A Three-Factor Model of Common Early Onset Psychiatric Disorders: Temperament, Adversity, and Dopamine

Maisha Iqbal, B.Sc.

Department of Neurology and Neurosurgery

McGill University

Montreal, Canada

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science in Neuroscience

March 2022

Maisha Iqbal©

Table of Contents

Abstract....4
Résumé....5
Acknowledgements....6
Contribution of Authors....7
Introduction....8
Categorical vs. Dimensional models of psychiatric nosology....8
Independently studied factors associated with mental illness....11
Early life adversity....11
Mechanisms linking early life adversity and psychopathology....12
Early life adversity on reward processing....13
Externalizing (EXT) traits....13
Interaction between EXT traits and adversity....14
The Dopamine System....15
Dopamine Synthesis, Release, and Metabolism....15
Dopaminergic Pathways....17
Dopamine's role in reward processing....18
Dopamine's role in psychiatric disorders....18
Measuring dopamine in humans....20
Sex and gender differences in psychiatric disorders....21
Importance of longitudinal cohorts and prospective studies....22
Aim and Hypotheses....22
Manuscript....23
Introduction....23
Methods....24
Participants....24
Measures....25
Externalizing (EXT) scores....25
Assessments....25
Magnetic resonance imaging (MRI)....26

PET imaging....26
MRI and PET analyses....27
Statistical analyses....28
Results....29
Lifetime psychiatric diagnoses....29
Three-factor model predicts lifetime psychiatric disorders at index interview....29
Three-factor model predicts lifetime EXT disorders at index interview....30
Three-factor model predicts lifetime psychiatric disorders at follow-up....30
Three-factor model is accurate in men and women....31
Discussion....31
Strengths and Limitations....34
Conclusions....35
General Discussion....37
Midbrain dopamine D2 autoreceptor availability: stable state or susceptible trait?....41
Strengths and Limitations....43
Practical applications and future directions……....46
Conclusion....47
References....48
Tables....83
Supplementary Tables....87

Abstract

The causes of psychiatric disorders are poorly understood. Recent models propose that many early onset disorders that are commonly comorbid might reflect the varying expression of overlapping risk factors. The mediating processes remain largely unknown, but three factors show some promise: adolescent externalizing traits, early life adversity, and midbrain dopamine D2 autoreceptors. To investigate whether these features acquire greater predictive power when combined, a longitudinal study was conducted in youth who have been followed since birth. Cohort members were invited to participate based on externalizing scores between 10 to 16 years of age. At age 18 (age 18.5 ± 0.6 y.o.), 52 volunteers who met the entry criteria had a 90-min positron emission tomography scan with [^{18}F]fallypride to image dopamine D2 autoreceptors, completed the Childhood Trauma Questionnaire, and were assessed with the Structured Clinical Interview for DSM-5. The three-factor model identified those with a lifetime history of DSM-5 disorders with an overall accuracy of 90.4% ($p = 2.4 \times 10^{-5}$) and explained 91.5% of the area under the receiver operating characteristic curve [95% CI: .824, 1.000]. Targeting externalizing disorders specifically did not yield a more powerful model than targeting all disorders ($p = 0.54$). The model remained significant when including data from participants who developed their first disorders during a three-year follow-up period ($p = 3.5 \times 10^{-5}$). Together, these results raise the possibility that a combination of temperamental traits, childhood adversity, and poorly regulated dopamine transmission increases risk for diverse, commonly comorbid, early onset psychiatric problems, predicting this susceptibility prospectively.

Résumé

Les troubles psychiatriques d'apparition précoce, couramment comorbides, pourraient refléter l'expression variable de facteurs de risque qui se chevauchent. Les processus médiateurs restent mal compris, mais trois facteurs semblent prometteurs: les traits d'extériorisation des adolescents, l'adversité au début de la vie et les auto-récepteurs de la dopamine D2 du mésencéphale. Pour déterminer si ces caractéristiques acquièrent un plus grand pouvoir prédictif lorsqu'elles sont combinées, une étude longitudinale a été menée auprès de jeunes suivis depuis la naissance. Les membres de la cohorte ont été invités à participer en fonction des scores d'externalisation entre 10 et 16 ans. À 18 ans (18,5 ± 0,6 ans), 52 volontaires répondant aux critères d'admission ont subi une tomographie par émission de positrons de 90 minutes avec [18F]fallypride pour imager les auto-récepteurs de la dopamine D2. Ces derniers, ont également rempli le questionnaire sur les traumatismes de l'enfance et ont été évalués à l'aide du questionnaire structuré entretien clinique pour le DSM-5. Le modèle à trois facteurs a identifié les personnes ayant des antécédents de troubles du DSM-5 avec une précision globale de 90,4 % ($p = 2,4 \times 10^{-5}$) et a expliqué 91,5 % de l'aire sous la courbe caractéristique du fonctionnement du récepteur [CI à 95 %: .824, 1.000]. Le ciblage spécifique des troubles extériorisés n'a pas produit un modèle plus puissant que le ciblage de tous les troubles ($p = 0,54$). Le modèle est resté significatif en incluant les données des participants qui ont développé leurs premiers troubles au cours d'une période de suivi de trois ans ($p = 3,5 \times 10^{-5}$). Ensemble, ces résultats soulèvent la possibilité qu'une combinaison de traits de tempérament, d'adversité infantile et de transmission mal régulée de dopamine augmente le risque de divers problèmes psychiatriques d'apparition précoce, généralement comorbides, prédisant cette susceptibilité de manière prospective.

Acknowledgements

I would like to send the biggest thank you to my supervisor Marco (Dr. Marco Leyton) for his continued support and supervision. Being able to complete this thesis during a global pandemic was possible largely due to his vested interest in my academic growth and success. Thank you to my committee members Drs. Alain Gratton and Claire-Dominique Walker for your insightful feedback along the way. I would also like to thank Syl (Dr. Sylvia Cox) for her help and guidance when I joined the lab, for her stats expertise during our data analysis days. I would also like to thank Val (Dr. Valérie D'Amour-Horvat) for the emotional support during the past two years, for her guidance in my career choices, and for introducing me to Laerd statistics. A big thank you to Laerd statistics, where I learned how to analyze and interpret all of the data reported in this thesis. This thesis would not have been possible without this invaluable resource, as I had no stats background coming into the lab. Thank you Paul (Dr. Paul Clarke) for your incredibly helpful stats course, which taught me how to be a better scientist.

Thank you to my best friend Trycia (Trycia Kouchache) for the unwavering support and companionship you have been throughout this entire masters journey. Finally, a huge thank you to my parents for being my closest friends during a time of isolation and a constant source of support in my endeavours.

Contribution of Authors

Manuscript

Study Conception and Design: Marco Leyton, Sylvia Cox, Jean Seguin

Data Collection: Maria Tippler, Sylvia Cox, Natalia Jaworska

Data Analysis: Maisha Iqbal, Sylvia Cox, Natalia Jaworska, Natalie Castellanos-Ryan

Data Interpretation : Maisha Iqbal, Sylvia Cox, Natalia Jaworska, Marco Leyton

Manuscript Writing and Feedback: Maisha Iqbal, Sylvia Cox, Natalia Jaworska, Maria Tippler, Natalie Castellanos-Ryan, Sophie Parent, Alain Dagher, Frank Vitaro, Mara Brendgen, Michel Boicin, Robert Pihl, Sylvana Cote, Richard Tremblay, Jean Seguin, Marco Leyton

Introduction

In any given year, as many as 20% of Canadians suffer from mental illnesses. By the time they are 40 years old, up to 50% currently have or previously had at least one psychiatric disorder (Smetanin et al., 2011), costing an estimated $46 billion dollars per year for substance use disorders (SUDs; *Substance Use in Canada Costs Almost $46 Billion a Year According to Latest Data | Canadian Centre on Substance Use and Addiction*, n.d.) and $51 for non-SUD disorders (Lim et al., 2008; Smetanin et al., 2011). The causes of these disorders remain poorly understood. This has hampered the discovery of treatments most of which were identified through serendipitous observations. With a better understanding of the causes of mental illness, it is hoped that better treatments and preventative strategies can be developed.

Categorical vs. dimensional models of psychiatric nosology

Psychiatric disorders are currently diagnosed using a categorical model where each disorder is viewed as a separate entity often assumed to have its own set of causes. In this model, having a psychiatric illness is viewed as a binary outcome; an individual either has a disorder or not (American Psychiatric Association & American Psychiatric Association, 2013). However, this categorical model has important limitations. First, its descriptions do not account for the high degree of heterogeneity in clinical presentations of a given disorder. For example, two patients with the same diagnosis may have completely different symptom profiles with minimal overlap. Second, this categorical model does not account for the high degree of co-morbidity seen in patients, as those who have one psychiatric illness are also at a much greater risk of developing a second mental illness either concurrently or subsequently (Kotov et al., 2017, 2021; Krueger,

1999). Twin studies suggest that this tendency to comorbidity includes a genetic component (Kendler et al., 2003).

The accumulating evidence in support of transdiagnostic risk factors also fits with observations that symptoms are shared across diagnoses. For example, thought disorder is a dimension of mania in bipolar disorder as well as schizophrenia and other psychoses (Harrow et al., 2000; Marengo & Harrow, 1985; Yalincetin et al., 2017). Someone who scores high on one dimension is at higher risk of having other disorders that share the same dimension (Eaton et al., 2011; The Brainstorm Consortium et al., 2018). If these superficially similar features are promoted by the same factors, this could explain the high degree of comorbidity between disorders.

The high level of comorbidity across nearly all common psychiatric disorders led to the proposal that there might be an overarching transdiagnostic p factor that affects risk for diverse problems (Caspi & Moffitt, 2018; Lahey et al., 2012). This hypothesized p factor is a single dimension that indicates one's risk for mental illness, comorbidity, duration of mental illness and severity of symptoms. The p factor is conceptually similar to the 'g' factor of general intelligence. The "g" factor indexes intelligence on a scale from low to high, similarly, the "p" factor indicates one's susceptibility to mental illness (Caspi et al., 2014; Caspi & Moffitt, 2018; Lahey et al., 2012). Also like the g factor, the postulated p factor could arise from multiple influences that converge to outcomes non-specifically. The p factor also helps explain the high degree of concurrent and sequential comorbidity seen in psychiatric patients, as well as the difficulty with finding causes, biomarkers and treatments that are unique for specific mental illnesses (Caspi et al., 2014; Kapur et al., 2012).

A second model builds on the p factor concept and proposes that there is a hierarchy of risk factors, a p factor on top that influences susceptibility to near all psychiatric disorders, and successive subfactors that shape progressively more specific problems and symptoms. This HiTOP (Hierarchical Taxonomy of Psychopathology) model views psychiatric disorders as a continuum with varying degrees of severity and overlap between disorders (Kotov et al., 2011, 2017, 2021). It puts mental health on a spectrum from consistently high functioning through to pathology, analogous to blood pressure or weight, addressing the great variability in clinical presentation of the nominally same disorder diagnosed by the categorical model.

The HiTOP model is composed of five levels. The lowest level consists of individual symptoms and maladaptive traits These components can be combined into subfactors, such as sexual problems, eating pathology, fear, distress and mania. One level further up, related subfactors are grouped to form larger spectra, including internalizing, externalizing and thought disorders. Lastly, these spectra are combined to form a superspectra, such as the hypothesized general p factor, that is common to all mental illnesses (Kotov et al., 2018; Latzman & DeYoung, 2020) (Figure 1).

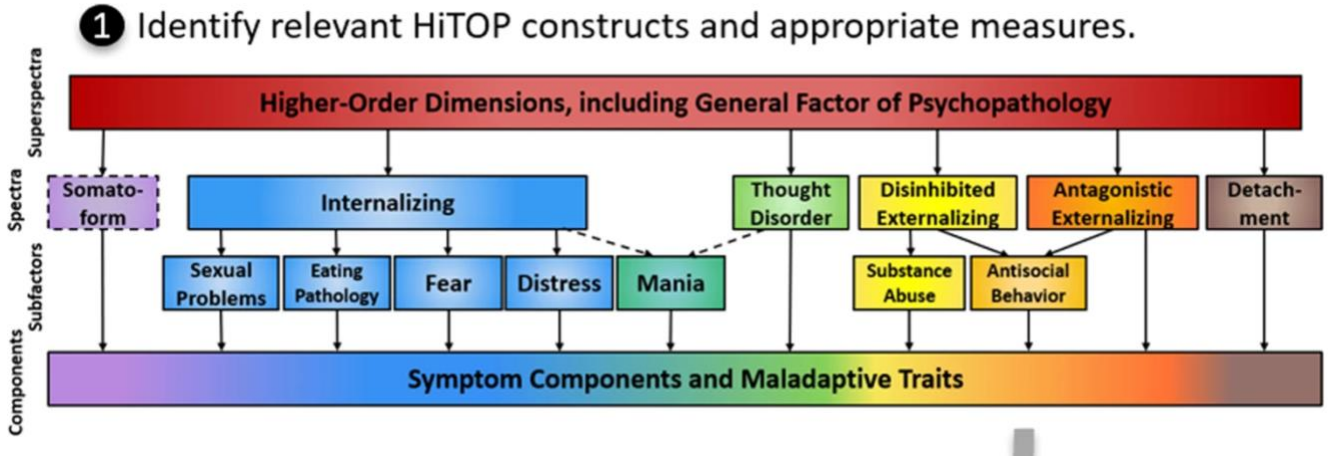

Figure 1. Hierarchical Taxonomy of Psychopathology (HiTOP) framework from Latzman & DeYoung (2020).

Independently studied factors associated with mental illness

The processes and mechanisms that construct the hypothesized p factor and other high level HiTOP factors are poorly understood. The following sections describe three factors that show some potential: early life adversity, adolescent EXT behavioural traits, and low midbrain dopamine cell autoregulation.

Early life adversity

Early life adversity is the prototypical transdiagnostic risk factor for poor mental and physical health outcomes throughout life, placing a large financial burden on the healthcare system. By some estimates, 23% of North Americans experience one early life adversity, and 35% experienced two or more (Bellis et al., 2019). Early life adversities contribute to 30% of anxiety cases in North America and 40% of depression cases. The total annual costs associated with early life adversities in the United States is $581 billion (Bellis et al., 2019).

Both physiological (i.e., prenatal substance exposure, premature birth, malnutrition and infections) and psychosocial stressors (i.e., abuse, poverty, and parental conflicts) may lead to biological changes such as epigenetic modifications, reprogramming of the stress response system and immune regulatory system, as well as neurodevelopmental impairments. These biological changes during childhood can then lead to behavioral problems and increase the risk of a wide range of physical and mental health issues including cardiovascular diseases, metabolic disorders, and psychiatric disorders (Nelson et al., 2020). The effect of early life adversity depends on contextual factors such as the nature, duration and number of adverse events, the developmental period during which the adversities took place, one's family environment, social

support, and coping abilities. Coping abilities, in turn, are related to diverse factors including pre-existing behavioral characteristics and temperament (Nelson et al., 2020).

Mechanisms linking early life adversity and psychopathology

One compelling model of how early life adversity increases risk of psychopathology transdiagnostically suggests that childhood trauma changes how youth process social and other emotionally relevant information (McLaughlin et al., 2020). Changes in social information processing include prioritizing threat related cues, such as increased sensitivity to perceiving threats, inaccurately interpreting neutral and negative emotions as anger, and increased attention biased toward threatening cues. Changes in emotional processing include low emotional awareness, increased emotional reactivity, difficulty with regulating emotions and emotional learning.

These changes in social and emotional processing are accompanied by changes in biological aging, including accelerated cellular aging and earlier onset of puberty. Some of these changes are thought to be an adaptive response, making it easier to detect threatening stimuli, however, they have also been associated with psychopathologies transdiagnostically including both internalizing and externalizing disorders (McLaughlin & Lambert, 2017).

Protective factors can be identified also. These include having supportive caregivers, higher sensitivity to rewarding and positive stimuli, and having a mature amygdala-prefrontal circuitry (McLaughlin & Lambert, 2017) , as well as greater family support, optimism and positive religious coping (such as looking to God for support, guidance and forgiveness) (Schaefer et al., 2018).

Effect of early life adversity on reward processing

Studies in both laboratory animals (Bolton et al., 2018; Lomanowska et al., 2006; Matthews et al., 1996; Matthews & Robbins, 2003) and humans (Boecker et al., 2014; Dennison et al., 2019; Nagy et al., 2021) suggest that a history of stressful life events can alter reward processing (Novick et al., 2018). In a longitudinal study where participants were followed from birth, Boecker et al. (2014) investigated the effect of early life adversity on processing reward anticipation and receipt in adulthood (mean age = 24 years). One hundred and sixty-two healthy participants completed a monetary incentive delay task in a functional magnetic resonance imaging scanner. It was found that participants with greater early life adversity had decreased activation in the ventral striatum, putamen, and thalamus during reward anticipation, and increased activation of the bilateral insula, right pallidum and bilateral putamen during reward delivery (Boecker et al., 2014).

Externalizing (EXT) traits

EXT behaviours are characterized by poor emotional control and behavioural disinhibition that is directed toward the external environment (*Externalization – APA Dictionary of Psychology*, n.d.). They appear early in life and are relatively stable throughout childhood and adolescence (Cox et al., 2021). EXT traits have been shown to increase risk for a wide range of mental health problems (Krueger et al., 2021), including prototypical EXT disorders, such as substance use (Cox et al., 2021; Foster et al., 2018) and cluster B personality disorders (Wolf et al., 2011), but also internalizing disorders such as anxiety and depression (Krueger, 1999; Willner et al., 2016).

Interaction between EXT traits and adversity

Not all children are equally sensitive to their environment. Children's temperament may signal which environment will allow them to thrive. Rioux et al. (2016) investigated whether children's temperament (such as impulsivity and inhibitory control) at age 6 and their parents' parenting style (coercive parenting at age 6 and/or high parental monitoring at age 14) interacted to influence the children's alcohol use at age 15. The authors also investigated whether this interaction supported a diathesis-stress model or a differential susceptibility model.

The diathesis-stress model proposes that children with difficult temperament are more susceptible to the negative effects of poor parental practices, compared with children with easy temperament (Monroe, 1992). In comparison, the differential susceptibility model proposes that impulsive children are more adversely affected by poor parental practices (such as coercion) compared to non-impulsive children, yet they are also more likely to benefit from healthy parental practices (e.g., absence of coercion) compared to non-impulsive children (Belsky & Pluess, 2009; Ellis et al., 2011).

Rioux and colleagues' 2016 study found that alcohol use at age 15 could be predicted by an interaction between the children's temperament and their parent's parenting practices. The interaction supported the differential susceptibility model. That is, compared to children with well-regulated temperamental features, more disinhibited children were at higher risk of alcohol use if they had coercive parents and at lower risk if their parents displayed good parental practices. These findings suggest that impulsive and disinhibited childhood temperament is not necessarily a risk factor for poor psychiatric outcomes, but an indicator of greater sensitivity to the environment (Belsky, 1997; Belsky & Pluess, 2009).

Based on this differential sensitivity model, Boyce and Ellis (2005) posited that children can be categorized as either "orchids", who are highly susceptible to their environments, or “dandelions,” who are less reactive and able to thrive regardless of their environment (Boyce & Ellis, 2005). More recently, Zhang, Widamann and Belsky (2021) extended this idea to propose that children’s susceptibility to their environment lies on a continuum from non-susceptible to highly susceptible.

The Dopamine System

Dopamine potently influences behavioral responses to rewards and punishments (Hu, 2016). Long-lasting changes in dopamine cell reactivity can develop following exposure to early life adversity (Brenhouse et al., 2013; Oswald et al., 2014; Pruessner et al., 2004) and these in turn could affect EXT related traits (Buckholtz, Treadway, Cowan, Woodward, Li, et al., 2010; Jaworska et al., 2020; Leyton et al., 2002). Through these processes, it is thought that poorly regulated dopamine transmission might increase risk for diverse psychiatric problems (Ashok et al., 2017; Cheng et al., 2020; de Beaurepaire, 1991).

Dopamine Synthesis, Release, and Metabolism

Dopamine synthesis begins with the essential amino acid, phenylalanine, which is converted to tyrosine, then *L*-DOPA, and finally dopamine. Cytosolic dopamine is taken up by the vesicular monoamine transporter (VMAT) for storage in vesicles. Upon receiving the appropriate neuronal input, the vesicles fuse with the presynaptic neuron’s plasma membrane and dopamine is expelled into the synaptic cleft. Released dopamine then binds to post synaptic receptors for signal transduction. Extracellular dopamine can then be catabolized to homovanillic acid (HVA)

in a two-step process by the enzymes catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO). Dopamine can also be taken back into the dopamine cell by the dopamine transporter (DAT) located on the cell's plasma membrane. Once inside the cell, dopamine can be metabolised by MAO-B into 3,4-dihydroxyphenylacetic acid (DOPAC) (Cooper et al., 2003; Juárez Olguín et al., 2016).

There are five identified dopamine receptor types (D1 – D5) which are categorized into the D1 family of receptors consisting of the D1 and D5 subtype, and the D2 family consisting of the D2, D3 and D4 subtypes. The D1-like receptors are found on non-dopaminergic cells and increase neuronal activity upon activation, whereas the D2-like receptors are also located on nondopaminergic cells but are inhibitory. The D2 receptor subtype also function as inhibitory autoreceptors (Ford, 2014). These autoreceptors can be found on the soma and dendrites of midbrain dopamine neurons and axons within their terminal regions. The majority of terminal region dopamine D2 receptors are heteroreceptors located on nondopaminergic neurons, whereas the majority of midbrain D2 receptors are autoreceptors (Ford, 2014; Sesack et al., 1994; Yung et al., 1995). Upon activation by circulating dopamine, midbrain D2 autoreceptors decrease dopamine synthesis, cell excitability and release via G-protein coupled inhibitory pathways.

There is evidence in both laboratory animals and humans that low levels of midbrain D2/D3 autoreceptors are associated with more novelty seeking (Bellés et al., 2020; Buckholtz, Treadway, Cowan, Woodward, Li, et al., 2010; Zald et al., 2008) and other impulsive personality traits (Buckholtz, Treadway, Cowan, Woodward, Li, et al., 2010; Jaworska et al., 2020), both of which can affect risk for psychopathology. These effects of midbrain autoreceptors appear to reflect their ability to regulate striatal dopamine release (Bellés et al., 2020; Buckholtz, Treadway, Cowan, Woodward, Li, et al., 2010; Leyton et al., 2002; Milella et al., 2016).

Dopaminergic Pathways

The primary ascending dopamine pathways have their cell bodies in the midbrain which includes the ventral tegmental area (VTA) and substantia nigra (SN). Dopamine neurons from the SN project to the neostriatum (primarily the caudate nucleus and putamen) forming the nigrostriatal pathway (Cooper et al., 2003). Neurons from the VTA primarily project to the most ventral parts of the striatum, including the nucleus accumbens (NAcc), though also to the amygdala and hippocampus, constituting the mesolimbic pathway (Juárez Olguín et al., 2016). Lastly, dopaminergic neurons from both the SN and VTA project to the prefrontal cortex forming the mesocortical pathway (Cooper et al., 2003; Williams & Goldman-Rakic, 1998; Wise, 2009).

The nigrostriatal pathway is thought to be involved in regulating movements (Antonelli & Strafella, 2014; Korchounov et al., 2010) and might also influence reward-related associative learning (Berridge & Robinson, 1998; Graybiel et al., 1994; Robinson et al., 2005). Degeneration of cells in the SN leads to reduced levels of dopamine in the striatum which contributes to movement disorders such as Parkinson's disease and Huntington's disease (Blaess et al., 2020; Graybiel et al., 1994). In comparison, the mesolimbic pathway has established roles in motivational states including responses to rewards and punishments (Blaess et al., 2020). Neurons in this pathway are activated during rewarding and aversive experiences (Pignatelli & Bonci, 2015). Dysregulation of the mesolimbic pathway may be associated with psychiatric disorders (Grace, 2016; Volkow & Morales, 2015) including addictions and depression (Van den Heuvel & Pasterkamp, 2008). Lastly, the mesocortical pathway plays a role in executive functions, the planning of actions, and both inhibitory control and delayed gratification (Floresco & Magyar, 2006; Jentsch et al., 2000). Dysfunction of this pathway is thought to contribute to schizophrenia (Jentsch et al., 2000).

Dopamine's role in reward processing

Dopamine influences behavioral responses to rewards but the proposal that dopamine is closely related to the pleasurable aspects of reward receipt has been largely abandoned. This reflects studies in both humans and laboratory animals. In rodents, depleting up to 99% of dopamine in the NAcc and neostriatum of rats does not lead to decreases in orofacial responses to sucrose thought to index pleasure (Berridge & Robinson, 1998). In both rodents and non-human primates, dopamine cell firing and release are more closely related to the expectation of rewards and the motivation to pursue them than the receipt of reward (Berridge & Robinson, 1998, 2003; Fiorillo et al., 2003; Mohebi et al., 2019; Romo & Schultz, 1990; Schultz et al., 1997; Stauffer et al., 2016) . In humans, neither dopamine receptor antagonists (Brauer & De Wit, 1997) nor decreased dopamine synthesis (Cawley et al., 2013; Venugopalan et al., 2011) reduces the subjective euphoria experienced from obtaining rewards but the latter does decrease the willingness to work for them. Lastly, dopamine cell firing is potently influenced by reward prediction errors. Dopamine neuron firing increases upon receiving a reward greater than expected, decreases following events that are worse than expected, and remains unchanged when rewards obtained are as expected. When these processes are working well, they are thought to facilitate the assignment of incentive value to environmental stimuli (Flagel et al., 2011) and the generation of situation-appropriate responses to rewards and punishments (Schultz, 1998).

Dopamine's role in psychiatric disorders

Disturbances in the dopaminergic system are implicated in a wide range of problems including mood, substance use, and impulse-control disorders (Ashok et al., 2017; Cheng et al., 2020; de Beaurepaire, 1991). The direction of the effect is often unclear (Buckholtz, Treadway, Cowan,

Woodward, Li, et al., 2010; Grace, 2016; Leyton & Vezina, 2014). For example, there is evidence that, in people at elevated risk for substance use problems, dopamine transmission is greater than that seen in healthy controls under some testing conditions and lower under other conditions (Leyton, 2021; Leyton & Vezina, 2014). Impulsivity regulation is disturbed in both high and low dopamine states (D'Amour-Horvat & Leyton, 2014; Leyton et al., 2007; Leyton & Vezina, 2014). In mood disorders also, the direction of the effect is less clear than initially proposed. Depression has been associated with decreased DAT availability in the striatum and midbrain (Dubol et al., 2020; Pizzagalli et al., 2019) and lower levels of HVA in their cerebrospinal fluid (Kasa et al., 1982; Papeschi & McClure, 1971; Roy et al., 1986). Additionally, several PET studies have reported evidence of increased striatal D2 availability in depressed patients, as compared to healthy controls (Hamilton et al., 2018; Meyer et al., 2006). The lack of conclusiveness on the direction of effect in dopamine levels may indicate that it is not the direction that is important, but dopamine dysregulation (Grace, 2016).

Some of the complexities of these associations between dopamine transmission and the regulation of affectively relevant behaviors were illustrated by an elegant optogenetic study in mice. Chaudhury et al. (2013) investigated how dopamine cell pathway firing patterns might affect susceptibility to depression. They showed that optogenetic activation of phasic firing in VTA dopaminergic neurons that project to the NAcc induced a stress sensitivity phenotype in mice exposed to chronic social defeat stress. In comparison, inhibiting the VTA – NAcc dopaminergic projection induced a resilient phenotype whereas inhibiting the VTA to mPFC projection induced a susceptible phenotype. This work sheds light on how the firing pattern of VTA dopaminergic neurons could affect susceptibility to depression related behaviors (Chaudhury et al., 2013).

Measuring dopamine in humans

Positron emission tomography (PET) imaging is the only available method to non-invasively measure features of the dopamine system in living human brain (Buckholtz, Treadway, Cowan, Woodward, Li, et al., 2010; Jaworska et al., 2020). A number of D2/3 tracers are available. Compared to other D2/3 tracers that are often preferred for measuring dopamine release, such as [^{11}C]raclopride and [^{11}C]PHNO, [^{18}F]fallypride has higher D2/3 receptor affinity (Slifstein et al., 2010). This feature makes [^{18}F]fallypride less sensitive to changing concentrations of extracellular dopamine and more suitable for estimating D2/3 receptor density.

PET measures these features following the administration of a small amount of the labeled tracer. A radioactive atom is tagged to a molecule used by the organ of interest (*Positron Emission Tomography (PET)*, n.d.). For example, the brain uses glucose for energy, therefore a radioactive atom can be attached to a glucose analog to measure how much is used by the brain. The specific radioactive ligand used depends on purpose of the scan and molecule being targeted.

As the radionuclide decays it collides with electrons and Gamma rays called annihilation photons are emitted. For every electron the radionuclide collides into, two photons are emitted 180 degrees from each other (Berger, 2003; *Positron Emission Tomography (PET)*, n.d.). The photons then travel at the speed of light, hitting diametrically opposed "coincidence" detectors near simultaneously. Each time a pair of photons hit the detector 180 degrees apart, this information is used to create a three-dimensional image of the organ being studied. The greater the amount of radionuclide collected in a given tissue, the brighter the tissue appears on the image, as constructed by the computer indicating a greater amount of molecular activity (*Positron Emission Tomography (PET)*, n.d.). From the PET image, binding potential non-

displaceable (BP_{ND}) values can be calculated which indicates the amount of bound to free tracer ratio (Guo et al., 2014). A higher BP_{ND} value indicates that a larger number of the radioligand is bound to the receptor compared to the amount of unbound (free) ligand, thus indicating greater receptor availability.

The PET image is often paired with a magnetic resonance imaging (MRI) or computerized tomography (CT) scan to obtain a structural image of the organ (*Positron Emission Tomography (PET)*, n.d.). The functional image obtained from the PET scan is then overlaid on the structural image to create an accurate map of the organ's activity. PET imaging is unique as it allows researchers to measure functional activity in vivo, in specific targets. While, functional MRI also allows in vivo measurement of functional activity, it is limited to measuring the blood-oxygen-level-dependent signal which indexes the amount of oxygenated blood in a region of interest. PET imaging allows researchers to image levels of molecular targets and ligand-target interactions (Long & Wong, 2015).

Sex and gender differences in psychiatric disorders

Overall, the lifetime prevalence of mental illness in males vs. females is similar (*Investing_in_Mental_Health_FINAL_Version_ENG.Pdf*, n.d.). This noted, some mental illnesses show evidence of sex differences, including mood and anxiety disorders, which are diagnosed in females twice as often as in males (Gater et al., 1998; Kessler et al., 1994, 1995; Weissman et al., 1996) and SUDs which are diagnosed two and a half times more often in males than females (McHugh et al., 2018). It remains unclear whether this reflects inherent sex-related differences in susceptibility to specific mental health problems, differential expressions of the

same core problems, or different life experiences that push males vs. females toward different problems.

Importance of longitudinal cohorts and prospective studies

Studying the role of risk factors for mental problems has been hampered by the use of cross-sectional research designs. In comparison, prospective, longitudinal studies are the gold standard for investigating the effects of diverse experiences and events on health outcomes. The advantage of this study design is that it allows researchers to establish the temporal sequence of events, the minimum for postulating cause-effect relationships. Longitudinally followed birth cohorts also provide higher quality information as the data are collected close in time to events of interest.

Aim and Hypotheses

Based on the above observations, we used the PET [^{18}F]fallypride method in a longitudinally followed birth cohort to test whether the combination of EXT behaviours, childhood trauma, and dopamine cell regulation predicts clinical outcomes. It was hypothesized that higher EXT traits, greater early life adversity, and lower midbrain dopamine autoreceptor availability would predict the presence of early onset commonly comorbid psychiatric conditions. Finally, we also investigated whether there is a sex difference in the prevalence of lifetime psychiatric illnesses, by adding sex as a predictor variable. Given the similar rates of prevalence of lifetime psychiatric disorders in males and females, we did not expect to find a sex difference..

Manuscript

Introduction

Converging epidemiological (Caspi & Moffitt, 2018; Castellanos-Ryan et al., 2016; Kapur et al., 2012; Krueger, 1999; S. H. Lee et al., 2013) and molecular genetic evidence (Smoller et al., 2019; The Brainstorm Consortium et al., 2018; H. Zhou et al., 2020) raises the possibility that many psychiatric disorders reflect the varying expression of overlapping developmental trajectories (Caspi & Moffitt, 2018; Krueger et al., 2018). One of the largest trajectories is characterized by diverse externalizing (EXT) behaviors (Castellanos-Ryan et al., 2016; Foster et al., 2018; Kendler et al., 2016; Krueger & Tackett, 2003). EXT refers to behaviors where thoughts and feelings are directed toward external targets in the environment (*Externalization – APA Dictionary of Psychology*, n.d.), often in ways that violate societal norms or the rights of others (American Psychiatric Association & American Psychiatric Association, 2013; Kauten & Barry, 2020). Examples include projecting anger toward another person, poor impulse control, dysregulated affect, and altered responses to rewards and punishments (Bjork & Pardini, 2015; Byrd et al., 2014). Examples of EXT disorders in the Diagnostic and Statistical Manual of Mental Disorders – 5th edition (DSM-5) include attention-deficit/hyperactivity disorder (ADHD), conduct disorder, oppositional defiant disorder, antisocial personality disorder and SUDs (American Psychiatric Association & American Psychiatric Association, 2013, p. 5).

EXT traits are likely mediated by multiple neurobiological systems (Dalley & Robbins, 2017; Miczek & Meyer-Lindenberg, 2014). One implicated system has shown associations between low midbrain dopamine autoreceptor levels (Meador-Woodruff et al., 1994; Sokoloff & Le Foll, 2017), increased dopamine release (Buckholtz, Treadway, Cowan, Woodward, Li, et al., 2010; Milella et al., 2016), and various EXT-related features, including impulsivity, novelty

seeking and sensitivity to punishment (Buckholtz, Treadway, Cowan, Woodward, Li, et al., 2010; Jaworska et al., 2020). In laboratory animals too, low midbrain autoreceptors and elevated dopamine transmission can increase the salience of both positive and negative stimuli (Bellés et al., 2020; Bello et al., 2011; Berridge & Robinson, 2003; Chaudhury et al., 2013; da Silva et al., 2018; Heymann et al., 2020; Marinelli & White, 2000; Mohebi et al., 2019; Tournier et al., 2013), promote novelty seeking and motor impulsivity (Bellés et al., 2020; Dalley & Robbins, 2017; D'Amour-Horvat & Leyton, 2014; Marinelli & White, 2000; Tournier et al., 2013), and reduce the ability to disambiguate optimal choices (Duvarci et al., 2018; Holroyd et al., 2015; Olivetti et al., 2020). Stressful events can aggravate these features, including the fomenting of dopaminergic (Booij et al., 2016; Matuszewich et al., 2014) and behavioral hyperreactivity (Leyton & Stewart, 1990; Matuszewich et al., 2014) and susceptibility to mental health problems (Jaekel et al., 2020; Keyes et al., 2012).

Methods

Participants

All participants were born between 1996-1998, lived in the Montreal or Quebec City area in Canada, and had been followed since birth (Boivin et al., 2013; Cox et al., 2021; Orri et al., 2020). Fifty-eight volunteers (36F/22M) underwent magnetic resonance imaging (MRI) and [^{18}F]fallypride positron emission tomography (PET) scans. Six were excluded from the current analyses: two due to not having Childhood Trauma Questionnaire (CTQ) data and four due to BP_{ND} values being outliers (± 3 SD) (**Table 1 & Supplementary Table 1**). The final sample consisted of 52 participants (30F/22M), mean age at the time of scanning was 18.5 (SD = 0.6 years). Forty-one participants (22F/19M) had one or more follow-up interview (age at last assessment: 21.0 ± 0.9 years). Ethics approval was obtained from McGill University and Sainte-

Justine University Hospital Research Ethics Boards, and all participants provided written informed consent. Further details are in Jaworska et al. 2020 (Jaworska et al., 2020).

Measures

Externalizing (EXT) scores

Externalizing trait scores were measured annually between ages 10 and 16 through self-report (Quebec Longitudinal Study of Child Development; QLSCD, n = 53) or teacher ratings (Quebec Newborn Twin Study; QNTS, n = 5) using the Social Behavior Questionnaire (SBQ) (Behar & Stringfield, 1974; Tremblay et al., 1992). Mean scores were calculated for the following SBQ subscales: hyperactivity, impulsivity, oppositional behavior, non-aggressive behavioral problems, physical aggression, proactive aggression, indirect aggression and reactive aggression. Composite EXT trait scores were aggregated using a minimum of two years' data between 10 and 16 years (Castellanos-Ryan et al., 2016; Cox et al., 2021). Mean EXT scores during these years correlated with those obtained earlier in life (1–5 and 6–10 years) (Cox et al., 2021). For the current study, cohort members were invited to participate if they scored in either the top or bottom 30% of EXT trait scores, as established in the first wave of QLSCD cohort members (n = 242, born in 1996) (Cox et al., 2021).

Assessments

At their index assessment prior to the PET and MRI scans, all participants were interviewed face-to-face with the Structured Clinical Interview for DSM-5 (SCID) (Glasofer et al., 2015) and administered the CTQ (Bernstein & Fink, 1998). Follow-up telephone assessments were then conducted annually for the next three years. The CTQ measures early life adversity, including

emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect (Bernstein & Fink, 1998). It has been validated in French (Paquette et al., 2004) and has good psychometric properties ("Initial Reliability and Validity of a New Retrospective Measure of Child Abuse and Neglect," 1994). Elevated CTQ scores are associated with poor cognitive function across multiple domains (Goltermann et al., 2020) and diverse psychiatric disorders (McLaughlin et al., 2020; McLaughlin & Sheridan, 2016).

Magnetic resonance imaging (MRI)

MRI scans were acquired on each participant for anatomical co-registration using a 3T Siemens Trio TIM scanner (McConnell Brain Imaging Centre, Montreal Neurological Institute) with a Magnetization Prepared Rapid Acquisition sequence (slice: 1mm, TR: 2300 ms, TE: 3.42 ms, flip angle: 9°, FOV: 256 mm, Matrix: 256 x 256). MRI and PET data were co-registered to aid anatomical precision when defining the regions of interest (ROIs).

PET imaging

Dopamine D2 receptor levels were measured using the high affinity dopamine D2/D3 receptor ligand, [^{18}F]fallypride, and a 90-minute PET scan on a high-resolution research tomograph (HRRT). Following cannula insertion into the left antecubital vein for tracer administration, a 6-min ^{137}Cs transmission scan was obtained for attenuation correction. The [^{18}F]fallypride tracer (prepared as previously described (Milella et al., 2016)) was administered as a 1-min intravenous bolus, with emission scans acquired concurrently in list mode over 90-min (participants were instructed to remain awake). The mean±SD injected [^{18}F]fallypride dose was 123.39 ± 7.59 MBq, injected mass was 1.46 ± 3.90 nmol, and molar activity at time of

injection was 381.08 ± 819.99 GBq/μmol. There were no statistically significant differences in injected dose, mass or molar activity between participants with and without psychiatric diagnoses (*p* values > 0.4; **Supplementary Table 2**).

PET images were reconstructed using the Ordinary Poisson Ordered Subset Expectation Maximization (OP-OSEM) reconstruction algorithm (10 iterations, 16 subsets). This included correction for non-uniformities, attenuation, scattered and random coincidences, and motion. To reduce partial volume effects, resolution modeling using the point spread function was implemented in image reconstruction. Motion correction was based on a data-driven motion estimation and correction method that estimates rigid-body motion between dynamic frames. Further details are in Jaworska et al. 2020 (Jaworska et al., 2020).

MRI and PET analyses

The imaging data set was obtained from previously analyzed images (Jaworska et al., 2020). Binding potential non-displacement (BP_{ND}) values were derived from the primary region of interest (ROI), the midbrain dopamine cell body region, consisting of the ventral tegmental area and substantia nigra, and seven exploratory regions of interest (ROIs) further implicated in the regulation of mood and motivational states and impulsive behaviors (superior frontal gyrus, medial frontal gyrus, medial orbito-frontal gyrus, middle frontal gyrus, insula, amygdala, and hippocampus) (Jaworska et al., 2020). ROI masks were defined using standard masks on the MNI152 template which were coregistered to each individual's MRI scan using linear and nonlinear transformations (Murty et al., 2014). These ROI masks were then applied to each summed PET image using non-linear co-registration. Time-activity curves were extracted from each ROI in native PET space using tools developed by the Turku PET Centre

(http://www.turkupetcentre.net/). BP_{ND} values (i.e., equilibrium ratio of specifically bound to non-displaceable radioligand in tissue) were derived from ROIs using the simplified reference tissue model (Lammertsma & Hume, 1996) with cerebellar grey matter as the reference region.

Statistical analyses

Binomial logistic regression analyses were conducted to test whether midbrain [^{18}F]fallypride BP_{ND} values, EXT and CTQ scores, converted to Z scores, predicted the presence of lifetime DSM-5 diagnoses. All analyses were run for diagnoses obtained at the time of or prior to the PET scan and again including diagnoses obtained during the follow-up interviews.

Linearity of the continuous variables with respect to the logit of the dependent variable was assessed via the Box-Tidwell (1962) procedure (Box & Tidwell, 1962). A Bonferroni correction was applied using all seven terms (midbrain BP_{ND}, EXT, CTQ, midbrain*ln_midbrain, EXT*ln_EXT, CTQ*ln_CTQ, and constant) in the overall model resulting in statistical significance being defined as $p < 0.0071$ (Tabachnick & Fidell, 2013). Based on this assessment, all continuous independent variables were linearly related to the logit of the dependent variable.

Receiver operating characteristic (ROC) curves were created for each model, and the area under the curve (AUC) was used to evaluate the overall model's strength. ROC curves illustrate the ability of a binary classifier to discriminate groups as the threshold is varied. The graph is created by plotting the true positive rate or sensitivity on the y axis, and the false positive rate or (1 – specificity) on the x axis. The area under the ROC curve measures how well the model can identify positive and negative cases. The AUC ranges between 0 and 1. The closer the AUC is to 1, the better the model. An AUC close to 1 is able to correctly identify patients with and without

diagnoses, an AUC close to 0 identifies group designation incorrectly, and an AUC close to 0.5 indicates that the model has no classification ability (Narkhede, 2021).

All hypotheses were tested using two-tailed statistics. Unless otherwise noted, all analyses were performed using IBM SPSS version 26 with the following add-ons: Complex Sampling & Testing, Forecasting & Decision Trees, and Custom Tables & Advanced Statistics.

Results

Lifetime psychiatric diagnoses

At their index interview, 23% of participants met criteria for one or more lifetime DSM-5 disorders. By their last interview, this had increased to 31%. The specific diagnoses included SUDs, unipolar mood disorders, attention deficit-hyperactivity disorder (ADHD), panic disorder, generalized anxiety disorder, adjustment disorders, dyslexia, binge eating disorder, and conduct disorder (**Supplementary Tables 3A & 3B**).

Three-factor model predicts lifetime psychiatric disorders at index interview

The three-factor model was statistically significant ($p = 2.4 \times 10^{-5}$), correctly classifying 90% of cases and explaining 56% (Nagelkerke R^2) of the variance in DSM-5 diagnoses. Sensitivity was 75%, specificity was 95%, positive predictive value was 82%, negative predictive value was 93%, and ROC AUC was 92% [95% CI: .824, 1.000], considered an outstanding level of discrimination (**Table 2**) (Hosmer et al., 2013).

All three factors contributed to the model. Adding CTQ total scores as the third factor strengthened the model (compared to EXT + midbrain BP_{ND}, $p = 0.05$). Adding midbrain [^{18}F]fallypride BP_{ND} values as the third factor strengthened the model (compared to EXT + CTQ,

$p = 0.03$). Adding EXT scores as the third factor strengthened the model (compared to CTQ + midbrain BP_{ND}, $p = 5.0 \times 10^{-6}$). In comparison, the model was not improved by the addition of BP_{ND} values from the seven exploratory ROIs ($p \geq 0.37$).

Within the three-factor model, standardized EXT scores (Wald = 9.880, $p = 0.002$) and midbrain [^{18}F]fallypride BP_{ND} values (Wald = 3.833, $p = 0.05$) were statistically significant after controlling for the influence of the two other factors. One standard deviation (SD) increases in CTQ and EXT scores were associated with two- and 10-times greater odds of having a lifetime DSM diagnosis, respectively. A one SD decrease in midbrain [^{18}F]fallypride BP_{ND} values was associated with three times higher odds (**Table 3**).

Three-factor model predicts lifetime EXT disorders at index interview

The three-factor model predicted lifetime EXT disorders alone at index interview. The model was primarily driven by EXT traits ($p = 0.008$). When adding midbrain BP_{ND} values and CTQ scores, the former strengthened the model (compared to EXT + CTQ, $p = 0.027$) while the latter did not (compared to EXT + midbrain BP_{ND}, $p = 0.225$). More importantly, this three-factor model for EXT disorders was not stronger than the one capturing all expressed DSM-5 disorders (AUC ROC curves for EXT vs. all disorders, $t(102) = 0.6191$, $p = 0.54$) (X. Zhou et al., 2002), plausibly reflecting the propensity of people with EXT disorders to develop internalizing disorders and vice versa (Lahey et al., 2014) (**Table 4A**).

Three-factor model predicts lifetime psychiatric disorders at follow-up

At the last follow-up interview, the logistic regression model was statistically significant ($p = 3.5 \times 10^{-5}$), explained 51% (Nagelkerke R^2) of the variance in DSM-5 diagnoses, and

correctly classified 81% of cases. Sensitivity was 63%, specificity was 89%, positive predictive value was 71% and negative predictive value was 84%. Of the three predictor variables only EXT trait score was statistically significant (Wald = 11.948, $p = 0.001$), but inclusion of CTQ scores and midbrain BP_{ND} values yielded what is considered an excellent level of discrimination (Hosmer et al., 2013) (EXT alone, AUC ROC = 0.855 [95% CI: .713, 0.998]; EXT + CTQ + midbrain BP_{ND}, AUC ROC = 0.898 [95% CI: .795, 1.000]).

Three-factor model is accurate in men and women

Male participants were more likely to have diagnoses of ADHD and SUDs while female participants more frequently met criteria for mood and anxiety disorders (**Supplementary Table 4**). Overall, lifetime psychopathology was observed in similar proportions of males and females (6/22 vs. 10/30; no significant difference, Fisher's exact test, $p = 0.76$). At the index interview, the model remained significant with the addition of sex as a fourth factor ($p = 3.4 \times 10^{-5}$). Sex itself was not a significant predictor of a lifetime DSM-5 diagnosis (Wald = 0.374, $p = 0.54$), nor was the four-factor model (EXT + CTQ + midbrain BP_{ND} + sex) significantly different from the three-factor model ($p = 0.54$) (**Table 4B**). When additional diagnoses from the follow-up interviews were included, the model with sex as a fourth variable remained significant ($p = 7.4 \times 10^{-5}$). Again, however, sex itself was not a significant predictor of lifetime DSM-5 diagnosis (Wald = 0.843, $p = 0.36$) and the four-factor model (EXT + CTQ + midbrain BP_{ND} + sex) was not significantly different from the three-factor model ($p = 0.35$).

Discussion

Our study's primary objective was to test whether a three-factor model, composed of features with modest transdiagnostic predictive value when tested in isolation, could more powerfully predict the presence of lifetime psychiatric disorders in young adults who have been followed from birth. As hypothesized, the combination of higher EXT traits, greater levels of childhood adversity, and lower levels of midbrain D2 receptors identified, with high accuracy and statistical robustness, participants with any lifetime history of psychiatric illness, both at the index interview and at follow-up.

Our second aim was to test whether there is a sex is a predictor of lifetime psychiatric history. As hypothesized, we found that sex is not a significant predictor of whether someone currently or previously had any psychiatric illness.

To our knowledge, this is the first investigation to study all three factors together. In comparison, each individual factor has been found to increase risk for psychopathology. As a start, both epidemiological (Caspi & Moffitt, 2018; Castellanos-Ryan et al., 2016; Kapur et al., 2012; Krueger, 1999; S. H. Lee et al., 2013) and molecular genetic (Smoller et al., 2019; The Brainstorm Consortium et al., 2018; H. Zhou et al., 2020) studies suggest that EXT traits reflect a developmental trajectory from which diverse psychiatric disorders can emerge. This includes substance use and cluster B personality disorders, as well as problems commonly considered internalizing disorders (Caspi & Moffitt, 2018; Castellanos-Ryan et al., 2016; Krueger, 1999; Lahey et al., 2014).

Childhood trauma is arguably the prototypical transdiagnostic risk factor, increasing the probability of both internalizing and EXT disorders in adolescence and adulthood (Copeland et

al., 2018; McLaughlin et al., 2020). The replicated associations with early life adversity noted, some people exhibit striking resilience (Amstadter et al., 2016; Rutter, 1981). The factors accounting for these different responses to adversity are thought to include variability in coping skills (Asselmann et al., 2017) and pre-existing temperament (Rioux et al., 2016). The present study raises the possibility that a third contributing factor is midbrain dopamine cell reactivity.

Midbrain D2 receptors are primarily autoreceptors (Chen et al., 2020). In humans, somatodendritic autoreceptors are present on dopamine cells that project to the striatum but not cells that project to the cerebral cortex (Galloway et al., 1986; Hoffmann et al., 1988; Holloway et al., 2019; M. E. Wolf et al., 1986). Despite this, there is evidence from studies in laboratory animals that altered mesostriatal dopamine transmission affects functioning within the larger mesocorticolimbic circuitry. In these studies, poorly regulated dopamine cell reactivity can lead to cognitive deficits (Arnsten et al., 2009; Duvarci et al., 2018; Vijayraghavan et al., 2017), sub-optimal choices (Duvarci et al., 2018; Olivetti et al., 2020), impulsivity (Bellés et al., 2020; Leyton & Vezina, 2014) , and susceptibility to depressive phenotypes (Chaudhury et al., 2013). Adverse outcomes might be particularly profound when elevated mesostriatal dopamine transmission is combined with reduced or asynchronous cortical dopamine function (Chaudhury et al., 2013; Duvarci et al., 2018; Leyton & Vezina, 2014). Indeed, across diagnostic categories, there is evidence of poorly regulated dopamine transmission (Buckholtz, Treadway, Cowan, Woodward, Benning, et al., 2010; Buckholtz, Treadway, Cowan, Woodward, Li, et al., 2010; Cherkasova et al., 2014; Jaworska et al., 2020; Sequeira et al., 2021; Vosberg et al., 2020; Wang et al., 2019) with *DRD2* variants constituting a transdiagnostic risk gene (P. H. Lee et al., 2019).

The study's fourth finding was related to sex. As expected, males were more likely than females to be diagnosed with attention deficit and substance use disorders and less likely to meet

criteria for mood and anxiety disorders. This noted, both in our study and in the general population, the lifetime prevalence of psychiatric illness overall is similar for men and women (*Gender and Women's Mental Health*, n.d.) and adding sex as a predictor did not improve the model's strength. These observations suggest that the three investigated factors influence susceptibility to psychiatric disorders in both males and females irrespective of how the susceptibility comes to be expressed.

The breadth of diagnoses predicted by the model raises the possibility that it contributes to the hypothesized p factor that has been proposed to affect risk for all common psychiatric disorders (Caspi & Moffitt, 2018; Castellanos-Ryan et al., 2016; Lahey et al., 2012; The Brainstorm Consortium et al., 2018). The specific processes composing p have been little studied, but some work suggests that they include poor impulse control over emotions and difficulties in reality testing (Caspi & Moffitt, 2018). The findings reported here might identify sources of these alterations.

Strengths and Limitations

The present research benefitted from prospectively collected behavioral traits and clinical outcomes. It is also, to our knowledge, the first PET study in a longitudinally followed birth cohort. These strengths noted, the results should be interpreted in light of the following considerations. First, all three factors contributed to the model's strength after controlling for the influence of the two other factors indicating that they are not interchangeable proxies of each other. This noted, only EXT was statistically significant as a standalone variable. This observation suggests that CTQ scores and midbrain D2 receptor availabilities contribute through interactions with the other variables. Although the present sample is reasonably large for a PET

study, it is not large enough to interrogate further these potential statistical interactions; we can therefore primarily conclude that high statistical power is provided by the model overall. Second, the three-factor model also predicted the presence of EXT disorders uniquely. In this analysis, the smaller number of affected cases decreased further the ability to disentangle contributions of each individual factor, but the effect appeared to be driven by EXT scores and midbrain [^{18}F]fallypride BP_{ND} values. Additional work will be needed to better capture the model's strength for EXT vs. internalizing disorders, but longitudinal research indicates that a history of disorders from one cluster predicts higher risk for both 'homotypic' and 'heterotypic' conditions (Lahey et al., 2014). Consistent with the proposition that the studied risk factors are not specific to a single cluster, the three-factor model was not significantly better at capturing EXT disorders than all occurring DSM-5 disorders. Third, much of the data was collected prospectively, but definitive statements about causality are not possible. Instead, the study identifies a model that predicts clinical outcomes. Fourth, the sample was relatively homogenous, composed primarily of francophone youth of European descent. Future studies should test whether the model generalizes to other populations. Fifth, the index interviews were conducted face-to-face, but the follow-up interviews were by telephone, potentially diminishing the quality of information from these later assessments. Sixth, participant attrition may not have been random. However, these sub-samples did not differ on key variables, including age, EXT score, or proportion with a lifetime history of DSM-5 disorders (**Supplementary Table 5**). Finally, the project's PET tracer, [^{18}F]fallypride, binds to both D2 and D3 receptors (Mukherjee et al., 1999). Midbrain D2 receptors are primarily located on mesostriatal dopamine neurons where they act to inhibit mesostriatal dopamine release (Bello et al., 2011; Meador-Woodruff et al., 1994; Milella et al., 2016). The majority of midbrain D3 receptors, in comparison, are on terminal regions of

descending striatal GABAergic neurons and their activation inhibits cortical dopamine release (Sokoloff & Le Foll, 2017). Since [^{18}F]fallypride has preferential affinity for D2 (Mukherjee et al., 1999), our PET data are likely dominated by effects relevant for mesostriatal dopamine transmission. This noted, to the extent that the effect could also include changes to D3 receptors, poorly synchronized striatal and cortical dopamine transmission erodes a wide range of cognito-affective processes (Chaudhury et al., 2013; Duvarci et al., 2018).

Conclusions

This first study of the three-factor model supports proposals that many common forms of early onset psychopathology emerge from the varying expression of shared intersecting dimensions (Caspi & Moffitt, 2018; Castellanos-Ryan et al., 2016; S. H. Lee et al., 2013). Obtaining a better understanding of the identified features could provide targets for early interventions with implications for both nosology and etiology.

General Discussion

The aim of this study was to determine whether the combination of EXT traits, midbrain dopamine D2 receptor availability and early life adversity could identify participants with a lifetime history of psychiatric illness. As predicted, the three-factor model identified participants with past or current psychiatric illness(es) with an overall accuracy of 90.4%, and this finding was statistically strong and robust ($p = 2.4 \times 10^{-5}$). The area under the receiver operating characteristic (ROC) curve was 0.915 [95% CI: 0.824 to 1.000], which is considered an outstanding level of discrimination (Hosmer et al., 2013). After including diagnoses obtained at follow-up interviews, which took place over the subsequent three years, the model remained statistically significant and robust ($p = 3.5 \times 10^{-5}$). The model correctly classified 80.8% of cases, and its area under the ROC curve was 0.870 [95% CI: 0.746 to 0.994], considered an excellent level of discrimination. The latter result further suggests that this three-factor model can prospectively identify participants who are susceptible to psychiatric disorders. Lastly, adding sex as a predictor variable did not improve the strength of the model consistent with an absence of sex differences in the prevalence of lifetime psychiatric disorders in the present sample and the general population.

These findings are in agreement with existing literature showing that each of the three predictor variables individually increase risk for psychiatric illnesses and their associated features. In humans, decreased midbrain D2 receptor availability is associated with increased novelty seeking (Zald et al., 2008), impulsivity (Buckholtz, Treadway, Cowan, Woodward, Li, et al., 2010) and decreased sensitivity to punishment (Jaworska et al., 2020). These overlapping traits are key features of many psychiataric disorders including mood disorders, SUDs, ADHD,

Cluster B personality disorders and conduct disorder (Kulacaoglu & Kose, 2018; Moeller et al., 2001).

The impulsivity related traits contribute prominently to EXT behaviors. The broader concept of EXT also includes poor regulation of emotions and behaviours. These are behaviors directed toward the external environment, and consist of actions that are commonly disruptive, hyperactive or aggressive (Liu, 2004). Individual differences in these EXT behaviors show high levels of heritability (Wichers et al 2013; Hicks et al 2004, 2013; Silberg et al 2007; Kendler et al 2003) and stability during adolescence (Stemmler & Lösel, 2012; Vrieze et al., 2012; Cox et al., 2021). High levels of these EXT traits have been linked with poor mental health outcomes (Castellanos-Ryan et al., 2016; Krueger & Tackett, 2003) including prototypical EXT disorders such as SUDs (Cox et al., 2021; Foster et al., 2018; Kendler et al., 2016) and cluster B personality disorders (Wolf et al., 2011), as well as internalizing disorders including anxiety and depression (Krueger, 1999; Willner et al., 2016). The latter association might reflect some overlap between EXT and internalizing features, particularly emotional dysregulation. For example, Foster et al. (2018) showed that the components of internalizing that overlap with EXT traits increase risk for alcohol use disorders; conversely, internalizing features that are mutually exclusive from EXT traits (e.g. social withdrawal and behavioural inhibition) are protective against alcohol use disorder. However, these unique internalizing features can increase risk for other psychiatric illnessses including depression and anxiety disorders (Svihra & Katzman, 2004; Tang et al., 2020). Taken together, EXT traits are a strong predictor of many forms of psychopathology. It is likely that high EXT behaviors are an early expression of vulnerability, in addition to having a causal role in the development of psychiatric disorders later in life. The exact outcome from these EXT traits might reflect their intersection with other individual (such

as genetics and epigenetic changes) and environmental factors (such as family stress, strict parenting, peer groups, and neighbourhood crime levels) (Campbell et al., 2000).

Lastly, early life adversity has been shown to be a transdiagnostic risk factor for nearly all mental illnesses (Copeland et al., 2018; McLaughlin et al., 2020). It is difficult to ascertain, in humans, whether early life adversity causes the development of psychiatric illness later in life. This is due to ethical concerns in experimental study designs, and recall biases in retrospective measures of early life adversity (Hardt & Rutter, 2004; Lewinsohn & Rosenbaum, 1987; Reuben et al., 2016; Sheikh, 2018). There are also limitations of prospectively collected data on early life adversity, including participant attrition, subjectivity of the reports, and inconsistencies between observers. In prospective studies, reports of early life adversity may be obtained from parents during early childhood, teachers during primary school years, as well as the participants during adolescence and adulthood (Orri et al., 2021). Obtaining reports from multiple individuals at various time points may result in inconsistencies and low inter-rater reliability. Given these limitations, it is difficult to conclude whether early life adversity has a causal role in psychiatric disorders.

The present study's findings have the potential to improve our understanding of the etiology of psychiatric illnesses, as arising from discrete or shared risk factors. They support dimensional models of psychiatric nosology and identify potential early intervention and treatment targets including externalizing behavioural traits, early life adversity and low levels of midbrain dopamine autoreceptors. This three-factor model can also prospectively identify youth at high risk of developing psychiatric disorders. These at-risk youth can be given early interventions in an effort to prevent them from developing psychiatric illnesses. Two early intervention programs that have been shown to be effective in preventing the development of

SUDs and improving classroom behaviours include PreVenture and the Good Behavior Game, respectively.

"PreVenture" is an evidence based mental health program for teens. It uses targeted interventions for specific personality traits to promote mental wellness and delay substance use (Conrod, Castellanos-Ryan, & Strang, 2010). This program works by teaching teens effective coping skills, long term goal setting, and how to use their personality strengths to achieve their goals. The program also teaches participants how to manage their personality traits that can increase their risk of substance use problems. PreVenture has been shown to be effective in reducing and preventing mental illness and SUDs across the world including Canada (Conrod et al., 2013), the Netherlands (Lammers et al., 2017), Australia (Newton et al., 2019) and the U.K. (Musiat et al., 2014).

"The Good Behavior Game" was developed to help teachers manage children's behavior in the classroom by providing positive reinforcement for appropriate behaviours. It has been shown to be an effective method for increasing task appropriate behaviour and decreasing disruptive behaviours in the classroom (Barrish, Saunders & Wolf, 1969; Harris & Sherman, 1973; Medland & Stachnik, 1972).

Adverse life experiences during childhood are common. The social and political changes that would be required to prevent these events are largely outside the scope of the present thesis, but much might be accomplished by providing support to troubled parents and families. If a childhood trauma occurs, interventions are available that can reduce the consequences. One example is Trauma-Focused Cognitive Behavioural Therapy (TF-CBT; Cohen et al., 2016; Ramirez de Arellano et al., 2014). This program's goals include educating the child and their

caregivers about trauma and helping them to process it, developing coping strategies and reducing the trauma related stress, and supporting the victim to develop a sense of safety and social skills. TF-CBT uses principles of cognitive behavioural therapy and exposure techniques to prevent and treat post-traumatic stress due to childhood trauma exposure, depressive symptoms, behavioural problems and caregiver difficulties. TF-CBT has been shown to be effective in numerous randomized-clinical trials and shows promise as an effective treatment for victims of childhood trauma (de Arellano et al., 2014; Goldbeck et al., 2016; Jensen et al., 2014; Konanur et al., 2015; Mannarino et al., 2012; Ramirez de Arellano et al., 2014; Webb, 2014).

Midbrain dopamine D2 autoreceptor availability: stable state or susceptible trait?

It is of interest to know whether midbrain dopamine autoreceptor levels, as measured with [^{18}F]fallypride, are a stable marker of psychopathology. To determine whether midbrain dopamine D2 autoreceptor levels are stable traits, participants need to be scanned at muliple time. Studies of this nature are currently sparsely available; however, two examples are Cropley et al. (2008) and Mukherjee et al. (2002). The authors of both studies investigated the test-retest variability of [^{18}F]fallypride in multiple brain regions including the substantia nigra by scanning participants at two time points (4 to 6 weeks apart). Both studies reported good test-retest reliability of [^{18}F]fallypride in the susbtantia nigra; 7.7% ± 2.0 in Cropley et al. and 10% in Mukherjee et al. The intraclass correlation coefficient (ICC) was 0.95, indicating excellent reliability (Cropley et al., 2008). Lastly, Mukherjee et al., also examined age related changes in midbrain [^{18}F]fallypride BP_{ND} values using a cross sectional design and reported a 10% decline per decade (Mukherjee et al., 2002). Given the insufficient data, it is difficult to conclude whether midbrain dopamine D2 autoreceptor are stable traits.

Some evidence suggests that midbrain [^{18}F]fallypride BP_{ND} values are responsive to acute drug ingestion but are relatively robust against stress. In the present study, participants were excluded if their urine drug test was positive for any substance, with the exception of tetrahydrocannabinol (THC). Five participants tested positive for THC, and there was no significant difference in the midbrain [^{18}F]fallypride BP_{ND} values between participants with and without positive urine tests for THC ($t(50) = -0.487$, $p = 0.628$). Therefore, it is unlikely that THC exposure altered midbrain dopamine D2 receptor levels in the participants during the PET scan. It is also improbable that midbrain dopamine D2 receptor levels in our participants were in response to acute drug exposure, as that was an exclusion criteria.

Next, it is plausible that our PET measure might have been affected by the psychological stress associated with undergoing a PET scan. Nagano-Saito et al. (2013) investigated whether psychological stress leads to changes in dopamine D2 receptor availability in humans using the Montreal Imaging Stress Task (MIST) and the radioligand [^{18}F]fallypride. It was found that psychological stress does alter mesocortical dopamine release as indicated by decreases in [^{18}F]fallypride binding values in the prefrontal cortex, but no significant changes were reported in the midbrain (Nagano-Saito et al., 2013). Similarly, Lataster et al. (2011) also reported that psychosocial stress induced changes in [^{18}F]fallypride binding in the prefrontal cortex but not in the midbrain. Given these findings, it is unlikely that PET scan related psychological stress altered midbrain [^{18}F]fallypride binding and therefore dopamine D2 receptor availability in our participants.

Strengths and Limitations

Strengths of this study include its longitudinal design which allowed researchers to get closer to establishing cause-effect relationships in humans ethically. Next, EXT trait scores were collected throughout childhood and adolescence, increasing our confidence in the derived score. This study also has a relatively large sample size for PET studies. However, the conclusions drawn from this study should be considered in light of its limitations.

To begin, this first test of the three-factor model needs to be replicated in larger samples that would allow greater statistical power to study the interactions among the predictor variables. Second, given that 22% of Canada's population is made up of visible minorities (Government of Canada, 2020) it will be important to test whether this model generalizes to more ethnically diverse samples. Third, the CTQ is a retrospective measure of early life adversity and it may be prone to recall bias (Lewinsohn & Rosenbaum, 1987; Sheikh, 2018). Therefore, having objective measures early life adversity such as official records, parent or teacher reports of adversity during childhood or prospectively measuring early life adversity, would be beneficial and this information can be used to investigate whether objective measures of early life adversity contribute to the model differently from CTQ scores. Given the recall bias that may be present when using retrospective measures, it is important to assess the correlation between prospective and retrospective measures of early life adversity.

Reuben et al. (2016) investigated this in addition to whether retrospective and prospectively measured early life adversity can predict health outcomes in adulthood. They found a moderate correlation ($r = 0.47$, $p < .001$) and fair association (weighted kappa = 0.31, 95% CI: 0.27 – 0.35) between their prospective and retrospective measures of ELA (consisting

of the CTQ and interviews). It was also found that retrospectively reported early life adversity had significant correlations with participants' subjective reports of their mental health outcomes, but not objectively measured health outcomes such as working memory and physiological markers of health (e.g. triglyceride levels, blood pressure, waist circumference). Moreover, participants with agreeable personalities under reported their early life adversities while participants scoring high on neuroticism over reported early life adversities. The authors concluded that using retrospective measures of early life adversity are warranted and have good predictive power for psychopathologies, but this does not imply a causal relationship between early life adversity and psychopathology in adulthood. Participants with poor mental health are more likely to report early life adversities, while mentally healthy participants under report their early life adversities. This suggests that subjective recall of early life adversity is a strong predictor of adult psychopathology (Reuben et al., 2016).

Next, a review by Hardt and Rutter (2004) concluded that retrospective reports of early life adversities underestimate their prevalence, based on the observation that 1/3 of people who have experienced early life adversities do not report so in adulthood. They also found that participants with poor mental health over-report the number of early life adversities they experienced. This recall bias, may exaggerate the differences between mentally healthy and non-healthy populations. The authors suggest that using retrospective measures of early life adversities is acceptable for very serious and operationalized adversities (Hardt & Rutter, 2004). Together, causal conclusions cannot be made about the association between early life adversity and psychiatric disorders, but a high CTQ score may be a good indicator of one's current mental health. Furthermore, in the present study, CTQ scores made only a modest contribution (ß = .80;

Wald = 3.48; p = .06) after being combined with midbrain [^{18}F]fallypride BP_{ND} values and EXT trait scores.

A similar issue arises with the EXT scores. That is, EXT scores in youth predicted EXT disorders in early adulthood. The adolescent EXT scores preceeded the EXT disorders, the bare minimum for demonstrating causation, but the earlier behaviors might be an early expression of the problem instead of a cause. In either case, there is value in the statistical prediction, and the combination of early life adversity, high EXT scores and low midbrain dopamine D2 receptor levels was a strong predictor of psychiatric problems.

Next, participants were not screened for personality disorders. This raises the possibility that our clinical assessments may have missed disorders that load heavily on EXT factors such as antisocial personality disorder. This noted, people diagnosed with severe personality disorders are at much elevated risk for other non-personality disorders (Crawford et al., 2008; Johnson et al., 1999; Kasen et al., 1999; Oldham et al., 1995; Pantoularis et al., 2008). This observation suggests that our participants would have a high probability of being identified as cases irrespective of whether their primary problem was or was not a personality disorder. This said, we cannot rule out the possibility that some "cases" were missed.

Sixth, a large body of literature suggests that prenatal maternal stress affects psychiatric outcomes in offspring (Glover et al., 2018; Huizink & Rooij, 2018; St-Hilaire et al., 2015; Ward, 1991; Yong Ping et al., 2020). Unfortunately, the present study did not examine the effects of prenatal stress in psychiatric outcomes. Seventh, not all follow-up interviews were conducted in-person, potentially diminishing the quality of the diagnoses obtained. Finally, [^{18}F]fallypride binds to both D2 and D3 receptors. Although it binds preferentially to D2 receptors (Mukherjee

et al., 1999), we cannot conclude unequivocally that the effect was driven by D2 instead of D3 receptor levels.

Practical applications and future directions

If replicated, the present study's findings can be used to prospectively identify at-risk youth. These findings may also contribute toward the development of early interventions and treatments such as behavioural therapy to decrease externalizing behaviours. This work supports a dimensional based psychiatric nosology and provides insight on which variables might contribute to the hypothesized overarching p factor. In comparison, evidence was not found either supporting or rejecting the concept of hierarchical factors contributing to successively more specific mental health problems. This will require additional work. Future studies should aim also to develop a questionnaire to measure EXT traits efficiently in a clinical setting. In the present study, EXT traits were measured using subscales from various questionnaires and they were completed by the participants themselves, as well as their parents and teachers. This gives a complete and thorough assessment, however, it is less practical to administer in a clinical setting as it is time consuming and clinicians don't always have access to the patients' caregivers or teachers. Additionally, our measures of EXT traits were taken over seven years (ages 10 to 16) and participants' EXT trait scores were created using a minimum of two years' data; however, is not possible to obtain this information during a single clinic visit. It would be clinically useful if a single standardized questionnaire to measure EXT traits can be developed. This would allow clinicians to accurately and quickly assess patients' EXT traits. If this EXT questionnaire can be developed and validated, then the CTQ and an EXT questionnaire may be used as screening tools to help clinicians identify youth at high risk of developing psychiatric disorders.

Next, given that the three-factor model's predictive ability is not limited to EXT disorders but extends to internalizing disorders, it will be important to determine whether this reflects a contribution of internalizing features that covary with EXT features. Finally, PET scans are both expensive and time consuming, and are not practically feasible to administer as a screening tool. Therefore, it will be important to either develop alternative imaging methods or a non-imaging method that can substitute for the PET measure, at least with respect to statistical prediction of the outcome measure.

Conclusion

This study provides the first evidence that the combination of EXT traits, early life adversity and poor mesolimbic dopamine autoregulation can identify youth with a lifetime history of psychiatric illness as well as youth at risk for developing psychiatric disorders. The three variables constituting the three-factor model are transdiagnostic risk factors for commonly comorbid early-onset psychiatric disorders. Efforts to target these transdiagnostic risk factors are warranted and could benefit society as a whole.

References

American Psychiatric Association, & American Psychiatric Association (Eds.). (2013). *Diagnostic and statistical manual of mental disorders: DSM-5* (5th ed). American Psychiatric Association.

Amstadter, A. B., Maes, H. H., Sheerin, C. M., Myers, J. M., & Kendler, K. S. (2016). The relationship between genetic and environmental influences on resilience and on common internalizing and externalizing psychiatric disorders. *Social Psychiatry and Psychiatric Epidemiology*, *51*(5), 669–678. https://doi.org/10.1007/s00127-015-1163-6

Antonelli, F., & Strafella, A. P. (2014). Behavioral disorders in Parkinson's disease: The role of dopamine. *Parkinsonism & Related Disorders*, *20*, S10–S12. https://doi.org/10.1016/S1353-8020(13)70005-1

Arnsten, A. F. T., Vijayraghavan, S., Wang, M., Gamo, N. J., & Paspalas, C. D. (2009). Dopamine's Influence on Prefrontal Cortical Cognition: Actions and Circuits in Behaving Primates. In L. Iversen, S. Iversen, S. Dunnett, & A. Bjorklund (Eds.), *Dopamine Handbook* (pp. 230–248). Oxford University Press. https://doi.org/10.1093/acprof:oso/9780195373035.003.0016

Ashok, A. H., Marques, T. R., Jauhar, S., Nour, M. M., Goodwin, G. M., Young, A. H., & Howes, O. D. (2017). The dopamine hypothesis of bipolar affective disorder: The state of the art and implications for treatment. *Molecular Psychiatry*, *22*(5), 666–679. https://doi.org/10.1038/mp.2017.16

Asselmann, E., Wittchen, H.-U., Lieb, R., & Beesdo-Baum, K. (2017). A 10-year prospective-longitudinal study of daily hassles and incident psychopathology among adolescents and young adults: Interactions with gender, perceived coping efficacy, and negative life

events. *Social Psychiatry and Psychiatric Epidemiology*, *52*(11), 1353–1362. https://doi.org/10.1007/s00127-017-1436-3

Behar, L., & Stringfield, S. (1974). A behavior rating scale for the preschool child. *Developmental Psychology*, *10*(5), 601–610. https://doi.org/10.1037/h0037058

Bellés, L., Dimiziani, A., Tsartsalis, S., Millet, P., Herrmann, F. R., & Ginovart, N. (2020). Dopamine D2/3 Receptor Availabilities and Evoked Dopamine Release in Striatum Differentially Predict Impulsivity and Novelty Preference in Roman High- and Low-Avoidance Rats. *International Journal of Neuropsychopharmacology*, pyaa084. https://doi.org/10.1093/ijnp/pyaa084

Bellis, M. A., Hughes, K., Ford, K., Ramos Rodriguez, G., Sethi, D., & Passmore, J. (2019). Life course health consequences and associated annual costs of adverse childhood experiences across Europe and North America: A systematic review and meta-analysis. *The Lancet Public Health*, *4*(10), e517–e528. https://doi.org/10.1016/S2468-2667(19)30145-8

Bello, E. P., Mateo, Y., Gelman, D. M., Noaín, D., Shin, J. H., Low, M. J., Alvarez, V. A., Lovinger, D. M., & Rubinstein, M. (2011). Cocaine supersensitivity and enhanced motivation for reward in mice lacking dopamine D2 autoreceptors. *Nature Neuroscience*, *14*(8), 1033–1038. https://doi.org/10.1038/nn.2862

Belsky, J. (1997). Variation in Susceptibility to Environmental Influence: An Evolutionary Argument. *Psychological Inquiry*, *8*(3), 182–186. https://doi.org/10.1207/s15327965pli0803_3

Belsky, J., & Pluess, M. (2009). Beyond diathesis stress: Differential susceptibility to environmental influences. *Psychological Bulletin*, *135*(6), 885–908. https://doi.org/10.1037/a0017376

Berger, A. (2003). Positron emission tomography. *BMJ : British Medical Journal*, *326*(7404), 1449. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1126321/

Bernstein, D. P., & Fink, L. (1998). *Childhood trauma questionnaire: A retrospective self-report : manual*. Harcourt Brace & Co.

Berridge, K. C., & Robinson, T. E. (1998). What is the role of dopamine in reward: Hedonic impact, reward learning, or incentive salience? *Brain Research. Brain Research Reviews*, *28*(3), 309–369. https://doi.org/10.1016/s0165-0173(98)00019-8

Berridge, K. C., & Robinson, T. E. (2003). Parsing reward. *Trends in Neurosciences*, *26*(9), 507–513. https://doi.org/10.1016/S0166-2236(03)00233-9

Bjork, J. M., & Pardini, D. A. (2015). Who are those "risk-taking adolescents"? Individual differences in developmental neuroimaging research. *Developmental Cognitive Neuroscience*, *11*, 56–64. https://doi.org/10.1016/j.dcn.2014.07.008

Blaess, S., Stott, S. R. W., & Ang, S.-L. (2020). Chapter 17—The generation of midbrain dopaminergic neurons. In J. Rubenstein, P. Rakic, B. Chen, & K. Y. Kwan (Eds.), *Patterning and Cell Type Specification in the Developing CNS and PNS (Second Edition)* (pp. 369–398). Academic Press. https://doi.org/10.1016/B978-0-12-814405-3.00017-5

Boecker, R., Holz, N. E., Buchmann, A. F., Blomeyer, D., Plichta, M. M., Wolf, I., Baumeister, S., Meyer-Lindenberg, A., Banaschewski, T., Brandeis, D., & Laucht, M. (2014). Impact of Early Life Adversity on Reward Processing in Young Adults: EEG-fMRI Results from a Prospective Study over 25 Years. *PLOS ONE*, *9*(8), e104185. https://doi.org/10.1371/journal.pone.0104185

Boivin, M., Brendgen, M., Dionne, G., Dubois, L., Pérusse, D., Robaey, P., Tremblay, R. E., & Vitaro, F. (2013). The Quebec Newborn Twin Study Into Adolescence: 15 Years Later. *Twin Research and Human Genetics*, *16*(1), 64–69. https://doi.org/10.1017/thg.2012.129

Bolton, J. L., Molet, J., Regev, L., Chen, Y., Rismanchi, N., Haddad, E., Yang, D. Z., Obenaus, A., & Baram, T. Z. (2018). Anhedonia Following Early-Life Adversity Involves Aberrant Interaction of Reward and Anxiety Circuits and Is Reversed by Partial Silencing of Amygdala Corticotropin-Releasing Hormone Gene. *Biological Psychiatry*, *83*(2), 137–147. https://doi.org/10.1016/j.biopsych.2017.08.023

Booij, L., Welfeld, K., Leyton, M., Dagher, A., Boileau, I., Sibon, I., Baker, G. B., Diksic, M., Soucy, J.-P., Pruessner, J. C., Cawley-Fiset, E., Casey, K. F., & Benkelfat, C. (2016). Dopamine cross-sensitization between psychostimulant drugs and stress in healthy male volunteers. *Translational Psychiatry*, *6*(2), e740–e740. https://doi.org/10.1038/tp.2016.6

Box, G. E. P., & Tidwell, P. W. (1962). Transformation of the Independent Variables. *Technometrics*, *4*(4), 531–550. https://doi.org/10.1080/00401706.1962.10490038

Boyce, W. T., & Ellis, B. J. (2005). Biological sensitivity to context: I. An evolutionary–developmental theory of the origins and functions of stress reactivity. *Development and Psychopathology*, *17*(2), 271–301. https://doi.org/10.1017/S0954579405050145

Brauer, L. H., & De Wit, H. (1997). High dose pimozide does not block amphetamine-induced euphoria in normal volunteers. *Pharmacology, Biochemistry, and Behavior*, *56*(2), 265–272. https://doi.org/10.1016/s0091-3057(96)00240-7

Brenhouse, H. C., Lukkes, J. L., & Andersen, S. L. (2013). Early Life Adversity Alters the Developmental Profiles of Addiction-Related Prefrontal Cortex Circuitry. *Brain Sciences*, *3*(1), 143–158. https://doi.org/10.3390/brainsci3010143

Buckholtz, J. W., Treadway, M. T., Cowan, R. L., Woodward, N. D., Benning, S. D., Li, R., Ansari, M. S., Baldwin, R. M., Schwartzman, A. N., Shelby, E. S., Smith, C. E., Cole, D., Kessler, R. M., & Zald, D. H. (2010). Mesolimbic dopamine reward system hypersensitivity in individuals with psychopathic traits. *Nature Neuroscience*, *13*(4), 419–421. https://doi.org/10.1038/nn.2510

Buckholtz, J. W., Treadway, M. T., Cowan, R. L., Woodward, N. D., Li, R., Ansari, M. S., Baldwin, R. M., Schwartzman, A. N., Shelby, E. S., Smith, C. E., Kessler, R. M., & Zald, D. H. (2010). Dopaminergic Network Differences in Human Impulsivity. *Science*, *329*(5991), 532–532. https://doi.org/10.1126/science.1185778

Byrd, A. L., Loeber, R., & Pardini, D. A. (2014). Antisocial behavior, psychopathic features and abnormalities in reward and punishment processing in youth. *Clinical Child and Family Psychology Review*, *17*(2), 125–156. https://doi.org/10.1007/s10567-013-0159-6

Campbell, S. B., Shaw, D. S., & Gilliom, M. (2000). Early externalizing behavior problems: Toddlers and preschoolers at risk for later maladjustment. *Development and Psychopathology*, *12*(3), 467–488. https://doi.org/10.1017/s0954579400003114

Caspi, A., Houts, R. M., Belsky, D. W., Goldman-Mellor, S. J., Harrington, H., Israel, S., Meier, M. H., Ramrakha, S., Shalev, I., Poulton, R., & Moffitt, T. E. (2014). The p Factor: One General Psychopathology Factor in the Structure of Psychiatric Disorders? *Clinical Psychological Science : A Journal of the Association for Psychological Science*, *2*(2), 119–137. PubMed. https://doi.org/10.1177/2167702613497473

Caspi, A., & Moffitt, T. E. (2018). All for One and One for All: Mental Disorders in One Dimension. *American Journal of Psychiatry*, *175*(9), 831–844. https://doi.org/10.1176/appi.ajp.2018.17121383

Castellanos-Ryan, N., Brière, F. N., O'Leary-Barrett, M., Banaschewski, T., Bokde, A., Bromberg, U., Büchel, C., Flor, H., Frouin, V., Gallinat, J., Garavan, H., Martinot, J.-L., Nees, F., Paus, T., Pausova, Z., Rietschel, M., Smolka, M. N., Robbins, T. W., Whelan, R., … The IMAGEN Consortium. (2016). The structure of psychopathology in adolescence and its common personality and cognitive correlates. *Journal of Abnormal Psychology*, *125*(8), 1039–1052. https://doi.org/10.1037/abn0000193

Cawley, E. I., Park, S., Rot, M. aan het, Sancton, K., Benkelfat, C., Young, S. N., Boivin, D. B., & Leyton, M. (2013). Dopamine and light: Dissecting effects on mood and motivational states in women with subsyndromal seasonal affective disorder. *Journal of Psychiatry & Neuroscience : JPN*, *38*(6), 388–397. https://doi.org/10.1503/jpn.120181

Chaudhury, D., Walsh, J. J., Friedman, A. K., Juarez, B., Ku, S. M., Koo, J. W., Ferguson, D., Tsai, H.-C., Pomeranz, L., Christoffel, D. J., Nectow, A. R., Ekstrand, M., Domingos, A., Mazei-Robison, M. S., Mouzon, E., Lobo, M. K., Neve, R. L., Friedman, J. M., Russo, S. J., … Han, M.-H. (2013). Rapid regulation of depression-related behaviours by control of midbrain dopamine neurons. *Nature*, *493*(7433), 532–536. https://doi.org/10.1038/nature11713

Chen, R., Ferris, M. J., & Wang, S. (2020). Dopamine D2 autoreceptor interactome: Targeting the receptor complex as a strategy for treatment of substance use disorder. *Pharmacology & Therapeutics*, *213*, 107583. https://doi.org/10.1016/j.pharmthera.2020.107583

Cheng, P. W. C., Chang, W. C., Lo, G. G., Chan, K. W. S., Lee, H. M. E., Hui, L. M. C., Suen, Y. N., Leung, Y. L. E., Au Yeung, K. M. P., Chen, S., Mak, K. F. H., Sham, P. C., Santangelo, B., Veronese, M., Ho, C.-L., Chen, Y. H. E., & Howes, O. D. (2020). The role of dopamine dysregulation and evidence for the transdiagnostic nature of elevated

dopamine synthesis in psychosis: A positron emission tomography (PET) study comparing schizophrenia, delusional disorder, and other psychotic disorders. *Neuropsychopharmacology*, *45*(11), 1870–1876. https://doi.org/10.1038/s41386-020-0740-x

Cherkasova, M. V., Faridi, N., Casey, K. F., O'Driscoll, G. A., Hechtman, L., Joober, R., Baker, G. B., Palmer, J., Dagher, A., Leyton, M., & Benkelfat, C. (2014). Amphetamine-Induced Dopamine Release and Neurocognitive Function in Treatment-Naive Adults with ADHD. *Neuropsychopharmacology*, *39*(6), 1498–1507. https://doi.org/10.1038/npp.2013.349

Cohen, J. A., Mannarino, A. P., & Deblinger, E. (2016). *Treating trauma and traumatic grief in children and adolescents*. Guilford Publications.

Cooper, J. R., Bloom, F. E., & Roth, R. H. (2003). *The biochemical basis of neuropharmacology* (8th ed). Oxford University Press.

Copeland, W. E., Shanahan, L., Hinesley, J., Chan, R. F., Aberg, K. A., Fairbank, J. A., van den Oord, E. J. C. G., & Costello, E. J. (2018). Association of Childhood Trauma Exposure With Adult Psychiatric Disorders and Functional Outcomes. *JAMA Network Open*, *1*(7), e184493. https://doi.org/10.1001/jamanetworkopen.2018.4493

Cox, S. M. L., Castellanos-Ryan, N., Parent, S., Benkelfat, C., Vitaro, F., Pihl, R. O., Boivin, M., Tremblay, R. E., Leyton, M., & Séguin, J. R. (2021). Externalizing Risk Pathways for Adolescent Substance Use and Its Developmental Onset: A Canadian Birth Cohort Study. *The Canadian Journal of Psychiatry*, 070674372098242. https://doi.org/10.1177/0706743720982429

Crawford, T. N., Cohen, P., First, M. B., Skodol, A. E., Johnson, J. G., & Kasen, S. (2008). Comorbid Axis I and Axis II Disorders in Early Adolescence: Outcomes 20 Years Later.

Archives of General Psychiatry, *65*(6), 641–648. https://doi.org/10.1001/archpsyc.65.6.641

Cropley, V. L., Innis, R. B., Nathan, P. J., Brown, A. K., Sangare, J. L., Lerner, A., Ryu, Y. H., Sprague, K. E., Pike, V. W., & Fujita, M. (2008). Small effect of dopamine release and no effect of dopamine depletion on [18F]fallypride binding in healthy humans. *Synapse*, *62*(6), 399–408. https://doi.org/10.1002/syn.20506

da Silva, J. A., Tecuapetla, F., Paixão, V., & Costa, R. M. (2018). Dopamine neuron activity before action initiation gates and invigorates future movements. *Nature*, *554*(7691), 244–248. https://doi.org/10.1038/nature25457

Dalley, J. W., & Robbins, T. W. (2017). Fractionating impulsivity: Neuropsychiatric implications. *Nature Reviews Neuroscience*, *18*(3), 158–171. https://doi.org/10.1038/nrn.2017.8

D'Amour-Horvat, V., & Leyton, M. (2014). Impulsive actions and choices in laboratory animals and humans: Effects of high vs. low dopamine states produced by systemic treatments given to neurologically intact subjects. *Frontiers in Behavioral Neuroscience*, *8*. https://doi.org/10.3389/fnbeh.2014.00432

de Arellano, M. A. R., Lyman, D. R., Jobe-Shields, L., George, P., Dougherty, R. H., Daniels, A. S., Ghose, S. S., Huang, L., & Delphin-Rittmon, M. E. (2014). Trauma-focused cognitive-behavioral therapy for children and adolescents: Assessing the evidence. *Psychiatric Services (Washington, D.C.)*, *65*(5), 591–602. https://doi.org/10.1176/appi.ps.201300255

de Beaurepaire, R. (1991). The Dopamine System and Mental Disorders: Clinical and Psychopharmacological Overview. In J. C. Baron, D. Comar, L. Farde, J. L. Martinot, &

B. Mazoyer (Eds.), *Brain Dopaminergic Systems: Imaging with Positron Tomography: Proceedings of a Workshop held in Caen, France within the framework of the European Community Medical and Public Health Research* (pp. 147–167). Springer Netherlands. https://doi.org/10.1007/978-94-011-3528-3_12

Dennison, M. J., Rosen, M. L., Sambrook, K. A., Jenness, J. L., Sheridan, M. A., & McLaughlin, K. A. (2019). Differential Associations of Distinct Forms of Childhood Adversity With Neurobehavioral Measures of Reward Processing: A Developmental Pathway to Depression. *Child Development*, *90*(1), e96–e113. https://doi.org/10.1111/cdev.13011

Dubol, M., Trichard, C., Leroy, C., Granger, B., Tzavara, E. T., Martinot, J.-L., & Artiges, E. (2020). Lower midbrain dopamine transporter availability in depressed patients: Report from high-resolution PET imaging. *Journal of Affective Disorders*, *262*, 273–277. https://doi.org/10.1016/j.jad.2019.10.041

Duvarci, S., Simpson, E. H., Schneider, G., Kandel, E. R., Roeper, J., & Sigurdsson, T. (2018). Impaired recruitment of dopamine neurons during working memory in mice with striatal D2 receptor overexpression. *Nature Communications*, *9*(1), 2822. https://doi.org/10.1038/s41467-018-05214-4

Eaton, N. R., Krueger, R. F., Keyes, K. M., Skodol, A. E., Markon, K. E., Grant, B. F., & Hasin, D. S. (2011). Borderline personality disorder co-morbidity: Relationship to the internalizing–externalizing structure of common mental disorders. *Psychological Medicine*, *41*(5), 1041–1050. https://doi.org/10.1017/S0033291710001662

Ellis, B. J., Boyce, W. T., Belsky, J., Bakermans-Kranenburg, M. J., & Ijzendoorn, M. H. van. (2011). Differential susceptibility to the environment: An evolutionary–

neurodevelopmental theory. *Development and Psychopathology*, *23*(1), 7–28. https://doi.org/10.1017/S0954579410000611

Externalization – APA Dictionary of Psychology. (n.d.). Retrieved September 15, 2021, from https://dictionary.apa.org/externalization

Fiorillo, C. D., Tobler, P. N., & Schultz, W. (2003). Discrete coding of reward probability and uncertainty by dopamine neurons. *Science (New York, N.Y.)*, *299*(5614), 1898–1902. https://doi.org/10.1126/science.1077349

Flagel, S. B., Clark, J. J., Robinson, T. E., Mayo, L., Czuj, A., Willuhn, I., Akers, C. A., Clinton, S. M., Phillips, P. E. M., & Akil, H. (2011). A selective role for dopamine in reward learning. *Nature*, *469*(7328), 53–57. https://doi.org/10.1038/nature09588

Floresco, S. B., & Magyar, O. (2006). Mesocortical dopamine modulation of executive functions: Beyond working memory. *Psychopharmacology*, *188*(4), 567–585. https://doi.org/10.1007/s00213-006-0404-5

Ford, C. P. (2014). The role of D2-autoreceptors in regulating dopamine neuron activity and transmission. *Neuroscience*, *282*, 13–22. https://doi.org/10.1016/j.neuroscience.2014.01.025

Foster, K. T., Hicks, B. M., & Zucker, R. A. (2018). Positive and negative effects of internalizing on alcohol use problems from childhood to young adulthood: The mediating and suppressing role of externalizing. *Journal of Abnormal Psychology*, *127*(4), 394–403. https://doi.org/10.1037/abn0000337

Galloway, M. P., Wolf, M. E., & Roth, R. H. (1986). Regulation of dopamine synthesis in the medial prefrontal cortex is mediated by release modulating autoreceptors: Studies in vivo. *The Journal of Pharmacology and Experimental Therapeutics*, *236*(3), 689–698.

Gater, R., Tansella, M., Korten, A., Tiemens, B. G., Mavreas, V. G., & Olatawura, M. O. (1998). Sex differences in the prevalence and detection of depressive and anxiety disorders in general health care settings: Report from the world health organization collaborative study on psychological problems in general health care. *Archives of General Psychiatry*, *55*(5), 405–413. Scopus. https://doi.org/10.1001/archpsyc.55.5.405

Gender and women's mental health. (n.d.). Retrieved October 22, 2021, from https://www.who.int/teams/control-of-neglected-tropical-diseases/yaws/diagnosis-and-treatment/mental-health-and-substances-use

Glasofer, D. R., Brown, A. J., & Riegel, M. (2015). Structured Clinical Interview for DSM-IV (SCID). In T. Wade (Ed.), *Encyclopedia of Feeding and Eating Disorders* (pp. 1–4). Springer Singapore. https://doi.org/10.1007/978-981-287-087-2_80-1

Glover, V., O'Donnell, K. J., O'Connor, T. G., & Fisher, J. (2018). Prenatal maternal stress, fetal programming, and mechanisms underlying later psychopathology—A global perspective. *Development and Psychopathology*, *30*(3), 843–854. https://doi.org/10.1017/S095457941800038X

Goldbeck, L., Muche, R., Sachser, C., Tutus, D., & Rosner, R. (2016). Effectiveness of Trauma-Focused Cognitive Behavioral Therapy for Children and Adolescents: A Randomized Controlled Trial in Eight German Mental Health Clinics. *Psychotherapy and Psychosomatics*, *85*(3), 159–170. https://doi.org/10.1159/000442824

Goltermann, J., Redlich, R., Grotegerd, D., Dohm, K., Leehr, E. J., Böhnlein, J., Förster, K., Meinert, S., Enneking, V., Richter, M., Repple, J., DeVillers, I., Kloecker, M., Jansen, A., Krug, A., Nenadić, I., Brosch, K., Meller, T., Stein, F., … Dannlowski, U. (2020). Childhood maltreatment and cognitive functioning: The role of depression, parental

education, and polygenic predisposition. *Neuropsychopharmacology*. https://doi.org/10.1038/s41386-020-00794-6

Government of Canada, S. C. (2020, July 17). *Updated content for the 2021 Census of Population: Immigration, ethnocultural diversity and languages in Canada*. https://www12.statcan.gc.ca/census-recensement/2021/ref/98-20-0001/982000012020002-eng.cfm

Grace, A. A. (2016). Dysregulation of the dopamine system in the pathophysiology of schizophrenia and depression. *Nature Reviews Neuroscience*, *17*(8), 524–532. https://doi.org/10.1038/nrn.2016.57

Graybiel, A. M., Aosaki, T., Flaherty, A. W., & Kimura, M. (1994). The Basal Ganglia and Adaptive Motor Control. *Science*, *265*(5180), 1826–1831. https://doi.org/10.1126/science.8091209

Guo, Q., Owen, D. R., Rabiner, E. A., Turkheimer, F. E., & Gunn, R. N. (2014). A Graphical Method to Compare the *in vivo* Binding Potential of PET Radioligands in the Absence of a Reference Region: Application to [^{11} C]PBR28 and [^{18} F]PBR111 for TSPO Imaging. *Journal of Cerebral Blood Flow & Metabolism*, *34*(7), 1162–1168. https://doi.org/10.1038/jcbfm.2014.65

Hamilton, J. P., Sacchet, M. D., Hjørnevik, T., Chin, F. T., Shen, B., Kämpe, R., Park, J. H., Knutson, B. D., Williams, L. M., Borg, N., Zaharchuk, G., Camacho, M. C., Mackey, S., Heilig, M., Drevets, W. C., Glover, G. H., Gambhir, S. S., & Gotlib, I. H. (2018). Striatal dopamine deficits predict reductions in striatal functional connectivity in major depression: A concurrent 11C-raclopride positron emission tomography and functional

magnetic resonance imaging investigation. *Translational Psychiatry*, *8*(1), 1–10. https://doi.org/10.1038/s41398-018-0316-2

Hardt, J., & Rutter, M. (2004). Validity of adult retrospective reports of adverse childhood experiences: Review of the evidence. *Journal of Child Psychology and Psychiatry*, *45*(2), 260–273. https://doi.org/10.1111/j.1469-7610.2004.00218.x

Harrow, M., Green, K. E., Sands, J. R., Jobe, T. H., Goldberg, J. F., Kaplan, K. J., & Martin, E. M. (2000). Thought Disorder in Schizophrenia and Mania: Impaired Context. *Schizophrenia Bulletin*, *26*(4), 879–891. https://doi.org/10.1093/oxfordjournals.schbul.a033502

Heymann, G., Jo, Y. S., Reichard, K. L., McFarland, N., Chavkin, C., Palmiter, R. D., Soden, M. E., & Zweifel, L. S. (2020). Synergy of Distinct Dopamine Projection Populations in Behavioral Reinforcement. *Neuron*, *105*(5), 909–920. https://doi.org/10.1016/j.neuron.2019.11.024

Hoffmann, I. S., Talmaciu, R. K., Ferro, C. P., & Cubeddu, L. X. (1988). Sustained high release at rapid stimulation rates and reduced functional autoreceptors characterize prefrontal cortex dopamine terminals. *The Journal of Pharmacology and Experimental Therapeutics*, *245*(3), 761–772.

Holloway, Z. R., Freels, T. G., Comstock, J. F., Nolen, H. G., Sable, H. J., & Lester, D. B. (2019). Comparing phasic dopamine dynamics in the striatum, nucleus accumbens, amygdala, and medial prefrontal cortex. *Synapse*, *73*(2), e22074. https://doi.org/10.1002/syn.22074

Holroyd, K. B., Adrover, M. F., Fuino, R. L., Bock, R., Kaplan, A. R., Gremel, C. M., Rubinstein, M., & Alvarez, V. A. (2015). Loss of Feedback Inhibition via D2

Autoreceptors Enhances Acquisition of Cocaine Taking and Reactivity to Drug-Paired Cues. *Neuropsychopharmacology*, *40*(6), 1495–1509. https://doi.org/10.1038/npp.2014.336

Hosmer, D. W., Lemeshow, S., & Sturdivant, R. X. (2013). *Applied logistic regression* (Third edition). Wiley.

Hu, H. (2016). Reward and Aversion. *Annual Review of Neuroscience*, *39*(1), 297–324. https://doi.org/10.1146/annurev-neuro-070815-014106

Huizink, A. C., & Rooij, S. R. de. (2018). Prenatal stress and models explaining risk for psychopathology revisited: Generic vulnerability and divergent pathways. *Development and Psychopathology*, *30*(3), 1041–1062. https://doi.org/10.1017/S0954579418000354

Initial reliability and validity of a new retrospective measure of child abuse and neglect. (1994). *American Journal of Psychiatry*, *151*(8), 1132–1136. https://doi.org/10.1176/ajp.151.8.1132

Investing_in_Mental_Health_FINAL_Version_ENG.pdf. (n.d.). Retrieved January 18, 2022, from https://www.mentalhealthcommission.ca/wp-content/uploads/drupal/2016-06/Investing_in_Mental_Health_FINAL_Version_ENG.pdf

Jaekel, J., Sorg, C., Breeman, L., Baumann, N., Bilgin, A., Bäuml, J. G., & Wolke, D. (2020). Early regulatory problems and parenting: Life-long risk, vulnerability or susceptibility for attention, internalizing and externalizing outcomes? *European Child & Adolescent Psychiatry*. https://doi.org/10.1007/s00787-020-01632-2

Jaworska, N., Cox, S. M. L., Tippler, M., Castellanos-Ryan, N., Benkelfat, C., Parent, S., Dagher, A., Vitaro, F., Boivin, M., Pihl, R. O., Côté, S. M., Tremblay, R. E., Séguin, J. R., & Leyton, M. (2020). Extra-striatal D2/3 receptor availability in youth at risk for

addiction. *Neuropsychopharmacology*, *45*(9), 1498–1505. https://doi.org/10.1038/s41386-020-0662-7

Jensen, T. K., Holt, T., Ormhaug, S. M., Egeland, K., Granly, L., Hoaas, L. C., Hukkelberg, S. S., Indregard, T., Stormyren, S. D., & Wentzel-Larsen, T. (2014). A Randomized Effectiveness Study Comparing Trauma-Focused Cognitive Behavioral Therapy With Therapy as Usual for Youth. *Journal of Clinical Child & Adolescent Psychology*, *43*(3), 356–369. https://doi.org/10.1080/15374416.2013.822307

Jentsch, J. D., Roth, R. H., & Taylor, J. R. (2000). Role for dopamine in the behavioral functions of the prefrontal corticostriatal system: Implications for mental disorders and psychotropic drug action. *Progress in Brain Research*, *126*, 433–453. https://doi.org/10.1016/S0079-6123(00)26028-7

Johnson, J. G., Cohen, P., Skodol, A. E., Oldham, J. M., Kasen, S., & Brook, J. S. (1999). Personality Disorders in Adolescence and Risk of Major Mental Disorders and Suicidality During Adulthood. *Archives of General Psychiatry*, *56*(9), 805–811. https://doi.org/10.1001/archpsyc.56.9.805

Juárez Olguín, H., Calderón Guzmán, D., Hernández García, E., & Barragán Mejía, G. (2016). The Role of Dopamine and Its Dysfunction as a Consequence of Oxidative Stress. *Oxidative Medicine and Cellular Longevity*, *2016*, 9730467. https://doi.org/10.1155/2016/9730467

Kapur, S., Phillips, A. G., & Insel, T. R. (2012). Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? *Molecular Psychiatry*, *17*(12), 1174–1179. https://doi.org/10.1038/mp.2012.105

Kasa, K., Otsuki, S., Yamamoto, M., Sato, M., Kuroda, H., & Ogawa, N. (1982). Cerebrospinal fluid gamma-aminobutyric acid and homovanillic acid in depressive disorders. *Biological Psychiatry*, *17*(8), 877–883.

Kasen, S., Cohen, P., Skodol, A. E., Johnson, J. G., & Brook, J. S. (1999). Influence of Child and Adolescent Psychiatric Disorders on Young Adult Personality Disorder. *American Journal of Psychiatry*, *156*(10), 1529–1535. https://doi.org/10.1176/ajp.156.10.1529

Kauten, R., & Barry, C. T. (2020). Externalizing Behavior. In V. Zeigler-Hill & T. K. Shackelford (Eds.), *Encyclopedia of Personality and Individual Differences* (pp. 1509–1512). Springer International Publishing. https://doi.org/10.1007/978-3-319-24612-3_894

Kendler, K. S., Ohlsson, H., Edwards, A. C., Sundquist, J., & Sundquist, K. (2016). A developmental model for alcohol use disorders in Swedish men. *Psychological Medicine*, *46*(13), 2759–2770. https://doi.org/10.1017/S0033291716001409

Kendler, K. S., Prescott, C. A., Myers, J., & Neale, M. C. (2003). The Structure of Genetic and Environmental Risk Factors for Common Psychiatric and Substance Use Disorders in Men and Women. *Archives of General Psychiatry*, *60*(9), 929–937. https://doi.org/10.1001/archpsyc.60.9.929

Kessler, R. C., McGonagle, K. A., Zhao, S., Nelson, C. B., Hughes, M., Eshleman, S., Wittchen, H.-U., & Kendler, K. S. (1994). Lifetime and 12-Month Prevalence of DSM-III-R Psychiatric Disorders in the United States: Results From the National Comorbidity Survey. *Archives of General Psychiatry*, *51*(1), 8–19. https://doi.org/10.1001/archpsyc.1994.03950010008002

Kessler, R. C., Sonnega, A., Bromet, E., Hughes, M., & Nelson, C. B. (1995). Posttraumatic Stress Disorder in the National Comorbidity Survey. *Archives of General Psychiatry*, *52*(12), 1048–1060. https://doi.org/10.1001/archpsyc.1995.03950240066012

Keyes, K. M., Eaton, N. R., Krueger, R. F., McLaughlin, K. A., Wall, M. M., Grant, B. F., & Hasin, D. S. (2012). Childhood maltreatment and the structure of common psychiatric disorders. *British Journal of Psychiatry*, *200*(2), 107–115. https://doi.org/10.1192/bjp.bp.111.093062

Konanur, S., Muller, R. T., Cinamon, J. S., Thornback, K., & Zorzella, K. P. M. (2015). Effectiveness of Trauma-Focused Cognitive Behavioral Therapy in a community-based program. *Child Abuse & Neglect*, *50*, 159–170. https://doi.org/10.1016/j.chiabu.2015.07.013

Korchounov, A., Meyer, M. F., & Krasnianski, M. (2010). Postsynaptic nigrostriatal dopamine receptors and their role in movement regulation. *Journal of Neural Transmission*, *117*(12), 1359–1369. https://doi.org/10.1007/s00702-010-0454-z

Kotov, R., Krueger, R. F., & Watson, D. (2018). A paradigm shift in psychiatric classification: The Hierarchical Taxonomy Of Psychopathology (HiTOP). *World Psychiatry*, *17*(1), 24–25. https://doi.org/10.1002/wps.20478

Kotov, R., Krueger, R. F., Watson, D., Achenbach, T. M., Althoff, R. R., Bagby, R. M., Brown, T. A., Carpenter, W. T., Caspi, A., Clark, L. A., Eaton, N. R., Forbes, M. K., Forbush, K. T., Goldberg, D., Hasin, D., Hyman, S. E., Ivanova, M. Y., Lynam, D. R., Markon, K., … Zimmerman, M. (2017). The Hierarchical Taxonomy of Psychopathology (HiTOP): A dimensional alternative to traditional nosologies. *Journal of Abnormal Psychology*, *126*(4), 454–477. https://doi.org/10.1037/abn0000258

Kotov, R., Krueger, R. F., Watson, D., Cicero, D. C., Conway, C. C., DeYoung, C. G., Eaton, N. R., Forbes, M. K., Hallquist, M. N., Latzman, R. D., Mullins-Sweatt, S. N., Ruggero, C. J., Simms, L. J., Waldman, I. D., Waszczuk, M. A., & Wright, A. G. C. (2021). The Hierarchical Taxonomy of Psychopathology (HiTOP): A Quantitative Nosology Based on Consensus of Evidence. *Annual Review of Clinical Psychology*, *17*(1), 83–108. https://doi.org/10.1146/annurev-clinpsy-081219-093304

Kotov, R., Ruggero, C. J., Krueger, R. F., Watson, D., Yuan, Q., & Zimmerman, M. (2011). New Dimensions in the Quantitative Classification of Mental Illness. *Archives of General Psychiatry*, *68*(10), 1003–1011. https://doi.org/10.1001/archgenpsychiatry.2011.107

Krueger, R. F. (1999). The Structure of Common Mental Disorders. *Archives of General Psychiatry*, *56*(10), 921. https://doi.org/10.1001/archpsyc.56.10.921

Krueger, R. F., Hobbs, K. A., Conway, C. C., Dick, D. M., Dretsch, M. N., Eaton, N. R., Forbes, M. K., Forbush, K. T., Keyes, K. M., Latzman, R. D., Michelini, G., Patrick, C. J., Sellbom, M., Slade, T., South, S. C., Sunderland, M., Tackett, J., Waldman, I., Waszczuk, M. A., … Workgroup, H. U. (2021). Validity and utility of Hierarchical Taxonomy of Psychopathology (HiTOP): II. Externalizing superspectrum. *World Psychiatry*, *20*(2), 171–193. https://doi.org/10.1002/wps.20844

Krueger, R. F., Kotov, R., Watson, D., Forbes, M. K., Eaton, N. R., Ruggero, C. J., Simms, L. J., Widiger, T. A., Achenbach, T. M., Bach, B., Bagby, R. M., Bornovalova, M. A., Carpenter, W. T., Chmielewski, M., Cicero, D. C., Clark, L. A., Conway, C., DeClercq, B., DeYoung, C. G., … Zimmermann, J. (2018). Progress in achieving quantitative classification of psychopathology. *World Psychiatry*, *17*(3), 282–293. https://doi.org/10.1002/wps.20566

Krueger, R. F., & Tackett, J. L. (2003). Personality and Psychopathology: Working Toward the Bigger Picture. *Journal of Personality Disorders*, *17*(2), 109–128. https://doi.org/10.1521/pedi.17.2.109.23986

Kulacaoglu, F., & Kose, S. (2018). Singing under the impulsiveness: Impulsivity in psychiatric disorders. *Psychiatry and Clinical Psychopharmacology*, *28*(2), 205–210. https://doi.org/10.1080/24750573.2017.1410329

Lahey, B. B., Applegate, B., Hakes, J. K., Zald, D. H., Hariri, A. R., & Rathouz, P. J. (2012). Is there a general factor of prevalent psychopathology during adulthood? *Journal of Abnormal Psychology*, *121*(4), 971–977. https://doi.org/10.1037/a0028355

Lahey, B. B., Zald, D. H., Hakes, J. K., Krueger, R. F., & Rathouz, P. J. (2014). Patterns of Heterotypic Continuity Associated With the Cross-Sectional Correlational Structure of Prevalent Mental Disorders in Adults. *JAMA Psychiatry*, *71*(9), 989. https://doi.org/10.1001/jamapsychiatry.2014.359

Lammertsma, A. A., & Hume, S. P. (1996). Simplified Reference Tissue Model for PET Receptor Studies. *NeuroImage*, *4*(3), 153–158. https://doi.org/10.1006/nimg.1996.0066

Latzman, R. D., & DeYoung, C. G. (2020). Using empirically-derived dimensional phenotypes to accelerate clinical neuroscience: The Hierarchical Taxonomy of Psychopathology (HiTOP) framework. *Neuropsychopharmacology*, *45*(7), 1083–1085. https://doi.org/10.1038/s41386-020-0639-6

Lee, P. H., Anttila, V., Won, H., Feng, Y.-C. A., Rosenthal, J., Zhu, Z., Tucker-Drob, E. M., Nivard, M. G., Grotzinger, A. D., Posthuma, D., Wang, M. M.-J., Yu, D., Stahl, E. A., Walters, R. K., Anney, R. J. L., Duncan, L. E., Ge, T., Adolfsson, R., Banaschewski, T., … Smoller, J. W. (2019). Genomic Relationships, Novel Loci, and Pleiotropic

Mechanisms across Eight Psychiatric Disorders. *Cell*, *179*(7), 1469-1482.e11. https://doi.org/10.1016/j.cell.2019.11.020

Lee, S. H., Ripke, S., Neale, B. M., Faraone, S. V., Purcell, S. M., Perlis, R. H., Mowry, B. J., Thapar, A., Goddard, M. E., Witte, J. S., Absher, D., Agartz, I., Akil, H., Amin, F., Andreassen, O. A., Anjorin, A., Anney, R., Anttila, V., Arking, D. E., … Cross-Disorder Group of the Psychiatric Genomics Consortium. (2013). Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nature Genetics*, *45*(9), 984–994. https://doi.org/10.1038/ng.2711

Lewinsohn, P. M., & Rosenbaum, M. (1987). Recall of parental behavior by acute depressives, remitted depressives, and nondepressives. *Journal of Personality and Social Psychology*, *52*(3), 611–619. https://doi.org/10.1037//0022-3514.52.3.611

Leyton, M. (2021). Ubiquitous Dopamine Deficit Hypotheses in Cocaine Use Disorder Lack Support. *American Journal of Psychiatry*, *178*(5), 469–469. https://doi.org/10.1176/appi.ajp.2021.20111581

Leyton, M., Boileau, I., Benkelfat, C., Diksic, M., Baker, G., & Dagher, A. (2002). Amphetamine-induced increases in extracellular dopamine, drug wanting, and novelty seeking: A PET/[11C]raclopride study in healthy men. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *27*(6), 1027–1035. https://doi.org/10.1016/S0893-133X(02)00366-4

Leyton, M., het Rot, M. aan, Booij, L., Baker, G. B., Young, S. N., & Benkelfat, C. (2007). Mood-elevating effects of d-amphetamine and incentive salience: The effect of acute dopamine precursor depletion. *Journal of Psychiatry & Neuroscience*, *32*(2), 129–136. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810580/

Leyton, M., & Stewart, J. (1990). Preexposure to foot-shock sensitizes the locomotor response to subsequent systemic morphine and intra-nucleus accumbens amphetamine. *Pharmacology Biochemistry and Behavior*, *37*(2), 303–310. https://doi.org/10.1016/0091-3057(90)90339-J

Leyton, M., & Vezina, P. (2014). Dopamine ups and downs in vulnerability to addictions: A neurodevelopmental model. *Trends in Pharmacological Sciences*, *35*(6), 268–276. https://doi.org/10.1016/j.tips.2014.04.002

Lim, K.-L., Jacobs, P., Ohinmaa, A., Schopflocher, D., & Dewa, C. S. (2008). A new population-based measure of the economic burden of mental illness in Canada. *Chronic Diseases in Canada*, *28*(3), 92–98.

Liu, J. (2004). Childhood Externalizing Behavior: Theory and Implications. *Journal of Child and Adolescent Psychiatric Nursing : Official Publication of the Association of Child and Adolescent Psychiatric Nurses, Inc*, *17*(3), 93–103. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1617081/

Lomanowska, A. M., Rana, S. A., McCutcheon, D., Parker, L. A., & Wainwright, P. E. (2006). Artificial rearing alters the response of rats to natural and drug-mediated rewards. *Developmental Psychobiology*, *48*(4), 301–314. https://doi.org/10.1002/dev.20139

Long, N. J., & Wong, W.-T. (Eds.). (2015). *The chemistry of molecular imaging*. Wiley.

Mannarino, A. P., Cohen, J. A., Deblinger, E., Runyon, M. K., & Steer, R. A. (2012). Trauma-focused cognitive-behavioral therapy for children: Sustained impact of treatment 6 and 12 months later. *Child Maltreatment*, *17*(3), 231–241. https://doi.org/10.1177/1077559512451787

Marengo, J., & Harrow, M. (1985). Thought disorder. A function of schizophrenia, mania, or psychosis? *The Journal of Nervous and Mental Disease*, *173*(1), 35–41.

Marinelli, M., & White, F. J. (2000). Enhanced Vulnerability to Cocaine Self-Administration Is Associated with Elevated Impulse Activity of Midbrain Dopamine Neurons. *The Journal of Neuroscience*, *20*(23), 8876–8885. https://doi.org/10.1523/JNEUROSCI.20-23-08876.2000

Matthews, K., & Robbins, T. W. (2003). Early experience as a determinant of adult behavioural responses to reward: The effects of repeated maternal separation in the rat. *Neuroscience & Biobehavioral Reviews*, *27*(1), 45–55. https://doi.org/10.1016/S0149-7634(03)00008-3

Matthews, K., Wilkinson, L. S., & Robbins, T. W. (1996). Repeated maternal separation of preweanling rats attenuates behavioral responses to primary and conditioned incentives in adulthood. *Physiology & Behavior*, *59*(1), 99–107. https://doi.org/10.1016/0031-9384(95)02069-1

Matuszewich, L., McFadden, L. M., Friedman, R. D., & Frye, C. A. (2014). Neurochemical and behavioral effects of chronic unpredictable stress. *Behavioural Pharmacology*, *25*(5 and 6), 557–566. https://doi.org/10.1097/FBP.0000000000000061

McHugh, R. K., Votaw, V. R., Sugarman, D. E., & Greenfield, S. F. (2018). Sex and Gender Differences in Substance Use Disorders. *Clinical Psychology Review*, *66*, 12–23. https://doi.org/10.1016/j.cpr.2017.10.012

McLaughlin, K. A., Colich, N. L., Rodman, A. M., & Weissman, D. G. (2020). Mechanisms linking childhood trauma exposure and psychopathology: A transdiagnostic model of risk and resilience. *BMC Medicine*, *18*(1), 96. https://doi.org/10.1186/s12916-020-01561-6

McLaughlin, K. A., & Lambert, H. K. (2017). Child trauma exposure and psychopathology: Mechanisms of risk and resilience. *Current Opinion in Psychology*, *14*, 29–34. https://doi.org/10.1016/j.copsyc.2016.10.004

McLaughlin, K. A., & Sheridan, M. A. (2016). Beyond Cumulative Risk: A Dimensional Approach to Childhood Adversity. *Current Directions in Psychological Science*, *25*(4), 239–245. https://doi.org/10.1177/0963721416655883

Meador-Woodruff, J. H., Damask, S. P., & Watson, S. J. (1994). Differential expression of autoreceptors in the ascending dopamine systems of the human brain. *Proceedings of the National Academy of Sciences*, *91*(17), 8297–8301. https://doi.org/10.1073/pnas.91.17.8297

Meyer, J. H., McNeely, H. E., Sagrati, S., Boovariwala, A., Martin, K., Verhoeff, N. P. L. G., Wilson, A. A., & Houle, S. (2006). Elevated Putamen D 2 Receptor Binding Potential in Major Depression With Motor Retardation: An [11 C]Raclopride Positron Emission Tomography Study. *American Journal of Psychiatry*, *163*(9), 1594–1602. https://doi.org/10.1176/ajp.2006.163.9.1594

Miczek, K. A., & Meyer-Lindenberg, A. (Eds.). (2014). *Neuroscience of Aggression* (1st ed. 2014). Springer Berlin Heidelberg : Imprint: Springer. https://doi.org/10.1007/978-3-662-44281-4

Milella, M. S., Fotros, A., Gravel, P., Casey, K. F., Larcher, K., Verhaeghe, J. A. J., Cox, S. M. L., Reader, A. J., Dagher, A., Benkelfat, C., & Leyton, M. (2016). Cocaine cue–induced dopamine release in the human prefrontal cortex. *Journal of Psychiatry & Neuroscience*, *41*(5), 322–330. https://doi.org/10.1503/jpn.150207

Moeller, F. G., Barratt, E. S., Dougherty, D. M., Schmitz, J. M., & Swann, A. C. (2001). Psychiatric Aspects of Impulsivity. *American Journal of Psychiatry*, *158*(11), 1783–1793. https://doi.org/10.1176/appi.ajp.158.11.1783

Mohebi, A., Pettibone, J. R., Hamid, A. A., Wong, J.-M. T., Vinson, L. T., Patriarchi, T., Tian, L., Kennedy, R. T., & Berke, J. D. (2019). Dissociable dopamine dynamics for learning and motivation. *Nature*, *570*(7759), 65–70. https://doi.org/10.1038/s41586-019-1235-y

Monroe, S. M. (1992). Diathesis-stress theories in the context of life stress research: Implications for the depressive disorders. *Psychological Bulletin*, *110*(3), 406. https://doi.org/10.1037/0033-2909.110.3.406

Mukherjee, J., Christian, B. T., Dunigan, K. A., Shi, B., Narayanan, T. K., Satter, M., & Mantil, J. (2002). Brain imaging of 18F-fallypride in normal volunteers: Blood analysis, distribution, test-retest studies, and preliminary assessment of sensitivity to aging effects on dopamine D-2/D-3 receptors. *Synapse*, *46*(3), 170–188. https://doi.org/10.1002/syn.10128

Mukherjee, J., Yang, Z. Y., Brown, T., Lew, R., Wernick, M., Ouyang, X., Yasillo, N., Chen, C. T., Mintzer, R., & Cooper, M. (1999). Preliminary assessment of extrastriatal dopamine D-2 receptor binding in the rodent and nonhuman primate brains using the high affinity radioligand, 18F-fallypride. *Nuclear Medicine and Biology*, *26*(5), 519–527. https://doi.org/10.1016/s0969-8051(99)00012-8

Murty, V. P., Shermohammed, M., Smith, D. V., Carter, R. M., Huettel, S. A., & Adcock, R. A. (2014). Resting state networks distinguish human ventral tegmental area from substantia nigra. *NeuroImage*, *100*, 580–589. https://doi.org/10.1016/j.neuroimage.2014.06.047

Nagano-Saito, A., Dagher, A., Booij, L., Gravel, P., Welfeld, K., Casey, K. F., Leyton, M., & Benkelfat, C. (2013). Stress-induced dopamine release in human medial prefrontal cortex—18F-Fallypride/PET study in healthy volunteers. *Synapse*, *67*(12), 821–830. https://doi.org/10.1002/syn.21700

Nagy, S. A., Kürtös, Z., Németh, N., Perlaki, G., Csernela, E., Lakner, F. E., Dóczi, T., Czéh, B., & Simon, M. (2021). Childhood maltreatment results in altered deactivation of reward processing circuits in depressed patients: A functional magnetic resonance imaging study of a facial emotion recognition task. *Neurobiology of Stress*, 100399. https://doi.org/10.1016/j.ynstr.2021.100399

Narkhede, S. (2021, June 15). *Understanding AUC - ROC Curve*. Medium. https://towardsdatascience.com/understanding-auc-roc-curve-68b2303cc9c5

Nelson, C. A., Bhutta, Z. A., Burke Harris, N., Danese, A., & Samara, M. (2020). Adversity in childhood is linked to mental and physical health throughout life. *BMJ*, m3048. https://doi.org/10.1136/bmj.m3048

Novick, A. M., Levandowski, M. L., Laumann, L. E., Philip, N. S., Price, L. H., & Tyrka, A. R. (2018). The effects of early life stress on reward processing. *Journal of Psychiatric Research*, *101*, 80–103. https://doi.org/10.1016/j.jpsychires.2018.02.002

Oldham, J. M., Skodol, A. E., Kellman, H. D., Hyler, S. E., Doidge, N., Rosnick, L., & Gallaher, P. E. (1995). Comorbidity of axis I and axis II disorders. *The American Journal of Psychiatry*, *152*(4), 571–578. https://doi.org/10.1176/ajp.152.4.571

Olivetti, P. R., Balsam, P. D., Simpson, E. H., & Kellendonk, C. (2020). Emerging roles of striatal dopamine D2 receptors in motivated behaviour: Implications for psychiatric

disorders. *Basic & Clinical Pharmacology & Toxicology*, *126*(S6), 47–55. https://doi.org/10.1111/bcpt.13271

Orri, M., Boivin, M., Chen, C., Ahun, M. N., Geoffroy, M.-C., Ouellet-Morin, I., Tremblay, R. E., & Côté, S. M. (2020). Cohort Profile: Quebec Longitudinal Study of Child Development (QLSCD). *Social Psychiatry and Psychiatric Epidemiology*. https://doi.org/10.1007/s00127-020-01972-z

Orri, M., Boivin, M., Chen, C., Ahun, M. N., Geoffroy, M.-C., Ouellet-Morin, I., Tremblay, R. E., & Côté, S. M. (2021). Cohort Profile: Quebec Longitudinal Study of Child Development (QLSCD). *Social Psychiatry and Psychiatric Epidemiology*, *56*(5), 883–894. https://doi.org/10.1007/s00127-020-01972-z

Oswald, L. M., Wand, G. S., Kuwabara, H., Wong, D. F., Zhu, S., & Brasic, J. R. (2014). History of Childhood Adversity is Positively Associated with Ventral Striatal Dopamine Responses to Amphetamine. *Psychopharmacology*, *231*(12), 2417–2433. https://doi.org/10.1007/s00213-013-3407-z

Pantoularis, I., Garyfallos, G., Lobtzianidou, M., Livanos, A., Dasoukis, I., & Adamopoulou, A. (2008). Axis I-Axis II comorbidity of borderline personality disorder: Gender-related differences. *Annals of General Psychiatry*, *7*(1), S226. https://doi.org/10.1186/1744-859X-7-S1-S226

Papeschi, R., & McClure, D. J. (1971). Homovanillic and 5-Hydroxyindoleacetic Acid in Cerebrospinal Fluid of Depressed Patients. *Archives of General Psychiatry*, *25*(4), 354–358. https://doi.org/10.1001/archpsyc.1971.01750160066012

Paquette, D., Laporte, L., Bigras, M., & Zoccolillo, M. (2004). [Validation of the French version of the CTQ and prevalence of the history of maltreatment]. *Sante Mentale Au Quebec*, *29*(1), 201–220. https://doi.org/10.7202/008831ar

Pignatelli, M., & Bonci, A. (2015). Role of Dopamine Neurons in Reward and Aversion: A Synaptic Plasticity Perspective. *Neuron*, *86*(5), 1145–1157. https://doi.org/10.1016/j.neuron.2015.04.015

Pizzagalli, D. A., Berretta, S., Wooten, D., Goer, F., Pilobello, K. T., Kumar, P., Murray, L., Beltzer, M., Boyer-Boiteau, A., Alpert, N., El Fakhri, G., Mechawar, N., Vitaliano, G., Turecki, G., & Normandin, M. (2019). Assessment of Striatal Dopamine Transporter Binding in Individuals With Major Depressive Disorder: In Vivo Positron Emission Tomography and Postmortem Evidence. *JAMA Psychiatry*, *76*(8), 854–861. https://doi.org/10.1001/jamapsychiatry.2019.0801

Positron Emission Tomography (PET). (n.d.). Retrieved January 6, 2022, from https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/positron-emission-tomography-pet

Pruessner, J. C., Champagne, F., Meaney, M. J., & Dagher, A. (2004). Dopamine Release in Response to a Psychological Stress in Humans and Its Relationship to Early Life Maternal Care: A Positron Emission Tomography Study Using [11C]Raclopride. *Journal of Neuroscience*, *24*(11), 2825–2831. https://doi.org/10.1523/JNEUROSCI.3422-03.2004

Ramirez de Arellano, M. A., Lyman, D. R., Jobe-Shields, L., George, P., Dougherty, R. H., Daniels, A. S., Ghose, S. S., Huang, L., & Delphin-Rittmon, M. E. (2014). Trauma-Focused Cognitive Behavioral Therapy: Assessing the Evidence. *Psychiatric Services (Washington, D.C.)*, *65*(5), 591–602. https://doi.org/10.1176/appi.ps.201300255

Reuben, A., Moffitt, T. E., Caspi, A., Belsky, D. W., Harrington, H., Schroeder, F., Hogan, S., Ramrakha, S., Poulton, R., & Danese, A. (2016). Lest we forget: Comparing retrospective and prospective assessments of adverse childhood experiences in the prediction of adult health. *Journal of Child Psychology and Psychiatry*, *57*(10), 1103–1112. https://doi.org/10.1111/jcpp.12621

Rioux, C., Castellanos-Ryan, N., Parent, S., Vitaro, F., Tremblay, R. E., & Séguin, J. R. (2016). Differential susceptibility to environmental influences: Interactions between child temperament and parenting in adolescent alcohol use. *Development and Psychopathology*, *28*(1), 265–275. https://doi.org/10.1017/S0954579415000437

Robinson, S., Sandstrom, S. M., Denenberg, V. H., & Palmiter, R. D. (2005). Distinguishing Whether Dopamine Regulates Liking, Wanting, and/or Learning About Rewards. *Behavioral Neuroscience*, *119*(1), 5. https://doi.org/10.1037/0735-7044.119.1.5

Romo, R., & Schultz, W. (1990). Dopamine neurons of the monkey midbrain: Contingencies of responses to active touch during self-initiated arm movements. *Journal of Neurophysiology*, *63*(3), 592–606. https://doi.org/10.1152/jn.1990.63.3.592

Roy, A., Agren, H., Pickar, D., Linnoila, M., Doran, A. R., Cutler, N. R., & Paul, S. M. (1986). Reduced CSF concentrations of homovanillic acid and homovanillic acid to 5-hydroxyindoleacetic acid ratios in depressed patients: Relationship to suicidal behavior and dexamethasone nonsuppression. *The American Journal of Psychiatry*, *143*(12), 1539–1545. https://doi.org/10.1176/ajp.143.12.1539

Rutter, M. (1981). Stress, coping and development: Some issues and some questions. *Journal of Child Psychology and Psychiatry*, *22*(4), 323–356. https://doi.org/10.1111/j.1469-7610.1981.tb00560.x

Schaefer, L. M., Howell, K. H., Schwartz, L. E., Bottomley, J. S., & Crossnine, C. B. (2018). A concurrent examination of protective factors associated with resilience and posttraumatic growth following childhood victimization. *Child Abuse & Neglect*, *85*, 17–27. https://doi.org/10.1016/j.chiabu.2018.08.019

Schultz, W. (1998). Predictive reward signal of dopamine neurons. *Journal of Neurophysiology*, *80*(1), 1–27. https://doi.org/10.1152/jn.1998.80.1.1

Schultz, W., Dayan, P., & Montague, P. R. (1997). A neural substrate of prediction and reward. *Science (New York, N.Y.)*, *275*(5306), 1593–1599. https://doi.org/10.1126/science.275.5306.1593

Sequeira, S. L., Silk, J. S., Ladouceur, C. D., Hanson, J. L., Ryan, N. D., Morgan, J. K., McMakin, D. L., Kendall, P. C., Dahl, R. E., & Forbes, E. E. (2021). Association of Neural Reward Circuitry Function With Response to Psychotherapy in Youths With Anxiety Disorders. *The American Journal of Psychiatry*, appiajp202020010094. https://doi.org/10.1176/appi.ajp.2020.20010094

Sesack, S. R., Aoki, C., & Pickel, V. M. (1994). Ultrastructural localization of D2 receptor-like immunoreactivity in midbrain dopamine neurons and their striatal targets. *Journal of Neuroscience*, *14*(1), 88–106. https://doi.org/10.1523/JNEUROSCI.14-01-00088.1994

Sheikh, M. A. (2018). Childhood adversities and chronic conditions: Examination of mediators, recall bias and age at diagnosis. *International Journal of Public Health*, *63*(2), 181–192. https://doi.org/10.1007/s00038-017-1021-2

Slifstein, M., Kegeles, L. S., Xu, X., Thompson, J. L., Urban, N., Castrillon, J., Hackett, E., Bae, S.-A., Laruelle, M., & Abi-Dargham, A. (2010). Striatal and extrastriatal dopamine

release measured with PET and [18F]fallypride. *Synapse (New York, N.Y.)*, *64*(5), 350–362. https://doi.org/10.1002/syn.20734

Smetanin, P., Stiff, D., Briante, C., Adair, C. E., Ahmad, S., & Khan, M. (2011). *The Life and Economic Impact of Major Mental Illnesses in Canada*. Risk Analytica. https://www.mentalhealthcommission.ca/wp-content/uploads/drupal/MHCC_Report_Base_Case_FINAL_ENG_0_0.pdf

Smoller, J. W., Andreassen, O. A., Edenberg, H. J., Faraone, S. V., Glatt, S. J., & Kendler, K. S. (2019). Psychiatric genetics and the structure of psychopathology. *Molecular Psychiatry*, *24*(3), 409–420. https://doi.org/10.1038/s41380-017-0010-4

Sokoloff, P., & Le Foll, B. (2017). The dopamine D3 receptor, a quarter century later. *European Journal of Neuroscience*, *45*(1), 2–19. https://doi.org/10.1111/ejn.13390

Stauffer, W. R., Lak, A., Kobayashi, S., & Schultz, W. (2016). Components and characteristics of the dopamine reward utility signal. *The Journal of Comparative Neurology*, *524*(8), 1699–1711. https://doi.org/10.1002/cne.23880

Stemmler, M., & Lösel, F. (2012). The stability of externalizing behavior in boys from preschool age to adolescence: A person-oriented analysis. *Psychological Test and Assessment Modeling*, *54*(2), 195–207.

St-Hilaire, A., Steiger, H., Liu, A., Laplante, D. P., Thaler, L., Magill, T., & King, S. (2015). A prospective study of effects of prenatal maternal stress on later eating-disorder manifestations in affected offspring: Preliminary indications based on the Project Ice Storm cohort. *The International Journal of Eating Disorders*, *48*(5), 512–516. https://doi.org/10.1002/eat.22391

Substance Use in Canada Costs Almost $46 Billion a Year According to Latest Data | Canadian Centre on Substance Use and Addiction. (n.d.). Retrieved February 13, 2022, from https://www.ccsa.ca/substance-use-canada-costs-almost-46-billion-year-according-latest-data

Svihra, M., & Katzman, M. A. (2004). Behavioural inhibition: A predictor of anxiety. *Paediatrics & Child Health*, *9*(8), 547–550. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2724161/

Tabachnick, B. G., & Fidell, L. S. (2013). *Using multivariate statistics* (6th ed). Pearson Education.

Tang, A., Crawford, H., Morales, S., Degnan, K. A., Pine, D. S., & Fox, N. A. (2020). Infant behavioral inhibition predicts personality and social outcomes three decades later. *Proceedings of the National Academy of Sciences*, *117*(18), 9800–9807. https://doi.org/10.1073/pnas.1917376117

The Brainstorm Consortium, Anttila, V., Bulik-Sullivan, B., Finucane, H. K., Walters, R. K., Bras, J., Duncan, L., Escott-Price, V., Falcone, G. J., Gormley, P., Malik, R., Patsopoulos, N. A., Ripke, S., Wei, Z., Yu, D., Lee, P. H., Turley, P., Grenier-Boley, B., Chouraki, V., … Neale, B. M. (2018). Analysis of shared heritability in common disorders of the brain. *Science*, *360*(6395). https://doi.org/10.1126/science.aap8757

Tournier, B. B., Steimer, T., Millet, P., Moulin-Sallanon, M., Vallet, P., Ibañez, V., & Ginovart, N. (2013). Innately low D2 receptor availability is associated with high novelty-seeking and enhanced behavioural sensitization to amphetamine. *International Journal of Neuropsychopharmacology*, *16*(8), 1819–1834. https://doi.org/10.1017/S1461145713000205

Tremblay, R. E., Vitaro, F., Gagnon, C., Piché, C., & Royer, N. (1992). A Prosocial Scale for the Preschool Behaviour Questionnaire: Concurrent and Predictive Correlates. *International Journal of Behavioral Development*, *15*(2), 227–245. https://doi.org/10.1177/016502549201500204

Van den Heuvel, D. M. A., & Pasterkamp, R. J. (2008). Getting connected in the dopamine system. *Progress in Neurobiology*, *85*(1), 75–93. https://doi.org/10.1016/j.pneurobio.2008.01.003

Venugopalan, V. V., Casey, K. F., O'Hara, C., O'Loughlin, J., Benkelfat, C., Fellows, L. K., & Leyton, M. (2011). Acute phenylalanine/tyrosine depletion reduces motivation to smoke cigarettes across stages of addiction. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *36*(12), 2469–2476. https://doi.org/10.1038/npp.2011.135

Vijayraghavan, S., Major, A. J., & Everling, S. (2017). Neuromodulation of Prefrontal Cortex in Non-Human Primates by Dopaminergic Receptors during Rule-Guided Flexible Behavior and Cognitive Control. *Frontiers in Neural Circuits*, *11*, 91. https://doi.org/10.3389/fncir.2017.00091

Volkow, N. D., & Morales, M. (2015). The Brain on Drugs: From Reward to Addiction. *Cell*, *162*(4), 712–725. https://doi.org/10.1016/j.cell.2015.07.046

Vosberg, D. E., Leyton, M., & Flores, C. (2020). The Netrin-1/DCC guidance system: Dopamine pathway maturation and psychiatric disorders emerging in adolescence. *Molecular Psychiatry*, *25*(2), 297–307. https://doi.org/10.1038/s41380-019-0561-7

Vrieze, S. I., Perlman, G., Krueger, R. F., & Iacono, W. G. (2012). Is the Continuity of Externalizing Psychopathology the Same in Adolescents and Middle–Aged Adults? A

Test of the Externalizing Spectrum's Developmental Coherence. *Journal of Abnormal Child Psychology*, *40*(3), 459–470. https://doi.org/10.1007/s10802-011-9571-x

Wang, G.-J., Wiers, C. E., Shumay, E., Tomasi, D., Yuan, K., Wong, C. T., Logan, J., Fowler, J. S., & Volkow, N. D. (2019). Expectation effects on brain dopamine responses to methylphenidate in cocaine use disorder. *Translational Psychiatry*, *9*(1), 93. https://doi.org/10.1038/s41398-019-0421-x

Ward, A. J. (1991). Prenatal stress and childhood psychopathology. *Child Psychiatry and Human Development*, *22*(2), 97–110. https://doi.org/10.1007/BF00707788

Webb, C. (2014). Trauma-focused cognitive behavioral therapy for youth: Effectiveness in a community setting. *Psychological Trauma: Theory, Research, Practice, and Policy*, *6*(5), 555. https://doi.org/10.1037/a0037364

Weissman, M. M., Bland, R. C., Canino, G. J., Faravelli, C., Greenwald, S., Hwu, H.-G., Joyce, P. R., Karam, E. G., Lee, C.-K., Lellouch, J., Lépine, J.-P., Newman, S. C., Rubio-Stipec, M., Wells, J. E., Wickramaratne, P. J., Wittchen, H.-U., & Yeh, E.-K. (1996). Cross-National Epidemiology of Major Depression and Bipolar Disorder. *JAMA*, *276*(4), 293–299. https://doi.org/10.1001/jama.1996.03540040037030

Williams, S. M., & Goldman-Rakic, P. S. (1998). Widespread origin of the primate mesofrontal dopamine system. *Cerebral Cortex*, *8*(4), 321–345. https://doi.org/10.1093/cercor/8.4.321

Willner, C. J., Gatzke-Kopp, L. M., & Bray, B. C. (2016). The Dynamics of Internalizing and Externalizing Comorbidity Across the Early School Years. *Development and Psychopathology*, *28*(4 Pt 1), 1033–1052. https://doi.org/10.1017/S0954579416000687

Wise, R. A. (2009). Roles for nigrostriatal—Not just mesocorticolimbic—Dopamine in reward and addiction. *Trends in Neurosciences*, *32*(10), 517–524. https://doi.org/10.1016/j.tins.2009.06.004

Wolf, E. J., Miller, M. W., Harrington, K. M., & Reardon, A. (2011). Personality-based latent classes of posttraumatic psychopathology: Personality disorders and the internalizing/externalizing model. *Journal of Abnormal Psychology*, *121*(1), 256. https://doi.org/10.1037/a0023237

Wolf, M. E., Galloway, M. P., & Roth, R. H. (1986). Regulation of dopamine synthesis in the medial prefrontal cortex: Studies in brain slices. *The Journal of Pharmacology and Experimental Therapeutics*, *236*(3), 699–707.

Yalincetin, B., Bora, E., Binbay, T., Ulas, H., Akdede, B. B., & Alptekin, K. (2017). Formal thought disorder in schizophrenia and bipolar disorder: A systematic review and meta-analysis. *Schizophrenia Research*, *185*, 2–8. https://doi.org/10.1016/j.schres.2016.12.015

Yong Ping, E., Laplante, D. P., Elgbeili, G., Jones, S. L., Brunet, A., & King, S. (2020). Disaster-related prenatal maternal stress predicts HPA reactivity and psychopathology in adolescent offspring: Project Ice Storm. *Psychoneuroendocrinology*, *117*, 104697. https://doi.org/10.1016/j.psyneuen.2020.104697

Yung, K. K. L., Bolam, J. P., Smith, A. D., Hersch, S. M., Ciliax, B. J., & Levey, A. I. (1995). Immunocytochemical localization of D1 and D2 dopamine receptors in the basal ganglia of the rat: Light and electron microscopy. *Neuroscience*, *65*(3), 709–730. https://doi.org/10.1016/0306-4522(94)00536-E

Zald, D. H., Cowan, R. L., Riccardi, P., Baldwin, R. M., Ansari, M. S., Li, R., Shelby, E. S., Smith, C. E., McHugo, M., & Kessler, R. M. (2008). Midbrain dopamine receptor

availability is inversely associated with novelty-seeking traits in humans. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *28*(53), 14372–14378. https://doi.org/10.1523/JNEUROSCI.2423-08.2008

Zhou, H., Sealock, J. M., Sanchez-Roige, S., Clarke, T.-K., Levey, D. F., Cheng, Z., Li, B., Polimanti, R., Kember, R. L., Smith, R. V., Thygesen, J. H., Morgan, M. Y., Atkinson, S. R., Thursz, M. R., Nyegaard, M., Mattheisen, M., Børglum, A. D., Johnson, E. C., Justice, A. C., … Gelernter, J. (2020). Genome-wide meta-analysis of problematic alcohol use in 435,563 individuals yields insights into biology and relationships with other traits. *Nature Neuroscience*, *23*(7), 809–818. https://doi.org/10.1038/s41593-020-0643-5

Zhou, X., Obuchowski, N. A., & McClish, D. K. (Eds.). (2002). *Statistical methods in diagnostic medicine*. Wiley-Interscience.

Tables

Table 1. Participant characteristics (means ± standard deviations).

N	52
Female/Male	30/22
Age (years)	18.5 ± 0.58
Ethnicity	N = 50 White European
Education (number of years)	11.92 ± 1.05
Externalizing trait score	1.40 ± 1.05
Age of alcohol use onset	14.77 ± 1.86
Lifetime occasions of binge drinking	28.52 ± 45.20
Lifetime occasions of alcohol use (including intoxication and non-intoxication)	88.29 ± 101.81
Lifetime occasions of cannabis use	149.15 ± 406.89, range: 0 to 2011
Age of onset of cannabis use	15.68 ± 1.45
Lifetime occasions of drug use, excluding cannabis	13.65 ± 64.33, range: 0 to 426
Current tobacco smoking status*	46No/5Yes

*missing data from one participant

Table 2. Comparison of overall model strength at each step of sequential binomial logistic regression. ROC AUC = receiver operating characteristic area under the curve.

	EXT	**EXT + CTQ**	**EXT + CTQ + Midbrain BP_{ND}**
Chi Squared	$\chi^2(1) = 18.359$ $p = 0.000018$	$\chi^2(2) = 19.435$ $p = 0.000060$	$\chi^2(3) = 24.109$ $p = 0.000024$
Nagelkerke R^2	0.450	0.472	0.562
Classification predictive accuracy	87% (45/52)	87% (45/52)	90% (47/52)
ROC AUC (95% CI)	0.855 (0.713 – 0.998)	0.872 (0.749 – 0.995)	0.915 (0.824 – 1.000)
Sensitivity	50% (6/12)	58% (7/12)	75% (9/12)
Specificity	98% (39/40)	95% (38/40)	95% (38/40)
Positive predictive value	86% (6/7)	78% (7/9)	82% (9/11)
Negative predictive value	87% (39/45)	88% (38/43)	93% (38/41)

Table 3. Role of each standardized predictor variable in binomial logistic regression, at index interview.

	EXT Score	**Midbrain BP_{ND}**	**CTQ Total**
	Score range 0 to 3.98	**Score range** 1.26 to 2.80	**Score range** 25 to 61
Beta ± Standard Error	2.258 ± .72	-1.129 ± .58	0.800 ± .43
Wald	9.880	3.833	3.484
p	0.002	0.050	0.062
Odds Ratio (95% CI)	9.567 (2.340 – 39.115)	3.096 (0.999 – 9.615)	2.225 (0.961 – 5.151)

Table 4A. Role of each standardized variable in predicting EXT disorders at index interview.

	EXT Score	Midbrain BP_{ND}	CTQ Total
Beta ± S.E.	2.679 ± 1.017	-1.411 ± 0.738	.674 ± .550
Wald	6.945	3.654	1.500
p	0.008	0.056	0.221

Table 4B. Comparison of model strength in predicting EXT disorders with vs. without sex as a factor. In the general population, EXT disorders exhibit a sex difference in incidence rates. Proportions similar to this population distribution were seen in the present study but adding sex as a fourth factor did not significantly strengthen the model targeting these EXT disorders (p = 0.061) or the model targeting all DSM-5 disorders (p = 0.54).

	Midbrain BP_{ND} + EXT + CTQ	Midbrain BP_{ND} + EXT + CTQ + sex
Chi Squared	$\chi^2(3) = 18.552$ $p = 0.000338$	$\chi^2(4) = 22.055$ $p = 0.000195$
Nagelkerke R^2	0.549	0.633
Classification predictive accuracy	90% (47/52)	90% (47/52)
ROC AUC (95% CI)	0.949 (.890 – 1.000)	0.956 (.902 – 1.000)
Sensitivity	43% (3/7)	57% (4/7)
Specificity	98% (44/45)	96% (43/45)
Positive predictive value	75% (3/4)	67% (4/6)
Negative predictive value	92% (44/48)	93% (43/46)

Supplementary Tables

Supplementary Table 1. Comparison of observed characteristics in participants with complete versus incomplete data.

	Participants with incomplete data (n=6)	**Participants with complete data (n=52)**	**Statistical test**	***p*-value**
Number of females and males	6 females and 0 males	30 females and 22 males	Fisher's exact	$p = 0.07$
Age (mean ± SD)	18.67 ± 0.82	18.48 ± 0.58	Independent samples t-test	$p = 0.47$
Number of participants with at least one DSM diagnosis at time of PET scan	2	12	Fisher's exact	$p = 0.62$
EXT score (mean ± SD)	1.09 ± 1.21	1.40 ± 1.05	Independent samples t-test	$p = 0.50$

Supplementary Table 2. Mean and standard deviation of injected [^{18}F]fallypride dose, mass and molar activity in patients with and without psychiatric disorders at index interview.*

	[^{18}F]fallypride dose (MBq)	**[^{18}F]fallypride mass (nmol)**	**[^{18}F]fallypride molar activity (GBq/µmol)**
With psychiatric diagnoses	123.78 ± 5.26	0.57 ± 0.28	280.45 ± 150.15
Without psychiatric diagnoses	123.26 ± 8.25	1.72 ± 4.42	409.02 ± 924.66
Group comparison	$t(44) = -0.196$, $p = 0.846$	$t(42) = 0.822$, $p = 0.416$	$t(44) = 0.435$, $p = 0.666$

*The groups did not differ statistically when including diagnoses obtained at the follow-up interviews (all p-values ≥ 0.33).

Supplementary Table 3A. List of participants and their DSM-5 diagnoses.

Subject ID	Past DSM-5 diagnoses	DSM-5 diagnoses at index interview	New lifetime DSM-5 diagnoses at last interview
1			
2*			
3*			
4*	Major Depressive Disorder		
5*			
6*	Attention Deficit Hyperactivity Disorder	Attention Deficit Hyperactivity Disorder	
7*		Cannabis Use Disorder	
8	Major Depressive Disorder, Adjustment Disorder		
9*			
10*			
11*			Attention Deficit Hyperactivity Disorder
12*			
13*	Conduct Disorder	Cannabis Use Disorder	
14*			
15*			
16*			
17		Persistent Depressive Disorder	
18			
19*			
20*			
21			
22*			
23*			
24*	Cannabis Use Disorder	Amphetamine Use Disorder	
25*			
26*			
27*			Generalized Anxiety Disorder, Panic Disorder
28	Attention Deficit Hyperactivity Disorder, Dyslexia	Dyslexia	

Supplementary Table 3A. List of participants and their DSM-5 diagnoses (contd).

Subject ID	Past DSM-5 diagnoses	DSM-5 diagnoses at index interview	New lifetime DSM-5 diagnoses at last interview
29*	Adjustment Disorder with Depressed Mood		Panic Disorder
30*			
31*			
32*			Major Depressive Disorder, Panic Disorder
33*			Panic Disorder, Generalized Anxiety Disorder
34*			
35*			
36*			
37*			
38			
39*			
40*			
41*			
42			
43*			
44			
45	Attention Deficit Hyperactivity Disorder		
46*			
47			
48*	Major Depressive Disorder		
49*			
50*			
51*	Binge Eating Disorder	Alcohol Use Disorder	
52*			

*Participant had one or more follow-up interviews (n=41)

Supplementary Table 3B. Distribution of participants with internalizing (INT) versus externalizing (EXT) diagnoses in the high versus low EXT groups.

Risk group	Lifetime psychiatric diagnosis at index interview	Lifetime psychiatric diagnosis at last interview
Low EXT group	1	2
High EXT group	11	14
	Lifetime EXT diagnosis (SUD, ADHD, conduct disorder) at index interview	**Lifetime EXT diagnosis (SUD, ADHD, conduct disorder) at last interview**
Low EXT group	0	1
High EXT group	7	7
	Lifetime INT diagnosis (mood and anxiety disorders) at index interview	**Lifetime INT diagnosis (mood and anxiety disorders) at last interview**
Low EXT group	1	1
High EXT group	4	7

Supplementary Table 4. Specific diagnoses in males vs. females at the index interview.

Diagnosis	Males vs. Females (% with diagnosis)	Fisher's Exact test result
Substance Use Disorder	13.6 vs. 3.3	$p = 0.299$
Mood Disorder	4.5 vs. 10.0	$p = 0.629$
Attention Deficit Hyperactivity Disorder	9.1 vs. 3.3	$p = 0.567$
Adjustment Disorder	0.0 vs. 6.7	$p = 0.502$
Dyslexia	4.5 vs. 0.0	$p = 0.423$
Binge Eating Disorder	4.5 vs. 0.0	$p = 0.423$
Conduct Disorder	4.5 vs. 0.0	$p = 0.423$

Supplementary Table 5. Characteristics of participants with versus without follow-up interviews.

	One or more follow-up interviews (n=41)	No follow-up interviews (n=11)	Statistical test	*p*-value
Number of females and males	22 females and 19 males	8 females and 3 males	Fisher's exact	$p = 0.32$
Age (mean ± SD)	18.49 ± 0.60	18.45 ± 0.52	Independent samples t- test	$p = 0.84$
Number of participants with at least one DSM diagnosis at time of PET scan	8	4	Fisher's exact	$p = 0.25$
EXT score (mean ± SD)	1.35 ± 0.93	1.58 ± 1.47	Independent samples t-test	$p = 0.53$