Abstract in English

This thesis presents a series of studies exploring the neurocognitive aspects of suicidal vulnerability using neuroimaging in both suicide attempters and first degree biological relatives of suicide completers. Through a systematic literature review, we demonstrated the association between suicidal acts and structural and functional alterations in several brain regions. We then examined structural neuroimaging measures in the prefrontal cortex of a large sample of suicide attempters and highlighted significant alterations in the left ventrolateral prefrontal cortex, independently from mood disorders. Moreover, we showed that the volume of the nucleus accumbens was negatively correlated with the lethality of previous suicidal acts, which suggests that this region may modulate the way suicidal acts are completed. We then used functional neuroimaging and the classical Go-NoGo task to examine cognitive inhibition among suicide attempters. Our results suggest that cognitive control deficits within suicide attempters, associated with the activation of the inferior frontal gyrus, thalamus, orbitofrontal cortex and parietal cortex, are more likely to be state-related than traits. Moreover, we examined relatives of suicide completers using a battery of cognitive measures and neuroimaging. We found decision-making deficits, but no cognitive control deficits, in suicide relatives who themselves never attempted suicide compared to patient relatives with no family history of suicidal acts and to healthy controls. These results suggest that risky decision-making could be a transmitted trait within families while normal cognitive control could be protective against suicide in these individuals. Furthermore, we showed that risky decision-making in sucide relatives was associated with significant reduction in ventromedial prefrontal cortex activity during decision-making and increased activity in precuneus during choice processing. Finally, both outcome processing during decision-making and angry faces processing (a proxy for social threat) were associated with altered activity in the cerebellum among suicide relatives. Overall, our findings strongly support a significant role for the ventral (both medial and lateral) prefrontal cortex, but they also highlight a network of brains regions beyond the prefrontal cortex. Moreover, they underline the importance and potential heritability of risky decision-making in suicidal vulnerability and the possibility that some cognitive deficits may be states while others are traits. These new findings expand our knowledge and allow us to propose an updated neurocognitive model of suicide.

Abstract in French

Cette thèse présente une série d'études explorant les aspects neurocognitifs de la vulnérabilité suicidaire grâce à l'imagerie cérébrale ches des suicidants et des apparentés au premier degré biologique de suicidés. Une revue systématique de la littérature nous a permis de montrer une association entre les actes suicidaires et des modifications structurelles et fonctionnelles dans plusieurs régions du cerveau. Nous avons ensuite examiné plusieurs mesures de neuroimagerie structurelle dans le cortex préfrontal d'un large échantillon de suicidants, et mis en évidence des modifications dans la cortex préfrontal ventrolatéral gauche, indépendamment des troubles de l'humeur. En outre, nous avons montré que le volume du nucleus accumbens était corrélé négativement avec la létalité des actes suicidaires antérieurs, suggèrant que cette région pourrait moduler la façon dont les actes suicidaires sont exécutés. Nous avons ensuite utilisé la neuroimagerie fonctionnelle et la tâche classique de Go-NoGo afin d'examiner l'inhibition cognitive chez les suicidants. Nos résultats suggèrent que les déficits de contrôle cognitif chez les suicidants, associés à l'activation du gyrus frontal inférieur, du thalamus, du cortex orbitofrontal et du cortex pariétal, sont susceptibles d'être des traits plus que liés à l'état. Par ailleurs, nous avons exploré des apparentés de suicidés en utilisant une batterie de mesures cognitives et la neuroimagerie. Nous avons trouvé des déficits de prise de décision, mais pas des déficits de contrôle cognitif, chez ces personnes n'ayant jamais tenté elles-même de se suicider, en comparaison d'apparentés de patients sans antécédents familiaux d'actes suicidaires et de témoins sains. Ces résultats suggèrent que la prise de décision risquée pourrait être un trait transmis au sein des familles tandis que le contrôle cognitif normal pourrait avoir un effet protecteur contre le suicide chez ces individus. En outre, nous avons montré que la prise de décision risquée chez les apparentés de suicidés était associée à une réduction significative de l'activité du cortex préfrontal ventromédian au cours de la prise de décision, et une augmentation de l'activité du precuneus pendant le traitement des choix. Enfin, le traitement des résultats des choix lors de la prise de décision ainsi que le traitement des visages en colère (un proxy pour la menace sociale) ont été associés à une activité modifiée dans le cervelet chez les apparentés de suicidés. Au total, nos résultats soutiennent un rôle important pour le cortex préfrontal ventral (à la fois médial et latéral), mais mettent également en évidence un réseau de régions cérébrales au-delà du cortex préfrontal. Ils

soulignent également l'importance et l'héritabilité potentielle de la prise de décision risquée pour la vulnérabilité suicidaire, et la possibilité que certains déficits cognitifs pourraient être des états alors que d'autres sont des traits. Ces nouveaux résultats élargissent nos connaissances et nous permettent de proposer une mise à jour de notre modèle neurocognitif du suicide.

Title Page

Neuroimaging of Suicidal Behaviour:

A Collection of Recent Studies in Suicide Attempters and Relatives

By

Yang Ding

A thesis submitted to McGill University in partial fulfillment of the requirements of the Doctor of Philosophy Degree in Neuroscience from the Integrated Program in Neuroscience Program 2015

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Dedication

This thesis is dedicated to all the anonymous caregivers providing mental health care.

"Wer mit Ungeheuern kämpft, mag zusehn, dass er nicht dabei zum Ungeheuer wird. Und wenn du lange in einen Abgrund blickst, blickt der Abgrund auch in dich hinein."

"He who fights with monsters might take care lest he thereby become a monster. And when you gaze long into an abyss the abyss also gazes into you."

- Friedrich Wilhelm Nietzsche, *Beyond Good and Evil*, Aphorism 146 (1886).

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List of Abbreviations

Footnotes: Abbreviations used in Table

5HT: serotonin
DA: dopamine
BOLD: blood oxygenation level dependent
MRI: magnetic resonance imaging
T: tesla
CT: computed tomography
ROI: region of interest
SPECT: single-photon emission computed tomography
DTI: diffusion tensor imaging
SC: suicide completers
SA: suicide attempters
SI: suicide ideators
PC: patient controls
HC: healthy controls
MDD: major depressive disorder
TBI: traumatic brain injury
ADHD: attention deficit / hyperactivity disorder
PTSD: post-traumatic stress disorder
MADRS: Montgomery-Åsberg depression rating scale
MCC: multiple comparison correction
HAMD / HDRS: Hamilton depression rating scale
BDI: Beck's depression inventory
YMRS: Young's mania rating scale
PANNS: positive and negative syndrome scale
R: right
L: left
BA: Brodmann's area
vmPFC: ventromedial prefrontal cortex
DLPFC: dorsolateral prefrontal cortex
ACC: anterior cingulate cortex
PCC: posterior cingulate cortex
STG: superior temporal gyrus
SMA: supplementary motor area
OFC: orbitofrontal cortex
GM: gray matter
WM: white matter
WMH: white matter hyperintensities
DWMH: deep white matter hyperintensities
PVH: periventricular hyperintensities

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As researchers, we typically forget to acknowledge the countless physical hours spent by ground work personnel in acquiring the data. Therefore, I must thank **Ms. Alexandra Hoehne, Ms. Annukka Jäkälä, and Ms. Marie-Martin Beaulieu** for their kind support with studies that were conducted at the McGill Group for Suicide Studies. They laid the ground work for the data collection that made my PhD study looks easy. I also thank all of the study participants for their time and effort in withstanding the often long and painful hours inside MRI machines and for enduring hours of endless questionnaires.

To make this thesis and numerous other manuscripts readable for human beings, I would like to thank **Ms. Corina Nagy** for helpful comments and proofreading time. In addition, **Mr. Michael Gollner** has kindly provided additional proofreading to help make this thesis readable.

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Contribution of Author

All of the experimental results and data included in the following section of this dissertation are considered original scholarship and a distinct contribution to human knowledge.

Any elements that are not my original scholarship have been properly attributed to the original authors and their publication sources.

Preliminary data and partial data were previously presented at the 2012, 2013 and 2015 Organization for Human Brain Mapping (OHBM) conferences, 2013 International Academy of Suicide Research (IASR) conferences, 2013 to 2015 Society of Biological Psychiatry (SOBP) conferences.

Chapter 2 reports a book chapter currently in press that will be published in *Neuroimaging markers in mental disorders*, edited by M. Wessa, J. Houenou. Springer.

Chapter 3 reports an article published in Translational Psychiatry (2015).

Chapter 4 and 5 report manuscripts currently in review.

Chapter 1 Introduction

In this introduction, I will give a brief overview of the main findings underlying the hypothesis and methods used in our research.

1.1 Definition

Suicidal behaviour encompasses a number of complex acts, whose definition may differ from one study or one research group to another. According to the revised nomenclature of Self-Injurious Thoughts and Behaviours (Silverman, Berman et al. 2007), we will use the following definitions in the present thesis: **suicide or suicide completion** is defined as any act carried out with some degree of suicidal intent and with fatal outcome; **suicide attempt** refers to any act carried out with some degree of suicidal intent and without fatal outcome, **suicide ideation or suicidal ideas** include thoughts with some level of suicidal intent but without any acting out; **self-harm** is often used to define acts carried out with and without suicidal intent, and it therefore includes **non-suicidal self injuries**.

Suicidal behaviour within the context of this thesis will include attempted and completed suicide but *not* self-harm—since suicidal behaviours are clearly delineated from self-harm behaviours by the intentional component of ending one's life (Silverman, Berman et al. 2007)—or suicidal ideas without acting out.

1.2 Scope of the Problem

According to the Centers for Disease Control and Prevention (CDC) in 2005, suicide has a far-reaching impact. Suicide is among the ten leading causes of deaths worldwide (!!! INVALID CITATION !!! (Hawton and van Heeringen 2009)), accounting for almost one million victims annually (Varnik 2012) and an estimated loss of 20.8 to 36.7 million disability-adjusted life years annually (Murray and Lopez 2013; Wolfram|Alpha 2013). According to the CDC 2010 Cost of Injury Report,[1] the overall financial cost per suicide has been estimated at

[1] Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. Web-based Injury Statistics Query and Reporting System (WISQARS).

$1,164,499 US dollars, and the annual combined cost for cumulative lost years of productivity from suicide is approximately $44.6 billion US dollars in the United States alone, a substantial increase over the 5 to 8 billion dollars estimated previously (Wyatt and Henter 1995; Greenberg, Kessler et al. 2003). Suicide not only leads to individual suffering, with families and friends left with grief and unbearable questions, but it also represents a significant financial burden to society.

Unfortunately, we currently lack effective prediction and prevention strategies (Mann, Currier et al. 2006). Suicide risk currently relies on the sole assessment of multiple socio-demographic and clinical risk factors, a method with relatively poor predictive power (Pokorny 1983; Goldstein, Black et al. 1991; Mann and Currier 2007). Improving our understanding of this preventable yet complex behaviour is therefore important. The identification of neurobiological markers and improved models for suicidal behaviour may provide more precise predictive markers and enable us to develop more efficient preventative interventions.

1.3 The Stress-Diathesis Model of Suicidal Behaviour

Suicide is commonly thought of as the tragic end of a severe mental disorder. This is supported by epidemiological studies revealing significantly increased likelihood of suicide among many psychiatric disorders, including but not limited to major depression, bipolar disorder, schizophrenia, substance abuse, and Cluster B personality disorder (Arsenault-Lapierre, Kim et al. 2004; Dumais, Lesage et al. 2005; McGirr, Paris et al. 2007; Hawton and van Heeringen 2009). Moreover, psychological autopsies, through proxy-based interviews and medical file assessment, reported the existence of mental disorders in more than 90% of cases of suicide (Isometsa 2001). However, it has also been shown that more than 90% of individuals with mental disorders will never commit suicide (Bostwick and Pankratz 2000), suggesting that a mental disorder alone is not a sufficient condition for suicide. Additional factors are necessary and suicidal behaviour is inherently multifactorial.

Over the past decade, a stress-diathesis model (Mann JJ 2003), similar to other fields of medicine (Hankin and Abela 2005) has been proposed to explain suicidal behaviour. This model postulates the existence of a vulnerability to suicidal acts with genetic and early developmental components (notably childhood abuse) interacting with proximal stressful events—e.g. negative social events like marital conflict or job loss, depression and other acute states of a mental disorder or alcohol abuse (Mann 2003)—to increase the risk of suicide. At the clinical level, this vulnerability is revealed in an increased suicidal risk in individuals with personality traits like impulsive-aggressiveness in adolescents and young adults, or in the propensity toward hopelessness and pessimism (Turecki 2005). Another argument is the demonstration that a past personal history of a suicidal act is significantly associated with an increased risk of future suicide completion (Horwitz, Czyz et al. 2015).

The earliest and most replicated known biological risk factor associated with suicidal acts is low 5-Hydroxyindoleacetic acid (5HIAA) levels, the main metabolite of serotonin, in cerebrospinal fluid (Asberg, Traskman et al. 1976; Nordstrom, Samuelsson et al. 1994). In addition, 5HIAA levels are relatively stable at adult age (Higley, King et al. 1996), which supports the idea of persistent, trait-like alterations. Another important biological alteration is the hyper-reactivity of the Hypothalamo-Pituitary Axis (HPA), one of the main systems supporting stress responses (Mann and Currier 2007). Studies have shown a lack of response suppression after dexamethasone intake in patients who ultimately died from suicide. Both low 5HIAA and poor response to the dexamethasone suppression test have been associated with a 4.5 times greater risk of death from suicide among individuals with mood disorders (Mann and Currier 2007). The vulnerability to suicidal acts would therefore be underlied by 1) a deficient modulation of the serotonergic system, a system implicated in homeostasis and various cognitive processes, and 2) a hypersensitivity of the HPA stress axis.

Subsequent studies have explored the biological aspects of suicidal diathesis using a variety of approaches. For instance, post-mortem brain bank tissue extracts from suicide completers vs. non-clinical populations have revealed cellular alterations including astrocytic hypertrophy (Torres-Platas, Hercher et al. 2011) and glial cell

density alterations in the anterior cingulate cortex of suicide completers with alcohol dependence (Hercher, Parent et al. 2009), genetic and epigenetic alterations (Guipponi, Deutsch et al. 2009), or spermine synthase and oxidase (Fiori and Turecki 2010), among other factors. Detailing these findings would go beyond the scope of this thesis. However, these findings point toward brain deficits associated with the risk of suicide, some of which support the concept of a specific suicidal vulnerability.

1.4 A Neurocognitive Perspective on Suicidal Acts

Over the last 10 years, several groups have investigated the neurocognitive basis of the vulnerability to suicidal acts in suicide attempters (Jollant, Lawrence et al. 2011). Neuro-cognition lies at the interface between psychological and biological mechanisms. There has been increasing interest in understanding suicidal behaviour in terms of cognitive processes using neuropsychology and neuroimaging. We will summarize below some of the most important findings.

1) **Risky decision-making,** assessed using economic tasks like the Iowa Gambling Task or the Cambridge Gamble Task, has been found in suicide attempters (Jollant, Bellivier et al. 2005; Clark, Dombrovski et al. 2011), notably those who used violent suicidal means (Jollant, Bellivier et al. 2005). This finding was recently confirmed by a meta-analysis of nine studies using the Iowa Gambling Task (Richard-Devantoy, Berlim et al. 2013). Importantly, risky decision-making has been found in euthymic (i.e. no longer depressed) suicide attempters, which suggests trait-like features (Jollant, Bellivier et al. 2005). Impaired decision-making has been related to genetic variants associated with the serotonergic system (Jollant, Buresi et al. 2007). Moreover, disadvantageous decision-making has been correlated with interpersonal difficulties, suggesting that this may also contribute to classical triggers of suicidal crisis (Jollant, Lawrence et al. 2008). Also, there is no clear argument for a link between risky decision-making and a clinical impulsivity-trait (as measured with questionnaires) in suicide attempters (Jollant, Guillaume et al. 2007), which suggests that disadvantageous decision-making is not directly related to impulsive choices in this population. Risky decision-making in suicide attempters has also been related to a decreased response of the ventrolateral prefrontal cortex during

risky options (Jollant, Lawrence et al. 2010) and to a decreased response of the ventromedial prefontal cortex during reward prediction (Dombrovski, Szanto et al. 2013). This suggests a major role for deficient valuation processing. Recently, social decision-making has started to be investigated with the Ultimatum Game (Szanto, Clark et al. 2014), which has demonstrated an inability of high-lethality attempters to modulate their decisions in an unfair context.

2) **Deficits in cognitive control** have also been reported in suicide attempters (Richard-Devantoy, Jollant et al. 2012), notably in terms of **higher sensitivity to interference** (Richard-Devantoy, Berlim et al. 2013) and in the context of verbal fluency. Among retrospective psychological autopsy study of suicide completers, most studies suggest such deficit may be more prominent in certain age or gender groups(Richard-Devantoy, Jollant et al. 2012). Our preliminary results have not been able to cognitive control deficits among healthy first degree relative of suicide completers (Hoehne, Richard-Devantoy et al. 2015) suggesting this may be a more proximal and state like risk factor to suicidal behaviour. More explorations of deficient cognitive control are needed in the context of suicidal behaviour, and we will later present the first neuroimaging study of cognitive inhibition in suicide attempters and an assessment of cognitive inhibition in relatives of suicide completers.

3) Suicide attempters tend to show more **memory deficits**, from working memory to long-term memory and more general autobiographical memory. This was confirmed by a recent meta-analysis conducted by our group (Richard-Devantoy, Berlim et al. 2015). These various deficits may underlie distinct disturbances. For instance, working memory is an important component of cognitive control, enabling one to maintain online information needed to execute a task (Richard-Devantoy, Olié et al. 2013). Reduced autobiographical and long-term memory may particularly impact the ability to solve problems as past experience is usually important for complex problems.

4) Finally, euthymic suicide attempters showed altered brain responses to angry faces in the orbitofrontal cortex and cerebellum (Jollant, Lawrence et al. 2008; Olie, Ding et al. 2015). Suicide attempters may therefore present a particular **sensitivity to signals of social threat**.

We are far from understanding the pathways linking neurocognitive deficits and the risk of suicidal acts. However, our current neurocognitive and neuroimaging analytical approach is an attempt to go beyond limited clinical observations and patients' introspections. Data presented in this thesis relies on this approach and contributes to the identification or validation of particular neurocognitive impairments in individuals at-risk of suicide. We focused in particular on two populations: 1) suicide attempters, as they are at increased risk of suicide completion and can be distinguished from patients with no personal history of suicidal act, and 2) relatives of suicide completers, for reasons explained below.

1.5 Heritability of Suicide Diathesis and the Concept of Endophenotype

The heritability of suicidal behaviour has been established through family, twin and adoption studies (Brent and Mann 2005). It is estimated that the heritability of suicide reaches 20% when accounting for comorbid disorders. Importantly, transmission of these behaviours seems to correlate more with personality traits than with mental disorders. Beyond personality traits, it has been suggested that biological traits could be transmitted within families, which brings up the notion of endophenotypes (Courtet, Gottesman et al. 2011). The endophenotype concept is useful for identifying and quantifying genetically-influenced biological traits. Practically, in the context of suicide, endophenotypes are defined as state-independent, heritable traits that highly co-segregate with suicidal behaviour and that are found in elevated proportion among non-affected members within families of suicide completers. Endophenotypes may shed light on important biological traits of vulnerability, and therefore improve our understanding of the mechanisms of suicidal behaviour genesis. Some of the aforementioned neurocognitive traits could potentially qualify as endophenotypes. This is particularly the case for impaired decision-making and sensitivity to social threat, both found in euthymic suicide attempters. This will be the focus of studies run in close biological relatives of suicide completers and that will be presented in the following chapters.

1.6 Hypotheses and Objectives

Suicide is a complex phenomenon that requires multi-disciplinary approaches. The focus of this PhD thesis is to apply an *in vivo* neuroimaging approach to improve our understanding of the neurocognitive deficits associated with suicidal behaviour. To this end, we have investigated both suicide attempters and first-degree biological relatives of suicide completers, which is a relatively new approach in the neurocognitive domain. To reach this general objective, we have examined the structural and functional alterations, as measured by neuroimaging, that may exist among relatives of suicide completers and among suicide attempters. We have had the chance to access data from five different studies conducted by Dr. F. Jollant in Montreal (Canada), London (UK) and Montpellier (France), and to run structural and functional analyses.

One specific objective will be to validate impaired decision-making as an endophenotype of suicidal behaviour. Our specific hypotheses postulate that healthy suicide relatives, who themselves never attempted suicide, exhibit riskier decision-making compared to both patient relatives and healthy controls. These behavioural impairments will be associated with abnormal functional brain activation during the decision-making task, notably in the ventral prefrontal cortex. In the same population, we will also assess responses to emotional faces previously described in suicide attempters. We hypothesize that this population will show a similar sensitivity to social threat. We will therefore have a large perspective on cognitive and emotional traits that may be heritable, which will allow us to identify potentially protective traits and confirm vulnerability traits. Moreover, we will also validate in a large sample of suicide attempters structural brain alterations previously found in the prefrontal cortex, and we will examine subcortical structures. Finally, in an attempt to continue the dissection of the neurocognitive components of suicidal behaviour, we have participated in the analyses of a neuroimaging study investigating cognitive inhibition in suicide attempters.

Each chapter within the thesis is dedicated to one article investigating specific aspects of suicide-related neuroimaging and neurocognitive alterations. First, we conducted a comprehensive review of neuroimaging literature related to suicidal behaviour (Chapter 2) to highlight the current understanding of the neurocognitive

and neuroanatomical bases of suicidal behaviour. This also allowed us to develop an online and free review database (http://bdsuicide.disten.com) that contains the latest breakdown of neuroimaging studies in suicide behaviour. Next, using data already collected in two European samples, we explored potential prefrontal structural alterations as potential markers of suicidal vulnerability in mood disorders using multiple analytical approaches that have never been done before (Chapter 3). We have also contributed to a study that investigated subcortical alterations in the same sample (7.2.1) and the brain response to cognitive control in depressed suicide attempters recruited in Montreal (7.2.3). Lastly, we will present findings from the first ever functional neuroimaging study in healthy first-degree relatives of suicide completers with respect to their behavioural performance (7.2.2), brain response during decision-making (Chapter 4), and during the social challenge (Chapter 5).

Chapter 2 Review of Literature: Neurocognitive Basis of Suicidal Behaviour

2.1 Introduction: A Stress-Diathesis Model of Suicidal Behaviour

Suicide is among the ten leading causes of death worldwide (2009) accounting for almost one million victims annually and a significant loss of life-years at the societal level (Murray and Lopez 2013). The current assessment of suicide risk primarily relies on assessments of multiple socio-demographic and clinical variables with relatively poor predictive power. Improving our understanding of this preventable yet complex behaviour is necessary.

Suicide is especially elevated among those with mental disorders. Epidemiological studies have revealed significantly increased likelihood of suicide among many psychiatric disorders, including but not limited to major depression, bipolar disorder, schizophrenia and borderline personality disorder (Skodol, Gunderson et al. 2002; Arsenault-Lapierre, Kim et al. 2004; Hawton and van Heeringen 2009). Moreover, post-mortem studies reported the existence of mental disorders in more than 90% of cases of suicide (Isometsa 2001). However, more than 90% of individuals with mental disorders will never commit suicide (Bostwick and Pankratz 2000), which suggests that a mental disorder is not a sufficient condition for suicide. Additional factors must be in play. At the clinical level, personality traits, most notably impulsive aggressive traits in younger adults, have been associated with an increased risk of suicide (Dumais, Lesage et al. 2005). Interestingly, family, twin and adoption studies have established that suicidal behaviour is heritable (Brent and Mann 2005), but transmission of these behaviours seems to correlate more with personality traits than with mental disorders.

These data and others support a stress-diathesis model, which postulates a vulnerability to suicidal acts with genetic and early developmental components (including childhood abuse) interacting with proximal stressful events, such as negative social events like marital conflict or job loss, depression or alcohol abuse (Mann 2003).

This lower ability to respond adequately to stress is also underlined by numerous studies showing deficient cognitive functioning, notably disadvantageous decision-making (Jollant, Bellivier et al. 2005; Richard-Devantoy, Berlim et al. 2013) or reduced cognitive inhibition (Richard-Devantoy, Gorwood et al. 2012). Decision-making deficits have been found in normothymic patients at a distance from their suicidal act in comparison to patient controls (i.e. patients without suicidal behaviour but share the same comorbidity pattern), which suggests this represents a cognitive marker of suicide vulnerability.

Over the past decades, a variety of studies have been conducted to support the concept of vulnerability at the neurobiological level, ranging from biochemical (Mann and Currier 2007) to genetic/epigenetic (Brent and Mann 2005; Fiori and Turecki 2010) and cell morphological studies (Hercher, Parent et al. 2009; Hercher, Turecki et al. 2009; Torres-Platas, Hercher et al. 2011). The earliest and most replicated known biological risk factor associated with suicidal acts is low 5-Hydroxyindoleacetic acid (5HIAA) levels, the main metabolite of serotonin, in cerebro-spinal fluid (Nordstrom, Samuelsson et al. 1994). Subsequent studies in this area have also investigated serotonergic alterations in post-mortem studies (Mann, Huang et al. 2000) and the genetics of serotonin synthesis mechanisms (e.g. tryptophan hydroxylase) and transportation (e.g. serotonin transporter) (Courtet, Picot et al. 2004; Courtet, Jollant et al. 2005) (see below for pharmacological neuroimaging studies). The general hypothesis derived from these findings is a deficient modulation of the prefrontal cortex and other brain regions by the serotonergic system, an alteration that may possess some trait-like characteristics including long-term stability and could underlie clinical and cognitive traits including a higher propensity for impulsivity (Booij, Swenne et al. 2006) or risky decision-making (Jollant, Buresi et al. 2007).

Hypothalamic-Pituitary-Adrenal (HPA) axis sensitivity has also been implicated in suicidal behaviour (Dwivedi and Coryell 2012). Recent data suggests that the HPA response is also increased during an inhibition task in relatives of suicide completers (McGirr, Diaconu et al. 2010) revealing another heritable biological trait. Serotonergic and HPA systems may synergistically contribute to suicidal behaviour (Caspi, Sugden et al. 2003).

Finally, a dynamic field of current research aims at investigating how life events may modulate genetic expression through epigenetic mechanisms (Turecki, Ernst et al. 2012). Early findings suggest that childhood abuse may have long-term brain effects in suicide victims, particularly alterations of the expression of receptors of the glucocorticoid system in the hippocampus (McGowan, Sasaki et al. 2009).

Post-mortem studies examining the brains of suicide completers and neuropsychological and neuroimaging studies of suicide attempters are currently the focal point of studies that are increasing our understanding of suicidal vulnerability. Neurobiological research generally suggests a model of vulnerability to suicidal behaviour that includes a defective emotional and cognitive processes associated with a sensitive stress system (e.g. HPA axis) that may partly result from the long-term effects of childhood abuse (at least in younger individuals) and genetic factors. In the next chapters, we will review the neuroimaging literature and examine how these studies shed light on the mechanisms of suicidal vulnerability.

2.2 Review of Neuroimaging Studies of Suicidal Behaviour

2.3 Search Process

Neuroimaging studies related to suicidal behaviour up to November 2013 have been included in this review. An OvidMedline portal search with the Medical Subject Heading (MeSH) keywords “suicide” and “neuroimaging” yielded 66 articles. Of these, 13 original articles related to suicide research were retained. A Scopus portal search with the same keywords yielded 256 articles, of which 32 original articles related to suicide research were retained. Additional articles identified from article references and from our own publicly accessible online database (http://www.bdsuicide.disten.com) were added. Single case reports, duplicated reference entries, commentaries, editorials, conference abstracts, unpublished studies, and reviews were not included. We only evaluated articles written in English or Chinese. We selected studies involving at least one of the following groups: suicide ideators (SI), who have seriously thought about suicide but never carried out any act; suicide attempters (SA), who have actually carried out an act with “some” intent to die; suicide completers (SC), who eventually committed the act of suicide and died. Of all selected studies, most focused

on either SA or mixed SA/SI with two studies examining only SC before their eventual suicide. Non-suicidal self-injury (i.e. self-harm) was not included in this review unless the article showed a significant number of SI or SA. Articles were reviewed by all the authors.

In the end, 69 studies were retained. We broke down the major categories of the neuroimaging studies that explored patients with suicidal behaviour in the following way: functional studies (**Table 1**), pharmacological studies (**Table 2**) and structural studies (**Table 3**). Thirty-eight studies investigated structural changes (including eight studies examining whole brain volumetry and morphometry, 15 studies examining region of interest volumetry and morphometry, white matter lesions in eight studies or white matter connectivity in five studies, and two studies using very novel methodologies). Functional alterations (using MRI, PET or SPECT) utilizing various tasks were assessed in 21 studies and pharmacological binding in 13 studies. The majority of studies were conducted in young and middle-aged adults (n=53) and only eight were conducted in adolescents/children and eight in the elderly.

2.4 Limitations

Some common limitations that apply to these studies have to be mentioned. A series of studies investigated the same population, resulting in a potential overall literature bias from a single dataset. Second, as it is frequently the case in neuroscience (Button, Ioannidis et al. 2013), many studies are underpowered and should consequently be carefully interpreted considering both Type 1 (with a risk of excessive effect size) and Type 2 (with the risk of false lack of association) errors. In addition, some results may largely rely on analysis methods used (Focke, Helms et al. 2011) or choice of various (often lenient) threshold. Very few studies applied multi-modal approaches. Third, few studies used the exact same methods and thus cannot be considered true replications. Fourth, definitions of suicidal behaviour vary, a classical issue in the suicide field. Fifth, not all groups included psychiatric comorbidity controls without any history of suicidal acts to control for the effect of related co-morbid disorders. Also, some studies did not clearly delineate a life time history of psychiatric disorders or current psychiatric disorders, or the delay since last suicidal act. Finally, few studies only

investigated one gender while most included both males and females with the classical difficulty to detect gender specific differences in secondary analyses.

2.5 Results

2.5.1 Pharmacological neuroimaging: linking brain and biochemistry *in vivo*

Three independent studies examined the receptor 5HT2A binding with various results. Relative to healthy controls, Soloff et al (2007) suggested increased binding in hippocampus, medial temporal cortex, occipital cortex, and lateral orbitofrontal cortex (OFC) in SA with borderline personality disorder. However, Audenaert (2001) and Van Heeringen et al. (2003) suggest decreased binding potential in dorsolateral prefrontal cortex (DLPFC) in SA with major depression. Meyer et al. (2003) did not report any significant differences. Only one study included patient controls (PC) (Soloff, Price et al. 2007), and no differences between SA and PC were reported.

Six independent studies investigated serotonin transporter binding potential (5HTT BP) with most positive findings implicating either the midbrain or anterior cingulate cortex (ACC). Although the latest results (Nye, Purselle et al. 2013) suggested an increase in 5HTT BP in midbrain/pons and putamen area in SA relative to HC, previous results showed conflicting findings. Parsey et al. (2006) reported a conflicting decrease in 5HTT BP in SA vs. HC in midbrain and amygdala among depressed patients, while Nye et al. (2013) and Cannon et al. (2006) both observed a 5HTT BP reduction in midbrain in SA relative to both PC and HC. As for ACC, two studies conducted by Cannon et al. (2006; 2007) found increased binding in anterior cingulate cortex (ACC) in SA, mostly compared to PC. However, Oquendo et al. (2007), Lindstrom et al. (2004) and Ryding et al. (2006) did not find any significant differences in SA relative to mostly HC control groups. Lastly, several studies (Cannon, Ichise et al. 2007; Oquendo, Hastings et al. 2007; Bah, Lindström et al. 2008) examined serotonin transporter polymorphisms and suggested an association between specific alleles (e.g. S allele of 5-HTTLPR and 12 repeat allele of STin2) and lower 5HTT BP in multiple brain regions in a subset of SA reported previously (Lindström, Ryding et al. 2004; Ryding, Ahnlide et al. 2006).

Finally, only one study (Leyton, Paquette et al. 2006) evaluated serotonin synthesis by examining radioligand trapping in serotonin synthesis pathways. The study found decreased serotonin synthesis in the medial OFC and increased synthesis in the right paracentral lobule, left thalamus, left middle occipital cortex, and left hippocampal gyrus. Again, without PC, it is difficult to discern the precise impact of depression comorbidity and suicide unique alterations. Taken together, reduction in midbrain and ACC 5HTT BP might be the most prominently suggested results based on the existing studies. However, this effect is not perfectly replicated or delineated, so it may be more attributable to the effect of depression, as suggested by Parsey et al. (2006), with elevated differences between SA and HC. Overall, the support for a deficient serotonergic system in suicidal vulnerability in pharmacological neuroimaging studies is relatively weaker compare to HIAA studies. However, this could largely be related to limitations in the design and power of the studies and the different ligands used in each studies.

2.5.2 Functional neuroimaging: linking brain, cognition and behaviour

According to the latest meta-analyses and review, a series of replicated neuropsychological deficits has been demonstrated in patients with suicidal behaviour compared to controls (Richard-Devantoy, Berlim et al. 2013). Notable deficits include disadvantageous decision-making (mainly measured by the Iowa Gambling Task) and reduced verbal fluency and cognitive control. The evidence of cognitive inflexibility (as tested by the Wisconsin Card Sorting Test) among first degree euthymic relatives of suicide completers (McGirr, Jollant et al. 2013) further strengthens the plausibility of some cognitive deficits being heritable. Moreover, it has been reported that decision-making deficits and deficient cognitive control do not show a strong correlation (Richard-Devantoy, Olié et al. 2013), which suggests that they may synergistically, yet independently, contribute to suicidal behaviour.

The advent of wider applications of MRI within the past two decades has complemented earlier PET/SPECT functional studies by providing enhanced temporal and spatial localizations (Huettel, Song et al. 2009) of specific functional alterations that may be associated with aforementioned suicidal vulnerabilities.

2.5.2.1 Impaired decision-making

Impaired decision-making is one of the most replicated deficits observed among SA from adolescents (Bridge, McBee-Strayer et al. 2012) and adults (Jollant, Bellivier et al. 2005) to the elderly (Clark, Dombrovski et al. 2011). Two recent studies specifically examined decision-making processes in SA using the identical fMRI-modified Iowa Gambling Task (Lawrence, Jollant et al. 2009). Jollant et al. (2010) observed a net score difference between SA and both control groups. Using a region of interest (ROI) approach, the studies showed a reduced activation in the left lateral OFC and occipital cortex in SA compared to PC in the contrast between risky and safe choices. This contrast was correlated with final performance suggesting a significant role of risk encoding in the OFC in modulating choices in this population. This result has been partly replicated (with a more medial part of the OFC) in an independent study (Olie, Ding et al. 2015). Overall, the OFC seems to play a major role in disadvantageous decision-making in SA, possibly through a deficient ability to valuate abstract risk.

A study in adolescent SA was not able to show the same effect, most likely because most adolescent participants were unable to finish the latter portion of the task. A different contrast was examined that looked at risky choices or safe choices alone and their respective activation differences across adolescent groups. The authors reported reduced activation in the right thalamus of SA in risk choices compared to PC and increased activity in the left caudate compared to HC. However, the lack of data regarding the last part of the task when preferences are formed limits the interpretation of these findings.

2.5.2.2 Reduced cognitive control/inhibition

Dombrovski et al. (Dombrovski, Szanto et al. 2013) evaluated reversal learning in an elderly population. They observed a lack of response to expected reward in the medial OFC. Matthews et al. (2012) utilized a stop signal task to demonstrate elevated activity among suicide ideators in the bilateral DLPFC and supramarginal gyrus during error trial, in addition to the left ACC, precentral, and superior temporal regions. In an adolescent population, Pan et al. (2011) observed a reduced activation in the right ACC in SA relative to PC during the

classical Go-NoGo inhibition task. Willeumieur et al. (2011) and Amen et al. (2009) retrospectively examined motor inhibition in individuals who later committed suicide using the continuous performance task. They observed global perfusion reduction in SC relative to HC with a much smaller reduction in SC relative to PC, which suggests mainly a decreased activation in the left DLPFC, right temporal, parietal regions and a potential increase only in the right ACC, cerebellar and occipital regions in SC.

The most commonly implicated regions, therefore, involve both the DLPFC and ACC. A plausible but preliminary explanation based on an earlier experiment examining cognitive control in HC suggests that the DLPFC may be more implicated in the implementation of control neural networks, while the ACC may be more involved with error detection and resolution related brain circuit (MacDonald, Cohen et al. 2000). It is vital to mindful of the limitation with regard to the imaging paradigms and the findings does not preclude these regions from being part of other neural networks underlying other cognitive facilities. Findings may be more indicative of key common vulnerable nodes underlying multiple cognitive processes.

2.5.2.3 Higher sensitivity to social rejection and mental pain

Previous models of suicide have underscored the central role of mental pain in the suicidal process (Olie, Guillaume et al. 2010). In addition, a higher sensitivity to social rejection is suspected from the high frequency of personality disorders among suicide victims. Reisch et al. (2010) explored the neural basis of mental pain in female SA using individualized suicide related scripts. They observed reduced activity in the medial prefrontal cortex (PFC) in suicide and mental pain scripts and increased activation in the parahippocampal gyrus, occipital, temporal regions and cerebellum. Jollant et al. (2008) conducted a simple gender identification task based on Ekman faces and noted an increased activation in angry (but not happy) vs. neutral faces in SA relative to PC in the right lateral OFC, cerebellum and a decrease in the right frontal gyrus. Pan et al. (2013) used the same task in adolescents and reported stronger activation in the right ACC and temporal regions in response to less intense angry faces in SA vs. PC and reduced connectivity to insular regions compared to both control groups.

Of note, both studies using Ekman's faces found increased activations in regions that have been implicated in value attribution (OFC) and conflict monitoring (ACC) and, more generally, in social rejection (Eisenberger, Lieberman et al. 2003). Mental pain may also be related to dorsomedial PFC processing.

2.5.2.4 Reduced verbal fluency

Two studies (Audenaert, Goethals et al. 2002; Oquendo, Placidi et al. 2003) looked at verbal fluency in SA, with Oquendo et al. comparing high vs. low lethality attempters at rest, while Audenaert et al. compared SA to HC during performance of the verbal fluency task. Even though both studies did not use the same methodology, they suggest similar findings of decreased regional perfusion in DLPFC and ACC regions. Oquendo et al. found a greater decrease among higher lethality SA, with the activity of these regions positively correlated to task performance. Audenaert et al. noted that ACC activity was decreased in SA compared to HC during both categorical and letter fluency task.

2.5.2.5 Correlation with suicidal lethality and intent

Oquendo et al. (2003), in a resting state PET study, found activity in dorsomedial and dorsolateral PFC regions to be correlated with suicidal intent and lethality. This was partially replicated by Sublette et al. (2013) from the same group that showed a negative correlation between the right medial OFC, DLPFC with suicide intent. Interestingly, analyses showed that lethality was mediated by both impulsivity (negatively) and intent (positively). In addition, both studies suggest that reduced activity in SA was exacerbated by fenfluramine challenge, suggesting a role for serotonin modulation. Overall, while replication is needed, it is suggested that dorsal PFC plays a role in forming suicidal intent and processing action.

2.5.2.6 Other functional neuroimaging studies

One research group has replicated studies using an identical motor activation task in mood disordered patients (Marchand, Lee et al. 2011; Marchand, Lee et al. 2012; Marchand, Lee et al. 2013; Marchand, Lee et al. 2013). Given the application of an identical task paradigm and similar study designs, they replicated findings in

suicidal behaviour associated with putamen activities, and implication of altered functional connectivity of precentral gyrus to globus pallidus, DLPFC and posterior cingulate cortex (PCC).

Divergent findings have been reported using multiple modalities to evaluate resting state activity and perfusion. Foutoulakis et al. (2004) noted no differences with PC in the elderly, while Amen at al. (2009) observed widespread reduction in perfusion rates during resting state. Soloff et al. (2000) also noted reduced perfusion in multiple regions including temporal, frontal and insular regions. Sublett et al. (2013) replicated the previous findings of Oquendo et al.(2003) that showed an exacerbated response in the DLPFC and reduced hyperperfusion in the left vmPFC, ACC when comparing SA with PC after fenfluramine challenge. Fan et al (2013) revealed the amplitude of low-frequency fluctuation in ventromedial PFC uniquely reduced in SA compared to PC.

Very few studies have explored effective connectivity between anatomical regions. The only study that has achieved that in the context of suicidal neuroimaging studies is Zhang et al. (2013) which revealed altered connectivity between medial PFC and PCC. This area of research exploring network properties of the brain regions is expected to reveal more interpretable findings as we shift our paradigm from regional specialization to network performance.

2.5.3 Structural neuroimaging: “simple” markers of suicidal behaviour?

Another major area in neuroimaging exploration is structural neuroimaging. Although functional neuroimaging may be very informative, these studies often utilize complicated tasks to predict the risk of suicide in a given patient, although these tasks may not be easily implemented in future clinical practice. Structural MRI offers a potentially interesting alternative tool to detect predictive markers in addition to revealing brain regions associated with suicidal acts.

2.5.3.1 Volumetric / surface

A number of studies have explored volume differences, frequently after accounting for global brain sizes (e.g. via modulation in VBM or co-varying for brain size). The OFC has shown relatively consistent gray matter volume reduction in several studies and different populations compared to control groups. In five of the eight whole brain volumetric and morphometric neuroimaging studies, reduced OFC gray matter (GM) volume in SA was found in schizoaffective (Giakoumatos, Tandon et al. 2013), depressed (Wagner, Koch et al. 2011; Wagner, Schultz et al. 2012), schizophrenic (Aguilar, Garcia-Marti et al. 2008) and bipolar (Benedetti, Radaelli et al. 2011) patients. Also, for every study that included the OFC as a region of interest in their ROI analysis, it was possible to show a significant difference between SA and PC: from high-lethality attempters (Soloff, Pruitt et al. 2012), current SI (Caplan, Siddarth et al. 2010), to depressed SA (Monkul, Hatch et al. 2007). Only one study (Rüsch, Spoletini et al. 2008), which evaluated white matter (WM), observed elevated bilateral posterior OFC volume.

Another key region that has been consistently replicated is the DLPFC, whose volume has been frequently reported to be reduced in SA compared to PC (Benedetti, Radaelli et al. 2011; Wagner, Schultz et al. 2012; Giakoumatos, Tandon et al. 2013). However, the only ROI analyses that involved DLPFC did not report significant differences between SI and PC (Caplan, Siddarth et al. 2010). This could potentially suggest that DLPFC is a more reliable indicator of suicide attempt than suicide ideation.

Three of the whole brain studies also reported ACC alterations (Benedetti, Radaelli et al. 2011; Wagner, Koch et al. 2011; Wagner, Schultz et al. 2012). However, of the three ROI studies that examined the ACC (Matsuo, Nielsen et al. 2010; Goodman, Hazlett et al. 2011; Soloff, Pruitt et al. 2012), only Goodman et al. reported reduced GM volume between a mixed group of SA and patients who self-harmed and HC.

Finally, temporal regions, although more broadly and less clearly defined (potentially bordering superior temporal and supramarginal temporal junctions) have been implicated in several whole brain studies (Hwang, Lee et al. 2010; Benedetti, Radaelli et al. 2011; Wagner, Schultz et al. 2012; Giakoumatos, Tandon et al. 2013),

which showed reduced volume compared to PC. Caplan et al. (2010) is the only ROI study that examined temporal regions and showed elevated GM volume in the temporal lobe of patients with epilepsy.

Overall, findings in OFC, DLPFC and ACC seem the most robust with a transnosographic feature.

2.5.3.2 Diffusion tensor imaging

Jia et al. (2010; 2013) noted significant regional differences in WM in the anterior limb of the internal capsule and subsequently linked this alteration to reduced projection to both the thalamus and OFC. This corresponds well with Mahon et al.'s report of reduced diffusivity in the OFC of SA (2012) and Lopez-Larson et al.'s report of increased thalamic volume and increased diffusivity alteration (2013). However, the different directions in diffusivity are not well understood. Yurgelun-Todd et al. (2011) focused on L genu and cingulum ROIs and observed a reduction of fractional anisotropy in SI compare to HC.

2.5.3.3 Lesion studies

White matter lesion (WML) studies have shown elevated frequencies of lesions in SA vs. PC. These lesions were even found to predict future suicidal acts in elderly depressed patients (Sachs-Ericsson, Hames et al. 2013). The hyperintensities found on T2 sequences mainly concern periventricular (Ehrlich, Noam et al. 2003; Ehrlich, Noam et al. 2004) and deep white matter hyperintensities (Lopez, Becker et al. 1997; Ehrlich, Breeze et al. 2005). The exact role of these lesions is not clear, although connectivity alterations are suspected.

2.6 Discussion

2.6.1 A synthesis of current findings

In this review, we highlighted a variety of changes found in patients with histories of suicidal behaviour across diverse comorbidities (yet mainly mood disorders), neuroimaging modalities, and paradigms. These studies globally support the stress-diathesis model described in the introduction by highlight numerous anatomical, functional and pharmacological findings suggesting trait/diathesis like alterations uniquely exhibited among suicidal populations. This adds interesting new directions for the understanding of these complex behaviours.

Several cognitive domains were found to exhibit potential deficits in preliminary functional neuroimaging studies, namely decision-making, cognitive control, social rejection sensitivity and verbal fluency. Brain regions implicated were mainly the OFC, DLPFC and ACC (and several other regions including the temporal cortex and sub-cortical nuclei).

The OFC has been associated with serotonin alterations both in terms of synthesis (Leyton, Paquette et al. 2006) and receptor binding (Soloff, Price et al. 2007) in *in vivo* pharmacological neuroimaging studies. In addition, several structural neuroimaging studies have shown gray matter impairments (Monkul, Hatch et al. 2007; Aguilar, Garcia-Marti et al. 2008; Benedetti, Radaelli et al. 2011; Soloff, Pruitt et al. 2012; Wagner, Schultz et al. 2012; Giakoumatos, Tandon et al. 2013) with arguments for transnosographic features. Some studies also revealed white matter alterations in both regional and diffusion approaches (Caplan, Siddarth et al. 2010; Mahon, Burdick et al. 2012; Jia, Wang et al. 2013). There is also a preliminary report of resting state differences (Fan, Wu et al. 2013). Finally, functional imaging has linked this region to risky decision-making (Jollant, Bellivier et al. 2005; Jollant, Lawrence et al. 2010) and deficits in processing negative social feedback (Jollant, Lawrence et al. 2008; Richard-Devantoy, Guillaume et al. 2013), further reinforcing our earlier assumption (Jollant, Lawrence et al. 2011) about a role for this region in deficit of value attribution to social feedback and risk in SA.

As for DLPFC, its decreased serotonin receptor binding (Audenaert, Van Laere et al. 2001; Van Heeringen, Audenaert et al. 2003) is supported by multiple structural neuroimaging studies (Benedetti, Radaelli et al. 2011; Wagner, Schultz et al. 2012; Giakoumatos, Tandon et al. 2013). Functional studies further suggest that DLPFC plays a significant role in cognitive control and verbal fluency. The decoupling of cognitive inhibition and decision-making (Richard-Devantoy, Olié et al. 2013) suggests their independent (and potentially synergistic) contribution to suicidal risk, and this is congruent with the observation that the ventral and dorsal PFC serve different functions, notably value-based decision-making and cognitive control (Glascher, Adolphs et al. 2012).

Lastly, we also observed serotonin transporter alterations in the ACC as well as gray matter alterations (Cannon, Ichise et al. 2006; Cannon, Ichise et al. 2007; Benedetti, Radaelli et al. 2011; Wagner, Koch et al. 2011; Wagner, Schultz et al. 2012). The ACC has traditionally been associated with error monitoring (MacDonald, Cohen et al. 2000). Its alteration in cognitive control tasks, verbal fluency tasks and social emotional processing suggests it may play a role in higher order process monitoring. The ACC may integrate and resolve conflicts (Bush, Vogt et al. 2002) from multiple inputs including both the OFC (where social and risk emotional weighting are applied to stimuli) and DLPFC (where inhibitory signals mainly come from). One possible role of the OFC could be to provide a very raw unfiltered stimuli weighting and the DLPFC could offer a "rational" inhibitory input. The OFC deficit in value attribution (from excessive inputs in social signals of rejection to insufficient inputs in abstract risk) may have great contirbution on the final suicidal behaviour outcome. In addition, the OFC makes the link with social life, a major component of triggering of suicide crisis (Foster 2011).

We would like to stress that suicidal behaviour most likely results from a distributed multifactorial complex deficit that cannot be grossly simplified to just a handful of brain regions. What we have presented here represents the most commonly replicated and discovered findings in suicide research to date, but, given the heterogeneity of suicidal behaviour, this proposal and our interpretation has limited applicability and requires much more in-depth testing and development.

2.6.2 Future directions

More neurocognitive investigations are necessary. Future studies should comprehensively evaluate both structural and functional deficits to improve our ability to model suicidal behaviour. Distinguishing sub-groups of patients on the basis of their neurocognitive profiles will be necessary to promote more efficient interventions. In addition, cross-modal validation (Mahon, Burdick et al. 2012) or analytical replication (Jia, Huang et al. 2010; Wagner, Schultz et al. 2012; Jia, Wang et al. 2013) promises to improve the internal validity of study findings and to ensure consistent findings. Longitudinal studies (Amen, Prunella et al. 2009;

Willeumier, Taylor et al. 2011; Sachs-Ericsson, Hames et al. 2013) will offer glimpses into the true predictive power of neuroimaging, although the cost of such studies for a rare event like suicide may be prohibitive. Finally, future studies should investigate how these findings may be used in intervention aimed at preventing suicide, which is the ultimate goal of suicide research.

2.7 Tables[2]

Table 2.1. Functional Neuroimaging Studies

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[2] **5HT:** serotonin
DA: dopamine
BOLD: blood oxygenation level dependent
MRI: magnetic resonance imaging
T: tesla
CT: computed tomography
ROI: region of interest
SPECT: single-photon emission computed tomography
DTI: diffusion tensor imaging
SC: suicide completers
SA: suicide attempters
SI: suicide ideators
PC: patient controls
HC: healthy controls
MDD: major depressive disorder
TBI: traumatic brain injury
ADHD: attention deficit / hyperactivity disorder
PTSD: post-traumatic stress disorder
MADRS: Montgomery-Åsberg depression rating scale
MCC: multiple comparison correction
HAMD / HDRS: Hamilton depression rating scale
BDI: Beck's depression inventory
YMRS: Young's mania rating scale
PANNS: positive and negative syndrome scale
R: right
L: left
BA: Brodmann's area
vmPFC: ventromedial prefrontal cortex
DLPFC: dorsolateral prefrontal cortex
ACC: anterior cingulate cortex

Study	Method	Population	Main results	Comment / Limitation
Task Based Functional Studies: Inhibition				
Dombrovski et al. 2013	- 3T MRI - probabilistic reversal learning task - ROI approach (vmPFC) + whole brain analyses.	- 20 HC, 18 PC, 15 SA - medicated, most participants during major depressive episode (HDRS > 7) - elderly males and females (41.5% female; SA age: 65.9 ± 6.3)	- SA: no paralimbic response to high expected reward. - SA < PC: response to expected reward in vmPFC. - SA + PC: weak paramlimbic activity is correlated with: 1) ignoring negative feedback after reversal, 2) bet against odds, 3) non-planning impulsivity, 4) impulsive/careless problem solving, 5) poor attempt planning	- some clinical data missing - sensitivity analyses were conducted - correlation analyses not specific to SA
Matthews et al. 2012	- 3T MRI - stop task (error processing, self monitoring, inhibition) - whole brain analyses	- 13 PC, 13 SI - combat war veterans with at least depression, PTSD, mild TBI, mostly medicated and currently depressed - adult males only; SI age: 29.5 ± 4.7	- similar between group performance - SI > PC during error trials in middle frontal gyrus, supramarginal gyrus, L ACC, R precentral, STG	- well-matched groups - no HC group - multiple comorbidity
Pan et al. 2011	- 3T MRI - Go/No-Go task (inhibition) - whole brain analysis	- 14 HC, 15 PC, 15 SA - mostly medicated and currently depressed - adolescent males and females (73% females; SA age: 16.2 ± 0.8)	- PC > SA: R ACC in Go/NoGo vs. Go response blocks - PC > HC: L insula - no difference between SA and HC	- circularity in ROI analyses - same population as Pan et al. 2013
Willeumier et al. 2011	- [99m]TC HMPAO SPECT - Conner's continuous performance test (motor inhibition) - whole brain perfusion evaluation - suicide completers data extracted from a database of over 64 000 cases	- 27 HC, 36 PC, 21 SC - some depressed at time of SPECT (12 SC), most medicated - adult males and females (23.8% females, SC age 35.9 ± 14.0)	- SC < PC: diffuse cluster at frontal, temporal, parietal areas, at uncorrected P < 0.01 - SC < HC: significant differences across the brain; main regions from factor analysis were the superior frontal lobes, R precuneus, rolandic operculum, postcentral gyrus and left caudate–thalamus	- extended population from Amen et al. 2009 - only study with completers - numerous comorbidities in SC incl. bipolar and unipolar disorders head trauma, ADHD, drug use
Amen et al. 2009	- [99m]TC HMPAO SPECT - Conner's continuous performance test (motor inhibition) - whole brain perfusion evaluation - suicide completers data extracted from a database of over 64 000 cases	- 12 HC, 12 PC, 12 SC - mostly medication free (9 PC, 8 SC) but depressed (BDI 27) - adults males and females (25% females; SA age: 33.8 ± 13.6)	- at rest: SA > PC in R temporal, frontal, cingulate, parietal, insular and occipital cortex (strongest at temporal parietal); SA < HC all over the cortex in general - during task: SA < PC in L frontal, R medial temporal lobe, R thalamus; SA > PC in R ACC, L cerebellar pyramid, R occipital Lobe	- population partly overlap with Willeumier et al. 2011 - only study with completers - lenient imaging statistic threshold - all right-handed - mean suicide delay: 9 month after - patients matched for disorders; all groups matched for age and gender
Task Based Functional Studies: Verbal Fluency				

PCC: posterior cingulate cortex
STG: superior temporal gyrus
SMA: supplementary motor area
OFC: orbitofrontal cortex
GM: gray matter
WM: white matter
WMH: white matter hyperintensities
DWMH: deep white matter hyperintensities
PVH: periventricular hyperintensities

Oquendo et al. 2003	- 18F-FDG PET (rCMRglu) with placebo on first session, and fenfluramine on second day (single-blind design); - verbal fluency task - ROI1 (ACC, BA32; medial frontal gyrus BA8) and ROI2 (ACC, BA24; and R superior frontal gyrus BA6) determined as the clusters with highest perfusion signal	- 16 high-lethality SA, 9 low-lethality SA - unipolar depression, medication free (14 days), depressed (HAMD 20) - adults males and females (62% females; low-lethality SA age=30.4 ± 8.7, high-lethality SA =42.9 ± 10.4)	- verbal fluency positively correlated with ROI2 - high-lethality SA < low lethality SA in both ROI1 and ROI2 - this difference is increased by fenfluramine - suicide intent negatively correlated with ROI1; suicide lethality negatively correlated with ROI2; lethality suggested to be mediated by intent; impulsivity positively correlated with ROI1	- no HC or PC group - circular analyses with regard to ROI choice mechanism - small group of low lethality SA
Audenaert et al. 2002	- [99m]TC-ECD SPECT - verbal fluency task (either category fluency or letter fluency) - whole brain cerebral perfusion analyses	- 20 HC, 20 recent SA (< 7 days) - unipolar depression, medication free (six weeks), depressed (HAMD>21) - adults males and females (60% females; SA mean age: 31.5 ± 7.6)	- task performance: SA < HC for both - category fluency: SA < HC in L inferior frontal gyrus (BA10), R inferior parietal gyrus (BA40) and R ACC (BA24/32) - letter fluency: SA < HC in medial temporal gyrus (BA37/39), R ACC (BA24), R hypothalamic region	- no PC group - random division of 2 x 10 SA subgroups, each completing either task - figure statistical threshold not consistent with text
Task Based Functional Studies: Decision-making				
Pan et al. 2013	- 3T MRI - Iowa Gambling Task (decision-making) - whole brain analyses	- 13 HC, 14 PC, 15 SA - some medicated (6 PC, 10 SA) and some participants are depressed. - adolescent males and females (54.8% females; SA age: 16.2 ± 0.8)	- SA > PC, HC in IGT performance - Trial 21-40: PC > HC during safe choices in middle-temporal gyrus, hippocampus; PC > HC for risky choices in hippocampus; PC > SA for safe choices in hippocampus - Trial 41-60: SA < PC for risky choices in R thalamus; SA > HC for safe choice in L caudate; PC > HC for safe choice in L hippocampus	- last 40 trials (60 to 100) not analysed due to too many dropouts, limited to decisions under uncertainty - may be underpowered for IGT - SA shows stronger symptom, not well-matched with PC - modified IGT version for fMRI - same population as Pan et al. 2011
Jollant et al. 2010	- 1.5T MRI - Iowa Gambling Task (decision-making) - 5 ROIs for risky vs. safe contrast in lateral OFC, ACC, occipital cortex; 13 ROIs for wins vs. losses contrast. ROIs defined from contrasts in HC	- 15 HC, 12 PC, 13 SA - mostly medication free (10 SA, 11PC), and all euthymic (HDRS < 7) - adult males only; SA mean age 38 (28-59)	- SA < PC, HC: lower IGT net scores - SA < PC for risky vs. safe choices in left lateral OFC (BA47) and occipital cortex (BA19); - no BOLD difference for wins vs. losses - no correlation with suicidal variables	- well-matched PC and SA - assessed distant from suicidal act - PC group includes both with and without suicidal ideation - all right-handed - modified IGT version for fMRI - same population as Jollant et al. 2008
Task Based Functional Studies: Motor Activation Paradigm				
Marchand et al. 2013	- 3T MRI - motor activation paradigm (motor behaviour and disinhibition) - ROI: R posterior cingulate	- 40 SI - 14 with bipolar II, 26 with major depressive disorder, medication free (3 months), depressed (mean MADRS = 25) - young adults males and females (12% females; MDD SI age: 27.8 ±5.0, BP II SI age: 29.5 ±8.1)	- R PCC differ between MDD and BPII - R PCC connectivity associated with suicide ideation and depression severity, only in MDD: 1) with L precentral mid, inferior frontal gyri, 2) with R midfrontal gyrus	- both groups show elevated suicidal ideation - overlap with population from Marchand et al. 2011.
Marchand et al. 2013	- 3T Siemens MRI - motor activation paradigm (motor behaviour and disinhibition) - Task used for ROI selection, second analysis run for functional connectivity analyses: ROI1: L middle frontal gyrus and ROI2: R precentral gyrus	- 21 HC, 13 PC, 7 SA - status: medication free (3 months), euthymic (mean MADRS = 2.2) - young adults males only, mean age: 27.5 ± 4.0	- SA vs. PC: no task performance differences - self-harm/suicide attempt associated with greater connectivity between ROI2 to L globus pallidus - SA+PC < HC: 1) connectivity from ROI1 to L parietal, R frontal, B temporal, putamen; 2) connectivity from ROI2 to cerebellum, ACC, R frontal, temporal cortex	- self-harm/suicide attempt mixed - no clear separation between SA/PC group in terms of study design and analyses - control for first degree relative with no mental disorder - corrected for physiological artefacts

Marchand et al. 2012	- 3T MRI - motor activation paradigm (motor behaviour and disinhibition) - ROI approach: putamen - correlation design	- 17 PC, 5 SA - unipolar depression, medication free (3 months), depressed (MADRS > 26) - adult males only; patient age: 28.1 ± 5.1	- suicide ideation: L Putamen to anterior CMS, R putamen - self-harm: L Putamen to L inferior parietal lobule; R primary sensory cortex - activation of both putamen correlated with history of self-harm	- no HC group - no group contrast - very few SA to run correlation with history of self-harm - accounted for physiological artefacts from heart rate and breathing rate
Marchand et al. 2011	- 3T MRI - motor activation paradigm (motor behaviour and disinhibition) - ROI: Putamen as seed to evaluate striatal and cortical midline structure functional connectivity	- 19 HC, 16 bipolar II patients - medication free (3 weeks), depressed (MADRS=27.5, YMRS=2.8) - adult males, SA age: 32.9 ±7.5	- suicidal ideation negatively correlated with L putamen activation, depression severity positively correlated with L thalamus, precentral activation	- no report of history of suicide attempt - dissociable components of brain activation associated with depression severity and SI - only right-handed
Task Based Functional Studies: Rejection, Mental Pain				
Pan et al. 2013	- 3 T MRI - Ekman faces task - whole brain analyses - functional connectivity analyses based on R ACC	- 15 HC, 15 PC,14 SA - many medicated (7PC, 9SA), few depressed (1PC, 3SA, BDI 20) - adolescent males and females (56.8% females); SA age: 16.2 ± 0.8	- no task performance differences - SA > PC: R ACC, L DLPFC, R mid temporal gyrus, bilateral primary sensory cortices (50% angry) - SA > HC: L primary sensory cortex (50% angry) - SA < PC: L fusiform gyrus (neutral) - SA < HC: R ACC, L medial frontal cortex (neutral) - SA < HC: L primary visual (100% happy) - SA < HC, PC: R ACC to B insula functional connectivity (50% angry, PPI)	- same population as that of Pan et al. 2013 - median time since last attempt: 26.1 - canonical HRF - movement parameter covariated - covariated for age - psychophysiological interaction - LOTS of analyses - SA: median time since last attempt: 26.1 (SD 29.1) months
Reisch et al. 2010	- 1.5T MRI - suicidal script listening (neutral, mental pain, suicidal acts) - ROIs: L middle frontal gyrus, L medial PFC (BOLD change only)	- 8 recent SA (< 30 days) - most medicated (7 SA), depressed (BDI = 26.8) - adult females only; mean age: 38.5 ± 13.1	- suicidal < neutral script in medial PFC (BA 6, 10 and 46) - suicidal > neutral script in parahippocampal gyrus, cuneus (BA19), middle temporal gyrus (BA4) and cerebellum - suicidal > mental pain script in medial PFC (BA6), ACC (BA32) and hippocampus	- within four weeks of suicidal act - all right-handed - small sample size - all attempted suicide via overdosing
Jollant et al. 2008	- 1.5T MRI - Ekman faces task (attention to gender; neutral, angry and happy faces; two intensities: 100 and 50%) - whole brain analyses	- 16 HC, 14 PC, 13 SA - mostly medication free (13PC, 10 SA) and all euthymic (HAMD 7) - adult males; mean age = 40.3 ± 11.3	- 100% angry vs. neutral faces: SA > PC in R lateral OFC (BA47) and SA < PC in R superior frontal gyrus (BA6) - 50% angry vs. neutral faces: SA > PC in R cerebellum - 50% happy vs. neutral faces: SA < PC in R cerebellum and SA > PC > HC in R ACC - no correlation with suicidal variables	- well-matched PC and SA - assessed distant from suicidal act - PC group includes both with and without suicidal ideation - all right-handed - no difference in gender recognition and reaction time suggesting no attention deficit - same population as Jollant et al. 2010
Resting State / Perfusion / Other Studies				
Sublette et al. 2013	- 18F-FDG-PET - perfusion (rCMRglu) - resting state with placebo, then fenfluramine - whole brain analyses	- 16 PC,13 SA - medication free (> 14 days), depressed (HAMD > 16) - adults males and females (65.5% females), SA age: 36 ± 11.5	- placebo: SA < PC in R DLPFC; SA > PC in L vmPFC/posterior medial OFC), L ACC, caudate, putamen - FEN: SA < PC in B DLPFC; - R medial OFC, R DLPFC negatively correlated with suicide intent	- mixture of prospective SA, past SA, past and prospective SA (+/- 2 years) - well controlled groups - small sample size - no HC - overlap with subjects from earlier Oquendo et al. 2003 study

Fan et al. 2013	- 3T MRI - resting state - ANOVA derived fMRI ROIs: R parahippocampal gyrus, R ventral medial frontal gyrus, L ACC, L middle occipital gyrus, R STG; L angular gyrus.	- 56 HC, 9 PC, 27 SA - medicated (26 SA, 3 PC) and depressed (HAMD>17) - adult males and females (56.5% females; SA age 34.4 ± 12.9)	- Most prominent results in ANOVA is the R vmPFC regions with SA, HC < PC - ROI Analyses: SA > PC, HC in R superior temporal gyrus; SA > HC in L ACC, L angular gyrus; SA, HC < PC in R parahippocampal gyrus, R ventral medial frontal cortex, L ACC, L angular gyrus; PC, SA < HC in L middle occipital gyrus	- small PC group. - vmPFC changes may be more likely related to PC alteration - ROI not defined independently from groups
Zhang et al. 2013	- 3T MRI - N-back task (working memory): 2 back vs. baseline used for analyses - whole brain analyses - suicide risk defined by the Schizophrenia Suicide Risk Scale - dynamic causal modelling (DCM) was used: five models considered	- 15 HC, 14 high suicide risk, 19 low suicide risk - schizophrenia, mostly medicated - young adults males and females (50% females, mean age: high risk SA= 22.9 ± 4.0, low risk SA: 12.2 ± 6.8)	- No difference in task performance - HC < high risk: L PCC - HC < both groups: L mPFC - With DCM: HC > both groups from MPFC to PCC; both groups > HC from PCC to mPFC	- not clear what suicidal risk really includes - only study using DCM analyses - circular SVC analyses on previously already liberal statistical threshold - results mainly related to patient status more than suicide risk
also Amen et al. 2009 (detailed above)				
Fountoulakis et al. 2004	- [99m]TC HMPAO SPECT - ROIs (cerebellum, thalamus, caudate nucleus and globus pallidus, B frontal, B parietal, B temporal lateral, medium, B occipital ROIs).	- sample size: 50 patients including 13 SA (5 recent SA, 7 lifetime SA) - medication free (2 weeks), depressed (HAMD > 20) - adult males and females (70% females; suicide ideator age: 37 ± 15.0	SA vs. PC: No between-group difference	- multimodal approaches with several other physiological measurements in addition to SPECT imaging. - SPECT analyses details missing
Soloff et al. 2000	- 18F-FDG PET - co-registered with T1 MRI - fenfluramine challenge - whole brain	- 8 HC, 5 patients including 4 SA + 1 self-mutilation - borderline personality disorder medication free (8 months+), euthymic - young female adult (yet comparing with a mixed gender HC group), SA age: 28.4 ± 10.1	Day 1: Placebo - HC > SA: L temporal lobe; L superior temporal gyrus, R frontal lobe, insula Day 2 vs. Day 1: - HC: decrease in L parietal, B temporal, increase in L parahippocampus, R frontal, Cerebellum, R caudate - SA: decrease in R occipital, increase in L caudate, ACC - HC > SA: L superior temporal gyri, R PFC, L parietal lobe, L caudate - HC < SA: pons, R occipital	- impossible to differentiate between borderline personality comorbidity and suicidal act - very small groups - potential gender confound

Table 2.2. Pharmacological Neuroimaging Studies

Study	Method	Population	Results	Comment / Limitation
5HT2A Receptor				
Soloff et al. 2007	- [18F] altanserin PET with 1.5 GE MRI - 5HT2A antagonist - ROIs: medial inferior OFC, medial superior frontal cortex, lateral OFC, ACC, pregenual ACC, subgenual ACC, hippocampus, medial temporal cortex	- 11 HC, 2 PC,12 SA - medication free (2 months), depressed (9 BPD, HAMD 16.3) - young adult females only, age: 27.7 ± 8.2	- BPD SA > HC in hippocampus, medial temporal cortex, occipital cortex, trend in lateral OFC - no BP correlation with lifetime suicide attempt number	- secondary analyses with primary focus on BPD - lenient statistics and circularity in analyses - no PC group
van Heeringen et al. 2003 **Audenaert et al. 2001**	- [123I]5-I-R91150 SPECT - 5HT2A receptor antagonist - 12 predefined yet unspecified ROIs.	- 12 HC, 9 recent SA - medication free (6 months), depressed (HAMD 10) - adult males and females (39% females; SA age: 32.4 ± 11.5)	- SA < HC: binding index in frontal cortex (mainly dorsolateral) - lower binding index in violent method vs. self-poisoning - SA: negative correlation between binding and hopelessness (-0.70)/harm avoidance (0.72), both variables being correlated to each other (0.72); positive correlation with self-directness, cooperativeness	- within 7 days of suicidal act, - groups matched for age and gender - small sample sizes - no PC group - same population as Audenaert et al. 2001
Meyer et al. 2003	- [18F] setoperone PET - co-registered with 1.5T MRI - 5HT2A antagonist - ROIs: middle frontal gyrus, lateral OFC, posterior MTC, rostral ACC	- 29 HC, 22 PC, 18 SA - status: medication free (3 months), most have MDD (HAMD 17) - males and females, SA age of 31 ± 7	- SA vs. HC: no significant difference - higher binding associated with higher dysfunctional attitudes in BA9 - 5HT2 binding 4% lower in self-harm, 10% lower in severe self-injury sub-group	- patients matched for age with HC, age controlled for in analyses - SA vs. PC not reported - lack basic sociodemographic information table
5HT and DA Transporter				
Nye et al. 2013	- [11C]-ZIENT PET - co-registered with 1.5T MRI - ROIs: midbrain/pons, thalamus, putamen, caudate nucleus, amygdala, cingulate cortex, frontal cortex, occipital cortex, cerebellar cortex, defined by atlas and hand drawing based on MRI data - resting state - serotonin transporter	- cross-sectional group comparisons with control in MDE at time of scanning. patients. - 10 HC, 11 SA - medication free (6 weeks), depressed (HAMD 7) - adults males and females (38.1% females) with SA age of 38.5 ± 13.6	- SA > HC: midbrain/pons, putamen in SERT BP	- No PC - lack differentiation between suicide and depression. - tiny sample size. Many ROI. Likely Type 2 error with MCC. - SA mostly violent attempters - not control for subject variation in ROI size - covariated for AGE
Bah et al. 2008	- [123I]-Beta-CIT SPECT - whole brain - SPSS - correlational. No morphometric - 5HTT, DAT - Amersham ROI system - ROIs: whole brain, cerebellum, pons, frontal-temporal, parietal, occipital lobe, thalamus, basal ganglia - ROI chosen based on atlas	- 9 HC, 9 SA - medication free (six months), 5 SA depressed - adults males only, mean SA age of 41.11 ± 15.24	- SA versus PC: no differences regarding genotype frequencies or regional 5HTT availability - SA: 12 repeat allele of STin2 related to reduction of 5HTT BP: in frontal cortex, temporal lob, parietal lobe, but not occipital lobe - SA: S allele of 5HTTLPR related to 5HTT binding potential reduction in frontal cortex, parietal lobes, and occipital lobe	- Evaluated two types of serotonin transporter polymorphism - pilot study - case matched controls, - A subset of earlier Ryding/Lindstrom dataset

Cannon et al. 2007	- [11C]DASB PET - coregistered with 1.5 or 3.0 T GE T - SPM2/MedX - serotonin transporter - ROIs: thalamus, striatum, insular cortex, subgenual ACC, pregeneual ACC, dorsal cingulate cortex, PCC, periaqueductal gray, midbrain raphe - ROIs based on prior publications	- 34 HC, 36 PC (12 MD, 10 BD), 14 SA: (6 MDD, 8 BD) - unmedicated (11 months), depressed (MADRS 26) - adults males and females (71.4% females) with MDD patients age 35 ± 8.9, BD patients age: 30 ± 9.2	MDD SA > MDD PC: - binding potential in anteroventral striatum BD SA > BD PC: - pgACC binding potential BD SA < BD PC: - midbrain binding potential	- mainly interested in differences between MDD and BD - both MDD and BD had SA - excluded recent SA or serious SI - coregistered PET and MRI - MDD SA are all females.
Oquendo et al. 2007	- [11C](+)-McNeil 5652 PET - coregistered with 1.5T GE T1 - MedX - 6 manually traced ROI	- 41 HC, 9 PC, 9 SA - medication free (2 weeks), depressed (HAMD 10) - adults males and females (50% females), patient age 39.3 ± 16	SA vs. PC no difference	- secondary analysis - small SA and PC group
Cannon et al. 2006	- [11C]DASB PET, - serotonin transporter binding - ROIs: thalamus, striatum, insula, midbrain, subgenual ACC, pregenual ACC, DCC, PCC	- 37 HC, 10 PC, 8 SA - unmedicated (3 to 8 weeks), depressed - adult males and females (65% females, age: 30 ± 9)	- SA < PC, HC: 5-HTT binding in the midbrain - SA > PC, HC: 5-HTT binding in ACC	- secondary analysis - small SA group
Ryding et al. 2006 **Lindstrom et al. 2004**	- [123I]-Beta-CIT SPECT - co-registered with 1.5 T MRI - serotonin and dopamine transporters - whole brain and ROIs (midbrain, inferior OFC, thalami, caudate, putamen)	- 12 HC, 12 recent SA (5 violent, 7 non-violent SA) - medication free (six months), 50% SA with mood disorder - adult males and females (17% females; SA age: 38.8 ± 14)	- no differences between SA and HC - violent attempters do not differ from non-violent attempters - in SA, negative correlation between serotonin transporter binding and impulsivity in R inferior frontal gyrus, bilateral temporal, midbrain, thalamic bilateral basal ganglia, L cerebellar regions	- groups matched for age, gender and season of year - mostly males - no PC - small SA subgroups - within 4 weeks of suicidal act - hospital staff may not be the most suitable control groups
Parsey et al. 2006	- [11C]McN 5652 PET - co-registered with 1.5T MRI - serotonin transporter - ROIs: midbrain, putamen, amygdala, thalamus, hippocampus, ACC	- 43 HC, 25 patients including 9 SA - MDD, PTSD, panic, dysthymia and social phobia, unmedicated (26.5 days), depressed (HAMD = 24.4) - adults males and females (57.4% females; MDD patients age 38.0 ± 13.4)	- MDD patients (PC + SA) < HC: amygdala and midbrain - SA vs. PC : no difference	- secondary analyses - no MCC

5HT "Synthesis"

Leyton et al. 2006	- Alpha[11C]Methyl L Tryptophan trapping PET - measure of serotonin synthesis - ROIs: medial OFC, lateral OFC, medial prefrontal gyri	- 16 HC, 10 SA - mostly medication free, depressed (BDI = 21.3) - adult males and females (30% females; SA age: 37.7 ± 6.4)	- SA < HC in ventromedial and ventrolateral PFC - SA > HC in R paracentral lobule, L thalamus, L middle occipital cortex, L hippocampal gyrus - negative correlation between binding in lateral OFC and R medial PFC and suicidal intent	- no PC group - small SA group - all right-handed

Table 2.3. Structural Neuroimaging Studies

Study	Method	Population	Results	Comment
Whole Brain Volumetric and Morphometric Studies				
Giakoumatos et al. 2013	- 1.5T MRI - volumetric - FreeSurfer	- 262 HC, 341 PC,148 SA (97 high-lethality, 51 low-lethality) - schizophrenia, schizoaffective, psychotic bipolar disorder I, most medicated, clinically stable - adult males and females (51.5% females, SA age: high-lethality 35.6 ± 11.7, Low Lethality 36.9 ± 12.2)	- SA < PC in multiple areas: R rostral middle frontal, R superior frontal, L superior parietal, L supramarginal, L thalamus, inferior/superior temporal, R Insula - schizophrenia: SA < PC: L thalamus - schizoaffective: SA < PC: L medial OFC, R lingual, L supramarginal, R accumbens, inferior temporal - psychotic bipolar I SA < PC: L supramarginal, R fusiform.	- large population - multi-site study - only volumetric analyses reported - more females in attempters. - mixed diagnoses. - larger differences between HC and SA in terms of effect size. - no mention of specific template used
Wagner et al. 2012	- 1.5T MRI - cortical thickness - Freesurfer - Whole brain	- 30 HC, 15 PC, 15 high risk patients (10 SA, 5 first degree relative of SC) - major depressive episode without psychotic features patients medication free, depressed (HDRS >18) - adult males and females (62.5% females; high risk SA age: 41 ± 12.5)	- high risk < PC: L VLPFC, DLPFC, dACC (extracted based on MDD < HC contrast) - MDD < HC: L parahippocampal gyrus, ACC, OFC; R mid frontal gyrus, mid temporal gyrus, sup frontal gyrus, insula	- high risk group is mixed - illness duration differ between SA and PC - similar population as Wagner et al. 2011
Wagner et al. 2011	- 1.5 MRI - whole brain voxel-based morphometry	- 30 HC, 15 PC, 15 high risk patients (10 SA, 5 first degree relative of SC) - major depressive episode without psychotic features patients medication free, depressed (HDRS >18) - adult males and females (62.5% females; high risk SA age: 41 ± 12.5)	- SA < HC: fronto-limbic gray matter reduction - SA < PC: caudate and rostral ACC - (SA + PC) < HC, L OFC, R inferior frontal gyrus, amygdala, L caudate	- high risk group is mixed - illness duration differ between SA and PC - similar population as Wagner et al. 2012
Benedetti et al. 2011	- 3T MRI - volumetric - whole brain voxel-based morphometry	- 38 PC, 19 SA - bipolar disorder, some medicated (18/57 use lithium), depressed. (HAMD > 20) - adult males and females (52% females, SA age: lithium- 43.6 ± 11.3, lithium+ SA: 45.6 ± 10.4	- SA < PC: GM volume in DLPFC, OFC, medial frontal gyrus, ACC, STG, parieto-occipital cortex (precuneus, and paracentral lobule), and basal ganglia - SA > PC: GM volume in superior temporal cortex - Li- SA < Li+ SA: in most of those regions mentioned above - SA: high early life stress	- assess correlation with lithium - small groups (n=10) - no healthy controls - history of other drugs - not the same number of affective episode - large number of small clusters scattered all over the brains - modulated VBM
(See below Jia, et al. 2010 entries)				
Hwang et al. 2010	- 2T MRI - whole brain voxel-based morphometry	- 26 HC, 43 PC, 27 SA - status: MDD, depressed (mean HAM-D > 29) with unknown medication status - elderly males only, SA age: 79.1 ± 5.6	- SA < PC: GM/WM volumes in the DLPFC, parietal, and temporal regions and also the insula, lentiform nucleus, midbrain, and the cerebellum - marked reduction in dorsomedial PFC	- lenient VBM statistics
Aguilar et al. 2008	- 1.5T MRI - volumetric - whole brain voxel-based morphometry	- 24 PC,13 SA - schizophrenia (PANSS < 15), all medicated - adult males only, SA age: 37.1 ± 10.0	- SA < PC: GM density in L OFC and L STG - no amygdala volume differences.	- no HC group - PC vs. SA: significant age differences but association not explained by age or severity of illness
Rusch et al. 2008	- 1.5T MRI - volumetric - whole brain voxel-based morphometry	- 50 HC, 45 PC,10 SA - medicated and symptomatic schizophrenia (PANSS scores > 25) - adult males and females (30% females; SA age: 30.3 ± 6.5)	- SA > PC, HC: WM volume in bilateral posterior orbital and inferior frontal gyri - no GM volume difference	- small size of the SA group - 11% left-handed - association not explained by substance abuse or positive symptoms - substance abuse comorbidity between group differences
Region of Interest Brain Volumetric and Morphometric Studies				

Lopez-Larson et al. 2013	- 3T MRI - volumetric and DTI - FreeSurfer and FSL for DTI (bilateral anterior thalamic radiation) - ROI: bilateral thalamus	- 15 HC, 40 PC, 19 SA - status: veterans with mild TBI, depressed (medication status unknown) - adult males only, SA age: 38 ± 7.8	- SA > HC, PC for B thalamic volumes - trend SA > PC in L anterior thalamic radiation fractional anisotropy - no suicide variables correlation with thalamic volume. - no suicide variables correlation with anterior thalamic radiation fractional anisotropy	- comorbid TBI, difficult to interpret. - similar lifetime history of mental disorder between groups but several differences between patient groups (e.g. more drug and stimulant use in SA)
Dombrovski et al. 2012	- 3T MRI - volumetric - ROI: putamen, caudate and pallidum - correlation with Monetary choice questionnaire and Cambridge Gamble Task	- 16 HC, 20 PC,13 SA - unipolar depression, medicated (ATHF 3.0) - elderly males and females (49% females; SA age: 66 ± 6.4)	- SA < PC: associative striatum, limbic/ventral striatum - SA < HC: associative striatum (after accounting for brain size) - SA < PC and HC: lower putamen but not caudate or pallidum gray matter voxels - SA: higher delay discounting associated with lower putamen (associative striatum) gray matter voxel counts	- voxel count analyses occasionally accounted effect of body size - gray matter differences may be mainly driven by low lethality SA.
Nery-Fernandes et al. 2012	- 1.5T MRI - volumetric - ROI: corpus callosum (manual segmented subregions: rostrum, genu, rostral body, anterior midbody, posterior midbody, isthmus, splenium) with Bonferroni correction	- 22 HC, 21 PC,19 SA - bipolar I patients, all medicated and euthymic - adult males and females (66.1% females; SA age: 39.8 +-11.4)	- no significant differences between SA PC	- family history of SA/SC in both SA and PC - SPSS MANOVA analyses on extracted corpus callosum subareas and total callosum area.
Soloff et al. 2012	- 1.5T MRI -volumetric - multiple ROIs (middle-inferior OFC, ACC, middle-superior temporal cortex, insula, hippocampus, parahippoc., fusiform gyrus, lingual gyrus and amygdala) based on previous studies in BPD	- 50 HC, 24 PC, 44 SA (25 high-lethality, 19 low-lethality) - status: borderline personality disorder, some medicated, depressed (mean HDRS = 17) - adult males and females (75% females, SA age: 29.6 ± 8)	- SA < HC: all ROIs except amygdala - PC < HC: lingual gyrus, mid. sup. temporal cortex, insula, - SA < PC: L insular cortex - SA > PC: mid sup temporal cortex, L lingual gyrus - high-lethality SA < low-lethality SA: R middle superior temporal gyrus, R middle inferior OFC, R insular cortex, L fusiform gyrus, L lingual gyrus and R parahippocampal gyrus	- a history of childhood sexual abuse (but not physical abuse) was more prevalent among SA vs. PC - lenient statistical threshold
Baldaçara et al. 2011	- 1.5T MRI - volumetric - ROI: Vermis, B cerebellar hemisphere	- 22 HC, 20 PC, 20 SA - status: bipolar disorder I, euthymic (YMRS, HAMD < 7) - adult males and females (65% females; SA age: 39.9 ± 11.1)	- no relationship between cerebellar volume and suicidal behaviour - no correlation with clinical variables	- reduced number of analyses. - data suggest there might be a trend differences between SA and HC in bilateral cerebellum volume.
Cyprien et al. 2011	- 1.5T MRI - mid sagittal area - ROIs: corpus callosum subregion (anterior 3rd, mid 3rd, posterior 3rd, total area) defined using manual segmentation	- 180 HC, 234 PC, 21 SA - various psychiatric condition, mainly mood disorders patients mostly unmediated, depressed - elderly males and females (76.2% females; SA age: 72.2 ± 4.3	- SA < PC, HC: posterior third part of corpus callosum - SA: more childhood abuse and head trauma but childhood abuse had no association with size - analyses adjusted for gender, age, head trauma, childhood abuse, and total brain volume	- secondary analyses - only right-handed - higher percentage of women in SA - only midsagittal area measurement (no volume or thickness) - suicidal acts committed at different age
Goodman et al. 2011	- 3T MRI - volumetric - ROI : BA 24 (ACC)	- 13 HC, 13 SA (including self-harm) - ADHD, oppositional defiant, substance abuse and PTSD patients, depressed (BDI > 25) - adolescent males and females (76.9% females; patient age: 15.8 ± 1.1)	- SA < HC: ACC, BA23, BA24 GM relative volume; BA24, ACC relative total volume - SA > HC: ACC, BA23, BA31 WM relative volume. - SA: number of suicide attempt associated with smaller BA24 GM+WM volume and greater BA23 WM	- secondary analyses. - group of interest not very clearly defined. - no PC group
Spoletini et al. 2011	- 3T MRI - volumetric - ROIs : lateral ventricles, thalamus, hippocampus, amygdala, caudate, putamen, pallidum and accumbens	- 50 HC, 36 PC,14 SA - schizophrenia, mostly medicated, symptomatic (PANSS > 40) - adult males and females (57% females; SA age: 42.9 ± 11.3)	- SA > PC, HC: right amygdala volume - increased volumes related positively to severity of self-aggression	- no depression scale as a confounding factor

Yurgelun-Todd et al. 2011	- 3T MRI - DTI 64 directions - FreeSurfer for Volume - volume ROI: lateral ventricle, frontal lobe, cingulate cortex - diffusion ROI: genu and cingulum	- 17 HC, 15 SI - TBI, PTSD, MDD, substance abuse patients medicated (12SI), depressed (mean HAM-D > 12.6) - adult males only, SI age: 34.93 ± 9.71	- Trend suggest reduced bilateral frontal GM reduction - no WM, or ventricular volume differences - SI < HC in DTI: L cingulum, L genu, bilateral genu - no mean diffusivity differences - in SI: DTI show positive correlation between a) total cingulum with suicidal ideation, BIS, BIS attention, b) right cingulum with suicidal ideation and BIS c) right genu with BIS	- suicide ideation only, no SA and with a very mixed comorbid TBI, psychiatric profile - HC group: one had PTSD, one with MDD - findings may be more depression than suicide related
Caplan et al. 2010	- 1.5T MRI - volumetric - ROIs : PFC, middle frontal gyrus, superior frontal gyrus, OFC and temporal lobe	- 40 PC,11 current SI - patients with epilepsy and various co-morbid disorders, medicated, mostly euthymic (2/11 SA with MDE) - children males and females (54% females, SI age: 11 ± 2.0)	- SI < PC: R OFC WM volume - SI > PC: L temporal lobe GM volume	- small SI group (n=11) - SI older than non SI - heterogeneity of diagnoses - different lateralization of epilepsy
Matsuo et al. 2010	- 1.5T MRI - midsagittal area measurement - ROIs: corpus callosum (genu, anterior body, posterior body, isthmus, splenium)	- 27 HC, 10 PC, 10 SA - bipolar disorder, often medicated (12 patients), depressed (patients mean HAM-D > 14) - adult females only, SA age: 36.2 ± 10.1	- SA versus PC: No between-group difference - SA: negative correlation between anterior genu area and BIS impulsivity, motor, non-planning scores in SA (Smaller ACC predict high impulsivity)	- no volume or cortical thickness - small samples of patient groups - did not covariate for Cluster B effect, family history of suicide
Vang et al. 2010	- 1.5T MRI - volumetric (FreeSurfer) - ROIs : amygdala, hippocampus, globus pallidus, caudate, accumbens, putamen	- 6 HC, 7 SA - MDD and adjustment disorder, unmedicated, mostly depressed (4/7 SA) - adult males and females (29% females, SA age: 38.1 ± 11.4)	- SA vs. HC: lower volume of bilateral globus pallidus, and R caudate - SA: correlation between globus pallidus volume and "solidity" temperament, and 5HTT binding.	- no PC group - small groups - groups matched for age and gender - subset of data published in Ryding, et al. 2006
Jovev et al. 2008	- 1.5T MRI - volumetric - ROI: pituitary gland - correlation analyses	- 20 patients including 18 parasuicides - borderline personality disorder, few medicated (3 SA), few depressed (6 SA) - adolescent males and females (75% females; parasuicidal patients age: 13.3 ± 2.4).	- positive correlation between pituitary gland volume and number of para-suicidal acts - age, gender, and internalizing problems all associated with pituitary gland volume	- most patients without current medication - minimally treated patients - no real PC group - missing demographic details - first presentation patients - suggests HPA hyperactivity
Monkul et al. 2007	- 1.5T MRI - volumetric - ROIs: OFC, ACC, amygdala, hippocampus	- 17 HC, 10 PC, 7 SA - MDD, medicated free (2 weeks) and depressed (HAMD > 10) - adult females only, SA age: 31.4 ± 13.9	- SA < HC: smaller GM volume in bilateral OFC - SA > PC: GM volume in R amygdala - no group difference for hippocampus and ACC - PC vs. HC: no significant GM volume differences	- small SA group - volumes not correlated with number of suicidal acts, duration of illness or age at onset
Schlegel et al. 1989	- CT ROI: ventricular area normalized to the brain size - correlation analyses	- 34 non-psychotic patients and 10 psychotic patients - medication free, depressed - adult males and females (59.1% females, age: 42.8 ± 13.0)	- no significant differences between suicidal impulses and any ventricular measurements	- limited sample size - no SA or HC. - limited generalizability - lack clinical information - CT lack contrasts to segment very effectively
Diffusion Studies				
Jia et al. 2013	- 3T MRI - DTI 15 directions - ROI: left anterior limb of internal capsule	- 46 HC, 40 PC, 23 recent SA (< 1 month) - MDD, medication free (2 weeks), depressed (HAMD > 18) - adult males and females (65.2% females; SA age: 36.3 ± 14.5)	- SA < PC: anterior limb of internal capsule projection percentage to L OFC, thalamus	- re-analysis of data with focus specifically on anterior limb of internal capsule. - one of the only structural connectivity studies - population overlaps with Jia et al. 2013
(see earlier section Lopez-Larson et al. 2013)				

Mahon et al. 2012	- 1.5 T MRI - DTI 21 directions - whole brain + ROI: L OFC for SA vs. PC contrast.	- 15 HC, 15 PC,14 SA - patients with various psychiatric disorder: PTSD, anxiety, phobia, panic, eating disorder, obsessive-compulsive disorder, panic disorder, medicated (76.9% SA, 93.3% PC), euthymic - adult males and females (40.91% females; SA age: 33.3 ± 14.1)	- SA < PC: L OFC - no differences between PC and HC, SA and HC - SA < HC for ROI, not significant between PC and HC. - SA > PC: impulsivity measure - SA: negative correlation between ROI and motor impulsivity (BIS-11)	- one of the few studies that use multi-modal validation approach - circular ROI analyses - TBSS finding confirmed using non-VBM multimodal T1/T2/PD voxel based analyses (0.001, 10 ET in the white matter mask) - No effect of antipsychotic medication
(see earlier section for Yurgelun-Todd, et al. 2011)				
Jia,et al. 2010	- 3T MRI - DTI 15 directions - whole brain + ROIs: bilateral lentifrom nucleus, hippocampus, thalamus	- 52 HC, 36 PC,16 SA - MDD, medication free (2 weeks+), depressed (HAM-D > 20) - adult males and females (69% females; SA age: 34.2 ± 13.7)	- SA < PC, HC in L anterior limb of the internal capsule of axial (not radial) diffusivity - SA < PC: R lentiform nucleus of increased radial diffusivity - SA < HC: reduced FA in R subgyral frontal lobe WM of increased radial diffusivity - ROI: SA < PC, R lentiform nucleus. - no differences in L lentiform nucleus, B hippocampus, B thalamus - no group difference in VBM GM/WM	- groups matched for age, gender, education and ethnicity but longer disease duration in SA - no correlation with symptom severity - comprehensively evaluated WM/GM - population overlaps with Jia et al. 2010
Lesion Studies				
Sachs-Ericsson et al. 2013	- 1.5T MRI (T2) - whole brain analyses - white matter - prospective	- 223 PC, 23 SA - MDD, depressed, medication status unknown - elderly males and females (77.2% females; SA age: 66.7 ± 6.6)	- baseline: SA > PC: for L white matter lesions - 2 years: SA > PC: suicidal ideations - overtime: SA > PC: growth of bilateral WML - WML predict cognitive decline in entire patients sample - suicide attempt does not predict change in cognitive functioning/cognitive decline	- only known longitudinal lesion neuroimaging study in suicide attempters - lack HC group - complicated analyses - mixed depression onset - small SA population. Large PC populations. Unbalanced. - more MDD symptoms in SA
Pompili et al. 2008	- 1.5T MRI (T2) - whole brain analyses - white matter hyperintensities (Fazekas scale)	- 55 PC,44 SA - mood disorders, half sample medicated, half sample depressed - adult males and females (49.1% females; SA age: 45.6 ± 16.1)	- SA > PC for periventricular hyperintensities (80 vs. 27%) - no differences in deep white matter hyperintensities	- age was associated with white matter hyper intensities but results not explained by age - no HC group - presence, absence of WMH only, no detailed morphometric or volumetric analyses. - overlap with Pompili et al. 2007
Pompili et al. 2007	- 1.5T MRI (T2) - whole brain analyses - white matter hyperintensities (Fazekas scale)	- 36 PC, 29 SA - unipolar and bipolar mood disorder, medicated, mostly depressed - adult males and females (63.1% females; SA age: 42.2 ± 13.5)	- SA > PC for white matter hyperintensities (58% vs. 28%) - Increased hyperintensities in mood disorder - MDD does not differ from bipolar disorder in terms of suicide frequency or hyperintensities	- not explained by gender, age or comorbidity, medication - no correlation with suicidal dimensions - no HC group - age differences
Ehrlich et al. 2005	- 1.5T MRI (T2) - whole brain analyses - Fazekas (modified scale) - periventricular hyperintensities (PVH), deep white matter hyperintensities (DWMH) and subcortical gray matter hyperintensities (SCH)	- 40 PC, 62 SA - mood disorder, unknown medication or mood status - adult males and females (67% females; SA age: 26.7 ± 5.5)	- SA > PC: More PVH (27% vs. 7%) - PVH mostly on the right side - SA versus PC: not significant different amount of DWMH	- no HC group - no covariation with regard to age/suicide severity - clinical MRI sequence - lack exploration of psychiatric comorbidity

Ehrlich et al. 2004	- 1.5T MRI (T2) - whole brain analyses - Coffey scale (modified) - periventricular hyperintensities (PVH)	- 110 PC, 43 SA - various diagnoses including unipolar and bipolar, psychosis, affective disorders, conduct/ADHD, unknown medication status, current presence of psychiatric disorder. - adolescent, children males and females (26% females; SA age: 14.6 ± 3.4)	- MDD PVH+ group has higher history of suicidal acts compare to MDD PVH - (75% vs. 40.6%) - MDD with WMH 18 times more likely to have suicide attempt. - other psychiatric disorder with WMH not influencing suicide attempt risk - DWMH R parietal lobe associated with high prevalence of suicide attempt	- association not explained by other demographic or clinical variables (including age, gender, substance abuse, head injury) - no HC group, - inpatients
Ehrlich et al. 2003	- MRI (T2) - qualitative neuroimaging analyses - DWMH, PVH	- 110 PC, 43 SA - unknown medication or mood status - adolescent and children males and females(25.8% females), patient age: 14.6 ± 3.4	- Only 26DWMH, 22PVH found among 153 patients screened - DWMH in R parietal poses 8.6 times higher risk to have suicidal history - controlled for covariates - All SA have DWMH in R posterior parietal lobe	- lack basic participant details
Ahearn et al. 2001	- 1.5T MRI (T2) - whole brain analyses - Boyko scale; Coffey scale - periventricular hyperintensities (PVH), subcortical gray matter hyperintensities (SCH)	- 20 PC, 20 SA - unipolar depression, unknown medication status, depressed (HAMD > 20) - elderly males and females (85% females; SA age: 66 ± 5.8)	- SA > PC: SCH and trend for PVH (prominently in basal ganglia)	- age at suicidal act not reported - suicide onset not available - MDE severity not available - clinical population also had family history of SA - some patients had ECT
Lopez et al. 1997	- 1.5T MRI (T2) - Schelten scale - deep white matter hyperintensities (DWMH) - correlation analyses	- 28 patients - Alzheimer disease, medication unknown, lightly depressed (HAMD > 7). - elderly males and females (64.3% females; patients age: 73.3 ± 6.8)	- DWMH global scores correlated with low self-esteem and suicidal ideation in the PFC area - DWMH did not correlate with anything else, including HAM-D - DWMH did not correlate with vascular disease	- Secondary analyses - no psychiatric disorders before Alzheimer disease - no control groups. Limited reliability, generalizability - frontal regions most severe WMH - suicide ideation not clearly quantified.
Others				
Budisic et al. 2010	- structural, transcranial sonography study - echogeneicity measured - freehand ultrasound system - averaging of two measures - manual segmentation - Ponto mesencephalic nuclei raphe(Freehand)	- 40 HC, 17 PC, 14 SI - unipolar depression, unknown medication status, depressed (HAMD > 24) - elderly males and females, SI age: 51.3 ± 9.42	- SI < PC, HC: raphe nuclei echogenicity - negative correlation between HAMD, depressive episodes, and echogenicity - reduced echogenicity is easier to interpret, absence of raphe nuclei is much harder.	- rare neuroimaging modality for psychiatric study - controlled for depression in PC - two blind raters - author does not disentangle suicide from MDD - 10% disqualification rate (modality) - gender effect
Li et al. 2009	- MRI Spectroscopy study - 3T MRI (1H-MRS) - ROI: bilateral hippocampus - NAA/Cr, Cho/Cr, mI/Cr	- 24 HC, 24 SA - MDD, unknown medication status, depressed (HAMD > 7) - adult males and females (84% females; SA age: 34.7 ± 12.1)	- SA < HC: NAA/Cr ratio in L hippocampus - SA vs. HC: No difference between of NAA/Cr in R Hippocampus, - HC: NAA/Cr hippocampus L > R - SA: NAA/Cr hippocampus no L/R differences - no correlation with MDE duration, HAMD	- rare neuroimaging modality for psychiatric study - mostly females - very well-matched HC - No PC group making inference to suicidal acts more than mood disorder impossible

Chapter 3 Prefrontal Cortex Markers of Suicidal Vulnerability in Mood Disorders: A Model-Based Structural Neuroimaging Study with a Translational Perspective

A version of this chapter was adapted and previously published in Translational Psychiatry in 2015, Volume 5, e516. The full list of co-author includes Dr. Natalia Lawrence[2], Dr. Emilie Olié[3], Dr. Fabienne Cyprien[3], Dr. Emmanuelle Le Bars[4], Dr. Alain Bonafé[4], Dr. Marie Phillips[5], Dr. Phillips Courtet[3] and Dr. Fabrice Jollant[1,6] with the follwing academic affiliations.

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3.1 Introduction

One million individuals commit suicide each year worldwide (Hawton and van Heeringen 2009). Improving our ability to predict and prevent suicide is an important priority. However, the current assessment of suicide risk is based upon numerous socio-demographic and clinical risk factors, which often yield a high sensitivity but a low specificity (Mann and Currier 2007). It is expected that using specific neurobiological markers in addition to clinical assessments may improve evaluations of suicide risk in future. Uncovering some of these biomarkers is the goal of the present study.

The current understanding of suicidal behaviour is based on a stress-vulnerability model, which suggests that some individuals are at higher risk of committing suicide in stressful situations like interpersonal conflicts or loss (Mann 2003). This model has been supported by *in vivo* neuroimaging studies. When

comparing suicide attempters (SA) with patient controls (PC) and/or healthy controls (HC), functional neuroimaging studies have revealed dysfunctional ventral, dorsomedial and dorsolateral prefrontal cortices among other regions in various conditions, from a resting state (Oquendo, Placidi et al. 2003) to viewing angry faces (Jollant, Lawrence et al. 2008), to making decisions (Jollant, Lawrence et al. 2010) or to listening to suicidal scripts (Reisch, Seifritz et al. 2010). Further, structural neuroimaging has reported various brain alterations in SA, affecting both gray and white matter (see below).

On the basis of this literature, we recently proposed a neuroanatomical model that accounts for the vulnerability to suicidal behaviour at the neurocognitive level (Jollant, Lawrence et al. 2011). In this model, we suggested that the ventral prefrontal cortex, including the orbitofrontal cortex (OFC), would be mainly implicated in valuation deficits, which explains decision-making impairments in SA (Richard-Devantoy, Berlim et al. 2013), while more dorsal parts of the prefrontal cortex (including anterior cingulate cortex, ACC) may explain deficits in cognitive control and emotion regulation processes (Richard-Devantoy, Jollant et al. 2012). In the present study, we attempted to confirm the involvement of these prefrontal brain regions and their potential as biomarkers by examining their morphometric properties using structural neuroimaging in a large sample. Certainly, the ease of implementing structural neuroimaging compared to functional neuroimaging is potentially a great advantage and highly relevant for future clinical application.

However, previous results using this technique suffer from various limitations. First, many studies assessed samples of small size, with as few as seven to ten SA (Monkul, Hatch et al. 2007; Vang, Ryding et al. 2010). Only one large study, in subjects with psychotic disorders, has been published to date (Giakoumatos, Tandon et al. 2013). Recent papers have highlighted a frequent lack of replication of findings in neuroscience, partly in relation to underpowered studies (Button, Ioannidis et al. 2013). Second, of the six published studies evaluating whole brain graywater alterations, six different types of statistical thresholds have been used (Aguilar, Garcia-Marti et al. 2008; Rüsch, Spoletini et al. 2008; Hwang, Lee et al. 2010; Jia, Huang et al. 2010; Benedetti, Radaelli et al. 2011; Wagner, Koch et al. 2011). However, recent discussions about the lack of reliability of the P-value suggest that calculating effect sizes may be a more relevant approach (Nuzzo 2014). Third, these studies have focused on one particular standard analysis

method, usually measuring brain volume differences using voxel-based morphometry (VBM), but they have seldom applied concurrent surface-based morphometry (SBM) analyses. To date, only two studies have explored cortical thickness (Wagner, Schultz et al. 2012; Giakoumatos, Tandon et al. 2013). To our knowledge, only one group has combined two analysis methods in two different publications (Wagner, Koch et al. 2011; Wagner, Schultz et al. 2012). Yet, recent analyses have suggested that different SBM measures account for VBM gray matter variation in different regions, but also that VBM may be more sensitive than SBM to detect some abnormalities (Palaniyappan and Liddle 2012). The combination of both analyses could therefore improve our understanding of structural neuroimaging markers of disease.

We addressed several of these issues in the present study. First, we pooled data from three separate studies conducted in two locations with identical study designs to increase power. This has resulted in the largest neuroimaging study conducted on vulnerability to suicidal behaviour in mood disorders to date. Second, we calculated effect sizes for the main contrasts, namely SA vs. PC, and SA vs. HC. Third, we used two complementary analysis approaches in tandem, namely VBM and SBM. Finally, we used a validated study group design to specifically examine the vulnerability to suicidal behaviour by including non-depressed patients to exclude the acute effects of the depressive state, and a group of patients with a history of mood disorder but no suicide attempt to exclude the effect of comorbid disorders.

On the basis of previous studies, we hypothesized that SA, when compared with control groups, would show a reduction in structural measures of prefrontal cortex. To test the potential clinical applicability of these measures, we also conducted sensitivity and specificity calculations.

3.2 Material and Methods

3.2.1 Samples and assessment

Three samples were recruited, one at the Institute of Psychiatry in London, UK (Sample 1) and two at the academic hospital of Montpellier, France (Samples 2 and 3). For all three samples, participants were recruited through advertisements and there was an initial screening via telephone interview or in clinical settings. They were then interviewed in person by experienced psychiatrists. All participants were right-handed (Oldfield 1971) and euthymic at the time of scanning, and all participants had a HDRS (Hamilton

Depression Rating Scale) score below nine (Hamilton 1960). Exclusion criteria included a lifetime history of severe head trauma, central nervous system disorders, schizophrenia and substance use disorder over the last 12 months, suicide attempt using firearms, pregnancy and contraindications to magnetic resonance imaging (MRI). Details on the exclusions from each sample are given in Supplementary Information.

The three samples differed in two selection criteria: (1) Samples 1 and 2 comprised only males aged between 18 and 60, whereas Sample 3 comprised only non-menopausal females aged between 18 and 50; (2) All patients in Sample 1 suffered from major depressive disorder, whereas Samples 2 and 3 included both major depressive disorder and bipolar disorders.

All diagnoses were made according to the Diagnostic and Statistical Manual of Mental Disorders IV criteria using the Mini-International Neuropsychiatric Interview, version 5.0.0 (Sheehan, Lecrubier et al. 1998) The French or English versions of the National Adult Reading Test (Beardsall and Brayne 1990) were used to provide an estimation of verbal IQ and the Beck Depression Inventory (Beck, Ward et al. 1961) for a subjective measure of current depressive state. Participants also completed the Barratt Impulsiveness Scale version 10 (Patton, Stanford et al. 1995).

Within each sample, three groups were recruited as described above: (1) SA, individuals with a personal history of both mood disorder and suicidal behaviour; (2) PC, individuals with a history of mood disorder but no lifetime history of suicidal behaviour; (3) HC, individuals with no current or past history of any Diagnostic and Statistical Manual of Mental Disorders IV Axis I diagnoses or suicidal behaviour or psychotropic medication. The overall population included 82 HC, 82 PC and 67 SA.

As in our previous studies, a suicidal act was defined as any nonfatal, self-directed potentially injurious behaviour with any intent to die as a result (Jollant, Lawrence et al. 2011). The last and the most severe suicidal acts were assessed using the Risk Rescue Rating Scale (Weisman and Worden 1972) and the Suicide Intent Scale (Beck, Morris et al. 1974).

Participants from Sample 3 also fulfilled the Childhood Trauma Questionnaire (Bernstein, Fink et al. 1994), and participants from Sample 1 played the Iowa Gambling Task, a decision-making test (Bechara, Damasio et al. 1999).

After a complete description of the study was presented to the subjects, written informed consent was obtained from all participants. The studies were approved by the respective Research Ethics Committee (Institute of Psychiatry and Montpellier Research Ethics Board). The participants were paid £30 and €100, respectively.

Functional neuroimaging and behavioural results (but not structural results) from Sample 1 have previously been published (Jollant, Lawrence et al. 2008; Jollant, Lawrence et al. 2010), but data from Samples 2 and 3 have not.

3.2.2 MRI acquisition procedures

For Sample 1, T1-weighted magnetic resonance images were acquired using a GE Signa 1.5 T Neuro-optimized MR system (General Electric, Milwaukee, WI, USA) at the Institute of Psychiatry, London, UK. A spoiled gradient echo sequence was used for the T1-weighted acquisition with the following parameters: isotropic voxel dimension of 1.1mm with field-of view at 280 × 180mm; TE (echo time) of 5ms and TR (repetition time) of 10.8ms. One hundred and fifty slices of images each with two-dimensional matrix 256 × 160 were acquired at bandwidth of 122 Hz per pixel.

For Samples 2 and 3, T1-weighted magnetic resonance images were acquired with a 1.5 T whole-body MRI system (MAGNETON AVANTO, Siemens, Erlangen, Germany) in Montpellier Academic Hospital, France. Sample 2 used a three-dimensional T1 FLASH sequence with voxel dimension of 0.93 × 0.93 × 1mm, field-of-view at 240mm × 240mm, matrix256 × 256, 15 degrees flip angle, TE of 5.2 ms and TR of 11 ms with 160 slices and a bandwidth of 130 Hz per pixel. Sample 3 used three-dimensional T1MPRAGE with voxel dimension of 0.98mm × 0.98mm × 1mm, field-of-view at 250 × 250mm, matrix 256 × 256 with 160 slices, 15 degrees flip angle, TE of 4.1ms, TR of 2100 ms and TI of 1100 ms, and a bandwidth of 140 Hz per pixel.

3.2.3 MRI analyses

We conducted VBM analyses using SPM8 v.4667 and SBM analyses with FreeSurfer 5.1.0 (details below in 3.5 Supplementary Material). In brief, after quality control checks, SPM segments the T1 structural data and produces a group template based on the entire group data set by nonlinearly warping each participant to the common brain template space while preserving local anatomical alterations. VBM analyses yield normalized gray matter volume measurement since it is sampled in template MNI space, not the individual space before normalization. In contrast, FreeSurfer registers each vertex at individual gyrus/sulcus levels to template but ultimately produces individualized measurements of volume, area and surface based on personally modeled brain morphometry and gray matter/white matter boundary contours. VBM data were smoothed using an 8mm full width at half maximum Gaussian kernel in volume space, where as SBM data were smoothed using 20mm full width at half maximum Gaussian kernel in surface space to maximize sensitivities to smaller clusters of structural differences as suggested by previous studies that tested a variety of full width at half maximum sizes in different sample sizes (Lerch and Evans 2005; Shen and Sterr 2013).

We used a region of interest (ROI) approach due to robust *a priori* hypotheses and its elevated statistical sensitivity. Four ROIs (Figure 3.1) were defined using independently defined *a priori* anatomical atlases (detailed in Supplementary Information) on the basis of regions previously reported to show structural and/or functional alterations associated with suicidal behaviour. The four regions were differentiated on the basis of different brain connections (Saleem, Miller et al. 2014) and functional roles, notably in valuation processes and cognitive control (Dixon and Christoff 2014; Banich and Depue 2015): (1) the OFC (Monkul, Hatch et al. 2007; Jollant, Lawrence et al. 2008; Jollant, Lawrence et al. 2010; Giakoumatos, Tandon et al. 2013) (corresponding to the lateral part of Brodmann areas [BAs] 11, and BA 47); (2) the ventrolateral prefrontal cortex (referred to as VLPFC and corresponding to BA 44 and 45) (Sublette, Milak et al. 2013); (3) the ventromedial prefrontal cortex (including the medial part of BA 11, BA 10 and the ACC, both rostral and dorsal parts [BA 24/32]; ROI referred to as medial prefrontal cortex, MPFC) (Wagner, Koch et al. 2011) and (4) the dorsal and lateral prefrontal cortex (referred to as DPFC and corresponding to BA46/8/9)

(Oquendo, Placidi et al. 2003; Hwang, Lee et al. 2010; Benedetti, Radaelli et al. 2011). Average measures of all the voxels (for VBM) or vertex (for SBM) measures within that ROI were used.

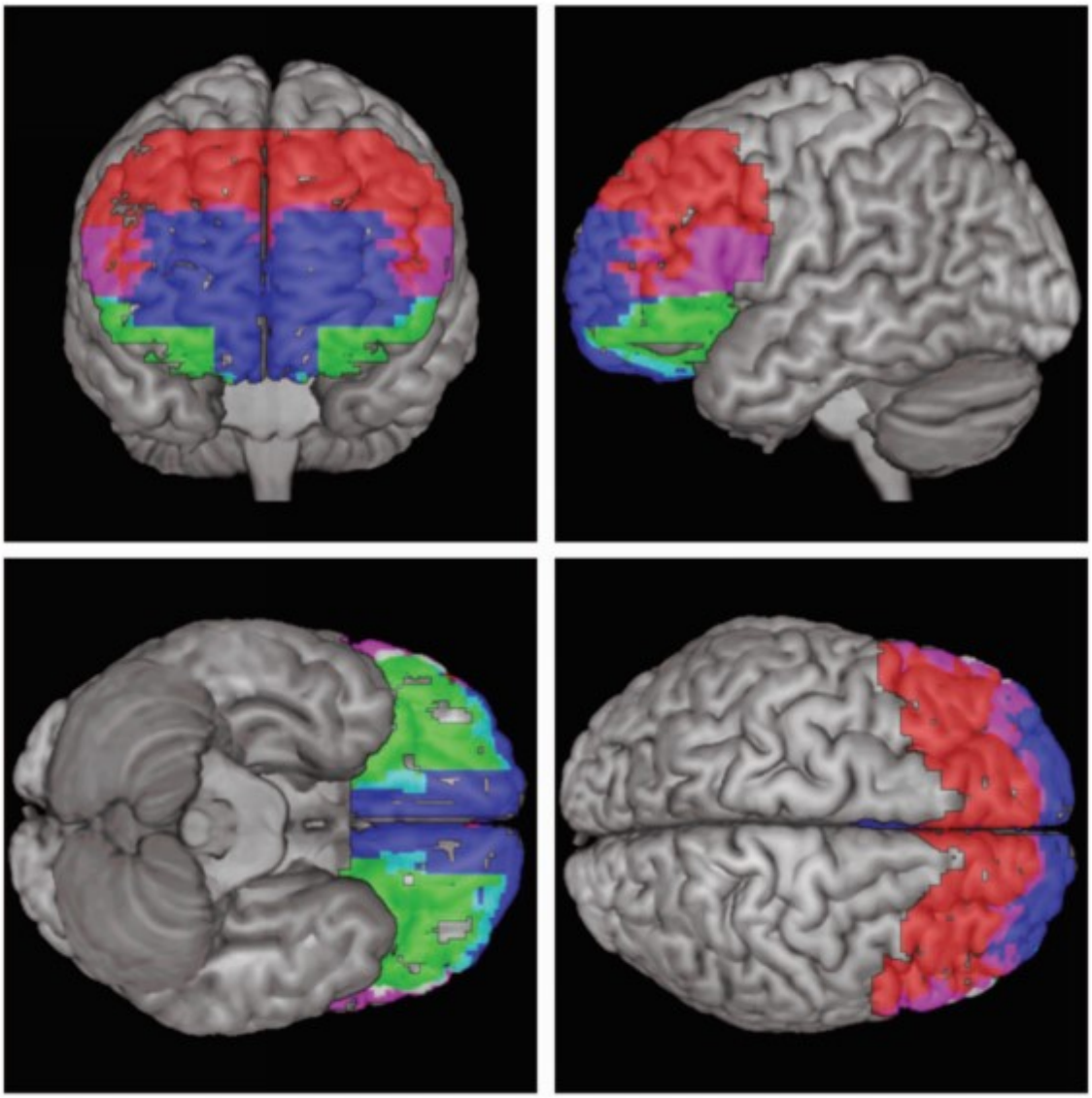

Figure 3.1. Representation of the four regions of interest of the prefrontal cortex examined in this article.

Blue: medial prefrontal cortex (MPFC; including anterior cingulate cortex, not shown). **Red**: dorsal prefrontal cortex (DPFC). **Green**: orbitofrontal cortex (OFC). **Violet**: ventrolateral prefrontal cortex (VLPFC). VBM, voxel-based morphometry.

Although multi-site neuroimaging poses challenges, samples can be combined and analyzed when groups are balanced across samples (which is the case here) and samples from multiple sites are properly controlled for in the analysis (Pardoe, Pell et al. 2008; Takao, Hayashi et al. 2014). The total volume and surface area, and the average thickness in individual space and normalized gray matter volume in the template space for each ROI were extracted and analyzed after covarying for relevant covariables consecutively. Group

comparisons in normalized gray matter volume, and SBM volumes/areas were systematically controlled for intracranial volume (Buckner, Head et al. 2004).

3.2.4 Statistical analyses

General linear model, followed by Tukey's post hoc, were used to compare quantitative variables between groups, and Pearson's correlation was used to examine associations between quantitative variables. Qualitative variables were compared using $\chi 2$ tests.

We also calculated effect sizes (Cohen's d) and its 95% confidence interval based on marginal means and standard error output from the general linear model (after accounting for the appropriate covariates) for the main contrasts between SA and both control groups.

A binary logistic regression model was used for sensitivity and specificity analyses.

In application, the alpha level was set at 0.05 unless a Bonferroni correction was necessary. The threshold for ROI analyses was set at a very conservative Bonferroni-corrected $P < 0.002$ ($P < 0.05$ divided by four ROIs, two sides and four different measures).

Statistical analyses were carried out with SPSS 20 (SPSS, Chicago, IL, USA).

3.3 Results

3.3.1 Socio-demographic and clinical variables

Table 3.1. Description and comparison of socio-demographic and clinical variables across the three groups in the pooled sample.

	Healthy controls (n = 82)	*Patient controls (n = 82)*	*Suicide attempters (n = 67)*	*Omnibus F/χ^2/t*	P	Post hoc
Male gender, *N* (%)	62 (75.6)	43 (52.4)	28 (41.8)	18.6	< 0.001	HC > PC, SA
Age, mean (s.d.)	37.8 (8.1)	39.4 (9.7)	39.2 (10.6)	0.8	0.5	
Years of education, *N* (%)	15.5 (2.1)	14.2 (2.5)	13.9 (2.2)	11.3	< 0.001	HC > PC, SA
NART (% correct), mean (s.d.)	0.73 (0.14)	0.72 (0.12)	0.69 (0.11)	2.0	0.1	
HDRS, mean (s.d.)	0.9 (1.4)	3.6 (2.2)	3.1 (2.3)	41.7	< 0.001	HC < PC, SA
BDI, mean (s.d.)	1.1 (2.5)	5.5 (5.3)	5.1 (4.6)	26.7	< 0.001	HC < PC, SA
Age at first mood episode, mean (s.d.)	—	25.6 (8.9)	25.3 (11.0)	0.2	0.9	
Number of depressive episodes, mean (s.d.)	—	5.0 (8.4)	5.6 (8.1)	2320	1.0	
Bipolar disorder, *N* (%)	—	30 (36.6)	30 (44.8)	1.0	0.3	
Number of hypo(manic) episodes, mean (s.d.)	—	3.2 (8.0)	3.8 (9.2)	2389.5	0.3	
Anxiety disorders, current, *N* (%)	—	28 (34.1)	27 (40.3)	0.6	0.4	
OCD, current, *N* (%)	—	3 (3.7)	0 (0)	2.5	0.1	
Alcohol/substance abuse, past, *N* (%)	—	26 (31.7)	16 (23.9)	1.1	0.3	
BIS10, mean (s.d.)	60.1 (13.8)	58.6 (16.7)	58.4 (16.6)	0.3	0.8	
Psychotropic medication, *N* (%)	—	47 (57.3)	46 (68.7)	2.0	0.2	
Antidepressant, *N* (%)	—	25 (30.5)	24 (35.8)	0.5	0.5	
Lithium, *N* (%)	—	14 (17.1)	13 (19.4)	0.1	0.7	
Antipsychotics, *N* (%)	—	6 (7.3)	17 (25.4)	9.2	0.002	PC < SA
Anticonvulsivants, *N* (%)	—	14 (17.1)	14 (20.9)	0.3	0.6	
Anxiolytics and hypnotics, *N* (%)	—	14 (17.1)	20 (29.9)	3.4	0.06	
Age at first suicide attempt, mean (min-max)	—	—	27.7 (11–59)	—	—	
Number of suicide attempts, mean (min-max)	—	—	2.7 (1–10)	—	—	
Suicide intent scale, total score, most severe act, mean (min-max)	—	—	16.2 (8–26)	—	—	
Risk rescue rating scale, total score, most severe act, mean (min-max)	—	—	41.2 (26–57)	—	—	

Abbreviations: BDI, Beck Depression Inventory; BIS10, Barratt Impulsivity Scale Version 10; HC, healthy control; HDRS, Hamilton Depression Rating Scale; NART, National Adult Reading Test; OCD, obsessive compulsive disorder; PC, patient control; SA, suicide attempter.

Groups were equally distributed across samples (see below 3.5 Supplementary Material). Similar between-group differences were observed across all three samples and the pooled sample (Table 3.1), although euthymic, HDRS and Beck Depression Inventory scores were higher in patients, as expected. These variables were not used as covariates as they are related to the group profile. Level of education was higher in HC than SA. Moreover, there were more males in HC than both patient groups.

SA did not differ significantly from PC on socio-demographic or clinical variables. However, they received significantly more antipsychotics with a trend for more anxiolytics/hypnotics. Most suicidal acts (85%) were drug overdoses.

3.3.2 Neuroimaging findings

Table 3.2. Region of interest analyses in the pooled sample comparing the three participant groups.

Regions	*Pipeline*	*Measures*	*Side*	*General linear model*		
				F	P	*Partial eta-squared*
Orbitofrontal cortex (OFC)	SPM	Normalized volume	Left	3.50	**0.03**	0.031
			Right	1.89	0.15	0.017
	Freesurfer	Cortical volume	Left	1.32	0.27	0.012
			Right	1.00	0.37	0.009
		Surface area	Left	1.27	0.28	0.011
			Right	0.97	0.38	0.009
		Cortical thickness	Left	0.37	0.70	0.003
			Right	0.24	0.79	0.002
Medial prefrontal cortex (MPFC)	SPM	Normalized volume	Left	1.78	0.17	0.016
			Right	2.29	0.10	0.020
	Freesurfer	Cortical volume	Left	0.66	0.52	0.006
			Right	1.29	0.28	0.012
		Surface area	Left	0.04	0.96	0.000
			Right	0.36	0.70	0.003
		Cortical thickness	Left	0.20	0.82	0.002
			Right	0.88	0.42	0.008
Ventrolateral prefrontal cortex (VLPFC)	SPM	Normalized volume	Left	4.73	**0.01**	0.041
			Right	2.56	0.08	0.023
	Freesurfer	Cortical volume	Left	7.70	**0.001**[a]	0.065
			Right	2.81	0.06	0.025
		Surface area	Left	4.39	**0.01**	0.038
			Right	1.14	0.32	0.010
		Cortical thickness	Left	0.21	0.40	0.008
			Right	4.36	**0.04**	0.029
Dorsal prefrontal cortex (DPFC)	SPM	Normalized volume	Left	2.70	0.07	0.024
			Right	3.41	**0.04**	0.030
	Freesurfer	Cortical volume	Left	2.85	0.06	0.025
			Right	3.55	**0.03**	0.031
		Surface area	Left	0.42	0.66	0.004
			Right	0.56	0.57	0.005
		Cortical thickness	Left	1.41	0.25	0.013
			Right	2.31	0.10	0.020

[a]Surviving multiple comparison correction. All analyses covarying for sample, and total intracranial volume, except for thickness with only sample as covariate. Bold entries indicate $P < 0.05$, uncorrected for multiple comparison.

Voxel-based morphometry. See Table 3.2 for group comparisons of all measures, Figure 3.2 for effect size analyses and Figure 3.3 for a correlation map between all measures examined here.

After covarying for sample and intracranial volume, general linear models based on normalized cortical gray matter volumes showed between-group differences in left VLPFC (P =0.01), left OFC (P =0.03) and right DPFC (P =0.04), but not MPFC, although this was not significant after multiple comparison correction. Post hoc analyses showed decreased normalized regional measures in SA relative to HC with no significant differences between SA and PC, and between HC and PC. Effect size calculation also suggests a significant effect between SA and HC for left DPFC, right VLPFC, right OFC and right MPFC (Figure 3.2).

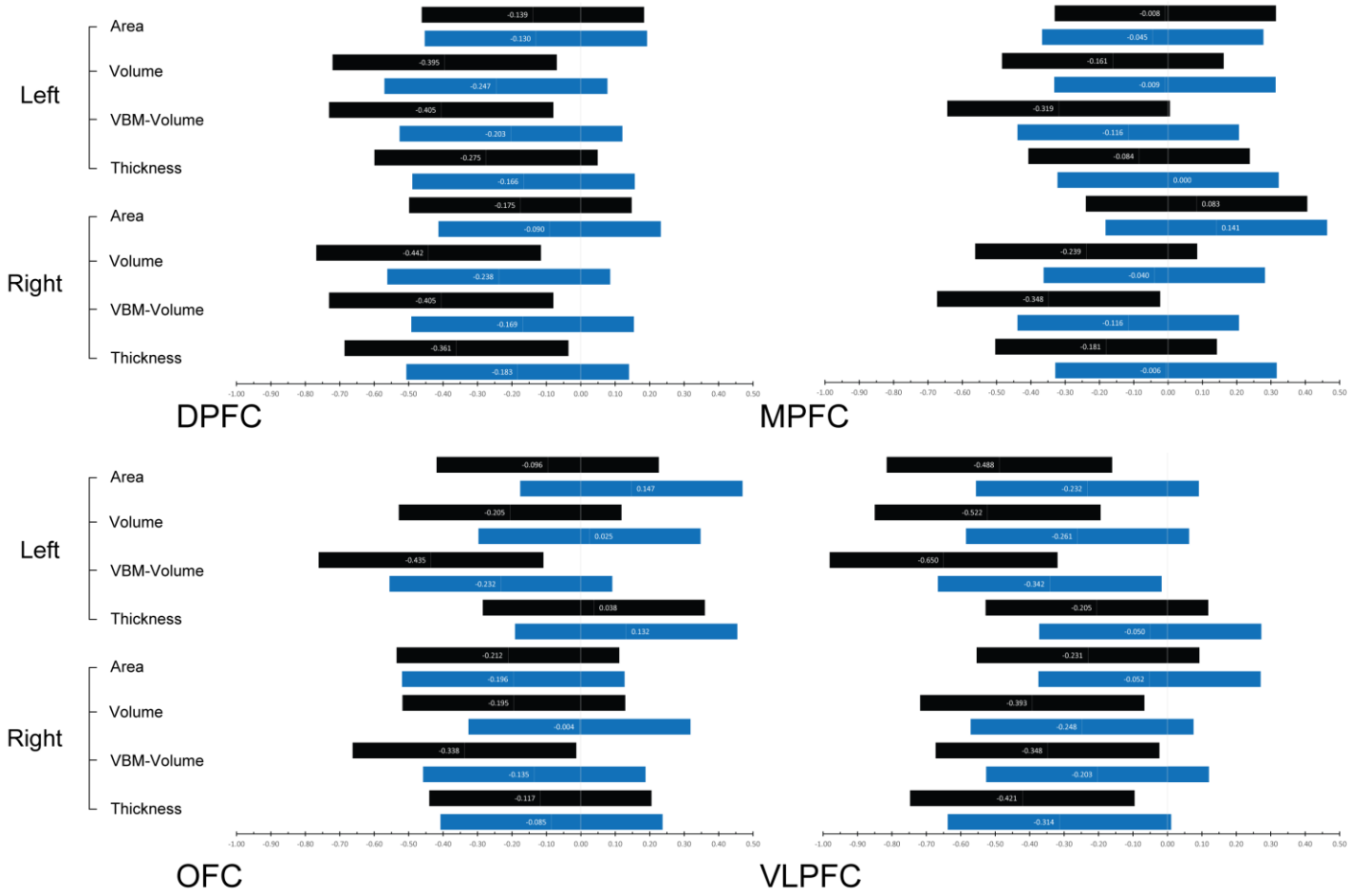

Figure 3.2. Effect sizes between suicide attempters and both control groups for the four regions of interest.

DPFC, dorsal prefrontal cortex; MPFC, medial prefrontal cortex; OFC, orbitofrontal cortex; VBM, voxel-based morphometry; VLPFC, ventrolateral prefrontal cortex. Blue: suicide attempters vs. patient controls; black: suicide attempters vs. healthy controls.

In exploratory whole brain VBM analyses, SPM revealed lower measures in SA than PC in right lateral OFC (BA 47; family-wise error-corrected cluster P-value=0.03; peak voxel=48,21,0; cluster size=1).

3.3.3 Surface-based morphometry

After covarying for sample and intracranial volume, there were group differences in gray matter volume in left VLPFC (P =0.001, surviving multiple comparison correction) with reduced volume in SA vs. both control groups, and between PC and HC, and right DPFC (P =0.03, not surviving multiple comparison correction), with reduced measures in SA vs. HC. There was no difference for OFC or MPFC. Effect size calculation also suggests a significant effect between SA and HC for left DPFC and right VLPFC.

After covarying for sample and intracranial volume, there were group differences in gray matter area in left VLPFC (P =0.01, not surviving multiple comparison correction), with reduced measures in SA vs. HC, but not in OFC, DPFC or MPFC.

After covarying for sample only, there were group differences in thickness in right VLPFC (P =0.04, not surviving multiple comparison correction) with reduced measures in SA vs. HC, but not in OFC, DPFC or MPFC. Effect size calculation also suggests a significant effect between SA and HC for right DPFC.

Figure 3.3 shows that structural measures were highly intercorrelated, notably SBM volumes together and area measures together. Only thickness measures were poorly correlated with area or volume measures as expected in most studies evaluation relationship between surface based measure and volume based measures (Winkler, Kochunov et al. 2010).

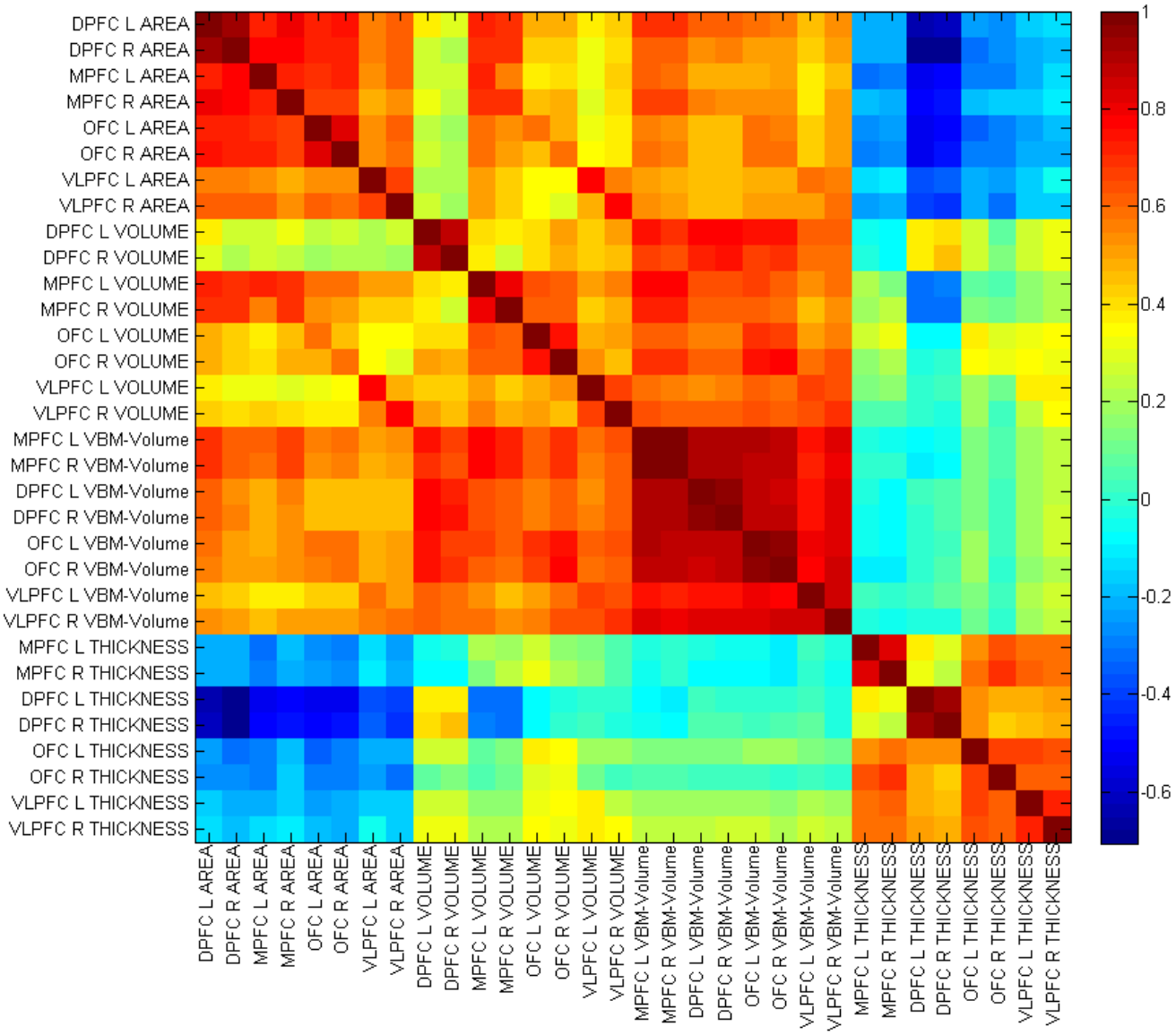

Figure 3.3. Correlation map between all magnetic resonance imaging measures for the four regions-of-interest.

DPFC, dorsal prefrontal cortex; L, left; MPFC, medial prefrontal cortex; OFC, orbitofrontal cortex; R, right; VBM, voxel-based morphometry; VLPFC, ventrolateral prefrontal cortex.

3.3.4 Effect of covariates

Only left VLPFC SBM volume and left VLPFC area remained significant after controlling for all main covariates (age, gender, level of education, bipolar disorder, lithium or antipsychotic intake). Left VLPFC VBM volume was no longer significant after covarying for gender or bipolar disorder; left OFC VBM volume was no longer significant after covarying for age, gender, bipolar disorder or lithium; right DPFC VBM or SBM volumes was no longer significant after covarying for age, gender or bipolar disorder; right VLPFC thickness was no longer significant after covarying for bipolar disorder or antipsychotics.

3.3.5 Correlation with clinical variables

In SA, lethality of the last suicidal act was correlated with all measures except left VLPFC area and right VLPFC thickness (all Po0.05; strongest correlations with right DPFC VBM and SBM volumes: r = -0.45; P $<10^{-3}$; left OFC: r = -0.38, P =0.001; left VLPFC SBM volume: r = -0.33; P =0.007). The number of suicidal acts was correlated with right DPFC VBM volume (r = -0.25, P =0.04) and left OFC VBM (r = -0.24; P =0.05); age at first suicidal act with right DPFC SBM volume (r = -0.40; P =0.001) and right VLPFC thickness (r = -0.26, P =0.03). No measure was correlated with the Suicide Intent Scale.

In patients, HDRS score was correlated with all measures except left VLPFC area and right VLPFC thickness (r between -0.15 and -0.21; all P < 0.07). Age at first mood episode was correlated with right VLPFC thickness only (r = -0.21; P =0.01); number of mood episodes with right DPFC SBM volume (r = -0.20, P =0.01). Barratt Impulsiveness Scale version 10 total score was correlated with all measures except right DPFC SBM volume (all Po0.07; strongest correlation with left VLPFC area: r =0.26, P =0.001; left OFC: r =0.23, P =0.005). And Childhood Trauma Questionnaire total score was correlated with right VLPFC thickness (r = -0.24; P =0.03). No measure was correlated with Beck Depression Inventory.

There was no significant association between the Iowa Gambling Task total score and any measure, but data were only available in the small Sample 1.

3.3.6 Potential for clinical application.

We examined the sensitivity and specificity of the neuroimaging measures in correctly classifying individuals with histories of suicide attempts among the 231 participants. As expected, a history of mood disorder had a 100% sensitivity (as all SA suffered from mood disorder in our study) but a lower specificity (71%). Adding left VLPFC area or volume into the model improved specificity in identifying attempters in a significant but limited manner, reaching 74.9% and 75.3%, respectively. Other measures had smaller effects. Of note, these findings cannot be generalized and may be inflated, and they should therefore be indicative of the clinical potential of these measures when added to clinical signs and symptoms.

3.4 Discussion

This study examined structural alterations associated with the vulnerability to suicidal behaviour in mood disorders using two complementary analyses in 231 subjects including 67 SA. It represents the largest neuroimaging study of suicidal behaviour in mood disorders to date and was specifically designed to investigate the neural basis of suicidal behaviour. After covarying for sample, intracranial volume, gender, age, education, bipolar disorder and medication intake, ROI analyses showed significant group differences in left VLPFC volume measured by FreeSurfer, the only measure that discriminated SA from both control groups in our study. Additional measures in VLPFC, OFC and DPFC, although not surviving a very conservative multiple comparison correction, were also different between SA and HC, with moderate effect sizes (Cohen's d up to 0.50). The link between these neuroimaging measures and the vulnerability to suicidal acts is further supported by significant correlations with suicidal variables including suicidal lethality, age at first suicidal act and number of previous acts. It is important to emphasize that patients were euthymic at the time of scanning, which suggests that these differences may reflect trait-like alterations. Our findings, therefore, tend to support the involvement of structural impairments in VLPFC, DPFC and OFC, but not MPFC (including ACC), in the pathophysiology of suicidal behaviour.

Our results are in agreement with results from several previous studies in mood disorders. For dorsal regions, reduced VBM volumes in DPFC in SA vs. PC have been reported in bipolar disorder and in elderly individuals with major depressive disorder (Hwang, Lee et al. 2010). Wagner et al. (2012) also reported reduced cortical thickness in the same region. Reduced volume of ACC in SA vs. PC has been found in depressive disorders (Wagner, Koch et al. 2011), bipolar disorder (Benedetti, Radaelli et al. 2011), but not in a small sample of depressed women (Monkul, Hatch et al. 2007). However, our study showed no structural differences in ACC. For ventral regions, previous studies have also shown reduced VBM measures (Benedetti, Radaelli et al. 2011) and thickness (Wagner, Schultz et al. 2012) in OFC in SA. Similarly, Wagner et al. (2012) reported reduced thickness in a region that encompassed our left VLPFC. Between-study differences in sample size, choice of threshold and lack of control for intracranial volume may explain some discrepancies with previous studies.

The role of these prefrontal regions in suicidal vulnerability has to be clarified. Two recent meta-analyses confirmed deficits in decision-making, cognitive control and working and long-term memory in SA (Richard-Devantoy, Berlim et al. 2013; Richard-Devantoy, Berlim et al. 2015). The OFC, which receives connections from the amygdala and thalamus, has a significant role in the interpretation of stimuli in the environment, notably in attributing value to stimuli (stimuli-outcome association) (Dixon and Christoff 2014), which may be important for the triggering of the suicidal crisis in the face of environmental stressors. The lateral PFC receives motivational inputs from ACC (Kouneiher, Charron et al. 2009) and represents cognitive information from memory, which is deficient in SA. Dorsal and lateral PFC notably confronts various information to outcomes and, therefore, exerts a cognitive control by ensuring the most advantageous choice in addition to some forms of behavioural flexibility (Dixon and Christoff 2014). Dysfunction of this interconnected prefrontal network may, therefore, be instrumental in the suicidal process by corrupting information acquisition and processing, resulting in impaired decision-making. At the clinical level, this would be reflected by negative assessments of life events and the automatic triggering of intense emotional responses. It would also be reflected by the inability to control the evoked emotional responses and particular negative thoughts (including hopelessness, ruminations and suicidal ideas) and the inability to prevent one from choosing to commit a suicidal act over alternative options.

At a translational level, our findings suggest that simple 1.5 T 10-min structural MRI sequences, which are relatively easy to implement in clinical practice, are unfortunately not sufficient to differentiate patients at higher risk of committing a suicidal act from non-attempters. Although some measures investigated here significantly improved within-sample specificity in identifying SA among patients with mood disorders, the improvement was not sufficiently large to support clinical application. Advancements in terms of acquisition (for example, higher field of multi-morphometric sequences), analysis methods (for example, quantitative MRI) or examination of particular subregions, are expected and may also increase accuracy.

One must keep in mind that patients who attempt suicide are likely a heterogeneous group. Different subgroups of SA (and PC) may, therefore, show different structural alterations. This has previously been suggested in SA when comparing decision-making performance in patients who committed violent vs. non-

violent suicidal acts (Jollant, Bellivier et al. 2005), and for resting-state activity in high vs. low lethality attempters (Jollant, Bellivier et al. 2005). It may be more relevant in future studies to focus on particular subgroups as some have suggested (Kapur, Phillips et al. 2012)—for example, those with particular neurocognitive alterations—and to assess the predictive value of neurocognitive alterations in prospective studies and clinical trials. This should be tested with the imaging markers revealed here. Our study presents several limitations. First, pooled data analysis adds heterogeneity when not designed *a priori* as a multicenter study, due to different acquisition parameters and scanners, which contributes to increased risk of Type II errors (Glover, Mueller et al. 2012) but not Type I error, and it does not undermine highlighted findings. Second, we included moderately to severely ill and often medicated patients to be more representative of the general clinical population. This may have added heterogeneity, although several clinical factors (including bipolar disorder and medication) were controlled for in analyses. Finally, determination of ROIs largely depends on their definition and the atlases, and these only partly overlap for SBM and VBM. This could explain the lack of convergence in statistically significant results between the two analysis methods. Our ROIs were also large in size, which may have reduced our ability to detect more localized differences.

In conclusion, we confirmed the role of several prefrontal regions in the vulnerability to suicidal behaviour. Further research is nonetheless required for the application of MRI in the prediction of suicidal behaviour.

3.5 Supplementary Material

3.5.1 Exclusion of participants

Sample 1, Institute of Psychiatry, London, UK

Forty-eight male participants were recruited, but two subjects were excluded due to claustrophobia during scanning; moreover, one subject was excluded due to current major depression and one subject due to motion artefacts.

Sample 2, CHU Montpellier, Montpellier, France

Eighty-nine male participants were recruited. Two suicide attempters were excluded due to claustrophobia and data from one patient control was incomplete.

Sample 3, CHU Montpellier, Montpellier, France

One hundred and five female participants were recruited. Three healthy controls were excluded due to excessive motion artefacts and panic attack. Two patient controls were excluded due to current depression. Three suicide attempters were excluded: one due to past head trauma, another due to a current manic episode and the third due to current depression.

3.5.2 Analyses

SPM8 VBM Analyses

For this VBM pipeline, structural data was analysed with SPM v.4667 without use of any other Matlab toolboxes or SPM plugins. SPM8 new segmentation function was used to segment participants' T1 scans into gray matter, white matter, and cerebral spinal fluid component before applying *Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra* (DARTEL) to create a study specific template. Individual subject data was subsequently normalized to MNI space while preserving tissue amount (modulation) such that ultimately modulated tissue volumes are compared. For the detailed step-by-step settings we used, see Ashburner (Ashburner 2010). VBM data were smoothed using a 3mm full width at half maximum Gaussian kernel based on previous investigations that suggested increased sensitivity for smaller kernel size in a larger sample size (Shen and Sterr 2013).

SPM8 VBM References:

FreeSurfer SBM Analyses

Surface-based morphometry (SBM) analyses were conducted using the FreeSurfer image analysis suite (version v 5.1.0) (http://surfer.nmr.mgh.harvard.edu). The technical details and references for these

procedures are described in prior publications listed online (http://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferWiki#References). Briefly, the processing includes motion correction (Reuter, Rosas et al. 2010), removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Segonne, Dale et al. 2004), automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (Fischl, Salat et al. 2002; Fischl, Salat et al. 2004) intensity normalization (Sled, Zijdenbos et al. 1998), tessellation of the gray matter/white matter boundary, automated topology correction (Fischl, Liu et al. 2001; Segonne, Pacheco et al. 2007), and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale, Fischl et al. 1999; Fischl and Dale 2000).

Once the cortical models are complete, a number of deformable procedures can be performed for further data processing and analysis including surface inflation (Fischl, Sereno et al. 1999), registration to a spherical atlas, which utilizes individual cortical folding patterns to match cortical geometry across subjects (Fischl, Sereno et al. 1999), parcellation of the cerebral cortex into units based on gyral and sulcal structure (Fischl, van der Kouwe et al. 2004; Desikan, Segonne et al. 2006), and creation of a variety of surface based data, including maps of surface area, curvature and sulcal depth. This method uses both intensity and continuity information from the entire three-dimensional MR volume in segmentation and deformation procedures to produce representations of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface (Fischl and Dale 2000). The maps are created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity. These maps were used to measure surface area and cortical thickness for the relevant SBM analyses.

SBM data were smoothed using 20mm full width at half maximum surface Gaussian kernel to optimize sensitive toward small structural alterations (Lerch and Evans 2005).

FreeSurfer SBM References

3.5.3 Definition of Regions of Interest

3.5.3.1 SPM ROI

For all MRI analyses, we performed an *a priori* region of interest (ROI) approach. Since no single anatomical atlas can provide regional definitions in both volume and vertex space respectively used in VBM and SBM approaches, similar but not exact matching ROIs were extracted based on the most commonly used atlases in each software.

SPM ROIs are anatomically defined with Anatomical Automatic Labelling (AAL) masks provided by the Wake Forest University PickAtlas software 3.0. (http://fmri.wfubmc.edu). This software implemented in SPM8 runs ROI analyses voxel by voxel and corrects for the number of voxels within the particular mask. Based on the AAL atlas in PickAtlas, we defined eight regions of interest resulting from left and right lateralized versions of four pairs of anatomical regions, namely: OFC as combined lateralized orbital parts of inferior frontal gyrus (Frontal_Inf_Orb), middle frontal gyrus (Frontal_Mid_Orb), superior frontal gyrus (Frontal_Sup_Orb) and medial frontal gyrus (Frontal_Med_Orb); DLPFC as the opercular parts of the inferior frontal gyrus (Frontal_Inf_Oper), and the middle frontal gyrus (Frontal_Mid); ACC as the anterior cingulate cortex (Cingulum_Ant).

3.5.3.2 Figures of SPM ROIs

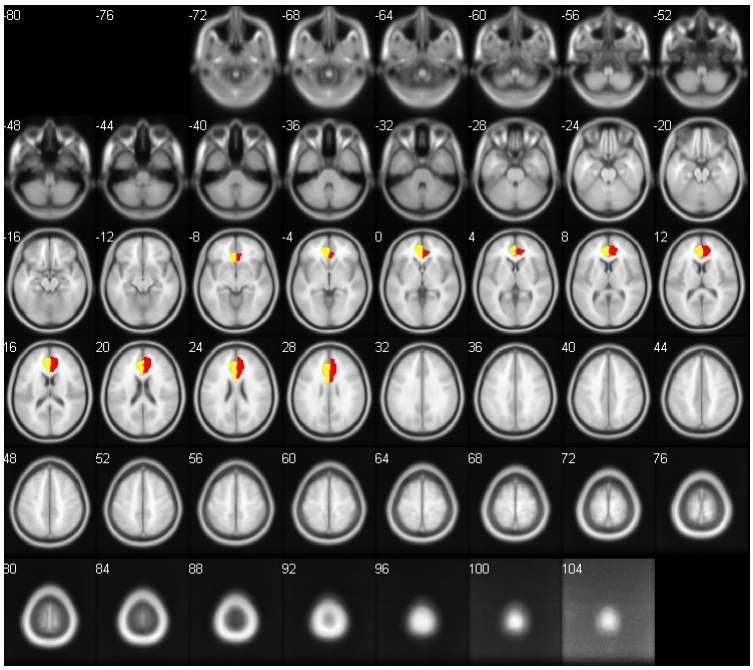

Figure 3.4. Bilateral anterior cingulate cortex regions of interest.

Yellow: Left. Red: Right

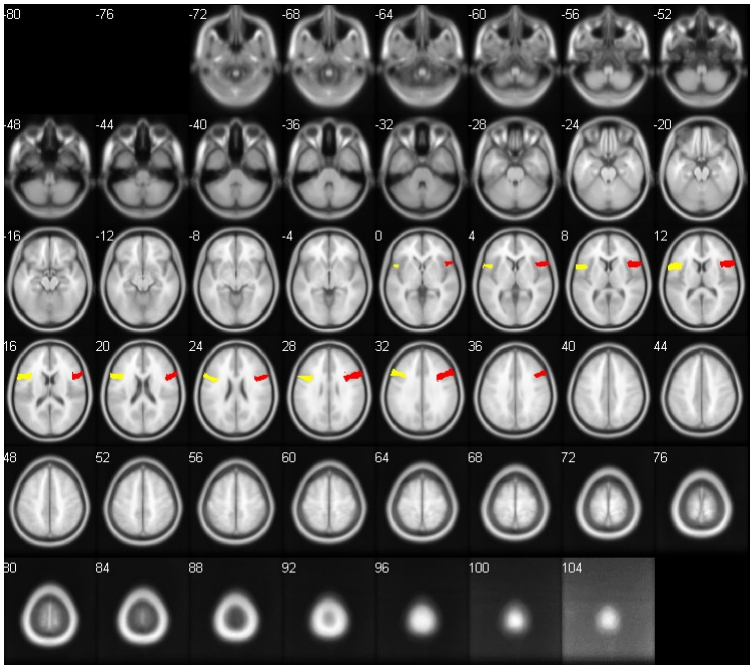

Figure 3.5. Bilateral pars opercularis inferior frontal gyrus regions of interest.

Yellow: Left. Red: Right

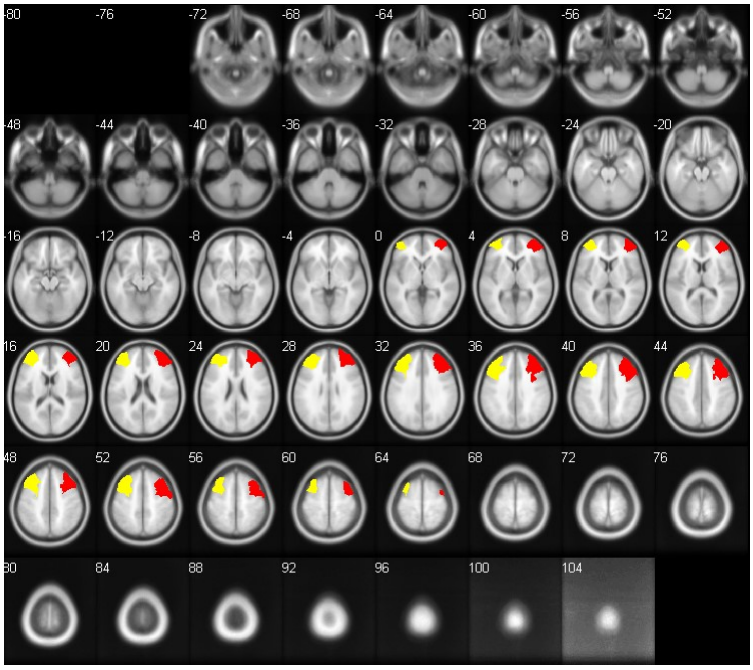

Figure 3.6. Bilateral middle frontal gyrus regions of interest.

Yellow: Left. Red: Right

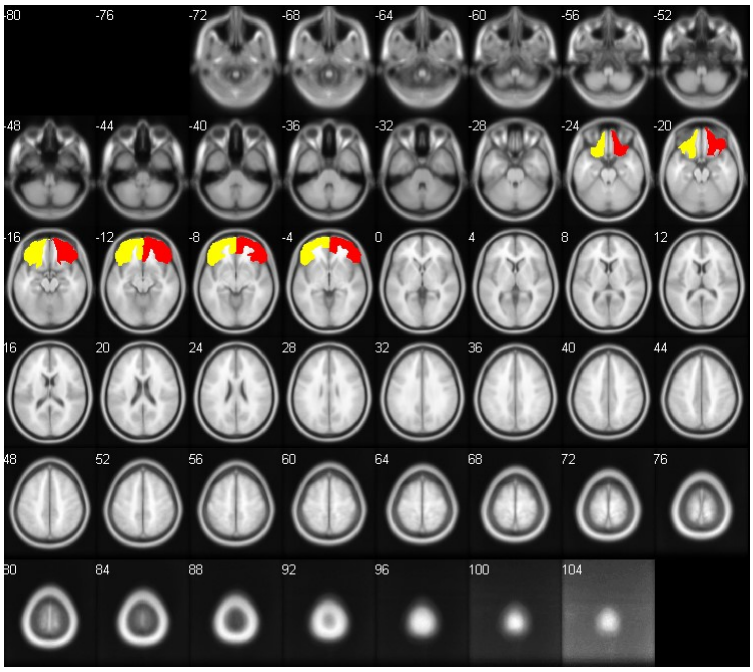

Figure 3.7: Bilateral orbitofrontal cortex regions of interest.

Yellow: Left. Red: Right

FreeSurfer requires different ROI definitions because the AAL atlas is only defined in volume space. There is no known equivalency in vertex/surface space, which is the basis of SBM analysis. The most commonly used atlases in SBM are the Desikan-Killiany Atlas for surface **area** and the Destrieux Atlas for **volume and thickness**. There is no known one-to-one matching between the corresponding regions of Destrieux, Desikan and AAL atlases.

For bilateral **volume** and **thickness** analyses with the Destrieux atlas (shown in brackets), we considered OFC to be composed of the orbital part of the inferior frontal gyrus (G_front_inf-Orbital) and the orbital gyrus (G_orbital); ACC is composed of of anterior cingulate gyrus/sulcus (G_and_S_cingul-Ant_volume); and DLPFC is composed of middle frontal gyrus (G_front_middle) and opercular part of inferior frontal gyrus. (G_front_inf-Opercular).

For bilateral **area** analyses with the Desikan atlas, OFC was considered to be a combination of the lateral orbital frontal ("lateralorbitofrontal") and orbital parts of the inferior frontal gyrus ("parsorbitalis"). ACC was composed of both its caudal and rostral components ("caudalanteriorcingulate", "rostralanteriorcingulate").

DLPFC consisted of the opercular part of the inferior frontal gyrus ("parsopercularis") and both rostral and caudal parts of the middle frontal gyrus (rostralmiddlefrontal, caudalmiddlefrontal).

Volume and **area** measures are **summed** across these atlases' defined sub-regions (i.e. giving total area, or volume of each ROI) whereas **thickness** is **averaged** across these sub-regions (i.e. average thickness within each ROI).

3.5.4 Supplementary tables[3]

Table 3.3. Comparison of socio-demographic and clinical variables across the three participant groups in Sample 1.

	Healthy Controls (n=18)		Patient Controls (n=14)		Suicide Attempters (n=12)		Omnibus F / χ^2 / t	p	Post-Hoc
Male Gender, N (%)	18	(100)	14	(100)	12	(100)	-	-	-
Age, mean (SD)	33.6	(10.9)	43.9	(10.5)	41.5	(11.1)	4.0	**0.03**	HC < PC
Years of education, N (%)	17.3	(1.8)	14.6	(2.7)	14.3	(2.6)	8.1	**0.001**	HC > PC, SA
NART, mean (SD)	0.79	(0.12)	0.81	(0.10)	0.70	(0.12)	3.4	**0.04**	PC > SA
HDRS, mean (SD)	1.1	(1.5)	2.9	(2.1)	2.2	(2.2)	3.7	**0.03**	HC < PC
BDI, mean (SD)	2.4	(4.5)	8.1	(5.3)	7.1	(6.5)	5.3	**0.009**	HC < PC
Age at first mood episode, mean (SD)	-	-	29.6	(10.7)	26.1	(14.7)	0.6	0.5	-
Number of depressive episodes, mean (SD)	-	-	3.8	(3.3)	2.7	(2.3)	8.4	0.3	-
Bipolar disorder, N (%)	-	-	-	-	-	-	-	-	-
Number of hypo/manic Episode, mean (SD)	-	-	-	-	-	-	-	-	-
Anxiety disorders	-	-	7	(50.0)	5	(41.7)	0.18	0.7	-
OCD, current, N (%)	-	-	0	(0.0)	0	(0.0)	-	-	-
Alcohol/substance abuse, past, N (%)	-	-	0	(0.0)	0	(0.0)	-	-	-
BIS10, mean (SD)	60	(9.4)	62	(9.3)	67	(10.8)	1.6	0.2	-
Psychotropic medication, N (%)	-	-	2	(14.3)	3	(25.0)	0.5	0.5	-
Antidepressant, N (%)	-	-	2	(14.3)	2	(16.7)	0.03	0.9	-
Lithium, N (%)	-	-	0	(0.0)	1	(8.3)	1.2	0.3	-
Antipsychotics, N (%)	-	-	0	(0.0)	0	(0.0)	-	-	-
Anticonvulsants, N (%)	-	-	0	(0.0)	0	(0.0)	-	-	-
Anxiolytics and hypnotics, N (%)	-	-	0	(0.0)	1	(8.3)	1.2	0.3	-
Age of first attempt, mean [min-max]	-	-	-	-	28.0	[13-52]	-	-	- -
Number of suicidal attempts, mean [min-max]	-	-	-	-	2.4	[1-6]	-	-	- -
Suicide intent scale, total score, most severe act, mean [min-max]	-	-	-	-	18.3	[13-26]	-	-	- -
Risk rescue rating scale, total score, most severe act, mean [min-max]	-	-	-	-	41.9	[26-57]	-	-	- -

[3] BIS10: Barratt Impulsivity Scale Version 10. NART: National Adult Reading Test. HDRS: Hamilton Depression Rating Scale. BDI: Beck Depression Inventory. HC: Healthy Controls. PC: Patient Controls. SA: Suicide Attempters. N.S.: not significant.

Table 3.4. Comparison of socio-demographic and clinical variables across the three participant groups in Sample 2.

	Healthy Controls (n=44)		Patient Controls (n=29)		Suicide Attempters (n=16)		Omnibus+ F / χ^2 / t	p	Post-Hoc
Male Gender, N (%)	44	(100.0)	29	(9.9)	16	(100)	-	-	-
Age, mean (SD)	40.2	(6.3)	42.1	(9.9)	40.4	(12)	0.5	0.6	-
Years of education, N (%)	14.9	(2.1)	13.6	(3.0)	13.5	(2.4)	3.5	**0.03**	-
NART, mean (SD)	0.74	(0.14)	0.75	(0.12)	0.73	(0.11)	0.07	0.9	-
HDRS, mean (SD)	0.55	(0.87)	3.1	(2.2)	2.3	(2.2)	22	**<0.001**	HC < PC, SA
BDI, mean (SD)	0.68	(1.6)	5.0	(5.1)	5.4	(4.7)	16	**<0.001**	HC < PC, SA
Age at first mood episode, mean (SD)	-	-	25.6	(9.2)	30.0	(13)	1.3	0.2	-
Number of depressive episodes, mean (SD)	-	-	7.1	(9.1)	6.4	(9.3)	3.3	0.9	-
Bipolar disorder, N (%)	-	-	16	(55)	9	(56)	0.0	0.9	-
Number of hypo/manic Episode, mean (SD)	-	-	6.1	(9.0)	7.2	(11)	7.7	0.4	-
Anxiety disorders	-	-	8	(28)	5	(31)	0.07	0.8	-
OCD, current, N (%)	-	-	1	(3.4)	0	(0.0)	0.6	0.4	-
Alcohol/substance abuse, past, N (%)	-	-	20	(69)	5	(31)	5.9	**0.02**	PC > SA
BIS10, mean (SD)	68	(8.5)	73	(12)	75	(11)	4.0	**0.02**	HC < SA
Psychotropic medication, N (%)	-	-	17	(59)	10	(63)	0.06	0.8	-
Antidepressant, N (%)	-	-	7	(24)	5	(31)	0.3	0.6	-
Lithium, N (%)	-	-	6	(21)	4	(25)	0.1	0.7	-
Antipsychotics, N (%)	-	-	4	(14)	6	(38)	3.4	0.07	-
Anticonvulsants, N (%)	-	-	6	(21)	3	(19)	0.02	0.9	-
Anxiolytics and hypnotics, N (%)	-	-	5	(17)	4	(25)	0.4	0.5	-
Age of first attempt, mean [min-max]	-	-	-	-	33.7	[14-59]	-	-	-
Number of suicidal attempts, mean [min-max]	-	-	-	-	1.5	[1-4]	-	-	-
Suicide intent scale, total score, most severe act, mean [min-max]	-	-	-	-	13.5	[2-25]	-	-	-
Risk rescue rating scale, total score, most severe act, mean [min-max]	-	-	-	-	38.6	[25-50]	-	-	-

Table 3.5. Comparison of socio-demographic and clinical variables across the three participant groups in Sample 3.

	Healthy Controls (n=20)	Patient Controls (n=39)	Suicide Attempters (n=39)	Omnibus+ F / χ^2 / t	p	Post-Hoc
Male Gender, N (%)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	-	-	-
Age, mean (SD)	36.1 (6.9)	35.9 (7.9)	38.0 (9.9)	0.7	0.5	-
Years of education, N (%)	15.3 (1.7)	14.5 (2.0)	13.9 (1.9)	3.4	**0.04**	HC > SA
NART, mean (SD)	0.65 (0.12)	0.67 (0.10)	0.67 (0.11)	0.2	0.8	-
HDRS, mean (SD)	1.6 (1.8)	4.2 (2.2)	3.8 (2.2)	11	**<0.001**	HC < PC, SA
BDI mean (SD)	0.7 (1.3)	5.0 (5.2)	4.4 (3.7)	7.7	**0.001**	HC < PC, SA
Age at first mood episode, mean (SD)	- -	24.5 (8.1)	23.2 (8.2)	0.7	0.5	-
Number of depressive episodes, mean (SD)	- -	3.9 (8.9)	6.1 (8.6)	27	**0.03**	PC < SA
Bipolar disorder, N (%)	- -	14 (36)	21 (54)	2.5	0.1	-
Number of hypo/manic Episode, mean (SD)	- -	2.2 (8.1)	3.6 (9.5)	10	0.5	-
Anxiety disorders	- -	13 (33)	17 (44)	0.9	0.4	-
OCD, current, N (%)	- -	2 (5.1)	0 (0.0)	2.1	0.2	-
Alcohol/substance abuse, past, N (%)	- -	6 (15)	11 (28)	1.9	0.2	-
BIS10, mean (SD)	44 (12)	48 (13)	49 (13)	1.2	0.3	-
Psychotropic medication, N (%)	- -	28 (72)	33 (85)	1.9	0.2	-
Antidepressant, N (%)	- -	16 (41)	17 (44)	0.05	0.8	-
Lithium, N (%)	- -	8 (21)	8 (21)	0.0	1.0	-
Antipsychotics, N (%)	- -	2 (5.1)	11 (28)	7.5	**0.006**	PC < SA
Anticonvulsants, N (%)	- -	8 (21)	11 (28)	0.6	0.4	-
Anxiolytics and hypnotics, N (%)	- -	9 (23)	15 (39)	2.2	0.1	-
Age of first attempt, mean [min-max]	- -	- -	25.1 [11-43]	-	-	-
Number of suicidal attempts, mean [min-max]	- -	- -	3.2 [1-10]	-	-	-
Suicide intent scale, total score, most severe act, mean [min-max]	- -	- -	13 [5-26]	-	-	-
Risk rescue rating scale, total score, most severe act, mean [min-max]	- -	- -	39 [28-57]	-	-	-

Chapter 4 Altered Brain Processing of Decision-Making in Healthy First-Degree Biological Relatives of Suicide Completers

A version of this chapter has been adapted and is currently under preparation to be submitted. The full list of co-author includes Yang Ding[1], Martin Lepage[2], Gustavo Turecki[1,2], Fabrice Jollant[1,3] with the follwing academic affiliations:

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4.1 Introduction

Over the last 15 years, a large number of studies have revealed neurocognitive deficits in suicide attempters (Jollant, Lawrence et al. 2011). A recent meta-analysis notably confirmed a significant association between suicidal behaviour and disadvantageous decision-making (Richard-Devantoy, Berlim et al. 2013), with more risky choices in patients with histories of suicidal behaviour compared to patients with no such history and healthy controls. Moreover, impaired decision-making was found more often in attempters who used a violent suicidal method (Jollant, Bellivier et al. 2005), a population at increased risk of subsequent suicide completion (Bergen, Hawton et al. 2012), and in normothymic suicide attempters, suggesting trait-like characteristics (Jollant, Bellivier et al. 2005). Disadvantageous decision-making may therefore represent a major component of the vulnerability to suicide completion. (Brent and Mann 2005)

Compelling evidence from family, twin and adoption studies also suggests that the vulnerability to suicidal behaviour is genetically mediated, with heritability reaching 50% (and 20% when comorbid psychiatric disorders were taken into account) (Brent and Mann 2005; Turecki and Brent 2015). Understanding factors of familial liability to suicide—e.g. through the assessment of first-degree biological relatives—is a relevant way to uncover or confirm mechanisms involved in the risk of suicide completion, beyond the limits of only studying suicide attempters and the difficulty of running prospective studies. Importantly, the transmission of suicide risk within

families is partly explained by the transmission of certain personality traits (McGirr, Alda et al. 2009), which suggests that trait-like cognitive deficits, notably risky decision-making, could run within families of suicide completers.

Several studies have supported the heritability of decision-making abilities. A twin study in the general population suggests that the heritability of decision-making during late adolescence is approximately 50% (Tuvblad, Gao et al. 2013). Other studies have also reported the heritability of this cognitive function in first-degree relatives of patients with alcoholism and obsessive-compulsive disorder (Lovallo, Yechiam et al. 2006; Cavedini, Zorzi et al. 2010). In the same subjects as for the current study, we showed that relatives of suicide completers, in comparison to both relatives of patients and healthy controls, display subtle but significant impairments in their ability to improve their performance during the Iowa Gambling Task, a value-based decision-making task (Hoehne, Richard-Devantoy et al. 2015). They notably continue to choose riskier options at the end of the task while controls have usually learned to avoid these options and switch to safer ones. Although prospective studies have yet to be conducted to fulfill the definition criteria, these findings suggest that risky decision-making could be an endophenotype of suicide.

In the present study, we investigated the neural basis of decision-making in first-degree relatives of suicide completers in order to identify the regions most likely associated with the genetic risk of suicide. Decision-making is a complex cognitive function that relies on various brain regions (Lawrence, Jollant et al. 2009). Disadvantageous decision-making in suicide attempters has been linked to reduced activity in the ventral prefrontal cortex during risk processing (Jollant, Lawrence et al. 2010). We previously suggested that the vulnerability to suicidal behaviour comprised an inadequate processing of risk and social values (Jollant, Lawrence et al. 2011), a hypothesis supported by imaging studies in suicide attempters using a reinforcement learning paradigm (Dombrovski, Szanto et al. 2013) and an emotional faces task (Jollant, Lawrence et al. 2008). Showing valuation deficits during decision-making in suicide relatives may strongly support this hypothesis.

To this end, we used the same neuroimaging protocol previously used in studies of suicide attempters (Jollant, Lawrence et al.). Moreover, in addition to healthy controls serving as the reference group, we recruited a group of relatives of depressed individuals with no personal or family history of suicidal behaviour. This enabled us to attribute differences between relatives of suicide completers and controls to traits specifically related to suicide and not to the familial transmission of depression. Finally, none of the participants were depressed at the time of scanning, which made it possible to identify neurocognitive traits independently of the acute effects of depression.

Based on previous findings, we hypothesized that relatives of suicide completers, although without any personal history of a suicidal act, will show a reduced response in the ventral prefrontal cortex during risky choices, an alteration associated with lower decision-making performance.

4.2 Material and Methods

4.2.1 Population

Three independent groups of participants aged 18 to 55 were recruited. 1) Seventeen first-degree biological relatives of suicides who died in a context of major depressive disorder, but not schizophrenia, bipolar disorder or unknown disorders (*suicide relatives*). Suicide relatives had no personal history of a suicide attempt themselves. 2) Sixteen first-degree biological relatives of depressed patients (*patient relatives*) with no personal or family (up to second biological degree) history of suicidal acts. Patients suffered from major depressive disorder, but not schizophrenia, bipolar disorder or unknown disorders. 3) Nineteen *healthy controls* with no personal or family (up to second biological degree) history of suicidal behaviour or major mental disorders. All participants had to be normothymic at the time of participation and free of psychotropic medication for the last six months.

Additional non-inclusion criteria for all participants included alcohol and substance dependence or abuse within the last 12 months, major comorbid psychiatric disorders such as schizophrenia and bipolar disorder, a lifetime history of severe head trauma or a central nervous system disorder, and any contra-indication to magnetic resonance imaging (MRI).

Suicide relatives had at least one first-degree biological relative who committed suicide, commonly defined as an act carried out with some intent to die and having led to death. The Family Interview for Genetics Studies (FIGS) was used to assess suicide on the basis of information given by the relative (https://www.nimhgenetics.org/interviews/figs/). Unclear cases (e.g. where there was doubt concerning an accident) were excluded.

4.2.2 Clinical assessment

All participants had to be normothymic at the time of participation as per the Structured Clinical Interview for Axis I DSM-IV (SCID-I) (First, Spitzer et al. 2002), and a 21-item Hamilton Depression Rating Scale (HAMD-21) (Hamilton 1960) score below 8. All participants also had to be right-handed as per the Edinburgh handedness inventory (Oldfield 1971).

Diagnoses were made in accordance with DSM IV criteria using the SCID-I (First, Spitzer et al. 2002) and SCID-II (First 1997). Level of depression was measured with the HAMD-21 (Hamilton 1960) and the Beck Depression Inventory (BDI) (Beck, Ward et al. 1961), and level of anxiety was measured with the Spielberger State Trait Inventory (STAXI)(Spielberger 1983). The Buss-Durkee Hostility Inventory (BDHI) (Buss and Durkee 1957), the Brown-Goodwin Assessment of Lifetime History of Aggression (BGLHA) (Brown, Goodwin et al. 1979), and the Barratt's Impulsivity Scale (BIS-11) (Patton, Stanford et al. 1995) were used to assess traits of hostility, aggression and impulsivity, respectively. Finally, the National Adult Reading Test (NART) was used as a measure of verbal IQ (Mackinnon 1999).

Informed written consent was obtained from all participants. This study was conducted at the Douglas Mental Health University Institute in Montréal and approved by the local ethics committee. Participants received 50 CAD for their time.

4.2.3 Statistical analyses

For all quantitative variables, normality of distribution was *a priori* assessed with a Shapiro-Wilk's test and equality of variance with Levene's test. As assumptions for their use were satisfied most of the time, ANOVA and general linear models (GLM) were used to investigate the association between group and quantitative

variables, including covariates where needed. Post-hoc analyses were conducted using Fisher's least significant difference (LSD). A Chi-square test was used to compare qualitative variables. P-values of less than 0.05 were considered statistically significant. A Pearson's test was used for correlations. All analyses were performed using SPSS version 21.0 (SPSS, Inc., Chicago, IL).

4.3 Iowa Gambling Task (IGT)

A previously validated and modified version of the IGT (Bechara, Damasio et al. 1999) was used to measure decision-making during the MRI session (for a detailed description of the task and changes, see Lawrence, Jollant et al. 2009). Briefly, the Iowa Gambling Task involves participants being asked to pick a card from among four decks presented on a screen. Each time they pick a card, they win or lose money. The goal of the game is to win as much money as possible. They do not know that they will have to pick 100 cards in total, nor that two decks are advantageous (safe), as gains overcome losses in the long-term, while two decks are disadvantageous (risky), as losses overcome gains in the long-term. However, they are informed that some decks are better than others. Contrary to the original version, the two safe decks and the two risky decks are similar in terms of frequency and level of outcomes (Supplementary Figure 1).

4.3.1 Imaging acquisition

Usually the same day or less than a week after the clinical evaluation, functional neuroimaging scans were carried out at the Brain Imaging Centre of the Douglas Institute using a 3T Siemens Magnetom Trio MRI scanner with a 12-channel head coil. Blood-oxygen-level dependent (BOLD) signals were acquired on 38 contiguous 3.5mm transversal slices with a T2-weighted gradient echo-planar imaging (EPI) sequence. Repetition time: 2.09 ms. Echo time: 30 ms. Field of view: 24mm. Base resolution: 64x64. In-plane resolution: 3.5mm × 3.5mm. GRAPPA acceleration: 2. Descending sequential acquisition. Stimuli were displayed on an MRI-compatible liquid crystal screen at the rear of the scanning bore, viewable via a mirror by the participant.

Structural scans consisted of a high resolution, whole brain T1-weighted acquisition. The data were acquired using a Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence with TR / TE / flip angle = 2300 ms

/ 2.98 ms / 9 degrees, and a base resolution of 256 × 256, with 1mm^3 isotropic voxels resulting in acquisition time of 9.25 minutes.

4.3.2 Image analyses

Functional MRI data were analyzed with SPM12 (Wellcome Department of Imaging Neuroscience, London, UK), implemented in Matlab 2014a (Mathworks, Inc., Natick, MA). A standard indirect normalization preprocessing routine was performed. This involved a slice-timing correction for the functional time-series using sinc function, realignment of functional data to its first volume within each individual, co-registration of functional and structural images, segmentation of structural images to produce a forward map to MNI template space, spatial normalizing to MNI template and smoothing with an isotropic 8mm full-width half maximum Gaussian Kernel. Low frequency temporal drifts in fMRI signal were removed by applying a high-pass filter with a cut-off of 128s.

A first-level fixed-effect event-related model for each individual was constructed for the following two temporally distinct conditions. 1) *Choice* when participants click on a specific deck. Choices were analyzed as safe or risky based on the deck chosen. 2) *Outcome* corresponding to the two-second outcome phase. Outcomes were analyzed as wins or losses. In both first-level models, motion parameters and the preparation phase prior to which participants made a choice were included as regressors. Canonical hemodynamic response function and its temporal and dispersion derivatives were regressed with the onsets and duration of the conditions, but only the canonical component was used to calculate the contrasts to compensate for hemodynamic response function variability (Supplementary Figures 2 & 3).

We then constructed separate second-level random-effect general linear models to compare the contrast images between the groups after including age or gender as covariates. Three-group comparisons were first conducted to assess the main effect of group, using an uncorrected voxel-wise p-value of 0.001 with a minimum extent threshold of 10 voxels, for purposes of visualization and exploration at the multi-group level. If significant voxels were found, pairwise comparisons were then conducted and only clusters with both FWE cluster-corrected $p < 0.05$ at the whole brain level and overlapping with significant findings from the three-group comparison were retained. FWE-correction followed a Gaussian random field theory.

We further evaluated task-dependent functional connectivity using psychophysiological interactions (PPI) analyses implemented in SPM12.[27] In short, a representative activity time course from the region of interest showing significant group differences is extracted and demeaned. Then, an interaction regressor is generated by convolving the extracted BOLD signal with the task time course and it is entered as a regressor in the GLM analyses after including covariates.

Results

4.3.3 Demographic and clinical variables

Table 4.1. Comparison of socio-demographic and clinical variables between the three groups.

	Healthy controls (HC) n=19		Patient relatives (PR) n=16		Suicide relatives (SR) n=17		F / χ^2	P	Post-Hoc
Male Gender, N (%)	13	(68.4)	6	(37.5)	8	(47.1)	3.6	0.2	
Age, mean (SD)	32.8	(9.9)	38.0	(8.7)	51.4	(9.4)	18.4	$<10^{-3}$	SR>PR, HC
NART ratio, mean (SD)	0.8	(0.1)	0.7	(0.2)	0.7	(0.2)	1.3	0.3	
Education, N (%)							8.0	0.1	
High school	0	(0)	3	(18.8)	2	(11.8)			
College	2	(12.5)	3	(18.8)	7	(41.2)			
University	14	(87.5)	10	(62.5)	8	(47.1)			
BDI score, mean (SD)	1.3	(1.5)	1.7	(2.2)	1.8	(3.0)	0.2	0.8	
HAM-D score, mean (SD)	1.7	(2.1)	1.4	(1.4)	2.3	(2.0)	0.9	0.4	
STAIA score, mean (SD)	25.5	(6.9)	26.9	(5.0)	22.6	(4.2)	1.0	0.4	
SCID I past history of depression, N (%)	1	(6.7)	3	(20.0)	5	(29.4)	2.7	0.3	
SCID I past substance abuse, N (%)	1	(6.7)	1	(6.7)	0	(0)	1.2	0.6	
SCID II personality disorders, N (%)	0	(0)	2	(13.3)	1	(6.3)	2.1	0.4	
BDHI score, mean (SD)	47.6	(9.1)	42.0	(13.4)	46.6	(6.0)	1.2	0.3	
STAIB score, mean (SD)	29.4	(4.6)	36.0	(8.3)	28.2	(6.4)	4.0	0.03	PR > HC, SR
BIS score, mean (SD)	73.1	(4.9)	72.4	(3.0)	72.9	(4.0)	0.1	0.9	

All groups were similar for most clinical variables. Suicide relatives were significantly older than both control groups; age was therefore used as a covariate in all neuroimaging analyses. Finally, patient relatives had higher levels of anxiety-traits than the two other groups.

Neuropsychological performances are detailed elsewhere (Hoehne, Richard-Devantoy et al. 2015). Briefly, suicide relatives showed a trend toward reduced ability to learn to avoid risky decks compared to both patient

relatives and healthy controls. In contrast, no significant group difference was found in terms of cognitive control with the exception of more corrected errors (taking into account the number of errors) at the Stroop test in suicide relatives. We hypothesized that risky decision-making was an endophenotype of suicide, while normal (or corrected) cognitive control may protect these individuals against suicide.

4.3.4 BOLD responses

Within-group contrasts are presented in Supplementary material.

4.3.4.1 Choice processing

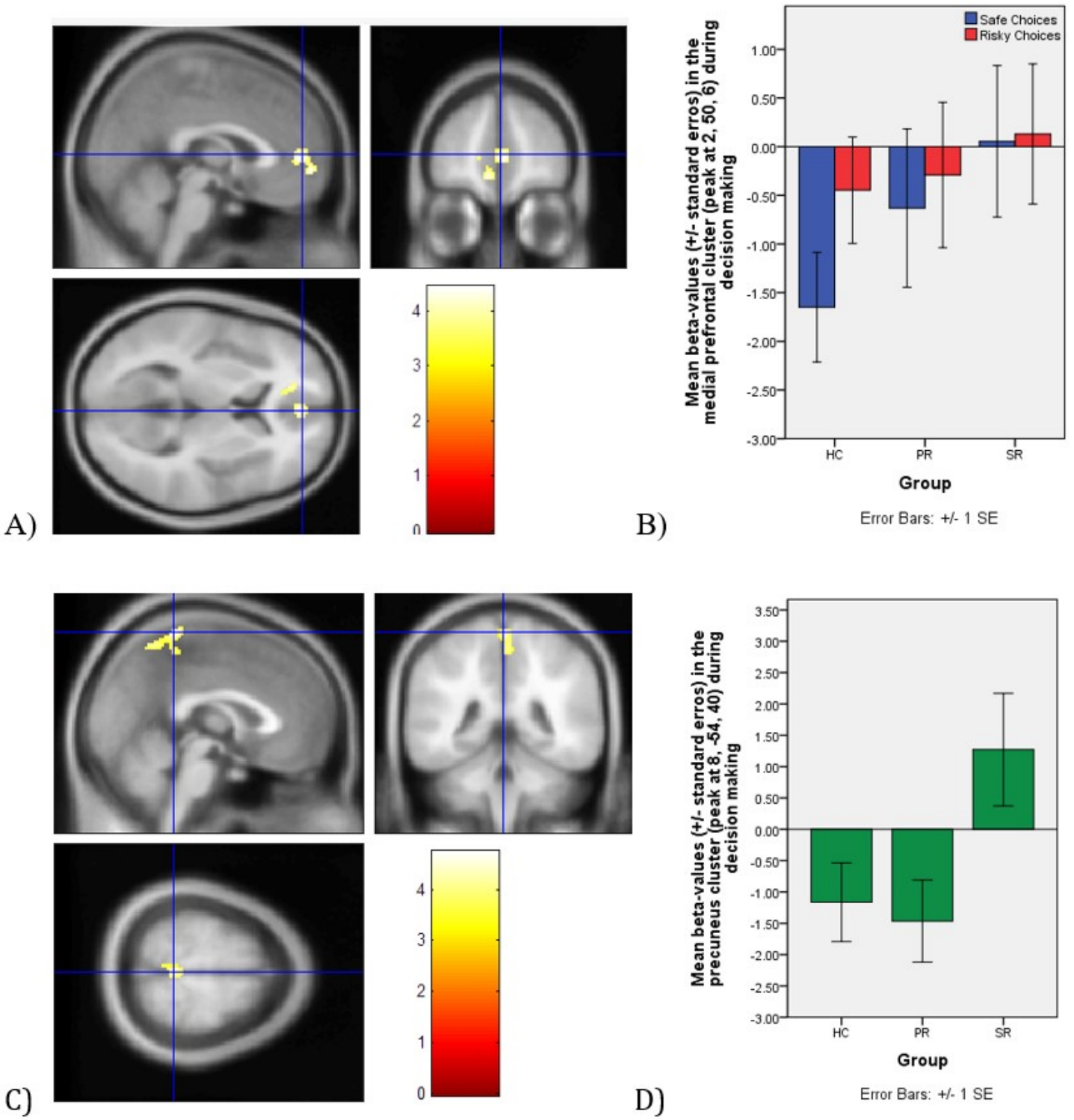

Figure 4.1. Blood-oxygen level dependent brain activation in relation to choice processing during Iowa Gambling Task.

A) Significant difference between suicide relatives and healthy controls in the ventromedial prefrontal cortex (mostly BA10) for the contrast between risky and safe choices. B) Representation of mean beta-values of safe choices and risky choices vs. baseline for the three groups in ventromedial prefrontal cortex. C) Significant difference between suicide relatives and patient relatives in precuneus (BA7) for the contrast all choices vs. baseline (co-variating for anxiety-trait). D) Representation of mean

beta-values of all choices vs. baseline for the three groups in precuneus. HC: Healthy Controls. PR: Patient Relatives. SR: Suicide Relatives.

Between-group comparisons for the risky vs. safe choice contrast across all three groups showed a significant difference in a cluster corresponding to bilateral ventral, anterior and medial prefrontal cortex (corresponding mainly to BA10 extending to BA32: $p_{unc} < 0.001$; DoF = 2, 48; 22 voxels; peak Z = 3.57 at 4, 50, 6). Pairwise comparisons showed a significant group difference for this cluster between healthy controls and suicide relatives ($p_{corrected} < 0.05$; DoF = 33; 285 voxels; peak Z = 3.90 at 2, 50, 6 extending toward -8, 48, -8) (Figure 1A) with no significant difference between healthy controls and patient relatives, or between patient relatives and suicide relatives. Extracted beta values from this region (Figure 1B**)** revealed no difference in activation level between risky and safe choices in suicide relatives, in contrast to the other two groups, where a more marked activation decrease was observed during safe choices compared to risky choices. Moreover, this difference tended to be correlated with the IGT total net score in all participants, after adjusting for age and group (r=-0.26; p=0.07).

Using this cluster as the seed region, PPI analyses showed significantly stronger functional connectivity in suicide relatives compared to healthy controls between the right ventromedial prefrontal cortex and bilateral cerebellum, right parietal cortex, and right inferior frontal gyrus (Supplementary Figure 5).

Finally, we contrasted all choices vs. baseline in suicide relatives vs. patient relatives in order to identify general processes implicated in choices that may not differ according to risk level. After co-variating for anxiety-trait, the right precuneus (BA7, $p_{corrected} < 0.05$; DoF = 30; 297 voxels; peak Z = 4.05 at 6, -60, 56) and right cerebellum (**$p_{corrected} < 0.05$**; DoF = 30; 303 voxels; peak Z = 3.65 at 16, -78, -32) were more activated in suicide relatives (Figures 1C and D).

4.3.4.2 Outcome processing

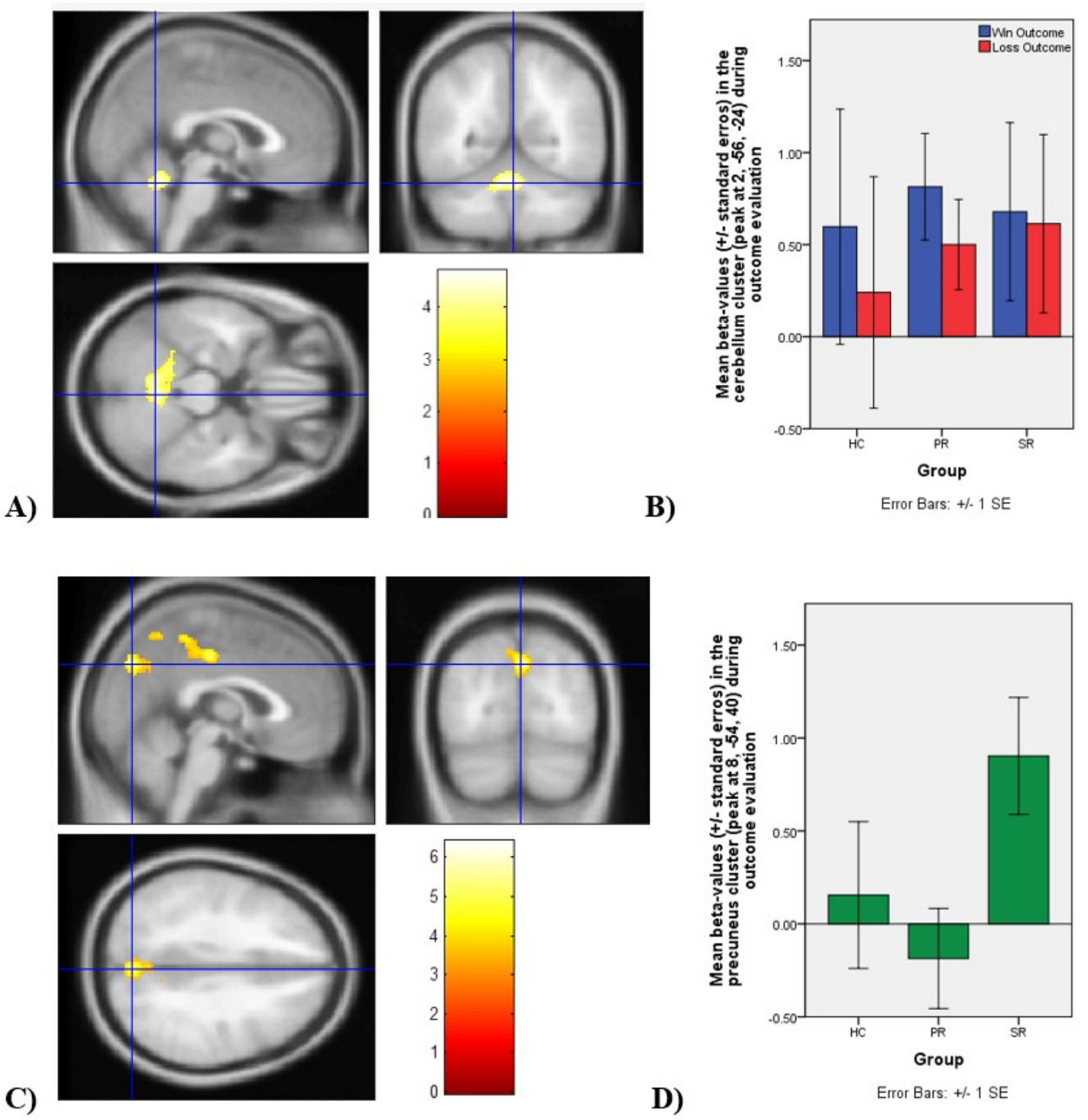

Figure 4.2. Blood-oxygen level dependent brain activation in relation to outcome processing during Iowa Gambling Task.

A) Significant difference between suicide relatives and healthy controls in the cerebellum for the contrast between wins and losses. B) Representation of mean beta-values of wins and losses vs. baseline for the three groups in the cerebellum. C) Significant difference between suicide relatives and patient relatives in the precuneus (BA7) for the contrast between wins and losses (co-variating for anxiety-trait). D) Representation of mean beta-values of all outcomes vs. baseline for the three groups in the precuneus. HC: Healthy Controls. PR: Patient Relatives. SR: Suicide Relatives.

Between-group comparison for the wins vs. losses contrast (Figure 2A) across all three groups showed regional differences in two clusters located in the right caudate ($p_{unc} < 0.001$; DoF = 2, 48; 10 voxels; peak Z = 3.54 at 0, 18, -2) and left cerebellum ($p_{unc} < 0•001$; DoF = 2, 48; 67 voxels; peak Z = 3.41 at -2, -56, -24). Pairwise corrected comparisons revealed a larger activation in healthy controls than suicide relatives in the right cerebellar cluster only ($p_{corrected} < 0.05$; DoF = 33; 525 voxels; peak Z = 4.09 at 2, -56, -24 mainly corresponding to lobule VI). Comparison between patient relatives and suicide relatives suggests a greater activation in patient relatives in the cerebellum at an uncorrected level but this did not survive whole brain correction. No other pairwise comparisons showed significant differences. Figure 2B shows a stronger contrast between wins and losses while this discrimination is lost in suicide relatives.

We also explored group differences in functional connectivity using the aforementioned significant cerebellum cluster as the seed region. No significant differences between suicide relatives and healthy controls were found after whole brain correction.

Finally, we contrasted all outcomes vs. baseline in suicide relatives vs. patient relatives in order to identify general processes implicated in outcome processing that cannot be found in the wins vs. losses contrast. After co-variating for anxiety-traits, we detected in suicide relatives increased activation in the bilateral precuneus (BA7; $p_{corrected} < 0.05$; DoF = 30; 271 voxels; peak Z = 4.72 at -2, -58, 58) extending to the right posterior cingulate (B31; $p_{corrected} < 0.05$; DoF = 30; 201 voxels; peak Z = 4.05 at 2, -22, 42) and right caudate ($p_{corrected} < 0.05$; DoF = 30; 350 voxels; peak Z = 5.00 at 20, -12, 28) (Figures 2C and 2D).

In all analyses, excluding the two healthy controls with past personal histories of substance abuse or depression did not modify the results. Finally, when the IGT total or last 20 choices net scores were used as covariates, none of the main results survived suggesting that our neuroimaging findings are related to decision-making performance.

4.4 Discussion

This study examined brain processing of decision-making in first-degree biological relatives of individuals who suffered from major depression and committed suicide. Investigating this population overcomes some of the limitation of studies conducted in suicide attempters (most attempters will never die from suicide; they are often medicated and symptomatic at inclusion). Although suicide relatives were healthy and had no personal history of a suicidal act, we identified a pattern of activation differences in comparison to control groups during risk and reward processing, affecting a network of functionally interconnected brain regions. Suicide relatives notably showed reduced activation contrast according to risk level (long-term disadvantageous vs. advantageous choices) in the ventromedial prefrontal cortex, and according to outcome (wins vs. losses) in the cerebellum in comparison to healthy controls. They also showed increased activation during choice and outcome processing in the cerebellum and precuneus in comparison to patient relatives. Our study, therefore, confirms that deficits in risk and reward processing, in relation to the ventral prefrontal cortex, precuneus and cerebellum, may be key mechanisms in the risk of suicide.

Previous studies have implicated the anterior and ventral medial prefrontal cortex in suicidal behaviour, notably a higher activation during resting state (Sublette, Milak et al. 2013) and a reduced trapping of a serotonergic synthesis marker (Leyton, Paquette et al. 2006), suggesting functional impairments in relation to altered serotonergic modulation. This region is also very close to the region (located in -7, 28, 5) identified in a previous study showing less activation for expected rewards in elderly suicide attempters (Dombrovski, Clark et al. 2010). The medial prefrontal cortex is part of a network of brain regions involved in decision-making (Lawrence, Jollant et al. 2009). It notably encodes the value of various reinforcing stimuli, including expected values to guide choices. In the current study, we found a greater reduction of activation in this region when controls made safe choices rather than risky choices. Moreover, the larger the difference in activation at time of choosing the better the final performance. This difference in activation was not observed in suicide relatives. Interestingly, we previously reported this lack of discrimination in risk level in suicide attempters using the exact same task (Jollant,

Lawrence et al. 2010), which suggests a similar inability of the ventral prefrontal cortex to encode the value of risk.

We also found the precuneus to be more activated during both choice and outcome processing (vs. baseline) in suicide relatives than in patient relatives. This region has previously been associated with suicidal behaviour in neuroimaging studies (Hwang, Lee et al. 2010; Benedetti, Radaelli et al. 2011; Willeumier, Taylor et al. 2011; Chen, Zhang et al. 2015). Its role in this context, however, is unknown. The precuneus is a major associative area with multiple connections including the medial prefrontal cortex and cerebellum and it has been implicated in various functions, notably self-representation (Cavanna and Trimble 2006). The posterior parietal cortex has also been involved in decision-making (Jocham, Furlong et al. 2014) and salience processing (Kahnt, Park et al. 2014). However, in our study, increased activation of this region in suicide relatives during decision-making, irrespective of the level of risk or type of outcome, may reflect global difficulties in attention switching or episodic memory retrieval, deficits also found in suicide attempters (Richard-Devantoy, Berlim et al. 2013; Richard-Devantoy, Berlim et al. 2015). These assumptions are nonetheless speculative at this stage.

Finally, the cerebellum showed a decreased activation difference between wins vs. losses in suicide relatives vs. healthy controls and an increased activation during choices in general in suicide relatives vs. patient relatives. Structural and functional alterations in the cerebellum have previously been associated with suicide vulnerability, but its role has usually been overlooked (Jollant, Lawrence et al. 2008; Hwang, Lee et al. 2010). While the participation of the cerebellum in cognitive processes is still subject of debate, it could be involved in learning, working memory, automaticity and behavioural adaptation—all of which are functions necessary for adaptive decision-making (Koziol, Budding et al. 2014). A more general role would be to monitor and regulate associative regions through reciprocal projections, and for the lobule identified in the present study, to participate in a salience network (Habas, Kamdar et al. 2009; Koziol, Budding et al. 2014). Again, more specific exploration of the role of this region will have to be conducted.

Several limitations of this study must be underlined. The main limitation is the relatively small sample size, which increases the risk of type I and II errors. This may explain the lack of an activation difference between suicide relatives and patient relatives for the contrasts between wins and losses and risky vs. safe choices. Moreover, no formal sample size calculation could be run prior to this study due to a lack of available data. While our experience has shown recruiting this population can be complicated, it is important that these findings be replicated. Investigating relatives of suicide attempters would also be interesting. Second, suicide relatives were older than both control groups, leading us to covariate for age. This may have reduced the chances of detecting subtle group differences.

In conclusion, this study supports a significant role for impaired decision-making in suicidal vulnerability. It notably confirms that heritable and persistent deficits in risk and reward processing may be key mechanisms. It also sheds light on potential brain areas underlying these complex behaviours, and it opens new avenues for the investigation and prevention of suicide.

4.5 Supplementary Material

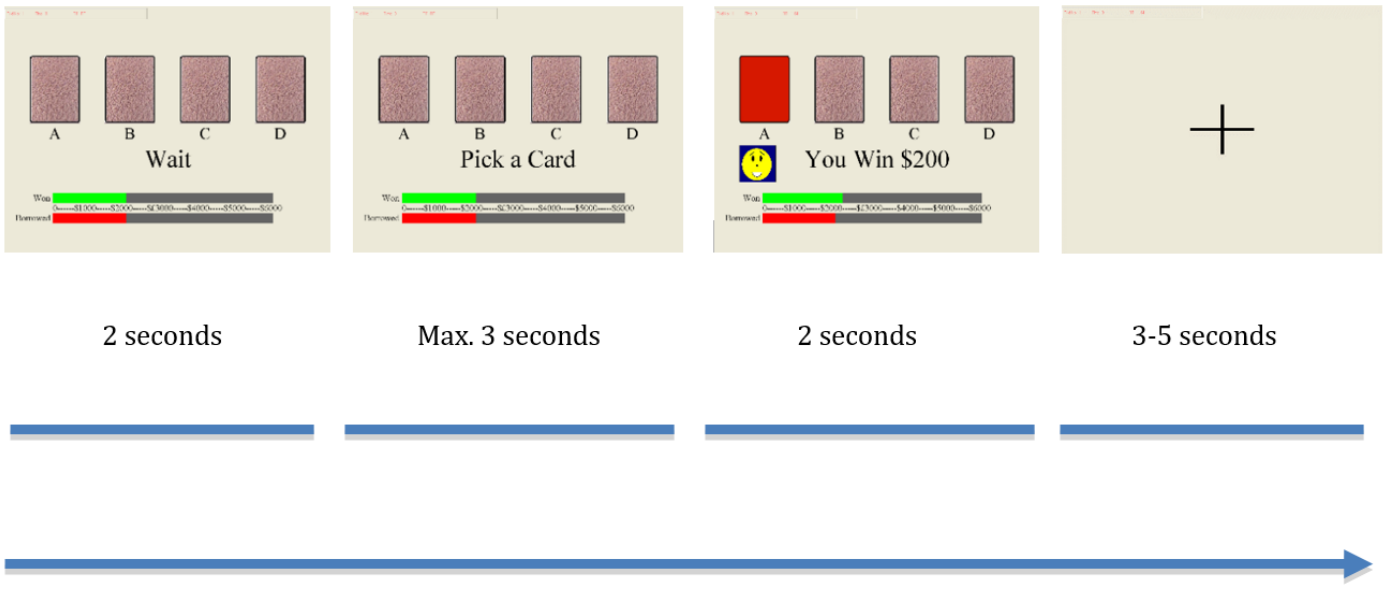

Figure 4.3. Presentation of the four consecutive sequences during the functional magnetic resonance imaging version of the Iowa Gambling Task used in this study.

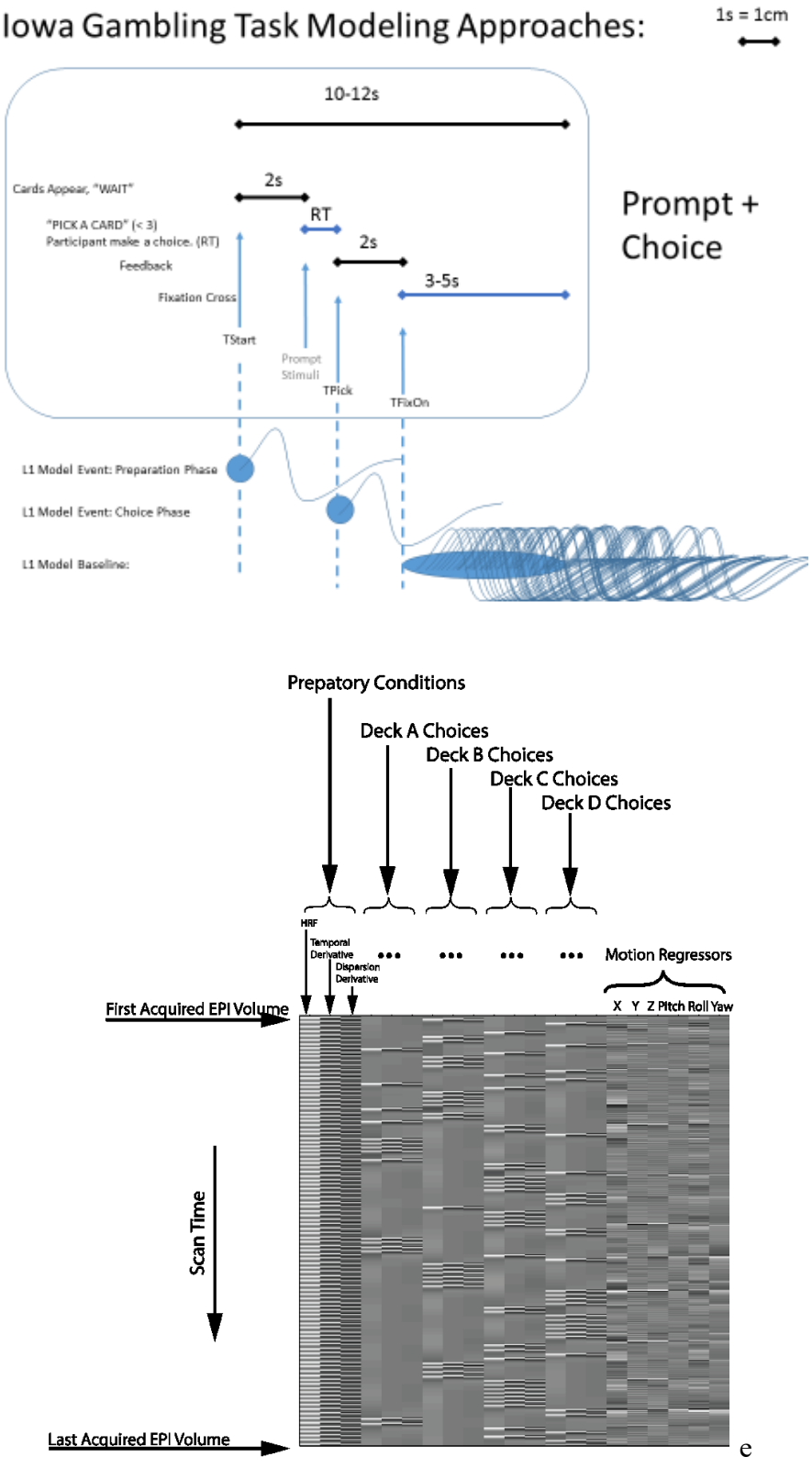

Figure 4.4. Modeling of the Iowa Gambling Task analyses for choices.

Top: timing diagram. Bottom: example single subject design matrix.

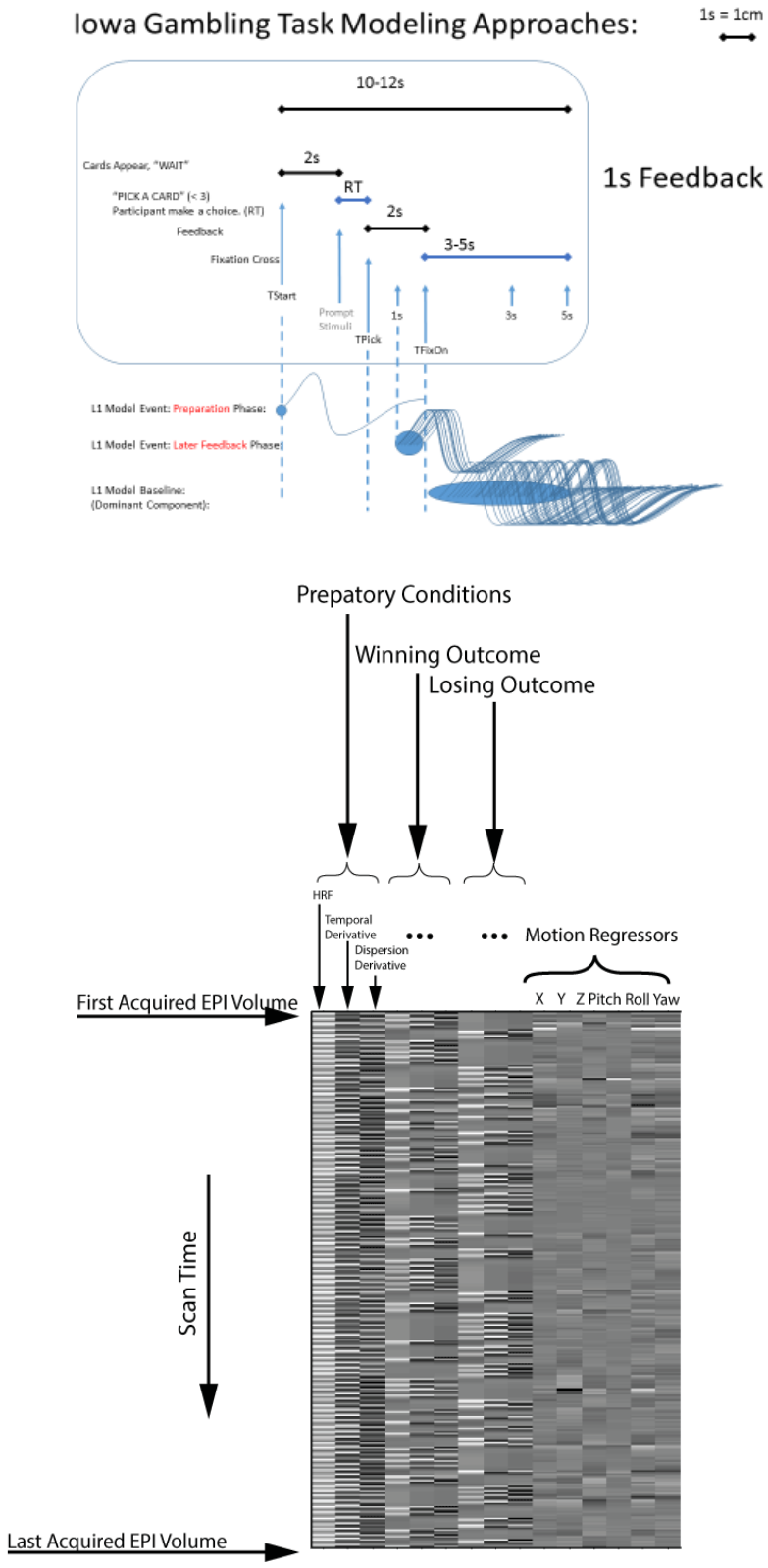

Figure 4.5. Modeling of the Iowa Gambling Task analyses for outcomes.

Top: Timing Diagram. Bottom: Example Single Subject Design Matrix

4.5.1 Supplementary Results

4.5.1.1 Choice processing

Within-group contrasts between risky and safe choices **(**Figure 4.6**)** in suicide relatives showed significant activation in the right dorsomedial prefrontal cortex (Brodmann Area [BA] 9 extending to the anterior cingulate; $p < 0.05$ corrected, 307 voxels, peak Z = 4.49; peak voxel: 8, 38, 28). In patient relatives, significant activation was observed only in the left occipital cortex (BA18; $p = 0.05$ corrected, 175 voxels, peak Z = 4.15 at -12, -92, 0). In healthy controls, significant activation was found in the anterior cingulate cortex (BA32; $p < 0.05$ corrected, 2052 voxels, peak Z = 4.71 at 0, 48, 4), left orbitofrontal cortex (BA47; $p < 0.05$ corrected, 298 voxels, peak Z = 4.03 at -42, 20, -6), and left occipital cortex (BA18; $p < 0.05$ corrected, 542 voxels, peak Z = 5.33 at -20, -92, 4).

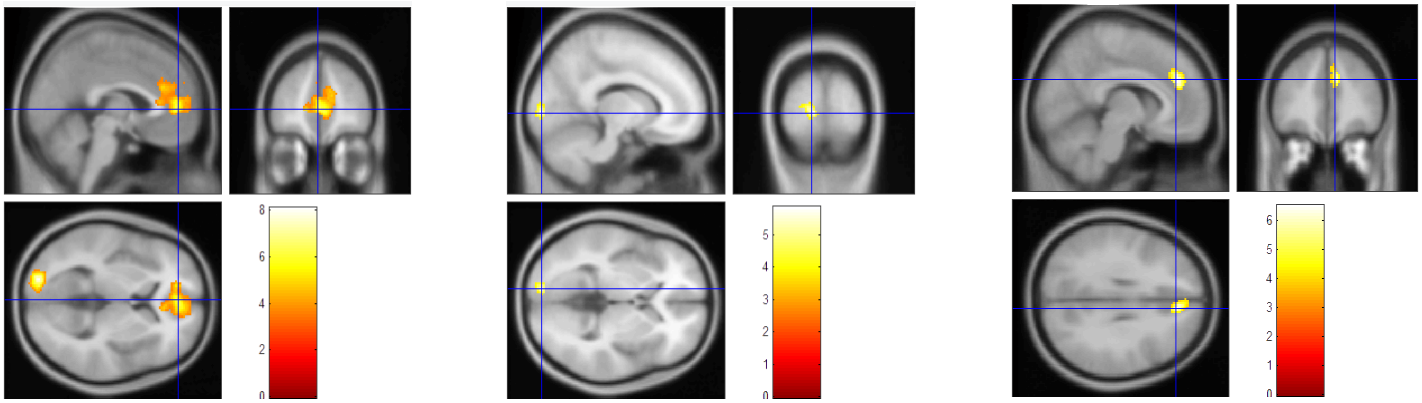

Figure 4.6. Within-group analyses for the contrast between risky and safe choices.
From left to right: healthy controls, patient relatives, and suicide relatives.

PPI analyses showed significantly stronger functional connectivity in suicide relatives compared to healthy controls between the ventromedial prefrontal cortex and left inferior occipital cortex/cerebellum ($P_{corrected} < 0.001$, 2635 voxels, with a peak Z value of 4.54 at -22, -70, -16), right cerebellum ($P_{corrected} < 0.001$, 1550 voxels, with a peak Z value of 4.98 at 26, -78, -18), left (BA7, $P_{corrected} = 0.004$, 403 voxels, with a peak Z value of 4.36 at -24, -62, 40) and right superior parietal cortex/precuneus (BA7, $P_{corrected} = 0.003$, 420 voxels, with a peak Z value of 3.98 at 22, -72, 50) and right inferior frontal gyrus, pars opercularis (BA44, $P_{corrected} = 0.001$, 497 voxels with a peak Z value of 3.93 at 56, 12, 34) (Figure 4.7).

Direct comparison between suicide relatives and patient relatives showed increased activation in bilateral caudate/thalamus regions in suicide relatives during **safe choices vs. baseline** ($p_{corrected} < 0.05$; DoF = 30; 373 voxels; peak Z = 4.22 at 10, 0, 16) (Figure 4.8**)** and during **risky choices vs. baseline (**$p_{corrected} < 0.05$; DoF = 30; 252 voxels; peak Z = 3.76 at -6, -8, 14) (Figure 4.9**)**. However, these significant clusters did not survive covariation with STAIB.

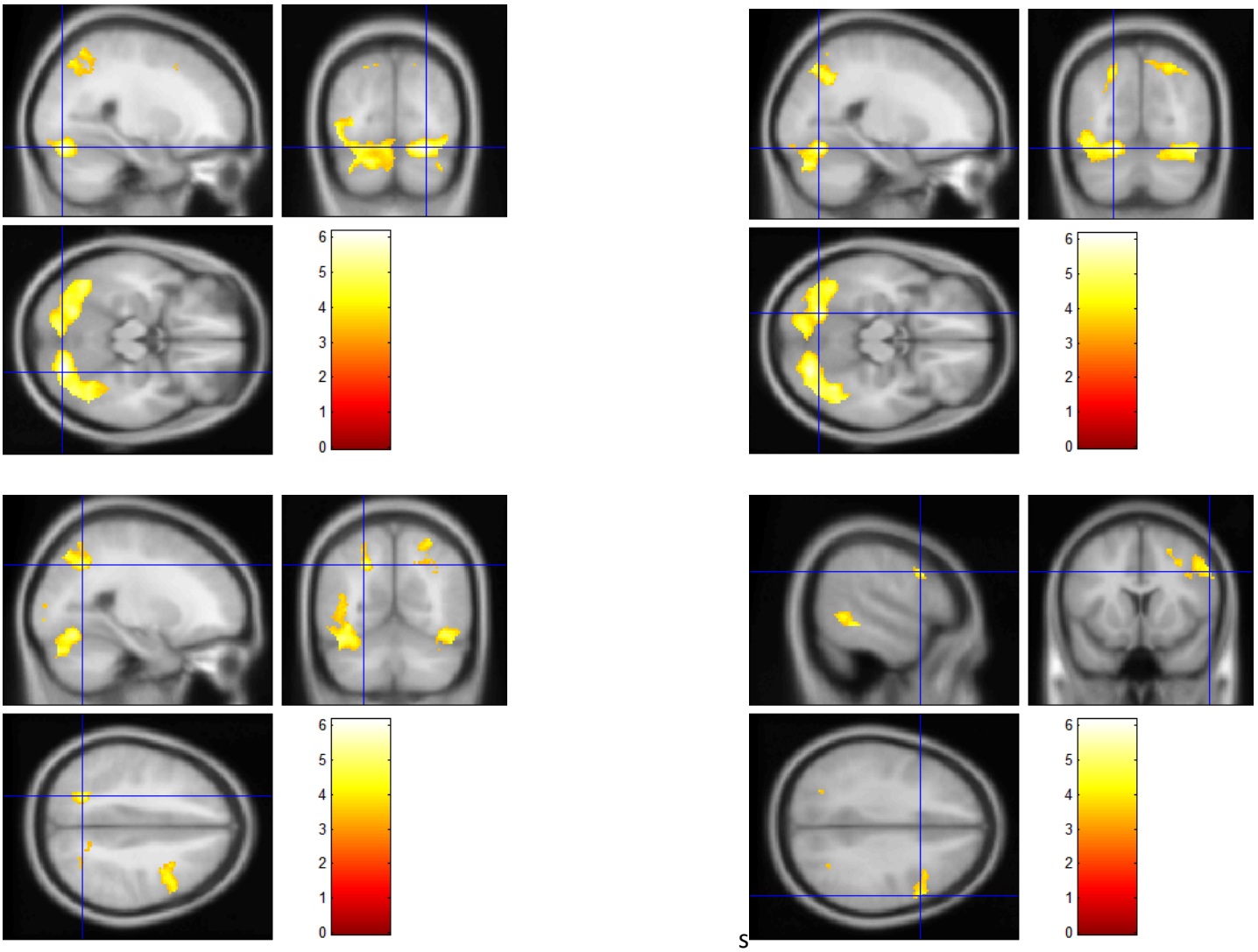

Figure 4.7. Comparison between **suicide relatives and healthy controls** in functional connectivity

Results are obtained using psychophysical interaction analyses with ventromedial prefrontal cortex region of interest which significantly differ between suicide relative and healthy control in the contrast risky vs. safe choices.

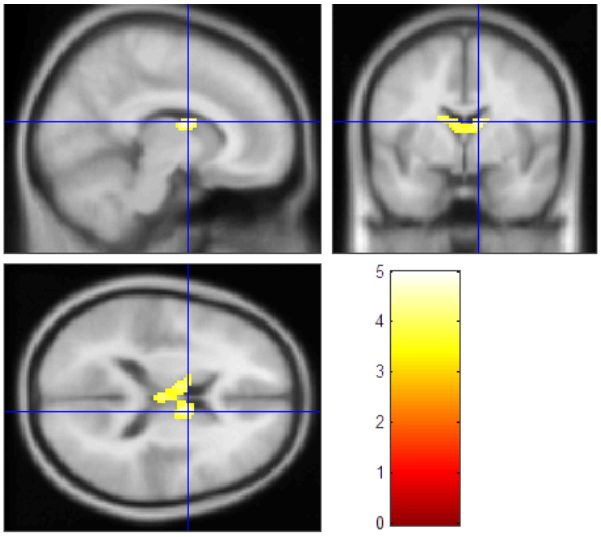

Figure 4.8. Comparison between suicide relatives and patient relatives for the **safe choices versus baseline** contrast without covariation for State Trait Anxiety Inventory: Trait.

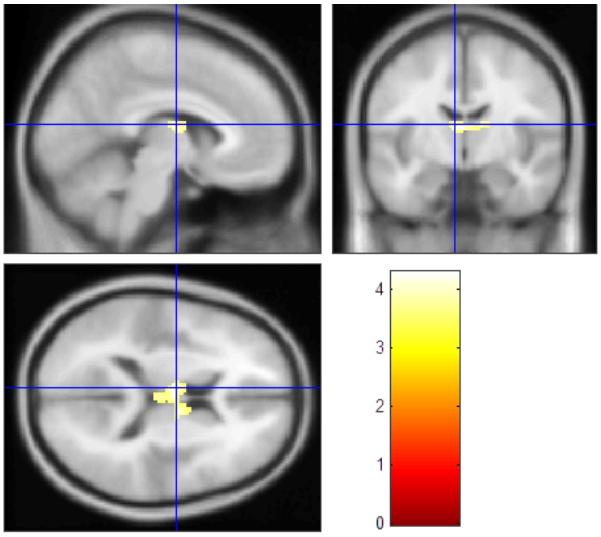

Figure 4.9. Comparison between suicide relatives and patient relatives for the risky choices versus baseline contrast without covariation for State Trait Anxiety Inventory: Trait.

4.5.1.2 Outcome processing

Within-group contrasts between wins and losses (Figure 4.10) showed activation in three clusters among suicide relatives: bilateral caudate/putamen and right pallidum ($p_{corrected} < 0.05$, 902 voxels, peak Z = 4.54 at 24, 0, -10), left fusiform and lingual gyrus in the occipital cortex (BA19; $p_{corrected} < 0.05$, 708 voxels, peak Z = 4.10 at -34, -70, -14), and right cerebellum ($p_{corrected} < 0.05$, 664 voxels, peak Z = 4.08 at 24, -64, -28). In patient relatives, greater activation was observed in bilateral caudate ($p_{corrected} < 0.05$, 950 voxels, peak Z = 4.94 at -12, 26, 0). In

healthy controls, greater activation was found in several large clusters, including one encompassing the left caudate, hippocampus, medial orbital gyrus, inferior frontal gyrus, cingulate cortex, amygdala and bilateral putamen ($p_{corrected} < 0.05$, 6919 voxels, peak Z = 5.46 at -18, -12, 20). Further, a large bilateral parietal activation cluster was found covering inferior and superior parietal regions ($p_{corrected} < 0.05$, 3648 voxels, peak Z = 4.90 at -48 -56, 50), and a large bilateral inferior activation cluster was found covering a large portion of inferior and middle temporal regions ($p_{corrected} < 0.05$, 4526 voxels, peak Z = 4.85 at 40, -38, -18); and numerous smaller activation clusters in the left superior frontal gyrus ($p_{corrected} < 0.05$, 634 voxels, peak Z of 4.57 = -14, 30, 40), right inferior, middle and superior frontal gyri ($p_{corrected} < 0.05$, 582 voxels, peak Z of 4.03 = 46, 40, 10) and right thalamus ($p_{corrected} < 0.05$, 210 voxels, peak Z = 4.38 at 20, -18, 18).

Direct comparison between suicide relatives and patient relatives showed greater activation in suicide relatives during wins vs. baseline in multiple regions, including the precuneus (BA7; $p_{corrected} < 0.05$; DoF = 30; 1205 voxels; peak Z = 4.41 at 2, -60, 38), anterior cingulate cortex (BA32; $p_{corrected} < 0.05$; DoF = 30; 217 voxels; peak Z = 3.8 at -4, 30, 24), left dorsolateral prefrontal cortex (BA6; $p_{corrected} < 0.05$; DoF = 30; 223 voxels, peak Z = 3.65 at -40, 8, 50) and right thalamus/caudate area ($p_{corrected} < 0.05$; DoF = 30; 212 voxels; peak Z = 3.65 at 10, 4, 18) (Figure 4.11). Most significant clusters remained significant after covariation with STAIB. During losses vs. baseline, greater activation was observed in suicide relatives compared to patient relatives in the precuneus (BA7; $p_{corrected} < 0.05$; DoF = 30; 324 voxels; peak Z = 4.05 at 10, -58, 48) (Figure 4.12), a difference that remained significant after co-variating with STAIB.

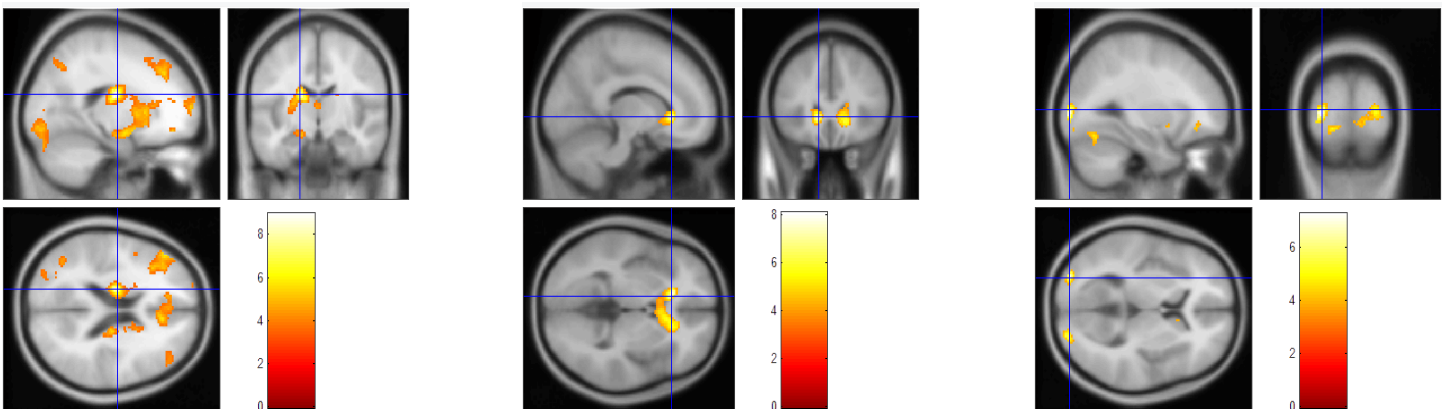

Figure 4.10. Within-group analyses for the contrast between wins and losses.

From left to right: healthy controls, patient relatives, and suicide relatives.

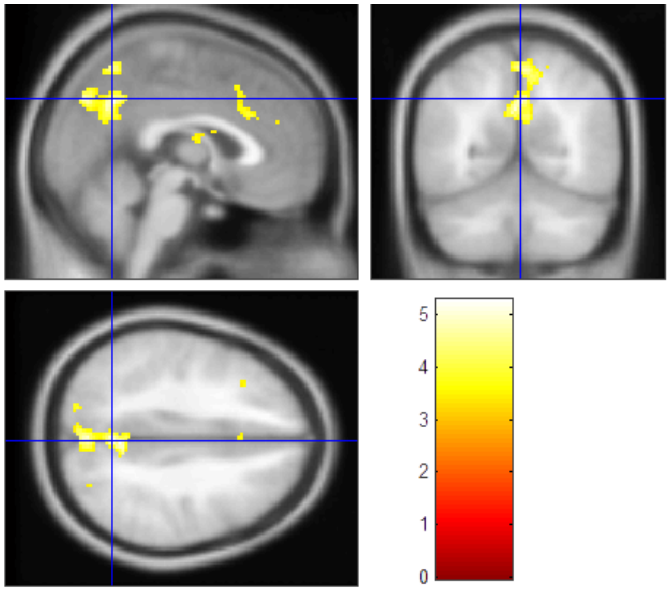

Figure 4.11. Comparison between suicide relatives and patient relatives for the wins vs. baseline contrast after co-variating for State Trait Anxiety Inventory: Trait.

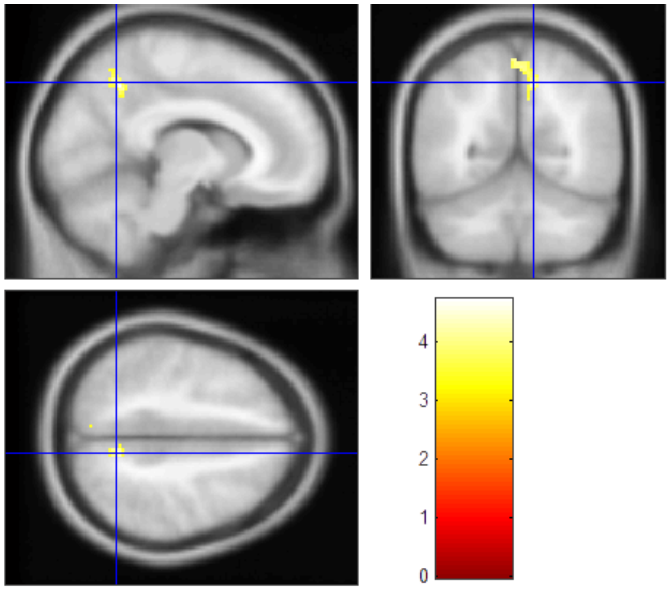

Figure 4.12. Comparison between suicide relatives and patient relatives for the losses vs. baseline contrast co-variating for State Trait Anxiety Inventory: Trait.

Chapter 5 Brain Responses to Social Threat in First-Degree Relatives of Suicide Completers: The Overlooked Role of the Cerebellum.

A version of this chapter has been adapted and is currently under preparation to be submitted. The full list of co-author includes Yang Ding[1], Alexandra Hoehne[1], Martin Lepage2, Gustavo Turecki[1,2], Fabrice Jollant[1,3] with the follwing academic affiliations:

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5.1 Introduction

Family, twin and adoption studies suggest that the vulnerability to suicidal acts is partly influenced by genetic factors, with a heritability estimated at around 50%, or 20% after adjusting for mental disorders (Brent and Mann 2005; Turecki and Brent 2015). The transmission of suicidal risk was found to be associated with the transmission of specific personality traits, notably impulsivity and aggression (McGirr, Alda et al. 2009). Over the last 15 years, numerous neuropsychological and neuroimaging studies have found that, beyond personality traits, deficits in neurocognitive functions also contribute to a vulnerability to suicidal acts (Jollant, Lawrence et al. 2011). Specifically, suicide attempters have shown risky decision-making and deficient cognitive control, among other factors (Jollant, Bellivier et al. 2005; Jollant, Lawrence et al. 2008; Richard-Devantoy, Berlim et al. 2013). It has been hypothesized that some of these neurocognitive deficits may be heritable traits found in unaffected relatives and that they represent an endophenotype of suicide (Courtet, Gottesman et al. 2011).

To date, very few neurocognitive investigations have been conducted in biological relatives of suicides (McGirr, Diaconu et al. 2010). Yet, the study of this population, notably those who have never attempted suicide, represents a valuable way of confirming specific traits of vulnerability transmitted within families, and it can serve as a means of uncovering potential protective factors. This approach also overcomes some of the limits of studies in

suicide attempters (sample heterogeneity, frequent medication use, variable risk of suicide completion) and the difficulty of running prospective studies. For example, in the same sample as in the present study, we found subtle deficits in decision-making (Hoehne, Richard-Devantoy et al. 2015), which suggests that impaired decision-making may be an endophenotype of suicide. However, this sample also showed no deficiencies in cognitive control measured in non-social conditions. We hypothesized that normal cognitive control may protect this population against suicide and counterbalance the effects of risky decision-making. Recent findings in suicide attempters also suggest that deficits in cognitive control in particular may be related to the depressive state and may therefore not be a heritable trait (7.2.3). Overall, research suggests a combination of state and trait neurocognitive abnormalities in relation to suicidal risk (Gujral, Ogbagaber et al. 2015).

In the present study, we explored the sensitivity to negative social stimuli, another aspect of the vulnerability to suicidal behaviour. Indeed, suicidal behaviour often occurs in a context of social disruption, whether at the marital, professional or legal level (Foster 2011). Variability in the way individuals respond to stressful social events provides important insights into the suicidal diathesis. Many studies used the presentation of angry faces as a robust and easy-to-use paradigm of response to social threat (Green and Phillips 2004). In middle-aged male euthymic patients, we found increased activation of the right ventrolateral prefrontal cortex and cerebellum during angry vs. neutral faces in suicide attempters compared to non-attempters (Jollant, Lawrence et al. 2008). Recently, a study focusing on the prefrontal cortex replicated the increased activation of the ventrolateral prefrontal cortex in euthymic suicide attempters (Olie, Ding et al. 2015). In depressed adolescents, Pan et al. (2013) reported different findings using the same paradigm but without contrasting with neutral faces: suicide attempters vs. patient controls showed increased response to mild angry faces in the right anterior cingulate gyrus, bilateral primary sensory cortices, left dorsolateral prefrontal cortex, and right middle temporal gyrus. Finally, using a task in which participants had to match angry or frightened faces, Vanyukov et al. (2014) did not find significant group differences between depressed elderly attempters and control groups. However, planning of a suicidal act was inversely related to activation during angry faces in the ventrolateral prefrontal cortex. Existing studies have

therefore not revealed consistent findings, which could be related to differences in methods and analyses, age and mood state of the population studied, and small sample sizes.

Our purpose in this study was to clarify brain responses to angry faces in relation to the vulnerability to suicidal behaviour by using the same paradigm and contrasts we previously used in middle-aged suicide attempters, but applied here to middle-aged relatives of suicides. Of note, this approach is supported by previous studies that have demonstrated the heritability of face processing among twins and family members of patients with various psychiatric conditions (Shannon, Patrick et al. 2013; Sully, Sonuga-Barke et al. 2015). In this study we also recruited a control group of individuals with a family history of depression and no history of suicidal acts to tease out vulnerabilities to depression. Another strength of this study is that only euthymic and unmedicated individuals were recruited, which would therefore exclude the direct effect of depression and medication on outcomes.

Based on our previous study in suicide attempters (Jollant, Lawrence et al. 2008), we hypothesized that relatives of suicide completers would show increased activation in the ventrolateral prefrontal cortex response to angry faces.

5.2 Methods and Materials

5.2.1 Population

Three groups of non-clinical participants aged 18 to 55 were recruited. 1) Seventeen first-degree biological relatives of suicides who died in a context of major depressive disorder, but not schizophrenia, bipolar disorder or unknown disorders (*suicide relatives*). Suicide relatives had no personal history of a suicide attempt themselves. 2) Sixteen first-degree biological relatives of depressed patients with no personal and family (up to second biological degree) history of suicidal acts (*patient relatives*). Patients suffered from major depressive disorder, but not schizophrenia, bipolar disorder or any unknown disorder. 3) Nineteen *healthy controls* with no personal or family (up to second biological degree) history of suicidal behaviour or major mental disorders.

Additional non-inclusion criteria for all participants included alcohol and substance dependence or abuse within the last 12 months, major comorbid psychiatric disorders such as schizophrenia and bipolar disorder, a lifetime

history of severe head trauma or a central nervous system disorder, and any contra-indication to magnetic resonance imaging (MRI). All participants had to be normothymic at the time of participation as per the Structured Clinical Interview for Axis I DSM-IV (First, Spitzer et al. 2002) and a 21-item Hamilton Depression Rating Scale (HAMD-21) (Hamilton 1960) score below 7. All participants also had to be right-handed as per the Edinburgh handedness inventory (Oldfield 1971), and they had to be free of psychotropic medication for at least six months.

Suicide relatives had at least one first-degree biological relative who committed suicide, commonly defined as an act carried out with some intent to die and having led to death. The Family Interview for Genetic Studies (FIGS) was used to assess suicide on the basis of information given by the relative (https://www.nimhgenetics.org/interviews/figs/). Unclear cases (e.g. where there was doubt concerning an accident) were excluded.

Informed written consent was obtained from all participants. This study was conducted at the Douglas Mental Health University Institute in Montréal and approved by the local ethics committee. Participants received 50 CAD for their time.

5.2.1.1 Clinical assessment

Diagnoses were made in accordance with DSM IV criteria using the SCID-I (First, Spitzer et al. 2002) and SCID-II (First 1997). Level of depression was measured with the HAMD-21 (Hamilton 1960) and the Beck Depression Inventory (BDI) (Beck, Ward et al. 1961). Anxiety level was assessed using the Spielberger State Trait Inventory (STAXI) (Spielberger). The Buss-Durkee Hostility Inventory (BDHI) (Buss and Durkee 1957), the Brown-Goodwin Assessment of Lifetime History of Aggression (BGLHA) (Brown, Goodwin et al. 1979), and the Barratt's Impulsivity Scale (BIS-11) (Patton, Stanford et al. 1995) were used to assess traits of hostility, aggression and impulsivity, respectively. Finally, the National Adult Reading Test (NART) was used as a measure of verbal IQ (Mackinnon 1999).

5.2.1.2 Statistical analyses

As the Shapiro-Wilk's test showed a normal or close to normal distribution for all main clinical and demographic dependent variables, ANOVA and general linear models (GLM) were used to investigate the association between groups and quantitative variables, including covariates where needed. A Chi-square test was used to compare qualitative variables. P-values of less than 0.05 were considered statistically significant. A Pearson's test was used for correlations. All analyses were performed using SPSS version 21.0 (SPSS, Inc., Chicago, IL).

5.2.2 Faces task

We used the same Ekman face task (Ekman, Friesen et al. 1975) as previously used in suicide attempters (Jollant, Lawrence et al. 2008). Briefly, in this task, participants were instructed to identify the gender of faces shown on the screen by pressing buttons with fingers from their right hand. No reference to the emotional features of the facial stimuli was made.

For each participant, three six-minute runs were conducted in a counterbalanced order. Each run consisted of 60 faces of neutral faces mixed with one particular emotion: happy, angry or sad. Of the 60 trials, 20 trials were neutral faces, 20 trials were faces at 50% emotional intensities and 20 trials at 100% emotional intensities. For all runs, the faces of the same 10 individuals (5 males and 5 females) were presented. Each face was presented for two seconds followed by a white cross on a black screen. The interstimulus interval followed a Poisson distribution from three to eight seconds (average interval of 4.9 seconds).

5.2.2.1 Imaging acquisition

Functional neuroimaging scans were carried out, usually the same day or a few days after the clinical evaluation, at the Cerebral Imaging Centre of the Douglas Mental Health University Institute on a 3T Siemens Magnetom Trio MRI scanner with a 12-channel head coil. Blood-oxygen-level dependent (BOLD) signals were acquired on 38 contiguous 3.5mm transversal slices with a T2-weighted gradient echo-planar imaging (EPI) sequence. Repetition time: 2090 ms. Echo time: 30 ms. Field of view: 224mm × 224mm × 133mm. Base resolution: 64 × 64. In-plane resolution: 3.5mm × 3.5mm. GRAPPA acceleration: 2. Descending sequential acquisition. 172 volumes were acquired for each run over 6:07 minutes. The bandwidth was 2442 Hz/Px. Stimuli were displayed

on an MRI-compatible liquid crystal screen at the rear of the scanning bore viewable by the participant through a mirror.

Structural scans consisted of a high resolution, whole brain T1-weighted acquisition following the ADNI T1 protocol. The data were acquired using a Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence with TR / TE / flip angle = 2300 ms / 2.98 ms / 9 degrees, with a field of view of 256mm × 240mm × 176mm, with $1mm^3$ isotropic voxels resulting in acquisition time of 9.25 minutes. The bandwidth was 240 Hz/Px.

5.2.2.2 Image analyses

Functional MRI data were analyzed with SPM12 (Wellcome Department of Imaging Neuroscience, London, UK) implemented in Matlab 2013b (Mathworks, Inc., Natick, MA). A standard indirect normalisation pre-processing routine was performed. This involved a slice-timing correction for the functional time series using sinc function, re-alignment of functional data to its first volume within each individual, co-registration of functional and structural images, segmentation of structural image to produce forward map to MNI template space, spatially normalizing to MNI template and smoothing with an isotropic 8mm full-width half maximum Gaussian Kernel. Low frequency temporal drifts in fMRI signal were removed by applying a high-pass filter with a cut-off of 128s.

A first-level fixed-effect event-related model for all three runs in each individual was constructed focusing on the following three temporally distinct conditions: 1) neutral faces; 2) 50% emotional faces; and 3) 100% emotional faces. The main contrast of interest was the difference between emotional (combining both 50% and 100% in order to increase power) facial stimuli and neutral faces. Motion parameters were included as regressors. Canonical hemodynamic response function and its temporal and dispersion derivatives were regressed with the onsets and duration of the conditions, but only the canonical component was used to calculate the contrasts.

We subsequently constructed a second-level random-effect general linear model (GLM) to compare the contrasting images between groups after including necessary covariates by first fitting multiple GLMs across all three groups, where any clusters with a voxel threshold of $p < 0.001$ uncorrected at the whole brain level with a minimum cluster size of 10 voxels were considered statistically significant. Subsequently, pairwise group

comparisons were conducted with the statistical threshold set for clusters at a $p < 0.05$ whole brain family-wise error corrected. Reported voxels correspond to standardized MNI coordinate space.

Finally, we examined functional connectivity using psychophysiological interaction (PPI) analyses with SPM (32). We first extracted the summary BOLD signal time course based on the first-level subject specific GLMs constructed previously. Then, we formed an interaction term based on the source signal and experimental condition before performing a second GLM analysis that evaluated the interaction term while controlling for the source ROIs extracted signal and experimental vector. This is done to evaluate the anatomical implication and network impact of the main regional findings.

5.3 Results

5.3.1 Demographical and clinical variables

Table 5.1. Description and comparison of socio-demographic and clinical variables between the three groups.[4]

	Healthy controls (HC) n=19		**Patient relatives (PR) n=17**		**Suicide relatives (SR) n=17**		**F / χ^2**	**P**	**Post-Hoc**
Male Gender, N (%)	13	(68)	7	(41)	8	(47)	3.5	0.2	
Age, mean (SD)	32.8	(9.9)	38.0	(8.4)	51.4	(9.4)	18.8	$<10^{-3}$	SR>PR, HC
NART ratio, mean (SD)	0.8	(0.1)	0.7	(0.2)	0.7	(0.2)	1.4	0.2	
Education, N (%)							8.0	0.1	
High school	0	(0)	4	(24)	2	(12)			
College	2	(11)	3	(18)	7	(41)			
University	14	(74)	10	(59)	8	(47)			
BDI score, mean (SD)	1.3	(1.5)	1.6	(2.2)	1.8	(3.0)	0.2	0.8	
HAM-D score, mean (SD)	1.7	(2.1)	1.8	(2.2)	2.3	(2.0)	0.3	0.7	
STAI-state score, mean (SD)	25.5	(6.9)	26.8	(4.9)	22.6	(4.2)	1.0	0.4	
SCID I past history of depression, N (%)	1	(7)	4	(25)	5	(29)	2.8	0.3	
SCID I past substance abuse, N (%)	1	(6.7)	1	(6.7)	0	(0)	1.2	0.6	
SCID II personality disorders, N (%)	0	(0)	3	(19)	1	(6)	3.5	0.0	
BDHI score, mean (SD)	47.6	(9.1)	42.0	(13.4)	46.6	(6.0)	1.2	0.3	
STAI-trait score, mean (SD)	29.4	(4.6)	36.4	(7.9)	28.2	(6.4)	4.8	0.02	PR > HC, SR
BIS score, mean (SD)	73.1	(4.9)	72.4	(3.0)	72.9	(4.0)	0.1	0.9	

[4] BIS-11: Barratt's Impulsivity Scale. BDHI: Buss-Durkee Hostility Inventory. BDI: Beck Depression Inventory. HAM-D-21: 21-item Hamilton Rating Scale for Depression. NART: National Adult Reading Test. SCID: structured Clinical Interview for Axis I DSM-IV (SCID I) and Axis II (SCID II). STAI-A: Spielberger State trait Anxiety Inventory – State. STAI: Spielberger State Trait Anxiety Inventory – Trait. SD: Standard deviation. *Data for the STAI were only available for 30 participants, 31 for STAI-state, and 39 for the BIS., 40 for Hamilton Reating Scale for Depression, 48 for NART, 50 for Education, and 51 for BDI.

The three groups were similar in terms of gender, education, verbal IQ, depression scores, past history of depression or substance abuse, rates of personality disorders, and hostility and impulsivity scores. Suicide relatives were significantly older than both control groups. They also had more past histories of psychotropic medication use than healthy controls. Finally, patient relatives had higher levels of anxiety traits than healthy controls.

5.3.2 Behavioural performance

After factoring for age, the reaction times and accuracies during the Ekman gender identification tasks were similar between participant groups regardless whether the tasks involved angry (reaction time: $F_{(2,50)} = 1.1$, $p = 0.3$ / accuracy: $F_{(2,50)} = 0.002$, $p = 1$), sad ($F_{(2,50)} = 0.3$, $p = 0.8$; and $F_{(2,50)} = 1.8$, $p = 0.2$) or happy ($F_{(2,50)} = 0.6$, $p = 0.5$; and $F_{(2,50)} = 0.5$, $p = 0.6$) facial stimuli.

5.3.3 BOLD responses to angry faces

5.3.3.1 Within group analyses

There was no significant difference in activation between angry and neutral faces in either suicide relatives or healthy controls. In patient relatives, we observed trends toward decreased activation at the right junction between lingual gyrus and cerebellum ($p_{corrected} = 0.053$, 149 voxels, peak $Z = 4.00$ at 4, -78, -14) and in the left posterior cerebellar lobe ($p_{corrected} = 0.051$, 150 voxels, peak $Z = 4.29$ at -34, -60, -32).

5.3.3.2 Between group comparisons

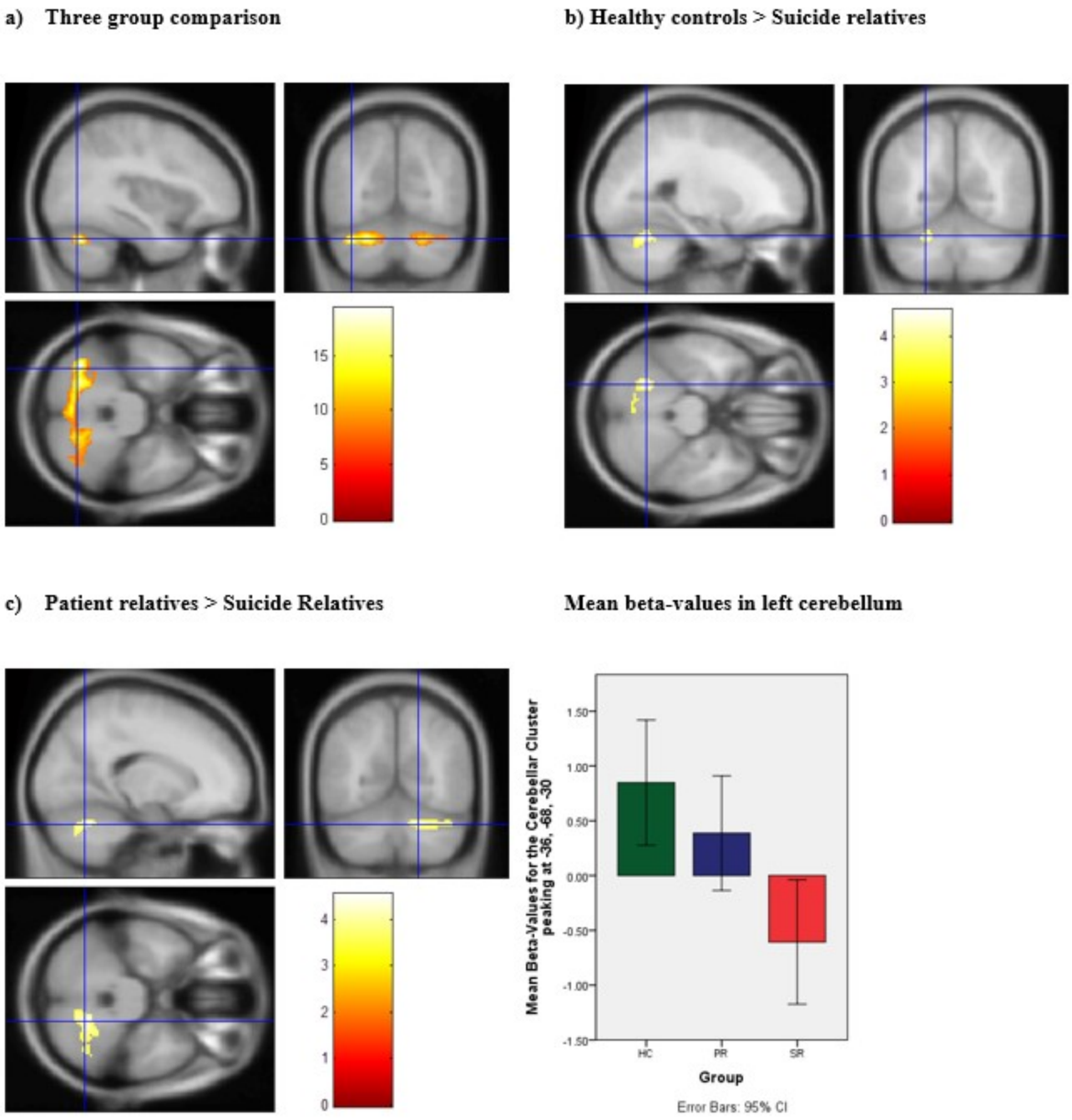

Figure 5.1. Contrasts between angry and neutral faces.[5]

After co-variating for age, a significant activation difference was observed in bilateral cerebellum ($P_{uncorrected} <$ 0.001, 766 voxels, peak Z = 4.49 at -38, -66, -30, **Figure 1a**). Pairwise comparisons including age as a covariate showed reduced activation of medial cerebellum (corresponding to lobule VI) in suicide relatives compared to

[5] HC: Healthy controls; PR: Patient relatives; SR: Suicide relatives. a) Peak voxel at -38, -66, -30; b) Peak voxel at -24, -60, -26; c) Peak voxel at 18, -62, -30.

healthy controls on the left side ($P_{corrected}$ = 0.027, 305 voxels, peak Z = 4.00 at -24, -60, -26, **Figure 1b**) and to patient relatives on the right side ($P_{corrected}$ = 0.009, 319 voxels, peak Z = 3.95 at 18, -62, -30; **Figure 1c**). Adjusting for anxiety trait scores, we did not observe any differences between healthy controls and patient relatives that survived whole brain correction.

To better illustrate these significant findings, we extracted the raw beta-values from the left cerebellum cluster and plotted them on a graph (**Figure 1d**). The graph suggests a linear trend between the three groups with a greater decrease in activation for suicide relatives compared to patient relatives and patient relatives compared to healthy controls. Second, to rule out the possible influence of age on group differences, we correlated the extracted parameter values with age and did not find any significant correlation (r = -0.04, p = 0.8).

5.3.3.3 Secondary analyses

First, as our previous study in suicide attempters showed group differences in cerebellar activation for 50% angry faces only, we explored the effect of intensities on cerebellar response. There was a significant decrease in activation between suicide relatives and healthy controls for 50% angry faces versus neutral faces in the left cerebellum ($P_{corrected}$ = 0.002, 456 voxels, peak Z of 4.27 at -36, -66, -30), but not between other groups. Nor was this observed for 100% angry faces versus neutral faces, which suggests a particular involvement of the cerebellum in processing subtle emotional intensities.

In addition, based on differences previously observed in the right orbitofrontal cortex for 100% angry faces vs. neutral faces between suicide attempters and patient controls, we extracted beta-values for all groups after drawing a 10mm sphere centered around the peak voxel detected in this earlier study at 29, 19, -24. There was no significant difference across the three groups ($F_{(2, 49)}$ = 0.1, p = 0.9).

5.3.3.4 Connectivity analyses

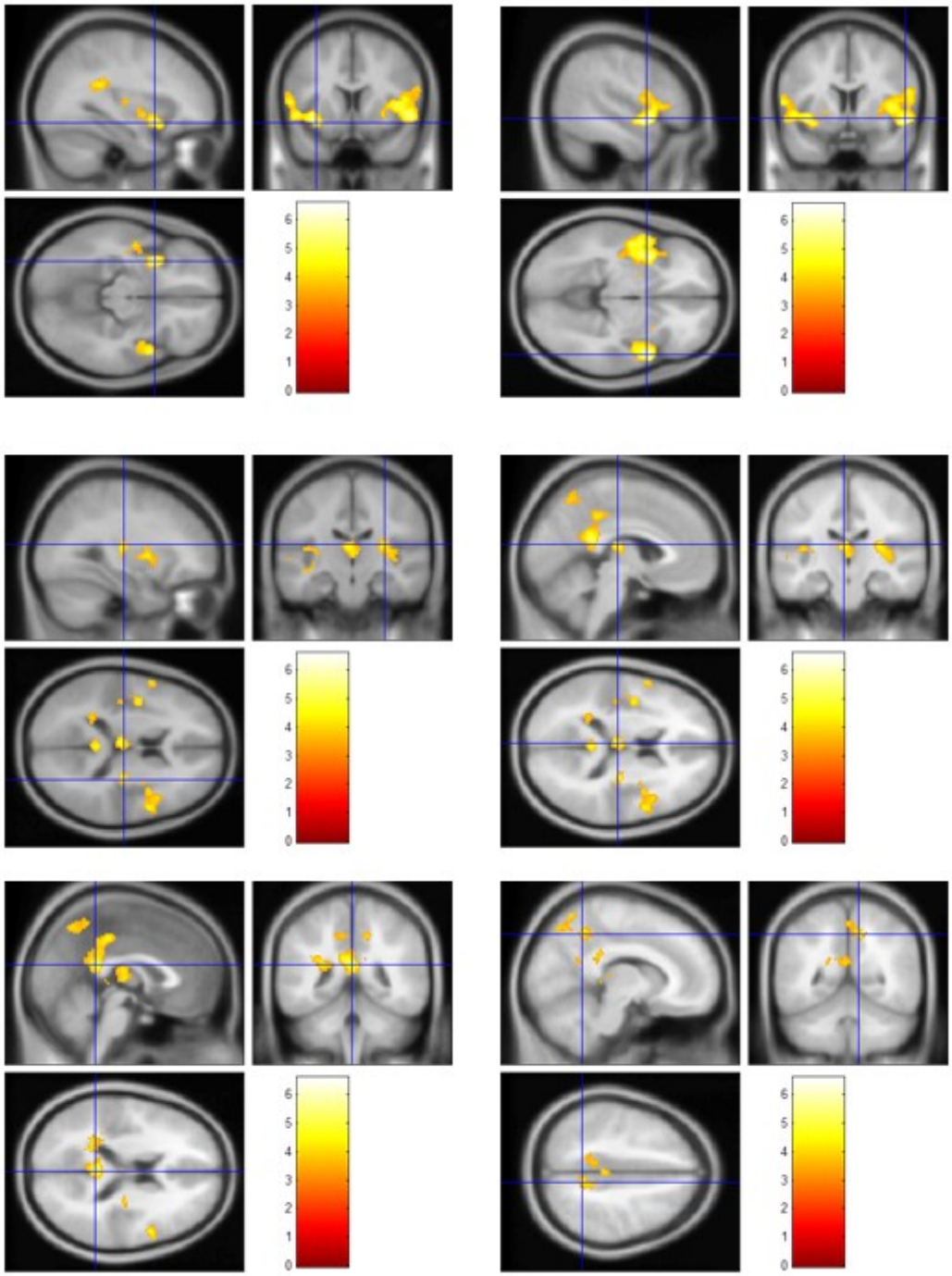

Figure 5.2. Functional connectivity with the left cerebellum in healthy controls vs. suicide relatives.

From top to bottom and left to right: left insula, right insula, right putamen, thalamus, right precuneus, posterior cingulate cortex.

First, we used the cluster that differed between healthy controls and suicide relatives shown in **Figure 1b** as the seed region. We found stronger functional connectivity in healthy controls than suicide relatives in bilateral insula (left: $P_{corrected} < 0.001$, 1619 voxels, peak Z of 5.01 at -32, 10, -12; right: $P_{corrected} < 0.001$, 1575 voxels, peak Z of

5.22 at 52, 6, -6), right putamen ($P_{corrected}$ = 0.037, 219 voxels, peak Z of 4.10 at 30, -18, 14), medial right thalamus ($P_{corrected}$ = 0.015, 274 voxels, peak Z of 4.12 at -4, -20, 14), mid-posterior cingulum ($P_{corrected}$ < 0.001, 1280 voxels, peak Z of 4.70 at 0, -44, 18) and right precuneus ($P_{corrected}$ < 0.001, 609 voxels, peak Z of 4.05 at 10, -52, 46) (**Figure 2**).

When we used the cluster that differed between patient relatives and suicide relatives shown in **Figure 1c** as the seed region, we did not find significant differences between these two groups in terms of functional connectivity.

5.3.4 BOLD responses to happy faces

Within-group analyses

In suicide relatives, no significance whole brain BOLD differences were observed between happy and neutral faces. Healthy controls showed reduced activation in the left inferior parietal sulci ($p_{corrected}$ = 0.051, 162 voxels, peak Z = 4.32, at -26, -48, 28) while patient relatives activated the left globus pallidus/caudate/putamen ($p_{corrected}$ = 0.03, 193 voxels, peak Z = 3.91 at -8, 8, -2), with trends for right inferior/middle frontal gyrus close to pars triangularis ($p_{corrected}$ = 0.057, 163 voxels, peak Z = 4.62 at 30, 24, 22) and right hippocampus/lingual gyrus/fusiform gyrus ($p_{corrected}$ = 0.089, 142 voxels, peak Z = 4.24 at 32, -48, 2).

Between-group analyses

Three group comparisons showed two significant clusters, one in the left middle temporal/angular gyrus region ($p_{uncorrected}$ < 0.001, 27 voxels, peak Z = 3.77 at -50, -70, 24) and one in the right inferior/middle frontal opercular regions ($p_{uncorrected}$ < 0.001, 63 voxels, peak Z = 4.14 at 32, 18, 18). Subsequent pairwise comparisons controlling for age showed increased activation in patient relatives compared to healthy controls in both the left occipital ($p_{corrected}$ < 0.05, 253 voxels, peak Z = 4.11 at -34, -50, -8) and right inferior occipital ($p_{corrected}$ < 0.05, 621 voxels, peak Z = 3.90 at 4, -60, -18). There was no significant difference between suicide relatives and control groups.

5.3.5 BOLD responses to sad faces

Within-group analyses

Contrasting sad and neutral faces did not yield a significant difference in either healthy controls or suicide relatives. Patient relatives showed activation in the left lentiform nucleus/putamen/caudate extending to the left inferior frontal gyrus and insula ($p_{corrected} < 0.05$, 870 voxels, Z = 5.59 at -34, 0, 14), right inferior frontal gyrus, pars triangularis and opercularis ($p_{corrected} < 0.05$, 605 voxels, Z = 4.75 at 50, 24, 8) and right lentiform nucleus/putamen ($p_{corrected} < 0.05$, 203 voxels, Z = 4.40 at 20, 0, 4)

Between-group analyses

There was no group difference between the three groups at $p_{uncorrected} < 0.001$.

5.4 Discussion

In this first study to explore heritable brain responses in relation to suicide, we found decreased activation of the cerebellum in close biological relatives of suicides compared to both patient relatives and healthy controls, when viewing angry faces. We also found decreased functional connectivity in suicide relatives between the cerebellum and the insula, precuneus, posterior cingulate cortex, putamen and thalamus. Importantly, group differences with suicide relatives were found for happy or sad face contrasts, suggesting (without confirming) a certain level of specificity for the kind of emotional cues capable of eliciting brain responses in this population. Contrary to our hypothesis, we found no group difference in ventral prefrontal cortex activation. Finally, as hypothesized, no group differences were observed in dorsomedial prefrontal cortex.

The cerebellum is often overlooked in neuroanatomical models of suicidal behaviour (Van Heeringen, Audenaert et al. 2003; Jollant, Lawrence et al. 2011). Yet, previous studies have shown increased responses in this region to suicidal vs. neutral script in suicide attempters (Reisch, Seifritz et al. 2010) and decreased activation during motor tasks in individuals who later committed suicide (Amen, Prunella et al. 2009). Decreased cerebellar white matter volume has been found in suicide attempters (Hwang, Lee et al. 2010), although a lack of group-difference using structural imaging has also been reported (Baldacara, Nery-Fernandes et al. 2011). Using the same task as in the current study, our group found increased activation of the cerebellum in response to 50% angry faces in suicide attempters vs. patient controls (Jollant, Lawrence et al. 2008). Finally, the same sample set as the one presented here also showed a reduced difference in cerebellar activation between wins and loses at a gambling task, increased activation of this region when making choices, and increased functional connectivity between the cerebellum and the ventromedial prefrontal cortex (Ding et al. in prep). Findings from the present study combined with previous studies summarized above therefore suggest a significant role of the cerebellum in suicidal vulnerability, although mechanisms at play are not yet clear at this stage.

Over the past several years, numerous studies have suggested that the cerebellum, beyond its motor role, may also be involved in cognitive and emotional functions (Koziol, Budding et al. 2014). Lesions of the cerebellum, for instance, have been implicated in a series of emotional and behavioural disturbances relevant for suicide,

including flattening of affects, disinhibition and impulsivity (Schmahmann 2004). The cerebellum is structurally and functionally connected with the neocortex and various subcortical regions, and it is organized in a modular fashion (Bernard, Seidler et al. 2012; Pelzer, Hintzen et al. 2013). The posterior part of the cerebellum, which encompasses the clusters differentially activated between groups in the present study, is connected to the prefrontal (both ventral and dorsal), temporal and parietal cortices, the posterior cingulate, the insula, the thalamus and basal ganglia (Bernard, Seidler et al. 2012; Diano, D'Agata et al. 2015). This large number of reciprocal connections makes the cerebellum ideally suited for various cognitive processes with possibly a regulatory or integrative role. Notably, one study using independent component analyses applied to resting state showed lobule VI of the cerebellum—the region showing decreased activation in suicide relatives—as part of a network of brain regions more specifically involved in salience detection, along with the orbitofrontal and dorsal prefrontal cortices, insula and thalamus (Habas, Kamdar et al. 2009).

One hypothesis may be that increased activation in the cerebellum and orbitofrontal cortex in *suicide attempters* reflects increased sensitivity and response to social threat in this population. In contrast, our sample of *suicide relatives*—a population at increased familial risk but who never attempted suicide—showed no activation of the orbitofrontal cortex, decreased activation of the cerebellum, nor diminished functional connectivity between the cerebellum and various cortical and subcortical regions. This could reflect reduced processing of negative social cues, a mechanism that may ultimately limit the emotional impact of these stimuli in these individuals. Of note, this opposite direction of activations between patients and relatives has previously been reported, for instance in bipolar disorder (Piguet, Fodoulian et al. 2015). Overall, these findings emphasize the importance of impaired brain processing of social threat in the vulnerability to suicidal behaviour. They also add up to previous neuroimaging and neuropsychological findings to help refine current models of suicidal behaviour, although replication studies and additional investigation are clearly necessary.

Several limitations of this study must be underlined. The main limitation is the relatively small sample size, which increases the risk of type I and II errors. Notably, this may have decreased our ability to detect additional differences. Of note, no formal sample size calculation could be run prior to this study due to a lack of available

data. While our experience has shown that recruiting this population can be complicated, it is important that these findings be replicated. Second, suicide relatives were older than both control groups, leading us to covariate for age where needed. This may have reduced the detection of subtler group differences. However, the lack of correlation between age and significant clusters suggests that our findings are not explained by age difference.

In conclusion, our study suggests a significant role for the cerebellum in suicide vulnerability in, but not limited to, the processing of threatening social cues. Future studies will determine if this brain region may be used as a marker of suicide risk and whether it represents an interesting target of preventative interventions.

5.5 Supplementary Material

5.5.1 Clinical assessment

Diagnoses were made in accordance with DSM IV criteria using the SCID-I (First, Spitzer et al. 2002) and SCID-II (First 1997). Level of depression was measured using the HAMD-21 (Hamilton 1960) and the Beck Depression Inventory (BDI) (Beck, Ward et al. 1961). Anxiety level was assessed using the Spielberger State Trait Inventory (STAXI) (Spielberger 1988). The Buss-Durkee Hostility Inventory (BDHI) (Buss and Durkee 1957), the Brown-Goodwin Assessment of Lifetime History of Aggression (BGLHA) (Brown, Goodwin et al. 1979), and the Barratt's Impulsivity Scale (BIS-11) (Barratt 1965) were used to assess traits of hostility, aggression and impulsivity, respectively. Finally, the National Adult Reading Test (NART) was used as a measure of verbal IQ (Nelson 1982).

5.5.2 BOLD responses to happy faces

Within-group analyses

In suicide relatives, no significance whole brain BOLD differences were observed between happy and neutral faces. Healthy controls showed deactivation in the left inferior parietal sulci ($p_{corrected}$ = 0.051, 162 voxels, peak Z = 4.32, at -26, -48, 28) while patient relatives activated the left globus pallidus/caudate/putamen ($p_{corrected}$ = 0.03, 193 voxels, peak Z = 3.91 at -8, 8, -2), with trends for right inferior/middle frontal gyrus close to pars triangularis ($p_{corrected}$ = 0.057, 163 voxels, peak Z = 4.62 at 30, 24, 22) and right hippocampus/lingual gyrus/fusiform gyrus ($p_{corrected}$ = 0.089, 142 voxels, peak Z = 4.24 at 32, -48, 2).

Between-group analyses

Three group comparisons showed two significant clusters, one in the left middle temporal/angular gyrus region ($p_{uncorrected} < 0.001$, 27 voxels, peak Z = 3.77 at -50, -70, 24) and one in the right inferior/middle frontal opercular regions ($p_{uncorrected} < 0.001$, 63 voxels, peak Z = 4.14 at 32, 18, 18). Subsequent pairwise comparisons controlling for age showed increased activation in patient relatives compared to healthy controls in both left occipital ($p_{corrected} < 0.05$, 253 voxels, peak Z = 4.11 at -34, -50, -8) and right inferior occipital ($p_{corrected} < 0.05$, 621 voxels, peak Z = 3.90 at 4, -60, -18). There was no significant difference between suicide relatives and control groups.

5.5.3 BOLD responses to sad faces

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Contrasting sad and neutral faces did not yield significant differences in either healthy controls or suicide relatives. Patient relatives showed bilateral activation in the left lentiform nucleus/putamen/caudate extending to the left inferior frontal gyrus and insula ($p_{corrected} < 0.05$, 870 voxels, Z = 5.59 at -34, 0, 14), right inferior frontal gyrus, pars triangularis and opercularis ($p_{corrected} < 0.05$, 605 voxels, Z = 4.75 at 50, 24, 8) and right lentiform nucleus/putamen ($p_{corrected} < 0.05$, 203 voxels, Z = 4.40 at 20, 0, 4)

Between-group analyses

There was no group difference between the three groups at $p_{uncorrected} < 0.001$ with a 10 voxels cluster size requirement.

Chapter 6 General Discussion

Over the duration of my PhD, I have participated in the exploration of both structural and functional aspects of suicidal vulnerability using neuroimaging among both suicide attempters and first-degree biological relatives of suicide completers. This has provided a unique opportunity to combine approaches and methods in order to improve our common understanding and perspective of new models of these complex behaviours.

The literature review (Chapter 2) showed a comprehensive perspective on the structural and functional association of several brain regions with suicidal acts, including but not limited to various sub-regions of the prefrontal cortex. These findings pave the way for a region of interest approach in subsequent analyses of suicide attempters and first-degree relatives of suicide completers, and it provides mechanistic explanations in relation to some of the regional alterations.

Our work with suicide attempters began with the examination of structural alterations in suicide attempters. This study, using a region of interest exploration of the prefrontal cortex (Chapter 3), highlighted a significant association between suicidal acts and the left ventrolateral region, independent from mood disorders and during normothymia (Figure 3.2). An association was also found between the orbitofrontal cortex and dorsolateral prefrontal cortex and suicidal acts, although the independence from mood disorders could not be affirmed (see Section 3.3.5). No association was found for the medial prefrontal cortex using this data set, although Dr. Anthony Gifuni and I continued structural explorations with a particular focus on subcortical structures (See Appendix 7.2.1). While most subcortical structures were not associated with suicidal vulnerability, volumes of the nucleus accumbens were significantly and negatively correlated with the lethality of suicidal acts. This finding suggests that this brain structure may modulate the way these acts are committed. More recently, Dr. Gifuni has examined this data set further with a focus on the corpus callosum, the main inter-hemispheric fiber bundle, but he could not find any association with suicidal acts (Gifuni et al. under preparation).

Although structural neuroimaging can tell us about potential structural abnormalities within the suicide attempter population, it cannot yet provide sufficient insight into the clinical, behavioral and functional implications of these

anatomical changes. Subsequently, I began working with Dr. Stéphane Richard-Devantoy using functional neuroimaging and a classical Go-NoGo task to examine cognitive inhibition among suicide attempters. Our functional neuroimaging study (see Appendix 7.2.3) suggests that cognitive control deficits within suicide attempters are more likely to be associated with the depressive state than with suicidal vulnerability. Specifically, cognitive inhibition was associated with activity in the inferior frontal gyrus, thalamus, OFC and parietal cortex. Activity in these regions was also correlated with suicidal ideas and psychological pain, suggesting a potential opportunity for intervention in the early stages of a suicidal crisis, before a suicide attempt.

In addition to these studies with suicide attempters, I have also conducted analyses exploring relatives of suicide completers. My earlier work, collaborating with Ms. Alexandra Hoehne and Dr. Stéphane Richard-Devantoy (see 7.2.2), examined measures of cognitive functions in first-degree biological relatives of suicide completers who never attempted suicide themselves. Our examination employed a battery of cognitive inhibition measures outside of the scanner and revealed no evidence to suggest any significant inhibition deficits were present among suicide relatives, unlike suicide attempters (Richard-Devantoy, Berlim et al. 2013). This finding suggests that cognitive inhibition may not be a robust heritable trait. This finding is also congruent with the aforementioned functional findings from the study of suicide attempters, which suggests that cognitive control deficits may only appear during a pathological state like depression and is additive to other state- and trait-deficits to create the conditions which facilitates suicidal act. Normal cognitive control in suicide relatives may be a protective factor in this population.

Contrary to cognitive inhibition, our study suggests that risky decision-making is likely transmitted within families and may therefore be a heritable trait and an endophenotype of suicide. This is in line with a previous study in normothymic suicide attempters (Jollant, Bellivier et al. 2005).

In the neuroimaging component of this study, we further explored the brain basis of risky decision-making in suicide relatives using functional magnetic resonance imaging (Chapter 4). Suicide relatives showed a significant reduction in ventromedial prefrontal cortex activity during decision-making when presented with contrasting

risky and safe choices (Figure 4.1). In addition, when using functional magnetic resonance imaging to examine choice and outcome processing, we also discovered increased activation in several regions including the precuneus and cerebellum (Figure 4.2). More in-depth studies using functional connectivity analyses via psychophysiological interaction suggest group differences, notably increased functional connectivity between the ventromedial prefrontal cortex and the inferior frontal gyrus, cerebellum and precuneus in suicide relatives vs. healthy controls (Figure 4.7). Overall, this first functional study in suicide relatives re-emphasized the significant role of the ventral prefrontal cortex in risky decision-making in suicidal behaviour (Jollant, Lawrence et al. 2010) and underlined the related significance of a network of brain regions, including the cerebellum and precuneus.

When we used Ekman's task to examine facial emotion processing (Chapter 5), reduced cerebellar activity was observed in suicide relatives when angry faces were presented (typically used as a proxy for social threat, Figure 5.1), which further reinforced the identification of the cerebellum as a key but overlooked player in the suicidal process. Moreover, subsequent psychophysical interaction analyses during the processing of angry emotion faces suggest a decreased functional connectivity between the cerebellum and various cortical (bilateral insula/inferior frontal gyri, posterior cingulate cortex, precuneus) and sub-cortical regions (putamen, thalamus) among suicide relatives compared to healthy controls. We theorized that a reduced response of the cerebellum, and reduced functional connectivity, in addition to a lack of ventral prefrontal activation to angry faces may reflect protective mechanisms against suicide.

In the next chapters, my aim is to rationalize these experimental findings into a theoretical framework. A preliminary working model (Jollant, Lawrence et al. 2011) has been proposed to unite the behavioural and neuroimaging alterations observed in suicide attempters (**Figure 6.1**). At the core of this working model are three major neurocognitive functions, which are proposed to be related to each clinical stage of the suicidal process (from a social trigger to suicidal ideas to suicidal act) with major underpinning anatomical regions: the ventrolateral prefrontal cortex for modulation of value attribution; the dorsal medial prefrontal cortex for regulation of emotional and cognitive response; and the dorsal lateral prefrontal cortex in response inhibition.

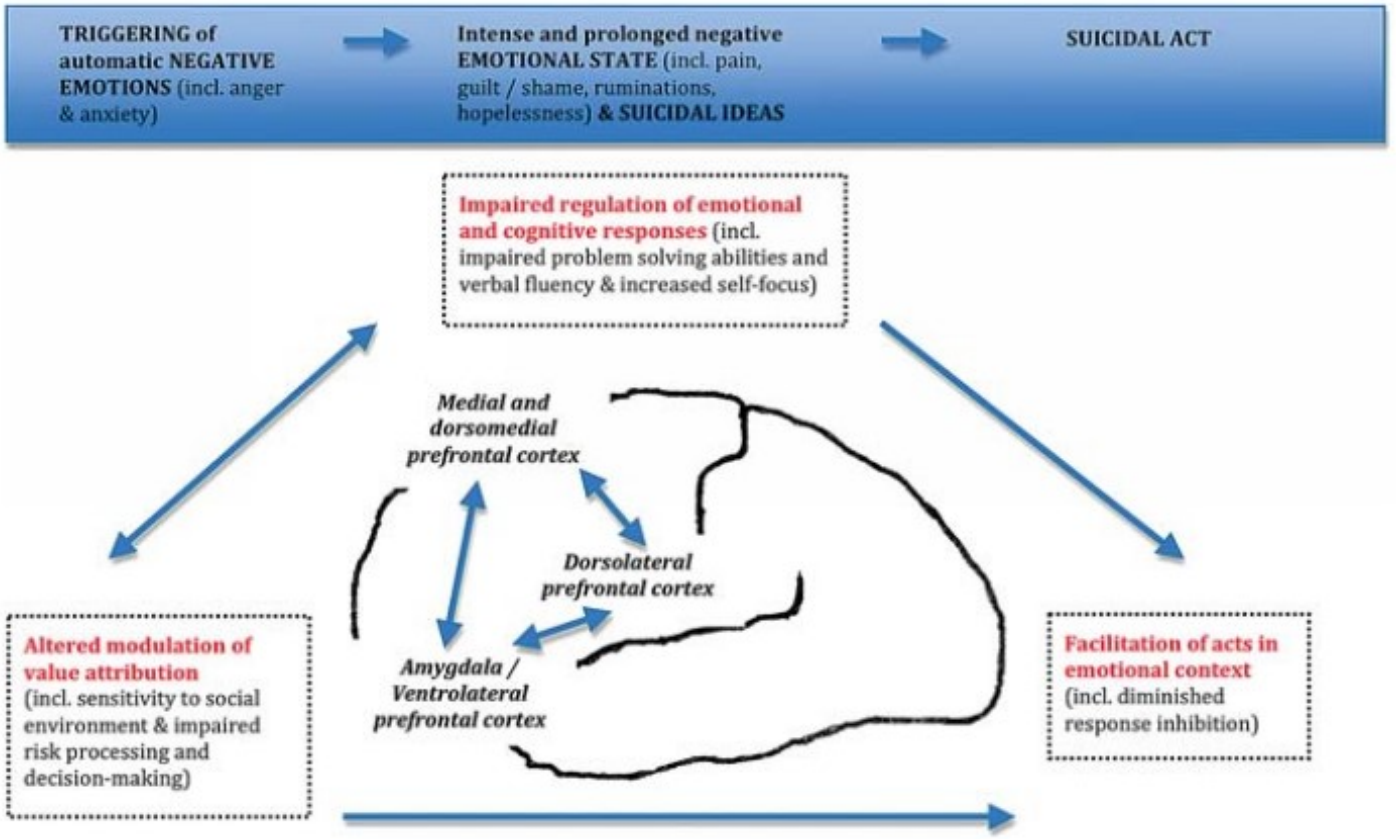

Figure 6.1. The three-step suicidal process and underlying cognitive and neuroanatomical dysfunctions, as described in Jollant et al. 2011.

Neuroanatomical alterations may be related to both gray matter and white fiber tracks. The main regions underlying the three general cognitive deficits are presented here.

However, the precise relation of each anatomical region to specific cognitive deficits and clinical measures remains to be clarified. Findings presented in this PhD thesis expand our understanding of these relationships and offer new information in terms of heritability and potential trait or state-characteristics. I will therefore build upon this preliminary model and complement it with a greater spatial localization emphasis.

In the following chapters, I will present findings summarized from two major neuroimaging approaches: anatomical (i.e. brain regions) and functional (i.e. the cognitive processes, connectivity, etc). I will also present findings based on the figures inspired by Van Heeringen et al. (2011) in order to facilitate discussion before providing a holistic synthesis integrating the various lines of these findings. The goal is to complement the earlier

working model of suicidal behaviour by providing a more higher resolution perspective with a more network based interpretation of the current literature and existing findings.

6.1 Anatomical Dimension

6.1.1 Ventrolateral prefrontal cortex

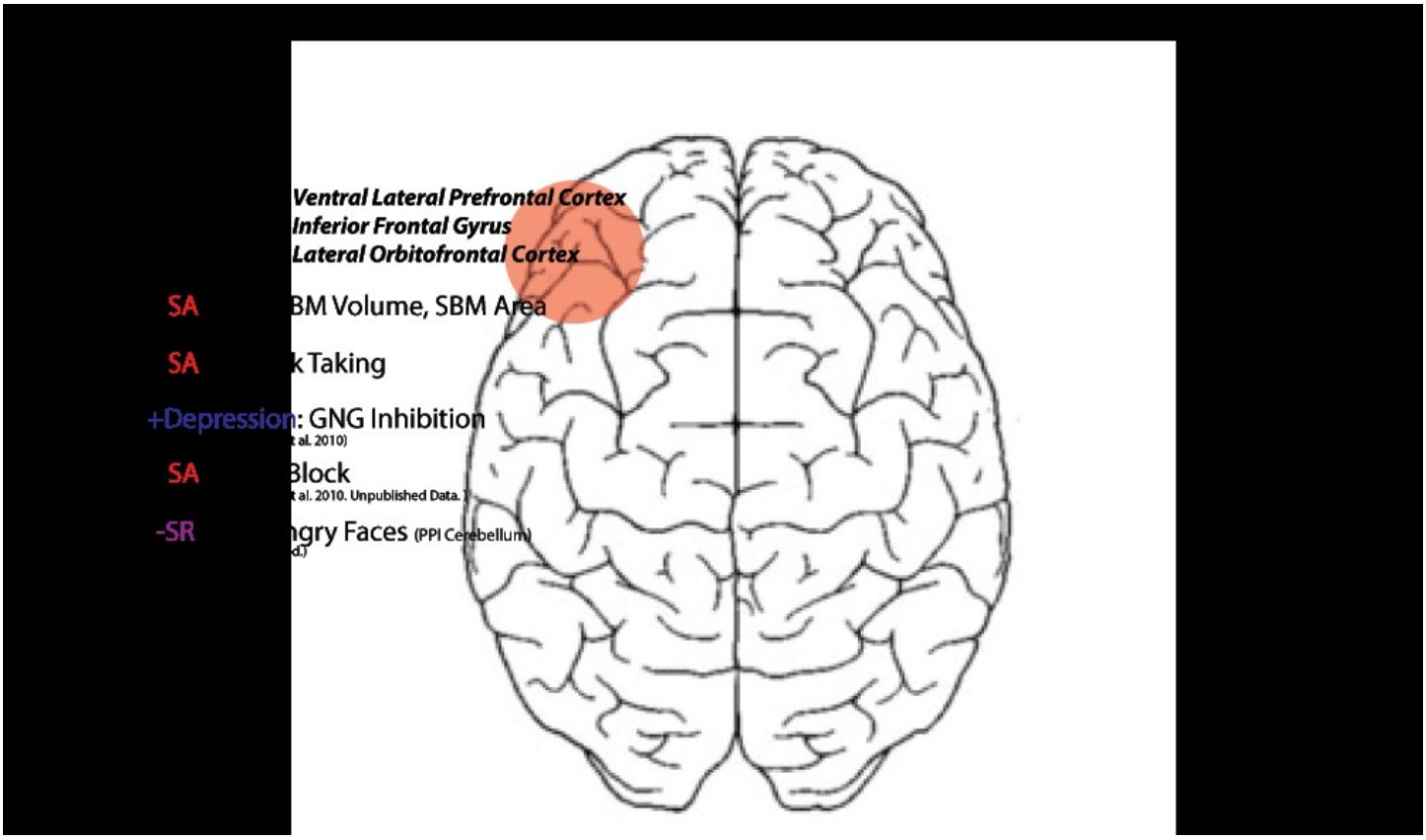

Figure 6.2. Current findings in the left ventrolateral prefrontal cortex.

SA: suicide attempters. SR: suicide relatives. SBM: surface-based morphometry. VBM: voxel-based morphometry. GNG: go-nogo task. PPI: psycho-physiological interaction.

A solid arrow implies statistically significant changes in the measurement. A plus or minus sign implies increased or decreased correlation.

The definition of the ventrolateral prefrontal cortex (VLPFC) is often ambiguous and can include anterior insula, parts of the inferior frontal gyrus (triangular, opercular and orbital), and the lateral part of the orbitofrontal cortex. It is typically difficult to clearly distinguish contributions from the insula in relation to the inferior frontal gyrus (Swick, Ashley et al. 2008). Although this region includes the Broca's area for speech production, interpreted in

the context of current findings, it most likely accounts for more than just verbal fluency difficulties among suicidal patients (Audenaert, Goethals et al. 2002), and alterations have been found in suicide attempters in non-verbal tasks like the Ekman's faces.

Jollant et al. (2010) first noted reduced activation of this region (mainly Brodmann's Area 47) during risk taking among suicide attempters. This functional alteration may find its basis in the structural analyses in which gray matter volumes have shown a very robust reduction in that region, most likely attributable to cortical area decrease (See 2.5.3.1). Richard-Devantoy's work (7.2.3) further implicates this region as positively correlated with an inhibition process among both depressed and suicidal patients. Moreover, a subset of his results specifically comparing suicide attempters to patient controls suggests that more pronounced activation during the NoGo block of the task is uniquely exhibited by suicide attempters. Meta-analyses of an inhibition related study (Swick, Ashley et al. 2008) suggest that this region may be as important as the dorsal lateral prefrontal cortex in the cognitive inhibition process. Lastly, suicide relatives have shown a reduced functional activity correlation between the VLPFC and cerebellum during the processing of mildly emotional angry faces (see 5.3.3.4).

While all of the aforementioned alterations emphasize the left hemisphere proximal to Broca's area, Jollant et al. (2008) demonstrate elevated activation during angry emotional processing on the right side, possibly as a contralateral compensatory mechanism such as seen in motor (Strens, Fogelson et al. 2003) or language systems (Thiel, Habedank et al. 2006). However, a replication of the initial study found increased responses to angry faces in suicide attempters vs. patient controls in the left OFC (defined as BA47 and 11) and VLPFC (defined as BA 44 and 45) (Olie, Ding et al. 2015). Collectively, these data suggest that there is a particular emphasis on the left VLPFC, but this does not preclude the possibility of a bilateral VLPFC functional contribution to emotional processing.

Despite these important findings that contribute to our understanding of the VLPFC as an important nexus involving cognitive control and emotion processing, the precise underpinning common low-level functioning mechanism that is disrupted in the higher-level processes remains unknown. One recently proposed mechanism

is value attribution and its related impairment as demonstrated by Dombrovski et al. in both past discounting and reversal learning (Dombrovski, Clark et al. 2010). The subsequent study implicated the ventral lateral prefrontal cortex as a predominant region that was activated in high ambiguity and low reward value situations(Dombrovski, Szanto et al. 2013). Lastly, these functional alterations may also be fundamentally related to processes reported in studies such as Amen, et al. (2009), which noted a reduced rate of cerebral blood flow both during baseline and concentrations in the regions.

The fact that all three key cognitive processes (i.e. decision-making, cognitive inhibition and emotional processing) show abnormal activity in this region highlights its important role in vulnerability to suicidal behaviour. The inferior frontal gyrus is a key hub region where multiple key cognitive networks interface (Menon and Uddin 2010) and where lesions and abnormalities could have the most important impact in terms of cognitive deficits and ultimately risk of suicidal behaviour. The precise functional impact of this region can be multifold given the dynamics of the networks involving this region and especially given its proximity to language processing. One way to study this region in the future may be to use non-invasive transcranial magnetic disruption and measure behavioural implications on task performance pre-and post-stimulation, beyond an impact on typical semantic performance (Devlin, Matthews et al. 2003). Similar approaches have already shown promising leads in the study of the dorsolateral prefrontal cortex (Knoch, Gianotti et al. 2006; Fecteau, Pascual-Leone et al. 2007).

6.1.2 Ventromedial prefrontal cortex

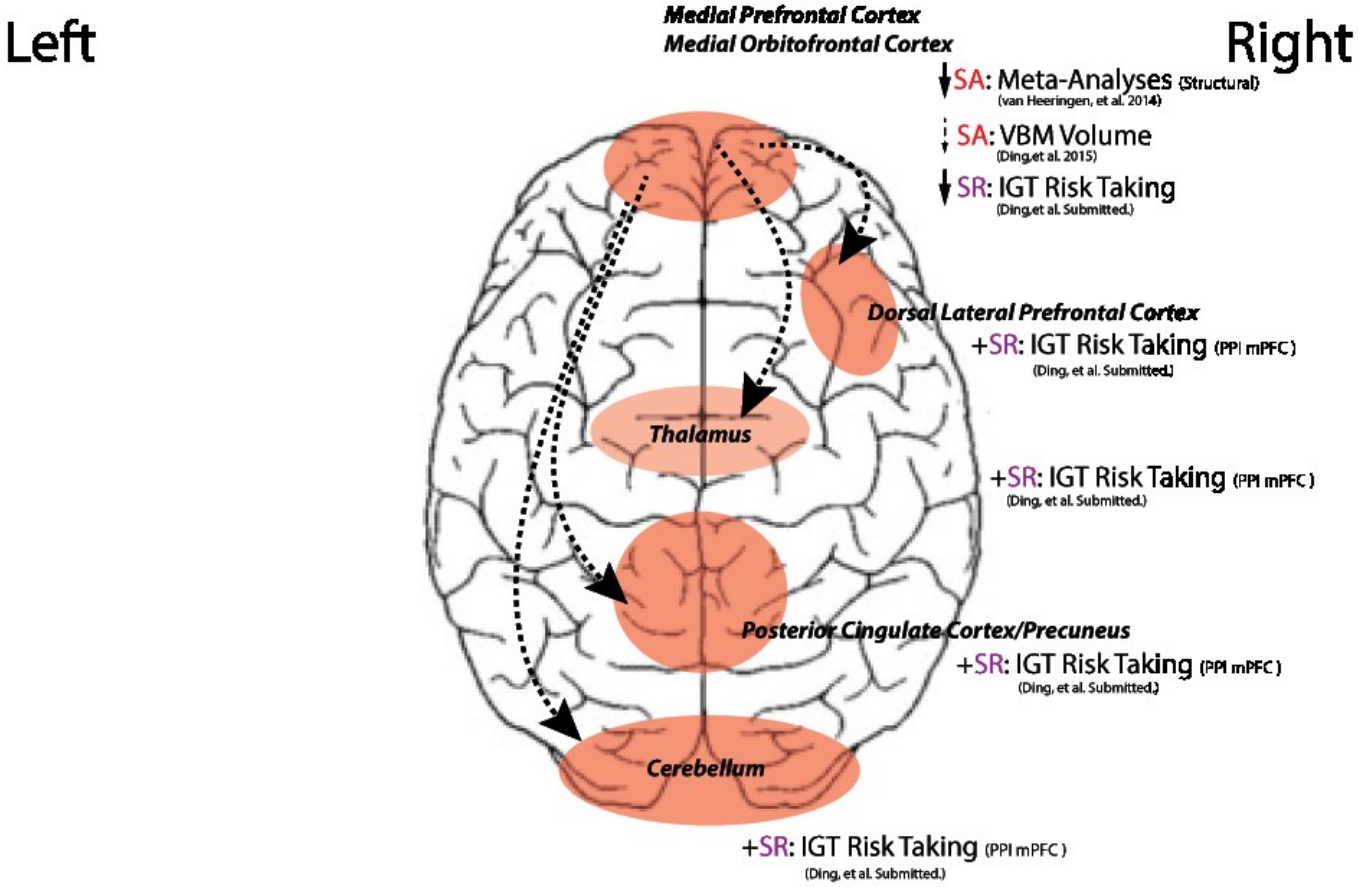

Figure 6.3. Current findings in the medial prefrontal cortex and orbitofrontal cortex.

SA: suicide attempters. SR: suicide relatives. VBM: voxel-based morphometry. IGT: Iowa gambling task.

A dashed line implies functional connectivity/correlation (as examined using psycho-physiological interaction) between the regions. An arrow source indicates the region of interest used for the PPI analyses and does not imply causation or effective connectivity. A solid arrow implies statistically significant changes in the measurement of PPI in the particular group. A dashed arrow suggests trend but non-statistically significant differences. A plus sign implies increased correlation.

The ventromedial prefrontal cortex (VMPFC) in conjunction with the medial part of orbitofrontal cortex have shown consistent alterations among suicide attempters and suicide relatives. Reduced gray matter volume was reported in a meta-analysis in suicide attempters (van Heeringen, Bijttebier et al. 2014) and this is congruent with our earlier structural analysis findings (Chapter 3), which suggests a strong trend in volume reduction on the left

medial OFC. Our subsequent study with suicide relatives suggests decreased Blood-Oxygen Level Dependent activities in this same region during risky decision-making processes was associated with a stronger functional correlation with the DLPFC, thalamus, precuneus and cerebellum among suicide relatives uniquely (4.5.1.1). An earlier pilot study using the same task in healthy controls revealed the medial PFC to be one of the primary regions activated during decision-making contrasts (Lawrence, Jollant et al. 2009). Similarly, Dombrovksi et al. (2013) showed a weaker response to reward in this region.

Finally, an early study by Leyton et al. (2006) measuring serotonin synthesis found reduced binding in suicide attempters in the same region, which suggests that reduced serotonergic inputs to this region may explain deficient functioning in suicide attempters and relatives. However, this still needs to be validated in suicide completers.

Interpreted in the context of current experimental results, VMPFC findings emphasize the importance of this regional deficit in its contribution to risky decision-making, mostly in suicide attempters. In-depth studies in healthy controls focusing on the medial prefrontal cortex have noted a strong ventral dorsal functional separation within the medial prefrontal cortex (Xue, Lu et al. 2009), whereas the ventral region shows a strong modulation of outcomes, and the rostral region modulates experienced risks. This is important because in our analysis (4.3.4.1), we examined risky versus safe decision-making contrasts yet observed differences in ventral regions that are more related to outcome modulation. This apparent paradoxical difference can potentially be explained by the fact that over the entire duration of the task, risky decks tend to have an overall net negative outcome (larger win amounts, and even larger loss amounts, with equivalent frequency distributions of both outcomes), whereas safe decks have an overall positive outcome (small win amounts, and even smaller loss amounts, with equivalent frequency distributions of both outcomes). Both outcomes, however, have an identical risk (win versus loss) probability due to the task design. Therefore, even though we measured risky versus safe risk-taking behaviour differences, we might inadvertently also incorporate outcome magnitude measurements especially after an explicit understanding of the probabilistic association between outcome and risk. Taken together with the aforementioned evidence of deficits in delayed discounting and possible value attribution bias in suicide

attempters, this suggests suicide relatives (and potentially suicide attempters, although this has not yet been confirmed at this stage) exhibit a diminished response to reward when compared to healthy control subjects.

6.1.3 Posterior cingulate and precuneus

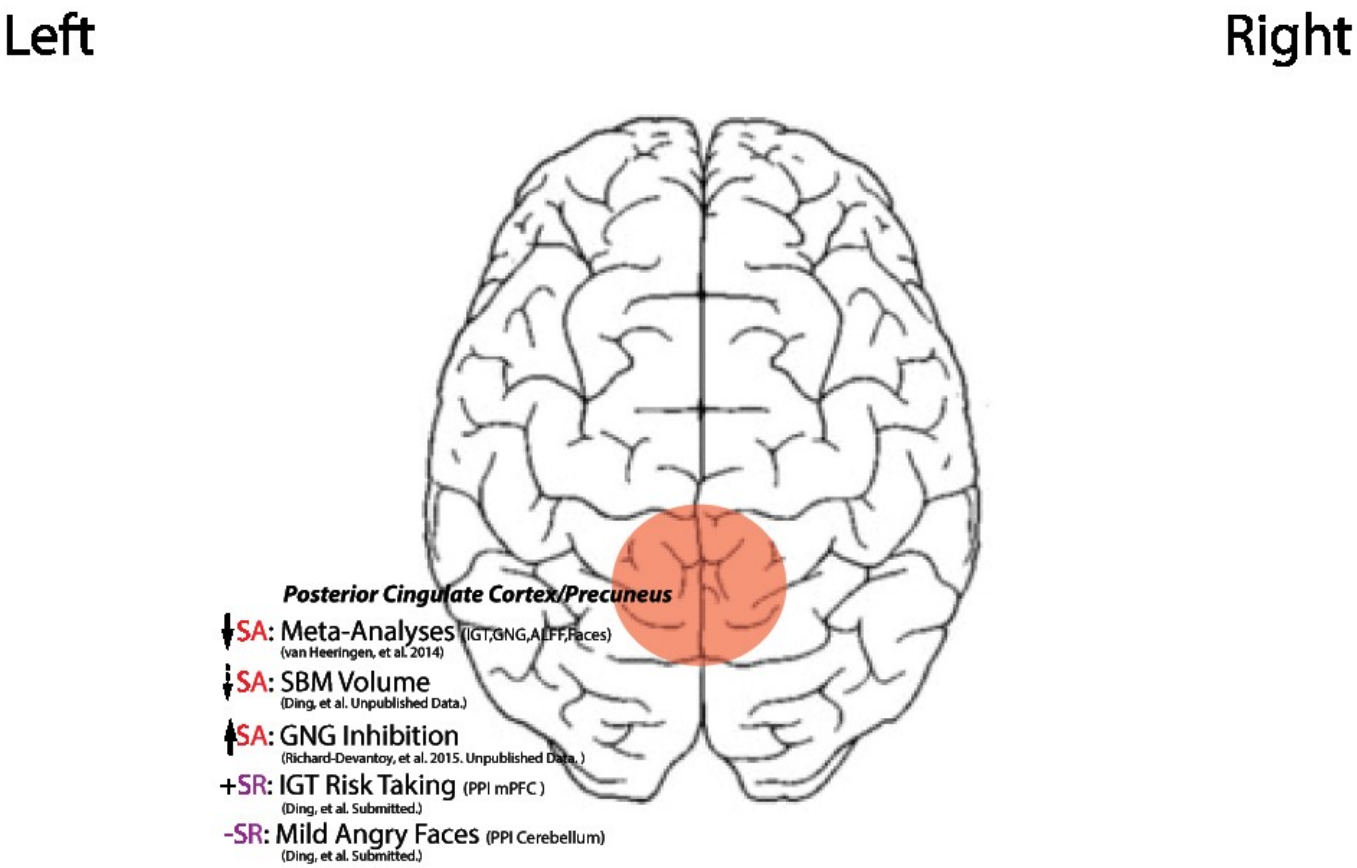

Figure 6.4. Current findings in the posterior cingulate cortex and precuneus.

SA: suicide attempters. SR: suicide relatives. SBM: surface-based morphometry. IGT: Iowa gambling task, a decision-making task. GNG: go-nogo task, a cognitive inhibition task. PPI: psycho-physiological interaction. ALFF: amplitude of low-frequency fluctuations, a resting state measure. Faces/Mild Angry Faces: Ekman faces task, an emotional processing task.

A solid arrow implies a significant increase or decrease in the measurement in the particular group. A plus or minus sign implies an increased or decreased correlation. A dashed arrow suggests a trend but non-statistically significant differences.

The posterior cingulate and precuneus (which is a part of the parietal cortex) are two adjacent regions typically activated collectively as one large overlapping cluster during self-referential processing (Andrews-Hanna,

Smallwood et al. 2014) and resting-state (Zhang and Li 2012) as a key node of the default mode network. In a recent meta-analysis of neuroimaging findings in suicide attempters (van Heeringen, Bijttebier et al. 2014), the posterior cingulate cortex exhibits reduced activity across different paradigms, especially in suicide attempters. One study not included in the meta-analysis reported the strongest perfusion reduction in this general region during baseline (Amen, Prunella et al. 2009) in prospective suicide completers compare to health controls. This is also supported by gray matter volume measurements in bipolar SA without lithium treatment that show volume reductions in numerous regions, including the PCC and precuneus, compared to bipolar SA treated with lithium (Benedetti, Radaelli et al. 2011).

Overall, the observed results across modalities are comparatively consistent and the plausible interpretation is that the reduced structural integrity may relate to the reduced perfusion during baseline that results in reduced functional activity during tasks, which may also be the consequence of an imbalance in resting state and task positive networks. Alternatively, it is also plausible that this signifies patients' inability to inhibit and supress intrinsic network activities and self-referential processes, a phenomenon typically found in depressed patients (Sheline, Barch et al. 2009). This region deactivates across a wide range of tasks (van Heeringen, Bijttebier et al. 2014) in suicide attempters mirroring its role as a key hub within the default mode network. This may explain why the a broad reaching range of functional deficiencies exhibited by suicide attempters and highly heterogeous nature of the findings among suicide attempters. Interestingly, however, a compensatory phenomenon has been observed in the precuneus in relation to the attentional network post cognitive rehabilitation (Kim, Yoo et al. 2009). Whether this is applicable in the context of suicide prevention therapy is an interesting avenue for further exploration. Resting network analyses targeting precuneus hub regions or task-based functional imaging tasks focusing on self-referential processes would be the optimal approaches to clearly delineate the contribution and impact of deficits within this region towards suicidal behaviours.

6.1.4 Cerebellum

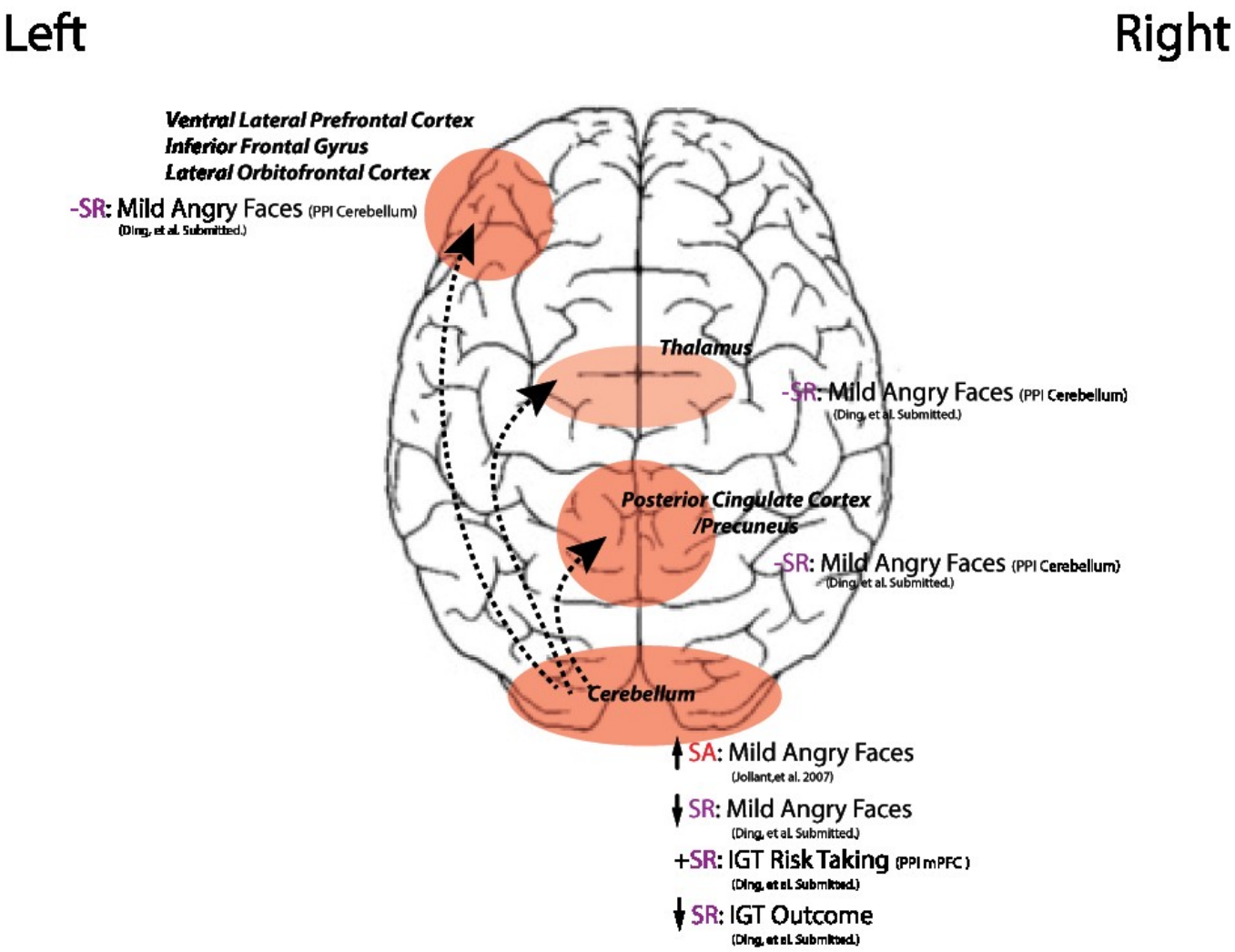

Figure 6.5. Current findings in the cerebellum.

SA: suicide attempters. SR: suicide relatives. IGT: Iowa gambling task, a decision-making task. PPI: psycho-physiological interaction. ALFF: amplitude of low-frequency fluctuations, a resting state measure. Faces/Mild Angry Faces: Ekman faces task, an emotional processing task. mPFC: medial prefrontal cortex.

A dashed line implies functional connectivity/correlation (as assessed using psycho-physiological interaction) between the regions. An arrow source indicates the region of interest used for the PPI analyses and does not imply causation or effective connectivity. A solid arrow implies a significant increase or decrease in the measurement in the particular group. A plus or minus sign implies increased or decreased correlation.

Jollant et al. (2008) found elevated activity in suicide attempters vs. patient controls while processing mild angry faces. We partially replicated this finding in the same anatomical region in suicide relatives, albeit in the opposite direction. In our study (Chapter 5), suicide relatives exhibited reduced activity while processing mild angry faces

compared to patient relatives and healthy controls. We postulated that reduced cerebellar activity in our sample of suicide relatives—a population at increased genetic risk of suicide but that never attempted suicide—may be a protective mechanism. In addition, this region is similarly deactivated during outcome processing after choices, which shares some commonality with the emotion processing context. On top of this reduced BOLD activity in both processing context, the cerebellum also shows a reduced functional correlation with the precuneus, thalamus and ventral lateral prefrontal cortex in suicide relatives. Lastly, we found an elevated positive correlation among suicide relatives with the medial PFC during the risky decision-making assessment. Cerebellar alterations have been reported in other studies of suicidal behaviour, not included in the recent meta-analyses: namely, Liu et al. (2016) showed a regional correlation with suicidal ideation; Amen, et al. (2009) reported a reduction in blood flow in propsective suicide completers at rest; Hwang, et al. (2010) found reductions in both gray and white matter volumes; lastly, Reisch, et al. (2010) demonstrated elevated cerebellar activation during suicidal stimuli. Apart from one study that specifically investigated cerebellar alterations in suicide attempters (Baldacara, Nery-Fernandes et al. 2011) and reported negative findings, the cerebellum has rarely been the primary focus of investigations in suicidal behaviour (some even use it as a control region for SPECT studies), and it remains a controversial topic even outside the field of suicide research. Classically, the cerebellum has been considered to be an important area for motor fine tuning activities. However, recent research has suggested that there are at least two independent circuits within the cerebellum (Krienen and Buckner 2009), one for motor activities and one for higher order cognitive processes. In the context of current research and findings in suicide attempters, the cerebellum is more likely to be involved through its implication in cognitive executive areas, which overlaps with areas where we have shown the greatest differences in the emotional facial recognition task. Earlier reports have shown cerebellar activity regardless of the affective valence of the stimuli (Small, Gregory et al. 2003), which is similar to the current observation when processing outcomes of the decision-making tasks. This suggest the potential involvement of the cerebellum in the valence evaluation process, though it may not be preferentially responsive to the actual valence. In the context of suicide attempers, it is possible that more effort is required to evaluate the valence of the context, while suicide relatives benefit from this protective alteration and require little effort (even compare to controls) to process ambigious valences. This postulate, however, is not able to fully

explain the paradoxical elevation in functional correlation during risk-taking seen in an earlier study of suicide attempters (Jollant, Lawrence et al. 2008). Overall, these findings pertaining to the cerebellum perhaps raise more questions than they answer, but its cognitive and functional implications should no longer be ignored.

6.1.5 Subcortical regions

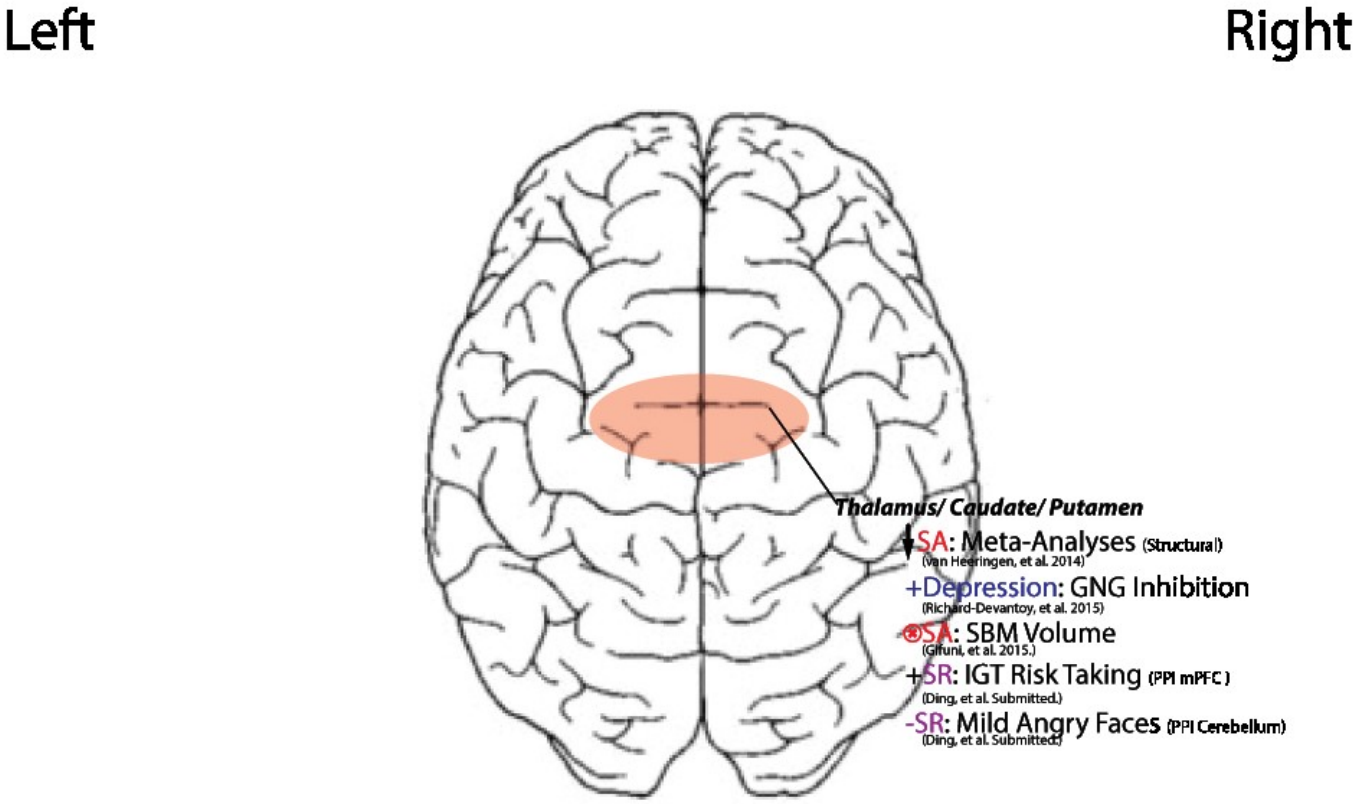

Figure 6.6. Current findings in the subcortical regions.

SA: suicide attempters. SR: suicide relatives. GNG: go-nogo task, a cognitive inhibition task. IGT: Iowa gambling task, a decision-making task. PPI: psycho-physiological interaction. ALFF: amplitude of low-frequency fluctuations, a resting state measure. Mild Angry Faces: a condition in Ekman faces task, an emotional processing task. mPFC: medial prefrontal cortex.

A solid arrow implies a significant increase or decrease in the measurement in the particular group. A plus or minus sign implies increased or decreased correlation. The ⊗ sign suggests no significant differences were found.

Even though the neuroimaging meta-review reported reduced volume in several subcortical regions (van Heeringen, Bijttebier et al. 2014), after taking age and other covariates into account, we did not observe evidence suggesting significant structural alterations in any subcortical structures in suicide attempters (7.2.1). Given the small number of studies in SA, several important regions have been reported that potentially reflect suicidal behaviour but without consistent replications. These studies should be cautiously interpreted given their numerous limitations, but this may present an important trend for future region of interest researches. We recently reported a significant negative correlation between nucleus accumbens volume and the lethality of suicidal acts (Gifuni, Ding et al. 2015). Findings in the lentiform nucleus suggest a decreased structural integrity in subcortical regions and a connection to suicidal vulnerability (Hwang, Lee et al. 2010). Taylor et al. (2015) has observed a white matter integrity reduction in the form of increased fractional anisotrophy and decreased radial diffusivity among depression groups with suicidal ideation in white matter adjacent to the basal ganglia and thalamus (Taylor, Boyd et al. 2015).

6.1.6 Dorsolateral prefrontal cortex

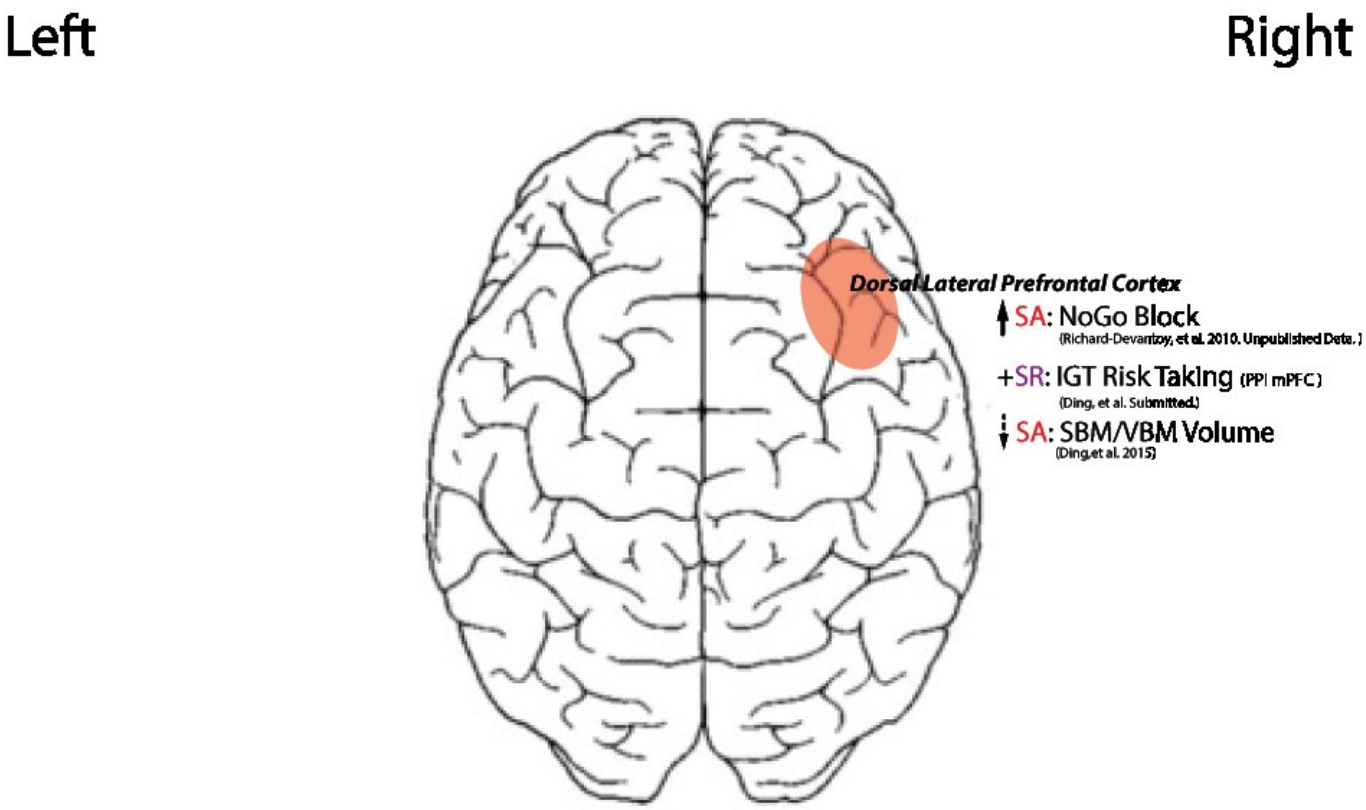

Figure 6.7. Current findings in the dorsolateral prefrontal cortex.

SA: suicide attempters. SR: suicide relatives. IGT: Iowa gambling task, a decision-making task. PPI: psycho-physiological interaction. mPFC: medial prefrontal cortex. NoGo Block: activation of nogo block within go-nogo task in the cognitive inhibition task. SBM: surface-based morphometry. VBM: voxel-based morphometry. mPFC: medial prefrontal cortex.

A solid arrow implies significant changes in the measurement in the particular group. A plus sign implies increased correlation. A dashed arrow implies a trend but statistically insignificant changes.

The DLPFC is associated with response inhibition (Shackman, McMenamin et al. 2009). This region has shown evidence of an assocation with inhibition of cognitive function, which is potentially related to serotonin in suicide attempters (Audenaert, Van Laere et al. 2001). Olié et al. (2015) reported an increased response to wins vs. losses during decision-making in the right DLPFC and a decreased response to risky vs. safe choices in the left DLPFC.

Moreover, there was a weak trend suggesting volume reduction in suicide attempters (Ding, Lawrence et al. 2015). It remains difficult to ascertain whether such DLPFC alteration is more trait- or state-like until its presence in suicide relatives is fully validated using the appropriate tasks such as Go-NoGo. One possible avenue of exploration might be through the application of novel paradigms such as transcranial magnetic stimulation, which has shown shown to increase risk-taking behaviour in gambling paradigms (Knoch, Gianotti et al. 2006).

Overall, current support of the DLPFC as a vulnerability marker is not strong, especially in the elderly population, despite showing correlation with suicidal ideation among healthy controls (Liu, Wang et al. 2016). One plausible interpretation is that the vulnerability is more subtle and may be more prevalent during stressful conditions instead of baseline (McGirr, Diaconu et al. 2010).

6.1.7 Anterior cingulate cortex

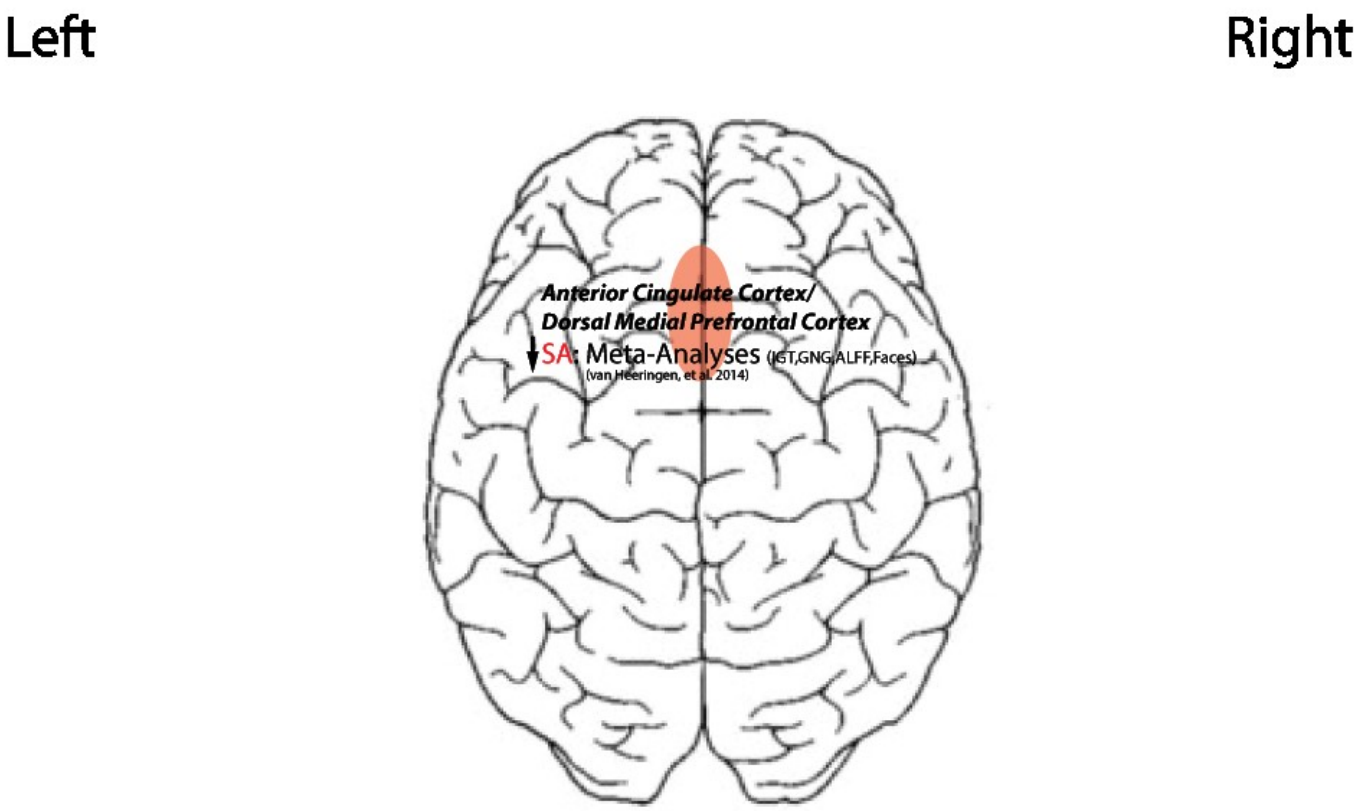

Figure 6.8. Current findings in the anterior cingulate cortex.

SA: suicide attempters. IGT: Iowa gambling task, a decision-making task. GNG: go-nogo task, a cognitive inhibition task. ALFF: amplitude of low-frequency fluctuations, a resting state measure. Faces: Ekman faces task, an emotional processing task. A solid arrow implies a significant increase or decrease in the measurement in the particular group.

The anterior cingulate cortex is typically associated with error detection (Carter, Braver et al. 1998) and has been reported to be altered in numerous studies included in the neuroimaging meta-analysis (van Heeringen, Bijttebier et al. 2014). However, no differences were observed in suicide attempters or suicide relatives under the decision-making or emotional processing tasks in our current studies. Neither was strong evidence of structural alterations observed, contrary to earlier reports (Wagner, Koch et al. 2011; Wagner, Schultz et al. 2012).

One interpretation of this finding and inconsistency across suicide relatives and suicide attempters could be that despite strong evidence of this as a vulnerability for suicide attempters, the familial transmission of this trait may be less pronounced than expected when compared to the transmission of decision-making deficits, assuming current findings in suicide relatives are representative of the sample as a whole. Another plausible interpretation is that both tasks are not eliciting sufficient error related detection activity from the ACC. Thus the IGT may be too difficult and ambiguous in terms of correct answers, and the Ekman gender identification faces task too simple (over 90% accuracy in suicide relatives).

6.2 Functional Dimension

6.2.1 Decision-making

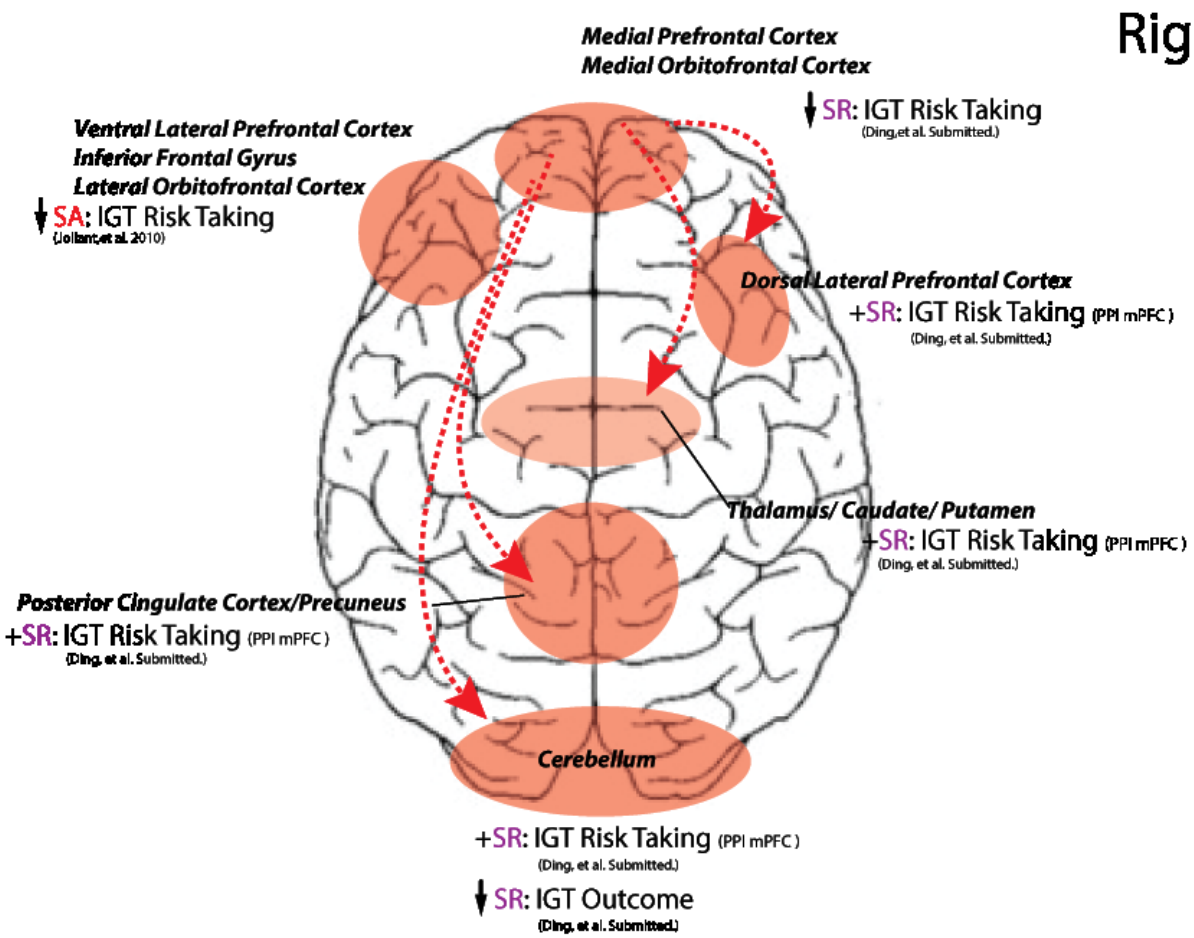

Figure 6.9. Findings related to decision-making.

SA: suicide attempters. SR: Suicide relatives. IGT: Iowa gambling task, a decision-making task. PPI: psycho-physiological interaction. mPFC: medial prefrontal cortex

A dashed line implies functional connectivity/correlation (as assessed using psycho-physiological interaction) between the regions. An arrow source indicates the region of interest used in the PPI analysis and does not imply causation or effective connectivity. A solid arrow implies significant changes in the measurement in the particular group. A plus sign implies increased functional correlation between regions indicated.

We revealed risky decision-making in suicide relatives (Hoehne, Richard-Devantoy et al. 2015) associated with ventromedial PFC alteration (Chapter 4). The most likely source of structural alteration related to this functional deficit, the ventral PFC, exhibits reliably consistent structural alterations observed in suicide attempters in our large scale study (Ding, Lawrence et al. 2015). This is in agreement with earlier reports linking the lateral OFC and decision-making in suicide attempters (Jollant, Lawrence et al. 2008), although a replication study using a

region of interest approach found a relationship between decision-making and the DLPFC but not the VLPFC (Olie, Ding et al. 2015).

Based on the evidence presented, decision-making has emerged as an important trait-like neurocognitive deficit that is readily demonstrated both behaviourally and through functional imaging means among suicide relatives and attempters. It currently represents one of the strongest neurocognitive endophenotypes of suicide. Future studies should assess the predictive power of functional, structural and behavioural measures of decision-making and its clinical impact. In terms of future research topics, clarification of the functional connectivity during decision-making in vulnerable individuals would greatly help validate the current hypothesis.

6.2.2 Angry faces processing

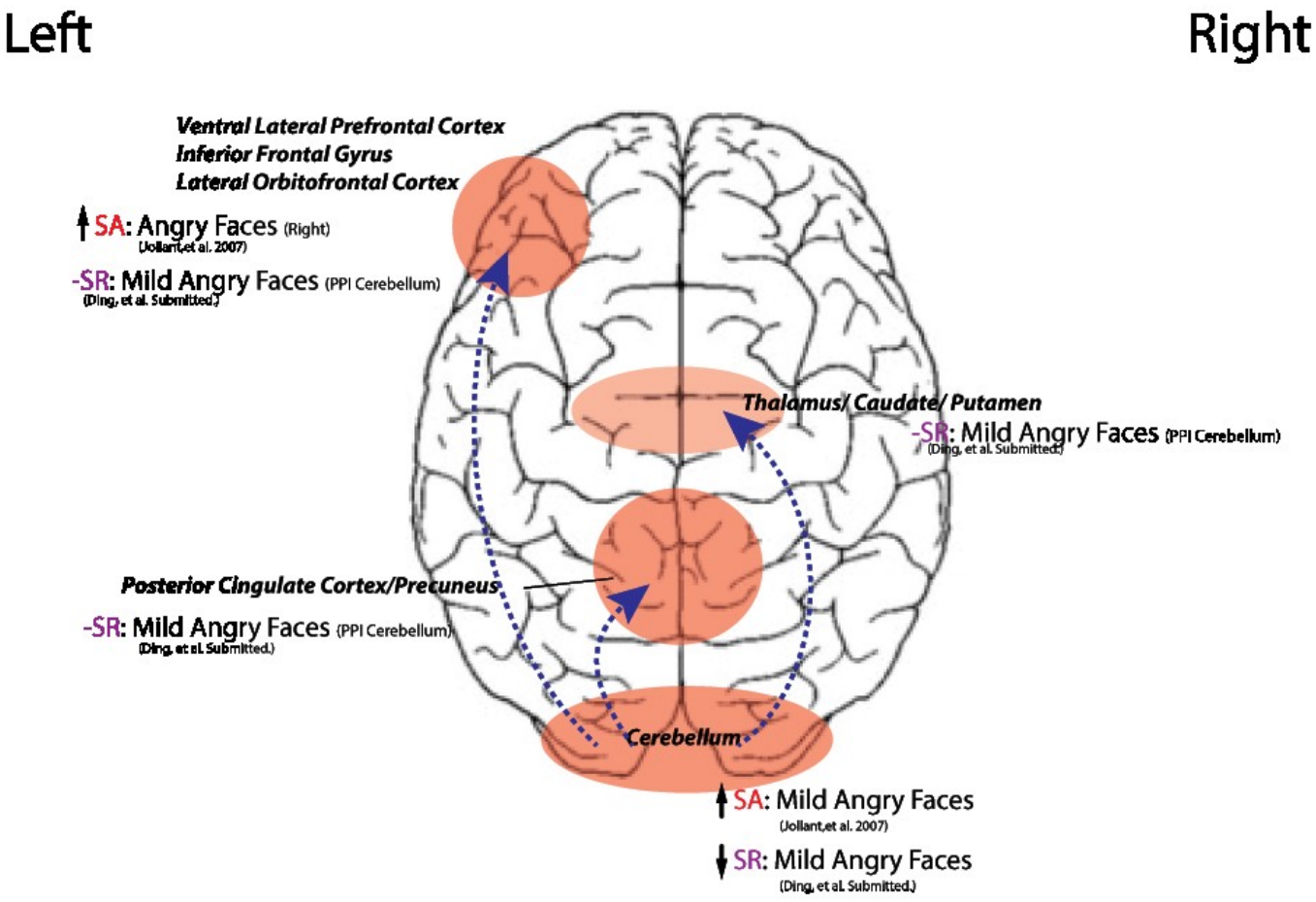

Figure 6.10. Findings related to emotional processing.

SA: suicide attempters. SR: suicide relatives. IGT: Iowa gambling task, a decision-making task. PPI: psycho-physiological interaction. Mild Angry Faces: Ekman faces task, an emotional processing task.

A dashed line implies functional connectivity/correlation (as assessed using psycho-physiological interaction) between the regions. An arrow source indicates the region of interest used in the PPI analysis and does not imply causation or effective connectivity. A solid arrow implies significant changes in the BOLD activity measurement in the particular group in the stated condition. A minus sign implies a decreased functional correlation between regions.

We explored emotional processing using the classical Ekman's faces task. We focused in particular on angry faces as a proxy for social threat. We observed a significant difference in the cerebellar activity of suicide relatives during angry faces (Chapter 5). The overall findings are congruent with the earlier report in suicide attempters (Jollant, Lawrence et al. 2008) and the replication study (Olie, Ding et al. 2015). Although this emotional processing alteration has been demonstrated in both suicide relatives and suicide attempters, suggesting its trait-like nature and its potential to be an endophenotype of suicide, there are still many questions that remain unanswered. These questions pertain especially to the behavioural manifestations of this emotional processing alteration, the mechanistic interpretation of cerebellar function and its connection to both decision-making and emotion processing.

6.2.3 Cognitive inhibition

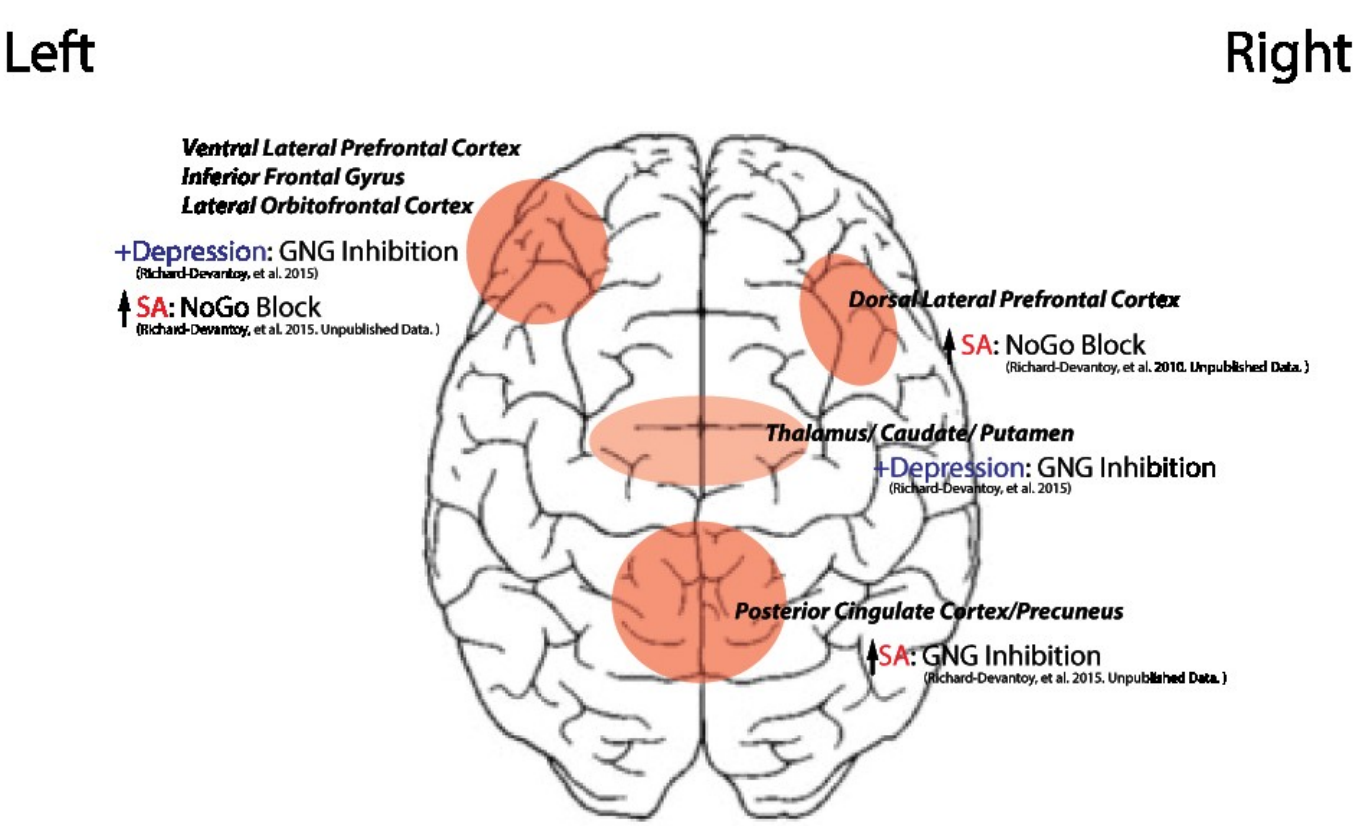

Figure 6.11. Findings related to cognitive inhibition.

SA: suicide attempters. IGT: Iowa gambling task, a decision-making task. GNG/NoGo Block: part of the go-nogo task, a cognitive inhibition task.

A solid arrow implies significant changes in the measurement in the particular group. A plus sign implies increased functional correlation between regions indicated.

Our findings suggest that cognitive inhibition may be a state alteration in the suicidal process. Indeed, there was no clear difference between suicide attempters and patient controls in terms of brain activation during the GoNoGo task, while activation differences were found between depressed patients and healthy controls in the left inferior frontal gyrus and medial thalamus during Go vs. NoGo, and in the bilateral parietal cortex and left orbitofrontal cortex during No-Go vs. baseline (Richard-Devantoy, Ding et al. 2016). Moreover, no cognitive control deficits were found in suicide relatives in the current study and they have not been studied as extensively

as suicide attempters. These findings sugggest that the neurocognitive risk of the suicidal act comprises a combination of state deficits (e.g. related to the depressive state) and trait-abnormalities transmitted within families. This is in agreement with a recent two-year longitudinal study in elderly suicide attempters (Gujral, Ogbagaber et al. 2015).

6.3 Limitation

There are several important limitations that need to be acknowledged in our investigation of suicide attempters and relatives.

First, there is a deliberate lack of emphasis on the direction of differences with regard to controls. The main reason for this is to emphasize that a difference exists within suicide related groups, but mostly details about the direction of differences was omitted. This was done since, in the context of fMRI contrast differences, when groups differ on the contrasts between two conditions, there are actually two equally plausible and equivalent interpretations of the results. In most circumstances, I attempted to clarify these differences and present the most plausible interpretation given the context. However, the opposite contrast of the opposite group differences can also be argued to exist. For instance, for contrasts between risky versus safe conditions, which show the suicide attempter group with greater differences than the healthy control group, it is perfectly reasonable to conclude that for the safe versus risky decision contrast (the opposite contrast), the suicide attempter group exhibit smaller differences than the healthy control group. Both interpretations are valid and in fact show the identical group relation. In most of the manuscript involving functional imaging I simplified the explanation by emphasizing only the easier to interpret contrasts and directionalities.

Another important limitation is the inclusion of earlier and present results acquired in 1.5 Tesla scanners with low resolution functional neuroimaging and reduced BOLD sensitivity. Practically, these limitations imply that designations such as the left VLPFC could well encompass regions such as the lateral OFC, triangularis, orbitalis, or opercularis parts of the inferior frontal gyrus or even parts of the anterior insula. With the typical 3mm voxel size in conjunction with the typical 8mm smoothing kernel, on top of individual anatomical variations and group

template formation process, the coordinates and the general anatomical interpretation of results needs to be taken with a degree of liberty and cautiousness. Hence, we restrict discussion mostly towards large anatomical regions to simplify the process. Without a doubt, among these regions there exist many sub-regions that are more intricate and that potentially possess layers of interactions, dependencies, and increasing complexities. For the functional discussions and the structural relations of existing findings, a vast simplifications and generalization has taken place to examine the high level functional architecture specialization of these regions. That does not mean that these regions will only carry out these functions, nor does it mean that no other region can carry out similar functions.

Thirdly, a lot of the results deal with group differences, such as group age differences, which may have nonlinear consequences in both behavioural and imaging data and that cannot be fully modelled effectively by simple covariates in the framework of linear models. Given the fact that the current nonlinear analysis of functional imaging data has not reached prominence, the full implications of group differences in age and their impact on other measures may be present and not yet fully appreciated.

Lastly, a few important clinical sampling limitations need to be acknowledged in terms of suicide comorbidity and incident proximity. Most suicidal behaviour considered within the scope of this thesis involves major depressive disorder (and bipolar disorder) as a comorbid (or familial comorbid) condition. Patients with schizophrenia may have different endophenotypic profiles and have very rarely been studied in neuroimaging studies of suicidal behaviour. In terms of incident proximity, we did not place any restriction on our recruitment in terms of duration of time since the suicidal act (and proband in suicide relative study).

With these important limitations in mind, I would like to propose a few additional updates to the preliminary model (Figure 6.1).

6.4 Synthesis of Current Findings

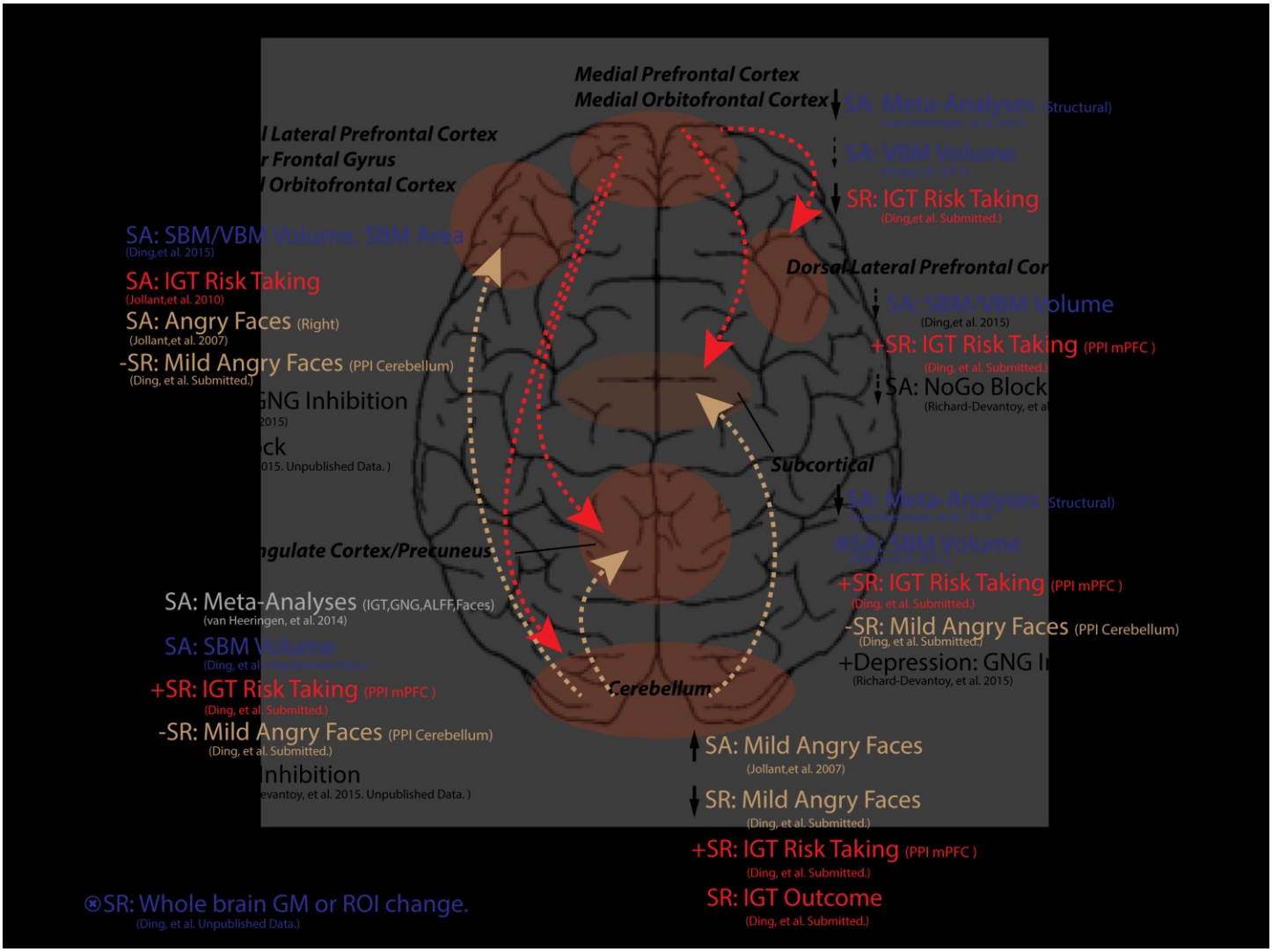

Figure 6.12. Summary of recent findings from the series of related experiments conducted before and during my PhD among of suicide attempters and their relatives on the topics of structural neuroimaging findings (**blue**), functional neuroimaging using the Iowa gambling task (**red**), Ekman's angry faces (**brown**), and cognitive inhibition (**black**).

A dashed line implies functional connectivity/correlation (as assessed using psycho-physiological interaction) between the regions. An arrow source indicates the region of interest used for the PPI analyses and does not imply causation or effective connectivity. A solid arrow implies a significant increase or decrease in the measurement in the particular group. A plus or minus sign implies increased or decreased correlation.

Above is a graphical recap of the most recent findings in suicide attempters and suicide relatives based on related projects covered in this thesis. Our series of studies on suicide attempters and suicide relatives begins to paint a holistic picture that brings together results from multiple sources on several specific anatomical regions, namely the VLPFC, medial PFC, cerebellum, PCC/precuneus and several other cortical structures. The main contribution

of this thesis to the current understanding of suicide behaviour is the following: the role of the PFC has been more segregated, with current findings strongly reinforcing the medial PFC as a major component of the decision-making process with attribution from and to multiple other brain regions. The left VLPFC, for its part, assumes a more integrative role across multiple networks such as decision-making, value attribution and inhibition—perhaps more so than any other regions in the brain—and is highly uniformly lateralized to the left side alone in most situations. Secondly, the cerebellum has shown a more prominent role in terms of emotional contextual processing than previously emphasized with potential implications for decision-making while taking risks. Lastly, subcortical structures, in addition to the precuneus/posterior cingulate cortex, show a potentially synergistic and plausibly mediatory relationship with each other, participating in both decision-making processes and emotional processing networks, which may serve as a potential interface/hub that exists between these two key separate networks. In summary, our findings shift the focus of brain imaging vulnerability exploration away from just the PFC and suggest that vulnerability may be more extensive and widely distributed than previously anticipated, spanning multiple function networks and anatomical regions. Although the PFC is very important for decision-making processes, other networks such as those implicated in emotional evaluation and cognitive inhibition may also be important, involving less commonly investigated structures, such as subcortical regions, the precuneus and the cerebellum. Current findings merely imply the importance of these regions in the performance of these cognitive functions. The precise relationship among these regions and their sub-granular components should be further elucidated using effective connectivity and resting state analyses combined with data-driven approaches to avoid interpretation biases. Only when such replications have been consistently achieved would we gain the substantial understanding of the implications of these regions and their impact on clinical detection and interventions.

6.5 Conclusion and Future Work

In this brief thesis, we explored several important functional and structural alterations in first-degree suicide relatives and in suicide attempters. Our findings 1) support a significant role for risky decision-making behaviour as an endophenotype of suicide, 2) highlighted the role of the left ventral PFC (both medial and lateral parts) but also the cerebellum and precuneus/posterior cingulate cortex in suicidal acts, especially in the context of angry

emotional context, and 3) suggest that cognitive inhibition may be a state specific alteration during depressive episodes. There are still many details that require further repeated validation.

There are still many unanswered questions, and current findings only add to the endless existing list. For instance, the precise impact of the medial PFC or cerebellum deficits on the rest of their respective networks, or the influence of external factors such as stress (McGirr, Diaconu et al. 2010) on the dynamics within these cognitive networks. Similarly, decision-making in social circumstances, such as in real life, represents a whole new field of exploration in the context of suicide research by necessitating the successful and concurrent integration of these two processes currently individually assessed. Questions such as these need to be answered, integrating not only neural imaging findings, but also clinical observations and neuropsychological evaluations. The contribution of neuroimaging findings alone, even when combined with advanced techniques is still insufficient to capture the dynamics and complicated nature of suicidal behaviour. There is still much work left to be done. My overall PhD contribution lies in the improved understanding of cognitive deficits among suicide relatives, but these remain unvalidated beyond the small sample of data collected. Future studies in suicide attempters need to carefully vet first-degree relatives and familial suicide status. Furthermore, cross-modal validation (Mahon, Burdick et al. 2012) or analytical replication (Jia, Huang et al. 2010; Wagner, Schultz et al. 2012; Jia, Wang et al. 2013) promises to improve internal validity of study findings and ensure a more thorough exploration of the precious data acquired. Lastly, to improve clinical intervention capabilities, especially with regard to predictive power, longitudinal studies (Amen, Prunella et al. 2009; Willeumier, Taylor et al. 2011; Sachs-Ericsson, Hames et al. 2013) will be more valuable and offer glimpses into the true predictive power of neuroimaging. For future studies, specifically in suicide relatives, I recommend including suicide attempters' relatives as a group as they offer simpler logistics and greater subject availabilities while providing an important validation for heritability of suicidal behaviour. Finally, the purpose of all these current researchers in suicide is to improve our clinical application and interventions in suicidal behaviour. Future studies should keep that in mind while investigating findings and traits that although statistically significant but only yield low effect size and low predictive power in relation to suicidal behaviour. Our ultimate goal is to save human lives through improved prediction and

prevention by better understanding risk factors that contribute to suicidal behaviour, not just chasing statistical significance. To that end, I hope my thesis has contributed to this higher purpose.

Chapter 7 Complete List of Bibliography and Appendices

7.1 Bibliography

7.2 Appendices

7.2.1 Dr. Gifuni's article: Subcortical nuclei volumes in suicidal behavior: nucleus accumbens may modulate the lethality of acts

Brain Imaging and Behavior
DOI 10.1007/s11682-015-9369-5

ORIGINAL RESEARCH

Subcortical nuclei volumes in suicidal behavior: nucleus accumbens may modulate the lethality of acts.

Anthony J. Gifuni · Yang Ding · Emilie Olié · Natalia Lawrence · Fabienne Cyprien · Emmanuelle Le Bars · Alain Bonafé · Mary L. Phillips · Philippe Courtet · Fabrice Jollant

Abstract Previously, studies have demonstrated cortical impairments in those who complete or attempt suicide. Subcortical nuclei have less often been implicated in the suicidal vulnerability. In the present study, we investigated, with a specific design in a large population, variations in the volume of subcortical structures in patients with mood disorders who have attempted suicide. We recruited 253 participants: 73 suicide attempters with a past history of both mood disorders and suicidal act, 89 patient controls with a past history of mood disorders but no history of suicidal act, and 91 healthy controls. We collected 1.5 T magnetic resonance imaging data from the caudate, pallidum, putamen, nucleus accumbens, hippocampus, amygdala, ventral diencephalon, and thalamus. Surface-based morphometry (Freesurfer) analysis was used to comprehensively evaluate gray matter volumes. In comparison to controls, suicide attempters showed no difference in subcortical volumes when controlled for intracranial volume. However, within attempters negative correlations between the left (r=−0.35, p=0.002), and right (r=−0.41, p<0.0005) nucleus accumbens volumes and the lethality of the last suicidal act were found. Our study found no differences in the volume of eight subcortical nuclei between suicide attempters and controls, suggesting a lack of association between these regions and suicidal behavior in general. However, individual variations in nucleus accumbens structure and functioning may modulate the lethality of suicidal acts during a suicidal crisis. The known role of nucleus accumbens in action selection toward goals determined by the prefrontal cortex, decision-making or mental pain processing are hypothesized to be potential explanations.

Keywords Suicidal behaviors · Markers · Subcortical structures · Magnetic resonance imaging (MRI) · Surface-based morphometry (SBM) · Neuroimaging · Mood disorders

Electronic supplementary material The online version of this article (doi:10.1007/s11682-015-9369-5) contains supplementary material, which is available to authorized users.

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Background

With one million deaths and 10–20 million suicide attempts every year, suicidal behavior is a major source of mortality and morbidity (Hawton and van Heeringen 2009; Lesage et al. 2012). In young adults, suicide ranks amongst the leading causes of premature death, and hence its prevention constitutes an important societal priority. The identification of factors facilitating suicide is one major avenue toward improved prevention. To date, the assessment of suicidal risk relies entirely on socio-demographic and clinical factors. These factors often have high sensitivity but limited specificity (Pokorny

1983). Consequently, more specific assessment tools are needed to substantiate suicidal risk in addition to the clinical assessment.

Suicide is often modeled as a complex behavior resulting from the interaction of acute stressors, such as interpersonal conflicts or loss, with predisposing factors (Mann 2003). Research has identified several elements of the suicidal diathesis, including brain alterations and neurocognitive dysfunctions (Jollant et al. 2011). Brain imaging is emerging as a promising way of improving the evaluation of suicidal risk through the identification of brain markers. Moreover, structural neuroimaging acquisition is widely available in Western countries, which could facilitate its clinical use. One goal of this study was, therefore, to test the ability of a "simple" 1.5 T structural neuroimaging sequence to discriminate suicide attempters from non-attempters.

Structural brain anomalies of suicide attempters have mainly been found in the prefrontal cortex (Jollant et al. 2011). However, differences in subcortical regions are suspected regarding their role in emotional and behavioral regulation (Herrero et al. 2002; Haber and Calzavara 2009; Ochsner et al. 2012). Not surprisingly, several studies have reported structural changes in these regions in suicide attempters and completers. Increased right amygdala volume has been associated with a history of suicide attempts in patients with depression (Monkul et al. 2007) and schizophrenia (Spoletini et al. 2011). Decreased volumes in the right caudate (Benedetti et al. 2011; Vang et al. 2010) and globus pallidus (Vang et al. 2010) have also been described in depressed patients with a history of at least one suicide attempt. Volumes in the right caudate were also found to be reduced when the experimental sample aggregated patients with a familial history of a suicidal gesture with patients with a history of a suicide attempt in a single group considered to be at a high risk of suicide (Wagner et al. 2011). Elderly suicide attempters showed reduced voxel counts in the putamen (Dombrovski et al. 2012). Moreover, the thalamus has similarly been implicated in a neuroimaging study (Benedetti et al. 2011) and in a volumetric post-mortem study (Young et al. 2008). Taken together, there is substantial evidence to suggest that several subcortical structures may be structurally altered in suicide attempters and completers, and may represent relevant biomarkers of suicidal behavior.

Despite specific findings associated with suicidal behavior, the hitherto published structural neuroimaging literature suffers from several limitations that the present study aims to address. Many recent studies assessed small sample sizes, as few as seven to ten suicide attempters (Vang et al. 2010; Monkul et al. 2007), which limit their statistical power and increase the risk of false positives and negatives. Our study constitutes the largest structural Magnetic Resonance Imaging (MRI) study specifically targeting suicidal behavior in mood disorders. Only one other large study, in psychotic disorders, has been conducted to date (Giakoumatos et al. 2013). Furthermore, we used previously validated and a priori-chosen study design (Jollant et al. 2005) with the inclusion of non-depressed patients to exclude the acute effect of the depressive state, and a group of patients with a history of mood disorder but not suicide attempt to exclude the effect of co-morbid disorders while specifically examining suicide vulnerability.

Based on previous findings, we hypothesized that suicide attempters vs. controls would show volumetric differences in subcortical nuclei, including the basal ganglia, the amygdala and the thalamus.

Materials and methods

Population

Participants were 73 suicide attempters (SA), 89 patient controls (PC) and 91 healthy controls (HC). SA were individuals with a personal history of both suicidal behavior and mood disorder; PC individuals with a personal history of mood disorder but no lifetime personal history of suicidal behavior; HC were individuals with no current or past history of any major DSM-IV Axis I diagnoses and no history of suicidal behavior. Suicidal acts were defined as any non-fatal, self-inflicted potentially injurious behavior committed with any intent to die as a result of the behavior (Mann 2003). This definition, therefore, excludes non-suicidal self-injuries and aborted suicidal acts. Psychiatric diagnoses were based on DSM-IV-TR criteria (APA 2000).

The study pools three samples, one recruited at the Institute of Psychiatry in London, United Kingdom (sample 1), and two recruited independently at the academic hospital of Montpellier, France (samples 2 and 3). The three samples only differed in two selection criteria: 1) Samples 1 and 2 comprised only males aged between 18 and 60 whereas Sample 3 comprised only non-menopausal females aged between 18 and 50; 2) All patients in Sample 1 suffered from major depressive disorder (MDD) whereas Samples 2 and 3 included both major depressive disorder and bipolar disorders. Participants were excluded if they had a lifetime history of severe head trauma, central nervous system disorders, schizophrenia, and substance use disorder over the last 12 months, suicide attempt using firearms, pregnancy, and contraindications to MRI. Only right-handed individuals checked by the Edinburgh handedness index (Oldfield 1971) were recruited. Details on excluded participants from each sample are given in Supplementary Material.

Assessment

For all samples, patients were enrolled through advertising and in outpatient clinics. After an initial screening interview, an experienced clinical psychiatrist interviewed selected participants. All DSM-IV diagnoses were made using the Mini-

International Neuropsychiatric Interview, version 5.0.0. (Sheehan et al. 1998). Symptom severity was assessed by the Hamilton Depression Rating Scale (HDRS) (Hamilton 1960) and the Beck Depression Inventory (BDI) (Beck et al. 1961). All subjects were euthymic during scanning, with a HDRS below 7. The last and the most severe suicidal acts were assessed using the Risk Rescue Rating Scale (RRRS) (Weisman and Worden 1972) and the Suicide Intent Scale (SIS) (Beck et al. 1974). The French or English versions of the National Adult Reading Test (NART) (Beardsall and Brayne 1990) were used to provide an estimation of verbal IQ. Barratt Impulsiveness Scale (BIS) version 10 was also used (Patton et al. 1995).

After complete description of the study to the subjects, written informed consent was obtained from all participants. The protocol was approved by respective site research ethics committees (Institute of Psychiatry or Montpellier Hospital research ethics board). Participants received compensation of £30 or 100€, respectively. A study with the same 3 samples has recently been published (Ding et al. in press).

MRI acquisition procedures and analysis

T1-weighted magnetic resonance images were acquired using a GE Signa 1.5 T Neuro-optimized MR system (General Electric, Milwaukee) in sample 1, and with a 1.5 whole-body MRI system (MAGNETON AVANTO, Siemens, Erlangen, Germany) in sample 2 and 3. Sample 1 used a spoiled gradient echo sequence with the following parameters: isotropic voxel dimension of 1.1 mm with field-of-view at 280×180 mm; TE of 5 ms and TR of 10.8 ms. 2D matrix 256×160 with 150 slices acquired, bandwidth of 122 Hz/pixel. Sample 2 used 3D T1 FLASH sequence with voxel dimension of 0.93×0.93×1 mm, field-of-view at 240×240 mm, matrix 256×256, 15 degrees Flip angle, TE of 5.2 ms and TR of 11 ms with 160 slices, bandwidth of 130 Hz/pixel. Sample 3 used 3DT1 MPRAGE with voxel dimension of 0.98 mm×0.98 mm×1 mm, field-of-view at 250×250 mm, matrix 256×256 with 160 slices, 15 degrees flip angle, TE of 4.1 ms, TR of 2100 ms and TI of 1100 ms, bandwidth of 140 Hz/pixel.

Surface-based morphometry (SBM) analyses were conducted using the Freesurfer image analysis suite (version v 5.1.0) (http://surfer.nmr.mgh.harvard.edu). The technical details and references for these procedures are described in prior publications listed online (http://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferWiki#References). Briefly, the processing includes motion correction (Reuter et al. 2010), removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Segonne et al. 2004), automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (Fischl et al. 2002, 2004) intensity normalization (Sled et al. 1998), tessellation of the gray matter/white matter boundary, automated topology correction (Fischl et al. 2001; Segonne et al. 2007), and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale et al. 1999; Fischl and Dale 2000). FreeSurfer results were evaluated using the QDEC, and TkSurfer tools.

This study examined 8 subcortical regions namely the amygdala, hippocampus, caudate, globus pallidus, putamen, nucleus accumbens, ventral diencephalon, and thalamus. FreeSurfer performs an automatic subcortical segmentation, where each voxel in the normalized brain volume is assigned a label (including the 8 subcortical regions studied). Automatic segmentation of subcortical structures is based on an atlas containing probabilistic information on the location of structures (Fischl et al. 2002). This automated classification technique compares in accuracy with manual labeling, and was shown to be sufficiently sensitive to robustly detect changes in subcortical structures that predispose to the onset of major neurocognitive disorder (Fischl et al. 2002).

Although multi-site neuroimaging poses challenges, samples can be combined and analyzed when groups are balanced across samples (which is the case here, see tables in Supplementary Material) and multi-site samples are properly controlled for in the analysis (Pardoe et al. 2008; Takao et al. 2014). Group comparisons in volumes were also systematically controlled for intracranial volume (Buckner et al. 2004). Additional covariates were used as needed (see below).

Statistical analyses

Unpaired *T*-tests and ANOVA (followed by Tukey post-hoc pairwise comparisons if significant) were used to compare quantitative variables across groups. Qualitative variables were compared using a chi-squared test. Confounding variables (sample, age, level of education, intracranial volume, bipolar disorder, medication) were controlled using a multivariate general linear model. The ANOVA threshold for statistical analyses was set at a very conservative $p<0.003$ ($p<0.05$ divided by 8 subcortical structures × 2 sides) for statistical significance. Statistical analyses were carried out with SPSS.21 (IBM Corp., Armonk, NY). As recent reports underlined the limits of using the *p*-value in group comparison (Nuzzo 2014), we additionally calculated Cohen's *d* effect sizes based on marginal means (taking into account the intracranial volume and sample) for each main comparisons i.e., between SA and PC. In order to parse the effect of different mood disorders, subanalyses were conducted with patients with unipolar depression only (from all 3 samples) or with patients with bipolar disorder only (from sample 2 and 3). Pearson product–moment correlation coefficients were computed to assess the relationship between the diverse sets of clinical measures (BDI, HDRS, NART, RSSS, SIS, BIS) and the subcortical volumes, using the same conservative statistical threshold ($p<0.003$). Finally, we also conducted a

multivariate ANCOVA to determine the effect of psychotropic medications on subcortical volumes in patients with mood disorders (PC and SA together), controlling for sample and intracranial volume.

Results

Socio-demographic and clinical comparisons

All three groups were equally distributed across the three samples. Comparison of socio-demographic and clinical variables across the three participant groups in the pooled sample (Table 1) showed that SA and PC were largely similar on all variables with the exception of higher use of antipsychotics and anxiolytics in SA. HC had a higher proportion of males and had more years of education. Also, patients had significantly higher HDRS and BDI scores than HC despite being below the threshold for depression. We did not covary for this latter variable as it was related to patient status.

Neuroimaging group comparisons

ANOVA revealed significant group differences (all $p<0.003$) for left amygdala, left ventral diencephalon, and right hippocampus. However, none of these differences survived corrections for intracranial volume and sample, even after covarying for age, gender, level of education, bipolar disorder, and medication intake. All subcortical brain regions had minimal and non-significant effect sizes (Table 2). Moreover, subanalyses restricted to patients with unipolar depression or to patient with bipolar disorder yielded similar negative results. Intracranial volume was significantly different between groups after accounting for sample ($F=3.2$, $p=0.04$), but did not differ between SA and PC.

Clinical correlations

The lethality of the last suicidal act (as measured with the first part of the RRRS) was negatively correlated with the left ($r=-0.35$, $n=73$, $p=0.002$), and right accumbens volume ($r=$

Table 1 Sociodemographic and clinical characteristics of the three groups

	Healthy Controls ($n=91$)	Patient Controls ($n=89$)	Suicide Attempters ($n=73$)	Omnibus F/Chi2/t	p	Post-hoc
Male Gender, N (%)	62 (68.1)	43 (48.3)	28 (38.4)	15.4	<0.001	HC>PC, SA
Age, mean (SD)	38.3 (8.2)	39.4 (9.5)	39.2 (10.6)	0.3	0.7	
Years of education, N (%)	15.2 (2.3)	14.3 (2.5)	13.9 (2.2)	7.3	0.001	HC>PC, SA
NART (% correct), mean (SD)	0.73 (0.14)	0.72 (0.11)	0.69 (0.11)	1.6	0.2	
HDRS, mean (SD)	0.9 (1.3)	3.6 (2.3)	3.1 (2.3)	43.9	<0.001	HC<PC, SA
BDI, mean (SD)	1.0 (2.4)	5.3 (5.2)	5.3 (4.7)	30.3	<0.001	HC<PC, SA
Age at first mood episode, mean (SD)	–	25.6 (8.8)	25.2 (11.2)	0.2	0.8	
Number of depressive episodes, mean (SD)	–	4.9 (8.0)	5.6 (7.8)	−0.6	0.6	
Bipolar disorder, N (%)	–	32 (36.0)	32 (43.8)	1.0	0.3	
Number of hypo(manic) episodes, mean (SD)	–	3.0 (7.7)	3.5 (8.8)	−0.4	0.7	
Anxiety disorders, current, N (%)	–	31 (34.8)	30 (41.1)	0.7	0.4	
OCD, current, N (%)	–	3 (3.4)	1 (1.4)	0.7	0.4	
Alcohol/substance abuse, past, N (%)	–	26 (29.2)	17 (23.3)	0.7	0.4	
BIS10, mean (SD)	58.2 (16.1)	57.2 (16.1)	58.3 (16.1)	0.1	0.9	
Psychotropic medication, N (%)	–	52 (58.4)	52 (71.2)	2.9	0.1	
Antidepressant, N (%)	–	28 (31.5)	27 (37.0)	0.6	0.5	
Lithium, N (%)	–	15 (16.9)	14 (19.2)	0.1	0.7	
Antipsychotics, N (%)	–	6 (6.7)	19 (26.0)	11.4	0.001	PC<SA
Anticonvulsivants, N (%)	–	15 (16.9)	17 (23.3)	1.1	0.3	
Anxiolytics and hypnotics, N (%)	–	16 (18.0)	23 (31.5)	4.0	0.05	PC<SA
Age at first suicide attempt, mean [min-max]	–	–	26.8 [11–59]	–	–	
Number of suicide attempts, mean [min-max]	–	–	2.7 [1–10]	–	–	
Suicide intent scale, total score, most severe act, mean [min-max]	–	–	414.5 [2–26]	–	–	
Risk rescue rating scale, total score, most severe act, mean [min-max]	–	–	39.5 [25–57]	–	–	

BIS10, barratt impulsivity scale version 10; *NART*, national adult reading test; *HDRS*, hamilton depression rating scale; *BDI*, beck depression inventory; *OCD*, obsessive compulsive disorder; *HC*, healthy controls; *PC*, patient controls; *SA*, suicide attempters; *SD*, standard deviation

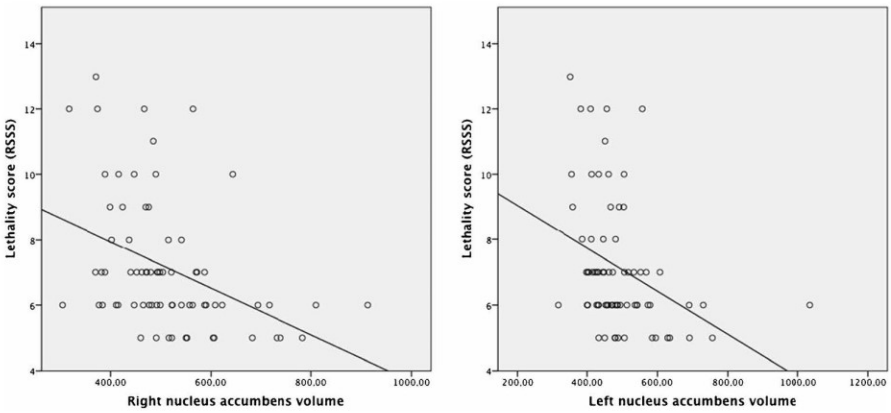

Fig. 1 Correlation between nucleus accumbens volumes and the lethality of the last suicidal act

PC and 29 HC, found no significant association with the right or left amygdala, nor any other subcortical regions. Spoletini et al. (Spoletini et al. 2011) with a larger sample of schizophrenic patients and using FSL, also reported increased amygdala volume (using 3 T magnetic field but similarly sized millimetric voxel). In contrast, Soloff et al. (Soloff et al. 2012) found no amygdalar differences between SA and PC in patients with borderline personality disorder using voxel-based morphometry (VBM).

Similarly, we found no volumetric differences in basal ganglia structures between SA and controls. This contrasts with reports of smaller right caudate nuclei (Vang et al. 2010; Wagner et al. 2011) and globus pallidus (Vang et al. 2010) using VBM or Freesurfer. Again, these prior reports had limited numbers of subjects which increase the likelihood of false positives: Wagner et al. (Wagner et al. 2011) had only 15 depressed subjects "at high risk for suicide" (some of them had never attempted suicide but had a family history of suicide) and Vang et al. (Vang et al. 2010) had only 7 SA, which were compared to 6 HC therefore limiting any definitive conclusion. In larger samples and using VBM, Benedetti et al. (Benedetti et al. 2011) reported smaller "basal ganglia" in 19 SA vs. 38 PC with bipolar disorder, and Dombrovski et al. (Dombrovski et al. 2012) found reduced putamen, but not pallidum or caudate, voxels counts in 13 elderly SA vs. 20 PC with depression. Only the report by Dombrovski et al. employed high magnetic filed (3 T), affording a better resolution, which could explain a difference with our findings.

The thalamus was previously implicated in the suicidal diathesis through neuroimaging studies showing reduced grey matter volumes in SA with bipolar (Benedetti et al. 2011) and psychotic disorders (Giakoumatos et al. 2013) (using VBM or Freesurfer, respectively). Our findings were not consistent with this in either our complete population or the bipolar patient sub-group. A lack of association was also reported by Spoletini and colleagues (Spoletini et al. 2011) whereas Lopez-Larson et al. (Lopez-Larson et al. 2013) reported *increased* thalamic volumes in SA vs PC in a complex population of depressed veterans with mild traumatic brain injury, using Freesurfer.

Finally, to our knowledge, hippocampal volume, although largely investigated in relation to mood disorders (Videbech and Ravnkilde 2004) and trauma history (Frodl and O'Keane 2013), was never directly associated with suicidal behavior (Soloff et al. 2012). Our study confirms the lack of a direct relationship. It is possible that hippocampal alterations are mainly the result of early traumatic events and, therefore, only affect a subset of SA (Turecki et al. 2012).

Although nucleus accumbens volumes did not discriminate attempters and non-attempters in general, our analyses suggest that this structure could modulate the lethality of the suicidal act i.e., medical consequences of the act. In as much as suicide is not a homogenous behavior at the clinical level, it is unlikely a homogenous phenomenon at the biological level. The common issue of phenotypic heterogeneity in psychiatry (Kapur et al. 2012) may explain the difficulty in finding reliable, reproducible group differences. Moreover, suicidal behaviors are complex acts varying in terms of intent, planification, or lethality.

Previous neuroimaging studies have suggested that some brain regions may modulate certain aspects of suicidal acts. Activity at rest in the medial prefrontal and anterior cingulate cortices has been correlated with impulsivity and suicidal intent (Oquendo et al. 2003). Correlations between basal ganglia structures and suicidal dimensions, or factors relevant to suicide, have also been found. For example, smaller putamen in elderly suicidal patients has been correlated with higher reward delay discounting (Dombrovski et al. 2012). Vang et al. (Vang et al. 2010) found a negative correlation between globus pallidus volumes and measures of impulsivity in suicidal patients (although we could not confirm this latter association in our study).

To date, the mechanisms linking the nucleus accumbens and the lethality of the suicidal act have not been investigated. However, based on related prior findings, some hypotheses can be suggested. Lethality reflects the consequences of different interacting factors including the level of suicidal intent, the choice of a suicidal method and, to a certain degree, the physical resistance of the individual. Of note, individuals committing more

lethal acts seem to be closer to suicide completers than low-lethality attempters (Giner et al. 2014). In terms of the role of the nucleus accumbens, it is located at "the interface between cognition, emotion and action" (Floresco 2014), receiving inputs from the prefrontal cortex, hippocampus, basolateral amygdala and ventral tegmental area, and projecting toward motor effectors. This region has been involved in action selection (Leotti and Delgado 2011), notably in situations of ambiguity, based on goals defined by cortical regions. The nucleus accumbens may particularly bias the intensity and direction of planned actions. In a situation of suicidal crisis, the nucleus accumbens could therefore be implicated, not in committing a suicidal act per se, but in selecting the specific actions associated with this act, with suicidal intent (the goal) being encoded by and transmitted from the prefrontal cortex (Oquendo et al. 2003). Moreover, the nucleus accumbens encodes positive prediction error (McGinty et al. 2013; Dombrovski et al. 2013), and is involved in decision-making (Kuhnen and Knutson 2005). Impaired decision-making has been robustly found in suicide attempters (Richard-Devantoy et al. 2014), notably those using a violent mean (Jollant et al. 2005). Use of violent suicidal means has in turn been associated with more lethality (Giner et al. 2014). Dysfunctional nucleus accumbens activity in some individuals may therefore underlie disadvantageous decision-making, but also the choice of a more violent mean in a stressful situation, increasing the risk of serious medical consequences and death. Finally, the nucleus accumbens has been associated with psychological pain processing (O'Connor et al. 2008). Increased psychological pain has been linked to increased risk of suicidal acts (Olie et al. 2010). Moreover, a recent study suggest that mental pain interacts with difficulty communicating to modulate lethality (Levi-Belz et al. 2014). Nucleus Accumbens may therefore be the link between mental pain and suicide lethality. The link between these various factors (lethality, mental pain, impaired decision-making, violent acts) and the functional and structural integrity of the nucleus accumbens should be further investigated in future studies.

Although not specifically designed to address this question, secondary analyses emphasize the importance of taking into account medication status when examining subcortical volumes. We found antipsychotics and benzodiazepines to be associated with reduced volumes of the hippocampus in all patients together. A recent study in schizophrenia demonstrated that atypical antipsychotics were associated with decreased left hippocampal volume, which correlated with a decrease in serum BDNF levels (Rizos et al. 2014). There is limited neuroimaging evidence of the effect of antipsychotics on subcortical volumes in mood disorders. This question necessitates specific investigation.

Our study had several methodological limitations. The main limitation in our analysis of subcortical nuclei was that our data were pooled across three sites. This procedure added supplementary heterogeneity because it was not designed as a priori multi-center study, which resulted in different acquisition parameters (slices, TE, TR) from two different scanners. Covarying for the sites was therefore necessary although it might have decreased the power to detect differences (Glover et al. 2012). Nonetheless, the risk of type II errors may have been counterbalanced by the large sample size (n=253) of our study, which was balanced across the three sites (see Supplementary Material). Indeed, analysis of cortical regions in the same samples revealed significant between-group differences in several prefrontal regions, despite covarying for the effect of the sample (Ding et al. in press). Secondly, given that data in males and females were obtained with different scanning procedures, examination of gender effects was not possible to distinguish from difference in scanning techniques. Our data were obtained with 1.5 T MRI scanners, which might lack the necessary power to detect subtle alterations. Higher isotropic resolution could theoretically render more accurate volumetric measurements of subcortical brain structures (Wu et al. 2010) and reduce systematic errors in registration (Simon et al. 1997). Fourth, different results among studies that have investigated volumetric differences may stem from the use of different analysis methods. Finally, we must take into account the heterogeneity in the psychiatric populations studied, which included moderately to severely ill and often medicated patients in order to be representative. Although, these medical factors were controlled for, this may have, nonetheless, resulted in additional heterogeneity.

In conclusion, this study adds new findings to the growing literature on the neurocognitive basis of suicidal behavior. No general association between subcortical volumes and suicidal behaviors could be confirmed contrary to what has been found in various cortical regions. New acquisition and analysis procedures may be necessary. However, our study also suggests that the nucleus accumbens may modulate the lethality of suicidal acts. More research is needed to understand the role of subcortical structures, and their link with cortical regions, in the development of the suicidal crisis and the modulation of this complex behavior.

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Informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, and the applicable revisions at the time of the investigation. Informed consent was obtained from all patients for being included in the study.

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7.2.2 Ms. Hoehne's article: First-degree relatives of suicide completers may have impaired decision-making but functional cognitive control

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First-degree relatives of suicide completers may have impaired decision-making but functional cognitive control

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ABSTRACT

Background: The heritability of suicide is well established. Transmission of risk appears to follow traits more than disorders like depression. In the present project, we aimed at investigating the potential for transmission of cognitive deficits previously observed in suicide attempters, specifically impaired decision-making and cognitive control.

Methods: Seventeen healthy first-degree relatives of suicide completers with no personal history of suicidal act were compared to 18 first-degree relatives of individuals with major depressive disorder but no family history of suicidal act, and 19 healthy controls. Decision-making was assessed with the Iowa Gambling Task, and cognitive control with the Stroop Task, the Hayling Sentence Completion Test, and the Trail-Making Test.

Results: Both suicide and depressed relatives showed lower gambling task net scores than healthy controls. However, there were trends toward lower learning abilities in suicide than depressed relatives (interaction: $p = 0.07$), with more risky choices at the end of the test. Suicide relatives also showed a higher number of self-corrected errors relative to the total number of errors in the Stroop colour test compared to both control groups, with no difference in interference scores. There was no group-difference for any other cognitive tests.

Conclusion: Our findings suggest that decision-making impairment may be found in healthy relatives of suicides and represent a cognitive endophenotype of suicidal behaviour. Normal cognitive control (or self-corrected deficits) may protect relatives against suicidal acts. Impairments in value-based and control processes may, therefore, be part of the suicide vulnerability and represent potential targets of preventative interventions.

1. Introduction

Suicidal behaviour is often modelled as the interaction between proximal stressful events such as job loss or marital conflicts, and vulnerability factors (Mann, 2003). Understanding this vulnerability is important in the hopes of improving preventative interventions. Family, twin and adoption studies have provided robust evidence of a familial transmission of the diathesis for suicidal behaviour with a heritability of suicidal behaviour estimated at 45–50% (Statham et al., 1998; Brent and Mann, 2005). There is also evidence that the transmission of suicide risk co-occurs with the transmission of particular personality traits, more than with categorical diagnoses such as major depressive disorder (Brent and Mann, 2005; Mcgirr et al., 2009). Given the relatively high heritability of suicidal behaviour, there is a growing interest in studying vulnerability factors of suicidal behaviour as endophenotypes i.e. heritable traits that are found both in patients and unaffected family members (Courtet et al., 2011). First-degree relatives of suicides represent a particularly interesting population to investigate toward this end.

Mounting evidence from a growing body of literature points to a number of neurocognitive impairments in suicide attempters that cannot be attributed to comorbid psychopathologies (Jollant et al., 2011). A recent meta-analysis of neuropsychological studies in mood disorders confirmed an association between suicide vulnerability and several cognitive deficits (Richard-Devantoy et al., 2014).

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This was notably the case of value-based decision-making (often measured by the Iowa Gambling Task) and cognitive control processes (particularly the interference effect measured by the Stroop test). This led us to a model of neurocognitive vulnerability to suicidal behaviour as being the combination of alterations in value-based and control processes (Jollant et al., 2011). These deficits may be partly heritable, and therefore represent endophenotypes of suicidal acts.

Previous studies have indeed suggested that cognitive skills are under substantial genetic modulation and are heritable. For instance, variants of genes expressed in the prefrontal cortex including COMT, dopamine receptor genes and BDNF, were previously associated with cognitive function (Savitz et al., 2006). Moreover, in a systematic review of literature, Hermo et al. (2014) found that different cognitive domains differed in their heritability in healthy individuals. This heritability and genetic modulation apply to cognitive measures previously linked to suicidal behaviour. For instance, performance in the Stroop test was found to be influenced by genetic variants (Stins et al., 2004). We also found that variants of several genes coding for the serotonergic system modulate decision-making in suicide attempters (Jollant et al., 2007a). Furthermore, a twin study using a behavioural economic design assessed the heritability of risk attitude at 57%, a measure indirectly related to decision-making performance in the Iowa Gambling Task (Zhong et al., 2009). Understanding the heritability of neurocognitive impairments previously found in suicide attempters would shed light on mechanisms of neurocognitive vulnerability to suicidal acts.

To our knowledge, only one study of cognitive function in relatives of suicide completers has been published to date. Mcgirr et al. (2010) reported that first-degree relatives of suicides, in comparison to healthy controls with no family history of mental disorders or suicidal behaviour, exhibited impaired cognitive inhibition but only following a psychosocial stress paradigm. In another article on the Wisconsin Card Sorting Test in the same sample, Mcgirr et al. (2013) found that first-degree relatives of suicides made more perseverative errors and had a lower level of conceptual responses. Evidence from this study, together with previous findings in healthy populations, suggests that neurocognitive impairments including deficits in cognitive inhibition and decision-making may represent cognitive endophenotypes of suicidal behaviour.

In the current paper, we investigated cognitive deficits in first-degree relatives of suicides with no personal history of suicidal acts. We recruited a new and slightly larger sample and, contrary to the previous study, we included a control group of first-degree relatives of individuals with major depressive disorder to distinguish cognitive deficits associated with suicidal behaviour from those associated with the vulnerability to depression. We hypothesized that the same cognitive deficits previously observed in suicide attempters, specifically in decision-making and cognitive control, would be found in first-degree suicide relatives.

2. Methods

2.1. Population

Three groups of participants aged between 18 and 55 years old were recruited through newspaper advertisement:

1) 17 biological first-degree relatives of suicide completers (*suicide relatives*). The suicide completers had suffered from major depressive disorder but not schizophrenia, bipolar disorder or unknown disorders. The relatives (participants) had no personal history of suicide attempt.
2) 18 biological first-degree relatives of individuals with major depressive disorder (*patient relatives*) with no personal and (second-degree) family history of suicidal acts.
3) 19 *healthy controls* with no (second-degree) family history of suicidal behaviour or major mental disorders.

Additional non-inclusion criteria for all participants included, alcohol and substance dependence or abuse within the last 12 months, major comorbid psychiatric disorders such as schizophrenia and bipolar disorder, lifetime history of severe head trauma or central nervous system disorder. All participants were right-handed as checked by the Edinburgh handedness inventory (Oldfield, 1971) and normothymic at time of participation as checked by the Structured Clinical Interview for Axis I DSM-IV (SCID-I).

Participants in the suicide relative group had at least one first-degree biological relative who committed suicide, commonly defined in the literature as an act carried out with some intent to die and having led to death (Mann, 2003). Suicide was assessed by the FIGS following information given by the relative (https://www.nimhgenetics.org/interviews/figs/). Unclear cases (e.g. if there is a doubt about an accident) were not included.

This study was carried out in accordance with the latest version of the Declaration of Helsinki. Written informed consent was obtained from all participants. This study was conducted at Douglas Mental Health University Institute, Montreal, and has been approved by the local ethics committee.

2.2. Clinical assessment

Diagnoses were made with the structured Clinical Interview for Axis I DSM-IV (SCID-I) (First and Spitzer, 2002) and Axis II DSM-IV (SCID-II) (First and Gibbon, 1997). Level of depression was rated with the 21-item Hamilton Rating Scale for Depression (HAMD-21) (Hamilton, 1960) and the Beck Depression Inventory (BDI) (Beck et al., 1961). The anxiety level was assessed with the Spielberger State Trait Inventory (Spielberger, 1983). The Buss-Durkee Hostility Inventory (BDHI) (Buss and Durkee, 1957), the Brown-Goodwin Assessment of Lifetime History of Aggression (BGLHA) (Brown and Goodwin, 1986), and the Barratt's Impulsivity Scale (BIS-11) (Barratt, 1965) were used to assess traits of hostility, aggression and impulsivity, respectively.

2.3. Neuropsychological assessment

The following neuropsychological domains were evaluated: 1) Verbal IQ with the National Adult Reading Test (NART) (Mackinnon et al., 1999); 2) Cognitive inhibition with the Stroop Colour Test (Stroop, 1935), the Trail Making Test (TMT), and the Hayling Sentence Completion Test (Burgess and Shallice, 1997); 3) Verbal fluency with the FAS verbal fluency test (Benton and Hamsher, 1976); 4) Working memory with the Digit Span number part 1 and 2 of the Weschler Adult Intelligence Scale 4th edition (WAIS-IV) (2008); and 5) decision-making with the Iowa Gambling Task (IGT) (Bechara et al., 1999). The order of the tasks was randomized.

In the first part of the *Stroop colour test*, (the "naming" sheet), participants are asked to name the colour of 100 coloured rectangles as fast as they can, without making any mistakes. In the second part (the "lecture" sheet), participants are asked to read words printed in black, all words naming colours. In the third part (the "interference" sheet), subjects are asked to name the colour of the ink of the words written on the page, all words naming colours that do not correspond to the colour of their ink (e.g. the word "green" printed in blue). We calculated an interference time index score corresponding to the time to read interference sheet minus naming

sheet. We also calculated the number of self-corrected errors in the interference sheet minus in the naming sheet.

In the *Trail Making Test (TMT)*, participants are asked to connect circles as quickly as possible, without lifting the pencil from the paper. Twenty-five circles are distributed over a sheet of paper. In Part A, the circles are numbered 1–25, and the participant must draw lines to connect the numbers in ascending order. In Part B, the circles include both numbers (1–13) and letters (A–L). Participants are asked to draw lines to connect the circles by alternating between the numbers and letters in ascending order (i.e., 1-A-2-B-3-C, etc.). Time to complete part A was used as a measure of information speed processing for this test.

The *Hayling Sentence Completion Test* consists of 30 sentences in which the final word is omitted but is highly predictable in everyday language situations. The task is made up of two sections (A and B), each one containing 15 sentences. In section A (response initiation, used as a measure of information speed processing), the sentences are read aloud to the individual, who has to complete each one with the missing word as quickly as possible. For example, in the sentence "He posted a letter and forgot to put a …," the correct response should be "stamp." In section B (response inhibition), the sentences are read aloud to the subject, who is asked to complete each one with an unexpected word that is absolutely unrelated to the sentence presented, as quickly as possible. For example, for the sentence "The farmer went to milk the …," participants might give the word "phone." During this inhibition section, participants who completed the sentence with a related word rather than an unrelated one are told that their word is related to the sentence, and ask to follow the task instructions, which are then repeated. If the participant does not produce a word within 30 s, the trial is terminated and a response latency of 30 s is recorded.

Finally, the computerized version of the *Iowa Gambling Task* (IGT) was used. Participants were presented with four decks of cards and prompted to pick a card from one of the decks. This action resulted in either a gain or a loss of a controlled randomized amount of money. Participants were not informed that there were two advantageous decks (that produced small gains and incurred even lower losses, resulting in a net gain over the long run) and two disadvantageous decks (that produced large gains and incurred much higher losses, resulting in a net loss over the long run). Participants were told that the goal of the game was to gain as much money as possible. They were also told that some decks were better than others, and that they had to figure it out as they played the game in order to win. They were told to play until the computer indicated that the game was over, and were not aware that the game ends after 100 choices. No real money was used in any parts of the simulated gambling process and the financial compensation of participants was not correlated to their task performance. All participants were presented a survey at the end of session to evaluate their level of engagement in the experiment. Task performance was measured through group average performance. Net scores were calculated as the difference between the number of safe minus risky choices, for the 100 choices (total score) and by blocks of 20 choices on the basis of previous findings (Jollant et al., 2005). We also calculated net scores for blocks of 50 choices representing two distinct decision-making phases, namely *decision under ambiguity*, then *decision under risk* when a certain knowledge about the task has been acquired (Jollant et al., 2007a).

2.4. Statistical analysis

As the Shapiro–Wilk's test showed a normal or close to normal distribution for all main dependent variables, a general linear model (GLM) was used to investigate the association between group and cognitive scores, including covariates where needed. A Chi-square test was used to compare qualitative values. For the correlation analysis, Pearson's correlation tests were used. A repeated-measures GLM was used for analyses of IGT net scores by consecutive blocks of 20 choices or blocks of 50 choices. P-values less than 0.05 were considered as statistically significant. No multiple comparison were conducted as the choice of tests was largely based on a priori hypotheses. All analyses were performed using SPSS version 21.0 (SPSS, Inc., Chicago, IL).

3. Results

3.1. Socio-demographic and clinical variables (Table 1)

The three groups did not differ significantly in terms of gender (although there was an obvious between group difference in sex ratio), level of education, current level of depressive or anxiety symptoms, levels of hostility, anger, or impulsivity traits, lifetime history of substance (drug and alcohol) abuse, personality disorders and verbal IQ. Suicide relatives were significantly older than the two other groups. Compared to healthy controls, suicide relatives were more likely to have used psychiatric medications in the past. Finally, patient relatives scored higher than healthy controls on STAI-B trait anxiety.

3.2. Neuropsychological performances (Table 2)

After controlling for age and gender (and information processing speed and total number of errors when needed), mean performances significantly differed between the three groups for the IGT and for the number of self-corrected errors in the Stroop test. In the Stroop colour test, suicide relatives corrected more errors made, after taking into account the total number of errors, compared to patient relatives and healthy controls.

In the IGT, the total net score was lower in both suicide relatives and patient relatives vs. healthy controls. However, the net score for the last 20 choices was lower only in suicide relatives vs. healthy controls, with a linear trend between the 3 groups ($F = 3.4$; $p = 0.04$). The learning effect during the IGT was assessed using a repeated-measures GLM for blocks of 20 choices (Fig. 1). Analyses showed a significant group*block interaction for the three groups ($F = 2.8$; $p = 0.008$) and a trend for the two relative groups ($F = 2.1$; $p = 0.07$) suggesting that the learning effect varies according to the group. Analyses per group showed significant effects in all 3 groups but a lower effect in suicide relatives compared to patient relatives and healthy controls ($F = 2.7$, $p = 0.04$, $\eta^2 = 0.1$ in suicide relatives; $F = 5.0$, $p = 0.001$, $\eta^2 = 0.2$ in patient relatives; $F = 11.9$, $p < 10^{-3}$, $\eta^2 = 0.4$ in healthy controls). Fig. 1 shows that, whereas suicide relatives and patient relatives followed a similar pattern of choice during the first 80 choices, they were distinguished during the last 20 choices, with safer choices in patient relatives. When changes in choices were assessed using two blocks of 50 trials, a significant group*block interaction was also found for the three groups ($F = 3.4$; $p = 0.04$) and a trend for the two relative groups ($F = 3.7$; $p = 0.06$), with significant learning effects in healthy controls ($F = 14.1$, $p = 0.001$; $\eta^2 = 0.4$) and patient relatives ($F = 9.5$, $p = 0.007$; $\eta^2 = 0.4$) but not in suicide relatives ($F = 1.4$, $p = 0.2$; $\eta^2 = 0.1$).

As previously found (Richard-Devantoy et al., 2013), decision-making (IGT total net score) did not correlate with any tests measuring cognitive control or memory (all $p > 0.1$), whereas tests of these two latter domains were largely correlated to each other (Stroop interference index and TMTB time: $rs = 0.30$, $p = 0.07$; Stroop and animal verbal fluency: $rs = -0.37$, $p = 0.02$; TMTB and memory span: $rs = 0.35$, $p = 0.03$; TMTB and animal verbal fluency: $rs = -0.38$; $p = 0.02$; memory span and animal verbal fluency:

Table 1
Description and comparison of socio-demographic and clinical variables between the three groups.

	Healthy controls (HC; n = 19)		Patient relatives (PR; n = 18)		Suicide relatives (SR; n = 17)		F/χ^2	P	Post-hoc
Male Gender, N (%)	13	(68.4)	7	(38.9)	8	(47.1)	1.7	0.19	
Age, mean (SD)	32.8	(9.9)	37.7	(8.3)	51.4	(9.4)	19.2	<10 [3]	SR > PR, HC
NART ratio, mean (SD)	0.8	(0.1)	0.7	(0.2)	0.7	(0.2)	1.1	0.35	
Education, N (%)							8.7	0.07	
High school	0	(0)	4	(22.2)	2	(11.8)			
College	2	(12.5)	4	(22.2)	7	(41.2)			
University	14	(87.5)	10	(55.6)	8	(47.1)			
BDI score, mean (SD)	1.3	(1.5)	1.5	(2.2)	1.8	(3.0)	0.2	0.79	
HAM-D score, mean (SD)	1.7	(2.1)	1.6	(2.2)	2.3	(2.0)	0.4	0.67	
STAI-A state score, mean (SD)*	25.5	(6.9)	26.3	(5.0)	22.6	(4.2)	0.8	0.48	
SCID I past history of depression, N (%)	1	(5.3)	4	(22.2)	5	(29.4)	3.7	0.16	
SCID I past substance abuse, N (%)	1	(5.3)	1	(5.6)	0	(0)	1.0	0.62	
SCID II personality disorders, N (%)	0	(0)	3	(16.7)	1	(5.9)	3.8	0.15	
Past use of psychotropic meds, N (%)	0	(0.0)	5	(27.8)	7	(41.2)	9.2	0.01	SR > HC
BDHI score, mean (SD)	47.6	(9.1)	42.0	(13.4)	46.6	(6.0)	1.2	0.33	
STAI-B trait score, mean (SD)*	29.4	(4.6)	35.8	(7.8)	28.2	(6.4)	4.2	0.03	PR > HC
BIS score, mean (SD)*	73.1	(4.9)	72.4	(3.0)	72.9	(4.0)	0.1	0.91	

Footnotes: BIS-11: Barratt's Impulsivity Scale; BDHI: Buss-Durkee Hostility Inventory; BDI: Beck Depression Inventory; HAM-D-21: 21-item Hamilton Rating Scale for Depression; NART: National Adult Reading Test; SCID: structured Clinical Interview for Axis I DSM-IV (SCID I) and Axis II (SCID II); STAI-A: Spielberger State trait Anxiety Inventory – State; STAI-B: Spielberger State trait Anxiety Inventory – Trait; SD: Standard deviation. Data for the STAI B were only available for 29 participants, 30 for STAI A, 39 for the BIS/BDHI/HDRS, 45 for SCID2, 47 for NART, 48 for SCID1, 49 for education, 50 for BDI.

Table 2
Neuropsychological Performances between the three groups.

	Healthy controls (HC; n = 19)		Patient relatives (PR; n = 18)		Suicide relatives (SR; n = 17)		Omnibus F/χ^2	P	Post-hoc
Stroop interference time index, mean (SE)	41.8	(5.4)	44.6	(4.5)	39.2	(5.4)	0.30	0.74	
Stroop self corrected errors (SE)*	0.6	(0.4)	−0.2	(0.3)	1.4	(0.4)	5.35	0.01	SR > PR
Hayling B corrected time (s), mean (SE)**	154.5	(28.8)	233.2	(25.0)	195.2	(40.8)	2.31	0.11	
TMT B reaction time, mean (SE)**	56.5	(7.7)	72.9	(6.3)	53.3	(7.7)	2.42	0.10	
Memory index, mean (SE)	5.0	(0.7)	4.1	(0.5)	3.2	(0.6)	1.66	0.20	
Verbal fluency (P + F), mean (SE)	22.3	(1.8)	22.6	(1.5)	26.6	(1.8)	1.57	0.22	
Verbal fluency (animals), mean (SE)	28.3	(2.6)	32.5	(2.1)	35.1	(2.5)	1.48	0.24	
IGT net score-total, mean (SE)	30.6	(7.2)	7.8	(6.5)	7.4	(7.6)	3.30	0.05	SR, PR < HC

Footnotes: Hayling: Hayling Sentence Completion Test; IGT: Iowa Gambling Task; TMT: Trail-Making Task; SE: Standard error.
All tests adjusted for age and gender, marginal means presented in table. * Additionally adjusted for number of errors. ** Additionally adjusted for information processing speed.

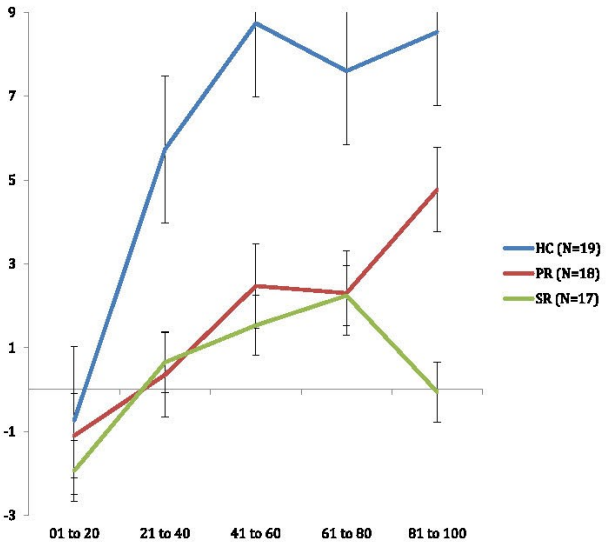

Fig. 1. Iowa Gambling Task net scores for the three groups, by block of 20 choices. *Footnotes*: HC: Healthy Controls; PR: Patient Relatives; SR: Suicide Relatives. Marginal means taking into account age and gender.

rs = −0.46, p = 0.004; all correlations adjusted for group). These results tend to support the proposed hypothesis that impairments in decision-making and cognitive control in suicidal behaviour rely partially on differential neural basis. Moreover, age was not correlated with any IGT scores (total, blocks of 20, blocks of 50) in any group or in the whole population after groups were controlled for (all p > 0.1). Finally, IGT performance was not correlated with reaction times during the IGT for all participants and within each group (all p > 0.3).

4. Discussion

In the present study, we evaluated the cognitive performance of first-degree biological relatives of individuals who committed suicide. Although suicide relatives did not differ from patient relatives in terms of total IGT net score, our analyses suggest that suicide relatives exhibit subtle decision-making deficits with a trend toward more difficulties to improve performance at the end of the task in comparison to patient relatives, and lower effect sizes in terms of learning effects. While group-differences are small for various possible reasons (see below), these results are in line with previous studies showing impaired decision-making in suicide attempters (Richard-Devantoy et al., 2014), even in normothymic phase (Jollant et al., 2005).

These findings are noteworthy for several reasons. First, it is important to keep in mind that all participants in the present study, including suicide relatives, were healthy individuals, taking no medication, most with no past history of depression and none with a personal history of suicidal act. Moreover, the heritability of decision-making is far from 100%, estimated at 46% during late adolescence in a twin study using the IGT (Tuvblad et al., 2013), and first-degree relatives only share 50% of genes, additionally limiting the capacity to detect impairments in this population. Finally, based on our previous study (Richard-Devantoy et al., 2014), we calculated that 70 individuals per group are necessary to show a significant difference between suicide attempters and patient controls in the IGT net score. Therefore, our ability to detect some differences between relatively small groups of healthy participants strongly supports the hypothesis that decision-making may be particularly heritable in families of suicide completers. Previous studies in different patient populations, including bipolar disorder, alcoholism, anorexia and obsessive-compulsive disorder, have also reported heritability of IGT performance (Lovallo et al., 2006; Cavedini et al., 2010; Kulkarni et al., 2010; Galimberti et al., 2013; Tuvblad et al., 2013). To date, the present study is the first to suggest heritability in decision-making impairment in families of suicide completers, adding important findings to the literature on transmissible cognitive impairments and underlining the significant role of risky decision-making in the vulnerability to suicidal behaviour.

Contrary to decision-making, we could not detect any major impairment in cognitive control. Yet, previous studies in suicide attempters have repeatedly reported decreased cognitive control compared to non-attempters (Richard-Devantoy et al., 2012; Richard-Devantoy et al., 2014), including lower performance in the Stroop test. Several explanations could account for our findings. First, cognitive control deficits may not be transmissible traits. While conceivable, this explanation is unlikely as the literature suggests otherwise. Cognitive inhibition performance in the Stroop test was previously found to be influenced by genetic variation (Stins et al., 2004). Schachar et al. (2011) revealed that measures of response inhibition in the Hybrid Stop Signal Task had substantial genetic influences: the heritability of response cancellation and response restraint was estimated at 50% and 27% respectively. Of note, some measures of cognitive control, like TMT, were not previously associated with the vulnerability to suicidal acts (Richard-Devantoy et al., 2014). It may also be that deficits in cognitive inhibition impairment in suicide relatives are subtle. Due to the small sample size in this study, it is unlikely that subtle impairments were fully captured. Additionally, these potential impairments may require specific conditions, such as stress to be uncovered. This was previously suggested by Mcgirr et al. (2010) who showed that suicide relatives exhibited normal cognitive control under non-stressful conditions, but revealed impairments when socially stressed. The sensitivity of cognitive functioning to stress or negative emotional states has previously been observed in suicide attempters (Williams et al., 2005). Finally, suicide relatives may possess skills that compensate some poorer cognitive abilities. Indeed, our findings suggest that suicide relatives have a greater tendency to self-correct errors in the Stroop test compared to the other two groups. Suicide relatives may, therefore, present increased sensitivity to interference (which would be heritable), but at the same time, a greater tendency to self-correct that could overcome some cognitive control deficits. This may balance the negative effects of impaired decision-making and, therefore, limit the level of vulnerability to suicidal behaviour, explaining their lack of personal histories of suicidal acts.

Taken together, we believe that decision-making deficits may constitute a cognitive endophenotype of suicidal behaviour, i.e. traits found in many patients, even in normothymic periods, and in many unaffected relatives. Cognitive control deficits, specifically sensitivity to interference, would also be part of the cognitive vulnerability to suicidal acts, as previously proposed (Jollant et al., 2011). The absence of major deficits in cognitive control and/or the ability to correct some of them, as observed in suicide relatives, may represent a protective factor against suicide and counterbalance deficits in decision-making.

In this particular study, we chose to evaluate decision-making using the IGT. Other measures of decision-making are available but have more rarely been used in studies of suicide attempters (Clark et al., 2011). Given the large battery of clinical and neuropsychological tests required in our study, we could only include one measure of decision-making in order to ensure a good acceptance. The IGT is a well-validated task that was previously used in studies of suicidal behaviour by our group and others, allowing for comparability between studies that is useful for testing the concept of endophenotype. Moreover, the IGT possesses certain strengths in terms of ecological validity. Similarly to real life situations where decisions are based on experience, the IGT uniquely includes a learning component. However, it is also a complex task that involves a number of separate mechanisms. As a result, the precise decision-making deficits associated with suicidal behaviour remain hard to pin-point. The current study and two previous studies in suicide attempters (Jollant et al., 2007b; Richard-Devantoy et al., 2013) suggest that impaired decision-making in suicidal vulnerability is not related to deficits in working memory, short-term memory, attention, cognitive control or motor impulsivity. Future investigations should integrate multiple measures of decision-making and relevant cognitive processes to inform the precise mechanisms involved in impaired decision-making in relation to suicidal behaviour.

Certain limitations have to be highlighted. Sample sizes were relatively small and our findings should be reproduced in larger samples in order to confirm their validity. In addition, we had to statistically control for the effect of age, as the suicide relatives group was significantly older than the other two groups. However, as age did not correlate with IGT scores, it is unlikely to explain group differences in IGT performance. Second, the influence of traumatic loss of a family member on cognitive function cannot be separated from other possible causative factors. However, these types of cognitive deficits observed in suicide relatives are closely related to those previously observed in suicide attempters, who have often not experienced this type of traumatic loss. We therefore hypothesize that the measured cognitive impairments, are more likely related to transmissible familial vulnerability than to the consequences of the loss itself. Finally, the motives for participating in such a study have to be questioned in relation to our findings. For example, trying to understand what led a beloved one to commit this tragic act was certainly the main objective of many if not all suicide relatives. However, the agreement to participate in a neurocognitive study may be motivated by the self-observation of one's own difficulties (therefore inflating deficits among suicide relatives), or to the contrary, an excellent cognitive functioning making suicide very unlikely and also difficult to "figure out" (therefore inflating negative results). A follow-up study is currently under way to explore these questions.

In conclusion, the present study investigated cognitive deficits previously associated with suicidal behaviour in suicide relatives. Using a unique research design including a group of patient relatives, our results suggest that decision-making impairment could be a cognitive endophenotype of suicidal behaviour. The lack of cognitive control deficits in suicide relatives may be understood as a protective factor against suicide in this population. Furthermore, this indirectly suggests that cognitive control deficits are also part

of the suicide vulnerability. While our results require replication in a larger sample size, notably to completely exclude the effect of the transmission of depression, our findings may shed new light on the familial transmission of suicide vulnerability and may help create opportunities for future targeted prevention.

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Contributors

A. Hoehne participated in recruitment and participant assessment, ran the analyses, and wrote the first draft. S. Richard-Devantoy ran the analyses and wrote the first draft. Y. Ding participated in study implementation and participant assessment. G. Turecki participated in the study implementation. F. Jollant wrote the protocol, secured funding for the study, coordinated the study, ran the analyses and wrote the manuscript. All authors read the manuscript and gave their consent.

Conflicts of interest

None to report.

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7.2.3 Dr. Richard-Devantoy's article: Cognitive Inhibition in Depression and Suicidal Behavior: A Neuroimaging Study

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ORIGINAL ARTICLE

Cognitive inhibition in depression and suicidal behavior: a neuroimaging study

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Background. Cognitive inhibition deficits have previously been found in suicide attempters. This study examined the neural basis for these deficits in depressed patients with and without a history of suicidal behavior.

Method. Functional magnetic resonance imaging was used to measure brain activation during the Go/No-Go response inhibition task in 25 unmedicated and depressed middle-aged suicide attempters, 22 unmedicated depressed patient controls with no personal or family history of suicidal behavior, and 27 healthy controls. Whole-brain analyses were conducted with SPM12.

Results. Suicide attempters exhibited an elevated number of commission errors relative to both control groups. However, suicide attempters did not differ from patient controls in terms of brain activation for any contrast. Analyses showed a significant association between depression and brain activation in the left inferior frontal gyrus and medial thalamus during Go *v.* No-Go, and in the bilateral parietal cortex and left orbitofrontal cortex during No-Go *v.* baseline. These regions were correlated with psychological pain, suicidal ideation and global functioning. There was no association between brain activation and personal histories of suicidal act.

Conclusions. Our study suggests that deficits in cognitive inhibition, in relation to the inferior frontal gyrus, thalamus, orbitofrontal cortex and parietal cortex, are related to the depressive state and not specifically to suicide vulnerability. We hypothesize that state-related deficits may add to trait-like cognitive impairments to facilitate suicidal acts. These different types of cognitive impairments may necessitate different therapeutic strategies for the prevention of suicide.

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Key words: Cognitive inhibition, depression, functional magnetic resonance imaging, Go/No-Go test, suicide.

Introduction

It is widely accepted that individuals who attempt suicide or die by suicide have a predisposition to this behavior (Mann, 2003; Turecki *et al.* 2012). According to this model, suicidal behaviors result from a complex interplay between vulnerability and contextual factors, including stressful proximal events, acute mental disorders such as major depression, and alcohol consumption or physical pain (Mann, 2003). This stress–vulnerability model has been borne out by clinical, cellular, molecular and genetic studies (Mann, 2003) and, more recently, by neuropsychological (Richard-Devantoy *et al.* 2012*a*, 2014*a*) and neuroimaging studies (Jollant *et al.* 2011). Neurocognitive deficits may represent relevant factors of vulnerability to suicide.

Impaired cognitive control, which is found across ages in suicide attempters (Keilp *et al.* 2001, 2008; Richard-Devantoy *et al.* 2012*b*, 2015), appears to be a promising avenue of investigation. Cognitive control is a general term underlying performance on tests measuring cognitive inhibition, task switching, error detection, response conflict and cognitive flexibility (Miller & Cohen, 2001). Cognitive control makes it possible to flexibly adapt one's behavior to meet current demands (Barch *et al.* 2009), especially in the face of ambiguous, complex and changing environments (Botvinick *et al.* 2001). Thus, deficient cognitive control is said to reduce one's ability to respond adaptively to stressors. Cognitive inhibition – a major component of cognitive control – refers to active suppression mechanisms that limit the processing of irrelevant stimuli for the ongoing task (Shallice & Burgess,

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1991). Cognitive inhibition deficits among suicide attempters may underlie inadequate regulation of emotional and cognitive responses (Jollant *et al.* 2011). We need to improve our understanding of the mechanisms underlying these deficits among suicide attempters.

Although we previously proposed a model suggesting a role for the dorsomedial (including the anterior cingulate) and dorsolateral prefrontal cortices in cognitive control deficits among suicide attempters (Jollant *et al.* 2011), the exact neural basis underlying cognitive inhibition deficits in this population is largely unknown. Only one neuroimaging study among adolescents has been conducted to date. Using a Go/No-Go task, it found greater activity in the right anterior cingulate gyrus and left insula among non-attempters compared with suicide attempters, but similar activation between attempters and healthy controls (Pan *et al.* 2011).

Here, we used functional magnetic resonance imaging (MRI) to measure brain activation in response to a cognitive inhibition paradigm among suicide attempters in comparison with controls. An *a priori* design was implemented with the specific aim of investigating vulnerability to suicidal behavior independently of co-morbid disorders. Unmedicated male and female depressed suicide attempters were compared with depressed individuals with no personal or family history of suicidal behavior and with healthy controls. The well-validated Go/No-Go task (Simmonds *et al.* 2008) was used as a classical measure of cognitive and response inhibition. Deficits on the Go/No-Go task have previously been found in suicide attempters. Among the elderly, Richard-Devantoy *et al.* (2012*b*) reported greater impairment in elderly depressed suicide attempters than in patient and healthy controls. Raust *et al.* (2007) found a trend toward more commission errors in middle-aged suicide attempters than in healthy controls, while Keilp *et al.* (2013) did not find any differences.

We hypothesized that suicide attempters would show (i) deficits in Go/No-Go performances in comparison with the control groups; and that (ii) these deficits would be related to impaired activation of the dorsomedial prefrontal cortex.

Method

Population

Three groups of participants aged 18–55 years were recruited: (1) 25 currently depressed patients with a personal history of attempted suicide (suicide attempters); (2) 22 currently depressed patient controls without a personal or first- or second-degree family history of suicidal behavior (patient controls); and (3) 27 healthy controls with no personal or first- or second-degree family history of suicidal behavior (healthy controls).

All participants were right-handed as confirmed by the Edinburgh Handedness Inventory (Oldfield, 1971). All suicide attempters and patient controls were depressed at the time of scanning, as determined by a Hamilton Depression Rating Scale (HAM-D) score higher than 20 (Hamilton, 1960), and all presented with a diagnosis of major depressive episode according to the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First *et al.* 2002). Only patients with a major depressive disorder were recruited. None of the participants was medicated at the time of the scanning. All participants were English- or French-speaking natives of Québec. Informed written consent was obtained from all participants. This study was conducted at the Douglas Mental Health University Institute in Montréal and approved by the local ethics committee. Participants received 100 Canadian dollars for their time.

Suicide attempts were defined as any acts carried out with the intent to die and thus did not include non-suicidal self-injuries (Mann, 2003). Furthermore, in order to reduce possible heterogeneity and eliminate acts with a low suicidal drive, we excluded dubious or low-intent attempts on the basis of a Suicide Intent Scale (SIS) score below 15/30 (Beck *et al.* 1974). Exclusion criteria included a lifetime history of schizophrenia or bipolar disorder, a history of alcohol/substance abuse or dependence spanning the previous 6 months, a major general medical condition requiring ongoing pharmacological treatment, a lifetime history of severe head trauma or central nervous system disorder, and contraindication to MRI.

No previous studies have been published on this population.

Clinical evaluation

Clinical assessment

Diagnoses were made using the SCID-I (First *et al.* 2002) and SCID-II (First *et al.* 1997). Level of depression was rated using the 24-item HAM-D (HAM-D-24) (Hamilton, 1960). Level of anxiety was assessed using the Hamilton Rating Scale for Anxiety (HAM-A) (Hamilton, 1959) and the Spielberger Anxiety State Trait Inventory (STAI) (Spielberger, 1983), and level of functioning with the Clinical Global Impressions (CGI) Scale (Guy, 2000). An analog scale measured current level of psychological pain, as this scale has been shown to discriminate suicide attempters from depressed non-attempters and to be correlated with suicidal ideas (Olie *et al.* 2010).

The Buss–Durkee Hostility Inventory (BDHI) (Buss & Durkee, 1957), the Brown–Goodwin Assessment of Lifetime History of Aggression (BGLHA) (Brown & Goodwin, 1986), and Barratt's Impulsivity Scale (BIS-11) (Barratt, 1965) were used to assess traits of hostility, aggression and impulsivity, respectively.

Suicidal history was assessed using the Colombia Suicide History Form (Posner *et al.* 2007), while suicide intent and current ideation were assessed, respectively, using the SIS (Beck *et al.* 1974) and the Scale for Suicidal Ideation (SSI) (Beck *et al.* 1979).

Neuropsychological assessment

Cognitive inhibition was assessed using the Stroop Color Test [Stroop, 1935; Godefroy & La GREFEX (Groupe de Réflexion pour l'Evaluation des Fonctions Exécutives), 2008], the Trail Making Test [Godefroy & La GREFEX (Groupe de Réflexion pour l'Evaluation des Fonctions Exécutives), 2008] and the Hayling Sentence Completion Test (Burgess & Shallice, 1996). The Iowa Gambling Task (IGT) was used to assess decision-making (Bechara *et al.* 1999), the FAS Verbal Fluency Test [Godefroy & La GREFEX (Groupe de Réflexion pour l'Evaluation des Fonctions Exécutives), 2008] to assess verbal fluency, the Wechsler Adult Intelligence Scale (WAIS)-IV Digit Span Test (forward and backward) (Wechsler, 2008) to assess working memory, and the National Adult Reading Test (NART) (Beardsall & Brayne, 1990; Mackinnon & Mulligan, 2005) to assess verbal intelligence quotient. The order of the tasks was randomized.

Statistical analyses

For continuous variables, distributions were tested with the Shapiro–Wilk test and showed a deviation from normality for most of the scores. Non-parametric tests were therefore used. Comparisons of quantitative values among groups were performed using the Kruskal–Wallis test (for three-group comparisons) or Mann–Whitney U test (for two-group comparisons). A χ^2 test was used to compare qualitative values. Spearman's correlations were used to assess the link between quantitative measures.

An α threshold of 0.05 was set *a priori* with Bonferroni corrections applied for multiple comparisons. SPSS 21.0 (SPSS, USA) was used.

Functional neuroimaging

Image acquisition

The functional neuroimaging scans were carried out on the same day as the clinical and neuropsychological assessment. The scans were conducted at the Douglas Mental Health University Institute's Cerebral Imaging Centre using a Siemens Magnetom Trio (Tim System 3T, MR B17) MRI scanner with a 12-channel head coil. For the blood oxygen-level dependent (BOLD) functional scans, 175 volumes consisting of 38 contiguous 3.5-mm transversal slices were acquired with a T2-weighted gradient echo-planar imaging sequence (repetition time 2.09 ms; echo time 30 ms; field of view 24 mm; base resolution 64 × 64; in-plane resolution 3.5 × 3.5 mm^2; GRAPPA acceleration 2; descending sequential acquisition). A structural sequence was also acquired consisting of a high-resolution, whole-brain T1-weighted acquisition using a magnetization prepared rapid gradient echo (MPRAGE) sequence with repetition time/echo time/flip angle = 2300/2.98 ms/9°, and a base resolution of 256 × 256, with 1 mm^3 isotropic voxels resulting in acquisition time of 9.25 min.

Go/No-Go task

A classical version of the Go/No-Go task (Simmonds *et al.* 2008) was implemented in E-Prime 2.0.10.182 (USA) as a measure of cognitive inhibition. Stimuli were displayed in an MRI-compatible liquid crystal display at the rear of the scanning bore, viewable via a mirror by the participant. Each task was composed of six blocks: three Go and three No-Go blocks were presented in an ABBAAB order interleaved with 20-s blank-screen resting periods and 5 s instructions prior to the start of each block. In the Go block, participants were instructed to respond to all letters (black letters on a white screen) indiscriminately by pressing the button with their right index finger as quickly as possible. In the No-Go block, participants were instructed to respond by pressing a button corresponding only to target letters (i.e. letters other than X) but not to an equally frequent non-target letter (letter X). See Fig. 1.

Each block (be it a Go or No-Go block) lasted 62 s and consisted of 24 trials. Each trial was composed of a fixation cross followed by a letter (target or non-target letter). The duration of the fixation cross varied between 700, 900, 1100 or 1300 ms, randomized to prevent habituation, six trials of each duration resulting in an average fixation cross duration of 1000 ms across the entire block and experiment. The target/non-target letters were always displayed for 500 ms. All blocks had 12 predetermined pseudo-randomly distributed target letters (50%) and 12 non-target letters (50%).

In all sequences, reaction times were recorded, as were omission errors (i.e. not pressing a target letter) in both conditions and commission errors (i.e. responding to a non-target letter) in the No-Go conditions. Omission scores are usually interpreted as reflecting attention abilities, while commission scores measure inhibitory processes.

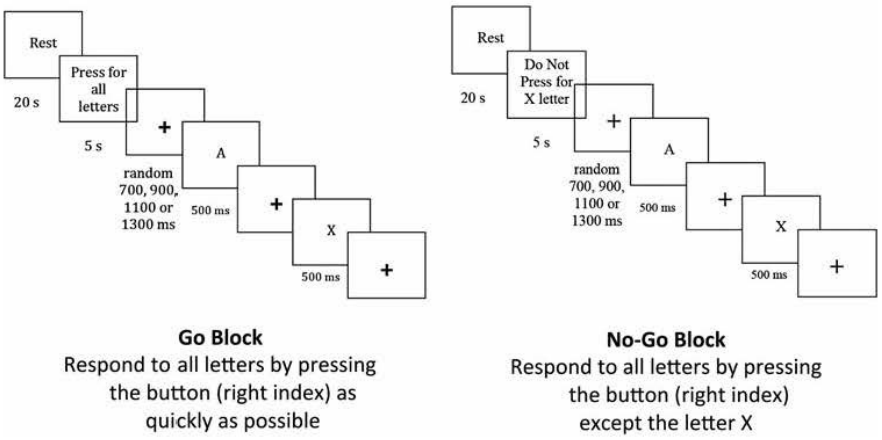

Fig. 1. Representation of the Go/No-Go paradigm used in this study.

Image analyses

MRI data were analysed with SPM12b (Wellcome Department of Imaging Neuroscience, UK) implemented in Matlab 2013b (Mathworks, Inc., USA). A standard indirect normalization preprocessing routine was performed: slice-timing correction for the functional time-series using sinc function, realignment of functional data to its first volume within each individual, co-registration of functional and structural images, segmentation of structural image to produce forward map Template-O-Matic (TOM) Montreal Neurological Institute (MNI) template space, spatially normalizing to MNI template, and smoothing with an isotropic 8 mm full-width half maximum Gaussian kernel. Low-frequency temporal drifts in functional MRI signal were removed by applying a high-pass filter with a cut-off of 128 s.

A first-level fixed-effect block-design model was constructed for each individual subject, including eight regressors composed of two block types (Go and No-Go). Canonical hemodynamic response function and its temporal and dispersion derivatives were used in the model. The following contrasts were conducted for the first-level fixed-effect model: Go *v.* No-Go, and No-Go *v.* baseline.

Then, we conducted three-group comparisons followed by direct pairwise comparisons by constructing separate second-level random-effect analyses (Friston *et al.* 1995). As these analyses yielded mixed results, we conducted a regression analysis with two factors: depression (both patient groups = 1, healthy controls = 0) and suicidal acts (suicide attempters = 1; both control groups = 0). For all analyses, statistical parametric maps were thresholded at an uncorrected voxel-wise p value of 0.001, with a minimum extent threshold of 10 voxels for exploration and visualization purposes. We then considered any clusters with family-wise error-corrected threshold of $p < 0.05$ as statistically significant. All results are reported using an MNI coordinate system.

Results

Clinical data (Table 1)

The three groups were similar in terms of gender. Healthy controls were younger than the two patient groups. As expected, they also showed lower levels of functional impairment at the CGI, lower depression (HAM-D) and anxiety (HAM-A) scores, and lower levels of impulsivity (BIS) and hostility (BDHI) than both patient groups, as well as a more infrequent history of aggression (BGLHA) and lower trait and state anxiety scores (STAI) than suicide attempters.

The two patient groups did not differ significantly in terms of the age at onset of mood disorder, number of previous depressive episodes, current levels of depressive or anxiety symptoms or suicidal ideation, impulsivity trait, past psychotropic exposure and burden of medical illness. Suicide attempters had higher levels of past suicidal ideas than patient controls but no difference in terms of psychological or physical pain levels (currently or over the past 15 days).

Eight patient controls and 11 suicide attempters had never received an antidepressant medication before starting the study. For those who previously received an antidepressant just before starting the study, the washout period was 8.4 (s.d. = 2.7) days for patient controls and 6.2 (s.d. = 3.3) days for suicide attempters. None of them used fluoxetine and lithium previously. All healthy controls had no previous exposure to medications.

Table 1. *Comparison of sociodemographic and clinical and neuropsychological variables between suicide attempters, patient controls and healthy controls*

	Suicide attempters ($n = 26$)	Patient controls ($n = 23$)	Healthy controls ($n = 28$)	χ^2/KW/*U*	df	*p*	*Post-hoc*
Sociodemographic and clinical characteristics							
Age, years	40.3 (9.7)	41.3 (11.4)	33.8 (7.1)	8.0	2	0.02	HC < SA, PC
Female gender, *n* (%)	15 (60)	15 (60)	17 (60)	0.3	2	0.7	–
CGI-E, score (out of 7)	4.6 (0.9)	4.7 (0.5)	0 (0)	53.2	2	<0.001	HC < SA, PC
HAM-D-24, score (out of 52)	29.0 (8.5)	29.6 (5.2)	0.8 (1.3)	51.2	2	<0.001	HC < SA, PC
Number of MDEs	2.3 (1.1)	2.1 (1.0)	–	177		0.5	–
Age at first MDE onset, years	30.6 (13.2)	37.9 (10.1)	–	135		0.1	–
HAM-A, score (out of 56)	18.3 (7.7)	17.0 (3.4)	0.7 (1.2)	51.5	2	<0.001	HC < SA, PC
BIS-11, score (out of 120)	76.4 (5.3)	76.0 (5.6)	71.8 (3.8)	11.6	2	0.003	HC < SA, PC
BGLHA, score (out of 120)	53.7 (11.7)	44.8 (12.1)	43.7 (9.4)	7.35	2	0.025	HC < SA
BDHI, score	28.5 (12.1)	37.6 (12.7)	46.3 (9.3)	21.4	2	<0.001	SA < PC < HC
STAI-A, score	56.2 (13.1)	56.8 (14.4)	26.1 (7.2)	41.7	2	<0.001	HC < SA
STAI-B, score	61.5 (11.9)	58.6 (12.3)	31.5 (8.2)	41.8	2	<0.001	HC < SA
SSI current, score	8.4 (8.0)	8.4 (7.9)	–	28.8	1	0.8	–
SSI past, score	19.9 (8.6)	10.1 (8.7)	–	47.1	1	<0.001	PC < SA
SIS most severe act, score	18.6 (5.1)	–	–	–	–	–	–
Psychological pain, current, score	5.3 (2.9)	5.5 (2.9)	0.4 (0.7)	43.7	2	<0.001	HC < SA, PC
Behavioral performances during the Go/No-Go task[a]							
Number of commission errors	5.6 (3.0)	4.0 (3.8)	3.3 (1.6)	10.6	2	0.001	HC, PC < SA
Reaction time, ms (Go blocks)	303.5 (51)	298.8 (55)	286.9 (38)	1.9	2	0.2	–
Reaction time, ms (No-Go blocks)	370.4 (44)	386.0 (38)	373.9 (23)	0.003	2	1.0	–
Number of omission errors (Go blocks)	12.2 (14.3)	10.6 (10.5)	4.0 (4.7)	10.0	2	0.002	HC < PC, SA
Number of omission errors (No-Go blocks)	7.5 (6.8)	6.7 (6.8)	2.9 (3.2)	13.4	2	<0.001	HC < PC, SA
Cognitive measures							
Memory index	4.8 (2.8)	4.5 (2.5)	3.7 (1.6)	1.9	2	0.4	–
NART ratio	71.8 (14.2)	71.4 (13.6)	75.5 (8.8)	4.8	2	0.1	–
IGT, net score	3.2 (32.5)	7 (28.5)	44.8 (26.9)	22.1	2	<0.001	HC > SA, PC
Verbal fluency, P	20.5 (6.6)	16.8 (2.4)	23.6 (4.9)	18.6	2	<0.001	HC > SA, PC
Verbal fluency, animals	26.8 (6.3)	24.7 (5.9)	33.0 (6.4)	18.9	2	<0.001	HC > SA, PC
Stroop interference time index	58.7 (26.7)	53.2 (28.2)	33.2 (15.2)	15.3	2	0.001	HC < SA, PC
Stroop interference uncorrected errors index	0.7 (2.3)	0.4 (0.8)	0.4 (0.8)	0.05	2	0.9	–
TMT B reaction time, ms	69.9 (18.4)	80.7 (34.1)	57.2 (23.2)	11.0	2	0.004	HC < PC
Hayling B choice reaction time, ms	226.7 (99.4)	188.1 (115)	80.0 (69.4)	28.8	2	<0.001	HC < SA, PC

Table 1 (*cont.*)

	Suicide attempters ($n = 26$)	Patient controls ($n = 23$)	Healthy controls ($n = 28$)	χ^2/KW/*U*	df	*p*	*Post-hoc*
Hayling penalties	5.7 (3.2)	4.25 (3.3)	1.3 (2.1)	28.9	2	<0.001	HC < SA, PC

Data are given as mean (standard deviation) unless otherwise indicated.

KW, Kruskal–Wallis; *U*, Mann–Whitney *U*; df, degrees of freedom; HC, healthy controls; SA, suicide attempters; PC, patient controls; CGI-E, Clinical Global Impressions scale, severity; HAM-D-24, 24-item Hamilton Rating Scale for Depression; MDE, major depressive episode; HAM-A, Hamilton Rating Scale for Anxiety; BIS-11, Barratt's Impulsivity Scale; BGLHA, Brown–Goodwin Assessment of Lifetime History of Aggression; BDHI, Buss–Durkee Hostility Inventory; STAI-A, Spielberger Trait Anger Inventory – State; STAI-B, Spielberger Trait Anger Inventory – Trait; SSI, Scale for Suicide Ideation; SIS, Suicidal Intent Scale; NART, National Adult Reading Test; IGT, Iowa Gambling Task; TMT, Trail Making Test.

[a] Analyses in 25 healthy controls.

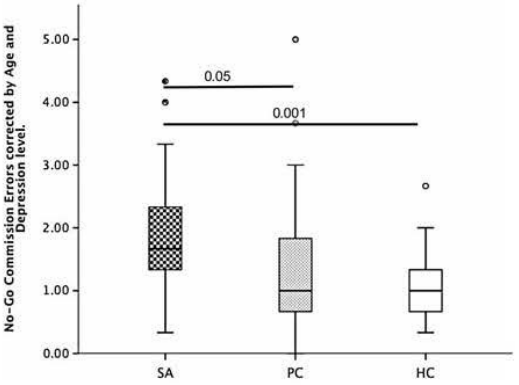

Fig. 2. Number of commission errors on the Go/No-Go task between the three groups. SA, Suicide attempters; PC, patient controls; HC, healthy controls. Values are means. Boxes are number of commission errors, error bars are standard deviations and circles are outliers; each point represents a participant.

Suicide attempters made a mean of 1.1 (s.d. = 1.3) suicide attempts, mainly using non-violent methods: overdose medication ($n = 20$; 80%); drowning ($n = 1$; 4%); jumping ($n = 1$; 4%); and wrist cutting ($n = 3$; 12%). None necessitated surgery or intensive unit care. Suicide ideation level (SSI score) was moderate for the most severe attempt (median = 16, on a maximum score of 38). The overall level of intent for the previous attempt was moderate (total SIS median score = 22.2, on a maximum score of 42), with moderate planning scores (planning SIS median score = 5.5, on a maximum score of 16).

Cognitive performance (Table 1)

Compared with healthy and patient controls, suicide attempters made a higher number of commission errors during the Go/No-Go task with age as a covariate (Fig. 2). Reaction times were similar between groups. The mean number of omission errors during the Go and No-Go blocks was lower in healthy controls compared with both suicide attempters and patient controls, with no difference between the two patient groups. Healthy controls performed better than the two patient groups on all other cognitive measures, with no difference between suicide attempters and patient controls. The three groups had similar memory capacities and NART scores.

Functional imaging

Within-group analyses

In healthy controls, contrast between Go *v.* No-Go conditions showed higher activation in a large network of

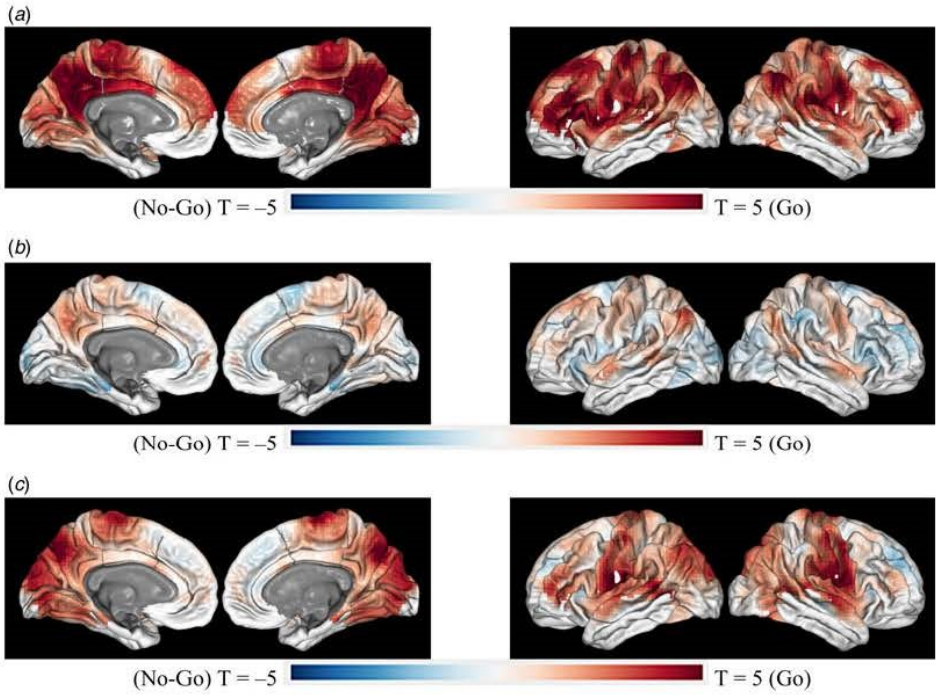

Fig. 3. Within-group analyses for the Go *v.* No-Go contrasts: (*a*) healthy controls; (*b*) patient controls; (*c*) suicide attempters.

multiple interconnected regions, including the precuneus, superior temporal gyrus, precentral gyrus, cingulate gyrus, insula and inferior frontal gyrus (Fig. 3*a*), which survived whole-brain correction. The greatest peak activational differences within that large network were observed in the right medial precuneus region ($p_{corrected} < 0.001$, 12297 voxels, peak $Z = 5.51$ at 6, −52, 14). Another cluster in the right cerebellum region also survived correction. We did not observe any significant differences in the No-Go *v.* Go contrast, even at a liberal threshold ($p_{uncorrected} < 0.001$).

In patient controls, no cluster survived whole-brain correction in either the Go *v.* No-Go or No-Go *v.* Go contrast (Fig. 3*b*).

In suicide attempters, the Go *v.* No-Go contrast showed increased activation difference in two large and four small clusters, surviving whole-brain corrections. The largest two clusters of activations were located in the precuneus/posterior cingulate gyrus ($p_{corrected} < 0.001$, 1466 voxels, peak $Z = 5.15$ at −3, −70, 32) and the right post-central gyrus/superior temporal gyrus region ($p_{corrected} < 0.001$, 730 voxels, peak $Z = 4.95$ at 63, −4, 32) (Fig. 3*c*). The smaller clusters covered the left temporal cortex ($p_{corrected} = 0.005$, 381 voxels, peak $Z = 4.98$ at −60, −16, 5), medial supplementary motor area ($p_{corrected} < 0.05$, 307 voxels, peak $Z = 4.33$ at 3, −13, 56), right cerebellum ($p_{corrected} = 0.18$, 266 voxels, peak $Z = 4.54$ at 39, −61, −37) and left putamen ($p_{corrected} < 0.05$, 201 voxels, peak $Z = 3.68$ at −33, −16, −7). There were no significant differences in the No-Go *v.* Go contrasts in the suicide attempter group.

Brain activation associated with depression and suicidal acts

Direct group comparisons yielded mixed results (detailed in the online Supplementary material). Briefly, in the whole-brain Go *v.* No-Go contrast, suicide attempters showed reduced activation in the precuneus and posterior cingulate cortex in comparison with healthy controls. However, there was no group difference between suicide attempters and patient controls, or between patient controls and healthy controls. Yet, online Supplementary Fig. S1*b* suggests a subthreshold difference in brain activation between patient controls and healthy controls, with no difference between suicide attempters and patient controls, which was confirmed by the following regression analyses.

For Go *v.* Go-No, we observed a positive association with depression (Fig. 4*a*) in the left inferior frontal gyrus (Brodmann area 45; $p_{corrected} < 0.05$, 292 voxels, peak $Z = 4.59$ at −57, 20, 2) and the medial thalamus ($p_{corrected} < 0.05$, 196 voxels, peak $Z = 4.21$ at 6, −4, 11). There was no association with suicide attempt.

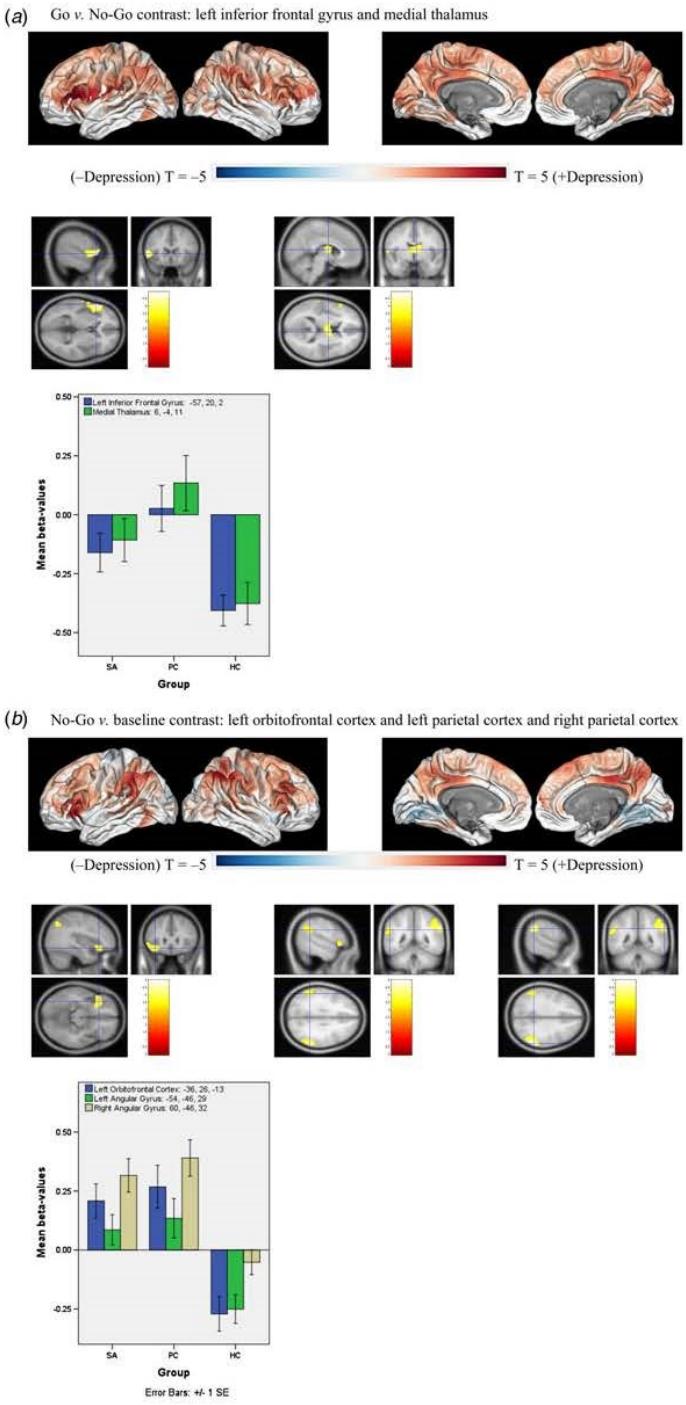

Fig. 4. Brain regions showing a significant association with depression. (*a*) Between-group comparisons for the Go *v.* No-Go contrasts. (*b*) Between-group comparisons for the No-Go *v.* baseline contrasts. SA, Suicide attempters; PC, patient controls; HC, healthy controls. Values are means, with standard errors (SE) represented by vertical bars.

For No-Go *v.* baseline, we found a positive association with depression (Fig. 4*b*) in a cluster encompassing bilateral inferior parietal lobules/angular gyrus/supramarginal regions (left: $p_{corrected} < 0.05$, 200 voxels, peak $Z = 3.70$ at −54, −46, 29; right: $p_{corrected} < 0.05$, 450 voxels, peak $Z = 4.65$ at 60, −46, 32) and in the left orbital part of the inferior frontal gyrus (Brodmann area 47; $p_{corrected} < 0.05$, 198 voxels, peak $Z = 4.08$ at −36, 26, −13). Again, there was no association with suicide attempt.

Clinical correlation

For the Go *v.* No-Go contrast, brain activation in the left inferior frontal gyrus was correlated with levels of psychological pain (current: $r_s = 0.31$, $p < 10–2$; last 15 days: $r_s = 0.30$, $p < 10–2$; worst over last 15 days: $r_s = 0.33$, $p < 10–2$) and CGI score ($r_s = 0.28$, $p < 0.05$). Activation in the medial thalamus was correlated with levels of psychological pain (current: $r_s = 0.31$, $p < 10–2$; last 15 days: $r_s = 0.40$, $p < 10–3$; worst over last 15 days: $r_s = 0.35$, $p < 10–2$), CGI score ($r_s = 0.32$, $p < 10–2$) and current SIS score ($r_s = 0.26$, $p < 0.05$).

For No-Go *v.* baseline, the left orbitofrontal cortex, and right and left angular gyri were both correlated with psychological pain (r_s between 0.33 and 0.49, all $p < 0.01$) and CGI score ($r_s = 0.44$ and 0.50, $p < 10^{-3}$).

Discussion

In this study, we explored cognitive inhibition, as measured by the Go/No-Go task, in relation to suicidal vulnerability among unmedicated depressed patients. First, we found that suicide attempters exhibited an elevated number of commission errors in comparison with both control groups. However, other cognitive inhibition measures showed lower performance between both patient groups and healthy controls, but not between suicide attempters and patient controls. These latter results were confirmed by neuroimaging analyses showing a significant association between depression and brain activation during the Go/No-Go task in the inferior frontal gyrus, medial thalamus, orbitofrontal cortex and parietal cortex, but no significant association with a personal history of suicidal act. All these clusters were significantly correlated with current levels of psychological pain, suicidal ideas and global functioning. Moreover, suicide attempters did not differ from patient controls in terms of activation for any contrast at the whole-brain corrected level. Overall, these findings therefore suggest that deficits in cognitive inhibition are associated with the depressive state more than vulnerability to the suicidal act.

Efforts to interpret our findings must take into account several difficulties, notably: (1) the complexity of cognitive inhibition, what it is and how it works; (2) the complexity of the neural network underlying this function; and (3) the complexity of the Go/No-Go task itself and the processes it mobilizes. Cognitive inhibition is a generic term that encompasses a series of interactive processes. These include conflict monitoring (Garavan *et al.* 2002; Graf *et al.* 2011), error detection (Simoes-Franklin *et al.* 2010), attention (Duann *et al.* 2009; Hampshire *et al.* 2010), working memory (Mostofsky & Simmonds, 2008; Simmonds *et al.* 2008), response selection and inhibition (Mostofsky & Simmonds, 2008; Simmonds *et al.* 2008), task setting (Vallesi *et al.* 2009) and the integration of bottom-up sensory information with top-down response-related information (Dodds *et al.* 2011). Not surprisingly, a considerable number of brain structures are involved in inhibitory control (Chikazoe, 2010; Swick *et al.* 2011). More specifically regarding the Go/No-Go task, a recent meta-analysis (Criaud & Boulinguez, 2013) highlighted the implication of the temporo-parietal regions and the inferior, middle and superior prefrontal gyri during the No-Go condition. Many of these regions are reported in the present study. This meta-analysis also underscored the fact that, beyond response inhibition, attention and working memory are likely to play a significant role during the No-Go condition through the activation of the dorsolateral prefrontal cortex, inferior frontal gyrus and parietal regions. It is therefore not excluded that deficits reported in the present study relate less to deficits in inhibition *per se*, than to deficits in working memory or attention.

While we found more commission errors in suicide attempters *v.* both patient groups at the Go/No-Go task, we could not identify specific impairments on other cognitive inhibition tests comparing suicide attempters with patient controls. This is in line with findings from a recent meta-analysis (Richard-Devantoy *et al.* 2014*a*) (tests included the Hayling Test and Trail Making Test in the present study; the Trail Making Test, Wisconsin Card Sorting Test, or the Continuous Performance Task in the meta-analysis cited above). Moreover, our neuroimaging analyses suggest that several brain regions differentially activated during response inhibition may be more associated with the depressive state than with suicidal vulnerability. These regions – the inferior frontal gyrus, thalamus, orbitofrontal cortex and parietal cortex – have previously been associated with depression (see the meta-analysis by Graham *et al.* 2013).

One hypothesis may be that, while vulnerability to suicidal acts is associated with a series of long-term (and possibly heritable) cognitive deficits, notably disadvantageous value-based decision-making and to a lesser extent a higher sensitivity to interference (as measured by the Stroop test), the acute depressive state may give rise to its own dysfunctional cognitive

load, including deficits in cognitive inhibition, attention and memory (Jollant *et al.* 2005; Richard-Devantoy *et al.* 2014*a*, *b*). The cognitive deficits accompanying the depressive state would be associated with increased risk of psychological pain (a measure correlated with suicidal ideas; Olie *et al.* 2010), suicidal ideas and impaired functioning. These deficits would add to the cognitive deficits already present as part of the long-term vulnerability, leading to conditions of increased risk of suicidal acts. This is somewhat supported by recent findings showing risky decision-making but normal cognitive control and memory in non-depressed relatives of suicide completers who never attempted suicide (Hoehne *et al.* 2015).

Several limitations should be underlined. First, although the number of participants was large for a neuropsychological/neuroimaging study, the size of the groups and the use of non-parametric tests – which are more robust but less sensitive than parametric tests – served to limit the statistical power of some comparisons. Replication in larger groups is required to validate these results. Moreover, while participants were not medicated, many patients had stopped taking their previous medication 1 week prior to the study, which may have modified the response in some brain structures. Finally, because suicide attempters and patient controls represent heterogeneous groups, there is a risk of variable findings based on sample selection. For instance, our sample of suicide attempters did not use violent suicidal means, and level of suicidal intent were scored moderate. This may explain the lack of difference in IGT performance between suicide attempters and patient controls. Findings may be different in different subgroups of attempters as it has been shown with risky decision-making (Gorlyn *et al.* 2013).

In conclusion, our findings suggest that deficits in cognitive inhibition, related to the inferior frontal gyrus, thalamus, orbitofrontal cortex and parietal cortex, are associated with the depressive state more than vulnerability to suicidal behavior. Deficits in cognitive inhibition may nonetheless add up to trait-like cognitive alterations to increase the risk of suicidal acts. Future research should therefore identify state and trait cognitive alterations, as improvements to these two kinds of deficits may necessitate different strategies.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291715002421

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Declaration of Interest

None.

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