanova, M. F., and Desarkar, P. (2016). Interoception in autism spectrum disorder: A review. *International Journal of Developmental Neuroscience*.

Dubois, J. and Adolphs, R. (2015). Neuropsychology: How many emotions are there? *Current Biology*, 25(15):R669–R672.

Dubois, J., Dehaene-Lambertz, G., Kulikova, S., Poupon, C., Hüppi, P., and Hertz-Pannier, L. (2014). The early development of brain white matter: a review of imaging studies in fetuses, newborns and infants. *Neuroscience*, 276:48–71.

Ducharme, S., Dougherty, D. D., and Drevets, W. C. (2016). Neuroimaging and neurocircuitry of obsessive. *Psychiatric Neurotherapeutics: Contemporary Surgical and Device-Based Treatments*, page 51.

Duchesne, A., Tessera, E., Dedovic, K., Engert, V., and Pruessner, J. (2012). Effects of panel sex composition on the physiological stress responses to psychosocial stress in healthy young men and women. *Biological psychology*, 89(1):99–106.

Dugas, M. J., Buhr, K., and Ladouceur, R. (2004). The role of intolerance of uncertainty in etiology and maintenance.

Dugas, M. J., Gagnon, F., Ladouceur, R., and Freeston, M. H. (1998). Generalized anxiety disorder: A preliminary test of a conceptual model. *Behaviour research and therapy*, 36(2):215–226.

Dugas, M. J., Gosselin, P., and Ladouceur, R. (2001). Intolerance of uncertainty and worry: Investigating specificity in a nonclinical sample. *Cognitive Therapy and Research*, 25(5):551–558.

Dugas, M. J. and Ladouceur, R. (2000). Treatment of gad targeting intolerance of uncertainty in two types of worry. *Behavior Modification*, 24(5):635–657.

Dugas, M. J., Marchand, A., and Ladouceur, R. (2005). Further validation of a cognitive-behavioral model of generalized anxiety disorder: diagnostic and symptom specificity. *Journal of anxiety disorders*, 19(3):329–343.

Dugas, M. J. and Robichaud, M. (2007). *Cognitive-behavioral treatment for generalized anxiety disorder: From science to practice*. Taylor & Francis.

Duits, P., Cath, D. C., Lissek, S., Hox, J. J., Hamm, A. O., Engelhard, I. M., Hout, M. A., and Baas, J. M. (2015). Updated meta-analysis of classical fear conditioning in the anxiety disorders. *Depression and anxiety*, 32(4):239–253.

Dunn, J. and Orr, S. (1984). Differential plasma corticosterone responses to hippocampal stimulation. *Experimental Brain Research*, 54(1):1–6.

Dunsmoor, J. E., Bandettini, P. A., and Knight, D. C. (2007). Impact of continuous versus intermittent cs-ucs pairing on human brain activation during pavlovian fear conditioning. *Behavioral neuroscience*, 121(4):635.

Dupree, C. H., Magill, M., and Apodaca, T. R. (2016). The pros and cons of drinking: A qualitative analysis of young adult drinking discussions within motivational interviewing. *Addiction Research & Theory*, 24(1):40–47.

Dupuy, M. and Chanraud, S. (2016). Imaging the addicted brain: Alcohol. *International Review of Neurobiology*.

Durazzo, T. C., Mon, A., Gazdzinski, S., and Meyerhoff, D. J. (2016). Regional brain volume changes in alcohol-dependent individuals during early abstinence: associations with relapse following treatment. *Addiction Biology*.

Durston, S., Mulder, M., Casey, B., Ziermans, T., and van Engeland, H. (2006). Activation in ventral prefrontal cortex is sensitive to genetic vulnerability for attention-deficit hyperactivity disorder. *Biological psychiatry*, 60(10):1062–1070.

Duvarci, S. and Pare, D. (2014). Amygdala microcircuits controlling learned fear. *Neuron*, 82(5):966–980.

Dysart, J. E., Lindsay, R., MacDonald, T. K., and Wicke, C. (2002). The intoxicated witness: Effects of alcohol on identification accuracy from showups. *Journal of Applied Psychology*, 87(1):170.

Easdon, C. and Vogel-Sprott, M. (2000). Alcohol and behavioral control: Impaired response inhibition and flexibility in social drinkers. *Experimental and Clinical Psychopharmacology*, 8(3):387–394.

Easterbrook, J. A. (1959). The effect of emotion on cue utilization and the organization of behavior. *Psychological review*, 66(3):183.

Eaton, D. K., Kann, L., Kinchen, S., Shanklin, S., Flint, K. H., Hawkins, J., Harris, W. A., Lowry, R., McManus, T., Chyen, D., et al. (2012a). Youth risk behavior surveillance-united states, 2011. *Morbidity and mortality weekly report. Surveillance summaries (Washington, DC: 2002)*, 61(4):1–162.

Eaton, N. R., Keyes, K. M., Krueger, R. F., Balsis, S., Skodol, A. E., Markon, K. E., Grant, B. F., and Hasin, D. S. (2012b). An invariant dimensional liability model of gender differences in mental disorder prevalence: evidence from a national sample. *Journal of Abnormal Psychology*, 121(1):282.

Eaton, W. W., Martins, S. S., Nestadt, G., Bienvenu, O. J., Clarke, D., and Alexandre, P. (2008). The burden of mental disorders. *Epidemiologic reviews*, 30(1):1–14.

Eckardt, M. J., File, S. E., Gessa, G. L., Grant, K. A., Guerri, C., Hoffman, P. L., Kalant, H., Koob, G. F., Li, T.-K., and Tabakoff, B. (1998). Effects of moderate alcohol consumption on the central nervous system*. *Alcoholism: Clinical and Experimental Research*, 22(5):998–1040.

Eckstein, M., Scheele, D., Weber, K., Stoffel-Wagner, B., Maier, W., and Hurlemann, R. (2014). Oxytocin facilitates the sensation of social stress. *Human brain mapping*, 35(9):4741–4750.

Edelman, S., Shalev, I., Uzefovsky, F., Israel, S., Knafo, A., Kremer, I., Mankuta, D., Kaitz, M., and Ebstein, R. P. (2012). Epigenetic and genetic factors predict women's salivary cortisol following a threat to the social self. *PLoS One*, 7(11):e48597.

Edlund, M. J., Booth, B. M., and Han, X. (2012). Who seeks care where? utilization of mental health and substance use disorder treatment in two national samples of individuals with alcohol use disorders. *Journal of studies on alcohol and drugs*, 73(4):635.

Edwards, A., Gardner, C., Hickman, M., and Kendler, K. (2016). A prospective longitudinal model predicting early adult alcohol problems: evidence for a robust externalizing pathway. *Psychological medicine*, 46(05):957–968.

Edwards, A. C., Aliev, F., Wolen, A. R., Salvatore, J. E., Gardner, C. O., McMahon, G., Evans, D. M., Macleod, J., Hickman, M., Dick, D. M., et al. (2015). Genomic influences on alcohol problems in a population-based sample of young adults. *Addiction*.

Edwards, A. C. and Kendler, K. S. (2012). Twin study of the relationship between adolescent attention-deficit/hyperactivity disorder and adult alcohol dependence. *Journal of studies on alcohol and drugs*, 73(2):185–194.

Ehret, P. J., LaBrie, J. W., Santerre, C., and Sherman, D. K. (2015). Self-affirmation and motivational interviewing: integrating perspectives to reduce resistance and increase efficacy of alcohol interventions. *Health psychology review*, 9(1):83–102.

Eippert, F., Veit, R., Weiskopf, N., Erb, M., Birbaumer, N., and Anders, S. (2007). Regulation of emotional responses elicited by threat-related stimuli. *Human brain mapping*, 28(5):409–423.

Eisenberg, D., Campbell, B., MacKillop, J., Lum, J., and Wilson, D. (2007). Season of birth and dopamine receptor gene associations with impulsivity, sensation seeking and reproductive behaviors. *PLoS ONE*, 2(11).

Eisenberger, N. I. (2012a). Broken hearts and broken bones a neural perspective on the similarities between social and physical pain. *Current Directions in Psychological Science*, 21(1):42–47.

Eisenberger, N. I. (2012b). The pain of social disconnection: examining the shared neural underpinnings of physical and social pain. *Nature Reviews Neuroscience*, 13(6):421–434.

Eisenberger, N. I. (2015a). Meta-analytic evidence for the role of the anterior cingulate cortex in social pain. *Social cognitive and affective neuroscience*, 10(1):1–2.

Eisenberger, N. I. (2015b). Social pain and the brain: Controversies, questions, and where to go from here. *Annual review of psychology*, 66:601–629.

Eisenberger, N. I., Lieberman, M. D., and Satpute, A. B. (2005). Personality from a controlled processing perspective: an fmri study of neuroticism, extraversion, and self-consciousness. *Cognitive, Affective, & Behavioral Neuroscience*, 5(2):169–181.

Eisenberger, N. I., Lieberman, M. D., and Williams, K. D. (2003). Does rejection hurt? an fmri study of social exclusion. *Science*, 302(5643):290–292.

Eisenegger, C., Haushofer, J., and Fehr, E. (2011). The role of testosterone in social interaction. *Trends in cognitive sciences*, 15(6):263–271.

Eisenlohr-Moul, T. A., Peters, J. R., Pond Jr, R. S., and DeWall, C. N. (2016). Both trait and state mindfulness predict lower aggressiveness via anger rumination: a multilevel mediation analysis. *Mindfulness*, 7(3):713–726.

Ekhtiari, H., Faghiri, A., Oghabian, M.-A., and Paulus, M. P. (2016). Functional neuroimaging for addiction medicine: From mechanisms to practical considerations. *Progress in brain research*, 224:129–153.

Ekman, P. (1993). Facial expression and emotion. *American psychologist*, 48(4):384.

Ekman, P. (1994). Strong evidence for universals in facial expressions: a reply to russell's mistaken critique.

Ekman, P. (2007). *Emotions revealed: Recognizing faces and feelings to improve communication and emotional life*. Macmillan.

Ekman, P., Friesen, W. V., O'Sullivan, M., Chan, A., Diacoyanni-Tarlatzis, I., Heider, K., Krause, R., LeCompte, W. A., Pitcairn, T., Ricci-Bitti, P. E., et al. (1987). Universals and cultural differences in the judgments of facial expressions of emotion. *Journal of personality and social psychology*, 53(4):712.

Elbogen, E. B. and Johnson, S. C. (2009). The intricate link between violence and mental disorder: results from the national epidemiologic survey on alcohol and related conditions. *Archives of general Psychiatry*, 66(2):152–161.

Eldreth, D. A., Matochik, J. A., Cadet, J. L., and Bolla, K. I. (2004). Abnormal brain activity in prefrontal brain regions in abstinent marijuana users. *Neuroimage*, 23(3):914–920.

Elfenbein, H. A., Mandal, M. K., Ambady, N., Harizuka, S., and Kumar, S. (2002). Cross-cultural patterns in emotion recognition: highlighting design and analytical techniques. *Emotion*, 2(1):75.

Elias, A. N., Meshkinpour, H., Valenta, L. J., and Grossman, M. K. (1982). Pseudo-cushing's syndrome: the role of alcohol. *Journal of clinical gastroenterology*, 4(2):137–140.

Elkins, I. J., McGue, M., Malone, S., and Iacono, W. G. (2004). The effect of parental alcohol and drug disorders on adolescent personality. *American Journal of Psychiatry*, 161(4):670–676.

Ellis, B. J., Boyce, W. T., Belsky, J., Bakermans-Kranenburg, M. J., and Van IJzendoorn, M. H. (2011). Differential susceptibility to the environment: An evolutionary–neurodevelopmental theory. *Development and psychopathology*, 23(01):7–28.

Ellison, A., Schindler, I., Pattison, L., and Milner, A. (2004). An exploration of the role of the superior temporal gyrus in visual search and spatial perception using tms. *Brain*, 127(10):2307–2315.

Elzinga, B. M., Spinhoven, P., Berretty, E., de Jong, P., and Roelofs, K. (2010). The role of childhood abuse in hpa-axis reactivity in social anxiety disorder: A pilot study. *Biological psychology*, 83(1):1–6.

Emmert, K., Kopel, R., Sulzer, J., Brühl, A. B., Berman, B. D., Linden, D. E., Horovitz, S. G., Breimhorst, M., Caria, A., Frank, S., et al. (2016). Meta-analysis of real-time fmri neurofeedback studies using individual participant data: How is brain regulation mediated? *NeuroImage*, 124:806–812.

Emrick, C. D. and Hansen, J. (1983). Assertions regarding effectiveness of treatment for alcoholism: Fact or fantasy? *American Psychologist*, 38(10):1078.

Engel, K., Bandelow, B., Gruber, O., and Wedekind, D. (2009). Neuroimaging in anxiety disorders. *Journal of Neural Transmission*, 116(6):703–716.

Engell, A. D., Haxby, J. V., and Todorov, A. (2007). Implicit trustworthiness decisions: automatic coding of face properties in the human amygdala. *Journal of Cognitive Neuroscience*, 19(9):1508–1519.

Engin, E., Smith, K. S., Gao, Y., Nagy, D., Foster, R. A., Tsvetkov, E., Keist, R., Crestani, F., Fritschy, J.-M., Bolshakov, V. Y., et al. (2016). Modulation of anxiety and fear via distinct intrahippocampal circuits. *eLife*, 5:e14120.

Enoch, M.-A. (2011). The role of early life stress as a predictor for alcohol and drug dependence. *Psychopharmacology*, 214(1):17–31.

Enoch, M.-A. (2014). Genetic influences on response to alcohol and response to pharmacotherapies for alcoholism. *Pharmacology Biochemistry and Behavior*, 123:17–24.

Epel, E. S., McEwen, B. S., and Ickovics, J. R. (1998). Embodying psychological thriving: Physical thriving in response to stress. *Journal of Social Issues*, 54(2):301–322.

Erblich, J. and Earleywine, M. (2003). Behavioral undercontrol and subjective stimulant and sedative effects of alcohol intoxication: independent predictors of drinking habits? *Alcoholism: Clinical and Experimental Research*, 27(1):44–50.

Eriksson, C. P. (2015). Genetic–epidemiological evidence for the role of acetaldehyde in cancers related to alcohol drinking. In *Biological Basis of Alcohol-Induced Cancer*, pages 41–58. Springer.

Erlich, N., Lipp, O. V., and Slaughter, V. (2013). Of hissing snakes and angry voices: human infants are differentially responsive to evolutionary fear-relevant sounds. *Developmental science*, 16(6):894–904.

Ernst, M., Nelson, E. E., Jazbec, S., McClure, E. B., Monk, C. S., Leibenluft, E., Blair, J., and Pine, D. S. (2005). Amygdala and nucleus accumbens in responses to receipt and omission of gains in adults and adolescents. *Neuroimage*, 25(4):1279–1291.

Ernst, M., Nelson, E. E., McClure, E. B., Monk, C. S., Munson, S., Eshel, N., Zarahn, E., Leibenluft, E., Zametkin, A., Towbin, K., et al. (2004). Choice selection and reward anticipation: an fmri study. *Neuropsychologia*, 42(12):1585–1597.

Ernst, M., Pine, D. S., and Hardin, M. (2006). Triadic model of the neurobiology of motivated behavior in adolescence. *Psychological medicine*, 36(03):299–312.

Errico, A. L., Parsons, O. A., King, A. C., and Lovallo, W. (1993). Attenuated cortisol response to biobehavioral stressors in sober alcoholics. *Journal of studies on alcohol*, 54(4):393–398.

Ersche, K., Barnes, A., Simon Jones, P., Morein-Zamir, S., Robbins, T., and Bullmore, E. (2011). Abnormal structure of frontostriatal brain systems is associated with aspects of impulsivity and compulsivity in cocaine dependence. *Brain*, 134(7):2013–2024.

Ersche, K., Turton, A., Pradhan, S., Bullmore, E., and Robbins, T. (2010a). Drug addiction endophenotypes: Impulsive versus sensation-seeking personality traits. *Biological Psychiatry*, 68(8):770–773.

Ersche, K. D., Hagan, C. C., Smith, D. G., Jones, P. S., Calder, A. J., and Williams, G. B. (2015). In the face of threat: neural and endocrine correlates of impaired facial emotion recognition in cocaine dependence. *Translational psychiatry*, 5(5):e570.

Ersche, K. D., Jones, P. S., Williams, G. B., Smith, D. G., Bullmore, E. T., and Robbins, T. W. (2013a). Distinctive personality traits and neural correlates associated with stimulant drug use versus familial risk of stimulant dependence. *Biological psychiatry*, 74(2):137–144.

Ersche, K. D., Turton, A. J., Pradhan, S., Bullmore, E. T., and Robbins, T. W. (2010b). Drug addiction endophenotypes: impulsive versus sensation-seeking personality traits. *Biological psychiatry*, 68(8):770–773.

Ersche, K. D., Williams, G. B., Robbins, T. W., and Bullmore, E. T. (2013b). Meta-analysis of structural brain abnormalities associated with stimulant drug dependence and neuroimaging of addiction vulnerability and resilience. *Current opinion in neurobiology*, 23(4):615–624.

Espejo, E. P., Gorlick, A., and Castriotta, N. (2016). Changes in threat-related cognitions and experiential avoidance in group-based transdiagnostic cbt for anxiety disorders. *Journal of Anxiety Disorders*.

Essau, C. A., Sasagawa, S., and Frick, P. J. (2006). Callous-unemotional traits in a community sample of adolescents. *Assessment*, 13(4):454–469.

Etkin, A., Büchel, C., and Gross, J. J. (2015). The neural bases of emotion regulation. *Nature Reviews Neuroscience*, 16(11):693–700.

Etkin, A., Büchel, C., and Gross, J. J. (2016). Emotion regulation involves both model-based and model-free processes. *Nature Reviews Neuroscience*.

Etkin, A., Egner, T., Peraza, D. M., Kandel, E. R., and Hirsch, J. (2006). Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. *Neuron*, 51(6):871–882.

Etkin, A., Klemenhagen, K., Dudman, J., Rogan, M., Hen, R., Kandel, E., and Hirsch, J. (2004). Individual differences in trait anxiety predict the response of the basolateral amygdala to unconsciously processed fearful faces. *Neuron*, 44(6):1043–1055.

Etkin, A., Prater, K., Schatzberg, A., Menon, V., and Greicius, M. (2009). Disrupted amygdalar subregion functional connectivity and evidence of a compensatory network in generalized anxiety disorder. *Archives of General Psychiatry*, 66(12):1361–1372.

Etkin, A. and Wager, T. D. (2007). Functional neuroimaging of anxiety: A meta-analysis of emotional processing in ptsd, social anxiety disorder, and specific phobia. *Am J Psychiatry*, 164(10):1476–1488.

Euser, A. S. and Franken, I. H. (2012). Alcohol affects the emotional modulation of cognitive control: an event-related brain potential study. *Psychopharmacology*, 222(3):459–476.

Evans, B. E., Greaves-Lord, K., Euser, A. S., Franken, I. H., and Huizink, A. C. (2012). The relation between hypothalamic–pituitary–adrenal (hpa) axis activity and age of onset of alcohol use. *Addiction*, 107(2):312–322.

Evans, B. E., Greaves-Lord, K., Euser, A. S., Franken, I. H., and Huizink, A. C. (2013). Cortisol levels in children of parents with a substance use disorder. *Psychoneuroendocrinology*, 38(10):2109–2120.

Evans, B. E., Greaves-Lord, K., Euser, A. S., Thissen, S., Tulen, J. H., Franken, I. H., and Huizink, A. C. (2016a). Stress reactivity as a prospective predictor of risky substance use during adolescence. *Journal of Studies on Alcohol and Drugs*, 77(2):208–219.

Evans, K. C., Wright, C. I., Wedig, M. M., Gold, A. L., Pollack, M. H., and Rauch, S. L. (2008). A functional mri study of amygdala responses to angry schematic faces in social anxiety disorder. *Depression and anxiety*, 25(6):496–505.

Evans, S. M. and Levin, F. R. (2011). Response to alcohol in women: Role of the menstrual cycle and a family history of alcoholism. *Drug and alcohol dependence*, 114(1):18–30.

Evans, T. C., Walukevich, K. A., and Britton, J. C. (2016b). Vigilance-avoidance and disengagement are differentially associated with fear and avoidant behaviors in social anxiety. *Journal of affective disorders*, 199:124–131.

Everaerd, D., Klumpers, F., van Wingen, G., Tendolkar, I., and Fernández, G. (2015). Association between neuroticism and amygdala responsivity emerges under stressful conditions. *Neuroimage*, 112:218–224.

Everitt, B. J. and Robbins, T. W. (2005). Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nature neuroscience*, 8(11):1481–1489.

Everitt, B. J. and Robbins, T. W. (2016). Drug addiction: updating actions to habits to compulsions ten years on. *Annual Review of Psychology*, 67:23–50.

Eysenck, H. (1967). The biological basis of behaviour. *CC Thomas, Springfield*.

Eysenck, H. J. (1983). A biometrical-genetical analysis of impulsive and sensation seeking behavior. *Biological bases of sensation seeking, impulsivity, and anxiety*, pages 1–27.

Eysenck, M. W. (1976). Arousal, learning, and memory. *Psychological Bulletin*, 83(3):389.

Fabiansson, E. C., Denson, T. F., Moulds, M. L., Grisham, J. R., and Schira, M. M. (2012). Don't look back in anger: Neural correlates of reappraisal, analytical rumination, and angry rumination during recall of an anger-inducing autobiographical memory. *NeuroImage*, 59(3):2974–2981.

Fahlke, C., Engel, J., Eriksson, C., Hård, E., and Söderpalm, B. (1994a). Involvement of corticosterone in the modulation of ethanol consumption in the rat. *Alcohol (Fayetteville, NY)*, 11(3):195–202.

Fahlke, C. and Hansen, S. (1999). Effect of local intracerebral corticosterone implants on alcohol intake in the rat. *Alcohol and Alcoholism*, 34(6):851–861.

Fahlke, C., Hansen, S., et al. (1996). Facilitation of ethanol consumption by intracerebroventricular infusions of corticosterone. *Psychopharmacology*, 127(1-2):133–139.

Fahlke, C., Hård, E., Hansen, S., Eriksson, C., and Engel, J. (1995). Consequence of long-term exposure to corticosterone or dexamethasone on ethanol consumption in the adrenalectomized rat, and the effect of type i and type ii corticosteroid receptor antagonists. *Psychopharmacology*, 117(2):216–224.

Fahlke, C., Hård, E., Thomasson, R., Engel, J. A., and Hansen, S. (1994b). Metyrapone-induced suppression of corticosterone synthesis reduces ethanol consumption in high-preferring rats. *Pharmacology Biochemistry and Behavior*, 48(4):977–981.

Fairbairn, C. E. and Sayette, M. A. (2014). A social-attributional analysis of alcohol response. *Psychological bulletin*, 140(5):1361.

Fairchild, G., Hagan, C. C., Walsh, N. D., Passamonti, L., Calder, A. J., and Goodyer, I. M. (2013). Brain structure abnormalities in adolescent girls with conduct disorder. *Journal of Child Psychology and Psychiatry*, 54(1):86–95.

Fairchild, G., Passamonti, L., Hurford, G., Hagan, C. C., von dem Hagen, E. A., van Goozen, S. H., Goodyer, I. M., and Calder, A. J. (2011). Brain structure abnormalities in early-onset and adolescent-onset conduct disorder. *American Journal of Psychiatry*.

Fairchild, G., van Goozen, S., Stollery, S., Brown, J., Gardiner, J., Herbert, J., and Goodyer, I. (2008). Cortisol diurnal rhythm and stress reactivity in male adolescents with early-onset or adolescence-onset conduct disorder. *Biological Psychiatry*, 64(7):599–606.

Fairchild, G., Van Goozen, S. H., Calder, A. J., Stollery, S. J., and Goodyer, I. M. (2009). Deficits in facial expression recognition in male adolescents with early-onset or adolescence-onset conduct disorder. *Journal of Child Psychology and Psychiatry*, 50(5):627–636.

Fanselow, M. S. and Dong, H.-W. (2010). Are the dorsal and ventral hippocampus functionally distinct structures? *Neuron*, 65(1):7–19.

Farley, F. H. (1981). Basic process individual differences: A biologically based theory of individualization for cognitive, affective, and creative outcomes. *Psychology and education: The state of the union*, pages 9–31.

Farmer, R. F., Gau, J. M., Seeley, J. R., Kosty, D. B., Sher, K. J., and Lewinsohn, P. M. (2016). Internalizing and externalizing disorders as predictors of alcohol use disorder onset during three developmental periods. *Drug and alcohol dependence*, 164:38–46.

Fauth-Bühler, M. and Kiefer, F. (2016). Alcohol and the human brain: a systematic review of recent functional neuroimaging and imaging genetics findings. *Current Addiction Reports*, 3(1):109–124.

Fedoroff, I. C. and Taylor, S. (2001). Psychological and pharmacological treatments of social phobia: a meta-analysis. *Journal of clinical psychopharmacology*, 21(3):311–324.

Fedulov, V., Rex, C. S., Simmons, D. A., Palmer, L., Gall, C. M., and Lynch, G. (2007). Evidence that long-term potentiation occurs within individual hippocampal synapses during learning. *The Journal of neuroscience*, 27(30):8031–8039.

Fein, G., Landman, B., Tran, H., McGillivray, S., Finn, P., Barakos, J., and Moon, K. (2006). Brain atrophy in long-term abstinent alcoholics who demonstrate impairment on a simulated gambling task. *Neuroimage*, 32(3):1465–1471.

Feinstein, J. S., Adolphs, R., Damasio, A., and Tranel, D. (2011). The human amygdala and the induction and experience of fear. *Current biology*, 21(1):34–38.

Feinstein, J. S., Buzza, C., Hurlemann, R., Follmer, R. L., Dahdaleh, N. S., Coryell, W. H., Welsh, M. J., Tranel, D., and Wemmie, J. A. (2013). Fear and panic in humans with bilateral amygdala damage. *Nature neuroscience*, 16(3):270–272.

Feldman, L. (1995). Valence focus and arousal focus: Individual differences in the structure of affective experience. *Journal of Personality and Social Psychology*, 69(1):153–166.

Feldman, S. and Conforti, N. (1980). Participation of the dorsal hippocampus in the glucocorticoid feedback effect on adrenocortical activity. *Neuroendocrinology*, 30(1):52–55.

Feldman, S. and Weidenfeld, J. (1993). The dorsal hippocampus modifies the negative feedback effect of glucocorticoids on the adrenocortical and median eminence crf-41 responses to photic stimulation. *Brain research*, 614(1):227–232.

Feldman, S. and Weidenfeld, J. (1999). Glucocorticoid receptor antagonists in the hippocampus modify the negative feedback following neural stimuli. *Brain research*, 821(1):33–37.

Feldman, S. and Weidenfeld, J. (2001). Electrical stimulation of the dorsal hippocampus caused a long lasting inhibition of acth and adrenocortical responses to photic stimuli in freely moving rats. *Brain research*, 911(1):22–26.

Felix-Ortiz, A., Burgos-Robles, A., Bhagat, N., Leppla, C., and Tye, K. (2016). Bidirectional modulation of anxiety-related and social behaviors by amygdala projections to the medial prefrontal cortex. *Neuroscience*, 321:197–209.

Felmingham, K. L., Tran, T. P., Fong, W. C., and Bryant, R. A. (2012). Sex differences in emotional memory consolidation: the effect of stress-induced salivary alpha-amylase and cortisol. *Biological psychology*, 89(3):539–544.

Feng, C., Luo, Y.-J., and Krueger, F. (2015). Neural signatures of fairness-related normative decision making in the ultimatum game: A coordinate-based meta-analysis. *Human brain mapping*, 36(2):591–602.

Feng, X., Wu, X., Morrill, R. J., Li, Z., Li, C., Yang, S., Li, Z., Cui, D., Lv, L., Hu, Z., et al. (2016). Social correlates of the dominance rank and long-term cortisol levels in adolescent and adult male rhesus macaques (macaca mulatta). *Scientific reports*, 6.

Ferguson, M. J. and Bargh, J. A. (2004). Liking is for doing: the effects of goal pursuit on automatic evaluation. *Journal of personality and social psychology*, 87(5):557.

Fernandez, K. C., Jazaieri, H., and Gross, J. J. (2016). Emotion regulation: A transdiagnostic perspective on a new rdoc domain. *Cognitive Therapy and Research*, 40(3):426–440.

Ferri, M., Amato, L., and Davoli, M. (2006). Alcoholics anonymous and other 12-step programmes for alcohol dependence. *The Cochrane Library*.

Fetzner, M. G., Horswill, S. C., Boelen, P. A., and Carleton, R. N. (2013). Intolerance of uncertainty and ptsd symptoms: exploring the construct relationship in a community sample with a heterogeneous trauma history. *Cognitive Therapy and Research*, 37(4):725–734.

Fialko, L., Bolton, D., and Perrin, S. (2012). Applicability of a cognitive model of worry to children and adolescents. *Behaviour research and therapy*, 50(5):341–349.

Fiddick, L. (2011). There is more than the amygdala: potential threat assessment in the cingulate cortex. *Neuroscience & Biobehavioral Reviews*, 35(4):1007–1018.

Field, M. and Cox, W. M. (2008). Attentional bias in addictive behaviors: a review of its development, causes, and consequences. *Drug and alcohol dependence*, 97(1):1–20.

Field, M. and Quigley, M. (2009). Mild stress increases attentional bias in social drinkers who drink to cope: a replication and extension. *Experimental and clinical psychopharmacology*, 17(5):312.

Fillmore, K. M., Hartka, E., Johnstone, B. M., Leino, E. V., Motoyoshi, M., and Temple, M. T. (1991). A meta-analysis of life course variation in drinking. *British journal of addiction*, 86(10):1221–1268.

Fillmore, M., Ostling, E., Martin, C., and Kelly, T. (2009). Acute effects of alcohol on inhibitory control and information processing in high and low sensation-seekers. *Drug and Alcohol Dependence*, 100(1-2):91–99.

Fink, G. R., Marshall, J. C., Shah, N. J., Weiss, P. H., Halligan, P. W., Grosse-Ruyken, M., Ziemons, K., Zilles, K., and Freund, H.-J. (2000). Line bisection judgments implicate right parietal cortex and cerebellum as assessed by fmri. *Neurology*, 54(6):1324–1331.

Fink, G. R., Marshall, J. C., Weiss, P. H., and Zilles, K. (2001). The neural basis of vertical and horizontal line bisection judgments: an fmri study of normal volunteers. *Neuroimage*, 14(1):S59–S67.

Finn, P., Justus, A., Mazas, C., and Steinmetz, J. (1999). Working memory, executive processes and the effects of alcohol on go/no- go learning: Testing a model of behavioral regulation and impulsivity. *Psychopharmacology*, 146(4):465–472.

Finn, P. and Pihl, R. (1987). Men at high risk for alcoholism: The effect of alcohol on cardiovascular response to unavoidable shock. *Journal of Abnormal Psychology*, 96(3):230–236.

Finn, P., Zeitouni, N., and Pihl, R. (1990). Effects of alcohol on psychophysiological hyperreactivity to nonaversive and aversive stimuli in men at high risk for alcoholism. *Journal of Abnormal Psychology*, 99(1):79–85.

Finn, P. R., Earleywine, M., and Pihl, R. O. (1992). Sensation seeking, stress reactivity, and alcohol dampening discriminate the density of a family history of alcoholism. *Alcoholism: Clinical and Experimental Research*, 16(3):585–590.

Finn, P. R. and Hall, J. (2004). Cognitive ability and risk for alcoholism: short-term memory capacity and intelligence moderate personality risk for alcohol problems. *Journal of Abnormal Psychology*, 113(4):569.

Finn, P. R. and Pihl, R. O. (1988). Risk for alcoholism: A comparison between two different groups of sons of alcoholics on cardiovascular reactivity and sensitivity to alcohol. *Alcoholism: Clinical and Experimental Research*, 12(6):742–747.

Fiorillo, C. D., Tobler, P. N., and Schultz, W. (2003). Discrete coding of reward probability and uncertainty by dopamine neurons. *Science*, 299(5614):1898–1902.

First, M., Spitzer, R., Gibbon, M., and Williams, J. (2002). Nonpatient edition (scid-i/np). *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-patient Edition (SCID-I/NP), Biometrics Research, New York State Psychiatric Institute, New York*.

Fishbein, D. H., Ridenour, T. A., Stahl, M., and Sussman, S. (2016a). The full translational spectrum of prevention science: facilitating the transfer of knowledge to practices and policies that prevent behavioral health problems. *Translational behavioral medicine*, 6(1):5–16.

Fishbein, D. H., Rose, E. J., Darcey, V. L., Belcher, A. M., and VanMeter, J. W. (2016b). Neurodevelopmental precursors and consequences of substance use during adolescence: Promises and pitfalls of longitudinal neuroimaging strategies. *Frontiers in Human Neuroscience*, 10.

Flagel, S., Robinson, T., Clark, J., Clinton, S., Watson, S., Seeman, P., Phillips, P., and Akil, H. (2010). An animal model of genetic vulnerability to behavioral disinhibition and responsiveness to reward-related cues: Implications for addiction. *Neuropsychopharmacology*, 35(2):388–400.

Foley, P. and Kirschbaum, C. (2010). Human hypothalamus–pituitary–adrenal axis responses to acute psychosocial stress in laboratory settings. *Neuroscience & Biobehavioral Reviews*, 35(1):91–96.

Fonzo, G., Ramsawh, H., Flagan, T., Simmons, A., Sullivan, S., Allard, C., Paulus, M., and Stein, M. (2016a). Early life stress and the anxious brain: evidence for a neural mechanism linking childhood emotional maltreatment to anxiety in adulthood. *Psychological medicine*, 46(05):1037–1054.

Fonzo, G. A., Huemer, J., and Etkin, A. (2016b). History of childhood maltreatment augments dorsolateral prefrontal processing of emotional valence in ptsd. *Journal of psychiatric research*, 74:45–54.

Fonzo, G. A., Ramsawh, H. J., Flagan, T. M., Sullivan, S. G., Letamendi, A., Simmons, A. N., Paulus, M. P., and Stein, M. B. (2015). Common and disorder-specific neural responses to emotional faces in generalised anxiety, social anxiety and panic disorders. *The British Journal of Psychiatry*, pages bjp–bp.

Fonzo, G. A., Simmons, A. N., Thorp, S. R., Norman, S. B., Paulus, M. P., and Stein, M. B. (2010). Exaggerated and disconnected insular-amygdalar blood oxygenation level-dependent response to threat-related emotional faces in women with intimate-partner violence posttraumatic stress disorder. *Biological psychiatry*, 68(5):433–441.

Ford, M. B. and Collins, N. L. (2010). Self-esteem moderates neuroendocrine and psychological responses to interpersonal rejection. *Journal of personality and social psychology*, 98(3):405.

Forscher, E. C., Zheng, Y., Ke, Z., Folstein, J., and Li, W. (2016). Decomposing fear perception: A combination of psychophysics and neurometric modeling of fear perception. *Neuropsychologia*, 91:254–261.

Forsyth, J. P., Palav, A., and Duff, K. (1999). The absence of relation between anxiety sensitivity and fear conditioning using 20% versus 13% co 2-enriched air as unconditioned stimuli. *Behaviour research and therapy*, 37(2):143–153.

Fortune, E. and Goodie, A. (2010). The relationship between pathological gambling and sensation seeking: The role of subscale scores. *Journal of Gambling Studies*, 26(3):331–346.

Foster, K. T., Hicks, B. M., Iacono, W. G., and McGue, M. (2014). Alcohol use disorder in women: Risks and consequences of an adolescent onset and persistent course. *Psychology of Addictive Behaviors*, 28(2):322.

Fouche, J.-P., Wee, N. J., Roelofs, K., and Stein, D. J. (2013). Recent advances in the brain imaging of social anxiety disorder. *Human Psychopharmacology: Clinical and Experimental*, 28(1):102–105.

Fowles, D. C., Fisher, A. E., and Tranel, D. T. (1982). The heart beats to reward: The effect of monetary incentive on heart rate. *Psychophysiology*, 19(5):506–513.

Fox, A. S., Oler, J. A., Tromp, D. P., Fudge, J. L., and Kalin, N. H. (2015). Extending the amygdala in theories of threat processing. *Trends in neurosciences*, 38(5):319–329.

Fox, E., Derakshan, N., and Shoker, L. (2008). Trait anxiety modulates the electrophysiological indices of rapid spatial orienting towards angry faces. *Neuroreport*, 19(3):259–263.

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., and Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America*, 102(27):9673–9678.

Franken, R. E., Gibson, K. J., and Rowland, G. (1992). Sensation seeking and the tendency to view the world as threatening. *Personality and Individual Differences*, 13(1):31–38.

Franklin, T., Acton, P., Maldjian, J., Gray, J., Croft, J., Dackis, C., O'Brien, C., and Childress, A. (2002). Decreased gray matter concentration in the insular, orbitofrontal, cingulate, and temporal cortices of cocaine patients. *Biological Psychiatry*, 51(2):134–142.

Fransson, P. and Marrelec, G. (2008). The precuneus/posterior cingulate cortex plays a pivotal role in the default mode network: Evidence from a partial correlation network analysis. *Neuroimage*, 42(3):1178–1184.

Fredrikson, M. (2016). Imaging genetics of anxiety disorders. *Neuroimaging Genetics: Principles and Practices*, page 223.

Fredrikson, M. and Faria, V. (2012). Neuroimaging in anxiety disorders. *Modern trends in pharmacopsychiatry*, 29:47–66.

Fredrikson, M., Wik, G., Annas, P., Ericson, K., and Stone-Elander, S. (1995). Functional neuroanatomy of visually elicited simple phobic fear: Additional data and theoretical analysis. *Psychophysiology*, 32(1):43–48.

Fredrikson, M., Wik, G., Greitz, T., Eriksson, L., Stone-Elander, S., Ericson, K., and Sedvall, G. (1993). Regional cerebral blood flow during experimental phobic fear. *Psychophysiology*, 30(1):126–130.

Freese, J. L. and Amaral, D. G. (2009). *Neuroanatomy of the primate amygdala*. na.

Freitas-Ferrari, M., Hallak, J., Trzesniak, C., Filho, A., Machado-de Sousa, J., Chagas, M., Nardi, A., and Crippa, J. (2010). Neuroimaging in social anxiety disorder: A systematic review of the literature. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 34(4):565–580.

Freud, A. (1965). Normality and pathology in children. *The Writings of Anna Freud*.

Frey, B. N., Andreazza, A. C., Nery, F. G., Martins, M. R., Quevedo, J., Soares, J. C., and Kapczinski, F. (2007). The role of hippocampus in the pathophysiology of bipolar disorder. *Behavioural pharmacology*, 18(5-6):419–430.

Friedman, J., Baross, Á., Delaney, A. D., Ally, A., Arbour, L., Asano, J., Bailey, D. K., Barber, S., Birch, P., Brown-John, M., et al. (2006). Oligonucleotide microarray analysis of genomic imbalance in children with mental retardation. *The American Journal of Human Genetics*, 79(3):500–513.

Frijling, J. L., van Zuiden, M., Koch, S. B., Nawijn, L., Veltman, D. J., and Olff, M. (2015). Effects of intranasal oxytocin on amygdala reactivity to emotional faces in recently trauma-exposed individuals. *Social cognitive and affective neuroscience*, page nsv116.

Frith, C. (2009). Role of facial expressions in social interactions. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*, 364(1535):3453–3458.

Frith, U. and Frith, C. (2010). The social brain: allowing humans to boldly go where no other species has been. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*, 365(1537):165–176.

Fuehrlein, B. S., Mota, N., Arias, A. J., Trevisan, L. A., Kachadourian, L. K., Krystal, J. H., Southwick, S. M., and Pietrzak, R. H. (2016). The burden of alcohol use disorders in us military veterans: results from the national health and resilience in veterans study. *Addiction*.

Fukushiro, D. and Frussa-Filho, R. (2011). Chronic amphetamine transforms the emotional significance of a novel but not a familiar environment: Implications for addiction. *International Journal of Neuropsychopharmacology*, 14(7):955–965.

Fulker, D. W., Eysenck, S. B., and Zuckerman, M. (1980). A genetic and environmental analysis of sensation seeking. *Journal of Research in Personality*, 14(2):261–281.

Funkenstein, D. H., King, S. H., and Drolette, M. (1954). The direction of anger during a laboratory stress-inducing situation. *Psychosomatic Medicine*, 16(5):404–413.

Furman, E. (1980). Transference and externalization in latency. *The Psychoanalytic study of the child*, 35:267.

Fusar-Poli, P., Placentino, A., Carletti, F., Landi, P., Allen, P., Surguladze, S., Benedetti, F., Abbamonte, M., Gasparotti, R., Barale, F., et al. (2009). Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. *Journal of psychiatry & neuroscience: JPN*, 34(6):418.

Gaab, J., Rohleder, N., Nater, U., and Ehlert, U. (2005). Psychological determinants of the cortisol stress response: the role of anticipatory cognitive appraisal. *Psychoneuroendocrinology*, 30(6):599–610.

Gabbay, F., Duncan, C., and McDonald, C. (2010). Brain potential indices of novelty processing are associated with preference for amphetamine. *Experimental and Clinical Psychopharmacology*, 18(6):470–488.

Gaffrey, M. S., Barch, D. M., and Luby, J. L. (2016). Amygdala reactivity to sad faces in preschool children: An early neural marker of persistent negative affect. *Developmental cognitive neuroscience*, 17:94–100.

Gallagher, K. E., Lisco, C. G., Parrott, D. J., and Giancola, P. R. (2014). Effects of thought suppression on provoked men's alcohol-related physical aggression in the laboratory. *Psychology of violence*, 4(1):78.

Gallagher, M. and Chiba, A. A. (1996). The amygdala and emotion. *Current opinion in neurobiology*, 6(2):221–227.

Gallagher, M. and Holland, P. (1994). The amygdala complex: Multiple roles in associative learning and attention. *Proceedings of the National Academy of Sciences of the United States of America*, 91(25):11771–11776.

Gallese, V. and Goldman, A. (1998). Mirror neurons and the simulation theory of mind-reading. *Trends in cognitive sciences*, 2(12):493–501.

Galvan, A., Hare, T. A., Parra, C. E., Penn, J., Voss, H., Glover, G., and Casey, B. (2006). Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents. *The Journal of Neuroscience*, 26(25):6885–6892.

Gamer, M., Schmitz, A. K., Tittgemeyer, M., and Schilbach, L. (2013). The human amygdala drives reflexive orienting towards facial features. *Current Biology*, 23(20):R917–R918.

Gan, G., Sterzer, P., Marxen, M., Zimmermann, U. S., and Smolka, M. N. (2015). Neural and behavioral correlates of alcohol-induced aggression under provocation. *Neuropsychopharmacology*.

Ganzel, B. L., Kim, P., Glover, G. H., and Temple, E. (2008). Resilience after 9/11: multimodal neuroimaging evidence for stress-related change in the healthy adult brain. *Neuroimage*, 40(2):788–795.

Gao, Q., Xu, Q., Duan, X., Liao, W., Ding, J., Zhang, Z., Li, Y., Lu, G., and Chen, H. (2013). Extraversion and neuroticism relate to topological properties of resting-state brain networks. *Frontiers in Human Neuroscience*, 7(MAY).

Garfinkel, S. N., Seth, A. K., Barrett, A. B., Suzuki, K., and Critchley, H. D. (2015). Knowing your own heart: distinguishing interoceptive accuracy from interoceptive awareness. *Biological psychology*, 104:65–74.

Garland, M. A., Parsons, O. A., and Nixon, S. J. (1993). Visual-spatial learning in nonalcoholic young adults with and those without a family history of alcoholism. *Journal of studies on alcohol*, 54(2):219–224.

Gartstein, M. A., Bridgett, D. J., Rothbart, M. K., Robertson, C., Iddins, E., Ramsay, K., and Schlect, S. (2010). A latent growth examination of fear development in infancy: Contributions of maternal depression and the risk for toddler anxiety. *Developmental Psychology*, 46(3):651.

Gartstein, M. A. and Rothbart, M. K. (2003). Studying infant temperament via the revised infant behavior questionnaire. *Infant Behavior and Development*, 26(1):64–86.

Gautam, P., Lebel, C., Narr, K. L., Mattson, S. N., May, P. A., Adnams, C. M., Riley, E. P., Jones, K. L., Kan, E. C., and Sowell, E. R. (2015). Volume changes and brain-behavior relationships in white matter and subcortical gray matter in children with prenatal alcohol exposure. *Human brain mapping*.

Gautam, P., Nuñez, S., Narr, K., Mattson, S., May, P., Adnams, C., Riley, E., Jones, K., Kan, E., and Sowell, E. (2014). Developmental trajectories for visuo-spatial attention are altered by prenatal alcohol exposure: A longitudinal fmri study. *Cerebral Cortex*, page bhu162.

Geiger, M. J., Domschke, K., Ipser, J., Hattingh, C., Baldwin, D. S., Lochner, C., and Stein, D. J. (2016). Altered executive control network resting-state connectivity in social anxiety disorder. *The World Journal of Biological Psychiatry*, 17(1):47–57.

Gentes, E. L. and Ruscio, A. M. (2011). A meta-analysis of the relation of intolerance of uncertainty to symptoms of generalized anxiety disorder, major depressive disorder, and obsessive–compulsive disorder. *Clinical Psychology Review*, 31(6):923–933.

Geoffroy, M.-C., Pereira, S. P., Li, L., and Power, C. (2016). Child neglect and maltreatment and childhood-to-adulthood cognition and mental health in a prospective birth cohort. *Journal of the American Academy of Child & Adolescent Psychiatry*, 55(1):33–40.

George, M. S. (2016). Is functional magnetic resonance imaging-inspired electroencephalogram feedback the next new treatment in psychiatry? *Biological Psychiatry*, 80(6):422–423.

George, S., Rogers, R., and Duka, T. (2005). The acute effect of alcohol on decision making in social drinkers. *Psychopharmacology*, 182(1):160–169.

George, W. H. and Stoner, S. A. (2000). Understanding acute alcohol effects on sexual behavior. *Annual review of sex research*, 11(1):92–124.

Gepner, Y., Golan, R., Harman-Boehm, I., Henkin, Y., Schwarzfuchs, D., Shelef, I., Durst, R., Kovsan, J., Bolotin, A., Leitersdorf, E., et al. (2015). Effects of initiating moderate alcohol intake on cardiometabolic risk in adults with type 2 diabetes: a 2-year randomized, controlled trial. *Annals of Internal Medicine*, 163(8):569–579.

Gepner, Y., Henkin, Y., Schwarzfuchs, D., Golan, R., Durst, R., Shelef, I., Harman-Boehm, I., Spitzen, S., Witkow, S., Novack, L., et al. (2016). Differential effect of initiating moderate red wine consumption on 24-h blood pressure by alcohol dehydrogenase genotypes: Randomized trial in type 2 diabetes. *American journal of hypertension*, 29(4):476.

Gerber, H., Borgwardt, S. J., Schmid, O., Gerhard, U., Joechle, W., Riecher-Rössler, A., Wiesbeck, G. A., and Walter, M. (2012). The impact of diacetylmorphine on hypothalamic-pituitary-adrenal axis activity and heroin craving in heroin dependence. *European addiction research*, 18(3):116–123.

Gerra, G., Angioni, L., Zaimovic, A., Moi, G., Bussandri, M., Bertacca, S., Santoro, G., Gardini, S., Caccavari, R., and Nicoli, M. (2004). Substance use among high-school students: Relationships with temperament, personality traits, and parental care perception. *Substance Use and Misuse*, 39(2):345–367.

Gerra, G., Bassignana, S., Zaimovic, A., Moi, G., Bussandri, M., Caccavari, R., Brambilla, F., and Molina, E. (2003). Hypothalamic–pituitary–adrenal axis responses to stress in subjects with 3, 4-methylenedioxy-methamphetamine ('ecstasy') use history: correlation with dopamine receptor sensitivity. *Psychiatry research*, 120(2):115–124.

Gerra, G., Zaimovic, A., Raggi, M. A., Moi, G., Branchi, B., Moroni, M., and Brambilla, F. (2007). Experimentally induced aggressiveness in heroin-dependent patients treated with buprenorphine: comparison of patients receiving methadone and healthy subjects. *Psychiatry research*, 149(1):201–213.

Ghashghaei, H. and Barbas, H. (2002). Pathways for emotion: interactions of prefrontal and anterior temporal pathways in the amygdala of the rhesus monkey. *Neuroscience*, 115(4):1261–1279.

Ghashghaei, H., Hilgetag, C., and Barbas, H. (2007). Sequence of information processing for emotions based on the anatomic dialogue between prefrontal cortex and amygdala. *NeuroImage*, 34(3):905–923.

Gianaros, P. J., Derbtshire, S. W., May, J. C., Siegle, G. J., Gamalo, M. A., and Jennings, J. R. (2005). Anterior cingulate activity correlates with blood pressure during stress. *Psychophysiology*, 42(6):627–635.

Gianaros, P. J., Horenstein, J. A., Cohen, S., Matthews, K. A., Brown, S. M., Flory, J. D., Critchley, H. D., Manuck, S. B., and Hariri, A. R. (2007). Perigenual anterior cingulate morphology covaries with perceived social standing. *Social Cognitive and Affective Neuroscience*.

Giancola, P., Levinson, C., Corman, M., Godlaski, A., Morris, D., Phillips, J., and Holt, J. (2009). Men and women, alcohol and aggression. *Experimental and Clinical Psychopharmacology*, 17(3):154–164.

Giancola, P. and Zeichner, A. (1995). An investigation of gender differences in alcohol-related aggression. *Journal of Studies on Alcohol*, 56(5):573–579.

Giancola, P. R., Helton, E. L., Osborne, A. B., Terry, M. K., Fuss, A. M., and Westerfield, J. A. (2002). The effects of alcohol and provocation on aggressive behavior in men and women. *Journal of studies on alcohol*.

Giedd, J. (2004). Structural magnetic resonance imaging of the adolescent brain. *Annals of the New York Academy of Sciences*, 1021:77–85.

Giedd, J. N. and Denker, A. H. (2015). The adolescent brain: Insights from neuroimaging. In *Brain Crosstalk in Puberty and Adolescence*, pages 85–96. Springer.

Gilam, G. and Hendler, T. (2015). Deconstructing anger in the human brain. *Current Topics in Behavioral Neurosciences*.

Gilbert, S. J., Dumontheil, I., Simons, J. S., Frith, C. D., and Burgess, P. W. (2007). Comment on "wandering minds: the default network and stimulus-independent thought". *Science*, 317(5834):43b–43b.

Gilman, J. M., Ramchandani, V. A., Crouss, T., and Hommer, D. W. (2012a). Subjective and neural responses to intravenous alcohol in young adults with light and heavy drinking patterns. *Neuropsychopharmacology*, 37(2):467–477.

Gilman, J. M., Ramchandani, V. A., Davis, M. B., Bjork, J. M., and Hommer, D. W. (2008). Why we like to drink: a functional magnetic resonance imaging study of the rewarding and anxiolytic effects of alcohol. *The Journal of Neuroscience*, 28(18):4583–4591.

Gilman, J. M., Smith, A. R., Ramchandani, V. A., Momenan, R., and Hommer, D. W. (2012b). The effect of intravenous alcohol on the neural correlates of risky decision making in healthy social drinkers. *Addiction biology*, 17(2):465–478.

Gilmore, A. K. and Bountress, K. E. (2016). Reducing drinking to cope among heavy episodic drinking college women: Secondary outcomes of a web-based combined alcohol use and sexual assault risk reduction intervention. *Addictive behaviors*, 61:104–111.

Gilmore, J. H., Schmitt, J. E., Knickmeyer, R. C., Smith, J. K., Lin, W., Styner, M., Gerig, G., and Neale, M. C. (2010). Genetic and environmental contributions to neonatal brain structure: a twin study. *Human brain mapping*, 31(8):1174–1182.

Gilpin, N. W., Herman, M. A., and Roberto, M. (2015). The central amygdala as an integrative hub for anxiety and alcohol use disorders. *Biological psychiatry*, 77(10):859–869.

Gingnell, M., Frick, A., Engman, J., Alaie, I., Björkstrand, J., Faria, V., Carlbring, P., Andersson, G., Reis, M., Larsson, E.-M., et al. (2016). Combining escitalopram and cognitive–behavioural therapy for social anxiety disorder: randomised controlled fmri trial. *The British Journal of Psychiatry*, 209(3):229–235.

Ginty, A. T. (2013). Blunted responses to stress and reward: Reflections on biological disengagement? *International Journal of Psychophysiology*, 90(1):90–94.

Giorgio, A., Watkins, K., Douaud, G., James, A., James, S., De Stefano, N., Matthews, P., Smith, S., and Johansen-Berg, H. (2008). Changes in white matter microstructure during adolescence. *Neuroimage*, 39(1):52–61.

Gjedde, A., Kumakura, Y., Cumming, P., Linnet, J., and Møller, A. (2010). Inverted-u-shaped correlation between dopamine receptor availability in striatum and sensation seeking. *Proceedings of the National Academy of Sciences of the United States of America*, 107(8):3870–3875.

Glahn, D. C., Lovallo, W. R., and Fox, P. T. (2007). Reduced amygdala activation in young adults at high risk of alcoholism: studies from the oklahoma family health patterns project. *Biological psychiatry*, 61(11):1306–1309.

Goeders, N. E. (2003). The impact of stress on addiction. *European Neuropsychopharmacology*, 13(6):435–441.

Gogtay, N., Giedd, J., Lusk, L., Hayashi, K., Greenstein, D., Vaituzis, A., Nugent III, T., Herman, D., Clasen, L., Toga, A., Rapoport, J., and Thompson, P. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences of the United States of America*, 101(21):8174–8179.

Gold, A. L., Shechner, T., Farber, M. J., Spiro, C. N., Leibenluft, E., Pine, D. S., and Britton, J. C. (2016). Amygdala–cortical connectivity: Associations with anxiety, development, and threat. *Depression and Anxiety*, 33(10):917–926.

Gold, P. and Chrousos, G. (2002). Organization of the stress system and its dysregulation in melancholic and atypical depression: High vs low crh/ne states. *Molecular Psychiatry*, 7(3):254–275.

Goldin, P. R., Manber-Ball, T., Werner, K., Heimberg, R., and Gross, J. J. (2009). Neural mechanisms of cognitive reappraisal of negative self-beliefs in social anxiety disorder. *Biological psychiatry*, 66(12):1091–1099.

Goldin, P. R., McRae, K., Ramel, W., and Gross, J. J. (2008). The neural bases of emotion regulation: Reappraisal and suppression of negative emotion. *BIOL PSYCHIATRY*, 63:577–586.

Goldstein, A. and Flett, G. (2009). Personality, alcohol use, and drinking motives: A comparison of independent and combined internal drinking motives groups. *Behavior Modification*, 33(2):182–198.

Goldstein, R. Z., Bechara, A., Garavan, H., Childress, A. R., Paulus, M. P., Volkow, N. D., et al. (2009). The neurocircuitry of impaired insight in drug addiction. *Trends in cognitive sciences*, 13(9):372–380.

Goldstein, R. Z. and Volkow, N. D. (2002). Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *American Journal of Psychiatry*.

Goldstein, R. Z. and Volkow, N. D. (2011). Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nature Reviews Neuroscience*, 12(11):652–669.

Gomez, P., Ratcliff, R., and Perea, M. (2007). A model of the go/no-go task. *Journal of Experimental Psychology: General*, 136(3):389.

Gonçalves, D. C. and Byrne, G. J. (2012). Interventions for generalized anxiety disorder in older adults: systematic review and meta-analysis. *Journal of anxiety disorders*, 26(1):1–11.

Gonzalez, R., Vassileva, J., Bechara, A., Grbesic, S., Sworowski, L., Novak, R. M., Nunnally, G., and Martin, E. M. (2005). The influence of executive functions, sensation seeking, and hiv serostatus on the risky sexual practices of substance-dependent individuals. *Journal of the International Neuropsychological Society*, 11(02):121–131.

González, R. A., Kallis, C., Ullrich, S., Barnicot, K., Keers, R., and Coid, J. W. (2016). Childhood maltreatment and violence: Mediation through psychiatric morbidity. *Child abuse & neglect*, 52:70–84.

Goodlett, C. R. and Horn, K. H. (2001). Mechanism of alcohol-induced damage to the developing nervous system. *Alcohol Research & Health*, 25(3):175–185.

Goodwin, D. W. (1985). Alcoholism and genetics: The sins of the fathers. *Archives of General Psychiatry*, 42(2):171–174.

Gordon, E. M., Lee, P. S., Maisog, J. M., Foss-Feig, J., Billington, M. E., VanMeter, J., and Vaidya, C. J. (2011). Strength of default mode resting-state connectivity relates to white matter integrity in children. *Developmental science*, 14(4):738–751.

Gordon, H. (2015). Laterality of brain activation for risk factors of addiction. *Current drug abuse reviews*, 9(1):1–18.

Gore, F., Schwartz, E. C., Brangers, B. C., Aladi, S., Stujenske, J. M., Likhtik, E., Russo, M. J., Gordon, J. A., Salzman, C. D., and Axel, R. (2015). Neural representations of unconditioned stimuli in basolateral amygdala mediate innate and learned responses. *Cell*, 162(1):134–145.

Gorka, S., Hee, D., Lieberman, L., Mittal, V., Phan, K., and Shankman, S. (2016a). Reactivity to uncertain threat as a familial vulnerability factor for alcohol use disorder. *Psychological Medicine*, pages 1–10.

Gorka, S. M. (2016). *Effects of Panic Symptoms and Problematic Alcohol Use on Sensitivity to Unpredictable Threat*. PhD thesis, Virginia Commonwealth University.

Gorka, S. M., Fitzgerald, D. A., King, A. C., and Phan, K. L. (2013). Alcohol attenuates amygdala–frontal connectivity during processing social signals in heavy social drinkers. *Psychopharmacology*, 229(1):141–154.

Gorka, S. M., Fitzgerald, D. A., Labuschagne, I., Hosanagar, A., Wood, A. G., Nathan, P. J., and Phan, K. L. (2015). Oxytocin modulation of amygdala functional connectivity to fearful faces in generalized social anxiety disorder. *Neuropsychopharmacology*, 40(2):278–286.

Gorka, S. M., Lieberman, L., Phan, K. L., and Shankman, S. A. (2016b). Association between problematic alcohol use and reactivity to uncertain threat in two independent samples. *Drug and alcohol dependence*, 164:89–96.

Gorka, S. M., Nelson, B. D., Phan, K. L., and Shankman, S. A. (2016c). Intolerance of uncertainty and insula activation during uncertain reward. *Cognitive, Affective, & Behavioral Neuroscience*, pages 1–11.

Gosselin, P., Ladouceur, R., Morin, C. M., Dugas, M. J., and Baillargeon, L. (2006). Benzodiazepine discontinuation among adults with gad: A randomized trial of cognitive-behavioral therapy. *Journal of consulting and clinical psychology*, 74(5):908.

Gottesman, I. and Gould, T. (2003). The endophenotype concept in psychiatry: Etymology and strategic intentions. *American Journal of Psychiatry*, 160(4):636–645.

Gottesman, I. I. and Shields, J. (1972). Schizophrenia and genetics: A twin study vantage point.

Goudriaan, A. E., Grekin, E. R., and Sher, K. J. (2007). Decision making and binge drinking: a longitudinal study. *Alcoholism: Clinical and Experimental Research*, 31(6):928–938.

Gould, R. A., Buckminster, S., Pollack, M. H., and Otto, M. W. (1997). Cognitive-behavioral and pharmacological treatment for social phobia: A meta-analysis. *Clinical Psychology: Science and Practice*, 4(4):291–306.

Goulden, R. (2016). Moderate alcohol consumption is not associated with reduced all-cause mortality. *The American journal of medicine*, 129(2):180–186.

Gourley, S. L., Zimmermann, K. S., Allen, A. G., and Taylor, J. R. (2016). The medial orbitofrontal cortex regulates sensitivity to outcome value. *The Journal of Neuroscience*, 36(16):4600–4613.

Grabner, R. H., Ansari, D., Reishofer, G., Stern, E., Ebner, F., and Neuper, C. (2007). Individual differences in mathematical competence predict parietal brain activation during mental calculation. *Neuroimage*, 38(2):346–356.

Gradin, V. B., Waiter, G., Kumar, P., Stickle, C., Milders, M., Matthews, K., Reid, I., Hall, J., and Steele, J. D. (2012). Abnormal neural responses to social exclusion in schizophrenia. *PloS one*, 7(8):e42608.

Graham, A. M., Buss, C., Rasmussen, J. M., Rudolph, M. D., Demeter, D. V., Gilmore, J. H., Styner, M., Entringer, S., Wadhwa, P. D., and Fair, D. A. (2016). Implications of newborn amygdala connectivity for fear and cognitive development at 6-months-of-age. *Developmental cognitive neuroscience*, 18:12–25.

Grant, B., Dawson, D., Stinson, F., Chou, S., Dufour, M., and Pickering, R. (2004a). The 12-month prevalence and trends in dsm-iv alcohol abuse and dependence: United states, 1991-1992 and 2001-2002. *Drug and Alcohol Dependence*, 74(3):223–234.

Grant, B. F., Goldstein, R. B., Saha, T. D., Chou, S. P., Jung, J., Zhang, H., Pickering, R. P., Ruan, W. J., Smith, S. M., Huang, B., et al. (2015a). Epidemiology of dsm-5 alcohol use disorder: Results from the national epidemiologic survey on alcohol and related conditions iii. *JAMA Psychiatry*.

Grant, B. F. and Harford, T. C. (1995). Comorbidity between dsm-iv alcohol use disorders and major depression: results of a national survey. *Drug and alcohol dependence*, 39(3):197–206.

Grant, B. F., Stinson, F. S., Dawson, D. A., Chou, S. P., Dufour, M. C., Compton, W., Pickering, R. P., and Kaplan, K. (2004b). Prevalence and co-occurrence of substance use disorders and independentmood and anxiety disorders: Results from the national epidemiologic survey on alcohol and relatedconditions. *Archives of general psychiatry*, 61(8):807–816.

Grant, D. M., Beck, J. G., and Davila, J. (2007a). Does anxiety sensitivity predict symptoms of panic, depression, and social anxiety? *Behaviour Research and Therapy*, 45(9):2247–2255.

Grant, M., Wood, K., Sreenivasan, K., Wheelock, M., White, D., Thomas, J., Knight, D., and Deshpande, G. (2015b). Influence of early life stress on intra- and extra-amygdaloid causal connectivity. *Neuropsychopharmacology*.

Grant, M. M., Cannistraci, C., Hollon, S. D., Gore, J., and Shelton, R. (2011). Childhood trauma history differentiates amygdala response to sad faces within mdd. *Journal of psychiatric research*, 45(7):886–895.

Grant, S., London, E. D., Newlin, D. B., Villemagne, V. L., Liu, X., Contoreggi, C., Phillips, R. L., Kimes, A. S., and Margolin, A. (1996). Activation of memory circuits during cue-elicited cocaine craving. *Proceedings of the National Academy of Sciences*, 93(21):12040–12045.

Grant, V. V., Stewart, S. H., and Birch, C. D. (2007b). Impact of positive and anxious mood on implicit alcohol-related cognitions in internally motivated undergraduate drinkers. *Addictive Behaviors*, 32(10):2226–2237.

Gray, J. (1981). A critique of eysenck's theory of personality. *A Model for Personality*, pages 246–276.

Gray, J. (1982). Precis of the neuropsychology of anxiety: An enquiry into the functions of the septo-hippocampal system. *Behav. Brain Sci.*, 5(3):469–534.

Gray, J. (1987a). The neuropsychology of emotion and personality. *Cognitive Neurochemistry*, pages 171–190.

Gray, J. (1987b). The psychology of fear and stress. *The Psychology of Fear and Stress*.

Gray, J. and Jeffrey, A. (1971). *The psychology of fear and stress*. McGraw-Hill, New York.

Gray, J. and McNaughton, N. (2000). Fundamentals of the septo-hippocampal system. *The Neuropsychology of Anxiety: An Enquiry into the Functions of Septo-hippocampal System, 2nd ed. Oxford University Press, Oxford*, pages 204–232.

Gray, J. A. (1975). *Elements of a two-process theory of learning.* Academic Press.

Gray, J. A. and McNaughton, N. (2003). *The neuropsychology of anxiety: An enquiry into the function of the septo-hippocampal system*. Number 33. Oxford university press.

Gray, M. A., Harrison, N. A., Wiens, S., and Critchley, H. D. (2007). Modulation of emotional appraisal by false physiological feedback during fmri. *PLoS one*, 2(6):e546.

Greco, V. and Roger, D. (2001). Coping with uncertainty: The construction and validation of a new measure. *Personality and individual differences*, 31(4):519–534.

Greco, V. and Roger, D. (2003). Uncertainty, stress, and health. *Personality and Individual differences*, 34(6):1057–1068.

Grecucci, A. and Sanfey, A. (2013). Emotion regulation and decision-making. *Handbook of emotion regulation (2nd ed.)*, pages 140–153.

Greeley, J. and Oei, T. (1999). Alcohol and tension reduction. *Psychological theories of drinking and alcoholism*, 2:14–53.

Green, J. G., McLaughlin, K. A., Berglund, P. A., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., and Kessler, R. C. (2010). Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication i: associations with first onset of dsm-iv disorders. *Archives of general psychiatry*, 67(2):113–123.

Greening, S. G. and Mitchell, D. G. (2015). A network of amygdala connections predict individual differences in trait anxiety. *Human brain mapping*, 36(12):4819–4830.

Grefkes, C., Ritzl, A., Zilles, K., and Fink, G. (2004). Human medial intraparietal cortex subserves visuomotor coordinate transformation. *NeuroImage*, 23(4):1494–1506.

Greicius, M., Krasnow, B., Reiss, A., and Menon, V. (2003). Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences of the United States of America*, 100(1):253–258.

Griep, E., Boersma, J., Lentjes, E., A Prins, A., Van Der Korst, J., and De Kloet, E. (1998). Function of the hypothalamic-pituitary-adrenal axis in patients with fibromyalgia and low back pain. *Journal of Rheumatology*, 25(7):1374–1381.

Griffiths, R. R., Johnson, M. W., Richards, W. A., Richards, B. D., McCann, U., and Jesse, R. (2011). Psilocybin occasioned mystical-type experiences: immediate and persisting dose-related effects. *Psychopharmacology*, 218(4):649–665.

Griffiths, R. R., Richards, W. A., Johnson, M. W., McCann, U. D., and Jesse, R. (2008). Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. *Journal of psychopharmacology*.

Grimm, S., Pestke, K., Feeser, M., Aust, S., Weigand, A., Wang, J., Wingenfeld, K., Pruessner, J. C., La Marca, R., Böker, H., et al. (2014). Early life stress modulates oxytocin effects on limbic system during acute psychosocial stress. *Social cognitive and affective neuroscience*, page nsu020.

Grodin, E. N. and Momenan, R. (2016). Decreased subcortical volumes in alcohol dependent individuals: effect of polysubstance use disorder. *Addiction biology*.

Groenewold, N. A., Opmeer, E. M., de Jonge, P., Aleman, A., and Costafreda, S. G. (2013). Emotional valence modulates brain functional abnormalities in depression: evidence from a meta-analysis of fmri studies. *Neuroscience & Biobehavioral Reviews*, 37(2):152–163.

Gross, J. (1998). The emerging field of emotion regulation: An integrative review. *Review of General Psychology*, 2(3):271–299.

Grosse Holtforth, M. (2008). Avoidance motivation in psychological problems and psychotherapy. *Psychotherapy Research*, 18(2):147–159.

Grossman, M. and Wood, W. (1993). Sex differences in intensity of emotional experience: a social role interpretation. *Journal of personality and social psychology*, 65(5):1010.

Gruenewald, T. L., Kemeny, M. E., Aziz, N., and Fahey, J. L. (2004). Acute threat to the social self: Shame, social self-esteem, and cortisol activity. *Psychosomatic medicine*, 66(6):915–924.

Grupe, D. W. and Nitschke, J. B. (2013). Uncertainty and anticipation in anxiety: an integrated neurobiological and psychological perspective. *Nature Reviews Neuroscience*, 14(7):488–501.

Grupe, D. W., Oathes, D. J., and Nitschke, J. B. (2012). Dissecting the anticipation of aversion reveals dissociable neural networks. *Cerebral Cortex*, page bhs175.

Guillory, S. A. and Bujarski, K. A. (2014). Exploring emotions using invasive methods: review of 60 years of human intracranial electrophysiology. *Social cognitive and affective neuroscience*, page nsu002.

Guillot, C., Fanning, J., Bullock, J., Mccloskey, M., and Berman, M. (2010). Effects of alcohol on tests of executive functioning in men and women: A dose response examination. *Experimental and Clinical Psychopharmacology*, 18(5):409–417.

Gulley, J. M. and Juraska, J. M. (2013). The effects of abused drugs on adolescent development of corticolimbic circuitry and behavior. *Neuroscience*, 249:3–20.

Gunnar, M., Larson, M., Hertsgaard, L., Harris, M., and Brodersen, L. (1992). The stressfulness of separation among nine-month-old infants: effects of social context variables and infant temperament. *Child development*, 63(2):290–303.

Gunnar, M., Morison, S., Chisholm, K., and Schuder, M. (2001). Salivary cortisol levels in children adopted from romanian orphanages. *Development and Psychopathology*, 13(3):611–628.

Guo, Y., Zhang, H., Gao, J., Wei, S., Song, C., Sun, P., and Qiao, M. (2015). Study of genes associated with the 'anger-in'and 'anger-out'emotions of humans using a rat model. *Experimental and therapeutic medicine*, 9(4):1448–1454.

Gur, A., Cevik, R., Nas, K., Colpan, L., and Sarac, S. (2004). Cortisol and hypothalamic-pituitary-gonadal axis hormones in follicular-phase women with fibromyalgia and chronic fatigue syndrome and effect of depressive symptoms on these hormones. *Arthritis Res Ther*, 6(3):R232–8.

Gur, R. C., Sara, R., Hagendoorn, M., Marom, O., Hughett, P., Macy, L., Turner, T., Bajcsy, R., Posner, A., and Gur, R. E. (2002). A method for obtaining 3-dimensional facial expressions and its standardization for use in neurocognitive studies. *Journal of neuroscience methods*, 115(2):137–143.

Gusnard, D. (2005). Being a self: Considerations from functional imaging. *Consciousness and Cognition*, 14(4):679–697.

Gusnard, D. and Raichle, M. (2001). Searching for a baseline: Functional imaging and the resting human brain. *Nature Reviews Neuroscience*, 2(10):685–694.

Gutiérrez-García, A. and Calvo, M. G. (2016). Social anxiety and trustworthiness judgments of dynamic facial expressions of emotion. *Journal of behavior therapy and experimental psychiatry*, 52:119–127.

Haas, B., Omura, K., Constable, R., and Canli, T. (2007). Emotional conflict and neuroticism: Personality-dependent activation in the amygdala and subgenual anterior cingulate. *Behavioral Neuroscience*, 121(2):249–256.

Haase, L., Stewart, J. L., Youssef, B., May, A. C., Isakovic, S., Simmons, A. N., Johnson, D. C., Potterat, E. G., and Paulus, M. P. (2016). When the brain does not adequately feel the body: Links between low resilience and interoception. *Biological psychology*, 113:37–45.

Habecker, E. L., Daniels, M. A., Canu, E., Rocca, M. A., Filippi, M., and Renshaw, P. F. (2016). fmri in psychiatric disorders. *fMRI Techniques and Protocols*, pages 657–697.

Haberstick, B. C., Young, S. E., Zeiger, J. S., Lessem, J. M., Hewitt, J. K., and Hopfer, C. J. (2014). Prevalence and correlates of alcohol and cannabis use disorders in the united states: results from the national longitudinal study of adolescent health. *Drug and alcohol dependence*, 136:158–161.

Habib, M., Cassotti, M., Moutier, S., Houdé, O., and Borst, G. (2015). Fear and anger have opposite effects on risk seeking in the gain frame. *Frontiers in psychology*, 6.

Haeny, A. M., Littlefield, A. K., and Sher, K. J. (2016). Limitations of lifetime alcohol use disorder assessments: A criterion-validation study. *Addictive behaviors*, 59:95–99.

Hagman, B. T. and Cohn, A. M. (2013). Using latent variable techniques to understand dsm-iv alcohol use disorder criteria functioning. *American journal of health behavior*, 37(4):565–574.

Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C. J., Wedeen, V. J., and Sporns, O. (2008). Mapping the structural core of human cerebral cortex. *PLoS Biol*, 6(7):e159.

Hagsand, A., Roos-af Hjelmsäter, E., Anders Granhag, P., Fahlke, C., and Söderpalm-Gordh, A. (2013). Do sober eyewitnesses outperform alcohol intoxicated eyewitnesses in a lineup? *The European journal of psychology applied to legal context*, 5(1):23–47.

Hall, J., Trent, S., Thomas, K. L., O'Donovan, M. C., and Owen, M. J. (2015). Genetic risk for schizophrenia: convergence on synaptic pathways involved in plasticity. *Biological psychiatry*, 77(1):52–58.

Hall, W., Degenhardt, L., and Teesson, M. (2009). Reprint of "understanding comorbidity between substance use, anxiety and affective disorders: Broadening the research base". *Addictive behaviors*, 34(10):795–799.

Halpern-Felsher, B. L., Millstein, S. G., and Ellen, J. M. (1996). Relationship of alcohol use and risky sexual behavior: a review and analysis of findings. *Journal of Adolescent Health*, 19(5):331–336.

Ham, L. S., Bacon, A. K., Carrigan, M. H., Zamboanga, B. L., and Casner, H. G. (2016). Social anxiety and alcohol use: The role of alcohol expectancies about social outcomes. *Addiction Research & Theory*, 24(1):9–16.

Ham, L. S., Bonin, M., and Hope, D. A. (2007). The role of drinking motives in social anxiety and alcohol use. *Journal of Anxiety Disorders*, 21(8):991–1003.

Ham, L. S. and Hope, D. A. (2003). College students and problematic drinking: A review of the literature. *Clinical psychology review*, 23(5):719–759.

Hamann, S. and Canli, T. (2004). Individual differences in emotion processing. *Current opinion in neurobiology*, 14(2):233–238.

Hamer, D. (2002). Rethinking behavior genetics. *Science*, 298(5591):71–72.

Hamilton, J. P., Etkin, A., Furman, D. J., Lemus, M. G., Johnson, R. F., and Gotlib, I. H. (2012). Functional neuroimaging of major depressive disorder: a meta-analysis and new integration of baseline activation and neural response data. *American Journal of Psychiatry*.

Hampson, S., Andrews, J., and Barckley, M. (2008). Childhood predictors of adolescent marijuana use: Early sensation-seeking, deviant peer affiliation, and social images. *Addictive Behaviors*, 33(9):1140–1147.

Han, H., Jung, W., Yun, J.-Y., Park, J., Cho, K., Hur, J.-W., Shin, N., Lee, T., and Kwon, J. (2016). Disruption of effective connectivity from the dorsolateral prefrontal cortex to the orbitofrontal cortex by negative emotional distraction in obsessive–compulsive disorder. *Psychological medicine*, 46(05):921–932.

Han, S. and Northoff, G. (2009). Understanding the self: a cultural neuroscience approach. *Progress in brain research*, 178:203–212.

Hankin, B. L., Badanes, L. S., Abela, J. R., and Watamura, S. E. (2010). Hypothalamic–pituitary–adrenal axis dysregulation in dysphoric children and adolescents: Cortisol reactivity to psychosocial stress from preschool through middle adolescence. *Biological psychiatry*, 68(5):484–490.

Hankin, B. L., Kassel, J. D., and Abela, J. R. (2005). Adult attachment dimensions and specificity of emotional distress symptoms: Prospective investigations of cognitive risk and interpersonal stress generation as mediating mechanisms. *Personality and Social Psychology Bulletin*, 31(1):136–151.

Hanlon, C., Dufault, D., Wesley, M., and Porrino, L. (2011). Elevated gray and white matter densities in cocaine abstainers compared to current users. *Psychopharmacology*, 218(4):681–692.

Hannigan, J. H., Chiodo, L. M., Sokol, R. J., Janisse, J., and Delaney-Black, V. (2015). Prenatal alcohol exposure selectively enhances young adult perceived pleasantness of alcohol odors. *Physiology & behavior*.

Hanson, J. D., Larson, M. E., and Snowdon, C. T. (1976). The effects of control over high intensity noise on plasma cortisol levels in rhesus monkeys. *Behavioral Biology*, 16(3):333–340.

Hanson, K. L., Medina, K. L., Nagel, B. J., Spadoni, A. D., Gorlick, A., and Tapert, S. F. (2010). Hippocampal volumes in adolescents with and without a family history of alcoholism. *The American journal of drug and alcohol abuse*, 36(3):161–167.

Harada, S., Agarwal, D., Goedde, H., Tagaki, S., and Ishikawa, B. (1982). Possible protective role against alcoholism for aldehyde dehydrogenase isozyme deficiency in japan. *The Lancet*, 320(8302):827.

Hardee, J. E., Benson, B. E., Bar-Haim, Y., Mogg, K., Bradley, B. P., Chen, G., Britton, J. C., Ernst, M., Fox, N. A., Pine, D. S., et al. (2013). Patterns of neural connectivity during an attention bias task moderate associations between early childhood temperament and internalizing symptoms in young adulthood. *Biological psychiatry*, 74(4):273–279.

Hardee, J. E., Weiland, B. J., Nichols, T. E., Welsh, R. C., Soules, M. E., Steinberg, D. B., Zubieta, J.-K., Zucker, R. A., and Heitzeg, M. M. (2014). Development of impulse control circuitry in children of alcoholics. *Biological psychiatry*, 76(9):708–716.

Harden, P. W. and Pihl, R. O. (1995). Cognitive function, cardiovascular reactivity, and behavior in boys at high risk for alcoholism. *Journal of Abnormal Psychology*, 104(1):94.

Hardie, T. L., Moss, H. B., Vanyukov, M. M., Yao, J. K., and Kirillovac, G. P. (2002). Does adverse family environment or sex matter in the salivary cortisol responses to anticipatory stress? *Psychiatry Research*, 112(2):121–131.

Hare, T., Tottenham, N., Galvan, A., Voss, H., Glover, G., and Casey, B. (2008). Biological substrates of emotional reactivity and regulation in adolescence during an emotional go-nogo task. *Biological Psychiatry*, 63(10):927–934.

Harel, N., Lee, S.-P., Nagaoka, T., Kim, D.-S., and Kim, S.-G. (2002). Origin of negative blood oxygenation level–dependent fmri signals. *Journal of cerebral blood flow & metabolism*, 22(8):908–917.

Harford, T. C., Yi, H.-y., and Grant, B. F. (2013). Other-and self-directed forms of violence and their relationships to dsm-iv substance use and other psychiatric disorders in a national survey of adults. *Comprehensive psychiatry*, 54(7):731–739.

Hariri, A., Tessitore, A., Mattay, V., Fera, F., and Weinberger, D. (2002). The amygdala response to emotional stimuli: A comparison of faces and scenes. *NeuroImage*, 17(1):317–323.

Hariri, A. R. (2009). The neurobiology of individual differences in complex behavioral traits. *Annual review of neuroscience*, 32:225.

Hariri, A. R., Bookheimer, S. Y., and Mazziotta, J. C. (2000). Modulating emotional responses: effects of a neocortical network on the limbic system. *Neuroreport*, 11(1):43–48.

Hariri, A. R., Gorka, A., Hyde, L. W., Kimak, M., Halder, I., Ducci, F., Ferrell, R. E., Goldman, D., and Manuck, S. B. (2009). Divergent effects of genetic variation in endocannabinoid signaling on human threat-and reward-related brain function. *Biological psychiatry*, 66(1):9–16.

Hariri, A. R. and Whalen, P. J. (2011). The amygdala: inside and out. *F1000 biology reports*, 3.

Harkness, K. L., Stewart, J. G., and Wynne-Edwards, K. E. (2011). Cortisol reactivity to social stress in adolescents: role of depression severity and child maltreatment. *Psychoneuroendocrinology*, 36(2):173–181.

Harmon-Jones, E. and Allen, J. J. (1998). Anger and frontal brain activity: Eeg asymmetry consistent with approach motivation despite negative affective valence. *Journal of personality and social psychology*, 74(5):1310.

Harrison, B. J., Fullana, M. A., Soriano-Mas, C., Via, E., Pujol, J., Martínez-Zalacaín, I., Tinoco-Gonzalez, D., Davey, C. G., López-Solà, M., Pérez Sola, V., et al. (2015). A neural mediator of human anxiety sensitivity. *Human brain mapping*, 36(10):3950–3958.

Hart, A. B., Lynch, K. G., Farrer, L., Gelernter, J., and Kranzler, H. R. (2015). Which alcohol use disorder criteria contribute to the association of adh1b with alcohol dependence? *Addiction biology*.

Hartman, C. A., Hermanns, V. W., de Jong, P. J., and Ormel, J. (2013). Self-or parent report of (co-occurring) internalizing and externalizing problems, and basal or reactivity measures of hpa-axis functioning: A systematic evaluation of the internalizing-hyperresponsivity versus externalizing-hyporesponsivity hpa-axis hypothesis. *Biological psychology*, 94(1):175–184.

Hartwigsen, G., Baumgaertner, A., Price, C. J., Koehnke, M., Ulmer, S., and Siebner, H. R. (2010). Phonological decisions require both the left and right supramarginal gyri. *Proceedings of the National Academy of Sciences*, 107(38):16494–16499.

Harvey, A. J., Kneller, W., and Campbell, A. C. (2013). The elusive effects of alcohol intoxication on visual attention and eyewitness memory. *Applied cognitive psychology*, 27(5):617–624.

Hashimoto, E., Tayama, M., Ishikawa, H., Yamamoto, M., and Saito, T. (2015). Influence of comorbid alcohol use disorder on treatment response of depressive patients. *Journal of Neural Transmission*, 122(2):301–306.

Hasin, D. S. and Grant, B. F. (2015). The national epidemiologic survey on alcohol and related conditions (nesarc) waves 1 and 2: review and summary of findings. *Social psychiatry and psychiatric epidemiology*, 50(11):1609–1640.

Hasin, D. S., O'Brien, C. P., Auriacombe, M., Borges, G., Bucholz, K., Budney, A., Compton, W. M., Crowley, T., Ling, W., Petry, N. M., et al. (2013). Dsm-5 criteria for substance use disorders: recommendations and rationale. *American Journal of Psychiatry*.

Hasin, D. S., Stinson, F. S., Ogburn, E., and Grant, B. F. (2007). Prevalence, correlates, disability, and comorbidity of dsm-iv alcohol abuse and dependence in the united states: results from the national epidemiologic survey on alcohol and related conditions. *Archives of general psychiatry*, 64(7):830–842.

Hastings, P. D., Fortier, I., Utendale, W. T., Simard, L. R., and Robaey, P. (2009). Adrenocortical functioning in boys with attention-deficit/hyperactivity disorder: Examining subtypes of adhd and associated comorbid conditions. *Journal of abnormal child psychology*, 37(4):565–578.

Haver, B., Gjestad, R., Lindberg, S., and Franck, J. (2009). Mortality risk up to 5 years after initiation of treatment among 420 swedish women with alcohol addiction. *Addiction*, 104(3):413–419.

Haxby, J. V., Hoffman, E. A., and Gobbini, M. I. (2000). The distributed human neural system for face perception. *Trends in cognitive sciences*, 4(6):223–233.

Haxby, J. V., Hoffman, E. A., and Gobbini, M. I. (2002). Human neural systems for face recognition and social communication. *Biological psychiatry*, 51(1):59–67.

Hearn, C. S., Donovan, C. L., Spence, S. H., and March, S. (2016). A worrying trend in social anxiety: To what degree are worry and its cognitive factors associated with youth social anxiety disorder? *Journal of Affective Disorders*, 208.

Heath, A. and Martin, N. (1992). Genetic differences in psychomotor performance decrement after alcohol: A multivariate analysis. *Journal of Studies on Alcohol*, 53(3):262–271.

Heatherton, T. F. and Wagner, D. D. (2011). Cognitive neuroscience of self-regulation failure. *Trends in cognitive sciences*, 15(3):132–139.

Hebb, D. O. (1955). Drives and the cns (conceptual nervous system). *Psychological review*, 62(4):243.

Heckman, C. J., Egleston, B. L., and Hofmann, M. T. (2010). Efficacy of motivational interviewing for smoking cessation: a systematic review and meta-analysis. *Tobacco control*, 19(5):410–416.

Heeger, D. J. and Ress, D. (2002). What does fmri tell us about neuronal activity? *Nature Reviews Neuroscience*, 3(2):142–151.

Heeren, A., Billieux, J., Philippot, P., De Raedt, R., Baeken, C., de Timary, P., Maurage, P., and Vanderhasselt, M.-A. (2016). Impact of transcranial direct current stimulation on attentional bias for threat: a proof-of-concept study among individuals with social anxiety disorder. *Social Cognitive and Affective Neuroscience*, page nsw119.

Heeren, A. and McNally, R. J. (2016). An integrative network approach to social anxiety disorder: The complex dynamic interplay among attentional bias for threat, attentional control, and symptoms. *Journal of Anxiety Disorders*, 42:95–104.

Hefner, K. R. and Curtin, J. J. (2012). Alcohol stress response dampening: selective reduction of anxiety in the face of uncertain threat. *Journal of psychopharmacology*, 26(2):232–244.

Hefner, K. R., Moberg, C. A., Hachiya, L. Y., and Curtin, J. J. (2013). Alcohol stress response dampening during imminent versus distal, uncertain threat. *Journal of abnormal psychology*, 122(3):756.

Hefner, K. R., Verona, E., Curtin, J., et al. (2016). Emotion regulation during threat: Parsing the time course and consequences of safety signal processing. *Psychophysiology*.

Hegedus, A. M., Alterman, A. I., and Tarter, R. E. (1984). Learning achievement in sons of alcoholics. *Alcoholism: Clinical and Experimental Research*, 8(3):330–333.

Heilbronner, S., Hayden, B. Y., and Platt, M. (2011). Decision salience signals in posterior cingulate cortex. *Frontiers in neuroscience*, 5:55.

Heilbronner, S. R. and Platt, M. L. (2013). Causal evidence of performance monitoring by neurons in posterior cingulate cortex during learning. *Neuron*, 80(6):1384–1391.

Heilig, M. and Leggio, L. (2016). What the alcohol doctor ordered from the neuroscientist: Theragnostic biomarkers for personalized treatments. *Progress in brain research*, 224:401–418.

Heilig, M. and Spanagel, R. (2015). Neurobiology of alcohol use disorder. *The American Psychiatric Publishing Textbook of Substance Abuse Treatment*.

Heim, C., Bradley, B., Mletzko, T., Deveau, T. C., Musselmann, D. L., Nemeroff, C. B., Ressler, K. J., and Binder, E. B. (2009). Effect of childhood trauma on adult depression and neuroendocrine function: sex-specific moderation by crh receptor 1 gene. *Frontiers in behavioral neuroscience*, 3:41.

Heim, C., Ehlert, U., Hanker, J., and Hellhammer, D. (1998). Abuse-related posttraumatic stress disorder and alterations of the hypothalamic-pituitary-adrenal axis in women with chronic pelvic pain. *Psychosomatic Medicine*, 60(3):309–318.

Heim, C. M., Mayberg, H. S., Mletzko, T., Nemeroff, C. B., and Pruessner, J. C. (2013). Decreased cortical representation of genital somatosensory field after childhood sexual abuse. *American Journal of Psychiatry*, 170(6):616–623.

Heinrich, A., Müller, K. U., Banaschewski, T., Barker, G. J., Bokde, A. L., Bromberg, U., Büchel, C., Conrod, P., Fauth-Bühler, M., Papadopoulos, D., et al. (2016). Prediction of alcohol drinking in adolescents: personality-traits, behavior, brain responses, and genetic variations in the context of reward sensitivity. *Biological psychology*, 118:79–87.

Heinrichs, M., Baumgartner, T., Kirschbaum, C., and Ehlert, U. (2003). Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. *Biological psychiatry*, 54(12):1389–1398.

Heinrichs, N. and Hofmann, S. G. (2001). Information processing in social phobia: A critical review. *Clinical psychology review*, 21(5):751–770.

Heinz, A., Beck, A., Grüsser, S., Grace, A., and Wrase, J. (2009). Identifying the neural circuitry of alcohol craving and relapse vulnerability. *Addiction Biology*, 14(1):108–118.

Heinz, A., Schlagenhauf, F., Beck, A., and Wackerhagen, C. (2016). Dimensional psychiatry: mental disorders as dysfunctions of basic learning mechanisms. *Journal of Neural Transmission*, pages 1–13.

Heinz, A. J., Beck, A., Meyer-Lindenberg, A., Sterzer, P., and Heinz, A. (2011). Cognitive and neurobiological mechanisms of alcohol-related aggression. *Nature Reviews Neuroscience*, 12(7):400–413.

Heitzeg, M., Nigg, J., Yau, W.-Y., Zubieta, J.-K., and Zucker, R. (2008). Affective circuitry and risk for alcoholism in late adolescence: Differences in frontostriatal responses between vulnerable and resilient children of alcoholic parents. *Alcoholism: Clinical and Experimental Research*, 32(3):414–426.

Heitzeg, M. M., Cope, L. M., Martz, M. E., and Hardee, J. E. (2015). Neuroimaging risk markers for substance abuse: Recent findings on inhibitory control and reward system functioning. *Current Addiction Reports*, pages 1–13.

Heitzeg, M. M., Nigg, J. T., Hardee, J. E., Soules, M., Steinberg, D., Zubieta, J.-K., and Zucker, R. A. (2014a). Left middle frontal gyrus response to inhibitory errors in children prospectively predicts early problem substance use. *Drug and Alcohol Dependence*, 141:51–57.

Heitzeg, M. M., Nigg, J. T., Yau, W.-Y. W., Zucker, R. A., and Zubieta, J.-K. (2010). Striatal dysfunction marks preexisting risk and medial prefrontal dysfunction is related to problem drinking in children of alcoholics. *Biological psychiatry*, 68(3):287–295.

Heitzeg, M. M., Villafuerte, S., Weiland, B. J., Enoch, M.-A., Burmeister, M., Zubieta, J.-K., and Zucker, R. A. (2014b). Effect of gabra2 genotype on development of incentive-motivation circuitry in a sample enriched for alcoholism risk. *Neuropsychopharmacology*.

Heleniak, C., Jenness, J. L., Vander Stoep, A., McCauley, E., and McLaughlin, K. A. (2016). Childhood maltreatment exposure and disruptions in emotion regulation: A transdiagnostic pathway to adolescent internalizing and externalizing psychopathology. *Cognitive Therapy and Research*, 40(3):394–415.

Helfritz-Sinville, L. E. and Stanford, M. S. (2014). Hostile attribution bias in impulsive and premeditated aggression. *Personality and individual differences*, 56:45–50.

Helfritz-Sinville, L. E. and Stanford, M. S. (2015). Looking for trouble? processing of physical and social threat words in impulsive and premeditated aggression. *The Psychological Record*, 65(2):301–314.

Hellhammer, D. H., Wüst, S., and Kudielka, B. M. (2009). Salivary cortisol as a biomarker in stress research. *Psychoneuroendocrinology*, 34(2):163–171.

Hellhammer, J. and Schubert, M. (2012). The physiological response to trier social stress test relates to subjective measures of stress during but not before or after the test. *Psychoneuroendocrinology*, 37(1):119–124.

Helzer, J., Burnam, A., and McEvoy, L. (1991). Alcohol abuse and dependence. *Psychiatric Disorders in America: The Epidemiologic Catchment Area Study*, pages 81–115.

Henckens, M. J., Klumpers, F., Everaerd, D., Kooijman, S. C., van Wingen, G. A., and Fernández, G. (2016). Interindividual differences in stress sensitivity: basal and stress-induced cortisol levels differentially predict neural vigilance processing under stress. *Social cognitive and affective neuroscience*, 11(4):663–673.

Hendershot, C. S., Wardell, J. D., McPhee, M. D., and Ramchandani, V. A. (2016). A prospective study of genetic factors, human laboratory phenotypes, and heavy drinking in late adolescence. *Addiction biology*.

Hendler, T. and Admon, R. (2016). Predisposing risk factors for ptsd: Brain biomarkers. *Comprehensive Guide to Post-Traumatic Stress Disorders*, pages 61–75.

Hendricks, P. S., Thorne, C. B., Clark, C. B., Coombs, D. W., and Johnson, M. W. (2015). Classic psychedelic use is associated with reduced psychological distress and suicidality in the united states adult population. *Journal of Psychopharmacology*, 29(3):280–288.

Henry, J. P. and Grim, C. E. (1990). Psychosocial mechanisms of primary hypertension. *Journal of hypertension*, 8(9):783–793.

Herman, A. I., Philbeck, J. W., Vasilopoulos, N. L., and Depetrillo, P. B. (2003a). Serotonin transporter promoter polymorphism and differences in alcohol consumption behaviour in a college student population. *Alcohol and Alcoholism*, 38(5):446–449.

Herman, J. (1993). Regulation of adrenocorticosteroid receptor mrna expression in the central nervous system. *Cellular and Molecular Neurobiology*, 13(4):349–372.

Herman, J. and Cullinan, W. (1997). Neurocircuitry of stress: Central control of the hypothalamo-pituitary-adrenocortical axis. *Trends in Neurosciences*, 20(2):78–84.

Herman, J., Cullinan, W., Morano, M., Akil, H., and Watson, S. (1995). Contribution of the ventral subiculum to inhibitory regulation of the hypothalamo-pituitary-adrenocortical axis. *Journal of Neuroendocrinology*, 7(6):475–482.

Herman, J., Figueiredo, H., Mueller, N., Ulrich-Lai, Y., Ostrander, M., Choi, D., and Cullinan, W. (2003b). Central mechanisms of stress integration: Hierarchical circuitry controlling hypothalamo-pituitary-adrenocortical responsiveness. *Frontiers in Neuroendocrinology*, 24(3):151–180.

Herman, J., Patel, P., Akil, H., and Watson, S. (1989a). Localization and regulation of glucocorticoid and mineralocorticoid receptor messenger rnas in the hippocampal formation of the rat. *Molecular Endocrinology*, 3(11):1886–1894.

Herman, J., Schafer, M.-H., Young, E., Thompson, R., Douglass, J., Akil, H., and Watson, S. (1989b). Evidence for hippocampal regulation of neuroendocrine neurons of the hypothalamo-pituitary-adrenocorticoid axis. *Journal of Neuroscience*, 9(9):3072–3082.

Herman, J. P., Chen, K.-C., Booze, R., and Landfield, P. W. (1998). Up-regulation of α 1d ca 2+ channel subunit mrna expression in the hippocampus of aged f344 rats. *Neurobiology of aging*, 19(6):581–587.

Herman, J. P., McKlveen, J. M., Ghosal, S., Kopp, B., Wulsin, A., Makinson, R., Scheimann, J., and Myers, B. (2016). Regulation of the hypothalamic-pituitary-adrenocortical stress response. *Comprehensive Physiology*.

Herman, J. P., Ostrander, M. M., Mueller, N. K., and Figueiredo, H. (2005). Limbic system mechanisms of stress regulation: hypothalamo-pituitary-adrenocortical axis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 29(8):1201–1213.

Hermann, A., Kress, L., and Stark, R. (2016). Neural correlates of immediate and prolonged effects of cognitive reappraisal and distraction on emotional experience. *Brain Imaging and Behavior*, pages 1–11.

Herold, D., Spengler, S., Sajonz, B., Usnich, T., and Bermpohl, F. (2015). Common and distinct networks for self-referential and social stimulus processing in the human brain. *Brain Structure and Function*, pages 1–11.

Herpers, P. C., Scheepers, F. E., Bons, D. M., Buitelaar, J. K., and Rommelse, N. N. (2014). The cognitive and neural correlates of psychopathy and especially callous–unemotional traits in youths: A systematic review of the evidence. *Development and psychopathology*, 26(01):245–273.

Herpertz, S., Dietrich, T., Wenning, B., Krings, T., Erberich, S., Willmes, K., Thron, A., and Sass, H. (2001). Evidence of abnormal amygdala functioning in borderline personality disorder: A functional mri study. *Biological Psychiatry*, 50(4):292–298.

Herrero, N., Gadea, M., Rodríguez-Alarcón, G., Espert, R., and Salvador, A. (2010). What happens when we get angry? hormonal, cardiovascular and asymmetrical brain responses. *Hormones and behavior*, 57(3):276–283.

Herringa, R. J., Burghy, C. A., Stodola, D. E., Fox, M. E., Davidson, R. J., and Essex, M. J. (2016). Enhanced prefrontal-amygdala connectivity following childhood adversity as a protective mechanism against internalizing in adolescence. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*.

Herrington, J. D., Miller, J. S., Pandey, J., and Schultz, R. T. (2016). Anxiety and social deficits have distinct relationships with amygdala function in autism spectrum disorder. *Social cognitive and affective neuroscience*, 11(6):907–914.

Herry, C., Bach, D. R., Esposito, F., Di Salle, F., Perrig, W. J., Scheffler, K., Lüthi, A., and Seifritz, E. (2007). Processing of temporal unpredictability in human and animal amygdala. *The Journal of Neuroscience*, 27(22):5958–5966.

Herting, M. M., Fair, D., and Nagel, B. J. (2011). Altered fronto-cerebellar connectivity in alcohol-naive youth with a family history of alcoholism. *Neuroimage*, 54(4):2582–2589.

Hess, U., Blairy, S., and Kleck, R. E. (1997). The intensity of emotional facial expressions and decoding accuracy. *Journal of Nonverbal Behavior*, 21(4):241–257.

Hesselbrock, V. M. and Hesselbrock, M. N. (1993). Alcoholism and subtypes of antisocial personality disorder. *Alcohol and alcoholism (Oxford, Oxfordshire). Supplement*, 2:479–484.

Hesslinger, B., Van Elst, L. T., Thiel, T., Haegele, K., Hennig, J., and Ebert, D. (2002). Frontoorbital volume reductions in adult patients with attention deficit hyperactivity disorder. *Neuroscience letters*, 328(3):319–321.

Hester, R. K. and Miller, W. R. (1989). *Self-control training.* Pergamon Press.

Het, S., Schoofs, D., Rohleder, N., and Wolf, O. T. (2012). Stress-induced cortisol level elevations are associated with reduced negative affect after stress: indications for a mood-buffering cortisol effect. *Psychosomatic Medicine*, 74(1):23–32.

Het, S. and Wolf, O. T. (2007). Mood changes in response to psychosocial stress in healthy young women: effects of pretreatment with cortisol. *Behavioral neuroscience*, 121(1):11.

Hettema, J., Steele, J., and Miller, W. R. (2005). Motivational interviewing. *Annu. Rev. Clin. Psychol.*, 1:91–111.

Hettema, J. E. and Hendricks, P. S. (2010). Motivational interviewing for smoking cessation: a meta-analytic review. *Journal of consulting and clinical psychology*, 78(6):868.

Heydayati, M., Dugas, M. J., Buhr, K., and Francis, K. (2003). The relationship between intolerance of uncertainty and the interpretation of ambiguous and unambiguous information. In *Poster presented at the Annual Convention of the Association for Advancement of Behaviour Therapy, Boston, MA*.

Heyman, G. M. (2013). Quitting drugs: quantitative and qualitative features. *Annual review of clinical psychology*, 9:29–59.

Hicks, B. M. and Zucker, R. A. (2014). Alcoholism: A life span perspective on etiology and course. In *Handbook of Developmental Psychopathology*, pages 583–599. Springer.

Hidalgo, V., Villada, C., Almela, M., Espín, L., Gómez-Amor, J., and Salvador, A. (2012). Enhancing effects of acute psychosocial stress on priming of non-declarative memory in healthy young adults. *Stress*, 15(3):329–338.

Hikida, T., Morita, M., and Macpherson, T. (2016). Neural mechanisms of the nucleus accumbens circuit in reward and aversive learning. *Neuroscience research*, 108:1–5.

Hill, S., De Bellis, M., Keshavan, M., Lowers, L., Shen, S., Hall, J., and Pitts, T. (2001). Right amygdala volume in adolescent and young adult offspring from families at high risk for developing alcoholism. *Biological Psychiatry*, 49(11):894–905.

Hill, S., Kostelnik, B., Holmes, B., Goradia, D., McDermott, M., Diwadkar, V., and Keshavan, M. (2007a). fmri bold response to the eyes task in offspring from multiplex alcohol dependence families. *Alcoholism: Clinical and Experimental Research*, 31(12):2028–2035.

Hill, S., Muddasani, S., Prasad, K., Nutche, J., Steinhauer, S., Scanlon, J., McDermott, M., and Keshavan, M. (2007b). Cerebellar volume in offspring from multiplex alcohol dependence families. *Biological Psychiatry*, 61(1):41–47.

Hill, S., Wang, S., Carter, H., Tessner, K., Holmes, B., McDermott, M., Zezza, N., and Stiffler, S. (2011). Cerebellum volume in high-risk offspring from multiplex alcohol dependence families: Association with allelic variation in gabra2 and bdnf. *Psychiatry Research - Neuroimaging*, 194(3):304–313.

Hill, S., Wang, S., Kostelnik, B., Carter, H., Holmes, B., McDermott, M., Zezza, N., Stiffler, S., and Keshavan, M. (2009). Disruption of orbitofrontal cortex laterality in offspring from multiplex alcohol dependence families. *Biological Psychiatry*, 65(2):129–136.

Hill, S. Y. and O'Brien, J. (2015). Psychological and neurobiological precursors of alcohol use disorders in high-risk youth. *Current Addiction Reports*, 2(2):104–113.

Hill, S. Y., Shen, S., Lowers, L., Locke-Wellman, J., Matthews, A. G., and McDermott, M. (2008). Psychopathology in offspring from multiplex alcohol dependence families with and without parental alcohol dependence: a prospective study during childhood and adolescence. *Psychiatry Research*, 160(2):155–166.

Hill, S. Y., Tessner, K., Wang, S., Carter, H., and McDermott, M. (2010). Temperament at 5years of age predicts amygdala and orbitofrontal volume in the right hemisphere in adolescence. *Psychiatry Research: Neuroimaging*, 182(1):14–21.

Hill, S. Y., Wang, S., Carter, H., McDermott, M. D., Zezza, N., and Stiffler, S. (2013). Amygdala volume in offspring from multiplex for alcohol dependence families: The moderating influence of childhood environment and 5-httlpr variation. *Journal of alcoholism and drug dependence*.

Himle, J. A. and Hill, E. M. (1991). Alcohol abuse and the anxiety disorders: Evidence from the epidemiologic catchment area survey. *Journal of Anxiety Disorders*, 5(3):237–245.

Hines, L. M., Ray, L., Hutchison, K., and Tabakoff, B. (2005). Alcoholism: the dissection for endophenotypes. *Dialogues Clin Neurosci*, 7(2):153–163.

Hittner, J. and Swickert, R. (2006). Sensation seeking and alcohol use: A meta-analytic review. *Addictive Behaviors*, 31(8):1383–1401.

Hobin, J. A., Goosens, K. A., and Maren, S. (2003). Context-dependent neuronal activity in the lateral amygdala represents fear memories after extinction. *The Journal of neuroscience*, 23(23):8410–8416.

Hodoson, R., Stockwell, T., and Rankin, H. (1979). Can alcohol reduce tension? *Behaviour Research and Therapy*, 17(5):459–466.

Hofer, M. A. (1994). Early relationships as regulators of infant physiology and behavior. *Acta Paediatrica*, 83(s397):9–18.

Hogeveen, J., Bird, G., Chau, A., Krueger, F., and Grafman, J. (2016). Acquired alexithymia following damage to the anterior insula. *Neuropsychologia*, 82:142–148.

Holahan, C., Moos, R., Holahan, C., Cronkite, R., and Randall, P. (2001). Drinking to cope, emotional distress and alcohol use and abuse: A ten-year model. *Journal of Studies on Alcohol*, 62(2):190–198.

Holaway, R. M., Heimberg, R. G., and Coles, M. E. (2006). A comparison of intolerance of uncertainty in analogue obsessive-compulsive disorder and generalized anxiety disorder. *Journal of Anxiety Disorders*, 20(2):158–174.

Holloway, F. A. (1995). Low-dose alcohol effects on human behavior and performance. *Alcohol, Drugs & Driving*.

Holmes, A. J., Hollinshead, M. O., Roffman, J. L., Smoller, J. W., and Buckner, R. L. (2016). Individual differences in cognitive control circuit anatomy link sensation seeking, impulsivity, and substance use. *The Journal of Neuroscience*, 36(14):4038–4049.

Holz, N. E., Boecker, R., Jennen-Steinmetz, C., Buchmann, A. F., Blomeyer, D., Baumeister, S., Plichta, M. M., Esser, G., Schmidt, M., Meyer-Lindenberg, A., et al. (2016). Positive coping styles and acc volume-two related mechanisms for conferring resilience? *Social cognitive and affective neuroscience*, page nsw005.

Holz, N. E., Laucht, M., and Meyer-Lindenberg, A. (2015). Recent advances in understanding the neurobiology of childhood socioeconomic disadvantage. *Current opinion in psychiatry*, 28(5):365–370.

Holzschneider, K. and Mulert, C. (2011). Neuroimaging in anxiety disorders. *Dialogues Clin. Neurosci*, 13(4):453–461.

Homberg, J. R. and Lesch, K.-P. (2011). Looking on the bright side of serotonin transporter gene variation. *Biological psychiatry*, 69(6):513–519.

Hooker, C. I., Verosky, S. C., Miyakawa, A., Knight, R. T., and D'Esposito, M. (2008). The influence of personality on neural mechanisms of observational fear and reward learning. *Neuropsychologia*, 46(11):2709–2724.

Hooks, M., Jones, G., Liem, B., and Justice, J. (1992). Sensitization and individual differences to ip amphetamine, cocaine, or caffeine following repeated intracranial amphetamine infusions. *Pharmacology Biochemistry and Behavior*, 43(3):815–823.

Hooks, M., Jones, G., Smith, A., Neill, D., and Justice, J. (1991a). Individual differences in locomotor activity and sensitization. *Pharmacology Biochemistry and Behavior*, 38(2):467–470.

Hooks, M. S., Jones, G. H., Smith, A. D., Neill, D. B., and Justice, J. B. (1991b). Response to novelty predicts the locomotor and nucleus accumbens dopamine response to cocaine. *Synapse*, 9(2):121–128.

Hooks, M. S., Juncos, J. L., Justice, J. B., Meiergerd, S. M., Povlock, S., Schenk, J., and Kalivas, P. (1994). Individual locomotor response to novelty predicts selective alterations in d1 and d2 receptors and mrnas. *The Journal of neuroscience*, 14(10):6144–6152.

Hopfer, C., Salomonsen-Sautel, S., Mikulich-Gilbertson, S., Min, S.-J., McQueen, M., Crowley, T., Young, S., Corley, R., Sakai, J., Thurstone, C., et al. (2013). Conduct disorder and initiation of substance use: a prospective longitudinal study. *Journal of the American Academy of Child & Adolescent Psychiatry*, 52(5):511–518.

Horstmann, G., Scharlau, I., and Ansorge, U. (2006). More efficient rejection of happy than of angry face distractors in visual search. *Psychonomic Bulletin & Review*, 13(6):1067–1073.

Houck, J. M. and Moyers, T. B. (2015). Within-session communication patterns predict alcohol treatment outcomes. *Drug and alcohol dependence*, 157:205–209.

Houtepen, L. C., Vinkers, C. H., Carrillo-Roa, T., Hiemstra, M., van Lier, P. A., Meeus, W., Branje, S., Heim, C. M., Nemeroff, C. B., Mill, J., et al. (2016). Genome-wide dna methylation levels and altered cortisol stress reactivity following childhood trauma in humans. *Nature Communications*, 7.

Howell, A. N., Buckner, J. D., and Weeks, J. W. (2016a). Fear of positive evaluation and alcohol use problems among college students: the unique impact of drinking motives. *Anxiety, Stress, & Coping*, 29(3):274–286.

Howell, B. R., McMurray, M. S., Guzman, D. B., Nair, G., Shi, Y., McCormack, K. M., Hu, X., Styner, M. A., and Sanchez, M. M. (2016b). Maternal buffering beyond glucocorticoids: impact of early life stress on corticolimbic circuits that control infant responses to novelty. *Social neuroscience*, pages 1–15.

Hoyt, L. T., Zeiders, K. H., Ehrlich, K. B., and Adam, E. K. (2016). Positive upshots of cortisol in everyday life. *Emotion*, 16(4):431.

Hsu, M., Bhatt, M., Adolphs, R., Tranel, D., and Camerer, C. F. (2005). Neural systems responding to degrees of uncertainty in human decision-making. *Science*, 310(5754):1680–1683.

Hu, C., Di, X., Eickhoff, S. B., Zhang, M., Peng, K., Guo, H., and Sui, J. (2016). Distinct and common aspects of physical and psychological self-representation in the brain: A meta-analysis of self-bias in facial and self-referential judgements. *Neuroscience & biobehavioral reviews*, 61:197–207.

Huang, J.-H., Jacobs, D. F., and Derevensky, J. L. (2010). Sexual risk-taking behaviors, gambling, and heavy drinking among us college athletes. *Archives of Sexual Behavior*, 39(3):706–713.

Huang, M.-X., Yurgil, K. A., Robb, A., Angeles, A., Diwakar, M., Risbrough, V. B., Nichols, S. L., McLay, R., Theilmann, R. J., Song, T., et al. (2014). Voxel-wise resting-state meg source magnitude imaging study reveals neurocircuitry abnormality in active-duty service members and veterans with ptsd. *NeuroImage: Clinical*, 5:408–419.

Huebner, T., Vloet, T. D., Marx, I., Konrad, K., Fink, G. R., Herpertz, S. C., and Herpertz-Dahlmann, B. (2008). Morphometric brain abnormalities in boys with conduct disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, 47(5):540–547.

Huettel, S. A. and McCarthy, G. (2001). The effects of single-trial averaging upon the spatial extent of fmri activation. *Neuroreport*, 12(11):2411–2416.

Huh, D., Mun, E.-Y., Larimer, M. E., White, H. R., Ray, A. E., Rhew, I. C., Kim, S.-Y., Jiao, Y., and Atkins, D. C. (2015). Brief motivational interventions for college

student drinking may not be as powerful as we think: An individual participant-level data meta-analysis. *Alcoholism: Clinical and Experimental Research*, 39(5):919–931.

Huhn, M., Tardy, M., Spineli, L. M., Kissling, W., Förstl, H., Pitschel-Walz, G., Leucht, C., Samara, M., Dold, M., Davis, J. M., et al. (2014). Efficacy of pharmacotherapy and psychotherapy for adult psychiatric disorders: a systematic overview of meta-analyses. *JAMA psychiatry*, 71(6):706–715.

Huibregtse, B., Corley, R., Wadsworth, S., Vandever, J., DeFries, J., and Stallings, M. (2016). A longitudinal adoption study of substance use behavior in adolescence. *Twin research and human genetics: the official journal of the International Society for Twin Studies*, pages 1–11.

Hull, J. (1987). Self-awareness model. *Psychological theories of drinking and alcoholism*, pages 272–304.

Hull, J. G. and Bond, C. F. (1986). Social and behavioral consequences of alcohol consumption and expectancy: a meta-analysis. *Psychological bulletin*, 99(3):347.

Hunt, W. A., Barnett, L. W., and Branch, L. G. (1971). Relapse rates in addiction programs. *Journal of clinical psychology*, 27(4):455–456.

Hur, Y.-M. and Bouchard Jr, T. J. (1997). The genetic correlation between impulsivity and sensation seeking traits. *Behavior genetics*, 27(5):455–463.

Hurley, T. and Edenberg, H. (2012). Genes encoding enzymes involved in ethanol metabolism. *Alcohol Res*, 34(3):339–344.

Hussong, A. M., Jones, D. J., Stein, G. L., Baucom, D. H., and Boeding, S. (2011). An internalizing pathway to alcohol use and disorder. *Psychology of Addictive Behaviors*, 25(3):390.

Hutchison, K., Wood, M., and Swift, R. (1999). Personality factors moderate subjective and psychophysiological responses to d-amphetamine in humans. *Experimental and Clinical Psychopharmacology*, 7(4):493–501.

Hwang, S., Nolan, Z., White, S., Williams, W., Sinclair, S., and Blair, R. (2016). Dual neurocircuitry dysfunctions in disruptive behavior disorders: emotional responding and response inhibition. *Psychological medicine*, pages 1–12.

Hyde, L. W., Gorka, A., Manuck, S. B., and Hariri, A. R. (2011). Perceived social support moderates the link between threat-related amygdala reactivity and trait anxiety. *Neuropsychologia*, 49(4):651–656.

Hyman, S. (1995). A man with alcoholism and hiv infection. *Journal of the American Medical Association*, 274(10):837–843.

Hyman, S. E. (2010). The diagnosis of mental disorders: the problem of reification. *Annual Review of Clinical Psychology*, 6:155–179.

Hyman, S. E. and Malenka, R. C. (2001). Addiction and the brain: the neurobiology of compulsion and its persistence. *Nature reviews neuroscience*, 2(10):695–703.

Hyytiä, P. and Koob, G. F. (1995). Gaba a receptor antagonism in the extended amygdala decreases ethanol self-administration in rats. *European journal of pharmacology*, 283(1):151–159.

Iacoboni, M. (2009). Imitation, empathy, and mirror neurons. *Annual Review of Psychology*, 60:653–670.

Iacono, W. G., Malone, S. M., and Vrieze, S. I. (2016). Endophenotype best practices. *International Journal of Psychophysiology*.

Iannetti, G. D. and Mouraux, A. (2010). From the neuromatrix to the pain matrix (and back). *Experimental brain research*, 205(1):1–12.

Iaria, G., Committeri, G., Pastorelli, C., Pizzamiglio, L., Watkins, K. E., and Carota, A. (2008). Neural activity of the anterior insula in emotional processing depends on the individuals' emotional susceptibility. *Human brain mapping*, 29(3):363–373.

ICAP (1998). What is a standard drink? *International Center for Alcohol Policies Reports, Washington, DC*.

Igelström, K. M., Webb, T. W., Kelly, Y. T., and Graziano, M. S. (2016). Topographical organization of attentional, social, and memory processes in the human temporoparietal cortex. *eneuro*, 3(2):ENEURO–0060.

Ilgen, M. A., Price, A. M., Burnett-Zeigler, I., Perron, B., Islam, K., Bohnert, A. S., and Zivin, K. (2011). Longitudinal predictors of addictions treatment utilization in treatment-naïve adults with alcohol use disorders. *Drug and alcohol dependence*, 113(2):215–221.

Ingvar, M. (1999). Pain and functional imaging. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 354(1387):1347–1358.

Insel, T. R. (2010). Rethinking schizophrenia. *Nature*, 468(7321):187–193.

Insel, T. R. and Wang, P. S. (2010). Rethinking mental illness. *Jama*, 303(19):1970–1971.

Ireland, M., Vandongen, R., Davidson, L., Beilin, L., and Rouse, I. (1984). Acute effects of moderate alcohol consumption on blood pressure and plasma catecholamines. *Clinical Science*, 66(6):643–648.

Isler, L., Liu, J. H., Sibley, C. G., and Fletcher, G. J. (2016). Self-regulation and personality profiles: Empirical development, longitudinal stability and predictive ability. *European Journal of Personality*, 30(3):274–287.

Issa, A. M., Rowe, W., Gauthier, S., and Meaney, M. J. (1990). Hypothalamic-pituitary-adrenal activity in aged, cognitively impaired and cognitively unimpaired rats. *The Journal of Neuroscience*, 10(10):3247–3254.

Ito, T., Miller, N., and Pollock, V. (1996). Alcohol and aggression: A meta-analysis on the moderating effects of inhibitory cues, triggering events, and self-focused attention. *Psychological Bulletin*, 122(1):60–82.

Ivanov, I., Liu, X., Shulz, K., Fan, J., London, E., Friston, K., Halperin, J. M., and Newcorn, J. H. (2012). Parental substance abuse and function of the motivation and behavioral inhibition systems in drug-naïve youth. *Psychiatry Research: Neuroimaging*, 201(2):128–135.

Izawa, S., Sugaya, N., Kimura, K., Ogawa, N., Yamada, K. C., Shirotsuki, K., Mikami, I., Hirata, K., Nagano, Y., and Nomura, S. (2013). An increase in salivary interleukin-6 level following acute psychosocial stress and its biological correlates in healthy young adults. *Biological psychology*, 94(2):249–254.

Izquierdo, A., Suda, R. K., and Murray, E. A. (2005). Comparison of the effects of bilateral orbital prefrontal cortex lesions and amygdala lesions on emotional responses in rhesus monkeys. *The Journal of Neuroscience*, 25(37):8534–8542.

Jabbar, S., Chastain, L. G., Gangisetty, O., Cabrera, M. A., Sochacki, K., and Sarkar, D. K. (2016). Preconception alcohol increases offspring vulnerability to stress. *Neuropsychopharmacology*.

Jackson, S. A., Horst, N. K., Pears, A., Robbins, T. W., and Roberts, A. C. (2016). Role of the perigenual anterior cingulate and orbitofrontal cortex in contingency learning in the marmoset. *Cerebral Cortex*, page bhw067.

Jacobson, L. (2005). Hypothalamic–pituitary–adrenocortical axis regulation. *Endocrinology and metabolism clinics of North America*, 34(2):271–292.

Jacobson, L. and Sapolsky, R. (1991). The role of the hippocampus in feedback regulation of the hypothalamic-pituitary-adrenocortical axis*. *Endocrine reviews*, 12(2):118–134.

Jacobus, J., Squeglia, L. M., Bava, S., and Tapert, S. F. (2013). White matter characterization of adolescent binge drinking with and without co-occurring marijuana use: a 3-year investigation. *Psychiatry Research: Neuroimaging*, 214(3):374–381.

Jacobus, J. and Tapert, S. F. (2013). Neurotoxic effects of alcohol in adolescence. *Annual review of clinical psychology*, 9.

Jacobus, J., Thayer, R., Trim, R., Bava, S., Frank, L., and Tapert, S. (2012). White matter integrity, substance use, and risk taking in adolescence. *Psychol Addict Behav*.

Jaffe, J., Babor, T., and Fishbein, D. (1988). Alcoholics, aggression and antisocial personality. *Journal of Studies on Alcohol*, 49(3):211–218.

Jaffee, S. R., Strait, L. B., and Odgers, C. L. (2012). From correlates to causes: can quasi-experimental studies and statistical innovations bring us closer to identifying the causes of antisocial behavior? *Psychological bulletin*, 138(2):272.

Jang, J. H., Jung, W. H., Kang, D.-H., Byun, M. S., Kwon, S. J., Choi, C.-H., and Kwon, J. S. (2011). Increased default mode network connectivity associated with meditation. *Neuroscience letters*, 487(3):358–362.

Jankord, R. and Herman, J. (2008). Limbic regulation of hypothalamo-pituitary-adrenocortical function during acute and chronic stress. *Annals of the New York Academy of Sciences*, 1148:64–73.

Jankowski, K. F. and Takahashi, H. (2014). Cognitive neuroscience of social emotions and implications for psychopathology: Examining embarrassment, guilt, envy, and schadenfreude. *Psychiatry and clinical neurosciences*, 68(5):319–336.

Jansen, A. G., Mous, S. E., White, T., Posthuma, D., and Polderman, T. J. (2015). What twin studies tell us about the heritability of brain development, morphology, and function: A review. *Neuropsychology review*, pages 1–20.

Janssen, I., Krabbendam, L., Bak, M., Hanssen, M., Vollebergh, W., Graaf, R. d., and Os, J. v. (2004). Childhood abuse as a risk factor for psychotic experiences. *Acta Psychiatrica Scandinavica*, 109(1):38–45.

Japee, S., Holiday, K., Satyshur, M. D., Mukai, I., and Ungerleider, L. G. (2015). A role of right middle frontal gyrus in reorienting of attention: a case study. *Frontiers in systems neuroscience*, 9:23.

Jasinski, M. J., Lumley, M. A., Latsch, D. V., Schuster, E., Kinner, E., and Burns, J. W. (2016). Assessing anger expression: Construct validity of three emotion expression-related measures. *Journal of personality assessment*, pages 1–9.

Javidi, H. and Yadollahie, M. (2011). Post-traumatic stress disorder. *The international journal of occupational and environmental medicine*, 3(1 January).

Jazaieri, H., Goldin, P. R., and Gross, J. J. (2016). Treating social anxiety disorder with cbt: Impact on emotion regulation and satisfaction with life. *Cognitive Therapy and Research*, pages 1–11.

Jellinek, E. (1960). Alcoholism, a genus and some of its species. *Canadian Medical Association Journal*, 83(26):1341.

Jensen, C. D., Cushing, C. C., Aylward, B. S., Craig, J. T., Sorell, D. M., and Steele, R. G. (2011). Effectiveness of motivational interviewing interventions for adolescent substance use behavior change: a meta-analytic review. *Journal of consulting and clinical psychology*, 79(4):433.

Jester, J. M., Buu, A., and Zucker, R. A. (2015). Longitudinal phenotypes for alcoholism: Heterogeneity of course, early identifiers, and life course correlates. *Development and psychopathology*, pages 1–16.

Joëls, M. and Baram, T. Z. (2009). The neuro-symphony of stress. *Nature Reviews Neuroscience*, 10(6):459–466.

Joëls, M., Fernandez, G., and Roozendaal, B. (2011). Stress and emotional memory: a matter of timing. *Trends in cognitive sciences*, 15(6):280–288.

Joëls, M., Karst, H., Krugers, H. J., and Lucassen, P. J. (2007). Chronic stress: implications for neuronal morphology, function and neurogenesis. *Frontiers in neuroendocrinology*, 28(2):72–96.

Johansen, P.-Ø. and Krebs, T. S. (2015). Psychedelics not linked to mental health problems or suicidal behavior: A population study. *Journal of Psychopharmacology*, 1:10.

Johanson, A., Gustafson, L., Passant, U., Risberg, J., Smith, G., Warkentin, S., and Tucker, D. (1998). Brain function in spider phobia. *Psychiatry Research - Neuroimaging*, 84(2-3):101–111.

John, O. P. and Gross, J. J. (2004). Healthy and unhealthy emotion regulation: Personality processes, individual differences, and life span development. *Journal of personality*, 72(6):1301–1334.

Johnson, B. A. (2010). Medication treatment of different types of alcoholism. *American Journal of Psychiatry*, 167(6):630–639.

Johnson, D. and Casey, B. (2015). Easy to remember, difficult to forget: The development of fear regulation. *Developmental Cognitive Neuroscience*, 11:42–55.

Joireman, J., Anderson, J., and Strathman, A. (2003). The aggression paradox: understanding links among aggression, sensation seeking, and the consideration of future consequences. *Journal of Personality and social Psychology*, 84(6):1287.

Jolles, D. D., van Buchem, M. A., Crone, E. A., and Rombouts, S. A. (2011). A comprehensive study of whole-brain functional connectivity in children and young adults. *Cerebral Cortex*, 21(2):385–391.

Jonah, B. A., Thiessen, R., and Au-Yeung, E. (2001). Sensation seeking, risky driving and behavioral adaptation. *Accident Analysis & Prevention*, 33(5):679–684.

Jones, A., Laurens, K., Herba, C., Barker, G., and Viding, E. (2009). Amygdala hypoactivity to fearful faces in boys with conduct problems and callous-unemotional traits. *American Journal of Psychiatry*, 166(1):95–102.

Jones, A., McMillan, M., Jones, R., Kowalik, G., Steeden, J., Deanfield, J., Pruessner, J., Taylor, A., and Muthurangu, V. (2012). Adiposity is associated with blunted cardiovascular, neuroendocrine and cognitive responses to acute mental stress. *PLoS ONE*, 7(6).

Jonker, F. A., Jonker, C., Scheltens, P., and Scherder, E. J. (2015). The role of the orbitofrontal cortex in cognition and behavior. *Reviews in the Neurosciences*, 26(1):1–11.

Jónsson, G. (2015). Culture is not your friend: Psychedelic literature of the 20th century and its subversive effect in an industrial world.

Joseph, J., Liu, X., Jiang, Y., Lynam, D., and Kelly, T. (2009). Neural correlates of emotional reactivity in sensation seeking. *Psychological Science*, 20(2):215–223.

Joslyn, G., Ravindranathan, A., Brush, G., Schuckit, M., and White, R. L. (2010). Human variation in alcohol response is influenced by variation in neuronal signaling genes. *Alcoholism: Clinical and Experimental Research*, 34(5):800–812.

Joslyn, G., Wolf, F. W., Brush, G., Wu, L., Schuckit, M., and White, R. L. (2011). Glypican gene gpc5 participates in the behavioral response to ethanol: Evidence from humans, mice, and fruit flies. *G3: Genes, Genomes, Genetics*, 1(7):627–635.

Jung, J., Goldstein, R. B., and Grant, B. F. (2016). Association of respondent psychiatric comorbidity with family history of comorbidity: Results from the national epidemiologic survey on alcohol and related conditions-iii. *Comprehensive Psychiatry*, 71:49–56.

Jünger, E., Gan, G., Mick, I., Seipt, C., Markovic, A., Sommer, C., Plawecki, M. H., O'Connor, S., Smolka, M. N., and Zimmermann, U. S. (2016). Adolescent women induce lower blood alcohol levels than men in a laboratory alcohol self-administration experiment. *Alcoholism: clinical and experimental research*.

Jupp, B. and Dalley, J. W. (2014). Behavioral endophenotypes of drug addiction: etiological insights from neuroimaging studies. *Neuropharmacology*, 76:487–497.

Jurk, S., Kuitunen-Paul, S., Kroemer, N. B., Artiges, E., Banaschewski, T., Bokde, A. L., Büchel, C., Conrod, P., Fauth-Bühler, M., Flor, H., et al. (2015). Personality and substance use: psychometric evaluation and validation of the substance use risk profile scale (surps) in english, irish, french, and german adolescents. *Alcoholism: Clinical and Experimental Research*, 39(11):2234–2248.

Juster, R.-P., Perna, A., Marin, M.-F., Sindi, S., and Lupien, S. J. (2012). Timing is everything: Anticipatory stress dynamics among cortisol and blood pressure reactivity and recovery in healthy adults. *Stress*, 15(6):569–577.

Kadden, R. M., Cooney, N. L., Getter, H., and Litt, M. D. (1989). Matching alcoholics to coping skills or interactional therapies: Posttreatment results. *Journal of Consulting and Clinical Psychology*, 57(6):698.

Kahle, S. S. and Hastings, P. D. (2015). The neurobiology and physiology of emotions: A developmental perspective. *Emerging Trends in the Social and Behavioral Sciences: An Interdisciplinary, Searchable, and Linkable Resource*.

Kahler, C. W., Caswell, A. J., Laws, M. B., Walthers, J., Magill, M., Mastroleo, N. R., Howe, C. J., Souza, T., Wilson, I., Bryant, K., et al. (2016). Using topic coding to understand the nature of change language in a motivational intervention to reduce alcohol and sex risk behaviors in emergency department patients. *Patient education and counseling*.

Kahler, C. W. and Strong, D. R. (2006). A rasch model analysis of dsm-iv alcohol abuse and dependence items in the national epidemiological survey on alcohol and related conditions. *Alcoholism: Clinical and Experimental Research*, 30(7):1165–1175.

Kahneman, D., Slovic, P., and Tversky, A. (1982). Judgment under uncertainty: Heuristics and biases.

Kajantie, E. and Phillips, D. I. (2006). The effects of sex and hormonal status on the physiological response to acute psychosocial stress. *Psychoneuroendocrinology*, 31(2):151–178.

Kaldewaij, R., Koch, S. B., Volman, I., Toni, I., and Roelofs, K. (2016). On the control of social approach–avoidance behavior: Neural and endocrine mechanisms. *Current Topics in Behavioral Neurosciences*.

Kalin, N., Shelton, S., and Davidson, R. (2004). The role of the central nucleus of the amygdala in mediating fear and anxiety in the primate. *Journal of Neuroscience*, 24(24):5506–5515.

Kalin, N. H., Shelton, S. E., Rickman, M., and Davidson, R. J. (1998). Individual differences in freezing and cortisol in infant and mother rhesus monkeys. *Behavioral Neuroscience*, 112(1):251.

Kalisch, R., Wiech, K., Herrmann, K., and Dolan, R. (2006). Neural correlates of self-distraction from anxiety and a process model of cognitive emotion regulation. *Journal of Cognitive Neuroscience*, 18(8):1266–1276.

Kalivas, P. W. and O'Brien, C. (2008). Drug addiction as a pathology of staged neuroplasticity. *Neuropsychopharmacology*, 33(1):166–180.

Kamphausen, S., Philipsen, A., van Elst, L. T., Lieb, K., and Tüscher, O. (2013). Emotional modulation of motor response inhibition in women with borderline personality disorder: an fmri study. *Journal of psychiatry & neuroscience: JPN*, 38(3):164.

Kanat, M., Heinrichs, M., Mader, I., Van Elst, L. T., and Domes, G. (2015). Oxytocin modulates amygdala reactivity to masked fearful eyes. *Neuropsychopharmacology*, 40(11):2632–2638.

Kang, D., Liu, Y., Miskovic, V., Keil, A., and Ding, M. (2016). Large-scale functional brain connectivity during emotional engagement as revealed by beta-series correlation analysis. *Psychophysiology*, 53(11):1627–1638.

Kanske, P., Heissler, J., Schönfelder, S., Bongers, A., and Wessa, M. (2010). How to regulate emotion? neural networks for reappraisal and distraction. *Cerebral Cortex*, page bhq216.

Kant, G. J., Meyerhoff, J. L., and Jarrard, L. E. (1984). Biochemical indices of reactivity and habituation in rats with hippocampal lesions. *Pharmacology Biochemistry and Behavior*, 20(5):793–797.

Kaplan, J. R., Manuck, S. B., Clarkson, T. B., Lusso, F. M., and Taub, D. M. (1982). Social status, environment, and atherosclerosis in cynomolgus monkeys. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 2(5):359–368.

Kaplan, M. S., McFarland, B. H., Huguet, N., Conner, K., Caetano, R., Giesbrecht, N., and Nolte, K. B. (2013). Acute alcohol intoxication and suicide: a gender-stratified analysis of the national violent death reporting system. *Injury prevention*, 19(1):38–43.

Kapp, B., Whalen, P., Supple, W., and Pascoe, J. (1992). Amygdaloid contributions to conditioned arousal and sensory information processing. *The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction*, pages 229–254.

Kapur, S., Craik, F. I., Jones, C., Brown, G. M., Houle, S., and Tulving, E. (1995). Functional role of the prefrontal cortex in retrieval of memories: a pet study. *Neuroreport*, 6(14):1880–1884.

Karatsoreos, I. N. and McEwen, B. S. (2011). Psychobiological allostasis: resistance, resilience and vulnerability. *Trends in cognitive sciences*, 15(12):576–584.

Karl, A., Schaefer, M., Malta, L. S., Dörfel, D., Rohleder, N., and Werner, A. (2006). A meta-analysis of structural brain abnormalities in ptsd. *Neuroscience & Biobehavioral Reviews*, 30(7):1004–1031.

Karnath, H.-O., Ferber, S., and Himmelbach, M. (2001). Spatial awareness is a function of the temporal not the posterior parietal lobe. *Nature*, 411(6840):950–953.

Karoly, H. C., Hagerty, S. L., and Hutchison, K. E. (2014). Developing neurobiological endophenotypes that reflect failure to control alcohol consumption and dependence. *Current Addiction Reports*, 1(1):10–18.

Karpyak, V. M., Biernacka, J. M., Geske, J. R., Abulseoud, O. A., Brunner, M. D., Chauhan, M., Hall-Flavin, D. K., Lewis, K. A., Loukianova, L. L., Melnyk, G. J., et al. (2016). Gender-specific effects of comorbid depression and anxiety on the propensity to drink in negative emotional states. *Addiction*.

Kasanova, Z., Hernaus, D., Vaessen, T., Van Amelsvoort, T., Winz, O., Heinzel, A., Pruessner, J., Mottaghy, F. M., Collip, D., and Myin-Germeys, I. (2016). Early-life stress affects stress-related prefrontal dopamine activity in healthy adults, but not in individuals with psychotic disorder. *PloS one*, 11(3):e0150746.

Kashdan, T. and Steger, M. (2006). Expanding the topography of social anxiety an experience-sampling assessment of positive emotions positive events, and emotion suppression. *Psychological Science*, 17(2):120–128.

Kashdan, T. B., Farmer, A. S., Adams, L. M., Ferssizidis, P., McKnight, P. E., and Nezlek, J. B. (2013). Distinguishing healthy adults from people with social anxiety disorder: Evidence for the value of experiential avoidance and positive emotions in everyday social interactions. *Journal of abnormal psychology*, 122(3):645.

Kashdan, T. B., Goodman, F. R., Machell, K. A., Kleiman, E. M., Monfort, S. S., Ciarrochi, J., and Nezlek, J. B. (2014). A contextual approach to experiential avoidance and social anxiety: Evidence from an experimental interaction and daily interactions of people with social anxiety disorder. *Emotion*, 14(4):769.

Kashdan, T. B. and Roberts, J. E. (2006). Affective outcomes in superficial and intimate interactions: Roles of social anxiety and curiosity. *Journal of Research in Personality*, 40(2):140–167.

Kassel, J. D., Jackson, S. I., and Unrod, M. (2000). Generalized expectancies for negative mood regulation and problem drinking among college students. *Journal of Studies on Alcohol*, 61(2):332–340.

Kawaguchi, A., Nemoto, K., Nakaaki, S., Kawaguchi, T., Kan, H., Arai, N., Shiraishi, N., Hashimoto, N., and Akechi, T. (2016). Insular volume reduction in patients with social anxiety disorder. *Frontiers in psychiatry*, 7.

Kawamoto, T., Ura, M., and Nittono, H. (2015). Intrapersonal and interpersonal processes of social exclusion. *Frontiers in neuroscience*, 9.

Kazén, M., Kuenne, T., Frankenberg, H., and Quirin, M. (2012). Inverse relation between cortisol and anger and their relation to performance and explicit memory. *Biological psychology*, 91(1):28–35.

Keding, T. J. and Herringa, R. J. (2014). Abnormal structure of fear circuitry in pediatric post-traumatic stress disorder. *Neuropsychopharmacology*.

Kelbaek, H., Gjørup, T., Brynjolf, I., Christensen, N. J., and Godtfredsen, J. (1985). Acute effects of alcohol on left ventricular function in healthy subjects at rest and during upright exercise. *The American journal of cardiology*, 55(1):164–167.

Kelleher, K., Chaffin, M., Hollenberg, J., and Fischer, E. (1994). Alcohol and drug disorders among physically abusive and neglectful parents in a community-based sample. *American Journal of Public Health*, 84(10):1586–1590.

Keller, D. L. (2016). Benefits of moderate alcohol consumption not disproven. *The American Journal of Medicine*, 129(8):e149.

Kelley, A., Macrae, C., Wyland, C., Caglar, S., Inati, S., and Heatherton, T. (2002). Finding the self? an event-related fmri study. *Journal of Cognitive Neuroscience*, 14(5):785–794.

Kelley, A. E. (2004). Ventral striatal control of appetitive motivation: role in ingestive behavior and reward-related learning. *Neuroscience & biobehavioral reviews*, 27(8):765–776.

Kelly, A. C., Di Martino, A., Uddin, L. Q., Shehzad, Z., Gee, D. G., Reiss, P. T., Margulies, D. S., Castellanos, F. X., and Milham, M. P. (2009). Development of anterior cingulate functional connectivity from late childhood to early adulthood. *Cerebral Cortex*, 19(3):640–657.

Kelly, C., Toro, R., Di Martino, A., Cox, C. L., Bellec, P., Castellanos, F. X., and Milham, M. P. (2012). A convergent functional architecture of the insula emerges across imaging modalities. *Neuroimage*, 61(4):1129–1142.

Kelly, M. M., Tyrka, A. R., Anderson, G. M., Price, L. H., and Carpenter, L. L. (2008). Sex differences in emotional and physiological responses to the trier social stress test. *Journal of behavior therapy and experimental psychiatry*, 39(1):87–98.

Kelly, O., Matheson, K., Martinez, A., Merali, Z., and Anisman, H. (2007). Psychosocial stress evoked by a virtual audience: relation to neuroendocrine activity. *CyberPsychology & Behavior*, 10(5):655–662.

Kelly, T., Robbins, G., Martin, C., Fillmore, M., Lane, S., Harrington, N., and Rush, C. (2006). Individual differences in drug abuse vulnerability: D-amphetamine and sensation-seeking status. *Psychopharmacology*, 189(1):17–25.

Keltner, D. and Gross, J. J. (1999). Functional accounts of emotions. *Cognition & Emotion*, 13(5):467–480.

Kemeny, M. E. and Schedlowski, M. (2007). Understanding the interaction between psychosocial stress and immune-related diseases: a stepwise progression. *Brain, behavior, and immunity*, 21(8):1009–1018.

Kemeny, M. E. and Shestyuk, A. (2008). Emotions, the neuroendocrine and immune systems, and health. *Handbook of emotions*, pages 661–675.

Kemmis, L., Hall, J., Kingston, R., and Morgan, M. (2007). Impaired fear recognition in regular recreational cocaine users. *Psychopharmacology*, 194(2):151–159.

Kendler, K., Ji, J., Edwards, A., Ohlsson, H., Sundquist, J., and Sundquist, K. (2015a). An extended swedish national adoption study of alcohol use disorder. *JAMA Psychiatry*, 72(3):211–218.

Kendler, K. and Neale, M. (2010). Endophenotype: a conceptual analysis. *Molecular psychiatry*, 15(8):789–797.

Kendler, K., Ohlsson, H., Edwards, A., Lichtenstein, P., Sundquist, K., and Sundquist, J. (2016a). A novel sibling-based design to quantify genetic and shared environmental effects: application to drug abuse, alcohol use disorder and criminal behavior. *Psychological medicine*, 46(8):1639.

Kendler, K., Ohlsson, H., Edwards, A., Sundquist, J., and Sundquist, K. (2016b). A developmental model for alcohol use disorders in swedish men. *Psychological Medicine*, pages 1–12.

Kendler, K. S. (2005a). Toward a philosophical structure for psychiatry. *American Journal of Psychiatry*.

Kendler, K. S. (2005b). "a gene for...": the nature of gene action in psychiatric disorders. *American Journal of Psychiatry*, 162(7):1243–1252.

Kendler, K. S. (2013). What psychiatric genetics has taught us about the nature of psychiatric illness and what is left to learn. *Molecular psychiatry*, 18(10):1058–1066.

Kendler, K. S. (2016). The nature of psychiatric disorders. *World Psychiatry*, 15(1):5–12.

Kendler, K. S., Chen, X., Dick, D., Maes, H., Gillespie, N., Neale, M. C., and Riley, B. (2012). Recent advances in the genetic epidemiology and molecular genetics of substance use disorders. *Nature neuroscience*, 15(2):181–189.

Kendler, K. S., Edwards, A., Myers, J., Cho, S. B., Adkins, A., and Dick, D. (2015b). The predictive power of family history measures of alcohol and drug problems and internalizing disorders in a college population. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 168(5):337–346.

Kendler, K. S., Ohlsson, H., Sundquist, J., and Sundquist, K. (2016c). Alcohol use disorder and mortality across the lifespan: A longitudinal cohort and co-relative analysis. *JAMA psychiatry*, 73(6):575–581.

Kendler, K. S., PirouziFard, M., Lönn, S., Edwards, A. C., Maes, H. H., Lichtenstein, P., Sundquist, J., and Sundquist, K. (2016d). A national swedish twin-sibling study of alcohol use disorders. *Twin Research and Human Genetics*, pages 1–8.

Kendler, K. S., Zachar, P., and Craver, C. (2011). What kinds of things are psychiatric disorders? *Psychological medicine*, 41(06):1143–1150.

Kennis, M., Rademaker, A. R., and Geuze, E. (2013). Neural correlates of personality: an integrative review. *Neuroscience & Biobehavioral Reviews*, 37(1):73–95.

Keough, M., Hines, S., Winslade, A., and O'Connor, R. (2015). Negative urgency and gender moderate the association between anxiety sensitivity and alcohol-related problems. *J Addict Prev*, 3(1):1–7.

Keough, M. T., Battista, S. R., O'Connor, R. M., Sherry, S. B., and Stewart, S. H. (2016). Getting the party started—alone: Solitary predrinking mediates the effect of social anxiety on alcohol-related problems. *Addictive behaviors*, 55:19–24.

Kerridge, B. T., Saha, T. D., Smith, S., Chou, P. S., Pickering, R. P., Huang, B., Ruan, J. W., and Pulay, A. J. (2011). Dimensionality of hallucinogen and inhalant/solvent abuse and dependence criteria: Implications for the diagnostic and statistical manual of mental disorders—fifth edition. *Addictive behaviors*, 36(9):912–918.

Kessels, R. P., Montagne, B., Hendriks, A. W., Perrett, D. I., and Haan, E. H. (2014). Assessment of perception of morphed facial expressions using the emotion recognition task: Normative data from healthy participants aged 8–75. *Journal of neuropsychology*, 8(1):75–93.

Kessler, R., Crum, R., Warner, L., Nelson, C., Schulenberg, J., and Anthony, J. (1997). Lifetime co-occurrence of dsm-iii-r alcohol abuse and dependence with other psychiatric disorders in the national comorbidity survey. *Archives of General Psychiatry*, 54(4):313–321.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., and Walters, E. E. (2005a). Lifetime prevalence and age-of-onset distributions of dsm-iv disorders in the national comorbidity survey replication. *Archives of general psychiatry*, 62(6):593–602.

Kessler, R. C., Chiu, W. T., Demler, O., and Walters, E. E. (2005b). Prevalence, severity, and comorbidity of 12-month dsm-iv disorders in the national comorbidity survey replication. *Archives of general psychiatry*, 62(6):617–627.

Keynan, J. N., Meir-Hasson, Y., Gilam, G., Cohen, A., Jackont, G., Kinreich, S., Ikar, L., Or-Borichev, A., Etkin, A., Gyurak, A., et al. (2016). Limbic activity modulation guided by functional magnetic resonance imaging–inspired electroencephalography improves implicit emotion regulation. *Biological psychiatry*.

Keysers, C. and Gazzola, V. (2007). Integrating simulation and theory of mind: from self to social cognition. *space*, 8:108–114.

Khalili-Mahani, N., Dedovic, K., Engert, V., Pruessner, M., and Pruessner, J. C. (2010). Hippocampal activation during a cognitive task is associated with subsequent neuroendocrine and cognitive responses to psychological stress. *Hippocampus*, 20(2):323–334.

Khalsa, S. S., Feinstein, J. S., Li, W., Feusner, J. D., Adolphs, R., and Hurlemann, R. (2016). Panic anxiety in humans with bilateral amygdala lesions: Pharmacological induction via cardiorespiratory interoceptive pathways. *The Journal of Neuroscience*, 36(12):3559–3566.

Khantzian, E. J. (1997). The self-medication hypothesis of substance use disorders: a reconsideration and recent applications. *Harvard review of psychiatry*, 4(5):231–244.

Khawaja, N. G. and McMahon, J. (2011). The relationship of meta-worry and intolerance of uncertainty with pathological worry, anxiety, and depression. *Behaviour Change*, 28(4):165–180.

Khemiri, L., Kuja-Halkola, R., Larsson, H., and Jayaram-Lindström, N. (2016). Genetic overlap between impulsivity and alcohol dependence: a large-scale national twin study. *Psychological medicine*, 46(05):1091–1102.

Kidwell, K. M., Van Dyk, T. R., Guenther, K. D., and Nelson, T. D. (2016). Anger and children's health: Differentiating role of inward versus outward expressed anger on sleep, medical service utilization, and mental health. *Children's Health Care*, pages 1–17.

Kiecolt-Glaser, J. K., Newton, T., Cacioppo, J. T., MacCallum, R. C., Glaser, R., and Malarkey, W. B. (1996). Marital conflict and endocrine function: are men really more physiologically affected than women? *Journal of Consulting and Clinical Psychology*, 64(2):324.

Kienast, T., Hariri, A. R., Schlagenhauf, F., Wrase, J., Sterzer, P., Buchholz, H. G., Smolka, M. N., Gründer, G., Cumming, P., Kumakura, Y., et al. (2008). Dopamine in amygdala gates limbic processing of aversive stimuli in humans. *Nature neuroscience*, 11(12):1381–1382.

Killgore, W. and Yurgelun-Todd, D. (2005). Social anxiety predicts amygdala activation in adolescents viewing fearful faces. *NeuroReport*, 16(15):1671–1675.

Killgore, W. D., Britton, J. C., Price, L. M., Gold, A. L., Deckersbach, T., and Rauch, S. L. (2011). Neural correlates of anxiety sensitivity during masked presentation of affective faces. *Depression and anxiety*, 28(3):243–249.

Killgore, W. D., Britton, J. C., Schwab, Z. J., Price, L. M., Weiner, M. R., Gold, A. L., Rosso, I. M., Simon, N. M., Pollack, M. H., and Rauch, S. L. (2014). Cortico-limbic responses to masked affective faces across ptsd, panic disorder, and specific phobia. *Depression and anxiety*, 31(2):150–159.

Killgore, W. D. and Yurgelun-Todd, D. A. (2001). Sex differences in amygdala activation during the perception of facial affect. *Neuroreport*, 12(11):2543–2547.

Killgore, W. D. and Yurgelun-Todd, D. A. (2004). Activation of the amygdala and anterior cingulate during nonconscious processing of sad versus happy faces. *Neuroimage*, 21(4):1215–1223.

Kim, E. J., Kyeong, S., Cho, S. W., Chun, J.-W., Park, H.-J., Kim, J., Kim, J., Dolan, R. J., and Kim, J.-J. (2016a). Happier people show greater neural connectivity during negative self-referential processing. *PloS one*, 11(2):e0149554.

Kim, H., Somerville, L. H., Johnstone, T., Alexander, A. L., and Whalen, P. J. (2003). Inverse amygdala and medial prefrontal cortex responses to surprised faces. *Neuroreport*, 14(18):2317–2322.

Kim, H., Somerville, L. H., Johnstone, T., Polis, S., Alexander, A. L., Shin, L. M., and Whalen, P. J. (2004). Contextual modulation of amygdala responsivity to surprised faces. *Journal of Cognitive Neuroscience*, 16(10):1730–1745.

Kim, J. J. and Diamond, D. M. (2002). The stressed hippocampus, synaptic plasticity and lost memories. *Nature Reviews Neuroscience*, 3(6):453–462.

Kim, M. J., Loucks, R. A., Palmer, A. L., Brown, A. C., Solomon, K. M., Marchante, A. N., and Whalen, P. J. (2011a). The structural and functional connectivity of the amygdala: from normal emotion to pathological anxiety. *Behavioural brain research*, 223(2):403–410.

Kim, M. J., Solomon, K. M., Neta, M., Davis, F. C., Oler, J. A., Mazzulla, E. C., and Whalen, P. J. (2016b). A face versus non-face context influences amygdala responses to masked fearful eye whites. *Social cognitive and affective neuroscience*, page nsw110.

Kim, S. and Hamann, S. B. (2007). Neural correlates of positive and negative emotion regulation. *Cognitive Neuroscience, Journal of*, 19(5):776–798.

Kim, S. H. and Hamann, S. (2012). The effect of cognitive reappraisal on physiological reactivity and emotional memory. *International Journal of Psychophysiology*, 83(3):348–356.

Kim, Y.-T., Kwon, D.-H., and Chang, Y. (2011b). Impairments of facial emotion recognition and theory of mind in methamphetamine abusers. *Psychiatry Research*, 186(1):80–84.

Kimbrel, N. A. (2008). A model of the development and maintenance of generalized social phobia. *Clinical Psychology Review*, 28(4):592–612.

Kimbrell, T. A., George, M. S., Parekh, P. I., Ketter, T. A., Podell, D. M., Danielson, A. L., Repella, J. D., Benson, B. E., Willis, M. W., Herscovitch, P., et al. (1999). Regional brain activity during transient self-induced anxiety and anger in healthy adults. *Biological psychiatry*, 46(4):454–465.

King, A. C., De Wit, H., McNamara, P. J., and Cao, D. (2011). Rewarding, stimulant, and sedative alcohol responses and relationship to future binge drinking. *Archives of general psychiatry*, 68(4):389–399.

King, A. C., Hasin, D., O'Connor, S. J., McNamara, P. J., and Cao, D. (2016). A prospective 5-year re-examination of alcohol response in heavy drinkers progressing in alcohol use disorder. *Biological psychiatry*, 79(6):489–498.

King, A. C., Houle, T., Wit, H., Holdstock, L., and Schuster, A. (2002). Biphasic alcohol response differs in heavy versus light drinkers. *Alcoholism: Clinical and Experimental Research*, 26(6):827–835.

Kingham, R. J. (1958). Alcoholism and the reinforcement theory of learning. *Quarterly journal of studies on alcohol*, 19(2):320–330.

Kinner, V. L., Wolf, O. T., and Merz, C. J. (2016). Cortisol alters reward processing in the human brain. *Hormones and behavior*.

Kinomura, S., Larsson, J., Gulyas, B., and Roland, P. E. (1996). Activation by attention of the human reticular formation and thalamic intralaminar nuclei. *Science*, 271(5248):512.

Kircher, T., Arolt, V., Jansen, A., Pyka, M., Reinhardt, I., Kellermann, T., Konrad, C., Lueken, U., Gloster, A., Gerlach, A., Ströhle, A., Wittmann, A., Pfleiderer, B., Wittchen, H.-U., and Straube, B. (2013). Effect of cognitive-behavioral therapy on neural correlates of fear conditioning in panic disorder. *Biological Psychiatry*, 73(1):93–101.

Kircher, T., Brammer, M., Bullmore, E., Simmons, A., Bartels, M., and David, A. (2002). The neural correlates of intentional and incidental self processing. *Neuropsychologia*, 40(6):683–692.

Kirov, G., Grozeva, D., Norton, N., Ivanov, D., Mantripragada, K. K., Holmans, P., Craddock, N., Owen, M. J., O'Donovan, M. C., Consortium, I. S., et al. (2009). Support for the involvement of large copy number variants in the pathogenesis of schizophrenia. *Human molecular genetics*, 18(8):1497–1503.

Kirov, G., Gumus, D., Chen, W., Norton, N., Georgieva, L., Sari, M., O'Donovan, M. C., Erdogan, F., Owen, M. J., Ropers, H.-H., et al. (2008). Comparative genome hybridization suggests a role for nrxn1 and apba2 in schizophrenia. *Human molecular genetics*, 17(3):458–465.

Kirsch, P., Schienle, A., Stark, R., Sammer, G., Blecker, C., Walter, B., Ott, U., Burkart, J., and Vaitl, D. (2003). Anticipation of reward in a nonaversive differential conditioning paradigm and the brain reward system: An event-related fmri study. *NeuroImage*, 20(2):1086–1095.

Kirschbaum, C., Kudielka, B. M., Gaab, J., Schommer, N. C., and Hellhammer, D. H. (1999). Impact of gender, menstrual cycle phase, and oral contraceptives on the activity of the hypothalamus-pituitary-adrenal axis. *Psychosomatic medicine*, 61(2):154–162.

Kirschbaum, C., Pirke, K.-m., and Hellhammer, D. (1995a). Preliminary evidence for reduced cortisol responsivity to psychological stress in women using oral contraceptive medication. *Psychoneuroendocrinology*, 20(5):509–514.

Kirschbaum, C., Pirke, K.-M., and Hellhammer, D. H. (1993). The 'trier social stress test'–a tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology*, 28(1-2):76–81.

Kirschbaum, C., Prussner, J. C., Stone, A. A., Federenko, I., Gaab, J., Lintz, D., Schommer, N., and Hellhammer, D. H. (1995b). Persistent high cortisol responses to repeated psychological stress in a subpopulation of healthy men. *Psychosomatic medicine*, 57(5):468–474.

Kirschbaum, C., Wüst, S., and Hellhammer, D. (1992). Consistent sex differences in cortisol responses to psychological stress. *Psychosomatic medicine*, 54(6):648–657.

Kjaer, T., Nowak, M., and Lou, H. (2002). Reflective self-awareness and conscious states: Pet evidence for a common midline parietofrontal core. *NeuroImage*, 17(2):1080–1086.

Klatsky, A. L., Friedman, G. D., Siegelaub, A. B., and Gérard, M. J. (1977). Alcohol consumption and blood pressure: Kaiser-permanente multiphasic health examination data. *New England Journal of Medicine*, 296(21):1194–1200.

Kleinhans, N. M., Richards, T., Weaver, K., Johnson, L. C., Greenson, J., Dawson, G., and Aylward, E. (2010). Association between amygdala response to emotional faces and social anxiety in autism spectrum disorders. *Neuropsychologia*, 48(12):3665–3670.

Klengel, T., Dias, B. G., and Ressler, K. J. (2015). Models of intergenerational and transgenerational transmission of risk for psychopathology in mice. *Neuropsychopharmacology*.

Klucken, T., Kagerer, S., Schweckendiek, J., Tabbert, K., Vaitl, D., and Stark, R. (2009). Neural, electrodermal and behavioral response patterns in contingency aware and unaware subjects during a picture–picture conditioning paradigm. *Neuroscience*, 158(2):721–731.

Klumpers, F., Morgan, B., Terburg, D., Stein, D. J., and van Honk, J. (2015). Impaired acquisition of classically conditioned fear-potentiated startle reflexes in humans with focal bilateral basolateral amygdala damage. *Social cognitive and affective neuroscience*, 10(9):1161–1168.

Klumpp, H., Fitzgerald, D. A., and Phan, K. L. (2013a). Neural predictors and mechanisms of cognitive behavioral therapy on threat processing in social anxiety disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 45:83–91.

Klumpp, H., Post, D., Angstadt, M., Fitzgerald, D. A., and Phan, K. L. (2013b). Anterior cingulate cortex and insula response during indirect and direct processing of emotional faces in generalized social anxiety disorder. *Biol Mood Anxiety Disord*, 3(1):7.

Klüver, H. and Bucy, P. C. (1937). " psychic blindness" and other symptoms following bilateral temporal lobectomy in rhesus monkeys. *American Journal of Physiology*.

Kneeland, E. T., Nolen-Hoeksema, S., Dovidio, J. F., and Gruber, J. (2016). Emotion malleability beliefs influence the spontaneous regulation of social anxiety. *Cognitive Therapy and Research*, pages 1–14.

Knop, J., Teasdale, T. W., Schulsinger, F., and Goodwin, D. W. (1985). A prospective study of young men at high risk for alcoholism: school behavior and achievement. *Journal of Studies on Alcohol*, 46(4):273–278.

Knutson, B., Adams, C. M., Fong, G. W., and Hommer, D. (2001). Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *J Neurosci*, 21(16):RC159.

Knutson, B. and Greer, S. (2008). Review. anticipatory affect: Neural correlates and consequences for choice. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 363(1511):3771–3786.

Kobayashi, Y. and Amaral, D. (2007). Macaque monkey retrosplenial cortex: Iii. cortical efferents. *Journal of Comparative Neurology*, 502(5):810–833.

Kobayashi, Y. and Amaral, D. G. (2003). Macaque monkey retrosplenial cortex: Ii. cortical afferents. *Journal of Comparative Neurology*, 466(1):48–79.

Koch, S. B., van Zuiden, M., Nawijn, L., Frijling, J. L., Veltman, D. J., and Olff, M. (2015). Intranasal oxytocin administration dampens amygdala reactivity towards emotional faces in male and female ptsd patients. *Neuropsychopharmacology*.

Kochanska, G., Gross, J. N., Lin, M.-H., and Nichols, K. E. (2002). Guilt in young children: Development, determinants, and relations with a broader system of standards. *Child development*, 73(2):461–482.

Kocijan, L. and Harris, L. M. (2016). Fear of positive evaluation and social anxiety. *Behaviour Change*, 33(01):15–26.

Kocovski, N. L. and Endler, N. S. (2000). Social anxiety, self-regulation, and fear of negative evaluation. *European Journal of Personality*, 14(4):347–358.

Koelega, H. (1995). Alcohol and vigilance performance: a review. *Psychopharmacology*, 118(3):233–249.

Koerner, N. and Dugas, M. J. (2006). A cognitive model of generalized anxiety disorder: The role of intolerance of uncertainty. *Worry and its psychological disorders: Theory, assessment and treatment*, pages 201–216.

Kogler, L., Gur, R. C., and Derntl, B. (2015a). Sex differences in cognitive regulation of psychosocial achievement stress: Brain and behavior. *Human brain mapping*, 36(3):1028–1042.

Kogler, L., Müller, V. I., Chang, A., Eickhoff, S. B., Fox, P. T., Gur, R. C., and Derntl, B. (2015b). Psychosocial versus physiological stress—meta-analyses on deactivations and activations of the neural correlates of stress reactions. *NeuroImage*, 119:235–251.

Kogler, L., Müller, V. I., Seidel, E.-M., Boubela, R., Kalcher, K., Moser, E., Habel, U., Gur, R. C., Eickhoff, S. B., and Derntl, B. (2016). Sex differences in the functional connectivity of the amygdalae in association with cortisol. *NeuroImage*, 134:410–423.

Kohler, S. and Hofmann, A. (2015). Can motivational interviewing in emergency care reduce alcohol consumption in young people? a systematic review and meta-analysis. *Alcohol and alcoholism*, 50(2):107–117.

Kohn, N., Eickhoff, S., Scheller, M., Laird, A., Fox, P., and Habel, U. (2014). Neural network of cognitive emotion regulation—an ale meta-analysis and macm analysis. *Neuroimage*, 87:345–355.

Koob, G. and Kreek, M. J. (2007). Stress, dysregulation of drug reward pathways, and the transition to drug dependence. *American Journal of Psychiatry*.

Koob, G. F. (2003). Neuroadaptive mechanisms of addiction: studies on the extended amygdala. *European Neuropsychopharmacology*, 13(6):442–452.

Koob, G. F. (2004). A role for gaba mechanisms in the motivational effects of alcohol. *Biochemical pharmacology*, 68(8):1515–1525.

Koob, G. F. (2013). Negative reinforcement in drug addiction: the darkness within. *Current opinion in neurobiology*, 23(4):559–563.

Koob, G. F. and Le Moal, M. (2006). *Neurobiology of addiction*. Academic Press.

Koob, G. F., Roberts, A. J., Schulteis, G., Parsons, L. H., Heyser, C. J., Hyytiä, P., Merlo-Pich, E., and Weiss, F. (1998). Neurocircuitry targets in ethanol reward and dependence. *Alcoholism: Clinical and Experimental Research*, 22(1):3–9.

Koob, G. F. and Volkow, N. D. (2010). Neurocircuitry of addiction. *Neuropsychopharmacology*, 35(1):217–238.

Koolhaas, J., Bartolomucci, A., Buwalda, B., de Boer, S., Flügge, G., Korte, S., Meerlo, P., Murison, R., Olivier, B., Palanza, P., Richter-Levin, G., Sgoifo, A., Steimer, T., Stiedl, O., van Dijk, G., Wöhr, M., and Fuchs, E. (2011). Stress revisited: A critical evaluation of the stress concept. *Neuroscience and Biobehavioral Reviews*, 35(5):1291–1301.

Koopmans, J. R., Boomsma, D. I., Heath, A. C., and van Doornen, L. J. (1995). A multivariate genetic analysis of sensation seeking. *Behavior genetics*, 25(4):349–356.

Kopin, I. J. (1995). Definitions of stress and sympathetic neuronal responses. *Annals of the New York Academy of Sciences*, 771(1):19–30.

Kowalski-Trakofler, K. M., Vaught, C., and Scharf, T. (2003). Judgment and decision making under stress: an overview for emergency managers. *International Journal of Emergency Management*, 1(3):278–289.

Krabbendam, L. and Van Os, J. (2005). Schizophrenia and urbanicity: a major environmental influence—conditional on genetic risk. *Schizophrenia bulletin*, 31(4):795–799.

Krach, S., Cohrs, J., de Echeverría Loebell, N., Kircher, T., Sommer, J., Jansen, A., and Paulus, F. (2011). Your flaws are my pain: Linking empathy to vicarious embarrassment. *PLoS ONE*, 6(4).

Kraemer, K. M., McLeish, A. C., and O'Bryan, E. M. (2015). The role of intolerance of uncertainty in terms of alcohol use motives among college students. *Addictive behaviors*, 42:162–166.

Kragel, P. A. and LaBar, K. S. (2016). Decoding the nature of emotion in the brain. *Trends in cognitive sciences*, 20(6):444–455.

Kramer, M. D., Krueger, R. F., and Hicks, B. M. (2008). The role of internalizing and externalizing liability factors in accounting for gender differences in the prevalence of common psychopathological syndromes. *Psychological Medicine*, 38(01):51–61.

Krampen, G. (1991). Competence and control questionnaire. *Göttingen: Göttingen*.

Krank, M., Stewart, S. H., O'Connor, R., Woicik, P. B., Wall, A.-M., and Conrod, P. J. (2011). Structural, concurrent, and predictive validity of the substance use risk profile scale in early adolescence. *Addictive behaviors*, 36(1):37–46.

Krebs, R., Schott, B., and Düzel, E. (2009). Personality traits are differentially associated with patterns of reward and novelty processing in the human substantia nigra/ventral tegmental area. *Biological Psychiatry*, 65(2):103–110.

Krebs, T. S. and Johansen, P.-Ø. (2013). Psychedelics and mental health: A population study. *PloS one*, 8(8):e63972.

Kret, M. E., Denollet, J., Grèzes, J., and de Gelder, B. (2011). The role of negative affectivity and social inhibition in perceiving social threat: an fmri study. *Neuropsychologia*, 49(5):1187–1193.

Krettek, J. and Price, J. (1978a). Amygdaloid projections to subcortical structures within the basal forebrain and brainstem in the rat and cat. *Journal of Comparative Neurology*, 178(2):225–253.

Krettek, J. and Price, J. (1978b). A description of the amygdaloid complex in the rat and cat with observations on intra-amygdaloid axonal connections. *Journal of Comparative Neurology*, 178(2):255–279.

Kringelbach, M. L. and Berridge, K. C. (2009). Towards a functional neuroanatomy of pleasure and happiness. *Trends in cognitive sciences*, 13(11):479–487.

Kringelbach, M. L. and Rolls, E. T. (2004). The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. *Progress in neurobiology*, 72(5):341–372.

Krogsrud, S. K., Fjell, A. M., Tamnes, C. K., Grydeland, H., Mork, L., Due-Tønnessen, P., Bjørnerud, A., Sampaio-Baptista, C., Andersson, J., Johansen-Berg, H., et al. (2016). Changes in white matter microstructure in the developing brain—a longitudinal diffusion tensor imaging study of children from 4 to 11years of age. *NeuroImage*, 124:473–486.

Kroll, D. S., Nieva, H. R., Barsky, A. J., and Linder, J. A. (2016). Benzodiazepines are prescribed more frequently to patients already at risk for benzodiazepine-related adverse events in primary care. *Journal of general internal medicine*, pages 1–8.

Krueger, R. F., Markon, K. E., Patrick, C. J., Benning, S. D., and Kramer, M. D. (2007). Linking antisocial behavior, substance use, and personality: an integrative quantitative model of the adult externalizing spectrum. *Journal of abnormal psychology*, 116(4):645.

Krugers, H. J., Lucassen, P., Karst, H., and Joëls, M. (2010). Chronic stress effects on hippocampal structure and synaptic function: relevance for depression and normalization by anti-glucocorticoid treatment. *Frontiers in synaptic neuroscience*, 2:24.

Kruschwitz, J. D., Simmons, A. N., Flagan, T., and Paulus, M. P. (2012). Nothing to lose: processing blindness to potential losses drives thrill and adventure seekers. *Neuroimage*, 59(3):2850–2859.

Kubota, K. and Niki, H. (1971). Prefrontal cortical unit activity and delayed alternation performance in monkeys. *Journal of Neurophysiology*.

Kuckertz, J. M., Strege, M. V., and Amir, N. (2016). Intolerance for approach of ambiguity in social anxiety disorder. *Cognition and Emotion*, pages 1–8.

Kudielka, B., Buske-Kirschbaum, A., Hellhammer, D., and Kirschbaum, C. (2004). Hpa axis responses to laboratory psychosocial stress in healthy elderly adults, younger adults, and children: impact of age and gender. *Psychoneuroendocrinology*, 29(1):83–98.

Kudielka, B. M., Hellhammer, D., and Wüst, S. (2009). Why do we respond so differently? reviewing determinants of human salivary cortisol responses to challenge. *Psychoneuroendocrinology*, 34(1):2–18.

Kudielka, B. M. and Kirschbaum, C. (2005). Sex differences in hpa axis responses to stress: a review. *Biological psychology*, 69(1):113–132.

Kuehn, E., Mueller, K., Lohmann, G., and Schuetz-Bosbach, S. (2016). Interoceptive awareness changes the posterior insula functional connectivity profile. *Brain Structure and Function*, 221(3):1555–1571.

Kühn, S. and Gallinat, J. (2013). Gray matter correlates of posttraumatic stress disorder: a quantitative meta-analysis. *Biological Psychiatry*, 73(1):70–74.

Kuhnen, C. and Knutson, B. (2005). The neural basis of financial risk taking. *Neuron*, 47(5):763–770.

Kuhns, J. B., Exum, M. L., Clodfelter, T. A., and Bottia, M. C. (2014). The prevalence of alcohol-involved homicide offending a meta-analytic review. *Homicide studies*, 18(3):251–270.

Kujawa, A., Swain, J. E., Hanna, G. L., Koschmann, E., Simpson, D., Connolly, S., Fitzgerald, K. D., Monk, C. S., and Phan, K. L. (2015). Prefrontal reactivity to social signals of threat as a predictor of treatment response in anxious youth. *Neuropsychopharmacology*.

Kujawa, A., Wu, M., Klumpp, H., Pine, D. S., Swain, J. E., Fitzgerald, K. D., Monk, C. S., and Phan, K. L. (2016). Altered development of amygdala-anterior cingulate cortex connectivity in anxious youth and young adults. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*.

Kumar, P., Berghorst, L., Nickerson, L., Dutra, S., Goer, F., Greve, D., and Pizzagalli, D. (2014). Differential effects of acute stress on anticipatory and consummatory phases of reward processing. *Neuroscience*, 266:1–12.

Kumar, R. A., KaraMohamed, S., Sudi, J., Conrad, D. F., Brune, C., Badner, J. A., Gilliam, T. C., Nowak, N. J., Cook, E. H., Dobyns, W. B., et al. (2008). Recurrent 16p11. 2 microdeletions in autism. *Human molecular genetics*, 17(4):628–638.

Kumar, S., Porcu, P., Werner, D., Matthews, D., Diaz-Granados, J., Helfand, R., and Morrow, A. (2009). The role of gabaa receptors in the acute and chronic effects of ethanol: A decade of progress. *Psychopharmacology*, 205(4):529–564.

Kumari, V., Das, M., Wilson, G. D., Goswami, S., Sharma, T., et al. (2007). Neuroticism and brain responses to anticipatory fear. *Behavioral neuroscience*, 121(4):643.

Kumsta, R., Entringer, S., Koper, J. W., van Rossum, E. F., Hellhammer, D. H., and Wüst, S. (2007). Sex specific associations between common glucocorticoid receptor gene variants and hypothalamus-pituitary-adrenal axis responses to psychosocial stress. *Biological Psychiatry*, 62(8):863–869.

Kuntsche, E., Knibbe, R., Gmel, G., and Engels, R. (2005). Why do young people drink? a review of drinking motives. *Clinical psychology review*, 25(7):841–861.

Kuntsche, E., Knibbe, R., Gmel, G., and Engels, R. (2006). Who drinks and why? a review of socio-demographic, personality, and contextual issues behind the drinking motives in young people. *Addictive Behaviors*, 31(10):1844–1857.

Kuntsche, E., Stewart, S., and Cooper, M. (2008). How stable is the motive - alcohol use link? a cross-national validation of the drinking motives questionnaire revised among adolescents from switzerland, canada and the united states. *Journal of Studies on Alcohol and Drugs*, 69(3):388–396.

Kuramoto, S. J. and Wilcox, H. C. (2016). Substance use disorders and intentional injury. In *The Oxford Handbook of Substance Use and Substance Use Disorders, Volume 2*.

Kushner, M., Mackenzie, T., Fiszdon, J., Valentiner, D., Foa, E., Anderson, N., and Wangensteen, D. (1996). The effects of alcohol consumption on laboratory-induced panic and state anxiety. *Archives of General Psychiatry*, 53(3):264–270.

Kushner, M. G., Abrams, K., and Borchardt, C. (2000). The relationship between anxiety disorders and alcohol use disorders: a review of major perspectives and findings. *Clinical psychology review*, 20(2):149–171.

Kushner, M. G., Maurer, E. W., Thuras, P., Donahue, C., Frye, B., Menary, K. R., Hobbs, J., Haeny, A. M., and Van Demark, J. (2013). Hybrid cognitive behavioral therapy versus relaxation training for co-occurring anxiety and alcohol disorder: A randomized clinical trial. *Journal of consulting and clinical psychology*, 81(3):429.

Kushner, M. G., Sher, K. J., and Beitman, B. D. (1990). The relation between alcohol problems and the anxiety disorders. *American Journal of Psychiatry*, 147(6):685–695.

Kushner, M. G., Thuras, P., Abrams, K., Brekke, M., and Stritar, L. (2001). Anxiety mediates the association between anxiety sensitivity and coping-related drinking motives in alcoholism treatment patients. *Addictive Behaviors*, 26(6):869–885.

Laakso, A., Pohjalainen, T., Bergman, J., Kajander, J., Haaparanta, M., Solin, O., Syvälahti, E., and Hietala, J. (2005). The a1 allele of the human d2 dopamine receptor gene is associated with increased activity of striatal l-amino acid decarboxylase in healthy subjects. *Pharmacogenetics and Genomics*, 15(6):387–391.

LaBar, K. S., Gatenby, J. C., Gore, J. C., LeDoux, J. E., and Phelps, E. A. (1998). Human amygdala activation during conditioned fear acquisition and extinction: a mixed-trial fmri study. *Neuron*, 20(5):937–945.

Labonté, B., Suderman, M., Maussion, G., Navaro, L., Yerko, V., Mahar, I., Bureau, A., Mechawar, N., Szyf, M., Meaney, M. J., et al. (2012). Genome-wide epigenetic regulation by early-life trauma. *Archives of general psychiatry*, 69(7):722–731.

LaBrie, J. W., Huchting, K., Tawalbeh, S., Pedersen, E. R., Thompson, A. D., Shelesky, K., Larimer, M., and Neighbors, C. (2008). A randomized motivational enhancement prevention group reduces drinking and alcohol consequences in first-year college women. *Psychology of Addictive Behaviors*, 22(1):149.

Lader, M. (2014). Benzodiazepine harm: how can it be reduced? *British journal of clinical pharmacology*, 77(2):295–301.

Ladouceur, R., Dugas, M. J., Freeston, M. H., Léger, E., Gagnon, F., and Thibodeau, N. (2000). Efficacy of a cognitive–behavioral treatment for generalized anxiety disorder: Evaluation in a controlled clinical trial. *Journal of consulting and clinical psychology*, 68(6):957.

Lahey, B. B. (2009). Public health significance of neuroticism. *American Psychologist*, 64(4):241.

Lai, H. M. X., Cleary, M., Sitharthan, T., and Hunt, G. E. (2015). Prevalence of comorbid substance use, anxiety and mood disorders in epidemiological surveys, 1990–2014: a systematic review and meta-analysis. *Drug and alcohol dependence*, 154:1–13.

Lamberts, S. and Rossum, E. (2004). Polymorphisms in the glucocorticoid receptor gene and their associations with metabolic parameters and body composition. *Recent Progress in Hormone Research*.

Lamblin, F. and De Witte, P. (1996). Adrenalectomy prevents the development of alcohol preference in male rats. *Alcohol*, 13(3):233–238.

Landers, M. S. and Sullivan, R. M. (2012). The development and neurobiology of infant attachment and fear. *Developmental neuroscience*, 34(2-3):101–114.

Lane, S. and Sher, K. (2015). Severity of dsm and criteria: consistency across studies is only "skim deep". In *Alcoholism-Clinical and experimental research*, volume 39, pages 303A–303A.

Lane, S., Steinley, D., and Sher, K. (2016). Meta-analysis of dsm alcohol use disorder criteria severities: structural consistency is only'skin deep'. *Psychological medicine*, 46(8):1769.

Lane, S. D., Cherek, D. R., Pietras, C. J., and Tcheremissine, O. V. (2004). Alcohol effects on human risk taking. *Psychopharmacology*, 172(1):68–77.

Lang, A., Shin, M., and Lee, S. (2005). Sensation seeking, motivation, and substance use: A dual system approach. *Media Psychology*, 7(1):1–29.

Laposa, J. M. and Rector, N. A. (2016). Can i really do this? an examination of anticipatory event processing in social anxiety disorder. *Journal of Cognitive Psychotherapy*, 30(2):94–104.

Laramée, P., Leonard, S., Buchanan-Hughes, A., Warnakula, S., Daeppen, J.-B., and Rehm, J. (2015). Risk of all-cause mortality in alcohol-dependent individuals: a systematic literature review and meta-analysis. *EBioMedicine*, 2(10):1394–1404.

Laufer, O., Israeli, D., and Paz, R. (2016). Behavioral and neural mechanisms of overgeneralization in anxiety. *Current Biology*, 26(6):713–722.

Lavoie, M.-A., Vistoli, D., Sutliff, S., Jackson, P. L., and Achim, A. M. (2016). Social representations and contextual adjustments as two distinct components of the theory of mind brain network: Evidence from the remics task. *Cortex*, 81:176–191.

Lawrence, E., Shaw, P., Giampietro, V., Surguladze, S., Brammer, M., and David, A. (2006). The role of 'shared representations' in social perception and empathy: An fmri study. *NeuroImage*, 29(4):1173–1184.

Lawson, A. L., Liu, X., Joseph, J., Vagnini, V. L., Kelly, T. H., and Jiang, Y. (2012). Sensation seeking predicts brain responses in the old–new task: Converging multimodal neuroimaging evidence. *International journal of psychophysiology*, 84(3):260–269.

Lawyer, S. R., Karg, R. S., Murphy, J. G., and McGlynn, F. D. (2002). Heavy drinking among college students is influenced by anxiety sensitivity, gender, and contexts for alcohol use. *Journal of anxiety disorders*, 16(2):165–173.

Lazareck, S., Robinson, J. A., Crum, R. M., Mojtabai, R., Sareen, J., and Bolton, J. M. (2012). A longitudinal investigation of the role of self-medication in the development of comorbid mood and drug use disorders: findings from the national epidemiologic survey on alcohol and related conditions (nesarc). *The Journal of clinical psychiatry*, 73(5):588–593.

Lazarus, R. (1999). Stress and emotion: A new synthesis. *Stress and Emotion: A New Synthesis*.

Lazarus, R. S. (1993). Why we should think of stress as a subset of emotion. *Annual Review Psychology*.

Lazarus, R. S. (2006). *Stress and emotion: A new synthesis*. Springer Publishing Company.

Lazarus, R. S. and Folkman, S. (1984). *Stress, appraisal, and coping*. Springer publishing company.

Leary, M. R. (2015). Emotional responses to interpersonal rejection. *Dialogues in clinical neuroscience*, 17(4):435.

Leary, M. R., Twenge, J. M., and Quinlivan, E. (2006). Interpersonal rejection as a determinant of anger and aggression. *Personality and Social Psychology Review*, 10(2):111–132.

Lebel, C. and Beaulieu, C. (2011). Longitudinal development of human brain wiring continues from childhood into adulthood. *Journal of Neuroscience*, 31(30):10937–10947.

Lebel, C., Gee, M., Camicioli, R., Wieler, M., Martin, W., and Beaulieu, C. (2012a). Diffusion tensor imaging of white matter tract evolution over the lifespan. *Neuroimage*, 60(1):340–352.

Lebel, C., Mattson, S. N., Riley, E. P., Jones, K. L., Adnams, C. M., May, P. A., Bookheimer, S. Y., O'Connor, M. J., Narr, K. L., Kan, E., et al. (2012b). A longitudinal study of the long-term consequences of drinking during pregnancy: heavy in utero alcohol exposure disrupts the normal processes of brain development. *The Journal of Neuroscience*, 32(44):15243–15251.

Lecic-Tosevski, D., Vukovic, O., and Stepanovic, J. (2011). Stress and personality. *Psychiatrike*, 22(4):290–297.

Lederbogen, F., Kirsch, P., Haddad, L., Streit, F., Tost, H., Schuch, P., Wüst, S., Pruessner, J. C., Rietschel, M., Deuschle, M., et al. (2011). City living and urban upbringing affect neural social stress processing in humans. *Nature*, 474(7352):498–501.

LeDoux, J. (1996). The emotional brain: The mysterious underpinnings of emotional life. *The Emotional Brain: The Mysterious Underpinnings of Emotional Life*.

LeDoux, J. (1998a). The emotional brain. weidenfeld & nicolson, london. tr. it. *Il cervello emotivo*.

LeDoux, J. (1998b). Fear and the brain: where have we been, and where are we going? *Biological psychiatry*, 44(12):1229–1238.

LeDoux, J. (2000a). The amygdala and emotion: A view through fear. *The Amygdala: A Functional Analysis*, pages 289–310.

LeDoux, J. (2000b). Emotion circuits in the brain. *Annual Review of Neuroscience*, 23:155–184.

Ledoux, J. (2002). Emotion, memory, and the brain. *Scientific American*.

LeDoux, J. (2003). The emotional brain, fear, and the amygdala. *Cellular and Molecular Neurobiology*, 23(4-5):727–738.

LeDoux, J. (2007). The amygdala. *Current Biology*, 17(20):R868–R874.

LeDoux, J. (2014a). Low roads and higher order thoughts in emotion. *Cortex; a journal devoted to the study of the nervous system and behavior*, 59:214–215.

LeDoux, J. (2015). *Anxious*. Oneworld Publications.

LeDoux, J. and Schiller, D. (2009). The human amygdala: Insights from other animals. *The Human Amygdala*, pages 43–60.

LeDoux, J. E. (2012). Evolution of human emotion: a view through fear. *Progress in brain research*, 195:431.

LeDoux, J. E. (2013). The slippery slope of fear. *Trends in cognitive sciences*, 17(4):155–156.

LeDoux, J. E. (2014b). Coming to terms with fear. *Proceedings of the National Academy of Sciences*, 111(8):2871–2878.

LeDoux, J. E., Cicchetti, P., Xagoraris, A., and Romanski, L. M. (1990). The lateral amygdaloid nucleus: sensory interface of the amygdala in fear conditioning. *The Journal of neuroscience*, 10(4):1062–1069.

Lee, M. R., Cacic, K., Demers, C. H., Haroon, M., Heishman, S., Hommer, D. W., Epstein, D. H., Ross, T. J., Stein, E. A., Heilig, M., et al. (2014). Gender differences in neural–behavioral response to self-observation during a novel fmri social stress task. *Neuropsychologia*, 53:257–263.

Lee, S. S., Humphreys, K. L., Flory, K., Liu, R., and Glass, K. (2011). Prospective association of childhood attention-deficit/hyperactivity disorder (adhd) and substance use and abuse/dependence: a meta-analytic review. *Clinical psychology review*, 31(3):328–341.

Lee, Y. and Bierman, A. (2016). A longitudinal assessment of perceived discrimination and maladaptive expressions of anger among older adults: Does subjective social power buffer the association? *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, page gbw110.

Leech, R., Braga, R., and Sharp, D. J. (2012). Echoes of the brain within the posterior cingulate cortex. *The Journal of Neuroscience*, 32(1):215–222.

Leech, R., Kamourieh, S., Beckmann, C. F., and Sharp, D. J. (2011). Fractionating the default mode network: distinct contributions of the ventral and dorsal posterior cingulate cortex to cognitive control. *The Journal of Neuroscience*, 31(9):3217–3224.

Leech, R. and Sharp, D. J. (2014). The role of the posterior cingulate cortex in cognition and disease. *Brain*, 137(1):12–32.

Leeman, R. F., Ralevski, E., Limoncelli, D., Pittman, B., O'Malley, S. S., and Petrakis, I. L. (2014). Relationships between impulsivity and subjective response in an iv ethanol paradigm. *Psychopharmacology*, 231(14):2867–2876.

Leggio, L., Kenna, G. A., Fenton, M., Bonenfant, E., and Swift, R. M. (2009). Typologies of alcohol dependence. from jellinek to genetics and beyond. *Neuropsychology review*, 19(1):115–129.

Legrand, D. and Ruby, P. (2009). What is self-specific? theoretical investigation and critical review of neuroimaging results. *Psychological review*, 116(1):252.

Lehman, B. J., Cane, A. C., Tallon, S. J., and Smith, S. F. (2015). Physiological and emotional responses to subjective social evaluative threat in daily life. *Anxiety, Stress, & Coping*, 28(3):321–339.

Lejuez, C., Magidson, J. F., Mitchell, S. H., Sinha, R., Stevens, M. C., and De Wit, H. (2010). Behavioral and biological indicators of impulsivity in the development of alcohol use, problems, and disorders. *Alcoholism: Clinical and Experimental Research*, 34(8):1334–1345.

Leland, D. S., Arce, E., Feinstein, J. S., and Paulus, M. P. (2006). Young adult stimulant users' increased striatal activation during uncertainty is related to impulsivity. *Neuroimage*, 33(2):725–731.

LeMarquand, D., Benkelfat, C., Pihl, R., Palmour, R., and Young, S. (1999). Behavioral disinhibition induced by tryptophan depletion in nonalcoholic young men with multigenerational family histories of paternal alcoholism. *American Journal of Psychiatry*, 156(11):1771–1779.

Lemche, E., Surguladze, S. A., Brammer, M. J., Phillips, M. L., Sierra, M., David, A. S., Williams, S. C., and Giampietro, V. P. (2016). Dissociable brain correlates for depression, anxiety, dissociation, and somatization in depersonalization-derealization disorder. *CNS spectrums*, 21(01):35–42.

Lenzenweger, M. F. (2013). Thinking clearly about the endophenotype–intermediate phenotype–biomarker distinctions in developmental psychopathology research. *Development and psychopathology*, 25(4pt2):1347–1357.

Leon, D. A., Chenet, L., Shkolnikov, V. M., Zakharov, S., Shapiro, J., Rakhmanova, G., Vassin, S., and McKee, M. (1997). Huge variation in russian mortality rates 1984–94: artefact, alcohol, or what? *The lancet*, 350(9075):383–388.

Leppänen, J. M. and Hietanen, J. K. (2004). Positive facial expressions are recognized faster than negative facial expressions, but why? *Psychological research*, 69(1-2):22–29.

Leppänen, J. M., Milders, M., Bell, J. S., Terriere, E., and Hietanen, J. K. (2004). Depression biases the recognition of emotionally neutral faces. *Psychiatry research*, 128(2):123–133.

Leppänen, J. M. and Nelson, C. A. (2012). Early development of fear processing. *Current Directions in Psychological Science*, 21(3):200–204.

Lerner, J. S. and Keltner, D. (2001). Fear, anger, and risk. *Journal of personality and social psychology*, 81(1):146.

Lesch, O. M., Walter, H., Wetschka, C., Hesselbrock, M. N., and Hesselbrock, V. (2011). *Aetiology of addiction*. Springer.

Leve, L. D., Khurana, A., and Reich, E. B. (2015). Intergenerational transmission of maltreatment: a multilevel examination. *Development and psychopathology*, 27(4pt2):1429–1442.

Levenson, R. (1980). Alcohol and stress response dampening: Pharmacological effects, expectancy, and tension reduction. *Journal of Abnormal Psychology*, 89(4):528–538.

Levenson, R., Oyama, O., and Meek, P. (1987). Greater reinforcement from alcohol for those at risk: Parental risk, personality risk, and sex. *Journal of Abnormal Psychology*, 96(3):242–253.

Levine, D. S. (2016). Certain and uncertain futures in the brain. In *Anticipation Across Disciplines*, pages 71–80. Springer.

Levy-Gigi, E., Szabó, C., Kelemen, O., and Kéri, S. (2013). Association among clinical response, hippocampal volume, and fkbp5 gene expression in individuals with posttraumatic stress disorder receiving cognitive behavioral therapy. *Biological psychiatry*, 74(11):793–800.

Lewis, A. H., Porcelli, A. J., and Delgado, M. R. (2014). The effects of acute stress exposure on striatal activity during pavlovian conditioning with monetary gains and losses. *Frontiers in behavioral neuroscience*, 8(179):24904331.

Lewis, B. A. and Vogeltanz-Holm, N. D. (2002). The effects of alcohol and anxiousness on physiological and subjective responses to a social stressor in women. *Addictive behaviors*, 27(4):529–545.

Lewis, G. W. and Fish, B. (1978). *I loved rogues*. Superior Publishing Company.

Lewis, M. and Ramsay, D. (2002). Cortisol response to embarrassment and shame. *Child development*, 73(4):1034–1045.

Leyton, M. (2010). The neurobiology of desire: dopamine and the regulation of mood and motivational states in humans. *Pleasures of the Brain*, pages 222–243.

Leyton, M. (2016). Changes in drug cue-induced dopamine release in the development of stimulant addictions in humans. In *INTERNATIONAL JOURNAL OF NEUROPSYCHOPHARMACOLOGY*, volume 19, pages 20–21. OXFORD UNIV PRESS GREAT CLARENDON ST, OXFORD OX2 6DP, ENGLAND.

Leyton, M., aan het Rot, M., Booij, L., Baker, G. B., et al. (2007). Mood-elevating effects of d-amphetamine and incentive salience: the effect of acute dopamine precursor depletion. *Journal of psychiatry & neuroscience: JPN*, 32(2):129.

Leyton, M., Boileau, I., Benkelfat, C., Diksic, M., Baker, G., and Dagher, A. (2002). Amphetamine-induced increases in extracellular dopamine, drug wanting, and novelty seeking: a pet/[11c] raclopride study in healthy men. *Neuropsychopharmacology*, 27(6):1027–1035.

Leyton, M. and Vezina, P. (2013). Striatal ups and downs: their roles in vulnerability to addictions in humans. *Neuroscience & Biobehavioral Reviews*, 37(9):1999–2014.

Leyton, M. and Vezina, P. (2014). Dopamine ups and downs in vulnerability to addictions: a neurodevelopmental model. *Trends in pharmacological sciences*, 35(6):268–276.

Li, C.-s. R., Huang, C., Constable, R. T., and Sinha, R. (2006). Gender differences in the neural correlates of response inhibition during a stop signal task. *Neuroimage*, 32(4):1918–1929.

Li, D., Zucker, N. L., Kragel, P. A., Covington, V. E., and LaBar, K. S. (2016a). Adolescent development of insula-dependent interoceptive regulation. *Developmental Science*.

Li, F. (2016). Significant up-regulated effect of positive emotion regulation. *Advances in Psychology*.

Li, L., Zhu, S., Tse, N., Tse, S., and Wong, P. (2016b). Effectiveness of motivational interviewing to reduce illicit drug use in adolescents: a systematic review and meta-analysis. *Addiction*, 111(5):795–805.

Li, Q., Sun, J., Guo, L., Zang, Y., Feng, Z., Huang, X., Yang, H., Lv, Y., Huang, M., and Gong, Q. (2010). Increased fractional anisotropy in white matter of the right frontal region in children with attention-deficit/hyperactivity disorder: a diffusion tensor imaging study. *Neuroendocrinology Letters*, 31(6):747.

Liang, C.-W., Tsai, J.-L., and Hsu, W.-Y. (2017). Sustained visual attention for competing emotional stimuli in social anxiety: An eye tracking study. *Journal of Behavior Therapy and Experimental Psychiatry*, 54:178–185.

Liang, W. and Chikritzhs, T. (2016). Alcohol use disorder hospitalisations over the last two decades: a population-based cohort study. *Internal medicine journal*, 46(3):301–306.

Lieberman, M., Eisenberger, N., Crockett, M., Tom, S., Pfeifer, J., and Way, B. (2006). Putting feelings into words: Affect labeling disrupts amygdala activity to affective stimuli. *Psychol. Sci.*

Lieberman, M. D. and Cunningham, W. A. (2009). Type i and type ii error concerns in fmri research: re-balancing the scale. *Social cognitive and affective neuroscience*, 4(4):423–428.

Liggins, J., Pihl, R. O., Benkelfat, C., and Leyton, M. (2012). The dopamine augmenter l-dopa does not affect positive mood in healthy human volunteers. *PLoS One*, 7(1):e28370.

Lighthall, N. R., Sakaki, M., Vasunilashorn, S., Nga, L., Somayajula, S., Chen, E. Y., Samii, N., and Mather, M. (2012). Gender differences in reward-related decision processing under stress. *Social Cognitive and Affective Neuroscience*, 7(4):476–484.

Lilienfeld, S. O. (2007). Psychological treatments that cause harm. *Perspectives on psychological science*, 2(1):53–70.

Lilienfeld, S. O. and Treadway, M. T. (2016). Clashing diagnostic approaches: Dsm-icd versus rdoc. *Annual review of clinical psychology*, 12:435–463.

Lim, S. S., Vos, T., Flaxman, A. D., Danaei, G., Shibuya, K., Adair-Rohani, H., AlMazroa, M. A., Amann, M., Anderson, H. R., Andrews, K. G., et al. (2013). A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the global burden of disease study 2010. *The lancet*, 380(9859):2224–2260.

Lindberg, S. and Ågren, G. (1988). Mortality among male and female hospitalized alcoholics in stockholm 1962–1983. *British journal of addiction*, 83(10):1193–1200.

Linden, W., Earle, T., Gerin, W., and Christenfeld, N. (1997). Physiological stress reactivity and recovery: conceptual siblings separated at birth? *Journal of psychosomatic research*, 42(2):117–135.

Lindquist, K., Satpute, A., Wager, T., Weber, J., and Barrett, L. (2016). The brain basis of positive and negative affect: Evidence from a meta-analysis of the human neuroimaging literature. *Cerebral cortex*, 26(5):1910–1922.

Lindquist, K. A., Wager, T. D., Bliss-Moreau, E., Kober, H., and Barrett, L. F. (2012a). What are emotions and how are they created in the brain? *Behavioral and Brain Sciences*, 35(03):172–202.

Lindquist, K. A., Wager, T. D., Kober, H., Bliss-Moreau, E., and Barrett, L. F. (2012b). The brain basis of emotion: a meta-analytic review. *Behavioral and Brain Sciences*, 35(03):121–143.

Linnen, A.-M., Ellenbogen, M. A., Cardoso, C., and Joober, R. (2012). Intranasal oxytocin and salivary cortisol concentrations during social rejection in university students. *Stress*, 15(4):393–402.

Linnet, K. M., Dalsgaard, S., Obel, C., Wisborg, K., Henriksen, T. B., Rodriguez, A., Kotimaa, A., Moilanen, I., Thomsen, P. H., Olsen, J., et al. (2003). Maternal lifestyle factors in pregnancy risk of attention deficit hyperactivity disorder and associated behaviors: review of the current evidence. *American Journal of Psychiatry*, 160(6):1028–1040.

Lipka, J., Hoffmann, M., Miltner, W. H., and Straube, T. (2014). Effects of cognitive-behavioral therapy on brain responses to subliminal and supraliminal threat and their functional significance in specific phobia. *Biological psychiatry*, 76(11):869–877.

Lipton, M. F., Augenstein, T. M., Weeks, J. W., and De Los Reyes, A. (2014). A multi-informant approach to assessing fear of positive evaluation in socially anxious adolescents. *Journal of Child and Family Studies*, 23(7):1247–1257.

Lissek, S., Baas, J., Pine, D., Orme, K., Dvir, S., Rosenberger, E., and Grillon, C. (2005). Sensation seeking and the aversive motivational system. *Emotion*, 5(4):396–407.

Litt, M., Babor, T., DelBoca, F., Kadden, R., and Cooney, N. (1992). Types of alcoholics, ii: Application of an empirically derived typology to treatment matching. *Archives of General Psychiatry*, 49(8):609–614.

Litten, R. Z., Egli, M., Heilig, M., Cui, C., Fertig, J. B., Ryan, M. L., Falk, D. E., Moss, H., Huebner, R., and Noronha, A. (2012). Medications development to treat alcohol dependence: a vision for the next decade. *Addiction biology*, 17(3):513–527.

Litten, R. Z., Falk, D. E., Ryan, M. L., and Fertig, J. B. (2016). Discovery, development, and adoption of medications to treat alcohol use disorder: Goals for the phases of medications development. *Alcoholism: Clinical and Experimental Research*.

Litten, R. Z., Ryan, M. L., Falk, D. E., Reilly, M., Fertig, J. B., and Koob, G. F. (2015). Heterogeneity of alcohol use disorder: Understanding mechanisms to advance personalized treatment. *Alcoholism: Clinical and Experimental Research*, 39(4):579–584.

Littlefield, A. K. and Sher, K. J. (2010). The multiple, distinct ways that personality contributes to alcohol use disorders. *Social and personality psychology compass*, 4(9):767–782.

Littlefield, A. K. and Sher, K. J. (2016). 10 personality and substance use disorders. *The Oxford Handbook of Substance Use and Substance Use Disorders: Two-Volume Set*, page 351.

Littlefield, A. K., Vergés, A., Rosinski, J. M., Steinley, D., and Sher, K. J. (2013). Motivational typologies of drinkers: do enhancement and coping drinkers form two distinct groups? *Addiction*, 108(3):497–503.

Liu, J. (2004). Childhood externalizing behavior: theory and implications. *Journal of child and adolescent psychiatric nursing*, 17(3):93–103.

London, E. D., Ernst, M., Grant, S., Bonson, K., and Weinstein, A. (2000). Orbitofrontal cortex and human drug abuse: functional imaging. *Cerebral cortex*, 10(3):334–342.

Longarzo, M., D'Olimpio, F., Chiavazzo, A., Santangelo, G., Trojano, L., and Grossi, D. (2015). The relationships between interoception and alexithymic trait. the self-awareness questionnaire in healthy subjects. *Frontiers in psychology*, 6.

Lopez, R. B., Hofmann, W., Wagner, D. D., Kelley, W. M., and Heatherton, T. F. (2014). Neural predictors of giving in to temptation in daily life. *Psychological science*, 25(7):1337–1344.

Lopez-Quintero, C., Hasin, D. S., de Los Cobos, J. P., Pines, A., Wang, S., Grant, B. F., and Blanco, C. (2011). Probability and predictors of remission from life-time nicotine, alcohol, cannabis or cocaine dependence: Results from the national epidemiologic survey on alcohol and related conditions. *Addiction*, 106(3):657–669.

Lorberbaum, J. P., Kose, S., Johnson, M. R., Arana, G. W., Sullivan, L. K., Hamner, M. B., Ballenger, J. C., Lydiard, R. B., Brodrick, P. S., Bohning, D. E., et al. (2004). Neural correlates of speech anticipatory anxiety in generalized social phobia. *Neuroreport*, 15(18):2701–2705.

Lou, H. C., Luber, B., Crupain, M., Keenan, J. P., Nowak, M., Kjaer, T. W., Sackeim, H. A., and Lisanby, S. H. (2004). Parietal cortex and representation of the mental self. *Proceedings of the National Academy of Sciences of the United States of America*, 101(17):6827–6832.

Lovallo, W. and Gerin, W. (2003). Psychophysiological reactivity: Mechanisms and pathways to cardiovascular disease. *Psychosomatic Medicine*, 65(1):36–45.

Lovallo, W., Wilson, M., Pincomb, G., Edwards, G., Tompkins, P., and Brackett, D. (1985). Activation patterns to aversive stimulation in man: Passive exposure versus effort to control. *Psychophysiology*, 22(3):283–291.

Lovallo, W. R. (2011). Do low levels of stress reactivity signal poor states of health? *Biological psychology*, 86(2):121–128.

Lovallo, W. R., Dickensheets, S. L., Myers, D. A., Thomas, T. L., and Nixon, S. J. (2000). Blunted stress cortisol response in abstinent alcoholic and polysubstance-abusing men. *Alcoholism: Clinical and Experimental Research*, 24(5):651–658.

Lovallo, W. R., Enoch, M.-A., Acheson, A., Cohoon, A. J., Sorocco, K. H., Hodgkinson, C. A., Vincent, A. S., Glahn, D. C., and Goldman, D. (2015). Cortisol stress response in men and women modulated differentially by the mu-opioid receptor gene polymorphism oprm1 a118g. *Neuropsychopharmacology*, 40(11):2546–2554.

Lovallo, W. R., Farag, N. H., Vincent, A. S., Thomas, T. L., and Wilson, M. F. (2006a). Cortisol responses to mental stress, exercise, and meals following caffeine intake in men and women. *Pharmacology Biochemistry and Behavior*, 83(3):441–447.

Lovallo, W. R. and Thomas, T. L. (2000). Stress hormones in psychophysiological research: Emotional, behavioral, and cognitive implications. *Handbook of psychophysiology (2nd ed.)*.

Lovallo, W. R., Yechiam, E., Sorocco, K. H., Vincent, A. S., and Collins, F. L. (2006b). Working memory and decision-making biases in young adults with a family history of alcoholism: Studies from the oklahoma family health patterns project. *Alcoholism: Clinical and Experimental Research*, 30(5):763–773.

Lubin, B. and Zuckerman, M. (1969). Level of emotional arousal in laboratory training. *The Journal of Applied Behavioral Science*, 5(4):483–490.

Lubman, D. I., Yücel, M., and Pantelis, C. (2004). Addiction, a condition of compulsive behaviour? neuroimaging and neuropsychological evidence of inhibitory dysregulation. *Addiction*, 99(12):1491–1502.

Luchtmann, M., Jachau, K., Tempelmann, C., and Bernarding, J. (2010). Alcohol induced region-dependent alterations of hemodynamic response: implications for the statistical interpretation of pharmacological fmri studies. *Experimental brain research*, 204(1):1–10.

Luczak, S., Glatt, S., and Wall, T. (2006). Meta-analyses of aldh2 and adh1b with alcohol dependence in asians. *Psychological Bulletin*, 132(4):607–621.

Lueken, U. and Hahn, T. (2016). Functional neuroimaging of psychotherapeutic processes in anxiety and depression: from mechanisms to predictions. *Current opinion in psychiatry*, 29(1):25–31.

Lueken, U., Straube, B., Konrad, C., Wittchen, H.-U., Ströhle, A., Wittmann, A., Pfleiderer, B., Uhlmann, C., Arolt, V., Jansen, A., and Kircher, T. (2013). Neural substrates of treatment response to cognitive-behavioral therapy in panic disorder with agoraphobia. *American Journal of Psychiatry*, 170(11):1345–1355.

Lueken, U., Zierhut, K. C., Hahn, T., Straube, B., Kircher, T., Reif, A., Richter, J., Hamm, A., Wittchen, H.-U., and Domschke, K. (2016). Neurobiological markers predicting treatment response in anxiety disorders: A systematic review and implications for clinical application. *Neuroscience & Biobehavioral Reviews*, 66:143–162.

Luijten, M., Machielsen, M. W., Veltman, D. J., Hester, R., Haan, L. d., and Franken, I. H. (2014). Systematic review of erp and fmri studies investigating inhibitory control and error processing in people with substance dependence and behavioural addictions. *Journal of Psychiatry & Neuroscience*.

Luisi, S., Tonetti, A., Bernardi, F., Casarosa, E., Florio, P., Monteleone, P., Gemignani, R., Petraglia, F., Luisi, M., and Genazzani, A. (1998). Effect of acute corticotropin releasing factor on pituitary-adrenocortical responsiveness in elderly women and men. *Journal of endocrinological investigation*, 21(7):449–453.

Luna, B., Garver, K. E., Urban, T. A., Lazar, N. A., and Sweeney, J. A. (2004). Maturation of cognitive processes from late childhood to adulthood. *Child development*, 75(5):1357–1372.

Luna, B., Padmanabhan, A., and O'Hearn, K. (2010). What has fmri told us about the development of cognitive control through adolescence? *Brain and Cognition*, 72(1):101–113.

Luna, B. and Sweeney, J. A. (2004). The emergence of collaborative brain function: Fmri studies of the development of response inhibition. *Annals of the New York Academy of Sciences*, 1021(1):296–309.

Lundahl, B. and Burke, B. L. (2009). The effectiveness and applicability of motivational interviewing: a practice-friendly review of four meta-analyses. *Journal of clinical psychology*, 65(11):1232–1245.

Lundahl, B., Moleni, T., Burke, B. L., Butters, R., Tollefson, D., Butler, C., and Rollnick, S. (2013). Motivational interviewing in medical care settings: a systematic review and meta-analysis of randomized controlled trials. *Patient education and counseling*, 93(2):157–168.

Lundahl, B. W., Kunz, C., Brownell, C., Tollefson, D., and Burke, B. L. (2010). A meta-analysis of motivational interviewing: Twenty-five years of empirical studies. *Research on Social Work Practice*.

Lundberg, U. and Frankenhaeuser, M. (1980). Pituitary-adrenal and sympathetic-adrenal correlates of distress and effort. *Journal of Psychosomatic Research*, 24(3):125–130.

Lundqvist, D., Flykt, A., and Öhman, A. (1998). The karolinska directed emotional faces (kdef). *CD ROM from Department of Clinical Neuroscience, Psychology section, Karolinska Institutet*, pages 91–630.

Lundsberg, L. S., Illuzzi, J. L., Belanger, K., Triche, E. W., and Bracken, M. B. (2015). Low-to-moderate prenatal alcohol consumption and the risk of selected birth outcomes: a prospective cohort study. *Annals of epidemiology*, 25(1):46–54.

Lundstrom, B., Petersson, K., Andersson, J., Johansson, M., Fransson, P., and Ingvar, M. (2003). Isolating the retrieval of imagined pictures during episodic memory: Activation of the left precuneus and left prefrontal cortex. *NeuroImage*, 20(4):1934–1943.

Lupien, S., Ouellet-Morin, I., Herba, C., Juster, R., and McEwen, B. (2016). From vulnerability to neurotoxicity: A developmental approach to the effects of stress on the brain and behavior. In *Epigenetics and Neuroendocrinology*, pages 3–48. Springer.

Lupien, S. J., McEwen, B. S., Gunnar, M. R., and Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience*, 10(6):434–445.

Lupis, S. B., Sabik, N. J., and Wolf, J. M. (2016). Role of shame and body esteem in cortisol stress responses. *Journal of behavioral medicine*, 39(2):262–275.

Lynskey, M. and Agrawal, A. (2007). Psychometric properties of dsm assessments of illicit drug abuse and dependence: results from the national epidemiologic survey on alcohol and related conditions (nesarc). *Psychological Medicine*, 37(09):1345–1355.

Lyons, A. and Thiele, T. (2010). Neuropeptide y conjugated to saporin alters anxiety-like behavior when injected into the central nucleus of the amygdala or basomedial hypothalamus in balb/cj mice. *Peptides*, 31(12):2193–2199.

Lyoo, I., Yoon, S., Kim, T., Lim, S., Choi, Y., Kim, J., Hwang, J., Jeong, H., Cho, H., Chung, Y., et al. (2015). Predisposition to and effects of methamphetamine use on the adolescent brain. *Molecular psychiatry*.

Lyvers, M. and Maltzman, I. (1991). Selective effects of alcohol on wisconsin card sorting test performance. *British Journal of Addiction*, 86(4):399–407.

MacDonald, A. B., Baker, J. M., Stewart, S. H., and Skinner, M. (2000a). Effects of alcohol on the response to hyperventilation of participants high and low in anxiety sensitivity. *Alcoholism: Clinical and Experimental Research*, 24(11):1656–1665.

MacDonald, A. W., Cohen, J. D., Stenger, V. A., and Carter, C. S. (2000b). Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science*, 288(5472):1835–1838.

MacDonald, G. and Leary, M. R. (2005). Why does social exclusion hurt? the relationship between social and physical pain. *Psychological bulletin*, 131(2):202.

Mackey, S., Kan, K. J., Chaarani, B., Alia-Klein, N., Batalla, A., Brooks, S., Cousijn, J., Dagher, A., de Ruiter, M., Desrivieres, S., et al. (2016). Neuroscience for addiction medicine: From prevention to rehabilitation-methods and interventions, 2016. In *Elsevier*.

Mackie, D. M., Devos, T., and Smith, E. R. (2000). Intergroup emotions: explaining offensive action tendencies in an intergroup context. *Journal of personality and social psychology*, 79(4):602.

Mackiewicz Seghete, K. L., Cservenka, A., Herting, M. M., and Nagel, B. J. (2013). Atypical spatial working memory and task-general brain activity in adolescents with a family history of alcoholism. *Alcoholism: Clinical and Experimental Research*, 37(3):390–398.

Madarasz, T. J., Diaz-Mataix, L., Akhand, O., Ycu, E. A., LeDoux, J. E., and Johansen, J. P. (2016). Evaluation of ambiguous associations in the amygdala by learning the structure of the environment. *Nature neuroscience*.

Maddock, R. J., Garrett, A. S., and Buonocore, M. H. (2001). Remembering familiar people: the posterior cingulate cortex and autobiographical memory retrieval. *Neuroscience*, 104(3):667–676.

Maddock, R. J., Garrett, A. S., and Buonocore, M. H. (2003). Posterior cingulate cortex activation by emotional words: fmri evidence from a valence decision task. *Human brain mapping*, 18(1):30–41.

Madson, M. B., Schumacher, J. A., Baer, J. S., and Martino, S. (2016a). Motivational interviewing for substance use: Mapping out the next generation of research. *Journal of substance abuse treatment*, 65:1–5.

Madson, M. B., Villarosa, M. C., Schumacher, J. A., and Mohn, R. S. (2016b). Evaluating the validity of the client evaluation of motivational interviewing scale in a brief motivational intervention for college student drinkers. *Journal of substance abuse treatment*, 65:51–57.

Maeng, L. Y. and Milad, M. R. (2015). Sex differences in anxiety disorders: interactions between fear, stress, and gonadal hormones. *Hormones and behavior*, 76:106–117.

Magarin, A., McEwen, B., et al. (1995). Stress-induced atrophy of apical dendrites of hippocampal ca3c neurons: comparison of stressors. *Neuroscience*, 69(1):83–88.

Magill, M., Gaume, J., Apodaca, T. R., Walthers, J., Mastroleo, N. R., Borsari, B., and Longabaugh, R. (2014). The technical hypothesis of motivational interviewing: A meta-analysis of mi's key causal model. *Journal of Consulting and Clinical Psychology*, 82(6):973.

Magill, M. and Ray, L. A. (2009). Cognitive-behavioral treatment with adult alcohol and illicit drug users: a meta-analysis of randomized controlled trials. *Journal of studies on alcohol and drugs*, 70(4):516–527.

Magrys, S. and Olmstead, M. (2015). Acute stress increases voluntary consumption of alcohol in undergraduates. *Alcohol and alcoholism*, 50(2):213–218.

Magrys, S., Olmstead, M., Wynne-Edwards, K., and Balodis, I. (2013). Neuroendocrinological responses to alcohol intoxication in healthy males: relationship with impulsivity, drinking behavior, and subjective effects. *Psychophysiology*, 50(2):204–209.

Mah, L., Arnold, M. C., and Grafman, J. (2004). Impairment of social perception associated with lesions of the prefrontal cortex. *American Journal of Psychiatry*, 161(7):1247–1255.

Mahabir, M., Tucholka, A., Shin, L. M., Etienne, P., and Brunet, A. (2015). Emotional face processing in post-traumatic stress disorder after reconsolidation impairment using propranolol: a pilot fmri study. *Journal of anxiety disorders*, 36:127–133.

Mahmood, O., Goldenberg, D., Thayer, R., Migliorini, R., Simmons, A., and Tapert, S. (2013). Adolescents' fmri activation to a response inhibition task predicts future substance use. *Addictive behaviors*, 38(1):1435–1441.

Maisto, S., Carey, K., and Bradizza, C. (1999). In leonard, ke and blane, ht. *Psychological theories of drinking and alcoholism*, pages 106–163.

Maj, M. (2016). The need for a conceptual framework in psychiatry acknowledging complexity while avoiding defeatism. *World Psychiatry*, 15(1):1–2.

Majewska, M. D. (2002). Hpa axis and stimulant dependence: an enigmatic relationship. *Psychoneuroendocrinology*, 27(1):5–12.

Mak, A., Hu, Z.-g., Zhang, J., Xiao, Z., and Lee, T. (2009). Sex-related differences in neural activity during emotion regulation. *Neuropsychologia*, 47(13):2900–2908.

Mäki-Marttunen, V., Castro, M., Olmos, L., Leiguarda, R., and Villarreal, M. (2016). Modulation of the default-mode network and the attentional network by self-referential processes in. patients with disorder of consciousness. *Neuropsychologia*.

Makovac, E., Meeten, F., Watson, D. R., Herman, A., Garfinkel, S. N., Critchley, H. D., and Ottaviani, C. (2015). Alterations in amygdala-prefrontal functional connectivity account for excessive worry and autonomic dysregulation in generalized anxiety disorder. *Biological psychiatry*.

Makris, N., Oscar-Berman, M., Jaffin, S. K., Hodge, S. M., Kennedy, D. N., Caviness, V. S., Marinkovic, K., Breiter, H. C., Gasic, G. P., and Harris, G. J. (2008). Decreased volume of the brain reward system in alcoholism. *Biological psychiatry*, 64(3):192–202.

Maller, R. G. and Reiss, S. (1992). Anxiety sensitivity in 1984 and panic attacks in 1987. *Journal of Anxiety Disorders*, 6(3):241–247.

Mann, F. D., Engelhardt, L., Briley, D. A., Grotzinger, A. D., Patterson, M. W., Tackett, J. L., Strathan, D. B., Heath, A., Lynskey, M., Slutske, W., et al. (2017). Sensation seeking and impulsive traits as personality endophenotypes for antisocial behavior: Evidence from two independent samples. *Personality and Individual Differences*, 105:30–39.

Mann, R. E., Sobell, L. C., Sobell, M. B., and Pavan, D. (1985). Reliability of a family tree questionnaire for assessing family history of alcohol problems. *Drug and alcohol dependence*, 15(1):61–67.

Månsson, K. N., Carlbring, P., Frick, A., Engman, J., Olsson, C.-J., Bodlund, O., Furmark, T., and Andersson, G. (2013). Altered neural correlates of affective processing after internet-delivered cognitive behavior therapy for social anxiety disorder. *Psychiatry Research: Neuroimaging*, 214(3):229–237.

Mantegazza, P. (1871). *Quadri della natura umana: feste ed ebbrezze*, volume 2. Bernardoni.

Manthey, J., Gual, A., Jakubczyk, A., Pieper, L., Probst, C., Struzzo, P., Trapencieris, M., Wojnar, M., and Rehm, J. (2016). Alcohol use disorders in europe: A comparison of general population and primary health care prevalence rates. *Journal of Substance Use*, 21(5):478–484.

Manzo, L., Gómez, M. J., Callejas-Aguilera, J. E., Donaire, R., Sabariego, M., Fernández-Teruel, A., Cañete, A., Blázquez, G., Papini, M. R., and Torres, C. (2014). Relationship between ethanol preference and sensation/novelty seeking. *Physiology & behavior*, 133:53–60.

Manzoni, G. M., Pagnini, F., Castelnuovo, G., and Molinari, E. (2008). Relaxation training for anxiety: a ten-years systematic review with meta-analysis. *BMC psychiatry*, 8(1):1.

Maoz, K., Eldar, S., Stoddard, J., Pine, D. S., Leibenluft, E., and Bar-Haim, Y. (2016). Angry-happy interpretations of ambiguous faces in social anxiety disorder. *Psychiatry research*, 241:122–127.

Maras, P. M. and Baram, T. Z. (2012). Sculpting the hippocampus from within: stress, spines, and crh. *Trends in neurosciences*, 35(5):315–324.

Marczinski, C. A., Abroms, B. D., Van Selst, M., and Fillmore, M. T. (2005). Alcohol-induced impairment of behavioral control: differential effects on engaging vs. disengaging responses. *Psychopharmacology*, 182(3):452–459.

Maren, S. (2001). Neurobiology of pavlovian fear conditioning. *Annual review of neuroscience*, 24(1):897–931.

Maren, S. (2016). Parsing reward and aversion in the amygdala. *Neuron*, 90(2):209–211.

Maren, S., Phan, K. L., and Liberzon, I. (2013). The contextual brain: implications for fear conditioning, extinction and psychopathology. *Nature Reviews Neuroscience*, 14(6):417–428.

Marganska, A., Gallagher, M., and Miranda, R. (2013). Adult attachment, emotion dysregulation, and symptoms of depression and generalized anxiety disorder. *American Journal of Orthopsychiatry*, 83(1):131–141.

Margulies, D. S., Kelly, A. C., Uddin, L. Q., Biswal, B. B., Castellanos, F. X., and Milham, M. P. (2007). Mapping the functional connectivity of anterior cingulate cortex. *Neuroimage*, 37(2):579–588.

Margulies, D. S., Vincent, J. L., Kelly, C., Lohmann, G., Uddin, L. Q., Biswal, B. B., Villringer, A., Castellanos, F. X., Milham, M. P., and Petrides, M. (2009). Precuneus shares intrinsic functional architecture in humans and monkeys. *Proceedings of the National Academy of Sciences*, 106(47):20069–20074.

Marin, M.-F., Morin-Major, J.-K., Schramek, T. E., Beaupré, A., Perna, A., Juster, R.-P., and Lupien, S. J. (2012). There is no news like bad news: women are more remembering and stress reactive after reading real negative news than men. *PloS one*, 7(10):e47189.

Marinelli, M. and White, F. (2000). Enhanced vulnerability to cocaine self-administration is associated with elevated impulse activity of midbrain dopamine neurons. *Journal of Neuroscience*, 20(23):8876–8885.

Marinkovic, K., Oscar-Berman, M., Urban, T., O'Reilly, C. E., Howard, J. A., Sawyer, K., and Harris, G. J. (2009). Alcoholism and dampened temporal limbic activation to emotional faces. *Alcoholism: Clinical and Experimental Research*, 33(11):1880–1892.

Marinkovic, K., Rickenbacher, E., Azma, S., and Artsy, E. (2012). Acute alcohol intoxication impairs top–down regulation of stroop incongruity as revealed by blood oxygen level-dependent functional magnetic resonance imaging. *Human brain mapping*, 33(2):319–333.

Marmot, M. (1984). Alcohol and coronary heart disease. *International Journal of Epidemiology*, 13(2):160–167.

Marmot, M. (2014). Commentary: Mental health and public health. *International journal of epidemiology*, page dyu054.

Márquez, C., Poirier, G. L., Cordero, M. I., Larsen, M. H., Groner, A., Marquis, J., Magistretti, P. J., Trono, D., and Sandi, C. (2013). Peripuberty stress leads to abnormal aggression, altered amygdala and orbitofrontal reactivity and increased prefrontal maoa gene expression. *Translational psychiatry*, 3(1):e216.

Marsh, A., Finger, E., Mitchell, D., Reid, M., Sims, C., Kosson, D., Towbin, K., Leibenluft, E., Pine, D., and Blair, R. (2008). Reduced amygdala response to fearful expressions in children and adolescents with callous-unemotional traits and disruptive behavior disorders. *American Journal of Psychiatry*, 165(6):712–720.

Marsh, A. A. (2015). Understanding amygdala responsiveness to fearful expressions through the lens of psychopathy and altruism. *Journal of Neuroscience Research*.

Marshall, E. J. (2014). Adolescent alcohol use: risks and consequences. *Alcohol and alcoholism*, 49(2):160–164.

Martens, M., Rocha, T., Martin, J., and Serrao, H. (2008). Drinking motives and college students: Further examination of a four-factor model. *Journal of Counseling Psychology*, 55(2):289–295.

Martin, C., Kelly, T., Rayens, M., Brogli, B., Brenzel, A., Smith, W., and Omar, H. (2002). Sensation seeking, puberty, and nicotine, alcohol, and marijuana use in adolescence. *Journal of the American Academy of Child and Adolescent Psychiatry*, 41(12):1495–1502.

Martin, C. S., Chung, T., and Langenbucher, J. W. (2008). How should we revise diagnostic criteria for substance use disorders in the dsm-v? *Journal of abnormal psychology*, 117(3):561.

Martin, C. S., Langenbucher, J. W., Chung, T., and Sher, K. J. (2014). Response to commentaries. *Addiction*, 109(11):1784–1785.

Martin, C. S., Steinley, D. L., Verges, A., and Sher, K. J. (2011). Letter to the editor: the proposed 2/11 symptom algorithm for dsm-5 substance-use disorders is too lenient. *Psychological medicine*, 41(09):2008–2010.

Martin, E., Ressler, K., Binder, E., and Nemeroff, C. (2009). The neurobiology of anxiety disorders: Brain imaging, genetics, and psychoneuroendocrinology. *Psychiatric Clinics of North America*, 32(3):549–575.

Martín-Albo, J., Núñez, J. L., Navarro, J. G., and Grijalvo, F. (2007). The rosenberg self-esteem scale: translation and validation in university students. *The Spanish journal of psychology*, 10(02):458–467.

Martinez, D., Broft, A., Foltin, R. W., Slifstein, M., Hwang, D.-R., Huang, Y., Perez, A., Frankel, W. G., Cooper, T., Kleber, H. D., et al. (2004). Cocaine dependence and d 2 receptor availabiltiy in the functional subdivisions of the striatum: Relationship with cocaine-seeking behavior. *Neuropsychopharmacology*, 29(6).

Marxen, M., Jacob, M. J., Müller, D. K., Posse, S., Ackley, E., Hellrung, L., Riedel, P., Bender, S., Epple, R., and Smolka, M. N. (2016). Amygdala regulation following fmri-neurofeedback without instructed strategies. *Frontiers in human neuroscience*, 10.

Mason, J. W. (1968). A review of psychoendocrine research on the pituitary-adrenal cortical system. *Psychosomatic medicine*, 30(5):576–607.

Mason, J. W. (1971). A re-evaluation of the concept of 'non-specificity'in stress theory. *Journal of Psychiatric research*, 8:323–333.

Mason, L., Peters, E., and Kumari, V. (2016). Functional connectivity predictors and mechanisms of cognitive behavioural therapies: A systematic review with recommendations. *Australian and New Zealand Journal of Psychiatry*, page 0004867415624970.

Mason, M. F., Norton, M. I., Van Horn, J. D., Wegner, D. M., Grafton, S. T., and Macrae, C. N. (2007). Wandering minds: the default network and stimulus-independent thought. *Science*, 315(5810):393–395.

Mather, M., Lighthall, N. R., Nga, L., and Gorlick, M. A. (2010). Sex differences in how stress affects brain activity during face viewing. *Neuroreport*, 21(14):933.

Mathers, C., Fat, D. M., and Boerma, J. T. (2008). *The global burden of disease: 2004 update*. World Health Organization.

Mathers, C. D. and Loncar, D. (2006). Projections of global mortality and burden of disease from 2002 to 2030. *PLoS medicine*, 3(11):e442.

Matheson, K. and Anisman, H. (2009). Anger and shame elicited by discrimination: Moderating role of coping on action endorsements and salivary cortisol. *European Journal of Social Psychology*, 39(2):163–185.

Matheson, S., Kariuki, M., Green, M., Dean, K., Harris, F., Tzoumakis, S., Tarren-Sweeney, M., Brinkman, S., Chilvers, M., Sprague, T., et al. (2016). Effects of maltreatment and parental schizophrenia spectrum disorders on early childhood social-emotional functioning: a population record linkage study. *Epidemiology and Psychiatric Sciences*, pages 1–12.

Matochik, J., London, E., Eldreth, D., Cadet, J.-L., and Bolla, K. (2003). Frontal cortical tissue composition in abstinent cocaine abusers: A magnetic resonance imaging study. *NeuroImage*, 19(3):1095–1102.

Matthews, B. A. and Norris, F. H. (2002). When is believing "seeing"? hostile attribution bias as a function of self-reported aggression1. *Journal of Applied Social Psychology*, 32(1):1–31.

Mattson, M. E., Allen, J. P., Longabaugh, R., Nickless, C. J., Connors, G. J., and Kadden, R. M. (1994). A chronological review of empirical studies matching alcoholic clients to treatment. *Journal of Studies on Alcohol, Supplement*, 12(12):16–29.

Mattson, W. I., Hyde, L. W., Shaw, D. S., Forbes, E. E., and Monk, C. S. (2016). Clinical neuroprediction: Amygdala reactivity predicts depressive symptoms 2 years later. *Social cognitive and affective neuroscience*, page nsw018.

May, J. C., Delgado, M. R., Dahl, R. E., Stenger, V. A., Ryan, N. D., Fiez, J. A., and Carter, C. S. (2004). Event-related functional magnetic resonance imaging of reward-related brain circuitry in children and adolescents. *Biological psychiatry*, 55(4):359–366.

Mayfield, D. (1976). Alcoholism, alcohol, intoxication and assaultive behavior. *Disease of the Nervous System*, 37(5):288–291.

Mayo-Wilson, E., Dias, S., Mavranezouli, I., Kew, K., Clark, D. M., Ades, A., and Pilling, S. (2014). Psychological and pharmacological interventions for social anxiety disorder in adults: a systematic review and network meta-analysis. *The Lancet Psychiatry*, 1(5):368–376.

Mazoyer, B., Zago, L., Mellet, E., Bricogne, S., Etard, O., Houde, O., Crivello, F., Joliot, M., Petit, L., and Tzourio-Mazoyer, N. (2001). Cortical networks for working memory and executive functions sustain the conscious resting state in man. *Brain research bulletin*, 54(3):287–298.

Mazur, A. (1995). Biosocial models of deviant behavior among male army veterans. *Biological Psychology*, 41(3):271–293.

McAlonan, K., Cavanaugh, J., and Wurtz, R. H. (2008). Guarding the gateway to cortex with attention in visual thalamus. *Nature*, 456(7220):391–394.

McBride, O., Cheng, H. G., Slade, T., and Lynskey, M. T. (2016). The role of specific alcohol-related problems in predicting depressive experiences in a cross-sectional national household survey. *Alcohol and alcoholism*, page agw010.

McBride, W. J. (2002). Central nucleus of the amygdala and the effects of alcohol and alcohol-drinking behavior in rodents. *Pharmacology Biochemistry and Behavior*, 71(3):509–515.

McCarter, K. L., Halpin, S. A., Baker, A. L., Kay-Lambkin, F. J., Lewin, T. J., Thornton, L. K., Kavanagh, D. J., and Kelly, B. J. (2016). Associations between personality disorder characteristics and treatment outcomes in people with co-occurring alcohol misuse and depression. *BMC psychiatry*, 16(1):210.

McCaul, M., Turkkan, J., Svikis, D., and Bigelow, G. (1991). Familial density of alcoholism: effects on psychophysiological responses to ethanol. *Alcohol*, 8(3):219–222.

McCloskey, M. S., Phan, K. L., Angstadt, M., Fettich, K. C., Keedy, S., and Coccaro, E. F. (2016). Amygdala hyperactivation to angry faces in intermittent explosive disorder. *Journal of psychiatric research*, 79:34–41.

McClure, E. B., Adler, A., Monk, C. S., Cameron, J., Smith, S., Nelson, E. E., Leibenluft, E., Ernst, M., and Pine, D. S. (2007). fmri predictors of treatment outcome in pediatric anxiety disorders. *Psychopharmacology*, 191(1):97–105.

McCoy, A. N. and Platt, M. L. (2005). Risk-sensitive neurons in macaque posterior cingulate cortex. *Nature neuroscience*, 8(9):1220–1227.

McCrae, R. R. and Costa, P. T. (1986). Personality, coping, and coping effectiveness in an adult sample. *Journal of personality*, 54(2):385–404.

McDonald, A. (1982). Cytoarchitecture of the central amygdaloid nucleus of the rat. *Journal of Comparative Neurology*, 208(4):401–418.

McDonald, A. (1991). Organization of amygdaloid projections to the prefrontal cortex and associated striatum in the rat. *Neuroscience*, 44(1):1–14.

Mcdonald, A. (1998). Cortical pathways to the mammalian amygdala. *Progress in Neurobiology*, 55(3):257–332.

McDougall, W. (1929). The chemical theory of temperament applied to introversion and extroversion. *The Journal of Abnormal and Social Psychology*, 24(3):293.

McEwen, B. (1998a). Seminars in medicine of the beth israel deaconess medical center: Protective and damaging effects of stress mediators. *New England Journal of Medicine*, 338(3):171–179.

McEwen, B. S. (1998b). Protective and damaging effects of stress mediators. *New England journal of medicine*, 338(3):171–179.

McEwen, B. S. (1999). Stress and hippocampal plasticity. *Annual review of neuroscience*, 22(1):105–122.

McEwen, B. S. (2015). Biomarkers for assessing population and individual health and disease related to stress and adaptation. *Metabolism*, 64(3):S2–S10.

McEwen, B. S. (2016). In pursuit of resilience: stress, epigenetics, and brain plasticity. *Annals of the New York Academy of Sciences*.

McEwen, B. S. and Gianaros, P. J. (2011). Stress-and allostasis-induced brain plasticity. *Annual review of medicine*, 62:431–445.

McEwen, B. S., Gray, J. D., and Nasca, C. (2015). Recognizing resilience: Learning from the effects of stress on the brain. *Neurobiology of Stress*, 1:1–11.

McEwen, B. S., Nasca, C., and Gray, J. D. (2016). Stress effects on neuronal structure: hippocampus, amygdala, and prefrontal cortex. *Neuropsychopharmacology*, 41(1):3–23.

McEwen, B. S. and Stellar, E. (1993). Stress and the individual: mechanisms leading to disease. *Archives of internal medicine*, 153(18):2093–2101.

McGlothlin, W. H. and Arnold, D. O. (1971). Lsd revisited: A ten-year follow-up of medical lsd use. *Archives of General Psychiatry*, 24(1):35–49.

McGrath, J. J., Petersen, L., Agerbo, E., Mors, O., Mortensen, P. B., and Pedersen, C. B. (2014). A comprehensive assessment of parental age and psychiatric disorders. *JAMA psychiatry*, 71(3):301–309.

McGrew, W. (2011). Natural ingestion of ethanol by animals: why. *Liquid bread: beer and brewing in cross-cultural perspective*, pages 13–19.

McHugh, R. K., Votaw, V. R., Bogunovic, O., Karakula, S. L., Griffin, M. L., and Weiss, R. D. (2016). Anxiety sensitivity and nonmedical benzodiazepine use among adults with opioid use disorder. *Addictive Behaviors*.

McKiernan, K. A., D'Angelo, B. R., Kaufman, J. N., and Binder, J. R. (2006). Interrupting the "stream of consciousness": an fmri investigation. *Neuroimage*, 29(4):1185–1191.

McLaughlin, K. J., Gomez, J. L., Baran, S. E., and Conrad, C. D. (2007). The effects of chronic stress on hippocampal morphology and function: an evaluation of chronic restraint paradigms. *Brain research*, 1161:56–64.

McLean, C. P., Asnaani, A., Litz, B. T., and Hofmann, S. G. (2011). Gender differences in anxiety disorders: prevalence, course of illness, comorbidity and burden of illness. *Journal of psychiatric research*, 45(8):1027–1035.

McLellan, A. T., Lewis, D. C., O'Brien, C. P., and Kleber, H. D. (2000). Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. *Jama*, 284(13):1689–1695.

McNair, D. (1971). *Manual profile of mood states*. Educational & Industrial testing service.

McNair, D. M., Lorr, M., and Droppleman, L. F. (1971). *Profile of mood states*. Univ.

McNally, R. (1989). Is anxiety sensitivity distinguishable from trait anxiety? reply to lilienfeld, jacob, and turner (1989). *Journal of Abnormal Psychology*, 98(2):193–194.

McNally, R. (1990). Psychological approaches to panic disorder: A review. *Psychological Bulletin*, 108(3):403–419.

McNally, R. J. (1999). Theoretical approaches to the fear of anxiety. *Anxiety sensitivity: Theory, research, and treatment of the fear of anxiety*, pages 3–16.

McNally, R. J. (2002). Anxiety sensitivity and panic disorder. *Biological psychiatry*, 52(10):938–946.

McNamee, R. L., Dunfee, K. L., Luna, B., Clark, D. B., Eddy, W. F., and Tarter, R. E. (2008). Brain activation, response inhibition, and increased risk for substance use disorder. *Alcoholism: Clinical and Experimental Research*, 32(3):405–413.

McQueeny, T., Schweinsburg, B., Schweinsburg, A., Jacobus, J., Bava, S., Frank, L., and Tapert, S. (2009). Altered white matter integrity in adolescent binge drinkers. *Alcoholism: Clinical and Experimental Research*, 33(7):1278–1285.

McRae, K. (2016). Cognitive emotion regulation: a review of theory and scientific findings. *Current Opinion in Behavioral Sciences*, 10:119–124.

McRae, K., Hughes, B., Chopra, S., Gabrieli, J. D., Gross, J. J., and Ochsner, K. N. (2010). The neural bases of distraction and reappraisal. *Journal of cognitive neuroscience*, 22(2):248–262.

Meadows, M.-E. and Kaplan, R. F. (1994). Dissociation of autonomic and subjective responses to emotional slides in right hemisphere damaged patients. *Neuropsychologia*, 32(7):847–856.

Meder, D., Madsen, K. H., Hulme, O., and Siebner, H. R. (2016). Chasing probabilities—signaling negative and positive prediction errors across domains. *NeuroImage*, 134:180–191.

Medina, K. L., Schweinsburg, A. D., Cohen-Zion, M., Nagel, B. J., and Tapert, S. F. (2007). Effects of alcohol and combined marijuana and alcohol use during adolescence on hippocampal volume and asymmetry. *Neurotoxicology and teratology*, 29(1):141–152.

Medina-Mora, M. E., Monteiro, M., Room, R., Rehm, J., Jernigan, D., Sánchez-Moreno, D., and Real, T. (2016). Alcohol use and alcohol use disorders. *Disease Control Priorities*, 4:127–43.

Meier, M. H., Caspi, A., Houts, R., Slutske, W. S., Harrington, H., Jackson, K. M., Belsky, D. W., Poulton, R., and Moffitt, T. E. (2013). Prospective developmental subtypes of alcohol dependence from age 18 to 32 years: Implications for nosology, etiology, and intervention. *Development and psychopathology*, 25(03):785–800.

Meier, S. E., Brigham, T. A., Ward, D. A., Myers, F., and Warren, L. (1996). Effects of blood alcohol concentrations on negative punishment: implications for decision making. *Journal of Studies on Alcohol*, 57(1):85–96.

Melis, M., Diana, M., Enrico, P., Marinelli, M., and Brodie, M. S. (2009). Ethanol and acetaldehyde action on central dopamine systems: mechanisms, modulation, and relationship to stress. *Alcohol*, 43(7):531–539.

Mellentin, A. I., Brink, M., Andersen, L., Erlangsen, A., Stenager, E., Bjerregaard, L. B., and Christiansen, E. (2016). The risk of offspring developing substance use disorders when exposed to one versus two parent (s) with alcohol use disorder: A nationwide, register-based cohort study. *Journal of Psychiatric Research*.

Mellings, T. M. and Alden, L. E. (2000). Cognitive processes in social anxiety: The effects of self-focus, rumination and anticipatory processing. *Behaviour research and therapy*, 38(3):243–257.

Meltzoff, A. N., Brooks, R., Shon, A. P., and Rao, R. P. (2010). "social" robots are psychological agents for infants: A test of gaze following. *Neural Networks*, 23(8):966–972.

Melzig, C. A., Holtz, K., Michalowski, J. M., and Hamm, A. O. (2011). Interoceptive threat leads to defensive mobilization in highly anxiety sensitive persons. *Psychophysiology*, 48(6):745–754.

Menary, K. R., Kushner, M. G., Maurer, E., and Thuras, P. (2011). The prevalence and clinical implications of self-medication among individuals with anxiety disorders. *Journal of anxiety disorders*, 25(3):335–339.

Méndez-Bértolo, C., Moratti, S., Toledano, R., Lopez-Sosa, F., Martínez-Alvarez, R., Mah, Y. H., Vuilleumier, P., Gil-Nagel, A., and Strange, B. A. (2016). A fast pathway for fear in human amygdala. *Nature neuroscience*.

Menon, V., Adleman, N. E., White, C. D., Glover, G. H., and Reiss, A. L. (2001). Error-related brain activation during a go/nogo response inhibition task. *Human brain mapping*, 12(3):131–143.

Menon, V. and Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Structure and Function*, 214(5-6):655–667.

Merikangas, K. R. and McClair, V. L. (2012). Epidemiology of substance use disorders. *Human genetics*, 131(6):779–789.

Merrill, J. E. and Read, J. P. (2010). Motivational pathways to unique types of alcohol consequences. *Psychology of Addictive Behaviors*, 24(4):705.

Merrill, J. E., Wardell, J. D., and Read, J. P. (2014). Drinking motives in the prospective prediction of unique alcohol-related consequences in college students. *Journal of studies on alcohol and drugs*, 75(1):93–102.

Merry, J. and Marks, V. (1969). Plasma-hydrocortisone response to ethanol in chronic alcoholics. *The Lancet*, 293(7601):921–923.

Metereau, E. and Dreher, J.-C. (2015). The medial orbitofrontal cortex encodes a general unsigned value signal during anticipation of both appetitive and aversive events. *Cortex*, 63:42–54.

Meuret, A. E., Chmielewski, M., Steele, A. M., Rosenfield, D., Petersen, S., Smits, J. A., Simon, N. M., Otto, M. W., Marques, L., Pollack, M. H., et al. (2016). The desire to belong: Social identification as a predictor of treatment outcome in social anxiety disorder. *Behaviour research and therapy*, 81:21–34.

Meyer-Lindenberg, A. and Tost, H. (2012). Neural mechanisms of social risk for psychiatric disorders. *Nature neuroscience*, 15(5):663–668.

Miczek, K. A., Yap, J. J., and Covington, H. E. (2008). Social stress, therapeutics and drug abuse: preclinical models of escalated and depressed intake. *Pharmacology & therapeutics*, 120(2):102–128.

Miech, R. A., Johnston, L. D., O'malley, P. M., Bachman, J. G., Schulenberg, J. E., et al. (2015). Monitoring the future national survey results on drug use, 1975–2014. *Institute for Social Research, The University of Michigan, Ann Arbor*.

Miedl, S. F., Blechert, J., Klackl, J., Wiggert, N., Reichenberger, J., Derntl, B., and Wilhelm, F. H. (2016). Criticism hurts everybody, praise only some: Common and specific neural responses to approving and disapproving social-evaluative videos. *NeuroImage*, 132:138–147.

Mihic, L., Wells, S., Graham, K., Tremblay, P., and Demers, A. (2009). Situational and respondent-level motives for drinking and alcohol-related aggression: A multilevel analysis of drinking events in a sample of canadian university students. *Addictive Behaviors*, 34(3):264–269.

Milad, M. R., Quinn, B. T., Pitman, R. K., Orr, S. P., Fischl, B., and Rauch, S. L. (2005). Thickness of ventromedial prefrontal cortex in humans is correlated with extinction memory. *Proceedings of the National Academy of Sciences of the United States of America*, 102(30):10706–10711.

Milad, M. R. and Quirk, G. J. (2002). Neurons in medial prefrontal cortex signal memory for fear extinction. *Nature*, 420(6911):70–74.

Milella, M. S., Fotros, A., Gravel, P., Casey, K. F., Larcher, K., Verhaeghe, J., Cox, S., Reader, A., Dagher, A., Benkelfat, C., et al. (2016). Cocaine cue–induced dopamine release in the human prefrontal cortex. *Journal of psychiatry & neuroscience: JPN*, 41(3):150207–150207.

Miller, G. A. (2010). Mistreating psychology in the decades of the brain. *Perspectives on Psychological Science*, 5(6):716–743.

Miller, G. A. and Rockstroh, B. (2013). Endophenotypes in psychopathology research: where do we stand? *Annual Review of Clinical Psychology*, 9:177–213.

Miller, M. A., Bershad, A. K., and de Wit, H. (2015). Drug effects on responses to emotional facial expressions: recent findings. *Behavioural pharmacology*, 26(6-Special Issue Pharmacological Approaches to the Study of Social Behaviour-Part 1: Reviews):571–579.

Miller, N. S. (1995). Liability and efficacy from long-term use of benzodiazepines: Documentation and interpretation. *Psychiatric Annals*, 25(3):166–173.

Miller, P. and Plant, M. (2002). Heavy cannabis use among uk teenagers: an exploration. *Drug and alcohol dependence*, 65(3):235–242.

Miller, W. and Rollnick, S. (2013a). Applications of motivational interviewing. *Motivational interviewing: Helping people change*.

Miller, W. R. (1983). Motivational interviewing with problem drinkers. *Behavioural Psychotherapy*, 11(02):147–172.

Miller, W. R. (1996). Motivational interviewing: research, practice, and puzzles. *Addictive behaviors*, 21(6):835–842.

Miller, W. R. and Heather, N. (2013). *Treating addictive behaviors: Processes of change*, volume 13. Springer Science & Business Media.

Miller, W. R. and Hester, R. K. (1986). The effectiveness of alcoholism treatment. In *Treating addictive behaviors*, pages 121–174. Springer.

Miller, W. R. and Rollnick, S. (2013b). *Motivational interviewing: Helping people change*. Guilford press.

Miller, W. R. and Rose, G. S. (2009). Toward a theory of motivational interviewing. *American psychologist*, 64(6):527.

Miller, W. R. and Rose, G. S. (2015). Motivational interviewing and decisional balance: contrasting responses to client ambivalence. *Behavioural and cognitive psychotherapy*, 43(02):129–141.

Miller, W. R., Yahne, C. E., Moyers, T. B., Martinez, J., and Pirritano, M. (2004). A randomized trial of methods to help clinicians learn motivational interviewing. *Journal of consulting and clinical psychology*, 72(6):1050.

Mills, K. L., Goddings, A.-L., Clasen, L. S., Giedd, J. N., and Blakemore, S.-J. (2014). The developmental mismatch in structural brain maturation during adolescence. *Developmental neuroscience*, 36(3–4):147–160.

Mills, R. S., Imm, G. P., Walling, B. R., and Weiler, H. A. (2008). Cortisol reactivity and regulation associated with shame responding in early childhood. *Developmental psychology*, 44(5):1369.

Mintzer, M. Z. (2007). The acute effects of alcohol on memory: A review of laboratory studies in healthy adults. *International Journal on Disability and Human Development*, 6(4):397–404.

Mintzer, M. Z. and Griffiths, R. R. (2001). Alcohol and false recognition: a dose-effect study. *Psychopharmacology*, 159(1):51–57.

Mitchell, I. J., Gillespie, S. M., and Abu-Akel, A. (2015). Similar effects of intranasal oxytocin administration and acute alcohol consumption on socio-cognitions, emotions and behaviour: Implications for the mechanisms of action. *Neuroscience & Biobehavioral Reviews*, 55:98–106.

Mitchell, J., Macrae, C., and Banaji, M. (2006). Dissociable medial prefrontal contributions to judgments of similar and dissimilar others. *Neuron*, 50(4):655–663.

Mitte, K. (2005). Meta-analysis of cognitive-behavioral treatments for generalized anxiety disorder: a comparison with pharmacotherapy. *Psychological Bulletin*, 131(5):785.

Mizuguchi, N., Nakata, H., and Kanosue, K. (2016). The right temporoparietal junction encodes efforts of others during action observation. *Scientific Reports*, 6:30274.

M.L., P., W.C., D., S.L., R., and R., L. (2003). Neurobiology of emotion perception i: The neural basis of normal emotion perception. *Biological Psychiatry*, 54(5):504–514.

Mobbs, D., Petrovic, P., Marchant, J. L., Hassabis, D., Weiskopf, N., Seymour, B., Dolan, R. J., and Frith, C. D. (2007). When fear is near: threat imminence elicits prefrontal-periaqueductal gray shifts in humans. *Science*, 317(5841):1079–1083.

Moberg, C. A. and Curtin, J. J. (2009). Alcohol selectively reduces anxiety but not fear: startle response during unpredictable versus predictable threat. *Journal of abnormal psychology*, 118(2):335.

Moberg, C. A., Weber, S. M., and Curtin, J. J. (2011). Alcohol dose effects on stress response to cued threat vary by threat intensity. *Psychopharmacology*, 218(1):217–227.

Mochcovitch, M. D., da Rocha Freire, R. C., Garcia, R. F., and Nardi, A. E. (2014). A systematic review of fmri studies in generalized anxiety disorder: Evaluating its neural and cognitive basis. *Journal of affective disorders*, 167:336–342.

Moeller, S. J., Bederson, L., Alia-Klein, N., and Goldstein, R. Z. (2016). Neuroscience of inhibition for addiction medicine: from prediction of initiation to prediction of relapse. *Progress in brain research*, 223:165–188.

Moffitt, T. E. (2005). The new look of behavioral genetics in developmental psychopathology: gene-environment interplay in antisocial behaviors. *Psychological bulletin*, 131(4):533.

Moffitt, T. E., Arseneault, L., Belsky, D., Dickson, N., Hancox, R. J., Harrington, H., Houts, R., Poulton, R., Roberts, B. W., Ross, S., et al. (2011). A gradient of childhood self-control predicts health, wealth, and public safety. *Proceedings of the National Academy of Sciences*, page 201010076.

Mogg, K. and Bradley, B. P. (1998). A cognitive-motivational analysis of anxiety. *Behaviour research and therapy*, 36(9):809–848.

Mokdad, A. H., Marks, J. S., Stroup, D. F., and Gerberding, J. L. (2004). Actual causes of death in the united states, 2000. *Jama*, 291(10):1238–1245.

Mole, T. B., Mak, E., Chien, Y., and Voon, V. (2016). Dissociated accumbens and hippocampal structural abnormalities across obesity and alcohol dependence. *International Journal of Neuropsychopharmacology*, page pyw039.

Möller, C., Wiklund, L., Sommer, W., Thorsell, A., and Heilig, M. (1997). Decreased experimental anxiety and voluntary ethanol consumption in rats following central but not basolateral amygdala lesions. *Brain research*, 760(1):94–101.

Monat, A., Averill, J. R., and Lazarus, R. S. (1972). Anticipatory stress and coping reactions under various conditions of uncertainty. *Journal of personality and social psychology*, 24(2):237.

Monk, C., Telzer, E., Mogg, K., Bradley, B., Mai, X., Louro, H., Chen, G., McClure-Tone, E., Ernst, M., and Pine, D. (2008a). Amygdala and ventrolateral prefrontal cortex activation to masked angry faces in children and adolescents with generalized anxiety disorder. *Archives of General Psychiatry*, 65(5):568–576.

Monk, C. S., Klein, R. G., Telzer, E. H., Schroth, E. A., Mannuzza, S., Moulton III, J. L., Guardino, M., Masten, C. L., McClure-Tone, E. B., Fromm, S., et al. (2008b). Amygdala and nucleus accumbens activation to emotional facial expressions in children and adolescents at risk for major depression. *American Journal of Psychiatry*.

Monk, C. S., Nelson, E. E., McClure, E. B., Mogg, K., Bradley, B. P., Leibenluft, E., Blair, R. J. R., Chen, G., Charney, D. S., Ernst, M., et al. (2006). Ventrolateral prefrontal cortex activation and attentional bias in response to angry faces in adolescents with generalized anxiety disorder. *American Journal of Psychiatry*.

Montoya, E. R., van Honk, J., Bos, P. A., and Terburg, D. (2015). Dissociated neural effects of cortisol depending on threat escapability. *Human Brain Mapping*, 36(11):4304–4316.

Moons, W. G., Eisenberger, N. I., and Taylor, S. E. (2010). Anger and fear responses to stress have different biological profiles. *Brain, behavior, and immunity*, 24(2):215–219.

Moor, B. G., Güroğlu, B., de Macks, Z. A. O., Rombouts, S. A., Van der Molen, M. W., and Crone, E. A. (2012). Social exclusion and punishment of excluders: neural correlates and developmental trajectories. *Neuroimage*, 59(1):708–717.

Morawetz, C., Bode, S., Baudewig, J., Jacobs, A. M., and Heekeren, H. R. (2016). Neural representation of emotion regulation goals. *Human brain mapping*, 37(2):600–620.

Morawetz, C., Bode, S., Baudewig, J., Kirilina, E., and Heekeren, H. (2015). Changes in effective connectivity between dorsal and ventral prefrontal regions moderate emotion regulation. *Cereb Cortex*.

Morean, M. E. and Corbin, W. R. (2010). Subjective response to alcohol: a critical review of the literature. *Alcoholism: Clinical and Experimental Research*, 34(3):385–395.

Morean, M. E., Corbin, W. R., and Treat, T. A. (2015). Differences in subjective response to alcohol by gender, family history, heavy episodic drinking, and cigarette use: Refining and broadening the scope of measurement. *Journal of studies on alcohol and drugs*, 76(2):287–295.

Moreno-López, L., Stamatakis, E. A., Fernández-Serrano, M. J., Gómez-Río, M., Rodríguez-Fernández, A., Pérez-García, M., and Verdejo-García, A. (2012). Neural correlates of the severity of cocaine, heroin, alcohol, mdma and cannabis use in polysubstance abusers: A resting-pet brain metabolism study. *PLoS One*, 7(6).

Morey, R. A., Haswell, C. C., Hooper, S. R., and De Bellis, M. D. (2016). Amygdala, hippocampus, and ventral medial prefrontal cortex volumes differ in maltreated youth with and without chronic posttraumatic stress disorder. *Neuropsychopharmacology*, 41(3):791–801.

Morgan, A. (2015). Is psychiatry dying? crisis and critique in contemporary psychiatry. *Social Theory & Health*, 13(2):141–161.

Morgan, C. J., Muetzelfeldt, L., Muetzelfeldt, M., Nutt, D. J., and Curran, H. V. (2009). Harms associated with psychoactive substances: findings of the uk national drug survey. *Journal of Psychopharmacology*.

Morgan, M. and Marshall, J. (2013). Deficient fear recognition in regular cocaine users is not attributable to elevated impulsivity or conduct disorder prior to cocaine use. *Journal of Psychopharmacology*, 27(6):526–532.

Morgenstern, J. and Longabaugh, R. (2000). Cognitive–behavioral treatment for alcohol dependence: A review of evidence for its hypothesized mechanisms of action. *Addiction*, 95(10):1475–1490.

Morie, K. P., Yip, S. W., Nich, C., Hunkele, K., Carroll, K. M., and Potenza, M. N. (2016). Alexithymia and addiction: A review and preliminary data suggesting neurobiological links to reward/loss processing. *Current Addiction Reports*, 3(2):239–248.

Morisano, D., Babor, T. F., and Robaina, K. A. (2014). Co-occurrence of substance use disorders with other psychiatric disorders: Implications for treatment services. *Nordic Studies on Alcohol and Drugs*, 31(1):5–25.

Morley, K., Baillie, A., Leung, S., Sannibale, C., Teesson, M., and Haber, P. (2015). Is specialized integrated treatment for comorbid anxiety, depression and alcohol dependence better than treatment as usual in a public hospital setting? *Alcohol and alcoholism*, page agv131.

Morozova, T. V., Goldman, D., Mackay, T., and Anholt, R. (2012). The genetic basis of alcoholism: multiple phenotypes, many genes, complex networks. *Genome Biol*, 13(2):239.

Morozova, T. V., Mackay, T. F., and Anholt, R. R. (2014). Genetics and genomics of alcohol sensitivity. *Molecular Genetics and Genomics*, 289(3):253–269.

Morris, A. B. and Albery, I. P. (2001). Alcohol consumption and hiv risk behaviours: Integrating the theories of alcohol myopia and outcome-expectancies. *Addiction Research & Theory*, 9(1):73–86.

Morris, D. H., Treloar, H., Tsai, C.-L., McCarty, K. N., and McCarthy, D. M. (2016). Acute subjective response to alcohol as a function of reward and punishment sensitivity. *Addictive behaviors*, 60:90–96.

Morris, J., Friston, K., Büchel, C., Frith, C., Young, A., Calder, A., and Dolan, R. (1998). A neuromodulatory role for the human amygdala in processing emotional facial expressions. *Brain*, 121(1):47–57.

Morrison, A. P., Frame, L., and Larkin, W. (2003). Relationships between trauma and psychosis: a review and integration. *British Journal of Clinical Psychology*, 42(4):331–353.

Morrison, A. S., Brozovich, F. A., Lee, I. A., Jazaieri, H., Goldin, P. R., Heimberg, R. G., and Gross, J. J. (2016). Anxiety trajectories in response to a speech task in social anxiety disorder: Evidence from a randomized controlled trial of cbt. *Journal of anxiety disorders*, 38:21–30.

Morriss, J., Macdonald, B., and van Reekum, C. M. (2016). What is going on around here? intolerance of uncertainty predicts threat generalization. *PloS one*, 11(5):e0154494.

Morzorati, S., Ramchandani, V., Flury, L., Li, T.-K., and O'Connor, S. (2002). Self-reported subjective perception of intoxication reflects family history of alcoholism when breath alcohol levels are constant. *Alcoholism: Clinical and Experimental Research*, 26(8):1299–1306.

Moscovitch, D. (2009). What is the core fear in social phobia? a new model to facilitate individualized case conceptualization and treatment. *Cognitive and Behavioral Practice*, 16(2):123–134.

Moss, H. (2013). The impact of alcohol on society: A brief overview. *Social Work in Public Health*, 28(3-4):175–177.

Moss, H., Yao, J., and Maddock, J. (1989). Responses by sons of alcoholic fathers to alcoholic and placebo drinks: Perceived mood, intoxication, and plasma prolactin. *Alcoholism: Clinical and Experimental Research*, 13(2):252–257.

Moss, H. B., Vanyukov, M. M., and Martin, C. S. (1995). Salivary cortisol responses and the risk for substance abuse in prepubertal boys. *Biological psychiatry*, 38(8):547–555.

Motley, M. T. (1990). Public speaking anxiety qua performance anxiety: A revised model and an alternative therapy. *Journal of Social Behavior and Personality*, 5(2):85.

Motzkin, J. C., Philippi, C. L., Wolf, R. C., Baskaya, M. K., and Koenigs, M. (2015). Ventromedial prefrontal cortex is critical for the regulation of amygdala activity in humans. *Biological psychiatry*, 77(3):276–284.

Muehlberger, C. W. (1957). *Medicolegal aspects of alcohol intoxication*, volume 35. National Safety Council.

Mueller, N. K., Dolgas, C. M., and Herman, J. P. (2004). Stressor-selective role of the ventral subiculum in regulation of neuroendocrine stress responses. *Endocrinology*, 145(8):3763–3768.

Mujica-Parodi, L., Carlson, J. M., Cha, J., and Rubin, D. (2014). The fine line between 'brave'and 'reckless': Amygdala reactivity and regulation predict recognition of risk. *NeuroImage*, 103:1–9.

Mujica-Parodi, L. R., Strey, H. H., Frederick, B., Savoy, R., Cox, D., Botanov, Y., Tolkunov, D., Rubin, D., and Weber, J. (2009). Chemosensory cues to conspecific emotional stress activate amygdala in humans. *PLoS One*, 4(7):e6415.

Müller, K. U., Gan, G., Banaschewski, T., Barker, G. J., Bokde, A. L., Büchel, C., Conrod, P., Fauth-Bühler, M., Flor, H., Gallinat, J., et al. (2015). No differences in ventral striatum responsivity between adolescents with a positive family history of alcoholism and controls. *Addiction biology*, 20(3):534–545.

Müller, V. I., Cieslik, E. C., Turetsky, B. I., and Eickhoff, S. B. (2012). Crossmodal interactions in audiovisual emotion processing. *Neuroimage*, 60(1):553–561.

Müller-Pinzler, L., Gazzola, V., Keysers, C., Sommer, J., Jansen, A., Frässle, S., Einhäuser, W., Paulus, F., and Krach, S. (2015). Neural pathways of embarrassment and their modulation by social anxiety. *Neuroimage*, 119:252–261.

Müller-Pinzler, L., Krach, S., Krämer, U. M., and Paulus, F. M. (2016a). The social neuroscience of interpersonal emotions. *Current Topics in Behavioral Neurosciences*.

Müller-Pinzler, L., Rademacher, L., Paulus, F. M., and Krach, S. (2016b). When your friends make you cringe: social closeness modulates vicarious embarrassment-related neural activity. *Social cognitive and affective neuroscience*, 11(3):466–475.

Mulligan, C. J., Robin, R. W., Osier, M. V., Sambuughin, N., Goldfarb, L. G., Kittles, R. A., Hesselbrock, D., Goldman, D., and Long, J. C. (2003). Allelic variation at alcohol metabolism genes (adh1b, adh1c, aldh2) and alcohol dependence in an american indian population. *Human genetics*, 113(4):325–336.

Mulligan, E. J., George, A. M., and Brown, P. M. (2016). Social anxiety and drinking game participation among university students: the moderating role of drinking to cope. *The American Journal of Drug and Alcohol Abuse*, pages 1–9.

Mullins, P. M., Mazer-Amirshahi, M., and Pines, J. M. (2016). Epidemiology of alcohol-related visits to united states emergency departments, 2001-2010.

Mullins-Sweatt, S. N., Lengel, G. J., and DeShong, H. L. (2016). The importance of considering clinical utility in the construction of a diagnostic manual. *Annual review of clinical psychology*, 12:133–155.

Mulvihill, L., Skilling, T., and Vogel-Sprott, M. (1997). Alcohol and the ability to inhibit behavior in men and women. *Journal of Studies on Alcohol*, 58(6):600–605.

Mun, E.-Y., Atkins, D. C., and Walters, S. T. (2015). Is motivational interviewing effective at reducing alcohol misuse in young adults? a critical review of foxcroft et al.(2014). *Psychology of Addictive Behaviors*, 29(4):836.

Munro, C. A., McCaul, M. E., Oswald, L. M., Wong, D. F., Zhou, Y., Brasic, J., Kuwabara, H., Kumar, A., Alexander, M., Ye, W., et al. (2006). Striatal dopamine release and family history of alcoholism. *Alcoholism: Clinical and Experimental Research*, 30(7):1143–1151.

Murdoch, D., Pihl, R., and Ross, D. (1990). Alcohol and crimes of violence: Present issues. *International Journal of the Addictions*, 25(9):1065–1081.

Murphy, C., Winters, J., Fals-Stewart, W., O'Farrell, T., and Murphy, M. (2005). Alcohol consumption and intimate partner violence by alcoholic men: Comparing violent and nonviolent conflicts. *Psychology of Addictive Behaviors*, 19(1):35–42.

Murphy, F. C., Nimmo-Smith, I., and Lawrence, A. D. (2003). Functional neuroanatomy of emotions: a meta-analysis. *Cognitive, Affective, & Behavioral Neuroscience*, 3(3):207–233.

Murray, E. A. and Izquierdo, A. (2007). Orbitofrontal cortex and amygdala contributions to affect and action in primates. *Annals of the New York Academy of Sciences*, 1121(1):273–296.

Murray, J., Burgess, S., Zuccolo, L., Hickman, M., Gray, R., and Lewis, S. J. (2015). Moderate alcohol drinking in pregnancy increases risk for children's persistent conduct problems: causal effects in a mendelian randomisation study. *Journal of child psychology and psychiatry*.

Muscatell, K., Dedovic, K., Slavich, G., Jarcho, M., Breen, E., Bower, J., Irwin, M., and Eisenberger, N. (2016). Neural mechanisms linking social status and inflammatory responses to social stress. *Social cognitive and affective neuroscience*.

Muscatell, K. A. and Eisenberger, N. I. (2012). A social neuroscience perspective on stress and health. *Social and personality psychology compass*, 6(12):890–904.

Muscatell, K. A., Morelli, S. A., Falk, E. B., Way, B. M., Pfeifer, J. H., Galinsky, A. D., Lieberman, M. D., Dapretto, M., and Eisenberger, N. I. (2012). Social status modulates neural activity in the mentalizing network. *Neuroimage*, 60(3):1771–1777.

Myers, K. M. and Davis, M. (2002). Behavioral and neural analysis of extinction. *Neuron*, 36(4):567–584.

Nachmias, M., Gunnar, M., Mangelsdorf, S., Parritz, R., and Buss, K. (1996). Behavioral inhibition and stress reactivity: The moderating role of attachment security. *Child Development*, 67(2):508–522.

Nadal, R., Armario, A., and Janak, P. (2002). Positive relationship between activity in a novel environment and operant ethanol self-administration in rats. *Psychopharmacology*, 162(3):333–338.

Nagahama, Y., Okada, T., Katsumi, Y., Hayashi, T., Yamauchi, H., Sawamoto, N., Toma, K., Nakamura, K., Hanakawa, T., Konishi, J., et al. (1999). Transient neural activity in the medial superior frontal gyrus and precuneus time locked with attention shift between object features. *Neuroimage*, 10(2):193–199.

Nagel, B., Herting, M. M., and Cservenka, A. (2012). Working memory and addictive behavior. *Alloway, Tracy Packiam and Alloway, Ross G (Eds.) Working memory: The connected intelligence*.

Nagel, B. J., Schweinsburg, A. D., Phan, V., and Tapert, S. F. (2005). Reduced hippocampal volume among adolescents with alcohol use disorders without psychiatric comorbidity. *Psychiatry Research: Neuroimaging*, 139(3):181–190.

Naghavi, H. R. and Nyberg, L. (2005). Common fronto-parietal activity in attention, memory, and consciousness: shared demands on integration? *Consciousness and cognition*, 14(2):390–425.

Naimi, T. S., Brewer, R. D., Mokdad, A., Denny, C., Serdula, M. K., and Marks, J. S. (2003). Binge drinking among us adults. *Jama*, 289(1):70–75.

Naqvi, N. H. and Bechara, A. (2009). The hidden island of addiction: the insula. *Trends in neurosciences*, 32(1):56–67.

Naqvi, N. H. and Bechara, A. (2010). The insula and drug addiction: an interoceptive view of pleasure, urges, and decision-making. *Brain Structure and Function*, 214(5-6):435–450.

Naqvi, N. H., Rudrauf, D., Damasio, H., and Bechara, A. (2007). Damage to the insula disrupts addiction to cigarette smoking. *Science*, 315(5811):531–534.

Naragon-Gainey, K. (2010). Meta-analysis of the relations of anxiety sensitivity to the depressive and anxiety disorders. *Psychological bulletin*, 136(1):128.

Narumoto, J., Okada, T., Sadato, N., Fukui, K., and Yonekura, Y. (2001). Attention to emotion modulates fmri activity in human right superior temporal sulcus. *Cognitive Brain Research*, 12(2):225–231.

Nasby, W., Hayden, B., and DePaulo, B. (1980). Attributional bias among aggressive boys to interpret unambiguous social stimuli as displays of hostility. *Journal of Abnormal Psychology*, 89(3):459–468.

Nater, U. M., Moor, C., Okere, U., Stallkamp, R., Martin, M., Ehlert, U., and Kliegel, M. (2007). Performance on a declarative memory task is better in high than low cortisol responders to psychosocial stress. *Psychoneuroendocrinology*, 32(6):758–763.

Nathan, P. E., Conrad, M., and Skinstad, A. H. (2016). History of the concept of addiction. *Annual review of clinical psychology*, 12:29–51.

Neal, J. A. and Edelmann, R. J. (2003). The etiology of social phobia: Toward a developmental profile. *Clinical Psychology Review*, 23(6):761–786.

Neale, M. and Martin, N. (1989). The effects of age, sex, and genotype on self-report drunkenness following a challenge dose of alcohol. *Behavior Genetics*, 19(1):63–78.

Nees, F., Tzschoppe, J., Patrick, C. J., Vollstädt-Klein, S., Steiner, S., Poustka, L., Banaschewski, T., Barker, G. J., Büchel, C., Conrod, P. J., et al. (2012). Determinants of early alcohol use in healthy adolescents: the differential contribution of neuroimaging and psychological factors. *Neuropsychopharmacology*, 37(4):986–995.

Nemeroff, C. B. (2016). Paradise lost: the neurobiological and clinical consequences of child abuse and neglect. *Neuron*, 89(5):892–909.

Neria, Y., Solomon, Z., Ginzburg, K., and Dekel, R. (2000). Sensation seeking, wartime performance, and long-term adjustment among israeli war veterans. *Personality and Individual Differences*, 29(5):921–932.

Nesse, R. M. and Stein, D. J. (2012). Towards a genuinely medical model for psychiatric nosology. *BMC medicine*, 10(1):1.

Neta, M., Davis, F. C., and Whalen, P. J. (2011). Valence resolution of ambiguous facial expressions using an emotional oddball task. *Emotion*, 11(6):1425.

Neta, M., Norris, C. J., and Whalen, P. J. (2009). Corrugator muscle responses are associated with individual differences in positivity-negativity bias. *Emotion*, 9(5):640.

Neta, M., Tong, T. T., Rosen, M. L., Enersen, A., Kim, M. J., and Dodd, M. D. (2016). All in the first glance: first fixation predicts individual differences in valence bias. *Cognition and Emotion*, pages 1–9.

Netter, P., Hennig, J., and Roed, I. (1996). Serotonin and dopamine as mediators of sensation seeking behavior. *Neuropsychobiology*, 34(3):155–165.

Newbury, J., Arseneault, L., Caspi, A., Moffitt, T. E., Odgers, C. L., and Fisher, H. L. (2016). Why are children in urban neighborhoods at increased risk for psychotic symptoms? findings from a uk longitudinal cohort study. *Schizophrenia bulletin*, page sbw052.

Newlin, D. B. and Renton, R. M. (2010). High risk groups often have higher levels of alcohol response than low risk: the other side of the coin. *Alcoholism: Clinical and Experimental Research*, 34(2):199–202.

Newlin, D. B. and Thomson, J. B. (1991). Chronic tolerance and sensitization to alcohol in sons of alcoholics. *Alcoholism: Clinical and Experimental Research*, 15(3):399–405.

Newlin, D. B. and Thomson, J. B. (1999). Chronic tolerance and sensitization to alcohol in sons of alcoholics: Ii. replication and reanalysis. *Experimental and clinical psychopharmacology*, 7(3):234.

Nezlek, J. B. and Leary, M. R. (2002). Individual differences in self-presentational motives in daily social interaction. *Personality and Social Psychology Bulletin*, 28(2):211–223.

Ngô, T.-L. (2012). [review of the effects of mindfulness meditation on mental and physical health and its mechanisms of action]. *Sante mentale au Quebec*, 38(2):19–34.

Nguyen, V. T., Breakspear, M., Hu, X., and Guo, C. C. (2016). The integration of the internal and external milieu in the insula during dynamic emotional experiences. *NeuroImage*, 124:455–463.

Nicholson, A. A., Rabellino, D., Densmore, M., Frewen, P. A., Paret, C., Kluetsch, R., Schmahl, C., Théberge, J., Neufeld, R. W., McKinnon, M. C., et al. (2016a). The neurobiology of emotion regulation in posttraumatic stress disorder: Amygdala downregulation via real-time fmri neurofeedback. *Human Brain Mapping*.

Nicholson, A. A., Sapru, I., Densmore, M., Frewen, P. A., Neufeld, R. W., Théberge, J., McKinnon, M. C., and Lanius, R. A. (2016b). Unique insula subregion resting-state functional connectivity with amygdala complexes in posttraumatic stress disorder and its dissociative subtype. *Psychiatry Research: Neuroimaging*, 250:61–72.

Nichter, B. and Chassin, L. (2015). Separate dimensions of anxiety differentially predict alcohol use among male juvenile offenders. *Addictive behaviors*, 50:144–148.

Nicol, A., Gunn, J., Gristwood, J., Foggitt, R., and Watson, J. (1973). The relationship of alcoholism to violent behaviour resulting in long term imprisonment. *British Journal of Psychiatry*, 123(572):47–51.

Nie, Z., Schweitzer, P., Roberts, A. J., Madamba, S. G., Moore, S. D., and Siggins, G. R. (2004). Ethanol augments gabaergic transmission in the central amygdala via crf1 receptors. *Science*, 303(5663):1512–1514.

Nie, Z., Zorrilla, E., Madamba, S., Rice, K., Roberto, M., and Siggins, G. (2009). Presynaptic crf1 receptors mediate the ethanol enhancement of gabaergic transmission in the mouse central amygdala. *TheScientificWorldJournal*, 9:68–85.

Niehoff, D. and Kuhar, M. (1983). Benzodiazepine receptors: localization in rat amygdala. *The Journal of Neuroscience*, 3(10):2091–2097.

Niehoff, D. L. and Whitehouse, P. J. (1983). Multiple benzodiazepine receptors: autoradiographic localization in normal human amygdala. *Brain research*, 276(2):237–245.

Nigg, J. T., Glass, J. M., Wong, M. M., Poon, E., Jester, J. M., Fitzgerald, H. E., Puttler, L. I., Adams, K. M., and Zucker, R. A. (2004). Neuropsychological executive functioning in children at elevated risk for alcoholism: findings in early adolescence. *Journal of abnormal psychology*, 113(2):302.

Nikolova, Y. S. and Hariri, A. R. (2012). Neural responses to threat and reward interact to predict stress-related problem drinking: A novel protective role of the amygdala. *Biology of mood & anxiety disorders*, 2(1):1.

Nikolova, Y. S., Knodt, A. R., Radtke, S. R., and Hariri, A. R. (2016). Divergent responses of the amygdala and ventral striatum predict stress-related problem drinking in young adults: possible differential markers of affective and impulsive pathways of risk for alcohol use disorder. *Molecular psychiatry*, 21(3):348–356.

Nillni, Y. I., Toufexis, D. J., and Rohan, K. J. (2011). Anxiety sensitivity, the menstrual cycle, and panic disorder: a putative neuroendocrine and psychological interaction. *Clinical psychology review*, 31(7):1183–1191.

Nitschke, J., Sarinopoulos, I., Oathes, D., Johnstone, T., Whalen, P., Davidson, R., and Kalin, N. (2009). Anticipatory activation in the amygdala and anterior cingulate in generalized anxiety disorder and prediction of reatment response. *American Journal of Psychiatry*, 166(3):302–310.

Nitschke, J. B., Sarinopoulos, I., Mackiewicz, K. L., Schaefer, H. S., and Davidson, R. J. (2006). Functional neuroanatomy of aversion and its anticipation. *Neuroimage*, 29(1):106–116.

Nixon, S. J. and Tivis, A. (1997). Neuropsychological responses in coa's. *Alcohol Research and Health*, 21(3):232.

Noël, X., Brevers, D., Bechara, A., Hanak, C., Kornreich, C., Verbanck, P., and Le Bon, O. (2011). Neurocognitive determinants of novelty and sensation-seeking in individuals with alcoholism. *Alcohol and alcoholism*, 46(4):407–415.

Nolan, S. A., Flynn, C., and Garber, J. (2003). Prospective relations between rejection and depression in young adolescents. *Journal of personality and social psychology*, 85(4):745.

Nolen-Hoeksema, S. (2012). Emotion regulation and psychopathology: The role of gender. *Annual review of clinical psychology*, 8:161–187.

Nolte, T., Bolling, D. Z., Hudac, C. M., Fonagy, P., Mayes, L., and Pelphrey, K. A. (2012). Brain mechanisms underlying the impact of attachment-related stress on social cognition. *Frontiers in human neuroscience*, 7:816–816.

Noordermeer, S. D., Luman, M., and Oosterlaan, J. (2016). A systematic review and meta-analysis of neuroimaging in oppositional defiant disorder (odd) and conduct disorder (cd) taking attention-deficit hyperactivity disorder (adhd) into account. *Neuropsychology review*, 26(1):44–72.

Norbury, A. and Husain, M. (2015). Sensation-seeking: Dopaminergic modulation and risk for psychopathology. *Behavioural brain research*, 288:79–93.

Norbury, A., Kurth-Nelson, Z., Winston, J. S., Roiser, J. P., and Husain, M. (2015). Dopamine regulates approach-avoidance in human sensation-seeking. *International Journal of Neuropsychopharmacology*, 18(10):pyv041.

Norman, A., Pulido, C., Squeglia, L., Spadoni, A., Paulus, M., and Tapert, S. (2011). Neural activation during inhibition predicts initiation of substance use in adolescence. *Drug and Alcohol Dependence*, 119(3):216–223.

Northoff, G. and Bermpohl, F. (2004). Cortical midline structures and the self. *Trends in cognitive sciences*, 8(3):102–107.

Northoff, G., Heinzel, A., de Greck, M., Bermpohl, F., Dobrowolny, H., and Panksepp, J. (2006). Self-referential processing in our brain-a meta-analysis of imaging studies on the self. *NeuroImage*, 31(1):440–457.

Novak, A., Burgess, E., Clark, M., Zvolensky, M., and Brown, R. (2003). Anxiety sensitivity, self-reported motives for alcohol and nicotine use, and level of consumption. *Journal of Anxiety Disorders*, 17(2):165–180.

Novick, J. and Kelly, K. (1970). Projection and externalization. *The psychoanalytic study of the child*.

Núñez, J. F., Ferré, P., Escorihuela, R. M., Tobeña, A., and Fernández-Teruel, A. (1996). Effects of postnatal handling of rats on emotional, hpa-axis, and prolactin reactivity to novelty and conflict. *Physiology & Behavior*, 60(5):1355–1359.

Nunn, J., Erdogan, M., and Green, R. S. (2016). The prevalence of alcohol-related trauma recidivism: A systematic review. *Injury*, 47(3):551–558.

Nutt, D. and Peters, T. (1994). Alcohol: the drug. *British medical bulletin*, 50(1):5–17.

Nutt, D. J., King, L. A., Phillips, L. D., et al. (2010). Drug harms in the uk: a multicriteria decision analysis. *The Lancet*, 376(9752):1558–1565.

Nutt, D. J., Lingford-Hughes, A., Erritzoe, D., and Stokes, P. R. (2015). The dopamine theory of addiction: 40 years of highs and lows. *Nature Reviews Neuroscience*, 16(5):305–312.

Nyberg, L. (1999). Functional neuroanatomy of component processes of episodic memory retrieval. *Cognitive neuroscience of memory. Seattle, WA: Hogrefe & Huber*.

Oades, R. D. and Halliday, G. M. (1987). Ventral tegmental (a10) system: neurobiology. 1. anatomy and connectivity. *Brain Research Reviews*, 12(2):117–165.

Oberlander, T. F., Weinberg, J., Papsdorf, M., Grunau, R., Misri, S., and Devlin, A. M. (2008). Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (nr3c1) and infant cortisol stress responses. *Epigenetics*, 3(2):97–106.

Oberlin, B. G., Dzemidzic, M., Tran, S. M., Soeurt, C. M., Albrecht, D. S., Yoder, K. K., and Kareken, D. A. (2013). Beer flavor provokes striatal dopamine release in male drinkers: mediation by family history of alcoholism. *Neuropsychopharmacology*, 38(9):1617–1624.

Obradović, J. (2012). How can the study of physiological reactivity contribute to our understanding of adversity and resilience processes in development? *Development and Psychopathology*, 24(02):371–387.

O'Brien, A., Terry, D. J., and Jimmieson, N. L. (2008). Negative affectivity and responses to work stressors: An experimental study. *Anxiety, stress, and coping*, 21(1):55–83.

O'Brien, C. P., Childress, A. R., Ehrman, R., and Robbins, S. J. (1998). Conditioning factors in drug abuse: can they explain compulsion? *Journal of Psychopharmacology*, 12(1):15–22.

Ochsner, K., Silvers, J., and Buhle, J. (2012). Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. *Annals of the New York Academy of Sciences*, 1251:E1–24.

Ochsner, K. N., Bunge, S. A., Gross, J. J., and Gabrieli, J. D. (2002). Rethinking feelings: an fmri study of the cognitive regulation of emotion. *Journal of cognitive neuroscience*, 14(8):1215–1229.

Ochsner, K. N. and Gross, J. J. (2005). The cognitive control of emotion. *Trends in cognitive sciences*, 9(5):242–249.

Ochsner, K. N., Hughes, B., Robertson, E. R., Cooper, J. C., and Gabrieli, J. D. (2009). Neural systems supporting the control of affective and cognitive conflicts. *Journal of cognitive neuroscience*, 21(9):1841–1854.

Ochsner, K. N., Ray, R. D., Cooper, J. C., Robertson, E. R., Chopra, S., Gabrieli, J. D., and Gross, J. J. (2004). For better or for worse: neural systems supporting the cognitive down-and up-regulation of negative emotion. *Neuroimage*, 23(2):483–499.

O'connor, R. M., Farrow, S., and Colder, C. R. (2008). Clarifying the anxiety sensitivity and alcohol use relation: Considering alcohol expectancies as moderators. *Journal of studies on alcohol and drugs*, 69(5):765–772.

Odlaug, B., Gual, A., DeCourcy, J., Perry, R., Pike, J., Heron, L., and Rehm, J. (2016). Alcohol dependence, co-occurring conditions and attributable burden. *Alcohol and alcoholism*, 51(2):201–209.

O'Doherty, J., Dayan, P., Schultz, J., Deichmann, R., Friston, K., and Dolan, R. J. (2004). Dissociable roles of ventral and dorsal striatum in instrumental conditioning. *Science*, 304(5669):452–454.

of Alcohol Abuse, N. I. and Alcoholism (2004). Niaaa council approves definition of binge drinking. *NIAAA newsletter*, 3(3).

of Health, U. D., Services, H., et al. (2005). National survey on drug use and health. *Rockville (MD): Substance Abuse and Mental Health Services Administration, Office of Applied Studies*.

O'Farrell, T., Fals-Stewart, W., Murphy, M., and Murphy, C. (2003). Partner violence before and after individually based alcoholism treatment for male alcoholic patients. *Journal of Consulting and Clinical Psychology*, 71(1):92–102.

Ogawa, S., Lee, T.-M., Kay, A. R., and Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences*, 87(24):9868–9872.

Ogino, Y., Nemoto, H., Inui, K., Saito, S., Kakigi, R., and Goto, F. (2007). Inner experience of pain: imagination of pain while viewing images showing painful events forms subjective pain representation in human brain. *Cerebral Cortex*, 17(5):1139–1146.

Oglesby, M. E., Albanese, B. J., Chavarria, J., and Schmidt, N. B. (2015). Intolerance of uncertainty in relation to motives for alcohol use. *Cognitive Therapy and Research*, 39(3):356–365.

Ohira, H., Nomura, M., Ichikawa, N., Isowa, T., Iidaka, T., Sato, A., Fukuyama, S., Nakajima, T., and Yamada, J. (2006). Association of neural and physiological responses during voluntary emotion suppression. *Neuroimage*, 29(3):721–733.

Öhman, A. (2002). Automaticity and the amygdala: Nonconscious responses to emotional faces. *Current directions in psychological science*, 11(2):62–66.

Öhman, A. and Mineka, S. (2001). Fears, phobias, and preparedness: toward an evolved module of fear and fear learning. *Psychological review*, 108(3):483.

O'Keeffe, L. M., Kearney, P. M., Greene, R. A., and Kenny, L. C. (2016). Alcohol use during pregnancy. *Obstetrics, Gynaecology & Reproductive Medicine*, 26(6):188–189.

Okon-Singer, H., Stout, D., Stockbridge, M., Gamer, M., Fox, A., and Shackman, A. (2016). The interplay of emotion and cognition. *The nature of emotion. Fundamental questions*.

Oler, J. A., Fox, A. S., Shackman, A. J., and Kalin, N. H. (2015). The central nucleus of the amygdala is a critical substrate for individual differences in anxiety. *Living without an amygdala*.

Oleson, T. D., Kroening, R. J., and Bresler, D. E. (1980). An experimental evaluation of auricular diagnosis: the somatotopic mapping of musculoskeletal pain at ear acupuncture points. *Pain*, 8(2):217–229.

Oliveira, L., Ladouceur, C. D., Phillips, M. L., Brammer, M., and Mourao-Miranda, J. (2013). What does brain response to neutral faces tell us about major depression? evidence from machine learning and fmri. *PloS one*, 8(4):e60121.

Olsen, S. O., Tudoran, A. A., Honkanen, P., and Verplanken, B. (2016). Differences and similarities between impulse buying and variety seeking: A personality-based perspective. *Psychology & Marketing*, 33(1):36–47.

O'Neill, M. and Schultz, W. (2010). Coding of reward risk by orbitofrontal neurons is mostly distinct from coding of reward value. *Neuron*, 68(4):789–800.

Onoda, K., Okamoto, Y., Nakashima, K., Nittono, H., Ura, M., and Yamawaki, S. (2009). Decreased ventral anterior cingulate cortex activity is associated with reduced social pain during emotional support. *Social Neuroscience*, 4(5):443–454.

Oorsouw, K. and Merckelbach, H. (2012). The effects of alcohol on crime-related memories: A field study. *Applied Cognitive Psychology*, 26(1):82–90.

Organization, W. H. (2007). World health organization expert committee on problems related to alcohol consumption. *Geneva: World Health Organisation*.

Organization, W. H. (2012). Alcohol in the european union: consumption, harm and policy approaches: Final report, copenhagen 27 march 2012. *Alcoholism and Drug Abuse*.

Ormel, J., Raven, D., van Oort, F., Hartman, C., Reijneveld, S., Veenstra, R., Vollebergh, W., Buitelaar, J., Verhulst, F., and Oldehinkel, A. (2014). Mental health in dutch adolescents: a trails report on prevalence, severity, age of onset, continuity and co-morbidity of dsm disorders. *Psychological medicine*, pages 1–16.

Ornish, D., Magbanua, M. J. M., Weidner, G., Weinberg, V., Kemp, C., Green, C., Mattie, M. D., Marlin, R., Simko, J., Shinohara, K., et al. (2008). Changes in prostate gene expression in men undergoing an intensive nutrition and lifestyle intervention. *Proceedings of the National Academy of Sciences*, 105(24):8369–8374.

Orsillo, S. M., Lilienfeld, S. O., and Heimberg, R. G. (1994). Social phobia and response to challenge procedures: Examining the interaction between anxiety sensitivity and trait anxiety. *Journal of Anxiety Disorders*, 8(3):247–258.

Orsini, C. A., Moorman, D. E., Young, J. W., Setlow, B., and Floresco, S. B. (2015). Neural mechanisms regulating different forms of risk-related decision-making: Insights from animal models. *Neuroscience & Biobehavioral Reviews*.

Ortner, C. N., MacDonald, T. K., and Olmstead, M. C. (2003). Alcohol intoxication reduces impulsivity in the delay-discounting paradigm. *Alcohol and Alcoholism*, 38(2):151–156.

Orwell, G. (1968). The collected essays, journalism and letters of george orwell: Volume ii: My country right or left, 1940-1943.

Oscar-Berman, M. and Marinković, K. (2007). Alcohol: effects on neurobehavioral functions and the brain. *Neuropsychology review*, 17(3):239–257.

Oshri, A., Carlson, M. W., Kwon, J. A., Zeichner, A., and Wickrama, K. K. (2016). Developmental growth trajectories of self-esteem in adolescence: associations with child neglect and drug use and abuse in young adulthood. *Journal of youth and adolescence*, pages 1–14.

Oshri, A., Sutton, T. E., Clay-Warner, J., and Miller, J. D. (2015). Child maltreatment types and risk behaviors: Associations with attachment style and emotion regulation dimensions. *Personality and Individual Differences*, 73:127–133.

Osman, A., Gutierrez, P. M., Smith, K., Fang, Q., Lozano, G., and Devine, A. (2010). The anxiety sensitivity index–3: analyses of dimensions, reliability estimates, and correlates in nonclinical samples. *Journal of Personality Assessment*, 92(1):45–52.

Ossewaarde, L., Hermans, E., van Wingen, G., Kooijman, S., Johansson, I.-M., Bäckström, T., and Fernández, G. (2010). Neural mechanisms underlying changes in stress-sensitivity across the menstrual cycle. *Psychoneuroendocrinology*, 35(1):47–55.

Öst, L.-G., Riise, E. N., Wergeland, G. J., Hansen, B., and Kvale, G. (2016). Cognitive behavioral and pharmacological treatments of ocd in children: A systematic review and meta-analysis. *Journal of Anxiety Disorders*.

O'Sullivan, S. S., Wu, K., Politis, M., Lawrence, A. D., Evans, A. H., Bose, S. K., Djamshidian, A., Lees, A. J., and Piccini, P. (2011). Cue-induced striatal dopamine release in parkinson's disease-associated impulsive-compulsive behaviours. *Brain*, page awr003.

Oswald, L., Mathena, J., and Wand, G. (2004). Comparison of hpa axis hormonal responses to naloxone vs psychologically-induced stress. *Psychoneuroendocrinology*, 29(3):371–388.

Ottaviani, C., Cevolani, D., Nucifora, V., Borlimi, R., Agati, R., Leonardi, M., De Plato, G., and Brighetti, G. (2012). Amygdala responses to masked and low spatial frequency fearful faces: a preliminary fmri study in panic disorder. *Psychiatry Research: Neuroimaging*, 203(2):159–165.

Otte, R., Donkers, F., Braeken, M., and Van den Bergh, B. (2015). Multimodal processing of emotional information in 9-month-old infants ii: Prenatal exposure to maternal anxiety. *Brain and cognition*, 95:107–117.

Otto, M. W., Smits, J. A., and Reese, H. E. (2004). Cognitive-behavioral therapy for the treatment of anxiety disorders. *Journal of Clinical Psychiatry*, 65:34–41.

Ozkaragoz, T., Satz, P., and Noble, E. P. (1997). Neuropsychological functioning in sons of active alcoholic, recovering alcoholic, and social drinking fathers. *Alcohol*, 14(1):31–37.

O'Connor, R. M., Colder, C. R., and Hawk, L. W. (2004). Confirmatory factor analysis of the sensitivity to punishment and sensitivity to reward questionnaire. *Personality and Individual Differences*, 37(5):985–1002.

O'Leary, M. M., Loney, B. R., and Eckel, L. A. (2007). Gender differences in the association between psychopathic personality traits and cortisol response to induced stress. *Psychoneuroendocrinology*, 32(2):183–191.

O'Leary-Barrett, M., Castellanos-Ryan, N., Pihl, R. O., and Conrod, P. J. (2016). Mechanisms of personality-targeted intervention effects on adolescent alcohol misuse, internalizing and externalizing symptoms. *Journal of Consulting and Clinical Psychology*.

O'Leary-Barrett, M. and Conrod, P. J. (2016). Young people and substance misuse. *Integrated Approaches to Drug and Alcohol Problems: Action on Addiction*, page 79.

O'Leary-Barrett, M., Pihl, R. O., Artiges, E., Banaschewski, T., Bokde, A. L., Büchel, C., Flor, H., Frouin, V., Garavan, H., Heinz, A., et al. (2015). Personality, attentional biases towards emotional faces and symptoms of mental disorders in an adolescent sample. *PloS one*, 10(6):e0128271.

O'Leary-Barrett, M., Topper, L., Al-Khudhairy, N., Pihl, R. O., Castellanos-Ryan, N., Mackie, C. J., and Conrod, P. J. (2013). Two-year impact of personality-targeted, teacher-delivered interventions on youth internalizing and externalizing problems: a cluster-randomized trial. *Journal of the American Academy of Child & Adolescent Psychiatry*, 52(9):911–920.

Pacak, K. and Palkovits, M. (2001). Stressor specificity of central neuroendocrine responses: implications for stress-related disorders. *Endocrine reviews*, 22(4):502–548.

Padula, C. B., Simmons, A. N., Matthews, S. C., Robinson, S. K., Tapert, S. F., Schuckit, M. A., and Paulus, M. P. (2011). Alcohol attenuates activation in the bilateral anterior insula during an emotional processing task: a pilot study. *Alcohol and alcoholism*, 46(5):547–552.

Paksarian, D., Cui, L., Angst, J., Ajdacic-Gross, V., Rössler, W., and Merikangas, K. R. (2016). Latent trajectories of common mental health disorder risk across 3 decades of adulthood in a population-based cohort. *Archives of general psychiatry*.

Palacio, A., Garay, D., Langer, B., Taylor, J., Wood, B. A., and Tamariz, L. (2016). Motivational interviewing improves medication adherence: a systematic review and meta-analysis. *Journal of general internal medicine*, pages 1–12.

Palermo, S., Benedetti, F., Costa, T., and Amanzio, M. (2015). Pain anticipation: An activation likelihood estimation meta-analysis of brain imaging studies. *Human brain mapping*, 36(5):1648–1661.

Pandey, S. C., Zhang, H., Roy, A., and Misra, K. (2006). Central and medial amygdaloid brain-derived neurotrophic factor signaling plays a critical role in alcohol-drinking and anxiety-like behaviors. *The Journal of neuroscience*, 26(32):8320–8331.

Paquette, V., Lévesque, J., Mensour, B., Leroux, J.-M., Beaudoin, G., Bourgouin, P., and Beauregard, M. (2003). "change the mind and you change the brain": effects of cognitive-behavioral therapy on the neural correlates of spider phobia. *Neuroimage*, 18(2):401–409.

Paquola, C., Bennett, M. R., and Lagopoulos, J. (2016). Understanding heterogeneity in grey matter research of adults with childhood maltreatment—a meta-analysis and review. *Neuroscience & Biobehavioral Reviews*.

Pardo, J. V., Fox, P. T., and Raichle, M. E. (1991). Localization of a human system for sustained attention by positron emission tomography. *Nature*, 349(6304):61–64.

Paret, C., Kluetsch, R., Zaehringer, J., Ruf, M., Demirakca, T., Bohus, M., Ende, G., and Schmahl, C. (2016a). Alterations of amygdala-prefrontal connectivity with real-time fmri neurofeedback in bpd patients. *Social cognitive and affective neuroscience*, 11(6):952–960.

Paret, C., Ruf, M., Gerchen, M. F., Kluetsch, R., Demirakca, T., Jungkunz, M., Bertsch, K., Schmahl, C., and Ende, G. (2016b). fmri neurofeedback of amygdala response to aversive stimuli enhances prefrontal–limbic brain connectivity. *NeuroImage*, 125:182–188.

Park, C. and Levenson, M. (2002). Drinking to cope among college students: Prevalence, problems and coping processes. *Journal of Studies on Alcohol*, 63(4):486–497.

Parker, G. (1983). *Parental overprotection: A risk factor in psychosocial development*. Grune & Stratton.

Parker, G. and Brotchie, H. (2010). Gender differences in depression. *International Review of Psychiatry*, 22(5):429–436.

Parker, G., Tupling, H., and Brown, L. (1979). A parental bonding instrument. *British journal of medical psychology*, 52(1):1–10.

Parkes, K. R. (1986). Coping in stressful episodes: The role of individual differences, environmental factors, and situational characteristics. *Journal of personality and social psychology*, 51(6):1277.

Parkinson, K., Newbury-Birch, D., Phillipson, A., Hindmarch, P., Kaner, E., Stamp, E., Vale, L., Wright, J., and Connolly, J. (2016). Prevalence of alcohol related attendance at an inner city emergency department and its impact: a dual prospective and retrospective cohort study. *Emergency medicine journal*, 33(3):187–193.

Parrott, D. J. and Giancola, P. R. (2004). A further examination of the relation between trait anger and alcohol-related aggression: The role of anger control. *Alcoholism: Clinical and Experimental Research*, 28(6):855–864.

Parvaz, M., Konova, A., Tomasi, D., Volkow, N., and Goldstein, R. (2012). Structural integrity of the prefrontal cortex modulates electrocortical sensitivity to reward. *Journal of Cognitive Neuroscience*, 24(7):1560–1570.

Parvizi, J., Van Hoesen, G. W., Buckwalter, J., and Damasio, A. (2006). Neural connections of the posteromedial cortex in the macaque. *Proceedings of the National Academy of Sciences*, 103(5):1563–1568.

Pascual, J., Soler, J., Baiget, M., Cortés, A., Menoyo, A., Barrachina, J., Ropero, M., Goma, M., Alvarez, E., and Perez, V. (2006). Association between the serotonin transporter gene and personality traits in borderline personality disorder patients evaluated with zuckerman-zuhlman personality questionnaire (zkpq). *Actas españolas de psiquiatría*, 35(6):382–386.

Passamonti, L., Fairchild, G., Fornito, A., Goodyer, I. M., Nimmo-Smith, I., Hagan, C. C., and Calder, A. J. (2012). Abnormal anatomical connectivity between the amygdala and orbitofrontal cortex in conduct disorder. *PloS one*, 7(11):e48789.

Paton, J. J., Belova, M. A., Morrison, S. E., and Salzman, C. D. (2006). The primate amygdala represents the positive and negative value of visual stimuli during learning. *Nature*, 439(7078):865–870.

Paulus, F., Müller-Pinzler, L., Jansen, A., Gazzola, V., and Krach, S. (2014). Mentalizing and the role of the posterior superior temporal sulcus in sharing others' embarrassment. *Cereb. Cortex*.

Paulus, F. M., Müller-Pinzler, L., Westermann, S., and Krach, S. (2013). On the distinction of empathic and vicarious emotions. *Frontiers in Human Neuroscience*.

Paulus, M. (2008). The role of neuroimaging for the diagnosis and treatment of anxiety disorders. *Depression and Anxiety*, 25(4):348–356.

Paulus, M., Feinstein, J., Castillo, G., Simmons, A., and Stein, M. (2005). Dose-dependent decrease of activation in bilateral amygdala and insula by lorazepam during emotion processing. *Archives of General Psychiatry*, 62(3):282–288.

Paulus, M. P., Rogalsky, C., Simmons, A., Feinstein, J. S., and Stein, M. B. (2003). Increased activation in the right insula during risk-taking decision making is related to harm avoidance and neuroticism. *Neuroimage*, 19(4):1439–1448.

Paulus, M. P., Schuckit, M. A., Tapert, S. F., Tolentino, N. J., Matthews, S. C., Smith, T. L., Trim, R. S., Hall, S. A., and Simmons, A. N. (2012). High versus low level of response to alcohol: Evidence of differential reactivity to emotional stimuli. *Biological psychiatry*, 72(10):848–855.

Paulus, M. P. and Stein, M. B. (2006). An insular view of anxiety. *Biological psychiatry*, 60(4):383–387.

Paulus, M. P. and Stewart, J. L. (2014). Interoception and drug addiction. *Neuropharmacology*, 76:342–350.

Paus, T. (2001). Primate anterior cingulate cortex: Where motor control, drive and cognition interface. *Nature Reviews Neuroscience*, 2(6):417–424.

Pearson, J. M., Hayden, B. Y., Raghavachari, S., and Platt, M. L. (2009). Neurons in posterior cingulate cortex signal exploratory decisions in a dynamic multioption choice task. *Current biology*, 19(18):1532–1537.

Pearson, J. M., Heilbronner, S. R., Barack, D. L., Hayden, B. Y., and Platt, M. L. (2011). Posterior cingulate cortex: adapting behavior to a changing world. *Trends in cognitive sciences*, 15(4):143–151.

Pedersen, S. L. (2016). Persisting differences in the sensitivity to the effects of alcohol: What we know and where to go from here. *Biological psychiatry*, 79(6):e15–e16.

Peele, S. and Brodsky, A. (2000). Exploring psychological benefits associated with moderate alcohol use: a necessary corrective to assessments of drinking outcomes? *Drug and alcohol dependence*, 60(3):221–247.

Peen, J., Schoevers, R., Beekman, A., and Dekker, J. (2010). The current status of urban-rural differences in psychiatric disorders. *Acta Psychiatrica Scandinavica*, 121(2):84–93.

Peeters, M., Janssen, T., Monshouwer, K., Boendermaker, W., Pronk, T., Wiers, R., and Vollebergh, W. (2015). Weaknesses in executive functioning predict the initiating of adolescents' alcohol use. *Developmental cognitive neuroscience*, 16:139–146.

Peirce, R. S., Frone, M. R., Russell, M., Cooper, M. L., and Mudar, P. (2000). A longitudinal model of social contact, social support, depression, and alcohol use. *Health Psychology*, 19(1):28.

Pejic, T., Hermann, A., Vaitl, D., and Stark, R. (2013). Social anxiety modulates amygdala activation during social conditioning. *Social cognitive and affective neuroscience*, 8(3):267–276.

Pell, S. and D'alonzo, C. (1973). A five-year mortality study of alcoholics. *Journal of Occupational and Environmental Medicine*, 15(2):120–125.

Pelphrey, K., Mitchell, T., McKeown, M., Goldstein, J., Allison, T., and McCarthy, G. (2003). Brain activity evoked by the perception of human walking: Controlling for meaningful coherent motion. *Journal of Neuroscience*, 23(17):6819–6825.

Peña-Gómez, C., Vidal-Piñeiro, D., Clemente, I. C., Pascual-Leone, Á., and Bartrés-Faz, D. (2011). Down-regulation of negative emotional processing by transcranial direct current stimulation: effects of personality characteristics. *PloS one*, 6(7):e22812.

Peraza, J., Cservenka, A., Herting, M. M., and Nagel, B. J. (2015). Atypical parietal lobe activity to subliminal faces in youth with a family history of alcoholism. *The American journal of drug and alcohol abuse*, 41(2):139–145.

Perez, D. L., Vago, D. R., Pan, H., Root, J., Tuescher, O., Fuchs, B. H., Leung, L., Epstein, J., Cain, N. M., Clarkin, J. F., et al. (2016). Frontolimbic neural circuit changes in emotional processing and inhibitory control associated with clinical improvement following transference-focused psychotherapy in borderline personality disorder. *Psychiatry and clinical neurosciences*, 70(1):51–61.

Pérez Benítez, C. I., Shea, M. T., Raffa, S., Rende, R., Dyck, I. R., Ramsawh, H. J., Edelen, M. O., and Keller, M. B. (2009). Anxiety sensitivity as a predictor of the clinical course of panic disorder: a 1-year follow-up study. *Depression and Anxiety*, 26(4):335–342.

Perna, E. D. S. F., Theunissen, E., Kuypers, K., Toennes, S., and Ramaekers, J. (2016). Subjective aggression during alcohol and cannabis intoxication before and after aggression exposure. *Psychopharmacology*, pages 1–10.

Pesold, C. and Treit, D. (1995). The central and basolateral amygdala differentially mediate the anxiolytic effects of benzodiazepines. *Brain research*, 671(2):213–221.

Pessoa, L. (2008). On the relationship between emotion and cognition. *Nature Reviews Neuroscience*, 9(2):148–158.

Pessoa, L. (2010). Emotion and cognition and the amygdala: from "what is it?" to "what's to be done?". *Neuropsychologia*, 48(12):3416–3429.

Peters, M. L., Godaert, G. L., Ballieux, R. E., van Vliet, M., Willemsen, J. J., Sweep, F. C., and Heijnen, C. J. (1998). Cardiovascular and endocrine responses to experimental stress: effects of mental effort and controllability. *Psychoneuroendocrinology*, 23(1):1–17.

Peterson, J., Pihl, R., Gianoulakis, C., Conrod, P., Finn, P., Stewart, S., LeMarquand, D., and Bruce, K. (1996). Ethanol-induced change in cardiac and endogenous opiate function and risk for alcoholism. *Alcoholism: Clinical and Experimental Research*, 20(9):1542–1552.

Peterson, J., Pihl, R., Séguin, J., Finn, P., and Stewart, S. (1993). Heart-rate reactivity and alcohol consumption among sons of male alcoholics and sons of non-alcoholics. *Journal of Psychiatry and Neuroscience*, 18(4):190.

Peterson, J., Rothfleisch, J., Zelazo, P., and Pihl, R. (1990). Acute alcohol intoxication and cognitive functioning. *Journal of Studies on Alcohol*, 51(2):114–122.

Peterson, J. B., Finn, P. R., and Pihl, R. O. (1992). Cognitive dysfunction and the inherited predisposition to alcoholism. *Journal of Studies on Alcohol*, 53(2):154–160.

Peterson, R. and Reiss, S. (1992). Anxiety sensitivity index revised test manualinternational diagnostic services. *Inc, Worthington, OH*.

Peterson, R. A. and Plehn, K. (1999). Measuring anxiety sensitivity. *Anxiety sensitivity: Theory, research, and treatment of the fear of anxiety*, pages 61–81.

Petit, G., Maurage, P., Kornreich, C., Verbanck, P., and Campanella, S. (2014). Binge drinking in adolescents: a review of neurophysiological and neuroimaging research. *Alcohol and alcoholism*, 49(2):198–206.

Petrican, R., Saverino, C., Rosenbaum, R. S., and Grady, C. (2015). Inter-individual differences in the experience of negative emotion predict variations in functional brain architecture. *NeuroImage*, 123:80–88.

Petrovic, P. and Ingvar, M. (2002). Imaging cognitive modulation of pain processing. *Pain*, 95(1-2):1–5.

Petrovic, P., Kalso, E., Petersson, K., and Ingvar, M. (2002). Placebo and opioid analgesia - imaging a shared neuronal network. *Science*, 295(5560):1737–1740.

Petrovic, P., Petersson, K. M., Ghatan, P., Stone-Elander, S., and Ingvar, M. (2000). Pain-related cerebral activation is altered by a distracting cognitive task. *Pain*, 85(1):19–30.

Pettinati, H. M., Oslin, D. W., Kampman, K. M., Dundon, W. D., Xie, H., Gallis, T. L., Dackis, C. A., and O'Brien, C. P. (2010). A double-blind, placebo-controlled trial combining sertraline and naltrexone for treating co-occurring depression and alcohol dependence. *American Journal of Psychiatry*, 167(6):668–675.

Pettinati, H. M., Pierce, J. D., Wolf, A. L., Rukstalis, M. R., and O'Brien, C. P. (1997). Gender differences in comorbidly depressed alcohol-dependent outpatients. *Alcoholism: Clinical and experimental research*, 21(9):1742–1746.

Peyron, R., García-Larrea, L., Grégoire, M.-C., Costes, N., Convers, P., Lavenne, F., Mauguière, F., Michel, D., and Laurent, B. (1999). Haemodynamic brain responses to acute pain in humans. *Brain*, 122(9):1765–1780.

Peyron, R., Laurent, B., and García-Larrea, L. (2000). Functional imaging of brain responses to pain. a review and meta-analysis (2000). *Neurophysiologie Clinique*, 30(5):263–288.

Pezawas, L., Meyer-Lindenberg, A., Drabant, E. M., Verchinski, B. A., Munoz, K. E., Kolachana, B. S., Egan, M. F., Mattay, V. S., Hariri, A. R., and Weinberger, D. R. (2005). 5-httlpr polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. *Nature neuroscience*, 8(6):828–834.

Phan, K., Wager, T., Taylor, S., and Liberzon, I. (2002). Functional neuroanatomy of emotion: A meta-analysis of emotion activation studies in pet and fmri. *NeuroImage*, 16(2):331–348.

Phan, K. L., Fitzgerald, D. A., Nathan, P. J., and Tancer, M. E. (2006). Association between amygdala hyperactivity to harsh faces and severity of social anxiety in generalized social phobia. *Biological psychiatry*, 59(5):424–429.

Phelps, E., Delgado, M., Nearing, K., and Ledoux, J. (2004). Extinction learning in humans: Role of the amygdala and vmpfc. *Neuron*, 43(6):897–905.

Phelps, E. and LeDoux, J. (2005). Contributions of the amygdala to emotion processing: From animal models to human behavior. *Neuron*, 48(2):175–187.

Phelps, E. A. (2004). Human emotion and memory: interactions of the amygdala and hippocampal complex. *Current opinion in neurobiology*, 14(2):198–202.

Phelps, E. A. (2006). Emotion and cognition: insights from studies of the human amygdala. *Annu. Rev. Psychol.*, 57:27–53.

Phillips, A., Hunt, K., Der, G., and Carroll, D. (2011). Blunted cardiac reactions to acute psychological stress predict symptoms of depression five years later: Evidence from a large community study. *Psychophysiology*, 48(1):142–148.

Piazza, P., Deminiere, J.-M., Le Moal, M., and Simon, H. (1989a). Factors that predict individual vulnerability to amphetamine self-administration. *Science*, 245(4925):1511–1513.

Piazza, P. V., Deminière, J.-M., Le Moal, M., and Simon, H. (1989b). Factors that predict individual vulnerability to amphetamine self-administration. *Science*, 245(4925):1511–1513.

Piazza, P. V., Deroche, V., Deminiere, J.-M., Maccari, S., Le Moal, M., and Simon, H. (1993). Corticosterone in the range of stress-induced levels possesses reinforcing properties: implications for sensation-seeking behaviors. *Proceedings of the National Academy of Sciences*, 90(24):11738–11742.

Pihl, Robert O, G. P. R. and Peterson, J. B. (1994). Cardiovascular reactivity as a predictor of alcohol consumption in taste test situation. *Journal of Clinical Psychology*, 50:280–286.

Pihl, R. (2010). Mental disorders are brain disorders: You think? *Canadian Psychology/Psychologie canadienne*, 51(1):40.

Pihl, R. (2014). Understanding the risk factors for substance abuse. *Childhood and Adolescent Pathways to Substance Use Disorders*, page 12.

Pihl, R., Finn, P., and Peterson, J. (1989). Autonomic hyperreactivity and risk for alcoholism. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 13(3-4):489–496.

Pihl, R. O. and Abu Shakra, M. (2014). Etiological considerations. *Oxford Textbook of Psychopathology*, page 275.

Pihl, R. O., Paylan, S. S., Gentes-Hawn, A., and Hoaken, P. N. (2003). Alcohol affects executive cognitive functioning differentially on the ascending versus descending limb of the blood alcohol concentration curve. *Alcoholism: Clinical and Experimental Research*, 27(5):773–779.

Pihl, R. O., Peterson, J., and Finn, P. R. (1990). Inherited predisposition to alcoholism: characteristics of sons of male alcoholics. *Journal of Abnormal Psychology*, 99(3):291.

Pihl, R. O. and Peterson, J. B. (1995). Alcoholism: the role of different motivational systems. *Journal of Psychiatry and Neuroscience*, 20(5):372.

Pihl, R. O. and Sutton, R. (2009). Drugs and aggression readily mix; so what now? *Substance use & misuse*, 44(9-10):1188–1203.

Pillay, S. S., Gruber, S. A., Rogowska, J., Simpson, N., and Yurgelun-Todd, D. A. (2006). fmri of fearful facial affect recognition in panic disorder: the cingulate gyrus–amygdala connection. *Journal of affective disorders*, 94(1):173–181.

Pingault, J.-B., Cecil, C., Murray, J., Munafò, M. R., and Viding, E. (2016). Causal inference in psychopathology: A systematic review of mendelian randomisation studies aiming to identify environmental risk factors for psychopathology. *Psychopathology Review*.

Pishnamazi, M., Tafakhori, A., Loloee, S., Modabbernia, A., Aghamollaii, V., Bahrami, B., and Winston, J. S. (2016). Attentional bias towards and away from fearful faces is modulated by developmental amygdala damage. *Cortex*, 81:24–34.

Pitkänen, A. (2000). Connectivity of the rat amygdaloid complex. *The Amygdala: A Functional Analysis*, pages 31–115.

Pitman, R. K., Rasmusson, A. M., Koenen, K. C., Shin, L. M., Orr, S. P., Gilbertson, M. W., Milad, M. R., and Liberzon, I. (2012). Biological studies of post-traumatic stress disorder. *Nature Reviews Neuroscience*, 13(11):769–787.

Plassmann, H., O'Doherty, J. P., and Rangel, A. (2010). Appetitive and aversive goal values are encoded in the medial orbitofrontal cortex at the time of decision making. *The Journal of neuroscience*, 30(32):10799–10808.

Platt, L., Melendez-Torres, G., O'Donnell, A., Bradley, J., Newbury-Birch, D., Kaner, E., and Ashton, C. (2016a). How effective are brief interventions in reducing alcohol consumption: do the setting, practitioner group and content matter? findings from a systematic review and metaregression analysis. *BMJ open*, 6(8):e011473.

Platt, L. M., Whitburn, A. I., Platt-Koch, A. G., and Koch, R. L. (2016b). Non-pharmacological alternatives to benzodiazepine drugs for the treatment of anxiety in outpatient populations: A literature review. *Journal of Psychosocial Nursing and Mental Health Services*, 54(8):35–42.

Plessow, F., Kiesel, A., and Kirschbaum, C. (2012). The stressed prefrontal cortex and goal-directed behaviour: acute psychosocial stress impairs the flexible implementation of task goals. *Experimental brain research*, 216(3):397–408.

Ploghaus, A., Becerra, L., Borras, C., and Borsook, D. (2003). Neural circuitry underlying pain modulation: Expectation, hypnosis, placebo. *Trends in Cognitive Sciences*, 7(5):197–200.

Ploghaus, A., Narain, C., Beckmann, C., Clare, S., Bantick, S., Wise, R., Matthews, P., Nicholas P Rawlins, J., and Tracey, I. (2001). Exacerbation of pain by anxiety is associated with activity in a hippocampal network. *Journal of Neuroscience*, 21(24):9896–9903.

Ploghaus, A., Tracey, I., Gati, J. S., Clare, S., Menon, R. S., Matthews, P. M., and Rawlins, J. N. P. (1999). Dissociating pain from its anticipation in the human brain. *Science*, 284(5422):1979–1981.

Poeggel, G., Helmeke, C., Abraham, A., Schwabe, T., Friedrich, P., and Braun, K. (2003). Juvenile emotional experience alters synaptic composition in the rodent cortex, hippocampus, and lateral amygdala. *Proceedings of the National Academy of Sciences*, 100(26):16137–16142.

Pohorecky, L. (1981). The interaction of alcohol and stress a review. *Neuroscience and Biobehavioral Reviews*, 5(2):209–229.

Pohorecky, L. (1990). Interaction of ethanol and stress: research with experimental animals—an update. *Alcohol and alcoholism*, 25(2-3):263–276.

Pohorecky, L. (1991). Stress and alcohol interaction: An update of human research. *Alcoholism: Clinical and Experimental Research*, 15(3):438–459.

Pol, H. E. H., Schnack, H. G., Mandl, R. C., van Haren, N. E., Koning, H., Collins, D. L., Evans, A. C., and Kahn, R. S. (2001). Focal gray matter density changes in schizophrenia. *Archives of General Psychiatry*, 58(12):1118–1125.

Polcin, D. L., Korcha, R. A., Nayak, M., and Bond, J. (2015). Methamphetamine dependence and intensive motivational interviewing. *Drug & Alcohol Dependence*, 146:e72.

Poletti, S., Radaelli, D., Cucchi, M., Ricci, L., Vai, B., Smeraldi, E., and Benedetti, F. (2015). Neural correlates of anxiety sensitivity in panic disorder: A functional magnetic resonance imaging study. *Psychiatry Research: Neuroimaging*.

Pollock, V. (1992). Meta-analysis of subjective sensitivity to alcohol in sons of alcoholics. *American Journal of Psychiatry*, 149(11):1534–1538.

Pollock, V., Teasdale, T., Gabrielli, W., and Knop, J. (1986). Subjective and objective measures of response to alcohol among young men at risk for alcoholism. *Journal of Studies on Alcohol*, 47(4):297–304.

Pomarol-Clotet, E., Salvador, R., Sarro, S., Gomar, J., Vila, F., Martinez, A., Guerrero, A., Ortiz-Gil, J., Sans-Sansa, B., Capdevila, A., et al. (2008). Failure to deactivate in the prefrontal cortex in schizophrenia: dysfunction of the default mode network? *Psychological medicine*, 38(8):1185–1194.

Pombo, S., da Costa, N. F., Figueira, M. L., Ismail, F., and Lesch, O. M. (2015). Multidimensional alcoholism typologies: could they guide clinical practice? results from a 3-month prospective study. *International journal of psychiatry in clinical practice*, 19(0):1–11.

Porjesz, B. and Rangaswamy, M. (2007). Neurophysiological endophenotypes, cns disinhibition, and risk for alcohol dependence and related disorders. *The Scientific World Journal*, 7:131–141.

Porrino, L., Crane, A., and Goldman-Rakic, P. (1981). Direct and indirect pathways from the amygdala to the frontal lobe in rhesus monkeys. *Journal of Comparative Neurology*, 198(1):121–136.

Portas, C. M., Rees, G., Howseman, A., Josephs, O., Turner, R., and Frith, C. D. (1998). A specific role for the thalamus in mediating the interaction of attention and arousal in humans. *The Journal of Neuroscience*, 18(21):8979–8989.

Posamentier, M. T. and Abdi, H. (2003). Processing faces and facial expressions. *Neuropsychology review*, 13(3):113–143.

Posner, M. and Raichle, M. (1994). Networks of attention. *Images of mind*, pages 153–179.

Post, R. M., Altshuler, L. L., Kupka, R., McElroy, S. L., Frye, M. A., Rowe, M., Leverich, G. S., Grunze, H., Suppes, T., Keck, P. E., et al. (2015). Verbal abuse, like physical and sexual abuse, in childhood is associated with an earlier onset and more difficult course of bipolar disorder. *Bipolar disorders*, 17(3):323–330.

Potgieter, A., Deckers, F., and Geerlings, P. (1999). Craving and relapse measurement in alcoholism. *Alcohol and alcoholism*, 34(2):254–260.

Powers, A. and Casey, B. (2015). The adolescent brain and the emergence and peak of psychopathology. *Journal of Infant, Child, and Adolescent Psychotherapy*, 14(1):3–15.

Powers, S. I., Laurent, H. K., Gunlicks-Stoessel, M., Balaban, S., and Bent, E. (2016). Depression and anxiety predict sex-specific cortisol responses to interpersonal stress. *Psychoneuroendocrinology*.

Pratto, F. and John, O. (1991). Automatic vigilance: The attention-grabbing power of negative social information. *Journal of Personality and Social Psychology*, 61(3):380–391.

Praud, D., Rota, M., Rehm, J., Shield, K., Zatoński, W., Hashibe, M., La Vecchia, C., and Boffetta, P. (2016). Cancer incidence and mortality attributable to alcohol consumption. *International Journal of Cancer*, 138(6):1380–1387.

Preuschoff, K., Bossaerts, P., and Quartz, S. R. (2006). Neural differentiation of expected reward and risk in human subcortical structures. *Neuron*, 51(3):381–390.

Preuschoff, K., Quartz, S. R., and Bossaerts, P. (2008). Human insula activation reflects risk prediction errors as well as risk. *The Journal of neuroscience*, 28(11):2745–2752.

Price, J. (2003). Comparative aspects of amygdala connectivity. *Annals of the New York Academy of Sciences*, 985:50–58.

Price, J. L. (2007). Definition of the orbital cortex in relation to specific connections with limbic and visceral structures and other cortical regions. *Annals of the New York Academy of Sciences*, 1121(1):54–71.

Prince van Leeuwen, A., Creemers, H. E., Verhulst, F. C., Vollebergh, W. A., Ormel, J., Oort, F., and Huizink, A. C. (2014). Legal substance use and the development of a dsm-iv cannabis use disorder during adolescence: the trails study. *Addiction*, 109(2):303–311.

Prokasky, A., Rudasill, K., Molfese, V. J., Putnam, S., Gartstein, M., and Rothbart, M. (2016). Identifying child temperament types using cluster analysis in three samples. *Journal of Research in Personality*.

Protopopescu, X., Pan, H., Altemus, M., Tuescher, O., Polanecsky, M., McEwen, B., Silbersweig, D., and Stern, E. (2005). Orbitofrontal cortex activity related to emotional processing changes across the menstrual cycle. *Proceedings of the National Academy of Sciences of the United States of America*, 102(44):16060–16065.

Pruessner, J., Baldwin, M., Dedovic, K., Renwick, R., Mahani, N., Lord, C., Meaney, M., and Lupien, S. (2005a). Self-esteem, locus of control, hippocampal volume, and cortisol regulation in young and old adulthood. *NeuroImage*, 28(4):815–826.

Pruessner, J., Champagne, F., Meaney, M., and Dagher, A. (2004). Dopamine release in response to a psychological stress in humans and its relationship to early life maternal care: A positron emission tomography study using [11c] raclopride. *Journal of Neuroscience*, 24(11):2825–2831.

Pruessner, J., Hellhammer, D., and Kirschbaum, C. (1999a). Burnout, perceived stress, and cortisol responses to awakening. *Psychosomatic Medicine*, 61(2):197–204.

Pruessner, J., Hellhammer, D., and Kirschbaum, C. (1999b). Low self-esteem, induced failure and the adrenocortical stress response. *Personality and Individual Differences*, 27(3):477–489.

Pruessner, J. C., Baldwin, M. W., Dedovic, K., Renwick, R., Mahani, N. K., Lord, C., Meaney, M., and Lupien, S. (2005b). Self-esteem, locus of control, hippocampal volume, and cortisol regulation in young and old adulthood. *Neuroimage*, 28(4):815–826.

Pruessner, J. C., Dedovic, K., Khalili-Mahani, N., Engert, V., Pruessner, M., Buss, C., Renwick, R., Dagher, A., Meaney, M. J., and Lupien, S. (2008). Deactivation of the limbic system during acute psychosocial stress: evidence from positron emission tomography and functional magnetic resonance imaging studies. *Biological psychiatry*, 63(2):234–240.

Pruessner, J. C., Dedovic, K., Pruessner, M., Lord, C., Buss, C., Collins, L., Dagher, A., and Lupien, S. J. (2010). Stress regulation in the central nervous system: evidence from structural and functional neuroimaging studies in human populations-2008 curt richter award winner. *Psychoneuroendocrinology*, 35(1):179–191.

Pruessner, J. C., Kirschbaum, C., Meinlschmid, G., and Hellhammer, D. H. (2003). Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. *Psychoneuroendocrinology*, 28(7):916–931.

Pujol, J., Harrison, B., Ortiz, H., Deus, J., Soriano-Mas, C., Lopez-Sola, M., Yücel, M., Perich, X., and Cardoner, N. (2009). Influence of the fusiform gyrus on amygdala response to emotional faces in the non-clinical range of social anxiety. *Psychological medicine*, 39(07):1177–1187.

Purcell, S. M., Wray, N. R., Stone, J. L., Visscher, P. M., O'Donovan, M. C., Sullivan, P. F., Sklar, P., Ruderfer, D. M., McQuillin, A., Morris, D. W., et al. (2009). Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*, 460(7256):748–752.

Purpura, K. P. and Schiff, N. D. (1997). The thalamic intralaminar nuclei: a role in visual awareness. *The Neuroscientist*, 3(1):8–15.

Putman, P., Hermans, E. J., and van Honk, J. (2010). Cortisol administration acutely reduces threat-selective spatial attention in healthy young men. *Physiology & Behavior*, 99(3):294–300.

Putman, P. and Roelofs, K. (2011). Effects of single cortisol administrations on human affect reviewed: Coping with stress through adaptive regulation of automatic cognitive processing. *Psychoneuroendocrinology*, 36(4):439–448.

Qi, M., Gao, H., Guan, L., Liu, G., and Yang, J. (2016). Subjective stress, salivary cortisol, and electrophysiological responses to psychological stress. *Frontiers in psychology*, 7.

Qiao, J., Wang, Z., Geronazzo-Alman, L., Amsel, L., Duarte, C., Lee, S., Musa, G., Long, J., He, X., Doan, T., et al. (2015). Brain activity classifies adolescents with and without a familial history of substance use disorders. *Frontiers in human neuroscience*, 9:219–219.

Quinn, P. D. and Fromme, K. (2016). Individual differences in subjective alcohol responses and alcohol-related disinhibition. *Experimental and clinical psychopharmacology*, 24(2):90.

Quirk, G. J., Repa, J. C., and LeDoux, J. E. (1995). Fear conditioning enhances short-latency auditory responses of lateral amygdala neurons: parallel recordings in the freely behaving rat. *Neuron*, 15(5):1029–1039.

Quitkin, F. M., Rifkin, A., Kaplan, J., and Klein, D. F. (1972). Phobic anxiety syndrome complicated by drug dependence and addiction: a treatable form of drug abuse. *Archives of General Psychiatry*, 27(2):159–162.

Rabellino, D., Densmore, M., Frewen, P. A., Théberge, J., and Lanius, R. A. (2016). The innate alarm circuit in post-traumatic stress disorder: Conscious and subconscious processing of fear-and trauma-related cues. *Psychiatry Research: Neuroimaging*, 248:142–150.

Rachman, S., Grüter-Andrew, J., and Shafran, R. (2000). Post-event processing in social anxiety. *Behaviour Research and Therapy*, 38(6):611–617.

Radua, J., Stoica, T., Scheinost, D., Pittenger, C., and Hampson, M. (2016). Neural correlates of success and failure signals during neurofeedback learning. *Neuroscience*.

Raichle, M., MacLeod, A., Snyder, A., Powers, W., Gusnard, D., and Shulman, G. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America*, 98(2):676–682.

Raichle, M. E. (1998). Behind the scenes of functional brain imaging: a historical and physiological perspective. *Proceedings of the National Academy of Sciences*, 95(3):765–772.

Raichle, M. E. (2015). The brain's default mode network. *Annual review of neuroscience*, 38:433–447.

Raine, A. (2013). *The psychopathology of crime: Criminal behavior as a clinical disorder*. Elsevier.

Rainville, P., Carrier, B., Hofbauer, R., Bushnell, M., and Duncan, G. (1999). Dissociation of sensory and affective dimensions of pain using hypnotic modulation. *Pain*, 82(2):159–171.

Rainville, P., Duncan, G., Price, D., Carrier, B., and Bushnell, M. (1997). Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science*, 277(5328):968–971.

Raison, C. L. and Miller, A. H. (2003). When not enough is too much: the role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. *American Journal of Psychiatry*, 160(9):1554–1565.

Rajchert, J. and Winiewski, M. (2016). The behavioral approach and inhibition systems' role in shaping the displaced and direct aggressive reaction to ostracism and rejection. *Personality and Individual Differences*, 88:272–279.

Ramage, A. E., Lin, A.-L., Olvera, R. L., Fox, P. T., and Williamson, D. E. (2015). Resting-state regional cerebral blood flow during adolescence: Associations with initiation of substance use and prediction of future use disorders. *Drug and alcohol dependence*, 149:40–48.

Ramchandani, V. A., Plawecki, M., Li, T.-K., and O'Connor, S. (2009). Intravenous ethanol infusions can mimic the time course of breath alcohol concentrations following oral alcohol administration in healthy volunteers. *Alcoholism: Clinical and Experimental Research*, 33(5):938–944.

Randall, C. L. and McNeil, D. W. (2016). Motivational interviewing as an adjunct to cognitive behavior therapy for anxiety disorders: A critical review of the literature. *Cognitive and Behavioral Practice*.

Rangaswamy, M. and Porjesz, B. (2008). Uncovering genes for cognitive (dys) function and predisposition for alcoholism spectrum disorders: a review of human brain oscillations as effective endophenotypes. *Brain research*, 1235:153–171.

Rangaswamy, M., Porjesz, B., Ardekani, B. A., Choi, S. J., Tanabe, J. L., Lim, K. O., and Begleiter, H. (2004). A functional mri study of visual oddball: evidence for frontoparietal dysfunction in subjects at risk for alcoholism. *Neuroimage*, 21(1):329–339.

Rao, U., Hammen, C., Ortiz, L. R., Chen, L.-A., and Poland, R. E. (2008). Effects of early and recent adverse experiences on adrenal response to psychosocial stress in depressed adolescents. *Biological psychiatry*, 64(6):521–526.

Rapee, R. M. and Heimberg, R. G. (1997). A cognitive-behavioral model of anxiety in social phobia. *Behaviour research and therapy*, 35(8):741–756.

Ratka, A., Sutanto, W., Bloemers, M., and De Kloet, E. (1989). On the role of brain mineralocorticoid (type i) and glucocorticoid (type ii) receptors in neuroendocrine regulation. *Neuroendocrinology*, 50(2):117–123.

Ratsma, J., Van Stelt, O., Schoffelmeer, A., Westerveld, A., and Boudewijn Gunning, W. (2001). P3 event-related potential, dopamine d2 receptor a1 allele, and sensation-seeking in adult children of alcoholics. *Alcoholism: Clinical and Experimental Research*, 25(7):960–967.

Rauch, S. L., Whalen, P. J., Shin, L. M., McInerney, S. C., Macklin, M. L., Lasko, N. B., Orr, S. P., and Pitman, R. K. (2000). Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional mri study. *Biological psychiatry*, 47(9):769–776.

Ray, L. A., Bujarski, S., and Roche, D. J. (2016). Subjective response to alcohol as a research domain criterion. *Alcoholism: Clinical and Experimental Research*, 40(1):6–17.

Ray, R. D. and Zald, D. H. (2012). Anatomical insights into the interaction of emotion and cognition in the prefrontal cortex. *Neuroscience & Biobehavioral Reviews*, 36(1):479–501.

Read, J., Os, J. v., Morrison, A., and Ross, C. A. (2005). Childhood trauma, psychosis and schizophrenia: a literature review with theoretical and clinical implications. *Acta Psychiatrica Scandinavica*, 112(5):330–350.

Reas, E. T., Laughlin, G. A., Kritz-Silverstein, D., Barrett-Connor, E., and McEvoy, L. K. (2016). Moderate, regular alcohol consumption is associated with higher cognitive function in older, community-dwelling adults. *The Journal of Prevention of ALzheimer's Diseasel*, 3(2).

Reed, E., Amaro, H., Matsumoto, A., and Kaysen, D. (2009). The relation between interpersonal violence and substance use among a sample of university students: Examination of the role of victim and perpetrator substance use. *Addictive behaviors*, 34(3):316–318.

Rees, E., Kendall, K., Pardiñas, A. F., Legge, S. E., Pocklington, A., Escott-Price, V., MacCabe, J. H., Collier, D. A., Holmans, P., O'Donovan, M. C., et al. (2016). Analysis of intellectual disability copy number variants for association with schizophrenia. *JAMA psychiatry*, 73(9):963.

Regier, D. A., Farmer, M. E., Rae, D. S., Locke, B. Z., Keith, S. J., Judd, L. L., and Goodwin, F. K. (1990). Comorbidity of mental disorders with alcohol and other drug abuse: results from the epidemiologic catchment area (eca) study. *Jama*, 264(19):2511–2518.

Rehm, J. (2011). The risks associated with alcohol use and alcoholism. *Alcohol research & health: the journal of the National Institute on Alcohol Abuse and Alcoholism*, 34(2):135.

Rehm, J., Allamani, A., Aubin, H.-J., Della Vedova, R., Elekes, Z., Frick, U., Jakubczyk, A., Kostogianni, N., Landsmane, I., Manthey, J., et al. (2015a). People with alcohol use disorders in specialized care in eight different european countries. *Alcohol and Alcoholism*, 50(3):310–318.

Rehm, J., Allamani, A., Della Vedova, R., Elekes, Z., Jakubczyk, A., Landsmane, I., Manthey, J., Moreno-España, J., Pieper, L., Probst, C., et al. (2015b). General practitioners recognizing alcohol dependence: a large cross-sectional study in 6 european countries. *The Annals of Family Medicine*, 13(1):28–32.

Rehm, J., Anderson, P., Barry, J., Dimitrov, P., Elekes, Z., Feijão, F., Frick, U., Gual, A., Gmel Jr, G., Kraus, L., et al. (2015c). Prevalence of and potential influencing factors for alcohol dependence in europe. *European addiction research*, 21(1):6–18.

Rehm, J., Baliunas, D., Brochu, S., Fischer, B., Gnam, W., Patra, J., Popova, S., Sarnocinska-Hart, A., Taylor, B., Adlaf, E., et al. (2006a). The costs of substance abuse in canada 2002. *Ottawa: Canadian Centre on Substance Abuse*, pages 1–14.

Rehm, J., Dawson, D., Frick, U., Gmel, G., Roerecke, M., Shield, K. D., and Grant, B. (2014). Burden of disease associated with alcohol use disorders in the united states. *Alcoholism: Clinical and Experimental Research*, 38(4):1068–1077.

Rehm, J., Mathers, C., Popova, S., Thavorncharoensap, M., Teerawattananon, Y., and Patra, J. (2009). Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *The Lancet*, 373(9682):2223–2233.

Rehm, J., Patra, J., Baliunas, D., Popova, S., Roerecke, M., and Taylor, B. (2006b). Alcohol consumption and the global burden of disease 2002. geneva: World health organization, department of mental health and substance abuse. *Management of Substance Abuse*.

Rehm, J. and Roerecke, M. (2013). Reduction of drinking in problem drinkers and all-cause mortality. *Alcohol and alcoholism*, 48(4):509–513.

Rehm, J., Shield, K., Gmel, G., Rehm, M., and Frick, U. (2013). Modeling the impact of alcohol dependence on mortality burden and the effect of available treatment interventions in the european union. *European Neuropsychopharmacology*, 23(2):89–97.

Rehm, J., Shield, K., Rehm, M., Gmel, G., and Frick, U. (2012). Alcohol consumption, alcohol dependence and attributable burden of disease in europe. *Centre for Addiction and Mental Health*.

Reichel, C. and Bevins, R. (2008). Competition between the conditioned rewarding effects of cocaine and novelty. *Behavioral Neuroscience*, 122(1):140–150.

Reichenberger, J., Wiggert, N., Agroskin, D., Wilhelm, F. H., and Blechert, J. (2017). No praise, please: Depressive symptoms, reactivity to positive social interaction, and fear of positive evaluation. *Journal of behavior therapy and experimental psychiatry*, 54:186–194.

Reiman, E. (1997). The application of positron emission tomography to the study of normal and pathologic emotions. *Journal of Clinical Psychiatry*, 58(SUPPL. 16):4–12.

Reiss, S. (1991). Expectancy model of fear, anxiety, and panic. *Clinical Psychology Review*, 11(2):141–153.

Reiss, S. and McNally, R. (1985). Expectancy model of fear. *Theoretical Issues in Behavior Therapy*, pages 107–121.

Reiss, S., Peterson, R. A., Gursky, D. M., and McNally, R. J. (1986). Anxiety sensitivity, anxiety frequency and the prediction of fearfulness. *Behaviour research and therapy*, 24(1):1–8.

Reul, J. and De Kloet, E. (1986). Anatomical resolution of two types of corticosterone receptor sites in rat brain with in vitro autoradiography and computerized image analysis. *Journal of steroid biochemistry*, 24(1):269–272.

Reul, J. and Kloet, E. d. (1985). Two receptor systems for corticosterone in rat brain: microdistribution and differential occupation. *Endocrinology*, 117(6):2505–2511.

Reuter, M., Stark, R., Hennig, J., Walter, B., Kirsch, P., Schienle, A., and Vaitl, D. (2004). Personality and emotion: test of gray's personality theory by means of an fmri study. *Behavioral neuroscience*, 118(3):462.

Reynolds, S. M. and Berridge, K. C. (2002). Positive and negative motivation in nucleus accumbens shell: bivalent rostrocaudal gradients for gaba-elicited eating, taste "liking"/"disliking" reactions, place preference/avoidance, and fear. *The Journal of Neuroscience*, 22(16):7308–7320.

Reynolds, S. M. and Zahm, D. S. (2005). Specificity in the projections of prefrontal and insular cortex to ventral striatopallidum and the extended amygdala. *The Journal of neuroscience*, 25(50):11757–11767.

Riccardi, P., Zald, D., Li, R., Park, S., Ansari, M., Dawant, B., Anderson, S., Woodward, N., Schmidt, D., Baldwin, R., and Kessler, R. (2006). Sex differences in amphetamine-induced displacement of [18f]fallypride in striatal and extrastriatal regions: A pet study. *American Journal of Psychiatry*, 163(9):1639–1641.

Rice, T. R. (2016). Commentary: The neural bases of emotion regulation. *Frontiers in psychology*, 7.

Richards, J. B., Zhang, L., Mitchell, S. H., and Wit, H. (1999). Delay or probability discounting in a model of impulsive behavior: effect of alcohol. *Journal of the experimental analysis of behavior*, 71(2):121–143.

Rickels, K., Schweizer, E., Case, W. G., and Greenblatt, D. J. (1990). Long-term therapeutic use of benzodiazepines: I. effects of abrupt discontinuation. *Archives of General Psychiatry*, 47(10):899–907.

Ridderinkhof, K. R., Van Den Wildenberg, W. P., Segalowitz, S. J., and Carter, C. S. (2004). Neurocognitive mechanisms of cognitive control: the role of prefrontal cortex in action selection, response inhibition, performance monitoring, and reward-based learning. *Brain and cognition*, 56(2):129–140.

Rietschel, M. and Treutlein, J. (2013). The genetics of alcohol dependence. *Annals of the New York Academy of Sciences*, 1282(1):39–70.

Rigoli, F., Ewbank, M., Dalgleish, T., and Calder, A. (2016). Threat visibility modulates the defensive brain circuit underlying fear and anxiety. *Neuroscience letters*, 612:7–13.

rinos, A., Somoza, G., and De Nicola, A. (1987). Glucocorticoid negative feedback and glucocorticoid receptors after hippocampectomy in rats. *Hormone and Metabolic Research*, 19(3):105–109.

Riva, P., Lauro, L. J. R., DeWall, C. N., Chester, D. S., and Bushman, B. J. (2014). Reducing aggressive responses to social exclusion using transcranial direct current stimulation (tdcs). *Social cognitive and affective neuroscience*, page nsu053.

Rivier, C., Bruhn, T., and Vale, W. (1984). Effect of ethanol on the hypothalamic-pituitary-adrenal axis in the rat: role of corticotropin-releasing factor (crf). *Journal of Pharmacology and Experimental Therapeutics*, 229(1):127–131.

Robbins, T. W. (2016). 13 different mechanisms of cognitive flexibility within the prefrontal cortex. *Scientists Making a Difference*, page 62.

Roberti, J. (2004). A review of behavioral and biological correlates of sensation seeking. *Journal of Research in Personality*, 38(3):256–279.

Roberto, M., Madamba, S., Moore, S., Tallent, M., and Siggins, G. (2003). Ethanol increases gabaergic transmission at both pre- and postsynaptic sites in rat central amygdala neurons. *Proceedings of the National Academy of Sciences of the United States of America*, 100(4):2053–2058.

Roberto, M., Madamba, S., Stouffer, D., Parsons, L., and Siggins, G. (2004). Increased gaba release in the central amygdala of ethanol-dependent rats. *Journal of Neuroscience*, 24(45):10159–10166.

Robinson, J., Sareen, J., Cox, B. J., and Bolton, J. (2009). Self-medication of anxiety disorders with alcohol and drugs: Results from a nationally representative sample. *Journal of anxiety disorders*, 23(1):38–45.

Robinson, O. J., Charney, D. R., Overstreet, C., Vytal, K., and Grillon, C. (2012). The adaptive threat bias in anxiety: amygdala–dorsomedial prefrontal cortex coupling and aversive amplification. *Neuroimage*, 60(1):523–529.

Rodrigo, A. H., Di Domenico, S. I., Ayaz, H., Gulrajani, S., Lam, J., and Ruocco, A. C. (2014). Differentiating functions of the lateral and medial prefrontal cortex in motor response inhibition. *Neuroimage*, 85:423–431.

Rodrigo, A. H., Di Domenico, S. I., Graves, B., Lam, J., Ayaz, H., Bagby, R. M., and Ruocco, A. C. (2016). Linking trait-based phenotypes to prefrontal cortex activation during inhibitory control. *Social cognitive and affective neuroscience*, 11(1):55–65.

Rodriguez, B. F., Bruce, S. E., Pagano, M. E., Spencer, M. A., and Keller, M. B. (2004). Factor structure and stability of the anxiety sensitivity index in a longitudinal study of anxiety disorder patients. *Behaviour Research and Therapy*, 42(1):79–91.

Roelofs, K., Bakvis, P., Hermans, E., van Pelt, J., and van Honk, J. (2007). The effects of social stress and cortisol responses on the preconscious selective attention to social threat. *Biological Psychology*, 75(1):1–7.

Roelofs, K., Elzinga, B., and Rotteveel, M. (2005). The effects of stress-induced cortisol responses on approach-avoidance behavior. *Psychoneuroendocrinology*, 30(7):665–677.

Roelofs, K., van Peer, J., Berretty, E., de Jong, P., Spinhoven, P., and Elzinga, B. M. (2009). Hypothalamus–pituitary–adrenal axis hyperresponsiveness is associated with increased social avoidance behavior in social phobia. *Biological psychiatry*, 65(4):336–343.

Roerecke, M. and Rehm, J. (2013). Alcohol use disorders and mortality: a systematic review and meta-analysis. *Addiction*, 108(9):1562–1578.

Roerecke, M. and Rehm, J. (2014). Cause-specific mortality risk in alcohol use disorder treatment patients: a systematic review and meta-analysis. *International journal of epidemiology*, page dyu018.

Rogan, M. T., Stäubli, U. V., and LeDoux, J. E. (1997). Fear conditioning induces associative long-term potentiation in the amygdala. *Nature*, 390(6660):604–607.

Rogers, J. C. and De Brito, S. A. (2016). Cortical and subcortical gray matter volume in youths with conduct problems: A meta-analysis. *JAMA psychiatry*, 73(1):64–72.

Rohde, P., Lewinsohn, P. M., and Seeley, J. R. (1996). Psychiatric comorbidity with problematic alcohol use in high school students. *Journal of the American Academy of Child & Adolescent Psychiatry*, 35(1):101–109.

Rohleder, N., Beulen, S., Chen, E., Wolf, J., and Kirschbaum, C. (2007). Stress on the dance floor: The cortisol stress response to social-evaluative threat in competitive ballroom dancers. *Personality and Social Psychology Bulletin*, 33(1):69–84.

Rohleder, N., Wolf, J. M., and Kirschbaum, C. (2003). Glucocorticoid sensitivity in humans-interindividual differences and acute stress effects. *Stress*, 6(3):207–222.

Rohsenow, D. J. and Bachorowski, J.-A. (1984). Effects of alcohol and expectancies on verbal aggression in men and women. *Journal of Abnormal Psychology*, 93(4):418.

Rolls, E. T. (2005). *Emotion explained*. Oxford University Press, USA.

Rolls, E. T. and Deco, G. (2016). Non-reward neural mechanisms in the orbitofrontal cortex. *Cortex*.

Rolls, E. T., McCabe, C., and Redoute, J. (2008). Expected value, reward outcome, and temporal difference error representations in a probabilistic decision task. *Cerebral Cortex*, 18(3):652–663.

Romano, E., Babchishin, L., Marquis, R., and Fréchette, S. (2015). Childhood maltreatment and educational outcomes. *Trauma, Violence, & Abuse*, 16(4):418–437.

Romano, M. and Peters, L. (2015). Evaluating the mechanisms of change in motivational interviewing in the treatment of mental health problems: A review and meta-analysis. *Clinical psychology review*, 38:1–12.

Romelsjö, A., Stenbacka, M., Lundberg, M., and Upmark, M. (2004). A population study of the association between hospitalization for alcoholism among employees in different socio-economic classes and the risk of mobility out of, or within, the workforce. *The European Journal of Public Health*, 14(1):53–57.

Ron, D. and Barak, S. (2016). Molecular mechanisms underlying alcohol-drinking behaviours. *Nature Reviews Neuroscience*.

Rose, N. (2016). Neuroscience and the future for mental health? *Epidemiology and psychiatric sciences*, 25(02):95–100.

Rosenberg, M. (1965). Rosenberg self-esteem scale (rse). *Acceptance and commitment therapy. Measures package*, 61.

Rosenberg, M. (1979). Conceiving the self new york: Basic. *RosenbergConceiving the Self1979*.

Rosenblitt, J. C., Soler, H., Johnson, S. E., and Quadagno, D. M. (2001). Sensation seeking and hormones in men and women: exploring the link. *Hormones and behavior*, 40(3):396–402.

Rösner, S., Hackl-Herrwerth, A., Leucht, S., Lehert, P., Vecchi, S., and Soyka, M. (2010a). Acamprosate for alcohol dependence. *The Cochrane Library*.

Rösner, S., Hackl-Herrwerth, A., Leucht, S., Vecchi, S., Srisurapanont, M., and Soyka, M. (2010b). Opioid antagonists for alcohol dependence. *The Cochrane Library*.

Rosso, I. M., Makris, N., Britton, J. C., Price, L. M., Gold, A. L., Zai, D., Bruyere, J., Deckersbach, T., Killgore, W. D., and Rauch, S. L. (2010). Anxiety sensitivity correlates with two indices of right anterior insula structure in specific animal phobia. *Depression and anxiety*, 27(12):1104–1110.

Rotge, J.-Y., Lemogne, C., Hinfray, S., Huguet, P., Grynszpan, O., Tartour, E., George, N., and Fossati, P. (2014). A meta-analysis of the anterior cingulate contribution to social pain. *Social cognitive and affective neuroscience*, page nsu110.

Rothbart, M. K. and Bates, J. (2006). *Temperament, development, and personality*, volume 3. Wiley, New York, NY.

Rousseau, G. S., Irons, J. G., and Correia, C. J. (2011). The reinforcing value of alcohol in a drinking to cope paradigm. *Drug and alcohol dependence*, 118(1):1–4.

Rubak, S., Sandbæk, A., Lauritzen, T., and Christensen, B. (2005). Motivational interviewing: a systematic review and meta-analysis. *Br J Gen Pract*, 55(513):305–312.

Rubia, K., Russell, T., Overmeyer, S., Brammer, M. J., Bullmore, E. T., Sharma, T., Simmons, A., Williams, S. C., Giampietro, V., Andrew, C. M., et al. (2001). Mapping motor inhibition: conjunctive brain activations across different versions of go/no-go and stop tasks. *Neuroimage*, 13(2):250–261.

Rubia, K., Smith, A., Woolley, J., Nosarti, C., Heyman, I., Taylor, E., and Brammer, M. (2006). Progressive increase of frontostriatal brain activation from childhood to adulthood during event-related tasks of cognitive control. *Human Brain Mapping*, 27(12):973–993.

Rubin, B. P. (2009). Changing brains: The emergence of the field of adult neurogenesis. *BioSocieties*, 4(4):407–424.

Rubin, R. T., Mandell, A. J., and Crandall, P. H. (1966). Corticosteroid responses to limbic stimulation in man: localization of stimulus sites. *Science*, 153(3737):767–768.

Ruby, P. and Decety, J. (2003). What you believe versus what you think they believe: A neuroimaging study of conceptual perspective-taking. *European Journal of Neuroscience*, 17(11):2475–2480.

Rudgley, R. et al. (1994). *Essential substances: a cultural history of intoxicants in society*. Kodansha International.

Rudolph, K. D., Miernicki, M. E., Troop-Gordon, W., Davis, M. M., and Telzer, E. H. (2016). Adding insult to injury: neural sensitivity to social exclusion is associated with internalizing symptoms in chronically peer-victimized girls. *Social cognitive and affective neuroscience*, page nsw021.

Rueger, S. Y., Hu, H., McNamara, P., Cao, D., Hao, W., and King, A. C. (2015). Differences in subjective response to alcohol in heavy-and light-drinking chinese men versus caucasian american men. *Addiction*, 110(1):91–99.

Rule, R. R., Shimamura, A. P., and Knight, R. T. (2002). Orbitofrontal cortex and dynamic filtering of emotional stimuli. *Cognitive, Affective, & Behavioral Neuroscience*, 2(3):264–270.

Russell, M. A., Smith, T. W., and Smyth, J. M. (2016). Anger expression, momentary anger, and symptom severity in patients with chronic disease. *Annals of Behavioral Medicine*, 50(2):259–271.

Rutter, M. (2013). Developmental psychopathology: A paradigm shift or just a relabeling?. *Development and psychopathology*, 25(4pt2):1201–1213.

Rutter, M. and Uher, R. (2012). Classification issues and challenges in child and adolescent psychopathology. *International Review of Psychiatry*, 24(6):514–529.

Ryali, S., Chen, T., Supekar, K., and Menon, V. (2013). A parcellation scheme based on von mises-fisher distributions and markov random fields for segmenting brain regions using resting-state fmri. *NeuroImage*, 65:83–96.

Ryan, S. R., Friedman, C. K., Liang, Y., Lake, S. L., Mathias, C. W., Charles, N. E., Acheson, A., and Dougherty, D. M. (2016). Family functioning as a mediator of relations between family history of substance use disorder and impulsivity. *Addictive disorders & their treatment*, 15(1):17–24.

Sabatinelli, D., Fortune, E. E., Li, Q., Siddiqui, A., Krafft, C., Oliver, W. T., Beck, S., and Jeffries, J. (2011). Emotional perception: meta-analyses of face and natural scene processing. *Neuroimage*, 54(3):2524–2533.

Sacks, J. J., Roeber, J., Bouchery, E. E., Gonzales, K., Chaloupka, F. J., and Brewer, R. D. (2013). State costs of excessive alcohol consumption, 2006. *American Journal of Preventive Medicine*, 45(4):474–485.

Saddoris, M. P., Gallagher, M., and Schoenbaum, G. (2005). Rapid associative encoding in basolateral amygdala depends on connections with orbitofrontal cortex. *Neuron*, 46(2):321–331.

Sadikaj, G., Moskowitz, D., Russell, J. J., and Zuroff, D. C. (2015). Submissiveness in social anxiety disorder: The role of interpersonal perception and embarrassment. *Journal of Social and Clinical Psychology*, 34(1):1.

Sah, P., Faber, E., De Armentia, M., and Power, J. (2003). The amygdaloid complex: Anatomy and physiology. *Physiological Reviews*, 83(3):803–834.

Saha, T. D., Chou, S. P., and Grant, B. F. (2006). Toward an alcohol use disorder continuum using item response theory: results from the national epidemiologic survey on alcohol and related conditions. *Psychological medicine*, 36(07):931–941.

Saha, T. D., Compton, W. M., Chou, S. P., Smith, S., Ruan, W. J., Huang, B., Pickering, R. P., and Grant, B. F. (2012). Analyses related to the development of dsm-5 criteria for substance use related disorders: 1. toward amphetamine, cocaine and prescription drug use disorder continua using item response theory. *Drug and alcohol dependence*, 122(1):38–46.

Saha, T. D., Compton, W. M., Pulay, A. J., Stinson, F. S., Ruan, W. J., Smith, S. M., and Grant, B. F. (2010). Dimensionality of dsm-iv nicotine dependence in a national sample: an item response theory application. *Drug and alcohol dependence*, 108(1):21–28.

Said, C. P., Baron, S. G., and Todorov, A. (2009). Nonlinear amygdala response to face trustworthiness: contributions of high and low spatial frequency information. *Journal of Cognitive Neuroscience*, 21(3):519–528.

Sakai, K., Rowe, J. B., and Passingham, R. E. (2002). Active maintenance in prefrontal area 46 creates distractor-resistant memory. *Nature neuroscience*, 5(5):479–484.

Sakai, Y., Kumano, H., Nishikawa, M., Sakano, Y., Kaiya, H., Imabayashi, E., Ohnishi, T., Matsuda, H., Yasuda, A., Sato, A., et al. (2005). Cerebral glucose metabolism associated with a fear network in panic disorder. *Neuroreport*, 16(9):927–931.

Salamone, J. (1994). The involvement of nucleus accumbens dopamine in appetitive and aversive motivation. *Behavioural Brain Research*, 61(2):117–133.

Saleem, K., Kondo, H., and Price, J. (2008). Complementary circuits connecting the orbital and medial prefrontal networks with the temporal, insular, and opercular cortex in the macaque monkey. *Journal of Comparative Neurology*, 506(4):659–693.

Salom, C. L., Betts, K. S., Williams, G. M., Najman, J. M., Scott, J. G., and Alati, R. (2014). Do young people with comorbid mental and alcohol disorders experience worse behavioural problems? *Psychiatry research*, 219(2):372–379.

Salvatore, J. E., Gottesman, I. I., and Dick, D. M. (2015). Endophenotypes for alcohol use disorder: An update on the field. *Current Addiction Reports*, 2(1):76–90.

SAMHSA (2011). Mental health services administration (2012) results from the 2010 national survey on drug use and health: Detailed tables. *Rockville, MD: Center for Behavioral Health Statistics and Quality*.

Samokhvalov, A. V., Popova, S., Room, R., Ramonas, M., and Rehm, J. (2010). Disability associated with alcohol abuse and dependence. *Alcoholism: Clinical and Experimental Research*, 34(11):1871–1878.

Samoluk, S. B. and MacDonald, A. B. (2014). Anxiety sensitivity and substance use and abuse. *Anxiety Sensitivity: Theory, Research, and Treatment of the Fear of Anxiety*, page 287.

Samorini, G. (2002). *Animals and psychedelics: The natural world and the instinct to alter consciousness*. Inner Traditions/Bear & Co.

Sanchez-Roige, S., Stephens, D. N., and Duka, T. (2016). Heightened impulsivity: associated with family history of alcohol misuse, and a consequence of alcohol intake. *Alcoholism: clinical and experimental research*, 40(10):2208–2217.

Sander, D., Grafman, J., and Zalla, T. (2003). The human amygdala: An evolved system for relevance detection. *Reviews in the Neurosciences*, 14(4):303–316.

Sandin, B., Chorot, P., and McNally, R. (1996). Validation of the spanish version of the anxiety sensitivity index in a clinical sample. *Behaviour Research and Therapy*, 34(3):283–290.

Sandín, B., Chorot, P., Valiente, R. M., Germán, M. A. S., and Lostao, L. (2004). Dimensiones de la sensibilidad a la ansiedad: evidencia confirmatoria de la estructura jerárquica. *Revista de Psicopatología y Psicología Clínica*, 9(1):19–33.

Sandler, I., Wolchik, S. A., Cruden, G., Mahrer, N. E., Ahn, S., Brincks, A., and Brown, C. H. (2014). Overview of meta-analyses of the prevention of mental health, substance use, and conduct problems*. *Annual review of clinical psychology*, 10:243–273.

Sang, H. and Hamann, S. (2007). Neural correlates of positive and negative emotion regulation. *Journal of Cognitive Neuroscience*, 19(5):776–798.

Sänger, J., Bechtold, L., Schoofs, D., Blaszkewicz, M., and Wascher, E. (2014). The influence of acute stress on attention mechanisms and its electrophysiological correlates. *Frontiers in behavioral neuroscience*, 8.

Sangha, S., Chadick, J. Z., and Janak, P. H. (2013). Safety encoding in the basal amygdala. *The Journal of Neuroscience*, 33(9):3744–3751.

Santesso, D. and Segalowitz, S. (2009). The error-related negativity is related to risk taking and empathy in young men. *Psychophysiology*, 46(1):143–152.

Sapolsky, R. (1990). Adrenocortical function, social rank, and personality among wild baboons. *Biological Psychiatry*, 28(10):862–878.

Sapolsky, R. M. (1992). *Stress, the aging brain, and the mechanisms of neuron death.* the MIT Press.

Sapolsky, R. M. (1993). Endocrinology alfresco: psychoendocrine studies of wild baboons. *Recent progress in hormone research*, 48:437.

Sapolsky, R. M. (2000). Stress hormones: good and bad. *Neurobiology of disease*, 7(5):540–542.

Sapolsky, R. M. (2015). Stress and the brain: individual variability and the inverted-u. *Nature Neuroscience*, 18(10):1344–1346.

Sapolsky, R. M., Krey, L. C., and McEwen, B. S. (1986). The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis*. *Endocrine reviews*, 7(3):284–301.

Sapolsky, R. M. and McEwen, B. S. (1986). Stress, glucocorticoids, and their role in degenerative changes in the aging hippocampus. *Treatment development strategies for Alzheimer's disease*, pages 151–172.

Sapolsky, R. M., Romero, L. M., and Munck, A. U. (2000). How do glucocorticoids influence stress responses? integrating permissive, suppressive, stimulatory, and preparative actions 1. *Endocrine reviews*, 21(1):55–89.

Sargent, J., Tanski, S., Stoolmiller, M., and Hanewinkel, R. (2010). Using sensation seeking to target adolescents for substance use interventions. *Addiction*, 105(3):506–514.

Sarinopoulos, I., Grupe, D., Mackiewicz, K., Herrington, J., Lor, M., Steege, E., and Nitschke, J. (2010). Uncertainty during anticipation modulates neural responses to aversion in human insula and amygdala. *Cerebral Cortex (New York, NY)*, 20(4):929.

Sarkar, S., Craig, M., Catani, M., Dell'Acqua, F., Fahy, T., Deeley, Q., and Murphy, D. G. (2013). Frontotemporal white-matter microstructural abnormalities in adolescents with conduct disorder: a diffusion tensor imaging study. *Psychological Medicine*, 43(02):401–411.

Sasson, J. M. (1994). The blood of grapes: Viticulture and intoxication in the hebrew bible. *Drinking in Ancient Societies*.

Sathe, N., Chen, P., Dai, L., Laufenberg, J., Gordek, H., Cribb, D., and Virag, T. G. (2013). National survey on drug use and health. *Substance Abuse and Mental Health Services Administration*.

Sato, W., Kubota, Y., Okada, T., Murai, T., Yoshikawa, S., and Sengoku, A. (2002). Seeing happy emotion in fearful and angry faces: qualitative analysis of facial expression recognition in a bilateral amygdala-damaged patient. *Cortex*, 38(5):727–742.

Satpute, A. B., Kang, J., Bickart, K. C., Yardley, H., Wager, T. D., and Barrett, L. F. (2015). Involvement of sensory regions in affective experience: A meta-analysis. *Frontiers in psychology*, 6.

Saunders, B., Farag, N., Vincent, A. S., Collins, F. L., Sorocco, K. H., and Lovallo, W. R. (2008). Impulsive errors on a go-nogo reaction time task: Disinhibitory traits in relation to a family history of alcoholism. *Alcoholism: Clinical and Experimental Research*, 32(5):888–894.

Saunders, B. and Robinson, T. (2010). A cocaine cue acts as an incentive stimulus in some but not others: Implications for addiction. *Biological Psychiatry*, 67(8):730–736.

Saunders, G. and Schuckit, M. (1981). Mmpi scores in young men with alcoholic relatives and controls. *The Journal of nervous and mental disease*, 169(7):456–458.

Saxe, R. (2006). Uniquely human social cognition. *Current Opinion in Neurobiology*, 16(2):235–239.

Saxe, R. and Wexler, A. (2005). Making sense of another mind: The role of the right temporo-parietal junction. *Neuropsychologia*, 43(10):1391–1399.

Sayed, B. A. and French, M. T. (2016). To your health!: Re-examining the health benefits of moderate alcohol use. *Social Science & Medicine*, 167:20–28.

Sayette, M. (1993). An appraisal-disruption model of alcohol's effects on stress responses in social drinkers. *Psychological Bulletin*, 114(3):459–476.

Sayette, M. A. (1999). Does drinking reduce stress? *Alcohol Research and Health*, 23(4):250–255.

Sayette, M. A., Breslin, F. C., Wilson, G. T., and Rosenblum, G. D. (1994). Parental history of alcohol abuse and the effects of alcohol and expectations of intoxication on social stress. *Journal of Studies on Alcohol*, 55(2):214–223.

Sayette, M. A., Martin, C. S., Perrott, M. A., Wertz, J. M., and Hufford, M. R. (2001). A test of the appraisal-disruption model of alcohol and stress. *Journal of studies on alcohol*, 62(2):247–256.

Sayette, M. A., Smith, D. W., Breiner, M. J., and Wilson, G. T. (1992). The effect of alcohol on emotional response to a social stressor. *Journal of studies on alcohol*, 53(6):541–545.

Scaini, S., Belotti, R., Ogliari, A., and Battaglia, M. (2016). A comprehensive meta-analysis of cognitive-behavioral interventions for social anxiety disorder in children and adolescents. *Journal of Anxiety Disorders*, 42:105–112.

Schacht, J., Anton, R., and Myrick, H. (2013). Functional neuroimaging studies of alcohol cue reactivity: A quantitative meta-analysis and systematic review. *Addiction Biology*, 18(1):121–133.

Schaeffer, K. W., Parsons, O. A., and Yohman, J. R. (1984). Neuropsychological differences between male familial and nonfamilial alcoholics and nonalcoholics. *Alcoholism: Clinical and Experimental Research*, 8(4):347–351.

Scheele, D., Mihov, Y., Kendrick, K. M., Feinstein, J. S., Reich, H., Maier, W., and Hurlemann, R. (2012). Amygdala lesion profoundly alters altruistic punishment. *Biological psychiatry*, 72(3):e5–e7.

Schellekens, A. (2016). Translational perspectives in addiction psychiatry. *European Psychiatry*, 33:S60.

Scher, C. D. and Stein, M. B. (2003). Developmental antecedents of anxiety sensitivity. *Journal of Anxiety Disorders*, 17(3):253–269.

Schienle, A., Köchel, A., Ebner, F., Reishofer, G., and Schäfer, A. (2010). Neural correlates of intolerance of uncertainty. *Neuroscience letters*, 479(3):272–276.

Schienle, A., Schäfer, A., Stark, R., Walter, B., and Vaitl, D. (2005a). Neural responses of ocd patients towards disorder-relevant, generally disgust-inducing and fear-inducing pictures. *International Journal of Psychophysiology*, 57(1):69–77.

Schienle, A., Schäfer, A., Walter, B., Stark, R., and Vaitl, D. (2005b). Brain activation of spider phobics towards disorder-relevant, generally disgust- and fear-inducing pictures. *Neuroscience Letters*, 388(1):1–6.

Schilbach, L., Bzdok, D., Timmermans, B., Fox, P. T., Laird, A. R., Vogeley, K., and Eickhoff, S. B. (2012). Introspective minds: using ale meta-analyses to study commonalities in the neural correlates of emotional processing, social & unconstrained cognition. *PloS one*, 7(2):e30920.

Schilbach, L., Eickhoff, S. B., Rotarska-Jagiela, A., Fink, G. R., and Vogeley, K. (2008). Minds at rest? social cognition as the default mode of cognizing and its putative relationship to the "default system" of the brain. *Consciousness and cognition*, 17(2):457–467.

Schlenker, B. and Leary, M. (1982). Social anxiety and self-presentation: A conceptualization model. *Psychological Bulletin*, 92(3):641–669.

Schlotz, W., Kumsta, R., Layes, I., Entringer, S., Jones, A., and Wüst, S. (2008). Covariance between psychological and endocrine responses to pharmacological challenge and psychosocial stress: a question of timing. *Psychosomatic medicine*, 70(7):787–796.

Schmahl, C., Vermetten, E., Elzinga, B., and Bremner, J. (2004). A positron emission tomography study of memories of childhood abuse in borderline personality disorder. *Biological Psychiatry*, 55(7):759–765.

Schmidt, A., Borgwardt, S., Gerber, H., Wiesbeck, G. A., Schmid, O., Riecher-Rössler, A., Smieskova, R., Lang, U. E., and Walter, M. (2014). Acute effects of heroin on negative emotional processing: relation of amygdala activity and stress-related responses. *Biological psychiatry*, 76(4):289–296.

Schmidt, L. A., Fox, N. A., Sternberg, E. M., Gold, P. W., Smith, C. C., and Schulkin, J. (1999). Adrenocortical reactivity and social competence in seven year-olds. *Personality and Individual Differences*, 26(6):977–985.

Schmidt, N. B. (1999). Examination of differential anxiety sensitivities in panic disorder: a test of anxiety sensitivity subdomains predicting fearful responding to a 35% co2 challenge. *Cognitive Therapy and Research*, 23(1):3–20.

Schmidt, N. B. and Zvolensky, M. J. (2007). Anxiety sensitivity and co2 challenge reactivity as unique and interactive prospective predictors of anxiety pathology. *Depression and Anxiety*, 24(8):527–536.

Schmidt, N. B., Zvolensky, M. J., and Maner, J. K. (2006). Anxiety sensitivity: prospective prediction of panic attacks and axis i pathology. *Journal of psychiatric research*, 40(8):691–699.

Schmithorst, V. J. and Yuan, W. (2010). White matter development during adolescence as shown by diffusion mri. *Brain and cognition*, 72(1):16–25.

Schoenbaum, G. and Shaham, Y. (2008). The role of orbitofrontal cortex in drug addiction: a review of preclinical studies. *Biological psychiatry*, 63(3):256–262.

Schoofs, D. and Wolf, O. T. (2011). Are salivary gonadal steroid concentrations influenced by acute psychosocial stress? a study using the trier social stress test (tsst). *International Journal of Psychophysiology*, 80(1):36–43.

Schooler, J. W., Smallwood, J., Christoff, K., Handy, T. C., Reichle, E. D., and Sayette, M. A. (2011). Meta-awareness, perceptual decoupling and the wandering mind. *Trends in cognitive sciences*, 15(7):319–326.

Schreckenberger, M., Amberg, R., Scheurich, A., Lochmann, M., Tichy, W., Klega, A., Siessmeier, T., Gründer, G., Buchholz, H.-G., Landvogt, C., Stauss, J., Mann, K., Bartenstein, P., and Urban, R. (2004). Acute alcohol effects on neuronal and

attentional processing: Striatal reward system and inhibitory sensory interactions under acute ethanol challenge. *Neuropsychopharmacology*, 29(8):1527–1537.

Schreiber Compo, N., Evans, J. R., Carol, R. N., Kemp, D., Villalba, D., Ham, L. S., and Rose, S. (2011). Alcohol intoxication and memory for events: A snapshot of alcohol myopia in a real-world drinking scenario. *Memory*, 19(2):202–210.

Schroder, K. E. and Perrine, M. W. (2007). Covariations of emotional states and alcohol consumption: evidence from 2 years of daily data collection. *Social science & medicine*, 65(12):2588–2602.

Schuch, J. J., Roest, A. M., Nolen, W. A., Penninx, B. W., and de Jonge, P. (2014). Gender differences in major depressive disorder: results from the netherlands study of depression and anxiety. *Journal of affective disorders*, 156:156–163.

Schuckit, M. (1980). Alcoholism and genetics: Possible biological mediators. *Biological Psychiatry*, 15(3):437–447.

Schuckit, M. (1984). Subjective responses to alcohol in sons of alcoholics and control subjects. *Archives of General Psychiatry*, 41(9):879–884.

Schuckit, M., Gold, E., and Risch, C. (1987). Plasma cortisol levels following ethanol in sons of alcoholics and controls. *Archives of General Psychiatry*, 44(11):942–945.

Schuckit, M., Risch, S., and Gold, E. (1988). Alcohol consumption, acth level, and family history of alcoholism. *American Journal of Psychiatry*, 145(11):1391–1395.

Schuckit, M. and Russell, J. (1984). An evaluation of primary alcoholics with histories of violence. *Journal of Clinical Psychiatry*, 45(1):3–6.

Schuckit, M. A. (2014). A brief history of research on the genetics of alcohol and other drug use disorders. *Journal of studies on alcohol and drugs. Supplement*, 75(Suppl 17):59.

Schuckit, M. A. and Smith, T. L. (1996). An 8-year follow-up of 450 sons of alcoholic and control subjects. *Archives of General Psychiatry*, 53(3):202–210.

Schuckit, M. A., Smith, T. L., Kalmijn, J., Skidmore, J., Clausen, P., Shafir, A., Saunders, G., Bystritsky, H., and Fromme, K. (2015). The impact of focusing a program to prevent heavier drinking on a pre-existing phenotype, the low level of response to alcohol. *Alcoholism: Clinical and Experimental Research*, 39(2):308–316.

Schuckit, M. A., Smith, T. L., Paulus, M. P., Tapert, S. F., Simmons, A. N., Tolentino, N. J., and Shafir, A. (2016). The ability of functional magnetic resonance imaging to predict heavy drinking and alcohol problems 5 years later. *Alcoholism: Clinical and Experimental Research*, 40(1):206–213.

Schuckit, M. A., Smith, T. L., and Tipp, J. E. (1997a). The self-rating of the effects of alcohol (sre) form as a retrospective measure of the risk for alcoholism. *Addiction*, 92(8):979–988.

Schuckit, M. A., Tipp, J. E., Smith, T. L., Wiesbeck, G. A., and Kalmijn, J. (1997b). The relationship between self-rating of the effects of alcohol and alcohol challenge results in ninety-eight young men. *Journal of studies on alcohol*, 58(4):397–404.

Schulkin, J., McEwen, B. S., and Gold, P. W. (1994). Allostasis, amygdala, and anticipatory angst. *Neuroscience & Biobehavioral Reviews*, 18(3):385–396.

Schulsinger, F., Knop, J., Goodwin, D. W., and Teasdale, T. W. (1986). A prospective study of young men at high risk for alcoholism: Social and psychological characteristics. *Archives of General Psychiatry*, 43(8):755–760.

Schulte, T., Oberlin, B. G., Kareken, D. A., Marinkovic, K., Müller-Oehring, E. M., Meyerhoff, D. J., and Tapert, S. (2012). How acute and chronic alcohol consumption affects brain networks: insights from multimodal neuroimaging. *Alcoholism: Clinical and Experimental Research*, 36(12):2017–2027.

Schultz, W. (2004). Neural coding of basic reward terms of animal learning theory, game theory, microeconomics and behavioural ecology. *Current opinion in neurobiology*, 14(2):139–147.

Schulz, S. M., Alpers, G. W., and Hofmann, S. G. (2008). Negative self-focused cognitions mediate the effect of trait social anxiety on state anxiety. *Behaviour research and therapy*, 46(4):438–449.

Schulze, L., Domes, G., Krüger, A., Berger, C., Fleischer, M., Prehn, K., Schmahl, C., Grossmann, A., Hauenstein, K., and Herpertz, S. C. (2011). Neuronal correlates of cognitive reappraisal in borderline patients with affective instability. *Biological psychiatry*, 69(6):564–573.

Schurz, M., Kogler, C., Scherndl, T., Kronbichler, M., and Kühberger, A. (2015). Differentiating self-projection from simulation during mentalizing: Evidence from fmri. *PloS one*, 10(3):e0121405.

Schwabe, L., , M., Roozendaal, B., Wolf, O., and Oitzl, M. (2011). Stress effects on memory: An update and integration. *Neurosci. Biobehav. Rev.*

Schwanenberg, E. (1974). Izard, ce: The face of emotion. new york (appleton-century-crofts) 1971, 468 seiten. *Psyche*, 28(9-10):919–920.

Schwartz, C. E., Snidman, N., and Kagan, J. (1999). Adolescent social anxiety as an outcome of inhibited temperament in childhood. *Journal of the American Academy of Child & Adolescent Psychiatry*, 38(8):1008–1015.

Schwartz, C. E., Wright, C. I., Shin, L. M., Kagan, J., and Rauch, S. L. (2003). Inhibited and uninhibited infants" grown up": adult amygdalar response to novelty. *Science*, 300(5627):1952–1953.

Schwarz, R. M., Burkhart, B. R., and Green, S. B. (1978). Turning on or turning off: sensation seeking or tension reduction as motivational determinants of alcohol use. *Journal of Consulting and Clinical Psychology*, 46(5):1144.

Schweinsburg, A. D., Paulus, M. P., Barlett, V. C., Killeen, L. A., Caldwell, L. C., Pulido, C., Brown, S. A., and Tapert, S. F. (2004). An fmri study of response inhibition in youths with a family history of alcoholism. *Annals of the New York Academy of Sciences*, 1021(1):391–394.

Schweizer, T., Vogel-Sprott, M., Danckert, J., Roy, E., Skakum, A., and Broderick, C. (2006). Neuropsychological profile of acute alcohol intoxication during ascending and descending blood alcohol concentrations. *Neuropsychopharmacology*, 31(6):1301–1309.

Scott, C. and Corbin, W. R. (2014). Influence of sensation seeking on response to alcohol versus placebo: implications for the acquired preparedness model. *Journal of studies on alcohol and drugs*, 75(1):136.

Scott, K. M., Smith, D. R., and Ellis, P. M. (2010). Prospectively ascertained child maltreatment and its association with dsm-iv mental disorders in young adults. *Archives of general psychiatry*, 67(7):712–719.

Sebastian, C. L., De Brito, S. A., McCrory, E. J., Hyde, Z. H., Lockwood, P. L., Cecil, C. A., and Viding, E. (2016). Grey matter volumes in children with conduct problems and varying levels of callous-unemotional traits. *Journal of abnormal child psychology*, 44(4):639–649.

Sebastian, C. L., Tan, G. C., Roiser, J. P., Viding, E., Dumontheil, I., and Blakemore, S.-J. (2011). Developmental influences on the neural bases of responses to social rejection: implications of social neuroscience for education. *Neuroimage*, 57(3):686–694.

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., Reiss, A. L., and Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *The Journal of neuroscience*, 27(9):2349–2356.

Seeman, T. E., Berkman, L. F., Gulanski, B. I., Robbins, R. J., Greenspan, S. L., Charpentier, P. A., and Rowe, J. W. (1995). Self-esteem and neuroendocrine response to challenge: Macarthur studies of successful aging. *Journal of psychosomatic research*, 39(1):69–84.

Selemon, L. D. and Goldman-Rakic, P. S. (1988). Common cortical and subcortical targets of the dorsolateral prefrontal and posterior parietal cortices in the rhesus monkey: evidence for a distributed neural network subserving spatially guided behavior. *The Journal of Neuroscience*, 8(11):4049–4068.

Selye, H. (1956). *The stress of life*. McGraw-Hill.

Selzer, M. L. (1971). The michigan alcoholism screening test: The quest for a new diagnostic instrument. *American journal of Psychiatry*, 127(12):1653–1658.

Sergerie, K., Chochol, C., and Armony, J. L. (2008). The role of the amygdala in emotional processing: a quantitative meta-analysis of functional neuroimaging studies. *Neuroscience & Biobehavioral Reviews*, 32(4):811–830.

Servaas, M. N., Geerligs, L., Renken, R. J., Marsman, J.-B. C., Ormel, J., Riese, H., and Aleman, A. (2015). Connectomics and neuroticism: An altered functional network organization. *Neuropsychopharmacology*, 40(2):296–304.

Service, S., Verweij, K., Lahti, J., Congdon, E., Ekelund, J., Hintsanen, M., Räikkönen, K., Lehtimäki, T., Kähönen, M., Widen, E., et al. (2012). A genome-wide meta-analysis of association studies of cloninger's temperament scales. *Translational psychiatry*, 2(5):e116.

Setiawan, E., Pihl, R. O., Cox, S. M., Gianoulakis, C., Palmour, R. M., Benkelfat, C., and Leyton, M. (2011). The effect of naltrexone on alcohol's stimulant properties and self-administration behavior in social drinkers: Influence of gender and genotype. *Alcoholism: Clinical and Experimental Research*, 35(6):1134–1141.

Shackman, A., Fox, A., Oler, J., Shelton, S., Oakes, T., Davidson, R., and Kalin, N. (2016a). Heightened extended amygdala metabolism following threat characterizes the early phenotypic risk to develop anxiety-related psychopathology. *Molecular Psychiatry*.

Shackman, A., Kaplan, C., Stockbridge, M., Tillman, R., Tromp, D., Fox, A., and Gamer, M. (2016b). The neurobiology of dispositional negativity and attentional biases to threat: Implications for understanding anxiety disorders in adults and youth.(in press). *Journal of Experimental Psychopathology*.

Shackman, A. J. and Fox, A. S. (2016). Contributions of the central extended amygdala to fear and anxiety. *The Journal of Neuroscience*, 36(31):8050–8063.

Shackman, A. J., Fox, A. S., Oler, J. A., Shelton, S. E., Davidson, R. J., and Kalin, N. H. (2013). Neural mechanisms underlying heterogeneity in the presentation of anxious temperament. *Proceedings of the National Academy of Sciences*, 110(15):6145–6150.

Shackman, A. J., Salomons, T. V., Slagter, H. A., Fox, A. S., Winter, J. J., and Davidson, R. J. (2011). The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nature Reviews Neuroscience*, 12(3):154–167.

Shackmana, A. J., Trompe, D. P., Stockbridgeb, M. D., Kaplana, C. M., Tillmana, R. M., and Foxe, A. S. (in press). Dispositional negativity: An integrative psychological and neurobiological perspective. *Psychological Bulletin*.

Shah, P., Hall, R., Catmur, C., and Bird, G. (2016). Alexithymia, not autism, is associated with impaired interoception. *cortex*, 81:215–220.

Shah, S. G. and Angstadt, M. (2009). Amygdala and insula response to emotional images in patients with generalized social anxiety disorder. *Journal of psychiatry & neuroscience: JPN*, 34(4):296.

Shalev, I., Heim, C. M., and Noll, J. G. (2016). Child maltreatment as a root cause of mortality disparities: a call for rigorous science to mobilize public investment in prevention and treatment. *JAMA psychiatry*.

Shalev, I., Lerer, E., Israel, S., Uzefovsky, F., Gritsenko, I., Mankuta, D., Ebstein, R. P., and Kaitz, M. (2009). Bdnf val66met polymorphism is associated with hpa axis reactivity to psychological stress characterized by genotype and gender interactions. *Psychoneuroendocrinology*, 34(3):382–388.

Shankman, S. A., Gorka, S. M., Nelson, B. D., Fitzgerald, D. A., Phan, K. L., and O'Daly, O. (2014). Anterior insula responds to temporally unpredictable aversiveness: an fmri study. *Neuroreport*, 25(8):596.

Sheldon, K., Ryan, R., and Reis, H. (1996). What makes for a good day? competence and autonomy in the day and in the person. *Personality and Social Psychology Bulletin*, 22(12):1270–1279.

Sher, K. J. (1987). Stress response dampening. *Psychological theories of drinking and alcoholism*, pages 227–271.

Sher, K. J. (1991). *Children of alcoholics: A critical appraisal of theory and research*. University of Chicago Press.

Sher, K. J., Bartholow, B. D., Peuser, K., Erickson, D. J., and Wood, M. D. (2007). Stress-response-dampening effects of alcohol: attention as a mediator and moderator. *Journal of Abnormal Psychology*, 116(2):362.

Sher, K. J., Grekin, E. R., and Williams, N. A. (2005). The development of alcohol use disorders. *Annu. Rev. Clin. Psychol.*, 1:493–523.

Sher, K. J. and Walitzer, K. S. (1986). Individual differences in the stress-response-dampening effect of alcohol: A dose-response study. *Journal of Abnormal Psychology*, 95(2):159.

Sher, K. J., T. T. J. B. B. and Vieth, A. (1999). Personality and alcoholism: Issues, methods, and etiological processes. *Psychological theories of drinking and alcoholism (2nd edn)*, pages 55–105.

Shiba, Y., Santangelo, A. M., and Roberts, A. C. (2016). Beyond the medial regions of prefrontal cortex in the regulation of fear and anxiety. *Frontiers in systems neuroscience*, 10.

Shibata, T. and Ioannides, A. A. (2001). Contribution of the human superior parietal lobule to spatial selection process: an meg study. *Brain research*, 897(1):164–168.

Shield, K. D., Taylor, B., Kehoe, T., Patra, J., and Rehm, J. (2012). Mortality and potential years of life lost attributable to alcohol consumption in canada in 2005. *BMC Public Health*, 12(1):1.

Shields, G. S., Sazma, M. A., and Yonelinas, A. P. (2016). The effects of acute stress on core executive functions: A meta-analysis and comparison with cortisol. *Neuroscience & Biobehavioral Reviews*, 68:651–668.

Shihata, S., McEvoy, P. M., Mullan, B. A., and Carleton, R. N. (2016). Intolerance of uncertainty in emotional disorders: What uncertainties remain? *Journal of anxiety disorders*.

Shimizu, M., Seery, M. D., Weisbuch, M., and Lupien, S. P. (2011). Trait social anxiety and physiological activation: Cardiovascular threat during social interaction. *Personality and Social Psychology Bulletin*, 37(1):94–106.

Shin, L., Kosslyn, S., McNally, R., Alpert, N., Thompson, W., Rauch, S., Macklin, M., and Pitman, R. (1997). Visual imagery and perception in posttraumatic stress disorder: A positron emission tomographic investigation. *Archives of General Psychiatry*, 54(3):233–241.

Shin, L. and Liberzon, I. (2010). The neurocircuitry of fear, stress, and anxiety disorders. *Neuropsychopharmacology*, 35(1):169–191.

Shin, L., Orr, S., Carson, M., Rauch, S., Macklin, M., Lasko, N., Peters, P., Metzger, L., Dougherty, D., Cannistraro, P., Alpert, N., Fischman, A., and Pitman, R. (2004). Regional cerebral blood flow in the amygdala and medial prefrontal cortex during traumatic imagery in male and female vietnam veterans with ptsd. *Archives of General Psychiatry*, 61(2):168–176.

Shin, L. M., Davis, F. C., VanElzakker, M. B., Dahlgren, M. K., and Dubois, S. J. (2013). Neuroimaging predictors of treatment response in anxiety disorders. *Biology of mood & anxiety disorders*, 3(1):1.

Shin, L. M., Wright, C. I., Cannistraro, P. A., Wedig, M. M., McMullin, K., Martis, B., Macklin, M. L., Lasko, N. B., Cavanagh, S. R., Krangel, T. S., et al. (2005). A functional magnetic resonance imaging study of amygdala and medial prefrontal cortex responses to overtly presented fearful faces in posttraumatic stress disorder. *Archives of general psychiatry*, 62(3):273–281.

Shin, S. H., Lee, S., Jeon, S.-M., and Wills, T. A. (2015). Childhood emotional abuse, negative emotion-driven impulsivity, and alcohol use in young adulthood. *Child abuse & neglect*.

Shlosberg, D. and Shoval, G. (2015). Suicide and substance abuse in adolescents. In *Textbook of Addiction Treatment: International Perspectives*, pages 2249–2278. Springer.

Shoham, V. and Insel, T. R. (2011). Rebooting for whom? portfolios, technology, and personalized intervention. *Perspectives on Psychological Science*, 6(5):478–482.

Shokri-Kojori, E., Tomasi, D., Wiers, C., Wang, G., and Volkow, N. (2016). Alcohol affects brain functional connectivity and its coupling with behavior: greater effects in male heavy drinkers. *Molecular psychiatry*.

Shollenbarger, S. G., Price, J., Wieser, J., and Lisdahl, K. (2015). Poorer frontolimbic white matter integrity is associated with chronic cannabis use, faah genotype, and increased depressive and apathy symptoms in adolescents and young adults. *NeuroImage: Clinical*, 8:117–125.

Shulman, E. P., Harden, K. P., Chein, J. M., and Steinberg, L. (2015). Sex differences in the developmental trajectories of impulse control and sensation-seeking from early adolescence to early adulthood. *Journal of youth and adolescence*, 44(1):1–17.

Shulman, G. L., Fiez, J. A., Corbetta, M., Buckner, R. L., Miezin, F. M., Raichle, M. E., and Petersen, S. E. (1997). Common blood flow changes across visual tasks: Ii. decreases in cerebral cortex. *Journal of cognitive neuroscience*, 9(5):648–663.

Siegel, R. K. (1989). *Intoxication: Life in pursuit of artificial paradise.* EP Dutton.

Siegel, R. K. and Brodie, M. (1984). Alcohol self-administration by elephants. *Bulletin of the Psychonomic Society*, 22(1):49–52.

Sierra, R. O., Nítola, L. P., Duran, J. M., Prieto, D. R., León, L. A., and Cardenas, F. P. (2016). Medial orbitofrontal cortex lesion prevents facilitatory effects of d-cycloserine during fear extinction. *Behavioural brain research*, 296:379–383.

Sikes, S. K. (1971). The natural history of the african elephant.

Silberman, Y., Ariwodola, O., and Weiner, J. (2009). Differential effects of gabab autoreceptor activation on ethanol potentiation of local and lateral paracapsular gabaergic synapses in the rat basolateral amygdala. *Neuropharmacology*, 56(5):886–895.

Silberman, Y., Shi, L., Brunso-Bechtold, J., and Weiner, J. (2008). Distinct mechanisms of ethanol potentiation of local and paracapsular gabaergic synapses in the rat basolateral amygdala. *Journal of Pharmacology and Experimental Therapeutics*, 324(1):251–260.

Silveri, M., Rogowska, J., McCaffrey, A., and Yurgelun-Todd, D. (2011). Adolescents at risk for alcohol abuse demonstrate altered frontal lobe activation during stroop performance. *Alcoholism: Clinical and Experimental Research*, 35(2):218–228.

Silveri, M. M., Dager, A. D., Cohen-Gilbert, J. E., and Sneider, J. T. (2016). Neurobiological signatures associated with alcohol and drug use in the human adolescent brain. *Neuroscience & Biobehavioral Reviews*.

Sim, M. E., Lyoo, I. K., Streeter, C. C., Covell, J., Sarid-Segal, O., Ciraulo, D. A., Kim, M. J., Kaufman, M. J., Yurgelun-Todd, D. A., and Renshaw, P. F. (2007). Cerebellar gray matter volume correlates with duration of cocaine use in cocaine-dependent subjects. *Neuropsychopharmacology*, 32(10):2229–2237.

Simmons, A., Matthews, S. C., Paulus, M. P., and Stein, M. B. (2008a). Intolerance of uncertainty correlates with insula activation during affective ambiguity. *Neuroscience letters*, 430(2):92–97.

Simmons, A., Strigo, I., Matthews, S. C., Paulus, M. P., and Stein, M. B. (2006). Anticipation of aversive visual stimuli is associated with increased insula activation in anxiety-prone subjects. *Biological psychiatry*, 60(4):402–409.

Simmons, A. N., Paulus, M. P., Thorp, S. R., Matthews, S. C., Norman, S. B., and Stein, M. B. (2008b). Functional activation and neural networks in women with posttraumatic stress disorder related to intimate partner violence. *Biological psychiatry*, 64(8):681–690.

Simmons, A. N., Stein, M. B., Strigo, I. A., Arce, E., Hitchcock, C., and Paulus, M. P. (2011). Anxiety positive subjects show altered processing in the anterior insula during anticipation of negative stimuli. *Human brain mapping*, 32(11):1836–1846.

Simmons, W. K., Martin, A., and Barsalou, L. W. (2005). Pictures of appetizing foods activate gustatory cortices for taste and reward. *Cerebral Cortex*, 15(10):1602–1608.

Simon, D., Adler, N., Kaufmann, C., and Kathmann, N. (2014). Amygdala hyperactivation during symptom provocation in obsessive–compulsive disorder and its modulation by distraction. *NeuroImage: Clinical*, 4:549–557.

Simon, E. W., Rosen, M., and Ponpipom, A. (1996). Age and iq as predictors of emotion identification in adults with mental retardation. *Research in Developmental Disabilities*, 17(5):383–389.

Simonetti, J. A., Mackelprang, J. L., Rowhani-Rahbar, A., Zatzick, D., and Rivara, F. P. (2014). Psychiatric comorbidity, suicidality, and in-home firearm access among a nationally representative sample of adolescents. *JAMA psychiatry*.

Simpson, J. R., Drevets, W. C., Snyder, A. Z., Gusnard, D. A., and Raichle, M. E. (2001). Emotion-induced changes in human medial prefrontal cortex: Ii. during anticipatory anxiety. *Proceedings of the National Academy of Sciences*, 98(2):688–693.

Sindelar, H., Barnett, N., and Spirito, A. (2004). Adolescent alcohol use and injury. *Minerva pediatrica*, 56:291–309.

Singer, T., Critchley, H. D., and Preuschoff, K. (2009). A common role of insula in feelings, empathy and uncertainty. *Trends in cognitive sciences*, 13(8):334–340.

Singh, T., Walters, J. T., Johnstone, M., Curtis, D., Suvisaari, J., Torniainen, M., Rees, E., Iyegbe, C., Blackwood, D., McIntosh, A. M., et al. (2016). Rare schizophrenia risk variants are enriched in genes shared with neurodevelopmental disorders. *bioRxiv*, page 069344.

Sinha, R. (2008). Chronic stress, drug use, and vulnerability to addiction. *Annals of the New York Academy of Sciences*, 1141(1):105–130.

Sinha, R., Fox, H. C., Hong, K. A., Bergquist, K., Bhagwagar, Z., and Siedlarz, K. M. (2009). Enhanced negative emotion and alcohol craving, and altered physiological responses following stress and cue exposure in alcohol dependent individuals. *Neuropsychopharmacology*, 34(5):1198–1208.

Sipe, J. C., Chiang, K., Gerber, A. L., Beutler, E., and Cravatt, B. F. (2002). A missense mutation in human fatty acid amide hydrolase associated with problem drug use. *Proceedings of the National Academy of Sciences*, 99(12):8394–8399.

Sjoerds, Z., Van Tol, M.-J., van den Brink, W., Van der Wee, N. J., Van Buchem, M. A., Aleman, A., Penninx, B. W., and Veltman, D. J. (2013). Family history of alcohol dependence and gray matter abnormalities in non-alcoholic adults. *The world journal of biological psychiatry*, 14(8):565–573.

Skinner, K. D. and Veilleux, J. C. (2016). The interactive effects of drinking motives, age, and self-criticism in predicting hazardous drinking. *Substance use & misuse*, pages 1–11.

Skinner, M. L., Hong, S., Herrenkohl, T. I., Brown, E. C., Lee, J. O., and Jung, H. (2016). Longitudinal effects of early childhood maltreatment on co-occurring substance misuse and mental health problems in adulthood: the role of adolescent alcohol use and depression. *Journal of studies on alcohol and drugs*, 77(3):464–472.

Slade, T., Chiu, W.-T., Glantz, M., Kessler, R. C., Lago, L., Sampson, N., Al-Hamzawi, A., Florescu, S., Moskalewicz, J., Murphy, S., et al. (2016). A cross-national examination of differences in classification of lifetime alcohol use disorder between dsm-iv and dsm-5: Findings from the world mental health survey. *Alcoholism: Clinical and Experimental Research*.

Sladky, R., Höflich, A., Küblböck, M., Kraus, C., Baldinger, P., Moser, E., Lanzenberger, R., and Windischberger, C. (2015). Disrupted effective connectivity between the amygdala and orbitofrontal cortex in social anxiety disorder during emotion discrimination revealed by dynamic causal modeling for fmri. *Cerebral Cortex*, 25(4):895–903.

Slutske, W., Heath, A., Madden, P., Bucholz, K., Statham, D., and Martin, N. (2002). Personality and the genetic risk for alcohol dependence. *Journal of Abnormal Psychology*, 111(1):124–133.

Slutske, W. S., Heath, A. C., Dinwiddie, S. H., Madden, P. A., Bucholz, K. K., Dunne, M. P., Statham, D. J., and Martin, N. G. (1998). Common genetic risk factors for conduct disorder and alcohol dependence. *Journal of abnormal psychology*, 107(3):363.

Smallwood, J. and Schooler, J. W. (2006). The restless mind. *Psychological bulletin*, 132(6):946.

Smart Richman, L. and Leary, M. R. (2009). Reactions to discrimination, stigmatization, ostracism, and other forms of interpersonal rejection: a multimotive model. *Psychological review*, 116(2):365.

Smith, B. D., Davidson, R. A., Perlstein, W., and Gonzalez, F. (1990). Sensation-seeking: Electrodermal and behavioral effects of stimulus content and intensity. *International Journal of Psychophysiology*, 9(2):179–188.

Smith, C. A. and Ellsworth, P. C. (1985). Patterns of cognitive appraisal in emotion. *Journal of personality and social psychology*, 48(4):813.

Smith, C. T., Dang, L. C., Cowan, R. L., Kessler, R. M., and Zald, D. H. (2016a). Variability in paralimbic dopamine signaling correlates with subjective responses to d-amphetamine. *Neuropharmacology*, 108:394–402.

Smith, D. G., Jones, P. S., Bullmore, E. T., Robbins, T. W., and Ersche, K. D. (2014). Enhanced orbitofrontal cortex function and lack of attentional bias to cocaine cues in recreational stimulant users. *Biological psychiatry*, 75(2):124–131.

Smith, J., Marciani, L., Humes, D., Francis, S., Gowland, P., and Spiller, R. (2016b). Anticipation of thermal pain in diverticular disease. *Neurogastroenterology and motility: the official journal of the European Gastrointestinal Motility Society*.

Smith, J. L., Iredale, J. M., and Mattick, R. P. (2016c). Sex differences in the relationship between heavy alcohol use, inhibition and performance monitoring: Disconnect between behavioural and brain functional measures. *Psychiatry Research: Neuroimaging*, 254:103–111.

Smith, Y. and Pare, D. (1994). Intra-amygdaloid projections of the lateral nucleus in the cat: Pha-l anterograde labeling combined with postembedding gaba and glutamate immunocytochemistry. *Journal of Comparative Neurology*, 342(2):232–248.

Smits, D., De Boeck, P., and Vansteelandt, K. (2004). The inhibition of verbally aggressive behaviour. *European Journal of Personality*, 18(7):537–555.

Smits, D. J. and Kuppens, P. (2005). The relations between anger, coping with anger, and aggression, and the bis/bas system. *Personality and Individual differences*, 39(4):783–793.

Smyth, A., Teo, K. K., Rangarajan, S., O'Donnell, M., Zhang, X., Rana, P., Leong, D. P., Dagenais, G., Seron, P., Rosengren, A., et al. (2015). Alcohol consumption and cardiovascular disease, cancer, injury, admission to hospital, and mortality: a prospective cohort study. *The Lancet*, 386(10007):1945–1954.

Snoek, H., Van Goozen, S. H., Matthys, W., Buitelaar, J. K., and Van Engeland, H. (2004). Stress responsivity in children with externalizing behavior disorders. *Development and psychopathology*, 16(02):389–406.

Soares, L. M., De Vry, J., Steinbusch, H. W., Milani, H., Prickaerts, J., and de Oliveira, R. M. W. (2016). Rolipram improves cognition, reduces anxiety-and despair-like behaviors and impacts hippocampal neuroplasticity after transient global cerebral ischemia. *Neuroscience*, 326:69–83.

Söderpalm, A. H. and Wit, H. (2002). Effects of stress and alcohol on subjective state in humans. *Alcoholism: Clinical and Experimental Research*, 26(6):818–826.

Sokolov, E. N., Vinogradova, O. S., et al. (1975). *Neuronal mechanisms of the orienting reflex*. L. Erlbaum Associates.

Soliman, A., O'Driscoll, G. A., Pruessner, J., Holahan, A.-L. V., Boileau, I., Gagnon, D., and Dagher, A. (2008). Stress-induced dopamine release in humans at risk of psychosis: a [11c] raclopride pet study. *Neuropsychopharmacology*, 33(8):2033–2041.

Soliman, A., O'Driscoll, G. A., Pruessner, J., Joober, R., Ditto, B., Streicker, E., Goldberg, Y., Caro, J., Rekkas, P. V., and Dagher, A. (2011). Limbic response to psychosocial stress in schizotypy: a functional magnetic resonance imaging study. *Schizophrenia research*, 131(1):184–191.

Solomon, Z., Ginzburg, K., Neria, Y., and Ohry, A. (1995). Coping with war captivity: The role of sensation seeking. *European Journal of Personality*, 9(1):57–70.

Somerville, L. H., Wagner, D. D., Wig, G. S., Moran, J. M., Whalen, P. J., and Kelley, W. M. (2013). Interactions between transient and sustained neural signals support the generation and regulation of anxious emotion. *Cerebral Cortex*, 23(1):49–60.

Somerville, L. H., Whalen, P. J., and Kelley, W. M. (2010). Human bed nucleus of the stria terminalis indexes hypervigilant threat monitoring. *Biological psychiatry*, 68(5):416–424.

Sommer, W., Moller, C., Wiklund, L., Thorsell, A., Rimondini, R., Nissbrandt, H., and Heilig, M. (2001). Local 5, 7-dihydroxytryptamine lesions of rat amygdala: release of punished drinking, unaffected plus-maze behavior and ethanol consumption. *Neuropsychopharmacology*, 24(4):430–440.

Soravia, L. M., Orosz, A., Schwab, S., Nakataki, M., Wiest, R., and Federspiel, A. (2016). Cbt reduces cbf: cognitive-behavioral therapy reduces cerebral blood flow in fear-relevant brain regions in spider phobia. *Brain and Behavior*.

Sorocco, K. H., Carnes, N. C., Cohoon, A. J., Vincent, A. S., and Lovallo, W. R. (2015). Risk factors for alcoholism in the oklahoma family health patterns project: Impact of early life adversity and family history on affect regulation and personality. *Drug and alcohol dependence*, 150:38–45.

Sorocco, K. H., Lovallo, W. R., Vincent, A. S., and Collins, F. L. (2006). Blunted hypothalamic–pituitary–adrenocortical axis responsivity to stress in persons with a family history of alcoholism. *International Journal of Psychophysiology*, 59(3):210–217.

Sosic-Vasic, Z., Ulrich, M., Ruchsow, M., Vasic, N., and Grön, G. (2012). The modulating effect of personality traits on neural error monitoring: Evidence from event-related fmri. *PLoS ONE*, 7(8).

Sotres-Bayon, F. and Quirk, G. J. (2010). Prefrontal control of fear: more than just extinction. *Current opinion in neurobiology*, 20(2):231–235.

Soufer, R., Arrighi, J., and Burg, M. (2002). Brain, behavior, mental stress, and the neurocardiac interaction. *Journal of Nuclear Cardiology*, 9(6):650–662.

Sowell, E., Peterson, B., Thompson, P., Welcome, S., Henkenius, A., and Toga, A. (2003). Mapping cortical change across the human life span. *Nature Neuroscience*, 6(3):309–315.

Spadoni, A., Norman, A., Schweinsburg, A., and Tapert, S. (2008). Effects of family history of alcohol use disorders on spatial working memory bold response in adolescents. *Alcoholism: Clinical and Experimental Research*, 32(7):1135–1145.

Spanagel, R., Montkowski, A., Allingham, K., Shoaib, M., Holsboer, F., and Landgraf, R. (1995). Anxiety: a potential predictor of vulnerability to the initiation of ethanol self-administration in rats. *Psychopharmacology*, 122(4):369–373.

Spear, L. P. (2014). Adolescents and alcohol: acute sensitivities, enhanced intake, and later consequences. *Neurotoxicology and teratology*, 41:51–59.

Spear, L. P. (2015). Adolescent alcohol exposure: are there separable vulnerable periods within adolescence? *Physiology & behavior*, 148:122–130.

Spear, L. P. and Swartzwelder, H. S. (2014). Adolescent alcohol exposure and persistence of adolescent-typical phenotypes into adulthood: a mini-review. *Neuroscience & Biobehavioral Reviews*, 45:1–8.

Spielberger, C. D., Johnson, E., and Jacobs, C. (1982). Anger expression scale manual. *University of South Florida, Tampa, FL.*

Spikman, J. M., Timmerman, M. E., Milders, M. V., Veenstra, W. S., and van der Naalt, J. (2012). Social cognition impairments in relation to general cognitive deficits, injury severity, and prefrontal lesions in traumatic brain injury patients. *Journal of neurotrauma*, 29(1):101–111.

Spillane, N., Muller, C., Noonan, C., Goins, R., Mitchell, C., and Manson, S. (2012). Sensation-seeking predicts initiation of daily smoking behavior among american indian high school students. *Addictive Behaviors*, 37(12):1303–1306.

Spitalnick, J. S., DiClemente, R. J., Wingood, G. M., Crosby, R. A., Milhausen, R. R., Sales, J. M., McCarty, F., Rose, E., and Younge, S. N. (2007). Brief report: Sexual sensation seeking and its relationship to risky sexual behaviour among african-american adolescent females. *Journal of adolescence*, 30(1):165–173.

Spreng, R. N., Sepulcre, J., Turner, G. R., Stevens, W. D., and Schacter, D. L. (2013). Intrinsic architecture underlying the relations among the default, dorsal attention, and frontoparietal control networks of the human brain. *Journal of cognitive neuroscience*, 25(1):74–86.

Spreng, R. N., Stevens, W. D., Chamberlain, J. P., Gilmore, A. W., and Schacter, D. L. (2010). Default network activity, coupled with the frontoparietal control network, supports goal-directed cognition. *NeuroImage*, 53:303–317.

Squeglia, L., Sorg, S., Schweinsburg, A., Wetherill, R., Pulido, C., and Tapert, S. (2012a). Binge drinking differentially affects adolescent male and female brain morphometry. *Psychopharmacology*, 220(3):529–539.

Squeglia, L. M., Ball, T. M., Jacobus, J., Brumback, T., McKenna, B. S., Nguyen-Louie, T. T., Sorg, S. F., Paulus, M. P., and Tapert, S. F. (2016). Neural predictors of initiating alcohol use during adolescence. *American Journal of Psychiatry*, pages appi–ajp.

Squeglia, L. M., Boissoneault, J., Van Skike, C. E., Nixon, S. J., and Matthews, D. B. (2014a). Age-related effects of alcohol from adolescent, adult, and aged populations using human and animal models. *Alcoholism: Clinical and Experimental Research*, 38(10):2509–2516.

Squeglia, L. M. and Gray, K. M. (2016). Alcohol and drug use and the developing brain. *Current psychiatry reports*, 18(5):1–10.

Squeglia, L. M., Jacobus, J., and Tapert, S. F. (2014b). The effect of alcohol use on human adolescent brain structures and systems. *Handbook of clinical neurology*, 125:501.

Squeglia, L. M., Pulido, C., Wetherill, R. R., Jacobus, J., Brown, G. G., and Tapert, S. F. (2012b). Brain response to working memory over three years of adolescence: influence of initiating heavy drinking. *Journal of studies on alcohol and drugs*, 73(5):749–760.

Squeglia, L. M., Rinker, D. A., Bartsch, H., Castro, N., Chung, Y., Dale, A. M., Jernigan, T. L., and Tapert, S. F. (2014c). Brain volume reductions in adolescent heavy drinkers. *Developmental cognitive neuroscience*, 9:117–125.

Squeglia, L. M., Schweinsburg, A. D., Pulido, C., and Tapert, S. F. (2011). Adolescent binge drinking linked to abnormal spatial working memory brain activation: differential gender effects. *Alcoholism: Clinical and Experimental Research*, 35(10):1831–1841.

Squeglia, L. M., Sorg, S. F., Jacobus, J., Brumback, T., Taylor, C. T., and Tapert, S. F. (2015). Structural connectivity of neural reward networks in youth at risk for substance use disorders. *Psychopharmacology*, pages 1–10.

Squire, L. R., Wixted, J. T., and Clark, R. E. (2007). Recognition memory and the medial temporal lobe: a new perspective. *Nature Reviews Neuroscience*, 8(11):872–883.

Sripada, C. S., Angstadt, M., McNamara, P., King, A. C., and Phan, K. L. (2011). Effects of alcohol on brain responses to social signals of threat in humans. *Neuroimage*, 55(1):371–380.

Starcke, K., Holst, R. J., Brink, W., Veltman, D. J., and Goudriaan, A. E. (2013). Physiological and endocrine reactions to psychosocial stress in alcohol use disorders:

duration of abstinence matters. *Alcoholism: Clinical and Experimental Research*, 37(8):1343–1350.

Stark, M. J. (1992). Dropping out of substance abuse treatment: A clinically oriented review. *Clinical psychology review*, 12(1):93–116.

Stautz, K. and Cooper, A. (2013). Impulsivity-related personality traits and adolescent alcohol use: a meta-analytic review. *Clinical psychology review*, 33(4):574–592.

Steele, C. M. and Josephs, R. A. (1990). Alcohol myopia: Its prized and dangerous effects. *American Psychologist*, 45(8):921.

Stein, J., Wiedholz, L., Bassett, D., Weinberger, D., Zink, C., Mattay, V., and Meyer-Lindenberg, A. (2007a). A validated network of effective amygdala connectivity. *NeuroImage*, 36(3):736–745.

Stein, M. B., Goldin, P. R., Sareen, J., Zorrilla, L. T. E., and Brown, G. G. (2002). Increased amygdala activation to angry and contemptuous faces in generalized social phobia. *Archives of general psychiatry*, 59(11):1027–1034.

Stein, M. B., Jang, K. L., and Livesley, W. J. (1999). Heritability of anxiety sensitivity: A twin study. *American Journal of Psychiatry*, 156(2):246–251.

Stein, M. B., Simmons, A. N., Feinstein, J. S., and Paulus, M. P. (2007b). Increased amygdala and insula activation during emotion processing in anxiety-prone subjects. *American Journal of Psychiatry*.

Stenberg, G., Wiking, S., and Dahl, M. (1998). Judging words at face value: Interference in a word processing task reveals automatic processing of affective facial expressions. *Cognition & Emotion*, 12(6):755–782.

Stephan, K. E., Bach, D. R., Fletcher, P. C., Flint, J., Frank, M. J., Friston, K. J., Heinz, A., Huys, Q. J., Owen, M. J., Binder, E. B., et al. (2016). Charting the landscape of priority problems in psychiatry, part 1: classification and diagnosis. *The lancet Psychiatry*, 3(1):77–83.

Stephens, M. A. C., Mahon, P. B., McCaul, M. E., and Wand, G. S. (2016). Hypothalamic–pituitary–adrenal axis response to acute psychosocial stress: Effects of biological sex and circulating sex hormones. *Psychoneuroendocrinology*, 66:47–55.

Stephenson, M. and Helme, D. (2006). Authoritative parenting and sensation seeking as predictors of adolescent cigarette and marijuana use. *Journal of Drug Education*, 36(3):247–270.

Steptoe, A., Fieldman, G., Evans, O., and Perry, L. (1996). Cardiovascular risk and responsivity to mental stress: the influence of age, gender and risk factors. *Journal of cardiovascular risk*, 3(1):83–93.

Stern, E. R. and Taylor, S. F. (2014). Cognitive neuroscience of obsessive-compulsive disorder. *Psychiatric Clinics of North America*, 37(3):337–352.

Sterzer, P., Stadler, C., Poustka, F., and Kleinschmidt, A. (2007). A structural neural deficit in adolescents with conduct disorder and its association with lack of empathy. *Neuroimage*, 37(1):335–342.

Stevens, J. S. and Hamann, S. (2012). Sex differences in brain activation to emotional stimuli: a meta-analysis of neuroimaging studies. *Neuropsychologia*, 50(7):1578–1593.

Stevens, M., Kiehl, K., Pearlson, G., and Calhoun, V. (2007). Functional neural networks underlying response inhibition in adolescents and adults. *Behavioural Brain Research*, 181(1):12–22.

Stevens, S., Gerlach, A. L., and Rist, F. (2008). Effects of alcohol on ratings of emotional facial expressions in social phobics. *Journal of anxiety disorders*, 22(6):940–948.

Stevens, S., Rist, F., and Gerlach, A. L. (2009). Influence of alcohol on the processing of emotional facial expressions in individuals with social phobia. *British Journal of Clinical Psychology*, 48(2):125–140.

Stewart, S., Grant, V. V., Mackie, C. J., and Conrod, P. J. (2016). Comorbidity of anxiety and depression with substance use disorders. In *The Oxford Handbook of Substance Use and Substance Use Disorders*.

Stewart, S., Taylor, S., and Baker, J. (1997a). Gender differences in dimensions of anxiety sensitivity. *Journal of Anxiety Disorders*, 11(2):179–200.

Stewart, S. H. (1996). Alcohol abuse in individuals exposed to trauma: a critical review. *Psychological bulletin*, 120(1):83.

Stewart, S. H., Karp, J., Pihl, R. O., and Peterson, R. A. (1997b). Anxiety sensitivity and self-reported reasons for drug use. *Journal of substance abuse*, 9:223–240.

Stewart, S. H., Knize, K., and Pihl, R. O. (1992). Anxiety sensitivity and dependency in clinical and non-clinical panickers and controls. *Journal of Anxiety Disorders*, 6(2):119–131.

Stewart, S. H. and Kushner, M. G. (2001). Introduction to the special issue on "anxiety sensitivity and addictive behaviors". *Addictive Behaviors*, 26(6):775–785.

Stewart, S. H., Morris, E., Mellings, T., and Komar, J. (2006). Relations of social anxiety variables to drinking motives, drinking quantity and frequency, and alcohol-related problems in undergraduates. *Journal of mental health*, 15(6):671–682.

Stewart, S. H. and Pihl, R. O. (1994). Effects of alcohol administration on psychophysiological and subjective-emotional responses to aversive stimulation in anxiety-sensitive women. *Psychology of Addictive Behaviors*, 8(1):29.

Stewart, S. H., Samoluk, S. B., and MacDonald, A. B. (1999). Anxiety sensitivity and substance use and abuse. *Anxiety sensitivity: Theory, research, and treatment of the fear of anxiety*, pages 287–319.

Stewart, S. H. and Zeitlin, S. B. (1995). Anxiety sensitivity and alcohol use motives. *Journal of Anxiety Disorders*, 9(3):229–240.

Stewart, S. H., Zvolensky, M. J., and Eifert, G. H. (2001). Negative-reinforcement drinking motives mediate the relation between anxiety sensitivity and increased drinking behavior. *Personality and Individual differences*, 31(2):157–171.

Stewart, S. H., Zvolensky, M. J., and Eifert, G. H. (2002). The relations of anxiety sensitivity, experiential avoidance, and alexithymic coping to young adults' motivations for drinking. *Behavior Modification*, 26(2):274–296.

Stice, E. and Yokum, S. (2014). Brain reward region responsivity of adolescents with and without parental substance use disorders. *Psychology of Addictive Behaviors*, 28(3):805.

Stiles, J. and Jernigan, T. L. (2010). The basics of brain development. *Neuropsychology review*, 20(4):327–348.

Stillman, P. E., Van Bavel, J. J., and Cunningham, W. A. (2015). Valence asymmetries in the human amygdala: Task relevance modulates amygdala responses to positive more than negative affective cues. *Journal of cognitive neuroscience*.

Stillman, T., Baumeister, R., Lambert, N., Crescioni, A., DeWall, C., and Fincham, F. (2009). Alone and without purpose: Life loses meaning following social exclusion. *Journal of Experimental Social Psychology*, 45(4):686–694.

Stoleru, S., Gregoire, M.-C., Gerard, D., Decety, J., Lafarge, E., Cinotti, L., Lavenne, F., Le Bars, D., Vernet-Maury, E., Rada, H., et al. (1999). Neuroanatomical correlates of visually evoked sexual arousal in human males. *Archives of sexual behavior*, 28(1):1–21.

Stoops, W. W., Lile, J. A., Robbins, C. G., Martin, C. A., Rush, C. R., and Kelly, T. H. (2007). The reinforcing, subject-rated, performance, and cardiovascular effects of d-amphetamine: influence of sensation-seeking status. *Addictive behaviors*, 32(6):1177–1188.

Storgaard, H., Nielsen, S. D., and Gluud, C. (1994). The validity of the michigan alcoholism screening test (mast). *Alcohol and Alcoholism*, 29(5):493–503.

Strang, N. M., Claus, E. D., Ramchandani, V. A., Graff-Guerrero, A., Boileau, I., and Hendershot, C. S. (2015). Dose-dependent effects of intravenous alcohol administration on cerebral blood flow in young adults. *Psychopharmacology*, 232(4):733–744.

Straube, B., Lueken, U., Jansen, A., Konrad, C., Gloster, A. T., Gerlach, A. L., Ströhle, A., Wittmann, A., Pfleiderer, B., Gauggel, S., et al. (2014). Neural correlates of procedural variants in cognitive-behavioral therapy: a randomized, controlled multicenter fmri study. *Psychotherapy and psychosomatics*, 83(4):222–233.

Straube, T. (2016). Effects of psychotherapy on brain activation patterns in anxiety disorders. *Zeitschrift für Psychologie*.

Straube, T., Kolassa, I.-T., Glauer, M., Mentzel, H.-J., and Miltner, W. (2004). Effect of task conditions on brain responses to threatening faces in social phobics: An event-related functional magnetic resonance imaging study. *Biological Psychiatry*, 56(12):921–930.

Straube, T., Mentzel, H.-J., and Miltner, W. (2007a). Waiting for spiders: Brain activation during anticipatory anxiety in spider phobics. *NeuroImage*, 37(4):1427–1436.

Straube, T., Preissler, S., Lipka, J., Hewig, J., Mentzel, H.-J., and Miltner, W. H. (2010). Neural representation of anxiety and personality during exposure to anxiety-provoking and neutral scenes from scary movies. *Human brain mapping*, 31(1):36–47.

Straube, T., Schmidt, S., Weiss, T., Mentzel, H.-J., and Miltner, W. H. (2009a). Dynamic activation of the anterior cingulate cortex during anticipatory anxiety. *Neuroimage*, 44(3):975–981.

Straube, T., Schmidt, S., Weiss, T., Mentzel, H.-J., and Miltner, W. H. (2009b). Sex differences in brain activation to anticipated and experienced pain in the medial prefrontal cortex. *Human brain mapping*, 30(2):689–698.

Straube, T., Weiss, T., Mentzel, H.-J., and Miltner, W. (2007b). Time course of amygdala activation during aversive conditioning depends on attention. *NeuroImage*, 34(1):462–469.

Strawn, J. R., Cotton, S., Luberto, C. M., Patino, L. R., Stahl, L. A., Weber, W. A., Eliassen, J. C., Sears, R., and DelBello, M. P. (2016). Neural function before and after mindfulness-based cognitive therapy in anxious adolescents at risk for developing bipolar disorder. *Journal of child and adolescent psychopharmacology*.

Stroud, L. R., Salovey, P., and Epel, E. S. (2002). Sex differences in stress responses: social rejection versus achievement stress. *Biological psychiatry*, 52(4):318–327.

Sturm, V., Lenartz, D., Koulousakis, A., Treuer, H., Herholz, K., Klein, J. C., and Klosterkötter, J. (2003). The nucleus accumbens: a target for deep brain stimulation in obsessive–compulsive-and anxiety-disorders. *Journal of chemical neuroanatomy*, 26(4):293–299.

Sturman, D. A. and Moghaddam, B. (2011). Reduced neuronal inhibition and coordination of adolescent prefrontal cortex during motivated behavior. *The Journal of Neuroscience*, 31(4):1471–1478.

Suckling, J. and Nestor, L. J. (2016). The neurobiology of addiction: the perspective from magnetic resonance imaging present and future. *Addiction*.

Suhara, T., Yasuno, F., Sudo, Y., Yamamoto, M., Inoue, M., Okubo, Y., and Suzuki, K. (2001). Dopamine d2 receptors in the insular cortex and the personality trait of novelty seeking. *Neuroimage*, 13(5):891–895.

Sullivan, P., Daly, M., and O'Donovan, M. (2012). Genetic architectures of psychiatric disorders: the emerging picture and its implications. *Nature reviews. Genetics*, 13(8):537–551.

Sullivan, P. F., Kendler, K. S., and Neale, M. C. (2003). Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. *Archives of general psychiatry*, 60(12):1187–1192.

Suslow, T., Kugel, H., Reber, H., Bauer, J., Dannlowski, U., Kersting, A., Arolt, V., Heindel, W., Ohrmann, P., and Egloff, B. (2010). Automatic brain response to facial emotion as a function of implicitly and explicitly measured extraversion. *Neuroscience*, 167(1):111–123.

Susman, E. J. (2006). Psychobiology of persistent antisocial behavior: Stress, early vulnerabilities and the attenuation hypothesis. *Neuroscience & Biobehavioral Reviews*, 30(3):376–389.

Sussman, T. J., Jin, J., and Mohanty, A. (2016). Top-down and bottom-up factors in threat-related perception and attention in anxiety. *Biological Psychology*.

Swailes, S. and McIntyre-Bhatty, T. (2002). The "belbin" team role inventory: reinterpreting reliability estimates. *Journal of Managerial Psychology*, 17(6):529–536.

Swanson, J., Holzer III, C., Ganju, V., and Jono, R. (1990). Violence and psychiatric disorder in the community: Evidence from the epidemiologic catchment area surveys. *Hospital and Community Psychiatry*, 41(7):761–770.

Swanson, L. W. (2003). The amygdala and its place in the cerebral hemisphere. *Annals of the New York Academy of Sciences*, 985(1):174–184.

Swanson, L. W. and Petrovich, G. D. (1998). What is the amygdala? *Trends in neurosciences*, 21(8):323–331.

Swartz, J. R., Knodt, A. R., Radtke, S. R., and Hariri, A. R. (2015). A neural biomarker of psychological vulnerability to future life stress. *Neuron*, 85(3):505–511.

Swenson, R. M. and Vogel, W. H. (1983). Plasma catecholamine and corticosterone as well as brain catecholamine changes during coping in rats exposed to stressful footshock. *Pharmacology Biochemistry and Behavior*, 18(5):689–693.

Sylvester, C., Corbetta, M., Raichle, M., Rodebaugh, T., Schlaggar, B., Sheline, Y., Zorumski, C., and Lenze, E. (2012). Functional network dysfunction in anxiety and anxiety disorders. *Trends in neurosciences*, 35(9):527–535.

Szatmari, P., Paterson, A. D., Zwaigenbaum, L., Roberts, W., Brian, J., Liu, X.-Q., Vincent, J. B., Skaug, J. L., Thompson, A. P., Senman, L., et al. (2007). Mapping autism risk loci using genetic linkage and chromosomal rearrangements. *Nature genetics*, 39(3):319–328.

Szczepanik, J., Nugent, A. C., Drevets, W. C., Khanna, A., Zarate, C. A., and Furey, M. L. (2016). Amygdala response to explicit sad face stimuli at baseline predicts antidepressant treatment response to scopolamine in major depressive disorder. *Psychiatry Research: Neuroimaging*, 254:67–73.

Szczepanski, S. M., Konen, C. S., and Kastner, S. (2010). Mechanisms of spatial attention control in frontal and parietal cortex. *The Journal of Neuroscience*, 30(1):148–160.

Sznycer, D., Tooby, J., Cosmides, L., Porat, R., Shalvi, S., and Halperin, E. (2016). Shame closely tracks the threat of devaluation by others, even across cultures. *Proceedings of the National Academy of Sciences*, page 201514699.

Szpunar, K., Watson, J., and McDermott, K. (2007). Neural substrates of envisioning the future. *Proceedings of the National Academy of Sciences of the United States of America*, 104(2):642–647.

Taber-Thomas, B. C., Morales, S., Hillary, F. G., and Pérez-Edgar, K. E. (2016). Altered topography of intrinsic functional connectivity in childhood risk for social anxiety. *Depression and anxiety*.

Taillieu, T. L., Brownridge, D. A., Sareen, J., and Afifi, T. O. (2016). Childhood emotional maltreatment and mental disorders: results from a nationally representative adult sample from the united states. *Child Abuse & Neglect*, 59:1–12.

Tajima-Pozo, K., Yus, M., Ruiz-Manrique, G., Lewczuk, A., Arrazola, J., and Montañes-Rada, F. (2016). Amygdala abnormalities in adults with adhd. *Journal of attention disorders*.

Takagi, M., Youssef, G., and Lorenzetti, V. (2016). Neuroimaging of the human brain in adolescent substance users. In *Drug Abuse in Adolescence*, pages 69–99. Springer.

Takahashi, H., Yahata, N., Koeda, M., Matsuda, T., Asai, K., and Okubo, Y. (2004). Brain activation associated with evaluative processes of guilt and embarrassment: an fmri study. *Neuroimage*, 23(3):967–974.

Takahashi, H. K., Kitada, R., Sasaki, A. T., Kawamichi, H., Okazaki, S., Kochiyama, T., and Sadato, N. (2015). Brain networks of affective mentalizing revealed by the tear effect: The integrative role of the medial prefrontal cortex and precuneus. *Neuroscience research*, 101:32–43.

Takahashi, T., Ikeda, K., Ishikawa, M., Kitamura, N., Tsukasaki, T., Nakama, D., and Kameda, T. (2005). Anxiety, reactivity, and social stress-induced cortisol elevation in humans. *Neuroendocrinology Letters*, 26(4):351–354.

Takai, N., Yamaguchi, M., Aragaki, T., Eto, K., Uchihashi, K., and Nishikawa, Y. (2007). Gender-specific differences in salivary biomarker responses to acute psychological stress. *Annals of the New York Academy of Sciences*, 1098(1):510–515.

Talalaenko, A., Abramets, I., Stakhovskii, Y., Shekhovtsov, A., Chernikov, A., and Shevchenko, S. (1994). The role of dopaminergic mechanisms of the brain in various models of anxious states. *Neuroscience and Behavioral Physiology*, 24(3):284–288.

Tamietto, M. and De Gelder, B. (2010). Neural bases of the non-conscious perception of emotional signals. *Nature Reviews Neuroscience*, 11(10):697–709.

Tang, A., Beaton, E. A., Tatham, E., Schulkin, J., Hall, G. B., and Schmidt, L. A. (2016). Processing of different types of social threat in shyness: Preliminary findings of distinct functional neural connectivity. *Social neuroscience*, 11(1):15–37.

Tangney, J. P., Stuewig, J., and Mashek, D. J. (2007). Moral emotions and moral behavior. *Annual review of psychology*, 58:345.

Tanner-Smith, E. E., Steinka-Fry, K. T., Hennessy, E. A., Lipsey, M. W., and Winters, K. C. (2015). Can brief alcohol interventions for youth also address concurrent illicit drug use? results from a meta-analysis. *Journal of youth and adolescence*, 44(5):1011–1023.

Tarter, R. E., Hegedus, A. M., Goldstein, G., Shelly, C., and Alterman, A. I. (1984). Adolescent sons of alcoholics: Neuropsychological and personality characteristics. *Alcoholism: Clinical and Experimental Research*, 8(2):216–222.

Tarter, R. E., Jacob, T., and Bremer, D. A. (1989). Cognitive status of sons of alcoholic men. *Alcoholism: Clinical and Experimental Research*, 13(2):232–235.

Tarullo, A. and Gunnar, M. (2006). Child maltreatment and the developing hpa axis. *Hormones and Behavior*, 50(4):632–639.

Taylor, J., Harris, N., and Vogel, W. (1990). Voluntary alcohol and cocaine consumption in "low" and "high" stress plasma catecholamine responding rats. *Pharmacology Biochemistry and Behavior*, 37(2):359–363.

Taylor, J. M. and Whalen, P. J. (2015). Neuroimaging and anxiety: the neural substrates of pathological and non-pathological anxiety. *Current psychiatry reports*, 17(6):1–10.

Taylor, S. (1993). The structure of fundamental fears. *Journal of behavior therapy and experimental psychiatry*, 24(4):289–299.

Taylor, S. (1995a). Anxiety sensitivity: Theoretical perspectives and recent findings. *Behaviour research and therapy*, 33(3):243–258.

Taylor, S. (1995b). Stimulus estimation and the overprediction of fear: A comment on two studies. *Behaviour research and therapy*, 33(6):699–700.

Taylor, S. (1996). Nature and measurement of anxiety sensitivity: Reply to lilienfeld, turner, and jacob (1996). *Journal of Anxiety Disorders*, 10(5):425–451.

Taylor, S. (1999). Anxiety sensitivity: Theory, research, and treatment ofthe fear ofanxiety.

Taylor, S., Jang, K. L., Stewart, S. H., and Stein, M. B. (2008). Etiology of the dimensions of anxiety sensitivity: A behavioral–genetic analysis. *Journal of anxiety disorders*, 22(5):899–914.

Taylor, S., Koch, W., McNally, R., and Crockett, D. (1992a). Conceptualizations of anxiety sensitivity. *Psychological Assessment*, 4(2):245–250.

Taylor, S., Koch, W., Woody, S., and McLean, P. (1996). Anxiety sensitivity and depression: How are they related? *Journal of Abnormal Psychology*, 105(3):474–479.

Taylor, S., Koch, W. J., and Crockett, D. J. (1991). Anxiety sensitivity, trait anxiety, and the anxiety disorders. *Journal of Anxiety Disorders*, 5(4):293–311.

Taylor, S., Koch, W. J., and McNally, R. J. (1992b). How does anxiety sensitivity vary across the anxiety disorders? *Journal of anxiety disorders*, 6(3):249–259.

Taylor, S., Zvolensky, M. J., Cox, B. J., Deacon, B., Heimberg, R. G., Ledley, D. R., Abramowitz, J. S., Holaway, R. M., Sandin, B., Stewart, S. H., et al. (2007). Robust dimensions of anxiety sensitivity: development and initial validation of the anxiety sensitivity index-3. *Psychological assessment*, 19(2):176.

Taylor, S. E. and Brown, J. D. (1988). Illusion and well-being: a social psychological perspective on mental health. *Psychological bulletin*, 103(2):193.

Taylor, S. E., Klein, L. C., Lewis, B. P., Gruenewald, T. L., Gurung, R. A., and Updegraff, J. A. (2000). Biobehavioral responses to stress in females: tend-and-befriend, not fight-or-flight. *Psychological review*, 107(3):411.

Taylor, S. P., Gammon, C. B., and Capasso, D. R. (1976). Aggression as a function of the interaction of alcohol and threat. *Journal of Personality and Social Psychology*, 34(5):938.

Taylor, S. P., Schmutte, G. T., Leonard, K. E., and Cranston, J. W. (1979). The effects of alcohol and extreme provocation on the use of a highly noxious electric shock. *Motivation and Emotion*, 3(1):73–81.

Taylor, S. P. and Sears, J. D. (1988). The effects of alcohol and persuasive social pressure on human physical aggression. *Aggressive Behavior*.

Teale Sapach, M. J., Carleton, R. N., Mulvogue, M. K., Weeks, J. W., and Heimberg, R. G. (2015). Cognitive constructs and social anxiety disorder: Beyond fearing negative evaluation. *Cognitive behaviour therapy*, 44(1):63–73.

Teger, A. I., Katkin, E. S., and Pruitt, D. G. (1969). Effects of alcoholic beverages and their congener content on level and style of risk taking. *Journal of personality and social psychology*, 11(2):170.

Teicher, M. H., Anderson, C. M., Ohashi, K., and Polcari, A. (2014). Childhood maltreatment: altered network centrality of cingulate, precuneus, temporal pole and insula. *Biological psychiatry*, 76(4):297–305.

Teicher, M. H., Anderson, C. M., and Polcari, A. (2012). Childhood maltreatment is associated with reduced volume in the hippocampal subfields ca3, dentate gyrus, and subiculum. *Proceedings of the National Academy of Sciences*, 109(9):E563–E572.

Teicher, M. H. and Samson, J. A. (2013). Childhood maltreatment and psychopathology: a case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. *American Journal of Psychiatry*, 170(10):1114–1133.

Teicher, M. H. and Samson, J. A. (2016). Annual research review: Enduring neurobiological effects of childhood abuse and neglect. *Journal of child psychology and psychiatry*.

Teicher, M. H., Samson, J. A., Anderson, C. M., and Ohashi, K. (2016). The effects of childhood maltreatment on brain structure, function and connectivity. *Nature Reviews Neuroscience*, 17(10):652–666.

Telch, M., Shermis, M., and Lucas, J. (1989). Anxiety sensitivity: Unitary personality trait or domain-specific appraisals? *Journal of Anxiety Disorders*, 3(1):25–32.

Terasawa, Y., Shibata, M., Moriguchi, Y., and Umeda, S. (2012). Anterior insular cortex mediates bodily sensibility and social anxiety. *Social cognitive and affective neuroscience*, page nss108.

Terner, J. M. and De Wit, H. (2006). Menstrual cycle phase and responses to drugs of abuse in humans. *Drug and alcohol dependence*, 84(1):1–13.

Terracciano, A., Sanna, S., Uda, M., Deiana, B., Usala, G., Busonero, F., Maschio, A., Scally, M., Patriciu, N., Chen, W.-M., et al. (2010). Genome-wide association scan for five major dimensions of personality. *Molecular psychiatry*, 15(6):647–656.

Tessner, K. D. and Hill, S. Y. (2010). Neural circuitry associated with risk for alcohol use disorders. *Neuropsychology review*, 20(1):1–20.

Thai, N., Taber-Thomas, B. C., and Pérez-Edgar, K. E. (2016). Neural correlates of attention biases, behavioral inhibition, and social anxiety in children: An erp study. *Developmental cognitive neuroscience*, 19:200–210.

Thayer, R. E., Callahan, T. J., Weiland, B. J., Hutchison, K. E., and Bryan, A. D. (2013). Associations between fractional anisotropy and problematic alcohol use in juvenile justice-involved adolescents. *The American journal of drug and alcohol abuse*, 39(6):365–371.

Theresa, S. and Betancourt, S. (2008). The intergenerational effect of war. *Psychiatry*, 20(3):317–328.

Thoma, P., Friedmann, C., and Suchan, B. (2013). Empathy and social problem solving in alcohol dependence, mood disorders and selected personality disorders. *Neuroscience & Biobehavioral Reviews*, 37(3):448–470.

Thomas, S., Bacon, A. K., Sinha, R., Uhart, M., and Adinoff, B. (2012). Clinical laboratory stressors used to study alcohol–stress relationships. *Alcohol research: current reviews*, 34(4):459.

Thomas, S. E., Merrill, J. E., von Hofe, J., and Magid, V. (2014). Coping motives for drinking affect stress reactivity but not alcohol consumption in a clinical laboratory setting. *Journal of studies on alcohol and drugs*, 75(1):115.

Thomas, S. E., Randall, C. L., and Carrigan, M. H. (2003). Drinking to cope in socially anxious individuals: A controlled study. *Alcoholism: Clinical and Experimental Research*, 27(12):1937–1943.

Thomasson, H. R., Beard, J. D., and Li, T.-K. (1995). Adh2 gene polymorphisms are determinants of alcohol pharmacokinetics. *Alcoholism: Clinical and Experimental Research*, 19(6):1494–1499.

Thomasson, H. R., Edenberg, H. J., Crabb, D. W., Mai, X.-L., Jerome, R. E., Li, T. K., Wang, S. P., Lin, Y. T., Lu, R. B., and Yin, S. J. (1991). Alcohol and aldehyde dehydrogenase genotypes and alcoholism in chinese men. *American journal of human genetics*, 48(4):677.

Thorpe, S., Rolls, E., and Maddison, S. (1983). The orbitofrontal cortex: neuronal activity in the behaving monkey. *Experimental Brain Research*, 49(1):93–115.

Tillfors, M., Furmark, T., Marteinsdottir, I., Fischer, H., Pissiota, A., Långström, B., and Fredrikson, M. (2001). Cerebral blood flow in subjects with social phobia during stressful speaking tasks: a pet study. *American Journal of Psychiatry*.

Tobler, P. N., Christopoulos, G. I., O'Doherty, J. P., Dolan, R. J., and Schultz, W. (2009). Risk-dependent reward value signal in human prefrontal cortex. *Proceedings of the National Academy of Sciences*, 106(17):7185–7190.

Toga, A., Thompson, P., and Sowell, E. (2006). Mapping brain maturation. *Trends in Neurosciences*, 29(3):148–159.

Toller, G., Adhimoolam, B., Grunwald, T., Huppertz, H.-J., Kurthen, M., Rankin, K. P., and Jokeit, H. (2015). Right mesial temporal lobe epilepsy impairs empathy-related brain responses to dynamic fearful faces. *Journal of neurology*, 262(3):729–741.

Tomkins, S. S. and McCarter, R. (1964). What and where are the primary affects? some evidence for a theory. *Perceptual and motor skills*, 18(1):119–158.

Tomoda, A., Suzuki, H., Rabi, K., Sheu, Y.-S., Polcari, A., and Teicher, M. H. (2009). Reduced prefrontal cortical gray matter volume in young adults exposed to harsh corporal punishment. *Neuroimage*, 47:T66–T71.

Tops, M., Boksem, M. A., Wester, A. E., Lorist, M. M., and Meijman, T. F. (2006). Task engagement and the relationships between the error-related negativity, agreeableness, behavioral shame proneness and cortisol. *Psychoneuroendocrinology*, 31(7):847–858.

Tops, M., Riese, H., Oldehinkel, A. J., Rijsdijk, F. V., and Ormel, J. (2008). Rejection sensitivity relates to hypocortisolism and depressed mood state in young women. *Psychoneuroendocrinology*, 33(5):551–559.

Toro, R., Fox, P. T., and Paus, T. (2008). Functional coactivation map of the human brain. *Cerebral cortex*, 18(11):2553–2559.

Torro-Alves, N., Bezerra, I. A. d. O., Rodrigues, M. R., Machado-de Sousa, J. P., Osório, F. d. L., Crippa, J. A., et al. (2016). Facial emotion recognition in social anxiety: The influence of dynamic information. *Psychology & Neuroscience*, 9(1):1.

Torrubia, R., Avila, C., Moltó, J., and Caseras, X. (2001). The sensitivity to punishment and sensitivity to reward questionnaire (spsrq) as a measure of gray's anxiety and impulsivity dimensions. *Personality and individual differences*, 31(6):837–862.

Torrubia, R., Avila, C., Moltó, J., and Grande, I. (1995). Testing for stress and happiness: The role of the behavioral inhibition system. *Stress and Emotion: Anxiety, Anger, and Curiosity*, 15:189–211.

Torvik, F. A., Welander-Vatn, A., Ystrom, E., Knudsen, G. P., Czajkowski, N., Kendler, K. S., and Reichborn-Kjennerud, T. (2016). Longitudinal associations between social anxiety disorder and avoidant personality disorder: A twin study. *Journal of abnormal psychology*, 125(1):114.

Tost, H., Champagne, F. A., and Meyer-Lindenberg, A. (2015). Environmental influence in the brain, human welfare and mental health. *Nature Neuroscience*, 18(10):1421–1431.

Tottenham, N., Hare, T. A., and Casey, B. (2009). *A developmental perspective on human amygdala function.*

Tottenham, N., Hare, T. A., and Casey, B. (2011). Behavioral assessment of emotion discrimination, emotion regulation, and cognitive control in childhood, adolescence, and adulthood. *Frontiers in psychology*, 2.

Touroutoglou, A., Lindquist, K. A., Dickerson, B. C., and Barrett, L. F. (2015). Intrinsic connectivity in the human brain does not reveal networks for "basic" emotions. *Social Cognitive and Affective Neuroscience*, page nsv013.

Tran, S., Nowicki, M., Fulcher, N., Chatterjee, D., and Gerlai, R. (2016). Interaction between handling induced stress and anxiolytic effects of ethanol in zebrafish: A behavioral and neurochemical analysis. *Behavioural brain research*, 298:278–285.

Tranel, D., Bechara, A., and Denburg, N. L. (2002). Asymmetric functional roles of right and left ventromedial prefrontal cortices in social conduct, decision-making, and emotional processing. *Cortex*, 38(4):589–612.

Tranel, D. and Damasio, H. (1989). Intact electrodermal skin conductance responses after bilateral amygdala damage. *Neuropsychologia*, 27(4):381–390.

Treit, S., Lebel, C., Baugh, L., Rasmussen, C., Andrew, G., and Beaulieu, C. (2013). Longitudinal mri reveals altered trajectory of brain development during childhood and adolescence in fetal alcohol spectrum disorders. *The Journal of Neuroscience*, 33(24):10098–10109.

Trela, C. J., Piasecki, T. M., Bartholow, B. D., Heath, A. C., and Sher, K. J. (2016). The natural expression of individual differences in self-reported level of response to alcohol during ecologically assessed drinking episodes. *Psychopharmacology*, 233(11):2185–2195.

Trim, R. S., Simmons, A. N., Tolentino, N. J., Hall, S. A., Matthews, S. C., Robinson, S. K., Smith, T. L., Padula, C. B., Paulus, M. P., Tapert, S. F., et al. (2010). Acute ethanol effects on brain activation in low-and high-level responders to alcohol. *Alcoholism: Clinical and Experimental Research*, 34(7):1162–1170.

Trofimova, I. and Robbins, T. W. (2016). Temperament and arousal systems: A new synthesis of differential psychology and functional neurochemistry. *Neuroscience & Biobehavioral Reviews*, 64:382–402.

Tseng, W.-L., Thomas, L. A., Harkins, E., Pine, D. S., Leibenluft, E., and Brotman, M. A. (2016). Neural correlates of masked and unmasked face emotion processing in youth with severe mood dysregulation. *Social cognitive and affective neuroscience*, 11(1):78–88.

Tulving, E., Kapur, S., Markowitsch, H., Craik, F., Habib, R., and Houle, S. (1994). Neuroanatomical correlates of retrieval in episodic memory: Auditory sentence recognition. *Proceedings of the National Academy of Sciences of the United States of America*, 91(6):2012–2015.

Twenge, J. M., Baumeister, R. F., Tice, D. M., and Stucke, T. S. (2001). If you can't join them, beat them: effects of social exclusion on aggressive behavior. *Journal of personality and social psychology*, 81(6):1058.

Tye, K., Prakash, R., Kim, S.-Y., Fenno, L., Grosenick, L., Zarabi, H., Thompson, K., Gradinaru, V., Ramakrishnan, C., and Deisseroth, K. (2011). Amygdala circuitry mediating reversible and bidirectional control of anxiety. *Nature*, 471(7338):358–362.

Tyrka, A., Price, L., Marsit, C., Walters, O., and Carpenter, L. (2012). Childhood adversity and epigenetic modulation of the leukocyte glucocorticoid receptor: Preliminary findings in healthy adults. *PLoS ONE*, 7(1).

Tyrka, A., Wier, L., Anderson, G., Wilkinson, C., Price, L., and Carpenter, L. (2007). Temperament and response to the trier social stress test. *Acta Psychiatrica Scandinavica*, 115(5):395–402.

Uddin, L. Q., Kinnison, J., Pessoa, L., and Anderson, M. L. (2014). Beyond the tripartite cognition–emotion–interoception model of the human insular cortex. *Journal of cognitive neuroscience*, 26(1):16–27.

Uhart, M. and Wand, G. S. (2009). Stress, alcohol and drug interaction: an update of human research. *Addiction biology*, 14(1):43–64.

Uhlhaas, P. J., Roux, F., Rodriguez, E., Rotarska-Jagiela, A., and Singer, W. (2010). Neural synchrony and the development of cortical networks. *Trends in cognitive sciences*, 14(2):72–80.

Ullsperger, M., Harsay, H. A., Wessel, J. R., and Ridderinkhof, K. R. (2010). Conscious perception of errors and its relation to the anterior insula. *Brain Structure and Function*, 214(5-6):629–643.

Ulrich-Lai, Y. M. and Herman, J. P. (2009). Neural regulation of endocrine and autonomic stress responses. *Nature Reviews Neuroscience*, 10(6):397–409.

UNODC (2011). World drug report. *World Drug Report 2011 (United Nations Publication, Sales No. E.11.XI.10)*.

Urošević, S., Collins, P., Muetzel, R., Schissel, A., Lim, K. O., and Luciana, M. (2015). Effects of reward sensitivity and regional brain volumes on substance use initiation in adolescence. *Social cognitive and affective neuroscience*, 10(1):106–113.

Ursa, F. (2016). The relationship between anxiety vulnerability factors, psychedelic drug use and trait anxiety.

Vaillant, G. E. (1983). *The natural history of alcoholism*. Cambridge, Mass.: Harvard University Press.

Valentin, V. and O'Doherty, J. (2009). Overlapping prediction errors in dorsal striatum during instrumental learning with juice and money reward in the human brain. *Journal of Neurophysiology*, 102(6):3384–3391.

Valet, M., Sprenger, T., Boecker, H., Willoch, F., Rummeny, E., Conrad, B., Erhard, P., and Tolle, T. R. (2004). Distraction modulates connectivity of the cingulo-frontal cortex and the midbrain during pain—an fmri analysis. *Pain*, 109(3):399–408.

Välimäki, M. J., Härkönen, M., Eriksson, C. P., and Ylikahri, R. H. (1984). Sex hormones and adrenocortical steroids in men acutely intoxicated with ethanol. *Alcohol*, 1(1):89–93.

Van Ameringen, M., Mancini, C., Oakman, J., Kamath, M., Nahmias, C., and Szechtman, H. (1998). A pilot study of pet in social phobia. *Biol Psychiatry*, 43(SUPPL.):31S.

Van Dam, N. T., Rando, K., Potenza, M. N., Tuit, K., and Sinha, R. (2014). Childhood maltreatment, altered limbic neurobiology, and substance use relapse severity via trauma-specific reductions in limbic gray matter volume. *JAMA psychiatry*, 71(8):917–925.

van den Bulk, B. G., Somerville, L. H., van Hoof, M.-J., van Lang, N. D., van der Wee, N. J., Crone, E. A., and Vermeiren, R. R. (2016). Amygdala habituation to emotional faces in adolescents with internalizing disorders, adolescents with childhood sexual abuse related ptsd and healthy adolescents. *Developmental Cognitive Neuroscience*, 21:15–25.

van den Oord, E. J., Kuo, P.-H., Hartmann, A. M., Webb, B. T., Möller, H.-J., Hettema, J. M., Giegling, I., Bukszár, J., and Rujescu, D. (2008). Genomewide association analysis followed by a replication study implicates a novel candidate gene for neuroticism. *Archives of general psychiatry*, 65(9):1062–1071.

van der Meer, L., Costafreda, S., Aleman, A., and David, A. (2010). Self-reflection and the brain: A theoretical review and meta-analysis of neuroimaging studies with implications for schizophrenia. *Neuroscience and Biobehavioral Reviews*, 34(6):935–946.

van der Meulen, M., van IJzendoorn, M. H., and Crone, E. A. (2016). Neural correlates of prosocial behavior: Compensating social exclusion in a four-player cyberball game. *PloS one*, 11(7):e0159045.

van Elst, L. T., Hesslinger, B., Thiel, T., Geiger, E., Haegele, K., Lemieux, L., Lieb, K., Bohus, M., Hennig, J., and Ebert, D. (2003). Frontolimbic brain abnormalities in patients with borderline personality disorder: a volumetric magnetic resonance imaging study. *Biological psychiatry*, 54(2):163–171.

Van Goozen, S., Matthys, W., Cohen-Kettenis, P., Gispen-De Wied, C., Wiegant, V., and Van Engeland, H. (1998). Salivary cortisol and cardiovascular activity during stress in oppositional-defiant disorder boys and normal controls. *Biological Psychiatry*, 43(7):531–539.

Van Honk, J., Tuiten, A., Van Den Hout, M., Koppeschaar, H., Thijssen, J., De Haan, E., and Verbaten, R. (1998). Baseline salivary cortisol levels and preconscious selective attention for threat: A pilot study. *Psychoneuroendocrinology*, 23(7):741–747.

Van Honk, J., Tuiten, A., Van Den Hout, M., Koppeschaar, H., Thijssen, J., De Haan, E., and Verbaten, R. (2000). Conscious and preconscious selective attention to social threat: Different neuroendocrine response patterns. *Psychoneuroendocrinology*, 25(6):577–591.

van Leeuwen, A. P., Creemers, H. E., Greaves-Lord, K., Verhulst, F. C., Ormel, J., and Huizink, A. C. (2011). Hypothalamic–pituitary–adrenal axis reactivity to social stress and adolescent cannabis use: the trails study. *Addiction*, 106(8):1484–1492.

Van Marle, H. J., Hermans, E. J., Qin, S., and Fernández, G. (2010). Enhanced resting-state connectivity of amygdala in the immediate aftermath of acute psychological stress. *Neuroimage*, 53(1):348–354.

van Os, J., Kenis, G., and Rutten, B. P. (2010). The environment and schizophrenia. *Nature*, 468(7321):203–212.

van Peer, J. M., Spinhoven, P., and Roelofs, K. (2010). Psychophysiological evidence for cortisol-induced reduction in early bias for implicit social threat in social phobia. *Psychoneuroendocrinology*, 35(1):21–32.

Van Reekum, C. M., Urry, H. L., Johnstone, T., Thurow, M. E., Frye, C. J., Jackson, C. A., Schaefer, H. S., Alexander, A. L., and Davidson, R. J. (2007). Individual differences in amygdala and ventromedial prefrontal cortex activity are associated with evaluation speed and psychological well-being. *Journal of Cognitive Neuroscience*, 19(2):237–248.

Van Schuerbeek, P., Baeken, C., Luypaert, R., De Raedt, R., and De Mey, J. (2014). Does the amygdala response correlate with the personality trait 'harm avoidance'while evaluating emotional stimuli explicitly? *Behavioral and Brain Functions*, 10(1):1.

van Tol, M.-J., Demenescu, L. R., Van der Wee, N. J., Kortekaas, R., Marjan, N., Den Boer, J., Renken, R. J., van Buchem, M. A., Zitman, F. G., Aleman, A., et al. (2012). Functional magnetic resonance imaging correlates of emotional word encoding and recognition in depression and anxiety disorders. *Biological psychiatry*, 71(7):593–602.

Van West, D., Claes, S., Sulon, J., and Deboutte, D. (2008). Hypothalamic-pituitary-adrenal reactivity in prepubertal children with social phobia. *Journal of affective disorders*, 111(2):281–290.

VanBuskirk, K. A. and Wetherell, J. L. (2014). Motivational interviewing with primary care populations: a systematic review and meta-analysis. *Journal of behavioral medicine*, 37(4):768–780.

Vanyukov, M. M., Moss, H. B., Plail, J. A., Blackson, T., Mezzich, A. C., and Tarter, R. E. (1993). Antisocial symptoms in preadolescent boys and in their parents: associations with cortisol. *Psychiatry research*, 46(1):9–17.

Varese, F., Smeets, F., Drukker, M., Lieverse, R., Lataster, T., Viechtbauer, W., Read, J., van Os, J., and Bentall, R. P. (2012). Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective-and cross-sectional cohort studies. *Schizophrenia bulletin*, 38(4):661–671.

Vasilaki, E. I., Hosier, S. G., and Cox, W. M. (2006). The efficacy of motivational interviewing as a brief intervention for excessive drinking: a meta-analytic review. *Alcohol and Alcoholism*, 41(3):328–335.

Veenema, A. H., Koolhaas, J. M., and KLOET, E. R. (2004). Basal and stress-induced differences in hpa axis, 5-ht responsiveness, and hippocampal cell proliferation in two mouse lines. *Annals of the New York Academy of Sciences*, 1018(1):255–265.

Velanova, K., Wheeler, M. E., and Luna, B. (2008). Maturational changes in anterior cingulate and frontoparietal recruitment support the development of error processing and inhibitory control. *Cerebral Cortex*, 18(11):2505–2522.

Velasco, R. V., Bakhshaie, J., Walker, R. L., Viana, A. G., Garza, M., Ochoa-Perez, M., Paulus, D. J., Robles, Z., Valdivieso, J., and Zvolensky, M. J. (2016). Synergistic effects of pain intensity and anxiety sensitivity in relation to anxiety and depressive symptoms and disorders among economically disadvantaged latinos in a community-based primary care setting. *Journal of Anxiety Disorders*, 43:23–31.

Verdejo-García, A., Albein-Urios, N., Molina, E., Ching-López, A., Martínez-González, J. M., and Gutiérrez, B. (2013). A maoa gene* cocaine severity interaction on impulsivity and neuropsychological measures of orbitofrontal dysfunction: Preliminary results. *Drug and alcohol dependence*, 133(1):287–290.

Verdejo-Garcia, A., Clark, L., and Dunn, B. D. (2012). The role of interoception in addiction: a critical review. *Neuroscience & Biobehavioral Reviews*, 36(8):1857–1869.

Verdejo-García, A., Rivas-Pérez, C., Vilar-López, R., and Pérez-García, M. (2007). Strategic self-regulation, decision-making and emotion processing in poly-substance abusers in their first year of abstinence. *Drug and alcohol dependence*, 86(2):139–146.

Verelst, S., Moonen, P.-J., Desruelles, D., and Gillet, J.-B. (2012). Emergency department visits due to alcohol intoxication: characteristics of patients and impact on the emergency room. *Alcohol and alcoholism*, 47(4):433–438.

Verheul, R., van den Brink, W., and Geerlings, P. (1999). A three-pathway psychobiological model of craving for alcohol. *Alcohol and Alcoholism*, 34(2):197–222.

Verhulst, B., Neale, M., and Kendler, K. (2015). The heritability of alcohol use disorders: A meta-analysis of twin and adoption studies. *Psychological Medicine*, 45(5):1061–1072.

Vermetten, E., Vythilingam, M., Southwick, S. M., Charney, D. S., and Bremner, J. D. (2003). Long-term treatment with paroxetine increases verbal declarative memory and hippocampal volume in posttraumatic stress disorder. *Biological psychiatry*, 54(7):693–702.

Versella, M. V., Piccirillo, M. L., Potter, C. M., Olino, T. M., and Heimberg, R. G. (2016). Anger profiles in social anxiety disorder. *Journal of anxiety disorders*, 37:21–29.

Verweij, K. J., Creemers, H. E., Korhonen, T., Latvala, A., Dick, D. M., Rose, R. J., Huizink, A. C., and Kaprio, J. (2016). Role of overlapping genetic and environmental factors in the relationship between early adolescent conduct problems and substance use in young adulthood. *Addiction*.

Verweij, K. J., Zietsch, B. P., Medland, S. E., Gordon, S. D., Benyamin, B., Nyholt, D. R., McEvoy, B. P., Sullivan, P. F., Heath, A. C., Madden, P. A., et al. (2010). A genome-wide association study of cloninger's temperament scales: implications for the evolutionary genetics of personality. *Biological psychology*, 85(2):306–317.

Via, E., Cardoner, N., Pujol, J., Alonso, P., López-Solà, M., Real, E., Contreras-Rodríguez, O., Deus, J., Segalàs, C., Menchón, J. M., et al. (2014). Amygdala activation and symptom dimensions in obsessive-compulsive disorder. *The British Journal of Psychiatry*, 204(1):61–68.

Viana, A. G., Kiel, E. J., Alfano, C. A., Dixon, L. J., and Palmer, C. A. (2016). The contribution of temperamental and cognitive factors to childhood anxiety disorder symptoms: A closer look at negative affect, behavioral inhibition, and anxiety sensitivity. *Journal of Child and Family Studies*, pages 1–11.

Viana, A. G. and Rabian, B. (2008). Perceived attachment: Relations to anxiety sensitivity, worry, and gad symptoms. *Behaviour Research and Therapy*, 46(6):737–747.

Viana, A. G. and Stevens, E. N. (2016). Parental threatening behaviors and offspring substance use: The moderating role of anxiety sensitivity. *Journal of Child & Adolescent Substance Abuse*, 25(3):212–221.

Victorio-Estrada, A., Mucha, R., and Stephan, E. (1996). Excessive drinking situations in german alcoholics: replication of a three-factor model used for north americans. *Drug and alcohol dependence*, 41(1):75–79.

Vincent, J. L., Kahn, I., Snyder, A. Z., Raichle, M. E., and Buckner, R. L. (2008). Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. *Journal of neurophysiology*, 100(6):3328–3342.

Vinogradova, O. (2001). Hippocampus as comparator: role of the two input and two output systems of the hippocampus in selection and registration of information. *Hippocampus*, 11(5):578–598.

Viviani, R. (2013). Emotion regulation, attention to emotion, and the ventral attentional network. *Frontiers in human neuroscience*, 7.

Voellmin, A., Winzeler, K., Hug, E., Wilhelm, F. H., Schaefer, V., Gaab, J., La Marca, R., Pruessner, J. C., and Bader, K. (2015). Blunted endocrine and cardiovascular reactivity in young healthy women reporting a history of childhood adversity. *Psychoneuroendocrinology*, 51:58–67.

Vogt, B. A. (2005). Pain and emotion interactions in subregions of the cingulate gyrus. *Nature Reviews Neuroscience*, 6(7):533–544.

Vogt, B. A. (2016). Midcingulate cortex: Structure, connections, homologies, functions and diseases. *Journal of chemical neuroanatomy*, 74:28–46.

Vogt, B. A., Finch, D. M., and Olson, C. R. (1992). Functional heterogeneity in cingulate cortex: the anterior executive and posterior evaluative regions. *Cerebral cortex*, 2(6):435–443.

Vogt, B. A. and Paxinos, G. (2014). Cytoarchitecture of mouse and rat cingulate cortex with human homologies. *Brain Structure and Function*, 219(1):185–192.

Vogt, B. A., Vogt, L., and Laureys, S. (2006). Cytology and functionally correlated circuits of human posterior cingulate areas. *Neuroimage*, 29(2):452–466.

Volkow, N. et al. (2016). Review article: Neurobiologic advances from the brain disease model of addiction. *The new england journal of medicine*.

Volkow, N., Wang, G.-J., Fowler, J., Tomasi, D., and Telang, F. (2011). Addiction: Beyond dopamine reward circuitry. *Proceedings of the National Academy of Sciences of the United States of America*, 108(37):15037–15042.

Volkow, N. D. and Fowler, J. S. (2000). Addiction, a disease of compulsion and drive: involvement of the orbitofrontal cortex. *Cerebral cortex*, 10(3):318–325.

Volkow, N. D., Ma, Y., Zhu, W., Fowler, J. S., Li, J., Rao, M., Mueller, K., Pradhan, K., Wong, C., and Wang, G.-J. (2008). Moderate doses of alcohol disrupt the functional organization of the human brain. *Psychiatry Research: Neuroimaging*, 162(3):205–213.

Volkow, N. D., Mullani, N., Gould, L., Adler, S. S., Guynn, R. W., Overall, J. E., and Dewey, S. (1988). Effects of acute alcohol intoxication on cerebral blood flow measured with pet. *Psychiatry research*, 24(2):201–209.

Völlm, B. A., Taylor, A. N., Richardson, P., Corcoran, R., Stirling, J., McKie, S., Deakin, J. F., and Elliott, R. (2006). Neuronal correlates of theory of mind and empathy: a functional magnetic resonance imaging study in a nonverbal task. *Neuroimage*, 29(1):90–98.

von dem Hagen, E. A., Stoyanova, R. S., Baron-Cohen, S., and Calder, A. J. (2013). Reduced functional connectivity within and between 'social'resting state networks in autism spectrum conditions. *Social Cognitive and Affective Neuroscience*, 8(6):694–701.

Vries-Bouw, D., Popma, A., Vermeiren, R., Doreleijers, T. A., Van De Ven, P. M., Jansen, L., et al. (2011). The predictive value of low heart rate and heart rate variability during stress for reoffending in delinquent male adolescents. *Psychophysiology*, 48(11):1597–1604.

Vuilleumier, P. and Pourtois, G. (2007). Distributed and interactive brain mechanisms during emotion face perception: Evidence from functional neuroimaging. *Neuropsychologia*, 45(1):174–194.

Vyssoki, B., Blüml, V., Gleiss, A., Friedrich, F., Kogoj, D., Walter, H., Zeiler, J., Höfer, P., Lesch, O., and Erfurth, A. (2011). The impact of temperament in the course of alcohol dependence. *Journal of affective disorders*, 135(1):177–183.

Wadiwalla, M., Andrews, J., Lai, B., Buss, C., Lupien, S., and Pruessner, J. (2010). Effects of manipulating the amount of social-evaluative threat on the cortisol stress response in young healthy women. *Stress*, 13(3):214–220.

Wagels, L., Bergs, R., Clemens, B., Bauchmüller, M., Gur, R. C., Schneider, F., Habel, U., and Kohn, N. (2016). Contextual exclusion processing: an fmri study of rejection in a performance-related context. *Brain Imaging and Behavior*, pages 1–13.

Wager, T., Phan, K., Liberzon, I., and Taylor, S. (2003). Valence, gender, and lateralization of functional brain anatomy in emotion: A meta-analysis of findings from neuroimaging. *NeuroImage*, 19(3):513–531.

Wager, T., Rilling, J., Smith, E., Sokolik, A., Casey, K., Davidson, R., Kosslyn, S., Rose, R., and Cohen, J. (2004). Placebo-induced changes in fmri in the anticipation and experience of pain. *Science*, 303(5661):1162–1167.

Wager, T. D., Davidson, M. L., Hughes, B. L., Lindquist, M. A., and Ochsner, K. N. (2008). Prefrontal-subcortical pathways mediating successful emotion regulation. *Neuron*, 59(6):1037–1050.

Wagner, A. J., Garbers, R., Lang, A., Borgert, A. J., and Fisher, M. (2016). Increasing follow-up outcomes of at-risk alcohol patients using motivational interviewing. *Journal of Trauma Nursing*, 23(3):165–168.

Wakefield, J. C. (2016). Diagnostic issues and controversies in dsm-5: Return of the false positives problem. *Annual review of clinical psychology*, 12:105–132.

Walker, D. L., Toufexis, D. J., and Davis, M. (2003). Role of the bed nucleus of the stria terminalis versus the amygdala in fear, stress, and anxiety. *European journal of pharmacology*, 463(1):199–216.

Wallace, S. T. and Alden, L. E. (1997). Social phobia and positive social events: The price of success. *Journal of Abnormal Psychology*, 106(3):416.

Wallhed Finn, S., Bakshi, A.-S., and Andréasson, S. (2014). Alcohol consumption, dependence, and treatment barriers: perceptions among nontreatment seekers with alcohol dependence. *Substance use & misuse*, 49(6):762–769.

Walsh, T., McClellan, J. M., McCarthy, S. E., Addington, A. M., Pierce, S. B., Cooper, G. M., Nord, A. S., Kusenda, M., Malhotra, D., Bhandari, A., et al. (2008). Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. *science*, 320(5875):539–543.

Walter, M., Bentz, D., Schicktanz, N., Milnik, A., Aerni, A., Gerhards, C., Schwegler, K., Vogel, M., Blum, J., Schmid, O., et al. (2015). Effects of cortisol administration on craving in heroin addicts. *Translational psychiatry*, 5(7):e610.

Walter, M., Gerber, H., Kuhl, H. C., Schmid, O., Joechle, W., Lanz, C., Brenneisen, R., Schächinger, H., Riecher-Rössler, A., Wiesbeck, G. A., et al. (2013). Acute effects of intravenous heroin on the hypothalamic-pituitary-adrenal axis response: a controlled trial. *Journal of clinical psychopharmacology*, 33(2):193–198.

Waltman, C., McCaui, M., and Wand, G. (1994). Adrenocorticotropin responses following administration of ethanol and ovine corticotropin-releasing hormone in the sons of alcoholics and control subjects. *Alcoholism: Clinical and Experimental Research*, 18(4):826–830.

Wandell, B. A. (2016). Clarifying human white matter. *Annual review of neuroscience*, 39(1).

Wang, B., Deveaux, L., Lunn, S., Dinaj-Koci, V., Li, X., and Stanton, B. (2016). The influence of sensation-seeking and parental and peer influences in early adolescence on risk involvement through middle adolescence a structural equation modeling analysis. *Youth & society*, 48(2):220–241.

Wang, G.-J., Volkow, N. D., Fowler, J. S., Cervany, P., Hitzemann, R. J., Pappas, N. R., Wong, C. T., and Felder, C. (1999). Regional brain metabolic activation during craving elicited by recall of previous drug experiences. *Life sciences*, 64(9):775–784.

Wang, G.-J., Volkow, N. D., Franceschi, D., Fowler, J. S., Thanos, P. K., Scherbaum, N., Pappas, N., Wong, C. T., Hitzemann, R. J., and Felder, C. A. (2000). Regional brain metabolism during alcohol intoxication. *Alcoholism: Clinical and Experimental Research*, 24(6):822–829.

Wang, J., Korczykowski, M., Rao, H., Fan, Y., Pluta, J., Gur, R. C., McEwen, B. S., and Detre, J. A. (2007a). Gender difference in neural response to psychological stress. *Social cognitive and affective neuroscience*, 2(3):227–239.

Wang, J., Rao, H., Wetmore, G., Furlan, P., Korczykowski, M., Dinges, D., and Detre, J. (2005a). Perfusion functional mri reveals cerebral blood flow pattern under psychological stress. *Proceedings of the National Academy of Sciences of the United States of America*, 102(49):17804–17809.

Wang, P. S., Angermeyer, M., Borges, G., Bruffaerts, R., Chiu, W. T., De Girolamo, G., Fayyad, J., Gureje, O., Haro, J. M., Huang, Y., et al. (2007b). Delay and failure in treatment seeking after first onset of mental disorders in the world health organization's world mental health survey initiative. *World Psychiatry*, 6(3):177.

Wang, P. S., Berglund, P., Olfson, M., Pincus, H. A., Wells, K. B., and Kessler, R. C. (2005b). Failure and delay in initial treatment contact after first onset of mental disorders in the national comorbidity survey replication. *Archives of general psychiatry*, 62(6):603–613.

Wang, S., Mason, J., Charney, D., Yehuda, R., Riney, S., and Southwick, S. (1997). Relationships between hormonal profile and novelty seeking in combat-related posttraumatic stress disorder. *Biological Psychiatry*, 41(2):145–151.

Waraczynski, M. (2016). Toward a systems-oriented approach to the role of the extended amygdala in adaptive responding. *Neuroscience & Biobehavioral Reviews*, 68:177–194.

Wardell, J. D., Ramchandani, V. A., and Hendershot, C. S. (2016). Drinking motives predict subjective effects of alcohol and alcohol wanting and liking during laboratory alcohol administration: a mediated pathway analysis. *Alcoholism: clinical and experimental research*, 40(10):2190–2198.

Wardle, J., Ahmad, T., and Hayward, P. (1990). Anxiety sensitivity in agoraphobia. *Journal of Anxiety Disorders*, 4(4):325–333.

Ware, A. L., Infante, M. A., O'Brien, J. W., Tapert, S. F., Jones, K. L., Riley, E. P., and Mattson, S. N. (2015). An fmri study of behavioral response inhibition in adolescents with and without histories of heavy prenatal alcohol exposure. *Behavioural brain research*, 278:137–146.

Warnock-Parkes, E., Wild, J., Stott, R., Grey, N., Ehlers, A., and Clark, D. M. (2016). Seeing is believing: Using video feedback in cognitive therapy for social anxiety disorder. *Cognitive and Behavioral Practice*.

Warren, S. L., Crocker, L. D., Spielberg, J. M., Engels, A. S., Banich, M. T., Sutton, B. P., Miller, G. A., and Heller, W. (2013). Cortical organization of inhibition-related functions and modulation by psychopathology. *Frontiers in Human Neuroscience*, 7.

Watson, D. (2000). *Mood and temperament*. Guilford Press.

Watson, D. and Friend, R. (1969). Measurement of social-evaluative anxiety. *Journal of consulting and clinical psychology*, 33(4):448.

Weafer, J. and Fillmore, M. T. (2016). Low-dose alcohol effects on measures of inhibitory control, delay discounting, and risk-taking. *Current Addiction Reports*, 3(1):75–84.

Weber, M. D., Graham, J. W., Hansen, W. B., Flay, B. R., and Johnson, C. A. (1989). Evidence for two paths of alcohol use onset in adolescents. *Addictive Behaviors*, 14(4):399–408.

Weeks, J. W. (2015). Replication and extension of a hierarchical model of social anxiety and depression: fear of positive evaluation as a key unique factor in social anxiety. *Cognitive behaviour therapy*, 44(2):103–116.

Weeks, J. W., Heimberg, R. G., and Rodebaugh, T. L. (2008a). The fear of positive evaluation scale: Assessing a proposed cognitive component of social anxiety. *Journal of anxiety disorders*, 22(1):44–55.

Weeks, J. W., Heimberg, R. G., Rodebaugh, T. L., and Norton, P. J. (2008b). Exploring the relationship between fear of positive evaluation and social anxiety. *Journal of Anxiety Disorders*, 22(3):386–400.

Weeks, J. W. and Howell, A. N. (2012). The bivalent fear of evaluation model of social anxiety: further integrating findings on fears of positive and negative evaluation. *Cognitive Behaviour Therapy*, 41(2):83–95.

Weeks, J. W. and Howell, A. N. (2014). Fear of positive evaluation: The neglected fear domain in social anxiety. *The Wiley Blackwell Handbook of Social Anxiety Disorder*, pages 433–453.

Weeks, J. W., Menatti, A. R., and Howell, A. N. (2015). Psychometric evaluation of the concerns of social reprisal scale: Further explicating the roots of fear of positive evaluation. *Journal of anxiety disorders*, 36:33–43.

Weeks, J. W. and Zoccola, P. M. (2015). "having the heart to be evaluated": The differential effects of fears of positive and negative evaluation on emotional and cardiovascular responses to social threat. *Journal of anxiety disorders*, 36:115–126.

Weidt, S., Lutz, J., Rufer, M., Delsignore, A., Jakob, N., Herwig, U., and Bruehl, A. (2016). Common and differential alterations of general emotion processing in obsessive-compulsive and social anxiety disorder. *Psychological medicine*, 46(7):1427.

Weiland, B. J., Nigg, J. T., Welsh, R. C., Yau, W.-Y. W., Zubieta, J.-K., Zucker, R. A., and Heitzeg, M. M. (2012). Resiliency in adolescents at high risk for substance abuse: flexible adaptation via subthalamic nucleus and linkage to drinking and drug use in early adulthood. *Alcoholism: Clinical and Experimental Research*, 36(8):1355–1364.

Weiland, B. J., Welsh, R. C., Yau, W.-Y. W., Zucker, R. A., Zubieta, J.-K., and Heitzeg, M. M. (2013). Accumbens functional connectivity during reward mediates sensation-seeking and alcohol use in high-risk youth. *Drug and alcohol dependence*, 128(1):130–139.

Weiland, B. J., Zucker, R. A., Zubieta, J.-K., and Heitzeg, M. M. (2016). Striatal dopaminergic reward response relates to age of first drunkenness and feedback response in at-risk youth. *Addiction biology*.

Weiner, H. (1992). *Perturbing the organism: The biology of stressful experience*. University of Chicago Press.

Weiner, J. and Valenzuela, C. (2006). Ethanol modulation of gabaergic transmission: the view from the slice. *Pharmacology & therapeutics*, 111(3):533–554.

Weiss, N. H., Tull, M. T., Anestis, M. D., and Gratz, K. L. (2013). The relative and unique contributions of emotion dysregulation and impulsivity to posttraumatic stress disorder among substance dependent inpatients. *Drug and Alcohol Dependence*, 128(1):45–51.

Weissenborn, R. and Duka, T. (2003). Acute alcohol effects on cognitive function in social drinkers: their relationship to drinking habits. *Psychopharmacology*, 165(3):306–312.

Weisz, D., Harden, D., and Xiang, Z. (1992). Effects of amygdala lesions on reflex facilitation and conditioned response acquisition during nictitating membrane response conditioning in rabbit. *Behavioral Neuroscience*, 106(2):262–273.

Weitzman, O., Kemeny, M., and Fahey, J. (2004). Hiv-related shame and guilt predict cd4 decline. *Manuscript submitted for publication*.

Werch, C. E. and Owen, D. M. (2002). Iatrogenic effects of alcohol and drug prevention programs. *Journal of studies on alcohol*, 63(5):581–590.

Westra, H. A., Constantino, M. J., and Antony, M. M. (2016). Integrating motivational interviewing with cognitive-behavioral therapy for severe generalized anxiety disorder: An allegiance-controlled randomized clinical trial.

Wetherill, R. R., Bava, S., Thompson, W. K., Boucquey, V., Pulido, C., Yang, T. T., and Tapert, S. F. (2012). Frontoparietal connectivity in substance-naive youth with and without a family history of alcoholism. *Brain research*, 1432:66–73.

Wetherill, R. R., Castro, N., Squeglia, L. M., and Tapert, S. F. (2013a). Atypical neural activity during inhibitory processing in substance-naïve youth who later experience alcohol-induced blackouts. *Drug and alcohol dependence*, 128(3):243.

Wetherill, R. R., Squeglia, L. M., Yang, T. T., and Tapert, S. F. (2013b). A longitudinal examination of adolescent response inhibition: neural differences before and after the initiation of heavy drinking. *Psychopharmacology*, 230(4):663–671.

Weymar, M. and Schwabe, L. (2016). Amygdala and emotion: The bright side of it. *Frontiers in neuroscience*, 10:224.

Whalen, P. J. (1998). Fear, vigilance, and ambiguity: Initial neuroimaging studies of the human amygdala. *Current directions in psychological science*, pages 177–188.

Whalen, P. J. (2007). The uncertainty of it all. *Trends in Cognitive Sciences*, 12(11):499–500.

Whalen, P. J., Bush, G., McNally, R. J., Wilhelm, S., McInerney, S. C., Jenike, M. A., and Rauch, S. L. (1998a). The emotional counting stroop paradigm: a functional magnetic resonance imaging probe of the anterior cingulate affective division. *Biological psychiatry*, 44(12):1219–1228.

Whalen, P. J., Johnstone, T., Somerville, L. H., Nitschke, J. B., Polis, S., Alexander, A. L., Davidson, R. J., and Kalin, N. H. (2008). A functional magnetic resonance imaging predictor of treatment response to venlafaxine in generalized anxiety disorder. *Biological psychiatry*, 63(9):858–863.

Whalen, P. J., Kagan, J., Cook, R. G., Davis, F. C., Kim, H., Polis, S., McLaren, D. G., Somerville, L. H., McLean, A. A., Maxwell, J. S., et al. (2004). Human amygdala responsivity to masked fearful eye whites. *Science*, 306(5704):2061–2061.

Whalen, P. J. and Phelps, E. A. (2009). *The human amygdala*. Guilford Press.

Whalen, P. J., Rauch, S. L., Etcoff, N. L., McInerney, S. C., Lee, M. B., and Jenike, M. A. (1998b). Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *The Journal of neuroscience*, 18(1):411–418.

Whalen, P. J., Shin, L. M., McInerney, S. C., Fischer, H., Wright, C. I., and Rauch, S. L. (2001). A functional mri study of human amygdala responses to facial expressions of fear versus anger. *Emotion*, 1(1):70.

Whalley, K. (2014). Learning and memory: Synapse remodelling extinguishes fear. *Nature Reviews Neuroscience*, 15(1):3–3.

Wheaton, M. G., Deacon, B. J., McGrath, P. B., Berman, N. C., and Abramowitz, J. S. (2012). Dimensions of anxiety sensitivity in the anxiety disorders: Evaluation of the asi-3. *Journal of Anxiety Disorders*, 26(3):401–408.

Whelan, R., Watts, R., Orr, C. A., Althoff, R. R., Artiges, E., Banaschewski, T., Barker, G. J., Bokde, A. L., Büchel, C., Carvalho, F. M., et al. (2014). Neuropsychosocial profiles of current and future adolescent alcohol misusers. *Nature*, 512(7513):185–189.

White, N. M. (2009). Some highlights of research on the effects of caudate nucleus lesions over the past 200 years. *Behavioural brain research*, 199(1):3–23.

Whiteford, H. A., Degenhardt, L., Rehm, J., Baxter, A. J., Ferrari, A. J., Erskine, H. E., Charlson, F. J., Norman, R. E., Flaxman, A. D., Johns, N., et al. (2013). Global burden of disease attributable to mental and substance use disorders: findings from the global burden of disease study 2010. *The Lancet*, 382(9904):1575–1586.

Whiteside, S. and Lynam, D. (2001). The five factor model and impulsivity: Using a structural model of personality to understand impulsivity. *Personality and Individual Differences*, 30(4):669–689.

Whiteside, S., Lynam, D., Miller, J., and Reynolds, S. (2005). Validation of the upps impulsive behaviour scale: A four-factor model of impulsivity. *European Journal of Personality*, 19(7):559–574.

Whitfield, J. (1997). Meta-analysis of the effects of alcohol dehydrogenase genotype on alcohol dependence and alcoholic liver disease. *Alcohol and Alcoholism*, 32(5):613–619.

Whitfield, J. B. (2002). Alcohol dehydrogenase and alcohol dependence: variation in genotype-associated risk between populations. *American journal of human genetics*, 71(5):1247.

Whitfield-Gabrieli, S., Ghosh, S., Nieto-Castanon, A., Saygin, Z., Doehrmann, O., Chai, X., Reynolds, G., Hofmann, S., Pollack, M., and Gabrieli, J. (2015). Brain connectomics predict response to treatment in social anxiety disorder. *Molecular psychiatry*.

Whittle, S., Dennison, M., Vijayakumar, N., Simmons, J. G., Yücel, M., Lubman, D. I., Pantelis, C., and Allen, N. B. (2013). Childhood maltreatment and psychopathology affect brain development during adolescence. *Journal of the American Academy of Child & Adolescent Psychiatry*, 52(9):940–952.

WHO, W. H. O. (2014). *Global status report on alcohol and health-2014*. World Health Organization.

Widom, C. S., Czaja, S. J., and DuMont, K. A. (2015). Intergenerational transmission of child abuse and neglect: Real or detection bias? *Science*, 347(6229):1480–1485.

Wiers, C. E., Cabrera, E., Skarda, E., Volkow, N. D., and Wang, G.-J. (2016). Pet imaging for addiction medicine: From neural mechanisms to clinical considerations. *Progress in brain research*, 224:175–201.

Wiers, C. E. and Wiers, R. W. (2016). Imaging the neural effects of cognitive bias modification training. *NeuroImage*.

Wiest, G., Lehner-Baumgartner, E., and Baumgartner, C. (2006). Panic attacks in an individual with bilateral selective lesions of the amygdala. *Archives of neurology*, 63(12):1798–1801.

Wik, G., Fredrikson, M., Ericson, K., Eriksson, L., Stone-Elander, S., and Greitz, T. (1993). A functional cerebral response to frightening visual stimulation. *Psychiatry Research*, 50(1):15–24.

Wikenheiser, A. M. and Schoenbaum, G. (2016). Over the river, through the woods: cognitive maps in the hippocampus and orbitofrontal cortex. *Nature Reviews Neuroscience*.

Wilensky, A. E., Schafe, G. E., Kristensen, M. P., and LeDoux, J. E. (2006). Rethinking the fear circuit: the central nucleus of the amygdala is required for the acquisition, consolidation, and expression of pavlovian fear conditioning. *The Journal of neuroscience*, 26(48):12387–12396.

Wiley, L. C. (2014). *Alcohol use trajectories & the transition from adolescence into young adulthood: An examination of crime, sex, and gender*.

Wilhelm, K., Niven, H., Parker, G., and Hadzi-Pavlovic, D. (2005). The stability of the parental bonding instrument over a 20-year period. *Psychological medicine*, 35(03):387–393.

Will, G.-J., van Lier, P. A., Crone, E. A., and Güroğlu, B. (2016). Chronic childhood peer rejection is associated with heightened neural responses to social exclusion during adolescence. *Journal of abnormal child psychology*, 44(1):43–55.

Williams, K. D. (2007). Ostracism. *Psychology*, 58(1):425.

Williams, L. M., Brown, K. J., Palmer, D., Liddell, B. J., Kemp, A. H., Olivieri, G., Peduto, A., and Gordon, E. (2006a). The mellow years?: neural basis of improving emotional stability over age. *The journal of Neuroscience*, 26(24):6422–6430.

Williams, L. M., Kemp, A. H., Felmingham, K., Liddell, B. J., Palmer, D. M., and Bryant, R. A. (2007). Neural biases to covert and overt signals of fear: dissociation by trait anxiety and depression. *Journal of Cognitive Neuroscience*, 19(10):1595–1608.

Williams, L. M., Liddell, B. J., Kemp, A. H., Bryant, R. A., Meares, R. A., Peduto, A. S., and Gordon, E. (2006b). Amygdala–prefrontal dissociation of subliminal and supraliminal fear. *Human brain mapping*, 27(8):652–661.

Williams, M., McGlone, F., Abbott, D., and Mattingley, J. (2005). Differential amygdala responses to happy and fearful facial expressions depend on selective attention. *NeuroImage*, 24(2):417–425.

Wills, T. A., McNamara, G., Vaccaro, D., and Hirky, A. E. (1996). Escalated substance use: a longitudinal grouping analysis from early to middle adolescence. *Journal of abnormal psychology*, 105(2):166.

Wilson, J. R. and Nagoshi, C. T. (1988). Adult children of alcoholics: Cognitive and psychomotor characteristics. *British Journal of Addiction*.

Windle, M. and Scheidt, D. (2004). Alcoholic subtypes: are two sufficient? *Addiction*, 99(12):1508–1519.

Winfrey, L. P. (1980). *The unforgettable elephant*. Walker and Company.

Wintemute, G. J. (2015). The epidemiology of firearm violence in the twenty-first century united states. *Annual review of public health*, 36:5–19.

Winzeler, K., Voellmin, A., Hug, E., Kirmse, U., Helmig, S., Princip, M., Cajochen, C., Bader, K., and Wilhelm, F. H. (2016). Adverse childhood experiences and autonomic regulation in response to acute stress: the role of the sympathetic and parasympathetic nervous systems. *Anxiety, Stress, & Coping*, (just-accepted):1–23.

Wise, R. (2000). Addiction becomes a brain disease. *Neuron*, 26(1):27–33.

Wise, R. and Bozarth, M. (1987). A psychomotor stimulant theory of addiction. *Psychological Review*, 94(4):469–492.

Wise, R. A. (1988). Psychomotor stimulant properties of addictive drugs. *Annals of the New York Academy of Sciences*, 537(1):228–234.

Witek-Janusek, L. (1988). Pituitary-adrenal response to bacterial endotoxin in developing rats. *American Journal of Physiology-Endocrinology and Metabolism*, 255(4):E525–E530.

Wittchen, H.-U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jönsson, B., Olesen, J., Allgulander, C., Alonso, J., Faravelli, C., et al. (2011). The size and burden of mental disorders and other disorders of the brain in europe 2010. *European Neuropsychopharmacology*, 21(9):655–679.

Wohlwill, J. (1984). What are sensation seekers seeking? *Behavioral and Brain Sciences*, 7.

Woicik, P. A., Stewart, S. H., Pihl, R. O., and Conrod, P. J. (2009). The substance use risk profile scale: A scale measuring traits linked to reinforcement-specific substance use profiles. *Addictive behaviors*, 34(12):1042–1055.

Wolfensberger, S. P., Veltman, D. J., Hoogendijk, W. J., Boomsma, D. I., and de Geus, E. J. (2008). Amygdala responses to emotional faces in twins discordant or concordant for the risk for anxiety and depression. *Neuroimage*, 41(2):544–552.

Wolitzky-Taylor, K., Guillot, C. R., Pang, R. D., Kirkpatrick, M. G., Zvolensky, M. J., Buckner, J. D., and Leventhal, A. M. (2015). Examination of anxiety sensitivity and distress tolerance as transdiagnostic mechanisms linking multiple anxiety pathologies to alcohol use problems in adolescents. *Alcoholism: Clinical and Experimental Research*, 39(3):532–539.

Wolitzky-Taylor, K., Operskalski, J. T., Ries, R., Craske, M. G., and Roy-Byrne, P. (2011). Understanding and treating comorbid anxiety disorders in substance users: review and future directions. *Journal of addiction medicine*, 5(4):233–247.

Wong, Q. J. and Rapee, R. M. (2016). The aetiology and maintenance of social anxiety disorder: A synthesis of complimentary theoretical models and formulation of a new integrated model. *Journal of affective disorders*, 203:84–100.

Woo, C.-W., Koban, L., Kross, E., Lindquist, M. A., Banich, M. T., Ruzic, L., Andrews-Hanna, J. R., and Wager, T. D. (2014). Separate neural representations for physical pain and social rejection. *Nature communications*, 5.

Woon, F. L., Sood, S., and Hedges, D. W. (2010). Hippocampal volume deficits associated with exposure to psychological trauma and posttraumatic stress disorder in adults: a meta-analysis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 34(7):1181–1188.

Wrase, J., Makris, N., Braus, D. F., Mann, K., Smolka, M. N., Kennedy, D. N., Caviness, V. S., Hodge, S. M., Tang, L., Albaugh, M., et al. (2008). Amygdala volume associated with alcohol abuse relapse and craving. *American Journal of Psychiatry*.

Wrase, J., Schlagenhauf, F., Kienast, T., Wüstenberg, T., Bermpohl, F., Kahnt, T., Beck, A., Ströhle, A., Juckel, G., Knutson, B., et al. (2007). Dysfunction of reward processing correlates with alcohol craving in detoxified alcoholics. *Neuroimage*, 35(2):787–794.

Wright, C. I., Martis, B., McMullin, K., Shin, L. M., and Rauch, S. L. (2003). Amygdala and insular responses to emotionally valenced human faces in small animal specific phobia. *Biological psychiatry*, 54(10):1067–1076.

Wright, K. D., Lebell, M. A. A., and Carleton, R. N. (2016). Intolerance of uncertainty, anxiety sensitivity, health anxiety, and anxiety disorder symptoms in youth. *Journal of Anxiety Disorders*, 41:35–42.

Wu, G., Feder, A., Cohen, H., Kim, J. J., Calderon, S., Charney, D. S., and Mathé, A. A. (2013). Understanding resilience. *Frontiers in behavioral neuroscience*, 7:10.

Wu, L. S.-H., Lee, C.-S., Weng, T.-Y., Wang, K. H.-T., and Cheng, A. T.-A. (2016a). Association study of gene polymorphisms in gaba, serotonin, dopamine, and alcohol metabolism pathways with alcohol dependence in taiwanese han men. *Alcoholism: Clinical and Experimental Research*, 40(2):284–290.

Wu, Y., Wang, J., Zhang, Y., Zheng, D., Zhang, J., Rong, M., Wu, H., Wang, Y., Zhou, K., and Jiang, T. (2016b). The neuroanatomical basis for posterior superior parietal lobule control lateralization of visuospatial attention. *Frontiers in neuroanatomy*, 10.

Wudarczyk, O. A., Kohn, N., Bergs, R., Goerlich, K. S., Gur, R. E., Turetsky, B., Schneider, F., and Habel, U. (2016). Chemosensory anxiety cues enhance the perception of fearful faces–an fmri study. *NeuroImage*.

Wyk, B., Hudac, C., Carter, E., Sobel, D., and Pelphrey, K. (2009). Action understanding in the superior temporal sulcus region. *Psychological Science*, 20(6):771–777.

Wylie, R. C. (1974). *The self-concept: Theory and research on selected topics*, volume 2. U of Nebraska Press.

Xiao, P., Dai, Z., Zhong, J., Zhu, Y., Shi, H., and Pan, P. (2015). Regional gray matter deficits in alcohol dependence: A meta-analysis of voxel-based morphometry studies. *Drug and alcohol dependence*, 153:22–28.

Xie, X., Bratec, S. M., Schmid, G., Meng, C., Doll, A., Wohlschläger, A., Finke, K., Förstl, H., Zimmer, C., Pekrun, R., et al. (2016). How do you make me feel better? social cognitive emotion regulation and the default mode network. *NeuroImage*, 134:270–280.

Xu, J. and Potenza, M. N. (2012). White matter integrity and five-factor personality measures in healthy adults. *Neuroimage*, 59(1):800–807.

Xu, Y., Schneier, F., Heimberg, R. G., Princisvalle, K., Liebowitz, M. R., Wang, S., and Blanco, C. (2012). Gender differences in social anxiety disorder: Results from the national epidemiologic sample on alcohol and related conditions. *Journal of Anxiety Disorders*, 26(1):12–19.

Yakovenko, I., Quigley, L., Hemmelgarn, B. R., Hodgins, D. C., and Ronksley, P. (2015). The efficacy of motivational interviewing for disordered gambling: systematic review and meta-analysis. *Addictive behaviors*, 43:72–82.

Yan, P. and Li, C.-S. R. (2009). Decreased amygdala activation during risk taking in non-dependent habitual alcohol users: a preliminary fmri study of the stop signal task. *The American journal of drug and alcohol abuse*, 35(5):284–289.

Yang, Y., Lueken, U., Wittmann, A., Holtz, K., Kleint, N. I., Herrmann, M. J., Sass, K., Jansen, A., Konrad, C., Ströhle, A., et al. (2016). Neural correlates of individual differences in anxiety sensitivity: an fmri study using semantic priming. *Social cognitive and affective neuroscience*, page nsw024.

Yap, K., Gibbs, A. L., Francis, A. J., and Schuster, S. E. (2016). Testing the bivalent fear of evaluation model of social anxiety: The relationship between fear of positive evaluation, social anxiety, and perfectionism. *Cognitive behaviour therapy*, 45(2):136–149.

Yap, Q. J., Teh, I., Fusar-Poli, P., Sum, M. Y., Kuswanto, C., and Sim, K. (2013). Tracking cerebral white matter changes across the lifespan: insights from diffusion tensor imaging studies. *Journal of Neural Transmission*, 120(9):1369–1395.

Yarkoni, T. (2009). Big correlations in little studies. *Perspectives on Psychological Science*, 4(3):294–298.

Yarosh, H. L., Hyatt, C. J., Meda, S. A., Jiantonio-Kelly, R., Potenza, M. N., Assaf, M., and Pearlson, G. D. (2014). Relationships between reward sensitivity, risk-taking and family history of alcoholism during an interactive competitive fmri task. *PloS one*, 9(2):e88188.

Yau, W.-Y., Zubieta, J.-K., Weiland, B., Samudra, P., Zucker, R., and Heitzeg, M. (2012). Nucleus accumbens response to incentive stimuli anticipation in children of alcoholics: Relationships with precursive behavioral risk and lifetime alcohol use. *Journal of Neuroscience*, 32(7):2544–2551.

Ying, L., Fu, S., Qian, X., and Sun, X. (2011). Effects of mental workload on long-latency auditory-evoked-potential, salivary cortisol, and immunoglobulin a. *Neuroscience letters*, 491(1):31–34.

Yook, K., Kim, K.-H., Suh, S. Y., and Lee, K. S. (2010). Intolerance of uncertainty, worry, and rumination in major depressive disorder and generalized anxiety disorder. *Journal of anxiety disorders*, 24(6):623–628.

Yoon, S. A. and Weierich, M. R. (2016). Salivary biomarkers of neural hypervigilance in trauma-exposed women. *Psychoneuroendocrinology*, 63:17–25.

Young, A. W., Aggleton, J. P., Hellawell, D. J., Johnson, M., Broks, P., and Hanley, J. R. (1995). Face processing impairments after amygdalotomy. *Brain*, 118(1):15–24.

Young, E., Korszun, A., Figueiredo, H., Solomon, M., and Herman, J. (2008). Sex differences in the brain: From genes to behavior. *New York: Oxford University Press. Berenbaum, SA (1999). Effects of early androgens on sex-typed activities and interests in adolescents with congenital adrenal hyperplasia. Hormones and Behavior*, 35:102110.

Young, G. (2016). Statistical concepts and networks in causality. In *Unifying Causality and Psychology*, pages 121–147. Springer.

Young, S. E., Friedman, N. P., Miyake, A., Willcutt, E. G., Corley, R. P., Haberstick, B. C., and Hewitt, J. K. (2009). Behavioral disinhibition: liability for externalizing spectrum disorders and its genetic and environmental relation to response inhibition across adolescence. *Journal of abnormal psychology*, 118(1):117.

Youssef, F. F., Dookeeram, K., Basdeo, V., Francis, E., Doman, M., Mamed, D., Maloo, S., Degannes, J., Dobo, L., Ditshotlo, P., et al. (2012). Stress alters personal moral decision making. *Psychoneuroendocrinology*, 37(4):491–498.

Ystrom, E., Kendler, K. S., and Reichborn-Kjennerud, T. (2014). Early age of alcohol initiation is not the cause of alcohol use disorders in adulthood, but is a major indicator of genetic risk. a population-based twin study. *Addiction*.

Yu, R. (2016). Stress potentiates decision biases: A stress induced deliberation-to-intuition (sidi) model. *Neurobiology of Stress*, 3:83–95.

Yuan, M., Zhu, H., Qiu, C., Meng, Y., Zhang, Y., Shang, J., Nie, X., Ren, Z., Gong, Q., Zhang, W., et al. (2016). Group cognitive behavioral therapy modulates the resting-state functional connectivity of amygdala-related network in patients with generalized social anxiety disorder. *BMC psychiatry*, 16(1):198.

Yuille, J. C. and Tollestrup, P. A. (1990). Some effects of alcohol on eyewitness memory. *Journal of Applied Psychology*, 75(3):268.

Yun, M. K., Park, E., Son, J. A., and Hyun, M. S. (2016). Influencing factors on externalized and internalized problem behaviors among adolescents: Focused on first grade high school students. *Journal of Korean Academic Society of Nursing Education*, 22(2):152–162.

Yung, A., Cotter, J., Wood, S., McGorry, P., Thompson, A., Nelson, B., and Lin, A. (2015). Childhood maltreatment and transition to psychotic disorder independently predict long-term functioning in young people at ultra-high risk for psychosis. *Psychological medicine*, 45(16):3453–3465.

Zachar, P. and Kendler, K. S. (2007). Psychiatric disorders: a conceptual taxonomy. *American Journal of Psychiatry*.

Zack, M., Poulos, C., Aramakis, V., Khamba, B., and MacLeod, C. (2007). Effects of drink-stress sequence and gender on alcohol stress response dampening in high and low anxiety sensitive drinkers. *Alcoholism: Clinical and Experimental Research*, 31(3):411–422.

Zacny, J. (2010). A possible link between sensation-seeking status and positive subjective effects of oxycodone in healthy volunteers. *Pharmacology Biochemistry and Behavior*, 95(1):113–120.

Zakowski, S. G. (1995). The effects of stressor predictability on lymphocyte proliferation in humans. *Psychology and Health*, 10(5):409–425.

Zald, D. (2003). The human amygdala and the emotional evaluation of sensory stimuli. *Brain Research Reviews*, 41(1):88–123.

Zaleski, Z. (1984). Sensation-seeking and risk-taking behaviour. *Personality and individual Differences*, 5(5):607–608.

Zhang, D. and Raichle, M. E. (2010). Disease and the brain's dark energy. *Nature Reviews Neurology*, 6(1):15–28.

Zhang, L., Kerich, M., Schwandt, M. L., Rawlings, R. R., McKellar, J. D., Momenan, R., Hommer, D. W., and George, D. T. (2013). Smaller right amygdala in caucasian alcohol-dependent male patients with a history of intimate partner violence: A volumetric imaging study. *Addiction biology*, 18(3):537–547.

Zheng, Y. and Liu, X. (2015). Blunted neural responses to monetary risk in high sensation seekers. *Neuropsychologia*, 71:173–180.

Zheng, Y., Sheng, W., Xu, J., and Zhang, Y. (2014). Sensation seeking and error processing. *Psychophysiology*, 51(9):824–833.

Zheng, Y., Tan, F., Xu, J., Chang, Y., Zhang, Y., and Shen, H. (2015). Diminished p300 to physical risk in sensation seeking. *Biological psychology*, 107:44–51.

Zhu, P. J. and Lovinger, D. M. (2006). Ethanol potentiates gabaergic synaptic transmission in a postsynaptic neuron/synaptic bouton preparation from basolateral amygdala. *Journal of neurophysiology*, 96(1):433–441.

Zhuo, M. (2016). Neural mechanisms underlying anxiety–chronic pain interactions. *Trends in neurosciences*, 39(3):136–145.

Zilverstand, A., Parvaz, M. A., and Goldstein, R. Z. (2016a). Neuroimaging cognitive reappraisal in clinical populations to define neural targets for enhancing emotion regulation. a systematic review. *NeuroImage*.

Zilverstand, A., Parvaz, M. A., Moeller, S. J., and Goldstein, R. Z. (2016b). Cognitive interventions for addiction medicine: Understanding the underlying neurobiological mechanisms. *Progress in brain research*, 224:285–304.

Zimmermann, U., Spring, K., Kunz-Ebrecht, S., Uhr, M., Wittchen, H.-U., and Holsboer, F. (2004). Effect of ethanol on hypothalamic-pituitary-adrenal system response to psychosocial stress in sons of alcohol-dependent fathers. *Neuropsychopharmacology*, 29(6):1156–1165.

Zinbarg, R. E., Barlow, D. H., and Brown, T. A. (1997). Hierarchical structure and general factor saturation of the anxiety sensitivity index: Evidence and implications. *Psychological Assessment*, 9(3):277.

Zinbarg, R. E., Brown, T. A., Barlow, D. H., and Rapee, R. M. (2001). Anxiety sensitivity, panic, and depressed mood: A reanalysis teasing apart the contributions of the two levels in the hierarchical structure of the anxiety sensitivity index. *Journal of abnormal psychology*, 110(3):372.

Zink, C. F., Stein, J. L., Kempf, L., Hakimi, S., and Meyer-Lindenberg, A. (2010). Vasopressin modulates medial prefrontal cortex–amygdala circuitry during emotion processing in humans. *The Journal of neuroscience*, 30(20):7017–7022.

Zlomke, K. R. and Jeter, K. M. (2014). Stress and worry: examining intolerance of uncertainty's moderating effect. *Anxiety, Stress & Coping*, 27(2):202–215.

Zoladz, P. R. and Diamond, D. M. (2009). Linear and non-linear dose-response functions reveal a hormetic relationship between stress and learning. *Dose-Response*, 7(2):dose–response.

Zucker, R. A., Heitzeg, M. M., and Nigg, J. T. (2011). Parsing the undercontrol–disinhibition pathway to substance use disorders: A multilevel developmental problem. *Child Development Perspectives*, 5(4):248–255.

Zucker, R. A., Hicks, B. M., and Heitzeg, M. M. (2016). Alcohol use and the alcohol use disorders over the life course: A cross-level developmental review. *Developmental Psychopathology*.

Zuckerman, M. (1971). Dimensions of sensation seeking. *Journal of consulting and clinical psychology*, 36(1):45.

Zuckerman, M. (1979). Sensation seeking: Beyond the optimal level of arousalerlbaum. *Hillsdale, NJ*.

Zuckerman, M. (1984). Sensation seeking: A comparative approach to a human trait. *Behavioral and Brain Sciences*, 7(03):413–434.

Zuckerman, M. (1985). Sensation seeking, mania, and monoamines. *Neuropsychobiology*, 13(3):121–128.

Zuckerman, M. (1990). The psychophysiology of sensation seeking. *Journal of personality*, 58(1):313–345.

Zuckerman, M. (1994). *Behavioral expressions and biosocial bases of sensation seeking*. Cambridge university press.

Zuckerman, M. (2005). Psychobiology of personality (revised and updated) cambridge university press. *New York*.

Zuckerman, M. (2007). The sensation seeking scale v (sss-v): Still reliable and valid. *Personality and Individual Differences*, 43(5):1303–1305.

Zuckerman, M. (2016). Sensation seeking: A biosocial dimension of personality. *Physiological correlates of human behavior*, 3:99–115.

Zuckerman, M., Bone, R. N., Neary, R., Mangelsdorff, D., and Brustman, B. (1972). What is the sensation seeker? personality trait and experience correlates of the sensation-seeking scales. *Journal of consulting and clinical psychology*, 39(2):308.

Zunhammer, M., Eberle, H., Eichhammer, P., and Busch, V. (2013). Somatic symptoms evoked by exam stress in university students: the role of alexithymia, neuroticism, anxiety and depression. *PLoS One*, 8(12):e84911.

Zvolensky, M. J. and Eifert, G. H. (2001). A review of psychological factors/processes affecting anxious responding during voluntary hyperventilation and inhalations of carbon dioxide-enriched air. *Clinical psychology review*, 21(3):375–400.