Investigating the Dissociable Roles of the Ventromedial and Dorsolateral Prefrontal Cortex Underlying Components of Decision-Making in Precariously Housed Chronic Substance Users

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Abstract

Homelessness is a complex societal issue affecting thousands across Canada, with Metro Vancouver experiencing a significant increase in homelessness in recent years. Single-room occupancy hotels in Vancouver's Downtown Eastside (DTES) neighbourhood provide housing for individuals at risk of homelessness. However, residents face numerous risks to brain health, including substance use disorders, traumatic brain injury (TBI), psychosis, and vascular disease, leading to high rates of cognitive and decision-making impairments. This study explores the relationship between prefrontal cortex (PFC) morphology (cortical thickness/surface area) and decision-making in a precariously housed population. Specifically, given the multiple threats to PFC integrity and the observed increased risky decision-making, this research seeks to identify whether decision-making processes on a laboratory-based decision-making task are uniquely associated with ventromedial (vmPFC) and dorsolateral (dlPFC) morphology. Using a sample of 272 precariously housed individuals facing numerous threats to prefrontal brain structure and function, the present study employed two unique computational models to decompose Iowa Gambling Task (IGT) performance into component processes. Using select components, we examined a potential morphological dissociation between regions of the PFC (vmPFC and dlPFC) and decision-making components (attention to gain/loss and memory). Bayesian linear regressions failed to reveal the predicted morphological dissociation between prefrontal regions; however, secondary analyses revealed an association between vmPFC morphology and perseveration and reversal learning. This finding is consistent with the known role of the vmPFC as an important substrate for reversal learning, suggesting that the relationship between vmPFC dysfunction and poor IGT performance may result from impaired reversal learning. These findings underscore the complexity of decision-making processes and highlight the need for a nuanced understanding of how cortical morphology influences risky decision-making, particularly in marginalized populations.

Keywords: decision-making; Iowa Gambling Task; precarious housing; risk factors; prefrontal cortex

Dedication

This dissertation is dedicated to my father, whose endless love, wisdom, and support have shaped the person I am today. Dad, I cannot thank you enough for everything you have given me. You have been with me through this entire process, through all the ups and the many downs, just as you have been with me my whole life. Your regular check-ins were so appreciated and always seemed to come at the perfect time. You always knew when I needed a little extra support. I am forever grateful you were able to be with me every step of the way and see me through to the finish line. I will miss you so deeply, but I will forever carry your spirit with me in everything I do. I love you Dad.

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List of Acronyms

dlPFC	Dorsolateral prefrontal cortex
DTES	Downtown Eastside neighbourhood of Vancouver, British Columbia
HBA	Hierarchical Bayesian analysis
IGT	Iowa Gambling Task
ORL	Outcome Representation Learning model
PFC	Prefrontal cortex
PVL-Delta	Prospect Valence Learning model with Delta rule
SRO	Single Room Occupancy
TBI	Traumatic brain injury
vmPFC	Ventromedial prefrontal cortex
VPP	Value Plus Perseverance model

Preface

The Hotel Study is a naturalistic, longitudinal observational study that tracks over 400 adults living in marginalized housing in Vancouver's Downtown Eastside (DTES). This study investigates the mental, physical, and social health of participants over an extended period, with a particular focus on mental health and cognitive function. The study aims to provide a comprehensive understanding of the interconnected biological, psychological, and social factors that influence mental health in this population.

Findings from the longitudinal HOTEL study highlight a high prevalence of mental illness among adults in marginalized housing, which significantly impacts their overall health. Mental health issues contribute to a range of compounding health challenges, including premature mortality. Elevated rates of multimorbidity (the presence of multiple chronic conditions) and cognitive impairment suggest an accelerated aging process among these individuals, who are marginalized by complex illness, poverty, and social inequities.

The current dissertation study was carried out as part of a collaborative, multidisciplinary team, and my role as a neuropsychology graduate student on the HOTEL project team was central to ensuring the integrity and accuracy of the cognitive data collected throughout the project. As a member of this team, I was responsible for the storage, management, and organization of all cognitive data, ensuring that participant records were securely maintained and accessible for future analysis. In this dissertation project, I was responsible for the conceptualization of the study and the development of the research hypotheses collaboratively with my research supervisor, Dr. Thornton. Regarding the neuroimaging analysis, the data analysis was completed with assistance from Dr. Panenka and Wayne Su. Dr. Campbell led the computational and statistical modelling aspects of the project, with ongoing consultation with both myself and Dr. Thornton to ensure the coherence and alignment of the modelling approach with the study's hypotheses and overall objectives.

Chapter 1. Introduction

1.1. Background

According to recent reports, as many as 235,000 Canadians experience homelessness in a year (Gaetz, 2016). A count completed in 2023 found that over 4,800 persons are currently homeless throughout Metro Vancouver, representing a 32% increase since 2020 and the highest number recorded to date (Homeless Services Association of BC, 2023). Unfortunately, homelessness is a complex societal problem with many underlying social factors, including (but not limited to) lack of adequate income, access to affordable housing and health support, and experiences of discrimination. Homelessness can also exacerbate existing health disparities and create barriers to accessing essential care and services. Individuals often face a combination of social, economic, and environmental factors that increase their vulnerability to physical and mental health issues. These include limited access to stable housing, inadequate nutrition, exposure to harsh weather conditions, and high rates of substance use and trauma. In the Downtown Eastside (DTES) neighbourhood of Vancouver, British Columbia, single-room occupancy (SRO) hotels often represent the only alternative to homelessness and provide affordable short or long-term housing for low-income individuals who are at risk of homelessness (Vila-Rodriguez et al., 2013).

The environment in which marginalized persons live is associated with a multitude of risks to brain structure and function (Cadet et al., 2014; Gicas et al., 2017; John, 2009; Stuss, 2011). Occupants typically have a high rate of neurological illnesses (Jones et al., 2020), infectious diseases (Ludwig et al., 2012; Vila-Rodriguez et al., 2013), and TBI (O'Connor et al., 2022; Schmitt et al., 2017; Stubbs et al., 2020). Rates of psychosis are also high (Barbic et al., 2018; Honer et al., 2017; Vila-Rodriguez et al., 2013), and substance use is ubiquitous, with upwards of 95% experiencing some form of substance dependence (Jones et al., 2020; Vila-Rodriguez et al., 2013). Our research team has extensively documented the risks to brain health in a group of highly marginalized individuals residing on the DTES of Vancouver. One of the most prevalent and salient threats to physical, neurological, and cognitive health in the DTES is substance use. In the DTES environment, polysubstance use is widespread, and past work from our research group suggests occupants in this environment have high rates of

stimulant, opioid, alcohol, and cannabis use (Honer et al., 2017; Jones et al., 2015; Vila-Rodriguez et al., 2013).

Substance use disorder (SUD) has been described as a chronic, relapsing brain disorder that produces long-term changes in the reward circuitry of the brain (Koob & Volkow, 2010). SUD can be conceptualized schematically as three stages: i) acute intoxication and binge, ii) withdrawal, and iii) anticipation/craving, with widespread neurological mechanisms and circuitry involved in each stage (Koob & Volkow, 2016). Within each of these three stages, there is potential for significant neuroplastic changes in the brain's reward, stress, and executive function systems. These systems are linked by three major neurobiological circuits: the basal ganglia-driven intoxication/binge stage, the extended amygdala-mediated withdrawal stage and the PFC-driven anticipation/craving stage (Koob & Volkow, 2016). Although the biochemical effects of each drug class differ from one another, each of these drugs increases dopamine in the brain's reward system through direct or indirect effects on neurons within the ventral tegmental area (VTA), which is the origin of dopaminergic cells located in the midbrain. The VTA projects to structures in the basal ganglia, such as the ventral striatum (containing the nucleus accumbens) and the dorsal striatum and also sends projections to the extended amygdala, which refers to the large basal forebrain structure containing the amygdala and the bed nucleus of the stria terminalis (Nestler et al., 2015). The ventral striatum, extended amygdala, and VTA have extensive connections with the PFC and collectively make up the brain's mesolimbic, or reward pathway. Common among these drugs is a convergence on the PFC, which is particularly sensitive to the negative effects of chronic substance use (Ceceli et al., 2021; Goldstein & Volkow, 2011). Neuroimaging studies have provided compelling evidence of PFC dysfunction and structural changes in individuals experiencing SUD, manifesting in lower PFC volume, thickness, and surface area in opioid (Lin et al., 2018; Liu et al., 2009; Pezawas et al., 1998), stimulant (Crunelle et al., 2014; Franklin et al., 2002; Meade et al., 2020), alcohol (Daviet et al., 2022; Jernigan et al., 1991; Jernigan et al., 1991; Lindberg et al., 2024; Pfefferbaum et al., 1997), and cannabis users (Churchwell et al., 2010; Wilson et al., 2000). Functional imaging has also documented widespread reduced cerebral blood flow in substance users, with the most prominent decreases in the PFC (Volkow et al., 1988). These structural and functional changes are plausibly a result of chronic hyperstimulation of PFC circuits due to drug use and a resulting hypoactivity of PFC

function in response. However, those with SUD are also at an increased risk of numerous other pathologies known to impair brain structure and function.

Brain injury

It is well known that acute drug intoxication increases the risk for traumatic brain injuries (Darke et al., 2012; O'Connor et al., 2022; Savola et al., 2005; Schmitt et al., 2017), and our group has previously reported remarkably high rates of TBI in the DTES (O'Connor et al., 2022; Schmitt et al., 2017). One of the most common deficits reported even after a mild TBI is in higher-order cognitive functions involving the PFC. The frontal lobes, particularly the PFC, are highly vulnerable to injury due to their location at the front of the brain and their exposure to forces during trauma (Stuss, 2011). The PFC might also be particularly vulnerable to metabolic cascades following TBI (Blanié et al., 2012), which have detrimental neurological impacts both globally and regionally (Bigler, 2007; Leunissen et al., 2014; Warner et al., 2010).

In addition to the increased risk of traumatic injury, substance use, especially alcohol (K. C. Wilson & Saukkonen, 2004) and opioids (Baldo & Rose, 2022), can depress respiratory function, impair oxygenation, or cause erratic breathing patterns, increasing the risk of hypoxia (low oxygen levels in the blood) or anoxia (complete absence of oxygen). For example, opioids can suppress the respiratory centers in the brainstem, leading to slower or irregular breathing (Kiyatkin, 2019), while alcohol can exacerbate respiratory depression, particularly when combined with other sedatives (Thomas et al., 2021). Furthermore, the risk of accidental overdose, particularly with drugs like heroin or fentanyl, can result in anoxic brain injury, as overdose episodes can deprive the brain of oxygen for extended periods (Kiyatkin, 2019; Kiyatkin & Choi, 2024).

The lack of consistent access to healthcare often results in these conditions going unrecognized and untreated, which in turn contributes to further neurological damage and an increased risk of long-term cognitive and physical health problems (Bedmar et al., 2022). Without sufficient oxygen, brain cells begin to deteriorate and die, causing irreversible damage to neural tissue. The brain is especially vulnerable to oxygen deprivation, and even brief episodes of anoxia can lead to significant impairments in cognitive, motor, and sensory functions. Over time, this damage can result in persistent neurological deficits, such as memory loss, impaired executive function, and, in severe cases, permanent brain injury or death (FitzGerald et al., 2010).

Immediate medical intervention is crucial to prevent or minimize these devastating outcomes. Brain regions with high metabolic activity, dense neuronal populations, or those that require substantial blood flow may be especially vulnerable to damage (Caine & Watson, 2000). This includes the hippocampus, cerebellum, and watershed areas of the parieto-occipital-temporal cortex (Cervós-Navarro & Diemer, 1991; Kaplan, 1999). The negative impact of oxygen deprivation is not restricted to these regions, however, and can extend throughout the brain, affecting a wide range of neural structures, including the PFC. In response to reduced oxygen levels, studies have shown that both hypoxia and anoxia can lead to thinning of PFC cortical gray matter (Joo et al., 2013; Winstanley et al., 2021) and decreased functional connectivity within the PFC (Peran et al., 2020). This thinning is thought to result from neuronal loss, decreased dendritic complexity, and impairments in neurogenesis, as oxygen is essential for cellular metabolism and synaptic plasticity (Cui et al., 2024).

Vascular risks

Previous work from our group has shown that the vascular risk burden is high in this population, leading to high rates of cerebral small vessel disease (cSVD) and brain infarcts (Zhou et al., 2019, 2020). It is known that cSVD can have significant negative impacts on prefrontal structure and function, particularly when secondary to stimulant drug use (Du et al., 2020b, 2020a). Stimulant-induced vasoconstriction increases the risk of ischemic events (Kevil et al., 2019), and cocaine's direct disruption of cerebral blood vessels and cerebral blood flow likely contributes to impaired frontal functioning by disrupting white matter connections within the frontoparietal network (Schaefer et al., 2014; Schroeter et al., 2007). Chronic use of stimulants can also accelerate the development of atherosclerosis (hardening and narrowing of arteries), further increasing the risk of cardiovascular events, which have been shown to result in structural and functional changes in the PFC.

Viral risks

On top of the increased risk of cerebrovascular events, viral infections (including human immunodeficiency virus (HIV) and hepatitis C virus (HCV)) represent additional neurological threats in chronic substance users. Unfortunately, the risk for viral infections is high in marginalized populations, where access to clean needles is limited or not readily available. Research has demonstrated that both HIV and HCV can cause atrophy

in the prefrontal cortex, especially in the absence of appropriate medical management (Everall et al., 1991; Hjerrild et al., 2016; Marciniewicz et al., 2019; Sanford et al., 2018). In particular, untreated HIV can lead to neurocognitive impairments through direct viral invasion of the brain and immune-mediated damage, resulting in PFC cortical thinning and a reduction in gray matter volume (du Plessis et al., 2016; Thompson et al., 2005). HIV-associated neurocognitive disorders (HAND) are characterized by impairments in a number of higher-order cognitive functions mediated by the PFC, including challenges with attention and concentration (Woods et al., 2009). Meanwhile, HCV is thought to induce neuroinflammation and alter brain metabolism, leading to widespread cortical thinning and volume loss (Adinolfi et al., 2015; Tagliapietra & Monaco, 2020), as well as impaired functional connectivity in the PFC (Zhang et al., 2020).

Psychosis

In addition to the risk factors already described, chronic substance use also conveys an increased risk for psychosis. It has been well established that exposure to illicit drugs in adolescence is associated with an increased risk of developing schizophrenia and other psychotic disorders (Barkus & Murray, 2010). Prolonged substance use also conveys an increased risk of conversion to schizophrenia in higher-risk individuals (e.g., those with schizotypal personality disorder; Li et al., 2020) with significant risks across opioids, cannabis, stimulants, and alcohol (Alderson et al., 2017; Hjorthoj et al., 2018). One of the most consistent functional neuroimaging findings associated with schizophrenia and other psychotic disorders includes altered PFC activation (Mamah, 2023), and PFC atrophy has been well-documented in psychotic disorders (Abé et al., 2015; Gur et al., 2000; Kikinis et al., 2010). Research from our group has also documented structural changes within the frontal circuitry in substance-induced psychosis (SIP; Alexander et al., 2019; Willi et al., 2017), including compromised white matter integrity in frontotemporal and frontothalamic tracts.

Seizure disorders

Homeless and marginally housed individuals with substance use disorders are at heightened risk for seizures due to a combination of factors related to substance abuse, poor living conditions, and limited access to healthcare (O'Reilly et al., 2015). Many substances commonly used in this environment, such as alcohol, stimulants, and sedatives (e.g., benzodiazepines), can lower the seizure threshold, making the brain

more prone to epileptic activity (Pisani et al., 2002). Chronic alcohol use, in particular, can lead to alcohol-related seizures, both during withdrawal and as a direct result of neurotoxicity from long-term drinking (Hillbom et al., 2003). The lack of stable housing and healthcare makes it more difficult for homeless individuals to manage substance use or seek treatment, leading to a cycle where seizures and substance abuse mutually reinforce each other, worsening both conditions over time. Consequently, recurrent seizures in this group may often go undiagnosed and untreated, contributing to significant morbidity.

Epilepsy is a chronic seizure disorder marked by recurrent seizures, which can be either focal (affecting a specific part of the body) or generalized (affecting the entire body). Unfortunately, the prevalence of epilepsy is notably higher among homeless and marginally housed individuals, with research indicating an eightfold increased risk compared to the general population (O'Reilly et al., 2015). One of the most common forms of focal epilepsy is frontal lobe epilepsy (Hart et al., 1992), which is associated with altered structural and functional connectivity, reduced brain volume (Klugah-Brown et al., 2019) and impairments in a number of frontal-mediated cognitive functions (Arrotta et al., 2022). Epilepsy, particularly in its chronic form, can lead to cortical thinning through a combination of direct and indirect mechanisms. Recurrent seizures, especially in cases of poorly controlled epilepsy, can cause structural changes in the brain due to repeated neuronal firing and subsequent neuronal damage (Galovic et al., 2019). The electrical disturbances associated with seizures can lead to excitotoxicity, where excessive neurotransmitter release (often glutamate) overstimulates neurons, causing them to become damaged. Over time, this neuronal loss can result in thinning of the cortical gray matter as the brain's neural networks are disrupted (Barker-Haliski & White, 2015). Additionally, repeated seizure activity may activate inflammatory pathways that further contribute to neurodegeneration and cortical thinning (Wolinski et al., 2022). Inflammatory cytokines and glial cell activation are commonly seen in the aftermath of seizures, and chronic inflammation can impair neuroplasticity and exacerbate cell death.

Taken together, each of these neurological threats converge on common prefrontal structures and circuitry in the brain. Regardless of etiology, threats to PFC structural integrity convey a multitude of cognitive risks, including an increased risk for decision-making impairments. These impairments have been shown to cause an exacerbation of risk-taking behaviour (Floden et al., 2008; Goswami et al., 2016;

Woodrow et al., 2018; Zhou et al., 2020), thus perpetuating a cycle of risky behaviours and greater marginalization in an already highly marginalized group. Given the high-risk environment of the DTES, the numerous threats to structural brain integrity in the PFC, and the associated effect on risky decision-making, it is critical to understand how individuals in this highly marginalized environment process risks and how the numerous threats to PFC structural integrity impact risky decision-making.

1.2. Decision-making and the PFC

Decision-making is a complex cognitive process that involves evaluating potential outcomes and weighing the benefits against the potential costs or risks associated with a particular choice (Rangel et al., 2008). This is fundamental to human behaviour and occurs in various contexts, from everyday life choices to complex financial or strategic decisions. Consequently, it is perhaps unsurprising that it relies on large-scale neural systems throughout the cerebral cortex and underlying subcortical structures (Damasio, 1996). Uncovering the neural substrates underlying decision-making has received considerable attention from various disciplines over the years (e.g., neuropsychology, cognitive psychology, economics, computer science), leading to a number of different proposed theoretical models. Common to each of these models is the prominent role of the PFC. From an anatomical viewpoint, the PFC is considered one of the most important brain regions during decision-making because it exerts top-down control, sending signals to other brain regions to guide attention, prioritize tasks, and regulate behaviour based on goals and intentions (Broche-Pérez et al., 2016; Rosenbloom et al., 2012). This top-down control allows for flexible and adaptive responses to changing environmental demands, helping individuals to navigate complex situations and achieve their objectives. The PFC exerts its top-down control through extensive cortico-cortical and subcortical connections, including the thalamus, amygdala, basal ganglia, hippocampus, and cerebellum (Rosenbloom et al., 2012). Classic case studies, such as that of Phineas Gage, underscore the importance of the PFC during decision-making. In the case of Gage, an unfortunate railroad accident caused a tamping iron to be projected through his skull, destroying most of his frontal lobe. While he survived the accident, he was reportedly a changed man, displaying markedly disinhibited behaviour with deficits in rational decision-making and processing of emotions (Damasio et al., 1994). The resulting clinical presentation has since been termed ‘frontal lobe syndrome’ and refers

to the clinical presentation resulting from damage and impaired functioning of the prefrontal cortex. Many subsequent examples of frontal lobe syndromes have been documented throughout the medical literature (Loring & Meador, 2006) and collectively support the important role of the PFC in the decision-making process.

Structurally and functionally, the PFC is composed of two major brain regions: the ventromedial prefrontal cortex (vmPFC) and the dorsolateral prefrontal cortex (dlPFC). Both have attracted particular attention for their contribution to impulsive, risky decision-making processes in numerous neurological and psychiatric conditions (Bechara et al., 1994, 1998; Fellows & Farah, 2005; Woodrow et al., 2018; Zhou et al., 2020). Damage to both brain regions has been linked to real-world risky and erratic behaviours such as physical altercations (Davis et al., 2021), poor economic investments (Eslinger & Damasio, 1985), and increased frequency and duration of stimulant drug use (Kaag et al., 2018; Mackey et al., 2019; Smith et al., 2013; Yip et al., 2018). Building on this, experimental work has shown that transient modulation of vmPFC and dlPFC function causes impairments in decision-making on the IGT (de Visser et al., 2011; He et al., 2016; Obeso et al., 2021), albeit in different ways. For example, excitation of the vmPFC has been shown to improve decision-making by modulating one's ability to assess the probability of gains and losses (Kroker et al., 2022), while excitation of the dlPFC improves a person's memory for past information, with no effect on reward sensitivity (He et al., 2016). Collectively, these findings suggest different underlying roles in decision-making for dlPFC versus the vmPFC. Along these lines, both areas have been implicated as part of a broad and highly interconnected network of brain regions that are critical for effective decision-making (Broche-Pérez et al., 2016; Fellows, 2004; Kable & Glimcher, 2009; Rosenbloom et al., 2012). This network of brain regions integrates and modulates two important aspects of decision-making: i) Valuation and reward processing, which involves the vmPFC and limbic system (including ventral striatum, amygdala, basal ganglia); and ii) Cognitive control, executive attention and working memory, which involves the dlPFC and the frontoparietal system (Bechara, 2013; Verdejo-García et al., 2019).

The vmPFC and limbic pathways

The vmPFC represents one of the key nodes in the decision-making circuitry and is located in the anterior and medial most part of the frontal lobe. This brain region is

involved in numerous cognitive functions related to reward, emotion, and motivation. This includes anticipation and response to reward (Jocham et al., 2014; Manuel et al., 2019; Pujara et al., 2016), reward valuation (Bechara et al., 1994; Bechara et al., 2000), self-evaluation (Salehinejad et al., 2020) and other aspects of emotional processing which have colloquially been termed “hot” cognitive processes. The prominent role of the vmPFC in decision-making is central to the Somatic Marker Hypothesis (SMH), a well-known theory of decision-making that suggests emotions play a critical role in the decision-making process, especially when guiding choices with uncertainty or risk. The SMH was collectively proposed by Antonio Damasio and Antoine Bechara to provide a neural explanation for the real-life decision-making defect of patients who had experienced vmPFC damage (Damasio, 1994). These patients demonstrated different patterns of decision-making, such that they prioritized immediate rewards and were insensitive to both positive and negative future consequences (Bechara, 2004; Bechara et al., 2000; Bechara et al., 1994). Many subsequent studies supporting the role of the vmPFC in emotional processing during decision-making have been published (Hiser & Koenigs, 2018).

Structurally, the vmPFC has extensive cortical connections to the dlPFC, the anterior cingulate cortex (ACC), and the medial temporal cortex. It also shares substantial bidirectional connections with subcortical limbic structures (Barbas, 2007; Carmichael & Price, 1995; Cavada et al., 2000; Hiser & Koenigs, 2018). The limbic system is a collective term for the nuclei, tracts, and cortical areas surrounding the boundary between the cerebral hemispheres and the brainstem. During decision-making, limbic structures, such as the amygdala, hypothalamus, and ventral striatum are involved in emotional coding of environmental stimuli (Cardinal et al., 2002; Cardinal & Howes, 2005; Haber & Knutson, 2010), while the vmPFC is believed to exert top-down control of this circuitry (Motzkin et al., 2015; Rosenkranz et al., 2003; Rosenkranz & Grace, 2001). Animal studies have shown direct structural connections between the vmPFC, ventral striatum, and amygdala (Gabbott et al., 2005; Sesack et al., 1989), and disconnection of these pathways impairs the ability to flexibly alter decision-making behaviour according to reward value (Baxter et al., 2000; Fiuzat et al., 2017). Functional neuroimaging studies in humans have also demonstrated robust functional connectivity between the vmPFC and ventral striatum (Cauda et al., 2011; Di Martino et al., 2008) and amygdala at rest (Feng et al., 2016), as well as co-activation during reward (Cauda

et al., 2011) and emotional processing (Delli Pizzi et al., 2017; Sun et al., 2023). Collectively, there is strong evidence that the vmPFC and limbic pathways modulate emotional responses and reward processing during decision-making.

The dlPFC and the frontoparietal network

A second hub of the decision-making network is the dlPFC, which occupies the lateral and superior areas of the frontal lobes (Broche-Pérez et al., 2016). Similar to the vmPFC, the dlPFC has extensive limbic and thalamic connections, in addition to strong cortical connections with the vmPFC, ACC, temporal, and occipital cortices (Petrides & Pandya, 1999; Rosenbloom et al., 2012). Unlike the vmPFC, which is responsible for emotionally driven "hot" cognition, the dlPFC is involved in "cold" cognitive processes, including cognitive control, executive attention, and working memory (Barbey et al., 2013; He et al., 2016). The dlPFC also provides top-down modulation of the frontoparietal network, which is a highly connected network between the dlPFC, parietal cortex, and dorsal striatum (Shen et al., 2020; Shirer et al., 2012). Functional neuroimaging has demonstrated coordinated activity of the dlPFC and parietal areas during complex decision-making tasks, which is believed to enable the cognitive control necessary to handle complex task conditions (Camilleri et al., 2018; Cocuzza et al., 2020; Matsui et al., 2022). Studies have also revealed that disruption of this network by repetitive transcranial magnetic stimulation impairs attention, working memory, and decision-making performance (Rogasch et al., 2015; Van't Wout et al., 2005; Wyczesany et al., 2022). Furthermore, lesions in the dlPFC and other areas of the frontoparietal network produce impairments in working memory, cognitive control, and decision-making (Fellows & Farah, 2005; Figueroa-Vargas et al., 2020; Szczepanski & Knight, 2014), which have clear and negative effects on decision-making (Bagneux et al., 2013; Bechara & Martin, 2004; Dretsch & Tipples, 2008; Wesley & Bickel, 2014).

In homeless and marginally housed persons, we know everyday decisions carry a high burden of risk, particularly in such a challenging environment, with numerous neurological threats such as substance use, vascular risk factors, psychotic disorders, and TBI. Morphological changes to the prefrontal circuitry may underlie core components of risky decision-making, such as heightened reward sensitivity and impaired inhibitory processes. It is, therefore, imperative to understand the link between

structural brain integrity and components of risky decision-making in order to elucidate the neurocognitive underpinnings of risky behaviours in this highly vulnerable population.

1.3. Assessing decision-making using the Iowa Gambling Task

One of the most common laboratory-based measures for assessing risky decision-making is a simulated gambling task known as the Iowa Gambling Task (IGT). The IGT is designed to simulate real-life decision-making by manipulating the possibilities and magnitudes of potential rewards and punishments (Bechara et al., 1994). Participants are informed that the aim of the task is to win as much money as possible and avoid losing money. The IGT requires participants to sequentially choose 100 cards across four card decks. (A, B, C, or D). Each card drawn results in either a reward or a loss of simulated money. Two decks (Deck A and Deck B) are considered high-risk, with high payoffs, but also high losses and two (Deck C and Deck D) are considered low-risk, with lower payoffs but smaller losses. Decks A and B both yield high payoffs on every trial but differ in their losses. Deck A yields more frequent losses (5 per 10 cards), whereas Deck B yields one very large loss per 10 cards. Both decks result in a net loss overall. Deck C yields a smaller payoff on every trial and is paired with frequent (5 per 10 cards) smaller losses. Deck D also yields smaller payoffs on every trial and a moderate loss every ten cards. Decks C and D both yield net gains in the long run. The net losses become larger as more cards are selected from Decks A and B (at a rate of $150 per ten cards). In contrast, as more cards are chosen from Decks C and D, the net gains become larger at a rate of $25 per ten cards. In order to succeed, individuals must learn to choose from the low-risk decks more often and from the high-risk decks less often, as they have high payoffs but even higher losses in the long run. The IGT is traditionally scored by subtracting the disadvantageous decks (A and B) from the advantageous decks (C and D).

Past work has shown that individuals with vmPFC damage exhibit impaired decision-making and fail to learn the optimal strategy (Bechara, 2001, 2004; Bechara et al., 1994). As a result, these individuals typically do not develop a preference for decks C and D over time. Subsequent studies have found that dlPFC damage produces similar decision-making impairments on the IGT as vmPFC damage (Fellows & Farah, 2005; Manes et al., 2002). In line with their categorization as brain regions responsible for “hot”

and “cold” cognitive functions, impairments in IGT due to vmPFC damage are thought to be related to impaired emotional processes and reward valuation (Bechara, 2004), while impairments due to dlPFC damage are believed to be reflective of deficits in working memory (Bechara et al., 1998), which is critical to decision-making (Bagneux et al., 2013; Del Missier et al., 2013).

1.4. Computational modelling and the IGT

Although the IGT is sensitive to detect decision-making deficits in various clinical populations, the traditional net score metric does not adequately capture specific cognitive, motivational, and response processes underlying decision-making. Consequently, the specific neurocognitive processes that underlie decision-making deficits are difficult to ascertain using standard net score metrics (Haines et al., 2018). In order to gain a better understanding of the cognitive processes underlying decision-making strategies on the IGT, computational models have been developed to break down the decision-making process into its component parts (Ahn et al., 2016; Haines et al., 2018). On complex decision-making tasks like the IGT, performance is determined by several different underlying components, including motivational, learning, and choice processes (Ahn et al., 2016; Busemeyer & Stout, 2002). Cognitive modelling aims to break down these choice processes into parameters that can then be used to understand the source of the decision-making deficits in clinical populations. Computational models contain parameters that govern how individuals learn from feedback and make decisions. These parameters are estimated by fitting the model to the data collected during the IGT to find the set of parameter values that best explain a participant’s decision patterns. This provides insights into the underlying cognitive processes involved in decision-making. Importantly, cognitive modelling has shown that impaired decision-making, rather than reflecting a single common deficit, is associated with different underlying processes that reflect the continuous influence of learning and memory effects (Yechiam et al., 2005). Research has shown that computational modelling of IGT parameters is more sensitive to dissociating neurocognitive profiles in various clinical populations than standard net score indices (Ahn et al., 2016). To our knowledge no studies have directly probed the associations between neuroanatomical integrity and computational markers of IGT performance in such a unique group of individuals, with numerous threats to prefrontal structure and function. As previously

stated, this is particularly important because considerable evidence suggests that prefrontal morphology is associated with risky decision-making. It remains unclear, however, if specific underlying cognitive processes drive this relationship.

In computational modelling, the unique component processes underlying decision-making depend on the model used. A component common to most models is an individual's attention paid to gains and losses (Ahn et al., 2008; Haines et al., 2018). Much of the work investigating component processes of decision-making in clinical populations has been done examining various SUDs, and results have consistently shown that substance users show a heightened sensitivity to immediate reward and a decreased sensitivity to losses on the IGT (Bechara et al., 2002; Fridberg et al., 2010; Stout et al., 2005). This is supported by computational modelling on other risky decision-making tasks, such as the Balloon Analog Risk Task (Lejuez et al., 2002) and the Angling Risk Task (Pleskac, 2008). Studies investigating sensitivity to gain and loss in non-IGT paradigms have also demonstrated a relationship between vmPFC volume and attention to losses in healthy (Li et al., 2020), gambling addiction (Lee et al., 2022), and substance-using populations (Gianelli et al., 2022), such that lower volume was related to decreased loss aversion and increased risky behaviour. Heightened sensitivity to immediate rewards and insensitivity to future consequences is also observed in individuals with vmPFC lesions (Bechara et al., 1994, 2002), which aligns with its classification as a "hot" cognitive region.

In addition to altered sensitivity to gains and losses, substance users have also been shown to be more influenced by recent outcomes, with rapid forgetting of past outcomes (Fridberg et al., 2010; Stout et al., 2005). This finding comes from another commonly modelled component: the effect of learning and memory on decision-making performance. It has been previously shown that IGT performance suffers when a working memory load is introduced (Dretsch & Tipples, 2008; Hinson et al., 2002; Jameson et al., 2004; Pecchinenda et al., 2006), and it has been suggested that working memory impairments may compromise the ability to retain active representations of previous outcomes on the IGT, resulting in poorer overall task performance (Fridberg et al., 2010). The important contribution of working memory during decision-making has also been highlighted by lesion studies of the dlPFC, which produces marked decision-making impairments (Bechara et al., 1998; Fellows & Farah, 2005), further supporting its role as a "cold" cognitive region.

Numerous cognitive models exist to break down IGT scores into component processes, and differing models will vary in terms of model assumption and complexity, as well as the distinct parameters that are revealed. To capture decision-making on the IGT, we will compare three candidate models: the Prospect Valence Learning with delta rule (PVL-Delta), Value-Plus-Perseverance (VPP), and Outcome Representation Learning (ORL) models. These models were selected as they vary in terms of model assumption and complexity (Lewandowsky & Farrell, 2021; Wilson & Collins, 2019; Zhang et al., 2020) and have been extensively studied and validated in substance-using populations (Baitz et al., 2021; Haines et al., 2018; Steingroever et al., 2013; Worthy et al., 2013). Moreover, these three models also contain parameters describing sensitivity to reward and losses and memory for past cards selected. These cognitive parameters are known to be important components of decision-making and have been implicated as sources of impairment in substance users.

From the ORL, the sensitivity to gains and losses are reflected in the reward learning (A_{rew}) and punishment learning (A_{pun}) rates. On the VPP and PVL-Delta, the attention to losses parameter (λ) reflects the relative attention paid to losses over gains. Regarding memory, the ORL, VPP, and PVL-Delta each contain a parameter reflecting how an individual's past selection influences future cards selected, though they are modelled in different ways. On the ORL, the decay parameter (*K*) describes how quickly decision-makers forget their past deck choices. Unlike the ORL, the VPP and PVL-Delta contain a learning rate (Recency, *A*), which describes how quickly decision-makers integrate recent outcomes into their expected value for a given deck. In other words, this parameter describes how much individuals are influenced by recent outcomes.

1.5. Neuroimaging

Historically, cortical volume has been a popular method of investigating brain morphology in normal aging and pathological conditions both cross-sectionally and longitudinally (Alexander et al., 2019; Churchwell et al., 2010; Crunelle et al., 2014; Dalwani et al., 2011; Fein et al., 2002; Kikinis et al., 2010; Lin et al., 2018; Nakamura et al., 2008). Cortical volume refers to the total amount of gray matter between the grey-white interface and the pia mater (Winkler et al., 2010). It represents the combined volume of neurons, glial cells, blood vessels, and neuropil (nerve fibres and synapses) in the cortical layers. Changes in cortical volume are nonlinear and regionally specific

across development. In the frontal lobe, gray matter volume increases during childhood and pre-adolescence, with peak volume occurring at approximately 11 years of age, followed by a decline across the lifespan (Giedd et al., 1999). As previously stated, both normal age-related as well as pathological decreases in prefrontal cortical volume have been shown to relate to altered risky decision-making (Churchwell et al., 2010; Conti & Baldacchino, 2021; Kobayakawa et al., 2017; Lee et al., 2022; Lim et al., 2021). Mounting evidence, however, suggests that assessing grey matter volume may not be optimal for characterizing cortical morphology (Winkler et al., 2018). This is because cortical thickness and surface area, which together make up the components of volume, are independent and genetically uncorrelated (Jha et al., 2018; Panizzon et al., 2009; Strike et al., 2019; Winkler et al., 2009), and follow different developmental trajectories over the lifespan (Abé et al., 2015; Hogstrom et al., 2012; Lemaître et al., 2012; Zhu et al., 2023), such that changes in cortical surface area and thickness are not uniform across region or age (Storsve et al., 2014). Furthermore, cortical thickness and surface area appear to be differentially associated with cognitive abilities and disorders (Schnack et al., 2015; Tadayon et al., 2020; Winkler et al., 2018). For instance, a study by Tadayon et al. (2020) found that fluid intelligence (i.e., the ability to think logically and solve problems in novel situations) is positively correlated with cortical surface area across multiple regions, including the dlPFC, while cortical thickness shows no association. Conversely, dlPFC thickness (but not surface area) is negatively associated with crystallized intelligence (i.e., the accumulation of knowledge, facts, and skills acquired through learning and experience; Tadayon et al., 2020).

Cortical thickness

Cortical thickness refers to the distance between the pial surface and the white matter surface of the cortex. It reflects the density and organization of neurons, glial cells, and neuropil within the cortical layers. Developmentally, cortical thickness increases rapidly after birth, reaches a peak at around 14 months of age, and then gradually decreases thereafter (Bethlehem et al., 2022; Wang et al., 2019). Throughout normal development, changes in cortical thickness can indicate changes in neuronal structure, such as dendritic arborization and pruning (Huttenlocher, 1990), or may reflect more pathological processes like those associated with the numerous risk factors present in the DTES. This includes neuronal loss, synaptic dysfunction, abnormal protein aggregation, inflammatory processes, or vascular changes. Pathological changes such

as these have been well described in both the vmPFC and dlPFC in psychosis (Abé et al., 2015; Hibar et al., 2018; Kuperberg et al., 2003), traumatic brain injury (Nolan et al., 2018; Stuss, 2011), substance use (Mackey et al., 2019) and vascular disease (Seo et al., 2010), and have shown to be predictive of decision-making impairments (Pehlivanova et al., 2018; Yamagishi et al., 2016).

Cortical surface area

Cortical surface area refers to the total area of the outer surface of the cerebral cortex. It reflects the intricate folding patterns of gyri and sulci in the cortex and is particularly sensitive to developmental changes during prenatal and postnatal brain development. As a result, changes in cortical surface area, such as those influenced by genetic factors, environmental stimuli, and neurodevelopmental processes, can provide insights into typical brain maturation as well as abnormalities or delays in neurodevelopment. In contrast to cortical thickness, which reaches its peak within the first year and a half of life, surface area undergoes rapid expansion (reaching almost 70% of its adult size by two years of age) but doesn't peak until roughly 11 years of age (Bethlehem et al., 2022; Lyall et al., 2015), and expansion of the cortex during this time occurs primarily in surface area rather than in thickness (Geschwind & Rakic, 2013).

By parsing cortical volume into thickness and surface area, past work has been able to demonstrate a differential association between brain measures and cognitive measures and highlight the benefit of studying cortical surface area and thickness separately. Studies like Tadayon et al. (2020) and others (e.g., Borgeest et al., 2021; Lee et al., 2015; Schnack et al., 2015; Vuoksimaa et al., 2016) support the idea that cortical thickness and surface area reflect complementary aspects of neuroanatomy relating to different underlying biological processes, and may therefore provide valuable information into the pathophysiological processes of neurological disorders (Ding et al., 2019). Collectively, this suggests that volumetric measurements may not be the optimal choice when investigating cortical morphology and that examining thickness and surface area separately yields more information about disease- and symptom-related neurobiology and the mechanisms underlying potential differences (Rimol et al., 2012). For these reasons, we have chosen to analyze cortical thickness and surface area separately.

1.6. Objectives

The objectives of the current study are two-fold. First, we will determine the best-fitting and most accurate computational model for the current sample. Each of the selected models contains a parameter or parameters describing a participant's sensitivity to gains and losses, as well as a parameter describing the effect of learning and memory on decision-making performance. Second, once we determine the best-fitting model, we will investigate the dissociable relationship between vmPFC and dlPFC morphology (cortical thickness/surface area) and components of IGT decision-making in a group of precariously housed persons. Given the numerous converging threats to PFC structural brain integrity and associated circuitry (Gicas et al., 2017, 2018; Guttman et al., 2018; Morey et al., 2012), as well as behavioural evidence of increased risky decision-making, the current study sought to understand whether underlying components of decision-making are uniquely related to vmPFC and dlPFC morphology. The relationship between PFC integrity and components of decision-making has not been systematically investigated in marginalized persons despite the multimorbid burden that is known to negatively impact frontal brain structure. By doing so, we may help to seed an appreciation of the genesis of risk-taking to inform stakeholders of productive prevention and intervention approaches and strategies that may be implemented.

1.7. Dissociation of prefrontal brain regions and IGT parameters

Historically, the relationship between brain structure and function has been deduced through case studies involving localized brain lesions that result in specific functional deficits. From Phineas Gage's frontal lobe injury to Paul Broca's and Carl Wernicke's independent discoveries of different speech impairments in patients with left frontal lobe and posterior temporal lobe lesions, respectively, many of the great discoveries of brain-behaviour relationships have come from individual or group case studies (Fama & Sullivan, 2014). Although undoubtedly invaluable in their contributions, single correlational case studies like these between anatomical structure and behavioural functioning have inherent limitations and are not sufficient to convey specificity between structure and function. As the English neurologist John Hughlings-Jackson once mused, "To locate the lesion which destroys speech and to locate speech

are two different things" (Hughlings-Jackson, 1879). In order to increase the specificity of correlational findings, one must first provide evidence that damage to the brain region of interest is associated with function X but simultaneously does not affect function Y. This is known as a single dissociation study and can provide additional information by showing that a lesion is related to a specific cognitive function and at the same time not related to a different cognitive function. In a single dissociation, a lesion to brain structure A disrupts function X but not function Y, thus allowing one to infer that function X and function Y are independent of each other. While the single dissociation provides stronger evidence for a unique relationship between brain structure and function, it is still inadequate for drawing conclusions about the specificity between brain structure and function (Fama & Sullivan, 2014). For example, differences between function X and function Y may be related to lesions of brain structure A, but they could also be related to differences in tests used to assess these functions (Young et al., 2000). To provide more evidence of a specific structure-function relationship, one must provide evidence that two functions are disrupted independently from one another. Thus, in order to establish a specificity of functions, a double dissociation of symptoms is necessary (Teuber, 1955). In a double dissociation model, brain structure and function relationships may be inferred when two functions are disrupted independently from each other. In other words, a lesion to brain region A is associated with impairments in function X but not in function Y. In contrast, a lesion to brain region B is associated with impairments in function Y but not in function X (Fama & Sullivan, 2014). Although double dissociations are traditionally thought of as lesion studies in neuropsychology, non-lesion morphometric double dissociations have also provided valuable insights into brain structure-function relationships (Borgeest et al., 2021; Cousins et al., 2016; Fama & Sullivan, 2014; Johnson et al., 2018). For example, morphometric double dissociation studies have revealed dissociable structure-function relationships between unique brain regions (vmPFC and hippocampus) and cognitive functions.

Using a morphometric double dissociation approach, we tested the unique association between regions of the PFC (vmPFC and dlPFC) and components of decision-making (attention to gains/losses and memory). As described in Table 1, we predicted that thinner vmPFC and smaller surface area would be associated with lower attention to losses (A_{pun}, λ). This is supported by the known deleterious effect of multiple morbidities (e.g., chronic substance use, psychosis, TBI, vascular disease etc.) on

vmPFC volume (Ceceli et al., 2022; Gur et al., 2000; Honea et al., 2005; Nakamura et al., 2008; Pomarol-Clotet et al., 2010; Tabara et al., 2024), as well as evidence suggesting chronic substance users are insensitive to losses on the IGT (Ahn et al., 2014; Baitz et al., 2021; Lake et al., 2020; Vassileva et al., 2013). We predict this association will be absent for dlPFC thickness/surface area. Next, we hypothesize that lower reward sensitivity (A_{rew}) will be associated with thinner vmPFC and smaller surface area but show no association with dlPFC thickness/surface area. This hypothesis is supported by evidence from human and primate work, which implicates the vmPFC as a critical component of the reward network in coding for stimulus reward value (O'Doherty, 2007) and the relationship between higher attention to reward on the IGT with greater frontal grey matter volume (Premkumar et al., 2008). Next, we hypothesize that higher decay (K) and recency parameters (A, indicative of rapid forgetting and strong recency effects) will be associated with a thinner dlPFC and smaller surface area but show no association with vmPFC thickness/surface area. This hypothesis is supported by evidence suggesting that dlPFC dysfunction (such as that observed in chronic substance use and psychiatric illness) negatively affects IGT performance (Fellows & Farah, 2005; Manes et al., 2002), which may be explained by impairments in working memory (Bechara & Martin, 2004).

Given the heterogeneity and uniqueness of our sample and the high rates of psychotic disorders, we sought to extend our investigation by examining whether a similar pattern of findings exists between those with psychosis and those without. As stated, participants in the current study live in highly marginalized environments where rates of neurological and psychiatric illness are high. While schizophrenia and other psychotic disorders are known to affect real-world decision-making and IGT performance (Woodrow et al., 2018), the relationship between brain structure and IGT performance in psychotic disorders is less well-known. Numerous studies have suggested that dlPFC, but not vmPFC function, is altered in those with schizophrenia, and there is evidence to suggest that those with psychotic disorders engage alternate brain networks during complex decision-making (Ramchandran et al., 2020). Functional imaging suggests that those on the psychosis spectrum do not perform like "typical" vmPFC patients (as described by Bechara (1994)) but rather primarily activate the Dorsal Attentional Network (DAN), which may be moderated by antipsychotic medications (Ramchandran et al., 2020). Many of the studies investigating components of decision-making in

substance users have excluded those presenting with a history of psychotic disorder (Ahn et al., 2014; Fridberg et al., 2010; Kjome et al., 2009; Robinson et al., 2022; Vassileva et al., 2013), so the effect of psychosis on components of decision-making in substance users remains unresolved, and are included as exploratory analyses.

While it is clear psychosis has a negative effect on prefrontal brain structure and function (Vieira et al., 2021), it appears that the etiology of psychosis contributes to different neuroanatomical markers and behavioural presentation. For example, differences in regional brain activity and white matter connectivity have been observed in individuals presenting with primary psychosis and those with substance-induced psychosis (Alexander et al., 2019; Zhang et al., 2018). Given the observed differences in frontal structural and functional morphology between types of psychotic disorder, we categorized individuals into one of three groups based on lifetime history of diagnoses: i) Primary Psychosis (schizophrenia, schizoaffective disorder, and bipolar with psychosis), ii) Substance Induce Psychosis (SIP), and iii) Psychosis not otherwise specified (PNOS). The No Psychosis group was modelled separately because it closely resembled methodologies used by other researchers, while the inclusion of the three psychosis groups was aimed at investigating whether similar patterns of decision-making were present compared to those with no history of psychosis. Each of the four groups (No Psychosis, Primary Psychosis, SIP, PNOS) was modelled separately and in the same manner.

1.8. Supplementary analysis of additional IGT parameters

As a supplementary analysis, we investigated other specific cognitive parameters that constitute the best-fitting models. On the ORL, the win frequency parameter (β_F) accounts for the effect of outcome frequency on total value with respect to the expected outcome of each deck (Haines et al., 2018). In other words, this parameter tracks the decision-maker's preference for selecting from decks with low or high win frequency. On the IGT, it has been reported that most decision-makers prefer decks that produce more frequent wins, even at the expense of long-term value (Chiu et al., 2012; Yechiam et al., 2005). This is supported by the original IGT studies by Bechara et al. (1994), which demonstrated a substantial preference for Deck B in those with vmPFC damage as well as those experiencing substance addiction (Bechara & Damasio, 2002). From a neuroanatomical perspective, vmPFC activity is associated with the size and frequency

of rewards and punishments in healthy individuals (Premkumar et al., 2008; Yarkoni et al., 2005), though it is unclear if this relationship extends to highly marginalized persons with numerous threats to PFC structure and function.

In addition to the win frequency parameter within the ORL, the perseverance parameter *(β_P)* reflects an individual's preference to switch or stay with recently chosen decks. A similar set of parameters are contained within the VPP, though they are split into perseverance after selecting a winning card (ε_{pos}) and perseverance after selecting a losing card (ε_{neg}). Both the vmPFC and dlPFC have been implicated as brain regions associated with perseverative behaviour. For example, lesions within the dlPFC are also known to produce perseverative behaviours (Szczepanski & Knight, 2014), described as a failure to shift attentional set, where patients could not shift their response even when they knew the rule was wrong (Nagahama et al., 1996). Likewise, lesions of the vmPFC have been linked to perseverative responding in animals and humans as well as deficits in reversal tasks (Quirk et al., 2000). Because of this, we have reason to believe that perseverative behaviour on the IGT may be related to vmPFC and dlPFC thickness/surface area. This is further supported by evidence of persistent perseverative behaviour observed in individuals experiencing chronic substance dependence (Jentsch et al., 2002; Woicik et al., 2011). Given this, we will explore whether perseveration of the IGT is related to vmPFC and dlPFC.

Table 1. Summary of predicted associations

Primary Hypotheses			
Hypothesis	IGT Component		Predicted Outcome/Association
1	Attention to losses	ORL $A_{pun;}$ VPP λ	Lower attention to losses will be associated with lower vmPFC thickness/ surface area and show no association with dlPFC thickness/ surface area.
2	Attention to gains	ORL A_{rew}	Higher attention to gains will be associated with greater vmPFC thickness/ surface area and show no association with dlPFC thickness/ surface area.
3	Memory for card selection	ORL $K;$ VPP A	Shorter memory for past card selection will be associated with lower dlPFC thickness/surface area and show no association with vmPFC thickness/surface area
Supplementary Analysis			
A	Win Frequency	β_F	A preference for decks with high win frequency will be associated with thinner/smaller vmPFC and show no association with dlPFC thickness/ surface area.
B	Perseveration	ORL $\beta_{P;}$ VPP ε_{pos}, ε_{neg}	More perseverative behaviour will be associated with lower vmPFC/dlPFC thickness and smaller surface area.

Chapter 2. Methods

2.1. Participants

As part of a longitudinal study, participants were recruited from four different SRO hotels and the local community district court in the DTES neighbourhood of Vancouver, British Columbia (Vila-Rodriguez et al., 2013). Inclusion for the larger longitudinal study was English fluency and either living in an SRO hotel or having contact with the community cohort within the previous six months. For the current study, a total of 409 participants (recruited between 2008 and 2017) met criteria for a lifetime history of substance dependence and valid IGT data. Of those, 66 had no valid imaging, 60 had imaging completed greater than three months from IGT completion, and 11 had significant brain pathology on T1 scan. As illustrated in Figure 1, a total of 272 individuals were included in the current study, including 91 with no history of psychotic disorder and 181 individuals with a lifetime history of psychotic disorder.

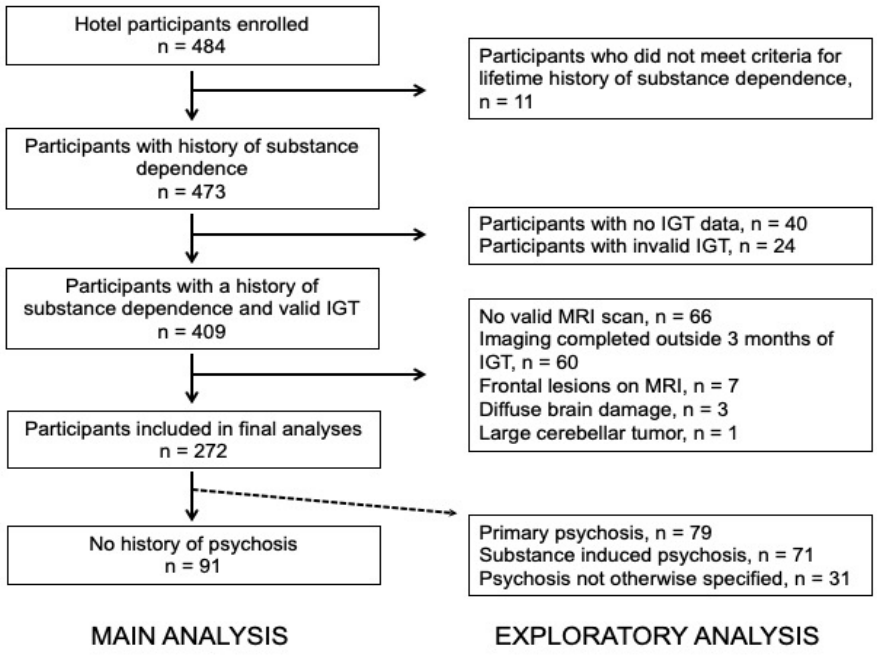

Figure 1. Flow diagram of participant inclusion.

2.2. Clinical measures

Demographic variables, including age, sex, education, and ethnicity, were self-reported during a structured baseline interview. For psychiatric diagnoses, hospitalization records were reviewed, and the Mini-International Neuropsychiatric Interview was conducted, complemented by a clinical interview and a mental status examination performed by a psychiatrist. All pertinent clinical data were utilized to establish psychiatric diagnoses and assess substance dependence using the Best Estimate Clinical Evaluation and Diagnosis methodology (BECED, Endicott, 1988), in accordance with criteria in the Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev., American Psychiatric Association (2000)). Because data collection for the study began prior to the publication of the DSM-5 and DSM-5-TR, psychiatric health and substance use disorders were assessed according to DSM-IV-TR diagnostic criteria. Blood samples were drawn, and serological testing for HIV and hepatitis C was completed to assess for viral infection. Objective history of traumatic brain injury was determined through a consensus review of anatomical MRI, as determined by a neuroradiologist.

2.3. Cognition

Trained research assistants and graduate students completed cognitive testing and scoring under the supervision of a Clinical Psychologist. Decision-making was assessed using the Iowa Gambling Task (IGT, Bechara et al., 1994). The monetary payoff for the IGT is illustrated in Table 2. Examiners rated the validity of IGT performance on a scale from 1 (clearly invalid) to 5 (clearly valid). Data for tests rated questionably valid (3) or lower were excluded from the analyses. Examples of reasons for invalid data include but are not limited to acute intoxication or inebriation, inability to comply with test instructions, fatigue, or testing equipment malfunction. Additional measures used to describe the overall cognitive functioning of the sample include the Hopkins Verbal Learning Test-Revised (HVLT; Brandt, 2001) to assess verbal learning and memory; the Stroop Color and Word Test, a measure of executive function and complex attention (Golden, 2002); the Cambridge Neuropsychological Test Automated Battery (CANTAB) Rapid Visual Information Processing Task (RVIP) to assess sustained attention (Fray et al., 1996), and the CANTAB Intradimensional-

extradimensional shift task (IDED) to assess mental flexibility and reversal learning. Intellectual functioning was estimated using the Wechsler Test of Adult Reading (WTAR; Wechsler, 2001).

Table 2. IGT payout

Card Selection	Deck A		Deck B		Deck C		Deck D	
1	100		100		50		50	
2	100		100		50		50	
3	100	-150	100		50	-50	50	
4	100		100		50		50	
5	100	-300	100		50	-50	50	
6	100		100		50		50	
7	100	-200	100		50	-50	50	
8	100		100		50		50	
9	100	-250	100	-1250	50	-50	50	
10	100	-350	100		50	-50	50	-250
Cumulative payoff	-250		-250		+250		+250	

2.4. Neuroimaging processing and acquisition

All neurocognitive tests were conducted within three months of MRI scan. Whole brain T1-weighted anatomic images were obtained using a Philips 3T Achieva scanner equipped with an eight-channel SENSE-Head coil and using a 3D FFE T1 weighted structural sequence applied in the sagittal plane with 190 1-mm thick slices (TR/TE = 7.6/3.5 ms; acquisition matrix = 256 × 250; field of view = 256 mm; flip angle = 8°; total acquisition time = 7:23 min). Images were visually inspected by trained raters for significant motion artifacts. Additionally, segmentations were visually inspected for failures and manually corrected where necessary. Structural MRI data was analyzed by Freesurfer V6.0 to calculate cortical thickness and surface area measures (Fischl et al., 2004) using the Desikan-Killiany Atlas for cortical parcellation (Desikan et al., 2006). The dlPFC was approximated as the rostral middle frontal gyrus (rMFG) and is defined by the Desikan-Killiany atlas as the rostral extent of the superior frontal sulcus, extending to the caudal extent of the middle frontal gyrus (as illustrated in Figures 2 and 4). The medial and lateral boundaries are defined as the superior and inferior frontal sulcus, respectively (Desikan et al., 2006). The vmPFC was approximated using the medial orbitofrontal cortex (mOFC; Bechara et al., 2000; Desikan et al., 2006). This region is defined at the rostral boundary as the rostral extent of the medial orbital gyrus, while the

caudal boundary is the caudal portion of the medial orbital gyrus/gyrus rectus (as illustrated in Figures 2 and 3). The medial boundary extends to the cingulate cortex on the inflated surface, while the lateral boundary is the medial bank of the superior frontal gyrus (or cingulate gyrus when visible) (Desikan et al., 2006). Left and right hemisphere cortical parameters were generated from the parcellation procedure and summed to create a bilateral index for the vmPFC (mOFC) and dlPFC (rMFG). The correlations between hemispheres for each region were between .65 and .89, suggesting these measures could be reasonably combined for evaluation. For surface area measures, we adjusted for intracranial volume by calculating the residual of a least-square derived linear regression between raw surface area and intracranial volume (Voevodskaya et al., 2014). Boundaries for the vmPFC and dlPFC are illustrated in Figures 2-4.

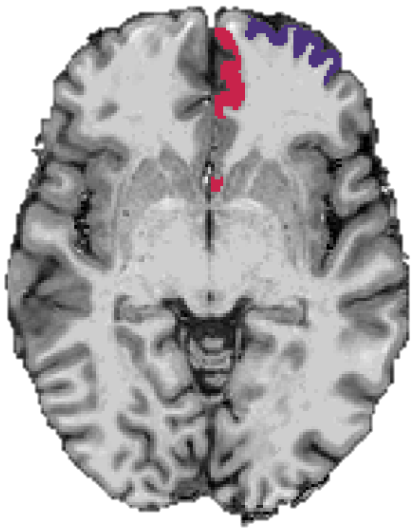

Figure 2. **Left hemisphere segmentation of the medial orbitofrontal cortex (vmPFC; red) and rostral middle frontal gyrus (dlPFC; purple).**

Figure 3. **Parcellation of the mOFC (vmPFC). This region is defined as the rostral extent of the medial orbital gyrus at its rostral boundary, and the caudal portion of the medial orbital gyrus/gyrus rectus at its caudal boundary. The medial boundary extends to the cingulate cortex on the inflated surface, while the lateral boundary is the medial bank of the superior frontal gyrus (or cingulate gyrus when visible).**

Figure 4. **Parcellation of the rMFG (dlPFC). The Desikan-Killiany atlas boundaries of the rMFG include the rostral extent of the superior frontal sulcus, extending to the caudal extent of the middle frontal gyrus. The medial and lateral boundaries are defined as the superior and inferior frontal sulcus, respectively.**

2.5. Statistical analysis

2.5.1. Parameter estimation

To estimate IGT parameters, we employed hBayesDM (hierarchical Bayesian modelling of Decision-Making tasks), a freely available software package for performing hierarchical Bayesian analysis (HBA) of various computational models on an array of decision-making tasks (Ahn et al., 2017). Using a Bayesian approach to estimate parameter values offers several advantages over individual-level estimation offered by the maximum likelihood estimation (MLE). In MLE, parameters are estimated by point estimates that maximize the likelihood of data for each individual separately (Ahn et al., 2017). The downside of this method is that MLE estimates can be noisy and unreliable, especially when working with smaller datasets. The HBA approach improves these shortcomings by introducing group-level parameters on top of individual parameters, leading to a "shrinkage" effect on individual estimates. This occurs as an individual's estimates inform group estimates, which in turn inform the estimates of all individuals (Ahn et al., 2017). The result means that individual parameter estimates are more stable and reliable than individual-level estimates in MLE. Furthermore, unlike MLE, the Bayesian approach uses a combination of two probability distributions to determine the likelihood of a model being true. These distributions are known as the prior and the posterior. The prior distribution allows the researcher to incorporate prior knowledge and assign a probability to each parameter before any data has been collected. The posterior probability refers to the updated probability distribution once data is collected. This is advantageous over the traditional MLE method as it produces a full posterior distribution instead of a point estimate, thus providing more information about the parameters. Following best practice guidelines (Ahn et al., 2016), the candidate models were evaluated to ensure optimal fit of the model to the data and ensure that the parameter interpretations are valid. Hierarchical Bayesian analysis was employed to estimate free parameters in the PVL-Delta, VPP, and ORL models, as described previously (Ahn et al., 2017; Haines et al., 2018; Steingroever et al., 2013; Worthy et al., 2013). The HBA was conducted using Stan (Stan Development Team, 2020), a probabilistic programming language that uses Hamiltonian Monte Carlo (HMC), a variant of Markov Chain Monte Carlo (MCMC), to efficiently sample from high-dimensional probabilistic models as specified by the user (Carpenter et al., 2017). Briefly, MCMC is a sampling

method for characterizing a probability distribution. This method draws a sequence of dependent samples such that the limiting distribution is the posterior of interest. The HMC uses Hamiltonian dynamics, which allows the Markov chain to explore the target distribution more efficiently, which results in faster convergence.

We ran MCMC for each of the models separately. Each MCMC was initialized from a warm start defined by the optimized parameters from a Variational Approximation to the posterior. Because of the complexity of the posterior, not all attempts produced the same starting point. Furthermore, not all the chains were sampling effectively or producing stationary, good-quality samples. At least 100 MCMC chains were run for each model. Each chain ran for 5,000 iterations, but 1,000 iterations were discarded as burn-in, leaving 4,000 per chain for further analysis. The median log-unnormalized posterior was used as a proxy for assessing which chains were sampling from better or worse parts of the posterior. Chains whose median log-unnormalized posterior was within 1% of the maximum across all 100 chains were kept. A maximum of 30 chains were kept for each model. Within each model, the Gelman-Rubin diagnostic was used to determine that all chains had converged to the same limiting distribution. Across all models, the Gelman-Rubin diagnostic was less than 1.01. The 30 chains, each with 4,000 iterations, were combined, resulting in 120,000 iterations per model. After fitting each Bayesian model, we measured its predictive accuracy for model comparison purposes. In order to evaluate model fit and prediction accuracy, we used the leave-one-out information criterion (LOOIC) to generate an estimate of the expected log predictive density (ELPD) for the dataset, which provides a comparison of the quality of the posterior predictions of the models.

2.5.2. Bayesian regressions

To assess the impact of covariates, X, on model parameters, Y, the regression model Y = XB + error was used. This was performed as a second-stage MCMC model to make the model computationally feasible. The Y values were the individual-level parameters (memory, attention to loss etc.) as appropriate for the model. The X values were brain covariates (cortical thickness and surface area). We controlled for age and sex, which are known to have a negative effect on IGT performance (Beitz et al., 2014) and brain structural integrity (Storsve et al., 2014). The model was run using MCMC. At each iteration, a value of Y was sampled from the 120,000 values output of the first

stage. The values of B were sampled using Metropolis-Hastings. Factors that may confound between-subject comparisons (age and sex) were incorporated into the multivariate Bayesian linear regression. Four MCMC chains were run, each with 100,000 iterations. Gelman-Rubin diagnostics were performed to assess convergence to a common posterior within each of the models for each psychosis group. All Gelman-Rubin diagnostics were less than 1.01.

Chapter 3. Results

3.1. Participant characteristics

Tables 3 and 4 show the demographic and clinical characteristics of participants for each group. In our main (No Psychosis) sample, 88.6% had a lifetime history of polysubstance use, with the predominant drug being cocaine (79% of the sample). MRI evidence of traumatic brain injury (TBI) was observed in 5 individuals (5.6% of the sample). Cognitively, premorbid IQ fell in the average range across participants, though other domains of cognitive functioning were below average compared to an age-matched normative sample. Notably, participants displayed impairments in sustained attention and verbal memory. With respect to decision-making, participants most frequently selected cards from deck B compared to other decks, and subjects showed a clear preference for decks with high win frequency (B and D) over alternatives (Figure 5).

A one-way analysis of variance (ANOVA) revealed a statistically significant difference in age ($F = 9.53$, $p = <0.001$) and education ($F = 3.69$, $p = 0.012$) between groups. Post-hoc t-tests revealed that the No Psychosis group ($M = 44.4$ years, $SD = 10.8$, $t = 5.13$, $p < 0.001$) was, on average, markedly older than the Primary Psychosis group ($M = 35.8$ years, $SD = 11$) and SIP group ($M = 39.2$, $SD = 9.8$, $t = 3.16$, $p = 0.002$). The SIP group ($M = 39.2$, $SD = 9.8$) was also older than the Primary Psychosis group ($M = 35.8$ years, $SD = 11$; $t = -2.01$, $p = 0.046$). Further, the No Psychosis group ($M = 10.7$, $SD = 2.5$, $t = 2.47$, $p = 0.015$) and Primary Psychosis group ($M = 10.9$, $SD = 1.9$, $t = 3.4$, p, 0.001) had, on average, more years formal education than the SIP group ($M = 9.8$, $SD = 2.1$). No other group differences were observed.

Table 3. Demographic and clinical characteristics for the No Psychosis group

	Total N	N	%N
Clinical Characteristic		**Mean (SD)**	
Demographics			
Age (years)	91	44.4 (11.0)	
Education (years)	91	10.7 (2.5)	
Premorbid IQ	88	98.0 (9.9)	
Sex			
Male		69	75.8
Female		22	24.2
Ethnicity			
White		55	60.4
Indigenous		26	28.6
Mixed		4	4.4
Other		6	6.6
Alcohol & Drug Dependence			
Alcohol		49	53.8
Cocaine		72	79.1
Methamphetamine		25	27.5
Opioid		55	60.4
Cannabis		31	34.1
Other		16	17.6
Psychiatric Illness			
Mood disorder		20	22.0
Viral Infection			
HIV		13	14.3
HCV active		28	30.8
HCV cleared		31	34.1
Traumatic brain injury			
MRI evidence of TBI		5	5.6
Cognition			
HVLT immediate recall score, t-score		32.3 (9.9)	
RVIP signal detection, A', standard score		-1.2 (1.1)	
Stroop color-word, t-score		50.0 (8.7)	
IDED total errors adjusted		55.0 (42.1)	
IGT Net score		-0.8 (30.4)	

Note. HVLT = Hopkin's Verbal Learning Test (learning and memory); RVIP = CANTAB Rapid Visual Information Processing Task (sustained attention); IDED = Intradimensional-extradimensional shift task (mental flexibility and reversal learning).

Table 4. Demographic and clinical characteristics for the psychosis groups

	Primary Psychosis			SIP			PNOS		
	Total N	N	%N	Total N	N	%N	Total N	N	%N
Clinical Characteristic		Mean (SD)			Mean (SD)			Mean (SD)	
Demographics									
Age (years)	79	35.8 (10.8)		71	39.2 (9.7)		31	41.7 (11.8)	
Education (years)	79	10.9 (1.9)		71	9.8 (2.1)		31	10.3 (2.1)	
Premorbid IQ	78	99.3 (9.0)		71	97.0 (9.1)		30	99.0 (10.4)	
Sex									
Male		63	80.0		58	82.0		27	87.1
Female		16	20.0		13	18.0		4	12.9
Ethnicity									
White		49	62.0		44	62.0		12	38.7
Indigenous		16	20.3		20	28.2		14	45.2
Mixed		3	3.8		3	4.2		2	6.5
Other		11	14.0		4	5.6		3	9.7
Alcohol & Drug Dependence									
Alcohol		36	45.5		41	57.7		19	61.3
Cocaine		58	73.4		60	84.5		23	74.2
Methamphetamine		44	55.7		36	50.7		12	38.7
Opioid		39	49.4		53	74.6		16	51.6
Cannabis		54	68.4		39	54.9		19	61.3
Other		15	19.0		8	11.3		5	16.1
Psychiatric Illness									
Mood disorder		20	25.3		19	26.8		12	38.7

Viral Infection						
HIV	7	8.9	9	12.7	6	19.4
HCV active	14	17.7	21	29.6	11	35.5
HCV cleared	15	19.0	28	39.4	7	22.6
Traumatic brain injury						
MRI evidence of TBI	1	1.3	2	2.8	0	0
Cognition						
HVLT immediate recall score, t-score	32.7 (12.7)		31.5 (10.4)		32.4 (13.5)	
RVIP signal detection, A', standard score	-1.0 (1.2)		-1.3 (1.3)		-1.3 (1.5)	
Stroop color-word, t-score	48.6 (10.8)		49.9 (7.8)		48.2 (11.4)	
IDED total errors adjusted	47.1 (38.6)		49.8 (47.0)		55.1 (53.6)	
IGT Net score	-6.6 (29.6)		-4.5 (33.9)		-4.5 (27.3)	

Note. HVLT = Hopkin's Verbal Learning Test (learning and memory); RVIP = CANTAB Rapid Visual Information Processing Task (sustained attention); Stroop color-word (response inhibition); IDED = Intradimensional-extradimensional shift task (mental flexibility and reversal learning); SIP = Substance induced psychosis; PNOS = Psychosis not otherwise specified.

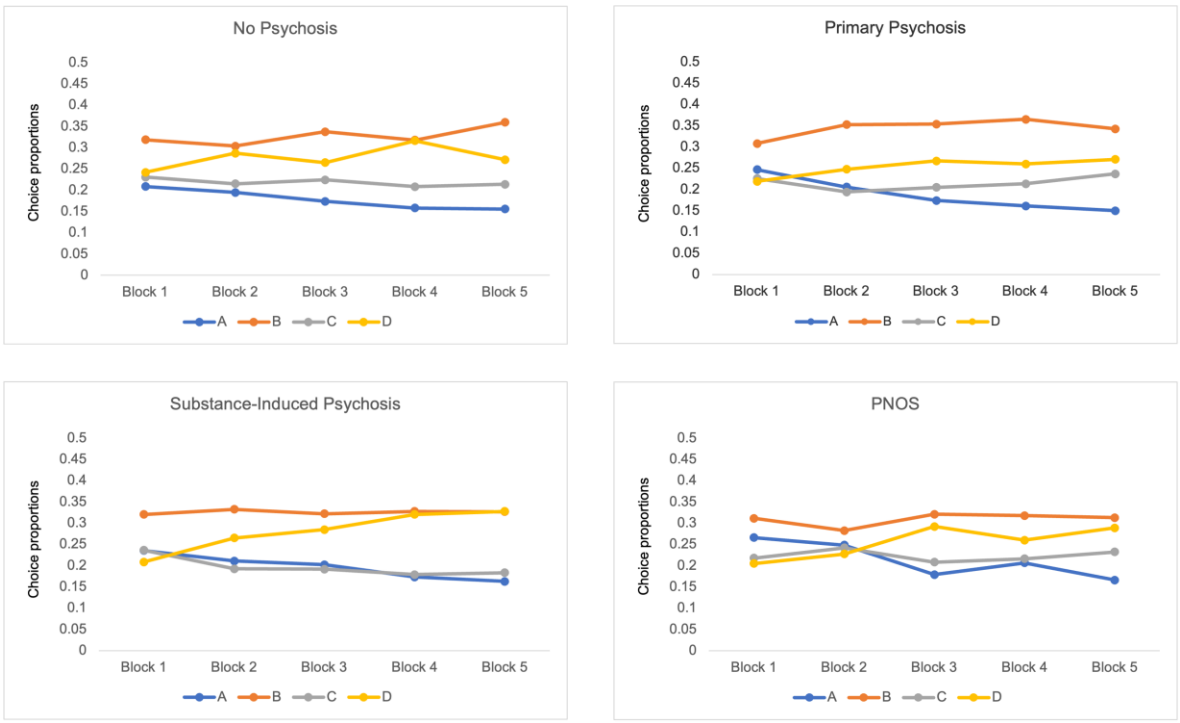

Figure 5. **Deck choice proportions over time. Participants show a preference for deck B throughout blocks, and a preference for decks with high win probability (decks B and D) on trials 21-100 (Blocks 2-5).**

3.2. Model evaluation

In order to evaluate the best-fitting model for our data, our approach was to compare one-step-ahead prediction accuracy across models as indexed by the LOOIC. Measures of predictive accuracy, such as LOOIC, are defined based on the deviance, which is the expected log predictive density of the fitted model multiplied by -2 (Gelman et al., 2014). As such, lower values indicate a better model fit. As illustrated in Figure 6, and consistent with Haines et al. (2018), results suggested that the VPP and ORL models outperform the PVL-Delta on one step ahead prediction accuracy.

Given these results, both the VPP and ORL models were included for the Bayesian regression. This decision was made for a few reasons. First, the ORL and VPP model different parameters that are of interest to the current study. In particular, the ORL captures differential valuation of gains versus losses, which may be particularly important in substance-using populations, which are known to have significantly reduced loss aversion and increased sensitivity to immediate rewards (Haines et al., 2018). Furthermore, the ORL accounts for win frequency effects, which have been shown to be

related to vmPFC functioning (O'Doherty, 2004). Although the PVL-Delta and VPP implicitly capture this effect, their parameters do not dissociate the effects of loss aversion or valuation (i.e., the utility shape) from that of win frequency (Haines et al., 2018). Furthermore, as stated previously, the ORL and VPP model memory for past deck selection with different parameters. The VPP uses a recency parameter (*A*) to quantify the memory for rewards and losses, where a low value indicates the most recent outcome has a low influence on the new expected value (Steingroever et al., 2014). In contrast, the ORL uses a decay (*K*) parameter, which describes how quickly decision-makers forget their past deck choices (Haines et al., 2018).

The second reason for selecting two models is that across the three psychosis groups, the VPP and ORL were statistically indistinguishable in the quality of predicting the decision process.

Figure 6. **LOOIC values indicating model fit.**
Note. Lower LOOIC values represent better fit compared to other models tested on the same data set. LOOIC values were baselined by the best model in each comparison (i.e., best model LOOIC = 0).

3.3. Parameter estimations

IGT population parameter distributions for the sample are presented in Figure 7. Visual analysis of trace plots for MCMC convergence shows acceptable mixing of chains. The extracted parameters for the ORL model in the No Psychosis group demonstrated that participants displayed a striking lack of sensitivity to losses (M = 0.043, 95% CI = 0.029 – 0.057) and a greater sensitivity to rewards (M = 0.2, 95% CI = 0.13 – 0.27). Furthermore, individuals tended to prefer decks that produced wins at higher frequency (M = 1.17, 95% CI = 0.76 – 1.59). With respect to memory, participants tended to remember longer histories of their deck selection (M = 0.97, 95% CI = 0.64 – 1.32) and did not display a clear preference to switch or stay with recently chosen cards (M = 1.0, 95% CI = -0.17 – 2.23). On the VPP, participants also demonstrated a lack of attention to losses (M = 0.39, 95% CI = 0.16 – 0.65). Consistent with the memory parameter on the ORL, the participants displayed slow forgetting and weak recency effects on the VPP (M = 0.01, 95% CI = 0.002 – 0.046). The perseverative parameters on the VPP suggest that participants tended to perseverate after selecting a winning card (M = 0.46, 95% CI = 0.062 – 1.26) and switch after selecting a losing card (M = -0.37, 95% CI = -1.1 – -0.029).

The three psychosis groups demonstrated a similar pattern of results, including a lack of sensitivity to losses and greater sensitivity to gains, with a preference for decks with a higher frequency of wins. They also tended to remember longer histories of their selections. One difference that emerged was that participants with a history of psychotic disorders did not tend to switch their deck selection after a loss.

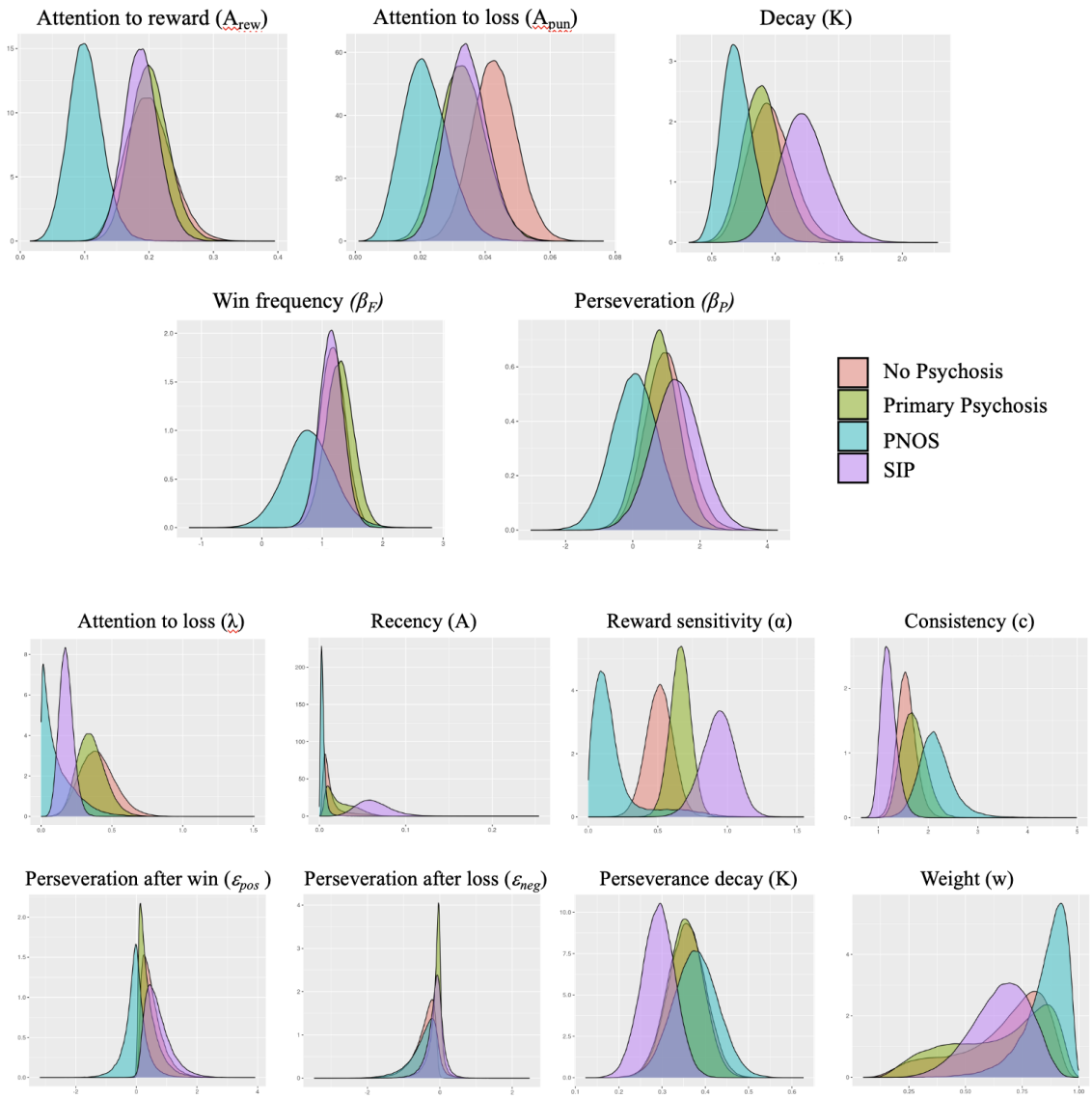

Figure 7. VPP and ORL group-level parameter distributions

3.4. Neuroimaging

Cortical thickness and surface area measures are presented in Table 5. For surface area measures, we adjusted for intracranial volume by calculating the residual of a least-square derived linear regression between raw surface area and intracranial volume (Voevodskaya et al., 2014). A one-way ANOVA revealed a statistically significant difference in vmPFC cortical thickness (F = 2.81, p = 0.04) and vmPFC surface area (F = 2.73, p = 0.044) between groups. Post-hoc t-tests revealed that the No Psychosis group had a significantly thinner vmPFC cortex than the Primary Psychosis group (t = -2.42, p

= 0.017) as well as thinner cortex (t = -2.64, p = 0.025) and smaller surface area (t = -2.4, p = 0.017) than the SIP group. The SIP group also had a larger vmPFC area than the Primary Psychosis (t = -2.42, p = 0.017) and PNOS (t = -2.08, p = 0.04) groups.

Table 5. Cortical thickness and surface area measures

Group	Region of interest	Mean (SD)	Range
No Psychosis (n = 91)	vmPFC		
	Cortical thickness (mm)	4.67 (0.028)	3.61 – 5.27
	Cortical surface area (mm^2)	4017.37 (29.11)	3247.21 – 4516.6
	dlPFC		
	Cortical thickness (mm)	4.55 (0.029)	3.56 – 5.14
	Cortical surface area (mm^2)	12281.52 (126.71)	9789.65 – 16023.02
Primary Psychosis (n = 79)	vmPFC		
	Cortical thickness (mm)	4.76 (0.023)	4.23 – 5.22
	Cortical surface area (mm^2)	4018.06 (28.8)	3485.1 – 4744.33
	dlPFC		
	Cortical thickness (mm)	4.58 (0.024)	4.01 – 5.11
	Cortical surface area (mm^2)	12500.62 (133.11)	9773.04 – 16657.53
SIP (n = 71)	vmPFC		
	Cortical thickness (mm)	4.76 (0.031)	3.82 – 5.63
	Cortical surface area (mm^2)	4119.98 (30.74)	3358.33 – 4697.69
	dlPFC		
	Cortical thickness (mm)	4.6 (0.036)	3.71 – 5.72
	Cortical surface area (mm^2)	12527.67 (114.19)	10907.78 – 14831.79
PNOS (n = 31)	vmPFC		
	Cortical thickness (mm)	4.76 (0.045)	4.27 – 5.29
	Cortical surface area (mm^2)	4000.13 (51.36)	3468.07 – 4553.74
	dlPFC		
	Cortical thickness (mm)	4.56 (0.043)	4.13 – 5.1
	Cortical surface area (mm^2)	12265.49 (207.2)	10037.25 – 15060.64

Note. SIP = Substance induced psychosis; PNOS = Psychosis not otherwise specified.

3.5. Dissociation of prefrontal brain regions and IGT parameters

Tables 6 and 7 show the results of the Bayesian linear regressions in the main (i.e., No Psychosis) group and three psychosis groups for both ORL and VPP models. The mean represents the estimate of the posterior distribution, and the credible interval (CI) represents the 95% probability that the coefficient falls within the described range. Wider intervals mean more uncertainty regarding the parameter. A credible interval

overlapping zero indicates uncertainty, while intervals that do not overlap zero indicate stronger evidence of an effect. Similar to prior studies, we use the term “strong evidence” to refer to group differences where the 95% credible interval excludes 0 (Haines et al., 2018; Kruschke, 2014)

As seen in Tables 6 and 7, we failed to reveal strong evidence for any of the predicted associations between PFC morphology and attention to loss/gains or memory in either of the selected models. With respect to our hypotheses, this means that, after accounting for age and sex, we did not observe the predicted dissociation between vmPFC and dlPFC regions (i.e., thickness or surface area) and these IGT parameters. Contrary to our hypothesis, we observed strong evidence of a positive relationship between the attention to rewards (A_{rew}) parameter and dlPFC, such that thicker dlPFC cortex was associated with more attention to rewards. No such relationship was observed between A_{rew} and vmPFC, though, as predicted, there was no association between vmPFC and memory components (see Table 8 for a summary of results).

Results from the psychosis groups demonstrated a similar pattern of findings. No association was observed between PFC brain metrics and attention to reward, attention to loss, or memory in either of the tested models.

Table 6. Posterior summary of Bayesian linear regression for ORL model parameters.

Dependent Variable	Group	vmPFC Thickness (95%CI)	vmPFC Surface area (95% CI)	dlPFC Thickness (95% CI)	dlPFC Surface area (95% CI)
A_{rew}	No Psychosis	$-2.42e^{-1}$	$-4.50e^{-5}$	**$3.43e^{-1}$***	$-6.10e^{-6}$
		($-6.24e^{-1}$ - $1.43e^{-1}$)	($-2.95e^{-4}$ - $2.07e^{-4}$)	**($1.55e^{-2}$ - $6.64e^{-1}$)**	($-6.43e^{-5}$ - $5.15e^{-5}$)
	Primary Psychosis	$-5.98e^{-2}$	$9.50e^{-5}$	$7.92e^{-1}$	$-3.27e^{-5}$
		($-3.81e^{-1}$ - $2.75e^{-1}$)	($-7.0e^{-4}$ - $8.7e^{-4}$)	($-3.4e^{-1}$ – 1.92)	($-2.24e^{-4}$ - $1.59e^{-4}$)
	SIP	$1.20e^{-3}$	$2.23e^{-5}$	$1.85e^{-2}$	$6.00e^{-6}$
		($-2.71e^{-1}$ - $2.58e^{-1}$)	($-1.69e^{-4}$ - $2.19e^{-4}$)	($-2.14e^{-1}$ - $2.66e^{-1}$)	($-4.46e^{-5}$ - $5.78e^{-5}$)
	PNOS	$1.87e^{-2}$	$-2.71e^{-5}$	$-1.83e^{-2}$	$7.0e^{-7}$
		($-2.27e^{-1}$ - $2.58e^{-1}$)	($-1.94e^{-4}$ - $1.45e^{-4}$)	($-2.77e^{-1}$ - $2.45e^{-1}$)	($-4.42e^{-5}$ - $4.47e^{-5}$)
A_{pun}	No Psychosis	$9.38e^{-3}$	$-2.39e^{-5}$	$-6.95e^{-3}$	$-2.30e^{-6}$
		($-8.15e^{-2}$ - $9.87e^{-2}$)	($-8.16e^{-5}$ - $3.25e^{-5}$)	($-9.29e^{-2}$ - $7.78e^{-2}$)	($-1.60e^{-5}$ - $1.10e^{-5}$)
	Primary Psychosis	$-5.46e^{-2}$	$3.98e^{-5}$	$8.26e^{-2}$	$7.00e^{-7}$
		($-1.51e^{-1}$ - $4.17e^{-2}$)	($-2.51e^{-5}$ - $1.06e^{-4}$)	($-9.30e^{-3}$ - $1.73e^{-1}$)	($-1.38e^{-5}$ - $1.57e^{-5}$)
	SIP	$8.34e^{-3}$	$-2.45e^{-5}$	$-1.72e^{-2}$	$7.30e^{-6}$
		$-8.19e^{-2}$ - $9.68e^{-2}$	$-9.02e^{-5}$ - $4.22e^{-5}$	$-9.64e^{-2}$ - $6.30e^{-2}$	$-1.02e^{-5}$ - $2.43e^{-5}$
	PNOS	$-1.35e^{-3}$	$6.20e^{-6}$	$2.37e^{-3}$	$4.30e^{-6}$
		$-8.55e^{-2}$ - $8.17e^{-2}$	$-5.38e^{-5}$ - $6.71e^{-5}$	$-9.04e^{-2}$ - $9.14e^{-2}$	$-1.14e^{-5}$ - $1.93e^{-5}$
K	No Psychosis	$-2.30e^{-1}$	$-4.80e^{-6}$	$3.72e^{-1}$	$1.71e^{-5}$
		(-1.84 - 1.41)	($-1.04e^{-3}$ - $1.01e^{-3}$)	(-1.14 - 1.91)	($-2.19e^{-4}$ - $2.49e^{-4}$)
	Primary Psychosis	$-2.03e^{-1}$	$8.21e^{-5}$	$2.54e^{-1}$	$3.17e^{-5}$
		-1.58 - 1.09	$-7.85e^{-4}$ - $9.45e^{-4}$	-1.07 - 1.49	$-1.8e^{-4}$ - $2.52e^{-4}$
	SIP	$4.14e^{-1}$	$-2.03e^{-4}$	$-3.96e^{-2}$	$1.21e^{-5}$
		-1.11 - 1.98	$-1.25e^{-3}$ - $8.7e^{-4}$	-1.55 - 1.4	$-3.1e^{-4}$ - $3.3e^{-4}$
	PNOS	$-2.64e^{-1}$	$-1.1e^{-4}$	$9.55e^{-2}$	$1.08e^{-4}$
		-1.57 - 1.08	$-9.5e^{-4}$ - $7.3e^{-4}$	-1.25 - 1.45	$-1.3e^{-4}$ - $3.4e^{-4}$
β_F	No Psychosis	$-1.78e^{-1}$	$-7.18e^{-4}$	1.08	$7.35e^{-5}$
		(-2.08 - 1.66)	($-1.94e^{-3}$ - $5.19e^{-4}$)	(-0.732 - 2.86)	($-2.11e^{-4}$ - $3.46e^{-4}$)

	Primary Psychosis	$-3.7e^{-1}$	$7.74e^{-4}$	$4.67e^{-1}$	$-7.2e^{-5}$
		$(-2.29 - 1.49)$	$(-4.85e^{-4} - 2.02e^{-3})$	$(-1.38 - 2.28)$	$(-3.88e^{-4} - 2.49e^{-4})$
	SIP	$8.16e^{-1}$	$3.56e^{-4}$	$-2.29e^{-1}$	$-1.9e^{-4}$
		$(-8.45e^{-1} - 2.49)$	$(-7.7e^{-4} - 1.52e^{-3})$	$(-1.83 - 1.35)$	$(-5.3e^{-4} - 1.6e^{-4})$
	PNOS	-2.15	$\mathbf{-2.7e^{-3}*}$	$\mathbf{3.07*}$	$\mathbf{7.51e^{-4}*}$
		$(-5.0 - 0.622)$	$\mathbf{(-4.46e^{-3} - -8.9e^{-4})}$	$\mathbf{(1.75e^{-1} - 5.87)}$	$\mathbf{(2.61e^{-4} - 1.25e^{-3})}$
β_P	No Psychosis	$\mathbf{-5.78*}$	$2.06e^{-3}$	2.83	$7.48e^{-5}$
		$\mathbf{(-10.2 - -1.26)}$	$(-8.78e^{-4} - 5.07e^{-3})$	$(-1.58 - 6.96)$	$(-6.13e^{-4} - 7.46e^{-4})$
	Primary Psychosis	$\mathbf{-5.56*}$	$4.09e^{-4}$	3.32	$4.27e^{-4}$
		$\mathbf{(-9.21 - -1.92)}$	$(-2.0e^{-3} - 2.85e^{-3})$	$(-0.202 - 6.81)$	$(-1.92e^{-4} - 1.04e^{-3})$
	SIP	1.83	$\mathbf{-4.95e^{-3}*}$	$-1.18e^{-1}$	$7.88e^{-4}$
		$(-3.27 - 6.94)$	$\mathbf{-(8.55e^{-3} - -1.31e^{-3})}$	$(-5.0 - 4.68)$	$(-3.2e^{-4} - 1.88e^{-3})$
	PNOS	2.81	$\mathbf{2.66e^{-3}*}$	$\mathbf{-6.59*}$	$1.38e^{-4}$
		$(-1.05 - 6.85)$	$\mathbf{(9.01e^{-5} - 5.18e^{-3})}$	$\mathbf{(-10.6 - -2.51)}$	$(-5.70e^{-4} - 8.6e^{-4})$

Table 7. Posterior summary of Bayesian linear regression for VPP model parameters.

Dependent Variable	Group	vmPFC Thickness (95%CI)	vmPFC Surface area (95% CI)	dlPFC Thickness (95% CI)	dlPFC Surface area (95% CI)
λ	No Psychosis	$6.0e^{-1}$	$-5.27e^{-5}$	$-3.09e^{-2}$	$-2.75e^{-5}$
		(-1.1 - 1.4)	($-8.0e^{-4}$ - $7.0e^{-4}$)	(-1.17 - 1.1)	($-2.03e^{-4}$ - $1.45e^{-4}$)
	Primary Psychosis	$-5.83e^{-1}$	$9.50e^{-5}$	$7.92e^{-1}$	$-3.27e^{-5}$
		(-1.8 – $5.9e^{-1}$)	($-7.0e^{-4}$ - $8.7e^{-4}$)	($-3.4e^{-1}$ – 1.92)	($-2.24e^{-4}$ - $1.59e^{-4}$)
	SIP	$6.30e^{-2}$	$-6.93e^{-5}$	$-6.6e^{-2}$	$1.02e^{-5}$
		($-5.47e^{-1}$ - $6.79e^{-1}$)	($-5.0e^{-4}$ - $3.6e^{-4}$)	($-6.51e^{-1}$ - $4.97e^{-1}$)	($-1.13e^{-4}$ - $1.35e^{-4}$)
	PNOS	$3.80e^{-3}$	$1.26e^{-5}$	$6.22e^{-3}$	$5.0e^{-7}$
		($-8.75e^{-1}$ - $8.68e^{-1}$)	($-5.58e^{-4}$ - $5.8e^{-4}$)	($-8.84e^{-1}$ - $9.17e^{-1}$)	($-1.51e^{-4}$ - $1.56e^{-4}$)
A	No Psychosis	$-3.7e^{-3}$	$-5.6e^{-6}$	$8.31e^{-3}$	$1.00e^{-7}$
		($-9.8e^{-2}$ - $9.0e^{-2}$)	($-6.5e^{-5}$ - $5.5e^{-5}$)	($-8.03e^{-2}$ - $9.74e^{-2}$)	($-1.42e^{-5}$ - $1.42e^{-5}$)
	Primary Psychosis	$-3.70e^{-3}$	$5.50e^{-6}$	$3.84e^{-3}$	$-2.30e^{-6}$
		($-1.22e^{-1}$ - $1.11e^{-1}$)	($-7.29e^{-5}$ - $8.57e^{-5}$)	($-1.06e^{-1}$ - $1.14e^{-1}$)	($-2.06e^{-5}$ - $1.54e^{-5}$)
	SIP	$2.05e^{-3}$	$-6.0e^{-7}$	$-6.73e^{-4}$	$1.0e^{-7}$
		($-1.57e^{-1}$ - $1.56e^{-1}$)	($-1.16e^{-4}$ - $1.15e^{-4}$)	($-1.40e^{-1}$- $1.38e^{-1}$)	($-2.98e^{-5}$ - $3.01e^{-5}$)
	PNOS	$-3.28e^{-3}$	$-8.80e^{-6}$	$1.44e^{-2}$	$2.20e^{-6}$
		($-3.93e^{-2}$ - $3.40e^{-2}$)	($-3.55e^{-5}$ - $1.79e^{-5}$)	($-2.69e^{-2}$ - $5.39e^{-2}$)	($-4.70e^{-6}$ - $9.10e^{-6}$)
ε_{pos}	No Psychosis	-1.3	$3.98e^{-5}$	$9.73e^{-1}$	$9.09e^{-5}$
		(-3.8 - 1.3)	($-1.6e^{-3}$ - $1.7e^{-3}$)	(-1.43 - 3.35)	($-2.67e^{-4}$ - $4.67e^{-4}$)
	Primary Psychosis	-1.41	$2.68e^{-4}$	1.04	$6.90e^{-5}$
		(-3.81 - $9.36e^{-1}$)	($-1.24e^{-3}$ - $1.79e^{-3}$)	(-1.19 – 3.33)	($-3.09e^{-4}$ - $4.59e^{-4}$)
	SIP	$5.26e^{-1}$	$-1.48e^{-3}$	$2.22e^{-1}$	$2.22e^{-4}$
		(-2.62 - 3.53)	($-3.70e^{-3}$ - $6.73e^{-4}$)	(-2.74 - 3.15)	($-4.35e^{-4}$ -$8.84e^{-4}$)
	PNOS	1.03	$3.17e^{-4}$	-2.44	$2.65e^{-4}$
		(-2.22 - 4.19)	($-1.68e^{-3}$ - $2.34e^{-3}$)	(-5.76 - $9.56e^{-1}$)	($-2.90e^{-4}$ - $8.42e^{-4}$)
ε_{neg}	No Psychosis	$-6.0e^{-1}$	$5.56e^{-4}$	$-1.23e^{-1}$	$-6.70e^{-6}$
		(-3.2 - 1.8)	($-1.0e^{-3}$ - $2.0e^{-3}$)	(-2.4 - 2.2)	($-3.69e^{-4}$ - $3.48e^{-4}$)
	Primary Psychosis	-1.1	$1.24e^{-5}$	$6.07e^{-1}$	$9.63e^{-5}$

	(-3.17 - 8.99e^{-1})	(-1.31e^{-3} - 1.28e^{-3})	(-1.28 – 2.56)	(-2.27e^{-4} - 4.23e^{-4})
SIP	-1.05e^{-1}	-3.34e^{-5}	1.30e^{-1}	-5.30e^{-6}
	(-1.93 - 1.78)	(-1.32e^{-3} - 1.25e^{-3})	(-1.66 - 1.88)	(-3.99e^{-4} - 3.76e^{-4})
PNOS	1.23	1.62e^{-3}	-2.50	-1.47e^{-4}
	(-2.05 - 4.52)	(-4.63e^{-4} - 3.80e^{-3})	(-5.98 - 8.24e^{-1})	(-7.28e^{-4} - 4.28e^{-4})

Note. vmPFC = ventromedial prefrontal cortex; dlPFC = dorsolateral prefrontal cortex; λ = attention to loss; *A* = memory for card selection; ε_{pos} = perseveration after a win; ε_{neg} = perseveration after a loss; A_{rew} = attention to gain; A_{pun} = attention to loss; K = memory for card selection; β_F = win frequency; β_P = perseveration/reversal learning.
*****Denotes strong evidence of a relationship.

Table 8. Summary of primary hypotheses

Primary Hypothesis	IGT Component	Predicted Association	Result
1	ORL A_{pun}, VPP λ	Lower attention to losses will be associated with lower vmPFC thickness/ surface area and show no association with dlPFC thickness/ surface area.	**Not supported**. Attention to loss parameters were not associated with vmPFC. Attention to loss was not associated with dlPFC morphology, as predicted.
2	ORL A_{rew}	Higher attention to reward will be associated with greater vmPFC thickness/ surface area and show no association with dlPFC thickness/ surface area.	**Not supported.** Attention to reward was not associated with vmPFC. Contrary to our hypothesis thicker dlPFC was associated with more attention to reward.
3	ORL K, VPP A	Shorter memory for past card selection will be associated with lower dlPFC thickness/surface area and show no association with vmPFC thickness/surface area	**Not supported.** Recency/decay parameters were not associated with dlPFC. Recency/decay parameters were not associated with dlPFC morphology, as predicted.

3.6. Supplemental IGT parameters

To further understand the nature of the relationship between PFC thickness/surface area and components of decision-making, we analyzed the win frequency and perseverative parameters within the ORL and VPP models. Regarding perseveration, on the ORL model, thinner vmPFC was associated with more perseveration. There was also strong evidence that older participants tended to perseverate more. We did not observe the predicted association between win frequency and vmPFC morphology. On the VPP, none of the perseveration parameters were associated with vmPFC of dlPFC morphology.

Results from the psychosis groups, on the ORL, strong evidence of an association emerged between the win frequency parameter and both the vmPFC and dlPFC in the PNOS group, such that larger vmPFC surface area was associated with less win frequency effect, while larger and thicker dlPFC was associated with greater win frequency effects. On the perseveration parameter, smaller and thinner vmPFC was associated with greater perseveration in the SIP and primary psychosis groups,

respectively. In the PNOS group, smaller vmPFC was associated with less perseveration, while thinner dlPFC was associated with greater perseveration.

Chapter 4. Discussion

Despite the widespread use of the IGT as a laboratory-based measure of decision-making in numerous healthy and clinical populations, there is a scarcity of studies examining the relationship between components of decision-making on the IGT and brain structural morphology. In the current study, we investigated the relationship between PFC morphology and components of decision-making on the IGT in a highly marginalized sample of homeless and precariously housed substance users where risks for PFC damage are pervasive. To our knowledge, this is the first study to directly investigate the relationship between IGT parameters and neuroanatomical substrates in a group of individuals with a history of substance use disorder and multimorbid illness.

4.1. IGT parameter estimations

In the current study, and as we previously reported in a highly overlapping sample using similar modelling approaches (Baitz et al. 2021), participants demonstrated a striking lack of attention to losses. This pattern has been reliably observed in persons with substance use disorder (Ahn et al., 2014; Baitz et al., 2021; Fridberg et al., 2010; Haines et al., 2018) and was consistent between models (ORL, VPP) and across all groups in the current study. In addition to a lack of attention to losses, participants were much more sensitive to rewards and preferred decks with higher win frequency. Taken together and consistent with past work in a large, overlapping group of marginalized individuals (Baitz et al., 2021), it appears that losses on the IGT are not registering and that learning was largely driven by positive outcomes. This finding has previously been reported in chronic drug users and may be associated with increased risk-taking behaviours (Haines et al., 2018; Lane et al., 2005; Lane & Cherek, 2002). According to the seminal work of Kahneman and Tversky (1979), when faced with an economic decision, holding all other things equal, losses tend to have a greater impact on behaviour than gains. Despite this, chronic substance users have consistently shown a reduced sensitivity to losses on the IGT, and our results further support this finding. Individuals with a history of substance use disorder are known to display impairments on the IGT similar to those with vmPFC damage (Bechara & Damasio, 2002), which has been described as a “myopia” for the future. However, previous work in an overlapping sample of marginalized persons on the DTES failed to

find a link between attention to losses and real-world risk-taking behaviour (Baitz et al., 2021). Our findings from the ORL suggest that attention to gains, or the difference between attention to gains and losses, might be a more important marker for real-world risk-taking behaviour.

Surprisingly, and counter to our expectation, results were suggestive of low decay and recency across groups, indicating that decisions were influenced by more distant, as opposed to more recent events. One explanation for this possibly counterintuitive finding is that distal events are interfering with more recent events during decision-making. Supporting this position, our team investigated serial position effects related to memory dysfunction in a highly overlapping sample of homeless and precariously housed individuals (Gicas et al., 2023). In this sample, the serial position profile was characterized by a diminished recency effect in relation to the primacy effect. In other words, individuals demonstrated poorer recall of recent verbally presented items relative to earlier presented (primacy) items. This was consistent with our sample of participants, who demonstrated clear impairments in their verbal learning abilities. It was proposed by Gicas et al. (2023) that a diminished recency effect may be secondary to impairments in working memory. Although this phenomenon has not been widely reported in the literature, other examples of diminished recency in those presenting with other neurological disorders, such as cerebral small vessel disease, indicate this may be related to compromised frontal-subcortical circuitry (Chander et al., 2018). Adding to this, high rates of cerebral small vessel disease have been observed among residents of the DTES and linked to impairments in cognition and decision-making on the IGT (Zhou et al., 2019, 2020).

In the current study, this means that decisions may be more strongly influenced by distant rather than recent events, as past experiences or ingrained habits take precedence over current information. This tendency may be partially explained by deficits in executive attention, which is responsible for focusing cognitive resources on the most relevant and immediate factors. When executive attention is compromised, individuals may excessively "think back" to past events, such as previous substance use rewards or past coping strategies, rather than focusing on more recent feedback or changing circumstances. As cognitive demands are increased and decision-making depletes mental resources, initial learning may be favoured at the expense of new learning, which results in a proactive interference effect. This tendency to ruminate on

past experiences can interfere with processing newer, more immediate information as the brain struggles to update its decision-making strategy. Consequently, distant events can dominate the decision-making process, leading to decisions that are based on outdated information and maladaptive behaviours, even when current events suggest that a different course of action would be more beneficial.

Regarding perseveration, we observed a general trend in results for perseveration parameters between the VPP and ORL. Data from the ORL suggest participants generally had a positive perseverance weight and engaged in less exploratory behaviour, though the evidence for this was weak, with credible intervals overlapping zero. Results from the VPP similarly suggest there was a tendency for participants to stay on a recently chosen deck if they had selected a win. On the other hand, participants tended to switch decks after selecting a losing card.

Collectively, these results may mirror decision-making strategies observed in real-world situations. Low attention to losses, high attention to rewards, and longer memory of past rewards or card selections can closely mirror patterns of decision-making seen in drug-using behaviour. Individuals often exhibit a tendency to focus on immediate rewards, such as the euphoric effects of drug use, while disregarding or underestimating the negative consequences, such as health risks or legal troubles. Similarly, individuals who focus excessively on potential rewards and have a heightened memory of past "wins" may continue to engage in risky behaviour despite repeated losses, much like a person with substance use disorder who continues to seek the "high" from a substance despite the accumulating costs and depreciating positive effects. This dynamic creates a cycle where the individual becomes increasingly fixated on immediate gratification, often at the expense of long-term consequences, making it harder to break free from substance dependence.

4.2. Dissociation of prefrontal brain regions and IGT parameters

Results from our primary hypotheses of a differential association between cognitive parameters and PFC regions was not supported, as the predicted associations between vmPFC morphology and attention to gains and losses on the VPP and ORL models was not observed. Furthermore, the predicted association between dlPFC and

memory parameters was also not observed. Interestingly, and counter to our prediction, we found strong evidence that thicker dlPFC was related to higher attention to gains, suggesting the dlPFC may also be involved in reward processing. Though unexpected, we know decision-making is a complex cognitive process involving highly integrated and overlapping neural networks of which the vmPFC and dlPFC are both a part of. Dysfunction within an interconnected system can have many different manifestations, meaning that dysfunction within either region may have consequences that extend to other parts of the neural circuitry. With respect to decision-making, this means that the vmPFC and dlPFC may not necessarily be bound by the restrictive view as “hot” and “cold” cognitive domains. Supporting this position, the dlPFC has been shown to modulate activity in vmPFC (Baumgartner et al., 2011; Hare et al., 2014), which may function to alter striatal reward encoding and drive dopaminergic activation during reward anticipation (Ballard et al., 2011). This means that the dlPFC may be an important substrate for both “hot” (e.g., reward-based) as well as “cold” processes.

Along these lines, the vmPFC may also have a function in reward-based memory, as it has been shown to integrate reward history to generate outcome expectancies associated with stimuli or responses (Riceberg & Shapiro, 2012; Schoenbaum et al., 2009). Damage to posterior aspects of the vmPFC has also been linked to an individual’s tendency to differently weigh recent compared to past experience on the IGT (Hochman et al., 2010). These findings collectively point to overlapping and non-dissociable roles of the vmPFC and dlPFC during value-based decision-making.

Results from our exploratory analyses demonstrate largely consistent results between individuals with no psychosis and those presenting with a history of primary psychosis and SIP. That is, no relationship was observed regarding vmPFC morphology and attention to gains or loss, or dlPFC morphology and memory. These findings are consistent with the only study we know that has investigated a relationship between PFC morphology and IGT parameters. In their study, Premkumar et al. (2008) observed that the relationship between components of IGT performance and frontotemporal grey matter volume was lost or attenuated in schizophrenia.

In contrast to Primary Psychosis and SIP groups, results from the PNOS group differed from the others across numerous parameters, and we observed strong evidence

of a positive relationship between vmPFC area and perseveration, as well as a negative relationship between dlPFC and perseveration. When interpreting these results, it is important to consider a number of factors within the PNOS group. First, we must consider the diagnostic nature of PNOS. Because a majority of the data for the current project was collected during the time the DSM-IV-TR was in use, we opted to remain consistent in using terminology and diagnoses from this version. The latest edition of the DSM, the DSM-5-TR, has recategorized PNOS as i) other specified schizophrenia spectrum and other psychotic disorders and ii) unspecified schizophrenia spectrum and other psychotic disorders. The diagnosis of PNOS was traditionally made when psychotic syndromes did not fit the description of any of the specific psychotic disorders or when inadequate information was available (Widing et al., 2020). This means that PNOS served as a temporary diagnosis with low diagnostic stability (Fusar-Poli et al., 2016). Therefore, the heterogeneity within this group will contribute to uncertainty in how clinically relevant the reported association is. Next, it should be noted that this was the smallest group, containing only 31 individuals, which impacts statistical inference. In a frequentist approach, we understand that low power reduces the likelihood that a statistically significant result reflects a true effect (Button et al., 2013). While the Bayesian approach lessens this concern and can traditionally perform better in small samples (Muthén & Asparouhov, 2012), we know that as sample sizes get smaller, the posterior distribution becomes more influenced by the prior (van de Schoot et al., 2014). Therefore, our selection of priors is likely more influential to the posterior distribution in the PNOS group than in the other groups. While it remains possible there is something unique in those with PNOS that contributes to the observed associations between brain morphometry and IGT parameters, it is perhaps more likely that heterogeneity and a small sample can better explain these findings.

4.3. Perseveration and reversal learning

An interesting result emerged from our supplementary analysis, which may partly explain the lack of an observed association between vmPFC and attention to gain/loss. We found strong evidence that lower vmPFC cortical thickness was associated with higher perseveration, a result that only emerged in the ORL model. A similar pattern of relationship existed between perseveration on the ORL and vmPFC morphology in the three psychosis groups. This is particularly interesting because, unlike the VPP, the ORL

accounts for reversal learning within the perseveration parameter as it controls switching from preference of riskier decks when large losses start to accumulate. Reversal learning, more broadly known as cognitive flexibility, refers to one's ability to modulate their behaviour to obtain a reward when reward contingencies (rules) change. On the IGT, a successful strategy requires reversal learning since the disadvantageous decks (decks A and B) begin with a series of wins, creating an initial preference for these decks, which must be overcome (or unlearned). The vmPFC's role in reversal learning is well-supported in the literature, and lesions to the vmPFC have been shown to result in increased perseverative responses to previously rewarded stimuli (Dias et al., 1996; Fellows & Farah, 2005), suggesting that this area plays an important role in flexible stimulus–reinforcement learning (Ami Tsuchida et al., 2010). Impairments in reversal learning have been well-documented in substance use disorders (Ersche et al., 2011; Izquierdo & Jentsch, 2012; Pilhatsch et al., 2020) and have also been documented in TBI (Fellows & Farah, 2003) vascular disease (Seidel et al., 2016) and psychosis (Baker et al., 2023; Suetani et al., 2022). These impairments are known to have detrimental impacts on decision-making since an inability to reverse previously learned outcomes might lead to repetition of choices that are no longer advantageous. This phenomenon was observed in the current study as participants failed to overcome an early preference for Deck B, even as losses mounted. Given the importance of reversal learning on decision-making tasks such as the IGT, as well as the prominent role of the vmPFC in reversal learning, it seems logical that this may be a mechanism contributing to poor decision-making on the IGT. Indeed, this idea has been proposed as a potential alternative to the theory that emotional processes (somatic markers) guide decision-making. In a study involving participants with localized vmPFC lesions, Fellows and Farah (2005) found that the relationship between vmPFC dysfunction and poor IGT performance was a result of impaired reversal learning, not attention to reward. A similar pattern of findings has been described in individuals with psychosis across both IGT and other paradigms of reversal learning (Mitchell et al., 2002).

On the surface, our failure to find a relationship between vmPFC and attention to reward and loss contrasts the classic view of the vmPFC as a substrate responsible for mediating somatic states, as described in the SMH (Bechara et al., 1994; Damasio et al., 1991). One of the main ideas behind the SMH is that individuals with vmPFC lesions demonstrate reduced autonomic responding to emotionally arousing stimuli. Digging a

bit deeper, it is possible that in our highly marginalized sample, individuals exposed to pervasive risk have adapted to process risk differently, such that the IGT is not registering somatic signals. Although the evidence supporting this is limited, given the uniqueness of our sample, there are examples of individuals and groups exhibiting IGT impairments in the absence of altered somatic states. For example, in a case study of patient RMB, an individual who experienced a left mesial-frontal cortex lesion, the authors report impaired performance on the IGT in the absence of any changes in their affective response system (Naccache et al., 2005). Along these same lines, in a study of persons with substance dependence, Bechara and Damasio (who originally conceptualized the SMH) concluded that although generally, substance users behaved similar to vmPFC patients across IGT and measures of somatic state activation, there existed a subgroup of individuals with SUD who had decision-making impairments, but showed normal somatic activation (Bechara & Damasio, 2002). These results support an alternative view that vmPFC integrity may be related to other processes (such as reversal learning) and may explain another mechanism by which threats to prefrontal integrity impact IGT performance and lead to riskier decision-making.

Whether these findings extend to other clinical populations remains unclear, though there is evidence that acute vmPFC damage in previously healthy adults results in a similar pattern of findings. A study by Fellows and Farah (2005) tested this through a modified version of the IGT that eliminated the initial preference for the disadvantageous decks and found that those with vmPFC lesions performed better on the modified version when they did not have to overcome an initial stimulus-reinforcement set. The authors concluded that poor performance on the IGT seen in vmPFC patients was indeed caused by impairments in reversal learning, and our results support these findings.

In addition to strong evidence of an association between lower vmPFC cortical thickness/surface area and higher perseveration, we also observed strong evidence of an association between older age and perseveration on the ORL, a finding that is consistent with prior work. In their paper examining IGT performance across ages (5-89 years), Beitz et al. (2014) revealed a lifelong trend involving decreasing win-shift behaviour, as well as decreased shifts after loss in older adults compared to children and younger adults. These results are also consistent with our knowledge of perseverative behaviour on other neuropsychological tests, such as the Wisconsin Card

Sorting Test (WCST). Interestingly, the association between older age and perseverative behaviour has been linked to PFC volume loss (Gunning-Dixon & Raz, 2003; Raz et al., 1998), which is, again, consistent with our results.

To summarize, in the current study, we report a negative relationship between perseveration and vmPFC thickness, a finding that was only present in the ORL, which accounts for reversal learning. This supports the view of reversal learning being an important function of the vmPFC.

4.4. Implications

The findings of the current study suggest that changes in the structural integrity of the vmPFC (e.g., cortical thinning) may be linked to impairments in reversal learning rather than deficits in reward learning, especially in individuals with a history of substance use and other comorbid conditions. These findings could have important real-world implications for both our understanding of decision-making in complex environments and for developing targeted interventions, particularly for vulnerable populations, such as homeless and precariously housed individuals.

For homeless and precariously housed persons, who often face rapidly changing and unpredictable environments, difficulties in reversal learning could contribute to poor decision-making, increased vulnerability to substance abuse, and challenges in adapting to changing social and environmental conditions. Impairments in reversal learning may manifest in a number of ways that significantly affect daily decision-making and behaviour. For example, individuals may persist in maladaptive behaviours, such as repeatedly seeking substances or remaining in harmful environments, despite negative consequences, reflecting a failure to adapt when previous strategies are no longer effective. They may also struggle to adjust to new opportunities or challenges, like entering rehabilitation or finding stable housing. Additionally, impaired reversal learning can lead to impulsivity, where individuals make quick, short-term decisions without considering the long-term consequences as they struggle to adjust to new feedback or changing situations.

Understanding that structural differences in the vmPFC related to reversal learning might underlie these patterns can inform the design of more effective

therapeutic interventions. For example, cognitive therapies aimed at improving cognitive flexibility and adaptive learning could be particularly beneficial for these individuals. Programs designed to target reversal learning, such as cognitive remediation therapy (CRT), could help individuals develop strategies for adapting to new situations and adjusting behaviour in response to changing contingencies (Wykes et al., 2011). Such interventions could be integrated into outreach programs or community mental health clinics, providing tailored support to individuals as they navigate complex and often unstable living conditions. In addition, training that focuses on enhancing executive functions like attention, inhibitory control, and cognitive flexibility could support these individuals in making healthier, more adaptive decisions, which may, in turn, improve long-term outcomes related to housing stability, mental health, and substance use recovery.

Moreover, understanding the role of the vmPFC in decision-making also suggests that interventions designed to enhance emotional regulation and reduce impulsivity, critical functions of this brain region, could be effective. Behavioural therapies that integrate techniques to foster better emotional control, such as dialectical behaviour therapy (DBT) or mindfulness-based interventions, could also be employed to support better decision-making in situations of stress or crisis, which are common in the lives of marginalized populations (Lynk et al., 2015).

4.5. Limitations and future directions

When interpreting the results of our study, some important limitations should be noted. Our sample was drawn from specific Hotels and community court in the DTES of Vancouver, British Columbia, which is an inherently heterogeneous population. Because of the many challenges faced by these individuals, the drivers of degradation in brain structure and neurocognitive functioning are apt to be multifactorial. We know substance use and psychotic disorders both affect brain structural integrity, and the presence of each increases the risk of many other potential threats. The current study focused on psychotic disorders as a potentially important moderator of the brain-behaviour relationship, but we did not control for other potentially unknown moderators that may contribute a significant amount of variance to the model. Therefore, it remains unclear what effect other untested variables may have on the observed brain-behaviour relationships. Potentially adding to this, selection bias may also have been introduced

through the requirement to undergo MRI neuroimaging, a criterion that approximately one-third of the total available sample did not meet. Therefore, this is not a random sample, which could limit the generalizability of our findings. Missing data analyses of the 212 participants that were excluded found that these individuals differed from the final sample on a number of demographic and clinical variables. More specifically, excluded participants had, on average, lower cognitive scores (including lower IGT net score), higher recent drug use, more TBIs, and higher rates of major mental illness. Excluded participants also had thinner cortex and smaller surface area in vmPFC and dlPFC regions. Collectively, this data suggests that we are capturing higher functioning individuals within the broader Hotel sample.

Another potential limitation is the somewhat ambiguous anatomical boundaries of the vmPFC and dlPFC. Because the vmPFC and dlPFC are not anatomically defined areas and are not restricted to specific Brodmann areas or standard MRI coordinates, the definition of these functional regions varies and remains open for debate (Wallis, 2011). For example, in our study, the vmPFC was constrained to the medial orbitofrontal cortex (mOFC), which is consistent with some studies but differs from others. According to some, the vmPFC comprises two regions defined by FreeSurfer, the mOFC and lateral orbitofrontal cortex (lOFC). We opted not to include the lOFC in our definition of vmPFC because past work has shown it may play a role in maintaining relevant information in working memory (Ronel, 2018). Guided by prior work, the dlPFC was constructed using the rostral portion of the middle frontal gyrus (MFG; Cox et al., 2014; Sanches et al., 2009; Shaked et al., 2018), which encompasses the region occupied by Brodmann area 46. According to many, the dlPFC is a broad area comprising the lateral superior frontal gyrus (SFG) and MFG (Petrides & Pandya, 1999). However, the dlPFC itself is not homogenous and contains various subregions with distinct structural-functional connectivity (Jung et al., 2021). We opted to focus on the rostral portion of the MFG as it is a region known to be associated with working memory. However, despite our best efforts to localize vmPFC and dlPFC, distinct morphological patterns exist between individuals, preventing the exact morphological alignment of vmPFC and dlPFC across individuals.

While this research provides valuable insights into the cortical structure of decision-making hubs, there are several limitations to consider that could offer a more comprehensive understanding of the neural underpinnings of decision-making. One

notable limitation is the focus on cortical structure alone, which may not fully capture the complexity of how brain regions communicate and cooperate during decision-making processes. Although the vmPFC and dlPFC are crucial for higher cognitive functions such as reasoning, impulse control, and reward evaluation, they do not operate in isolation. The underlying white matter tracts that connect these cortical areas to other regions of the brain and the integrity of these connections play a vital role in facilitating the network dynamics involved in decision-making. White matter integrity is essential for efficient information processing and communication between distant brain regions, and alterations in white matter can significantly affect decision-making performance. Moreover, a network-based approach, incorporating methods like resting-state functional MRI (fMRI) or diffusion tensor imaging (DTI), could provide deeper insight into how the vmPFC and dlPFC integrate with other regions involved in complex decision-making, such as the anterior cingulate cortex, insula, and striatum. We know interactions between the vmPFC and dlPFC occur during decision-making (Hare et al., 2009; Rudorf & Hare, 2014), and in the present study, we found a strong correlation between vmPFC and dlPFC in both cortical thickness and surface area measures, suggesting they are functionally connected (He et al., 2007). Since these prefrontal regions are part of a highly integrated network, it follows that their functions during the decision-making process are not as rigidly defined. Decision-making is a complex cognitive process that arises from large-scale systems comprised of many cortical and subcortical components. Indeed, the PFC is a highly distributed network, and localized regions are connected not only to the immediately surrounding regions but also to other areas spread throughout much of the frontal lobe and beyond (Pucak et al., 1996). For instance, on laboratory-based decision-making tasks, functioning of the amygdala (Zeeb & Winstanley, 2011), insular cortex (Clark et al., 2008; Lin et al., 2008), ventral striatum (Linnet et al., 2011), lentiform nucleus (Lin et al., 2008) and hippocampus (Gupta et al., 2009) have all shown to play important and sometimes overlapping roles in the decision-making process. In animal models, functional connectivity in reward-related networks is associated with individual differences in gambling strategies (Tjernström et al., 2022), implying different individual strategies on the IGT may be related to different connectivity of reward circuits. This network, with many distributed parts, suggests there may be no clear regional specialization as predicted. Adding to this, dysfunction within frontostriatal white matter has been linked to impaired decision-making in a similar overlapping sample of substance users (Gicas et al., 2019) and provides evidence that large-scale circuitry

may be a more important predictor of IGT performance than regional morphology alone. Examining functional connectivity across these networks could reveal how disruptions in specific pathways, whether due to structural damage, neurodegenerative processes, or other factors, affect decision-making performance and cognitive control. Future research could benefit from a more holistic perspective that incorporates both cortical structural analysis and white matter network connectivity, as this would allow for a more nuanced understanding of the brain's dynamic interactions during decision-making tasks. By integrating both structural and functional perspectives, future studies could provide a clearer picture of the neural circuits underlying individual differences in decision-making, as well as the impact of various neuropathologies or psychological conditions on cognitive functioning.

Another potential limitation is specific to the use of computational modelling to understand behavioural decision-making task performance. The standard practice when using computational modelling on the IGT is to select a single model that is best able to capture the decision-making processes of many different individuals. This one-size-fits-all approach represents a challenge, given the range of strategies that are commonly employed in laboratory-based decision-making tasks, particularly in such a heterogeneous sample. We attempted to mitigate this by testing multiple models that have shown to be valid and accurate in substance-using populations and including two unique models to decompose component processes. It remains possible, however, that a different, untested model performs better in terms of model fit and accuracy. This also represents a potential area of future research, where different models may be selected at the individual and parameter level.

Computational constraints also precluded us from between-group comparisons of the effect of psychosis on the relationship between brain and IGT parameters. To mitigate this, we opted for a replication analysis whereby we tested the same hypothesis across groups (No Psychosis, Primary, SIP, PNOS). Given this, we were unable to make any conclusions regarding a differential effect of psychosis on the relationship between brain and IGT parameters.

4.6. Conclusions

In this highly marginalized group, where individuals face numerous and constant threats to their physical and mental health, our results suggest decision-making on the IGT is marked by a lack of attention to losses. Furthermore, more distant outcomes tended to be weighed heavier regarding decision-making behaviour than more recent outcomes. Our results also suggest that a history of psychotic disorder does not demonstrably alter decision-making on the IGT in the context of a history of substance use disorder and other comorbid factors. Regarding our hypotheses, our results don't support a dissociation between prefrontal brain regions and "hot" and "cold" cognitive parameters, as we failed to find the predicted dissociations between selected IGT parameters (attention to gains/loss and memory for deck selection) and respective prefrontal cortical morphology. Rather, our results are consistent with the view that impairments in reversal learning may explain the impact of the vmPFC on IGT performance, particularly in this marginalized population. This could have particularly important implications for intervention as it suggests that cognitive inflexibility, rather than impaired emotional processing, may better explain what contributes to risky, impaired decision-making in these highly vulnerable individuals, who live in a challenging environment with constant exposure to numerous risk factors affecting brain structure and function.

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Appendix A. Supplementary tables and figures

Table A1. Summary of parameters for PVL-Delta, VPP and ORL models.

Model Parameters	Parameter values	Interpretation of parameters
PVL-Delta		
α	0 – 1	Reward sensitivity. Values approaching zero indicate the magnitude of the outcome (positive or negative) has little impact on its subjective value. As α approaches 1, the subjective value is proportional to the magnitude of the gain or loss.
λ	0 – 5	Reflects the relative attention paid to losses over gains. If λ < 1 then losses will be neglected by the decision-maker, whereas when λ > 1 a greater attention is paid to losses than gains. If λ = 1 then the decision-maker values gains and losses equally.
A	0 – 1	Describes the weight given to the recent outcomes in updating expectancies. When *A* approaches zero, the most recent outcome has low influence on the new expected value. As *A* approaches 1, the decision-maker displays rapid forgetting and strong recency effects.
c	0 – 5	The response consistency parameter. Larger values of *c* indicate a greater tendency to select options with higher expected values, while smaller values indicate a greater tendency explore options with lower expected values.
VPP		
α	0 – 1	Same as PVL-Delta above
λ	0 – 5	Same as PVL-Delta above
A	0 – 1	Same as PVL-Delta above
c	0 – 5	Same as PVL-Delta above
ε_{pos}	-1 – 1	The tendency to perseverance after a win. Positive values indicate a tendency to persevere by picking the same option on succeeding trials, while negative values indicate a tendency to switch.
ε_{neg}	-1 – 1	The tendency to perseverance after a loss. Positive values indicate a tendency to persevere by picking the same option on succeeding trials, while negative values indicate a tendency to switch.
K	0 – 1	K is the perseverance decay parameter and indicates how much the perseverance value decays on each trial.
ω	0 – 1	The weight parameter determines how much weight is given to the expected value and perseveration signals for each option. If ω is above 0.5, greater weight is put on the expected value of each option. Conversely, a value less than 0.5 indicates greater weight based on the perseverance strength.
ORL		
A_{rew}	0 – 1	The learning rate which is used to update expectations after a positive outcome (reward)
A_{pun}	0 – 1	The learning rate which is used to update expectations after a negative outcome (punishment)

K	0 – 5	K is the decay parameter and represents how quickly decision-makers forget their past choices. Low values of K suggest a decision maker that remembers long history of their own deck selection.
β_F	$-\infty - \infty$	The win frequency parameter. A β_F greater than 0 indicates an individuals' preference for decks with high win frequency.
β_P	$-\infty - \infty$	The perseverance parameter. A value less than 0 indicates a decision-makers preference for switching from recently chosen decks, while a value above 0 indicates their preference to stay on recently chosen decks.

Table A2. Summary of components of decision-making for VPP model.

				95% Credible Interval	
Group	**Dependent Variable**	**Median**	**Mean**	**Lower**	**Upper**
No Psychosis	α	0.512	0.512	0.323	0.7
	λ	0.393	0.402	0.163	0.649
	A	0.01	0.015	0.002	0.046
	c	1.552	1.563	1.202	1.941
	εpos	0.456	0.542	0.062	1.256
	εneg	-0.37	-0.45	-1.096	-0.029
	K	0.358	0.358	0.273	0.441
	ω	0.716	0.665	0.26	0.933
Primary Psychosis	α	0.663	0.662	0.515	0.809
	λ	0.349	0.356	0.171	0.556
	A	0.02	0.025	0.004	0.056
	c	1.692	1.707	1.256	2.187
	εpos	0.303	0.408	0.009	1.124
	εneg	-0.072	-0.115	-0.6	0.246
	K	0.354	0.354	0.271	0.435
	ω	0.692	0.647	0.257	0.952
SIP	α	0.94	0.936	0.692	1.165
	λ	0.175	0.178	0.084	0.276
	A	0.061	0.063	0.026	0.101
	c	1.192	1.208	0.908	1.528
	εpos	0.625	0.71	0.06	1.598
	εneg	-0.103	-0.13	-0.658	0.343
	K	0.292	0.291	0.216	0.368
	ω	0.669	0.658	0.409	0.883
PNOS	α	0.128	0.186	0	0.654
	λ	0.082	0.122	0	0.364
	A	0.003	0.004	0	0.01
	c	2.125	2.16	1.486	2.901
	εpos	-0.032	-0.041	-0.873	0.742
	εneg	-0.363	-0.441	-1.367	0.208
	K	0.377	0.377	0.275	0.479
	ω	0.879	0.856	0.665	0.993

Note. SIP = Substance induced psychosis; PNOS = Psychosis not otherwise specified.

Table A3. Summary of components of decision-making for ORL model.

				95% Credible Interval	
Group	**Dependent Variable**	**Median**	**Mean**	**Lower**	**Upper**
No Psychosis	A_{rew}	0.198	0.2	0.133	0.27
	A_{pun}	0.043	0.043	0.029	0.057
	K	0.958	0.968	0.639	1.317
	β_F	1.169	1.169	0.764	1.592
	β_P	1.001	1.013	-0.173	2.229
Primary Psychosis	A_{rew}	0.201	0.202	0.145	0.26
	A_{pun}	0.033	0.033	0.02	0.047
	K	0.896	0.903	0.605	1.214
	β_F	1.283	1.282	0.813	1.731
	β_P	0.798	0.805	-0.274	1.93
SIP	A_{rew}	0.188	0.189	0.137	0.242
	A_{pun}	0.034	0.034	0.022	0.047
	K	1.22	1.229	0.863	1.607
	β_F	1.148	1.148	0.754	1.542
	β_P	1.295	1.298	-0.1	2.726
PNOS	A_{rew}	0.1	0.102	0.051	0.153
	A_{pun}	0.021	0.022	0.009	0.036
	K	0.695	0.706	0.462	0.961
	β_F	0.774	0.78	-0.013	1.609
	β_P	0.068	0.074	-1.284	1.455

Note. SIP = Substance induced psychosis; PNOS = Psychosis not otherwise specified.

Table A4. Comparison of group sample characteristics

Variable	Group				Test statistic (p-value)	Difference
	No Psychosis (n = 91)	Primary Psychosis (n = 79)	SIP (n = 71)	PNOS (n = 31)		
Age, M (SD)	44.4 (11.0)	35.8 (10.8)	39.2 (9.7)	41.7 (11.8)	F = 9.53 (<0.001)	2 < 1,3; 3 < 1
Education, M (SD)	10.7 (2.5)	10.9 (1.9)	9.8 (2.1)	10.3 (2.1)	F = 3.69 (0.01)	3 < 1,2
Premorbid, IQ M (SD)	98.0 (9.9)	99.2 (9.0)	97.0 (9.1)	98.9 (10.4)	ns	-
Sex (M:F)	69:22	63:16	58:13	27:4	ns	-
IGT Net score, M (SD)	-0.8 (30.4)	-6.6 (29.6)	-4.5 (33.9)	-4.5 (27.3)	ns	-
HVLT immediate recall, M (SD)	32.3 (9.9)	32.7 (12.7)	31.5 (10.4)	32.4 (13.5)	ns	-
RVIP A', M (SD)	-1.2 (1.1)	-1.0 (1.2)	-1.3 (1.3)	-1.3 (1.5)	ns	-
Stroop color-word, M (SD)	50.0 (8.7)	48.6 (10.8)	50.0 (7.8)	48.2 (11.4)	ns	-
IDED total errors adjusted, M (SD)	55.0 (42.1)	47.1 (38.6)	50.0 (47.0)	55.1 (53.6)	ns	-

1 = No Psychosis; 2 = Primary Psychosis; 3 = SIP; 4 = PNOS; ns = no significant difference

Appendix B. IGT modelling

The first computational decision model used to extract cognitive parameters from IGT data was known as the Expectancy-Valence Learning (EVL) model (Ahn et al., 2016; Busemeyer & Stout, 2002). In this model, a decision-maker will integrate the gains and losses from each trial into a valence, which is an affective (or emotional) reaction to the experienced result. Different amounts of attention (or weights) may be given to the losses compared to gains. The decision-maker uses this utility function to evaluate positive and/or negative payoffs related to each card selection. A reinforcement learning rule is used to update expectations for each deck based on the utility of the positive or negative payoff produced by the choice. These expectancies are updated for each chosen deck and remain unchanged for each not chosen. The learning model produces expectancies that are a weighted average of past valences, and the weight given to each valence decreases the more distant it becomes in time. In other words, more recently experienced valences receive more weight than more distantly experienced valences. Individuals may differ in the rate at which they update their expectancies as they learn. Large rates are indicative of stronger recency effects and rapid forgetting, whereas small rates produce weak recency effects and slow forgetting (Busemeyer & Stout, 2002). In addition to weight and learning rate parameters, the EVL also includes a sensitivity parameter, which reflects the sensitivity of the choice probabilities to the expectancies, where the choice probability is a probabilistic function of the expectancies associated with each deck. If sensitivity is zero, then choices are completely random and independent of expectancies (Busemeyer & Stout, 2002). Taken together, this model assumes that decisions are made based on the expectation of valence and that three processes (motivation, memory/learning, and response consistency) are involved in this process (Busemeyer & Stout, 2002; Yechiam et al., 2005). While the EVL model provided early insights into the underlying components of decision-making on the IGT, subsequent cognitive models have been developed that provide a more accurate understanding of IGT performance (Ahn et al., 2014; Haines et al., 2018; Worthy et al., 2013).

Prospect Valence Learning with Delta Learning rule (PVL-Delta)

The PVL-Delta model uses the prospect utility function- a non-linear utility function from prospect theory, which is used by the decision-maker to evaluate positive

and/or negative payoffs related to each card selection (Kahneman & Tversky, 1979; Steingroever et al., 2013). Prospect theory is a theory of behavioural economics, which, in its simplest terms, describes how individuals make choices between probabilistic alternatives where risk and probability of outcomes are unknown. The theory assumes that gains and losses are valued differently and that individuals make decisions based on perceived gains rather than perceived losses. On the IGT, the PVL-Delta model assumes that after participants choose a card from deck $j \in \{1, 2, 3, 4\}$ on trial t, they will evaluate the net outcome according to a non-linear function from prospect theory (Kahneman & Tversky, 1979; Steingroever et al., 2013). According to the prospect utility function, the subjective utility (or value, $u(t)$) of the net outcome $x(t)$ is calculated based on the outcome of the card selected (i.e., the amount gained or lost), the shape of the utility function (α, reward sensitivity), and the attention to losses (λ).

$$u_j(t) = \begin{cases} x(t)^a, & x(t) \geq 0 \\ -\lambda \cdot |x(t)^a|, & x(t) < 0 \end{cases}$$

As α [0,1] approaches zero, the magnitude of the outcome (positive or negative) has little impact on its subjective value. In other words, all gains and losses are valued equally. In contrast, as α approaches 1, the subjective value is proportional to the magnitude of the gain or loss. The attention to losses parameter λ [0,5] reflects the relative attention paid to losses over gains. If $\lambda < 1$, then losses will be neglected by the decision-maker, whereas when $\lambda > 1$, greater attention is paid to losses than gains. If $\lambda = 1$, then the decision-maker values gains and losses equally.

The PVL-Delta model also assumes that on every trial, decision-makers update the expected utilities of every deck according to the Delta learning rule, also known as the Rescorla and Wagner rule (Rescorla & Wagner, 1972). This means that the expected utility of the chosen deck is adjusted upward if the experienced utility is higher than expected.

$$E_j = E_j(t-1) + A \cdot [u_j(t) - E_j(t-1)]$$

For the chosen deck (j), the expected utility is increased if the experienced utility ($u_j(t)$) *is* higher than expected. Conversely, if the experienced utility is lower, the expected utility is adjusted downward. Updating is influenced by the updating or recency

parameter (*A*), which quantifies memory for gains and losses. When *A* [0,1] approaches zero, the decision-maker has slow forgetting and weak recency effects. In other words, the most recent outcome has low influence on the new expected value. As *A* approaches 1, the decision-maker displays rapid forgetting and strong recency effects.

Next, the model assumes that the expected utilities of each deck guide participants' choices on the following trial (t+1). This probability, explained by the ratio-of-strength choice rule, is used to compute the probability of choosing each deck on each trial (Luce, 1959).

$$P[S_j(\mathrm{t}+1)] = \frac{e^{\theta \cdot E_j(t)}}{\sum_{j=1}^{4} e^{\theta \cdot E_j(t)}}$$

The trial-independent sensitivity parameter (θ) reflects the trade-off between exploration of new options (more random choices) and exploitation of high expected values (less random choices). This depends on an individual's response consistency *c* [0,5], which reflects a random or deterministic approach to card selection, where a small c value indicates a random choice pattern.

$$\theta = 3^c - 1$$

In all, the PVL-Delta model uses four parameters to capture assumptions about participants' performance on the IGT: the shape parameter (α), the attention to losses parameter (λ), the updating/recency parameter (*A*), and the response consistency parameter (*c*), (Steingroever et al., 2013). The PVL-Delta has been shown to perform better than previous models, particularly in individuals experiencing drug addiction (Baitz et al., 2021; Fridberg et al., 2010; Steingroever et al., 2014). Despite this, a criticism of this model is that it does not consider an individual's tendency to perseverate on decks. As such, the tendency to select an option with the highest expected value is conflated with the tendency to persevere on decks because the model uses a single value to represent these tendencies (Worthy et al., 2013). To address this concern, Worthy et al., (2013) developed the Value-Plus-Perseverance (VPP) model, which uses separate terms to represent expected value and perseverance.

Value Plus Perseverance (VPP)

Like the PVL-Delta, the VPP is a hybrid model that tracks expected values according to the PVL-Delta model. Unlike the PVL-Delta model, the VPP contains a separate term to account for perseveration. On a decision-making task like the IGT, individuals will vary in both their tendency to select more advantageous options and in their tendency to "stay" or "switch" on successive trials. It has been suggested that models should account for a participant's tendency to persevere or stay with the same option over consecutive trials. While a perseverance term exists in other models, namely the win-stay-lose-shift (WSLS) model and the PVL model with a decay learning rate (PVL-Decay), there are critical shortcomings of these models. For example, the WSLS model assumes that participants do not use information about the relative value of each option but rather only respond based on the binary positive/negative outcome of the prior selection (Worthy et al., 2013). Furthermore, unlike the Delta learning rule, the Decay learning rule assumes that expected values for each option decay on each trial (Erev & Roth, 1998). This means that decks not chosen will decline in expected value, while a deck will be increasingly more likely to be selected the more frequently it has been selected in the recent past (Worthy et al., 2013). The consequence is that the tendency to persevere may be conflated with the tendency to select the option with the highest expected value since a single term is used to represent both of these tendencies. In order to address these limitations, Worthy et al., (2013) developed the VPP model, which separates the expected value and perseverance terms. The result is a model containing eight free parameters. Four parameters representing the expected value come from the PVL-Delta model, and an additional four parameters representing perseverance, which include perseverance after gain, perseverance after loss, the perseverance decay rate, and the weight the individual places on reinforcement learning vs perseverance (Ahn et al., 2014; Worthy et al., 2013). In this model, the perseverance strengths for each option are determined by a more general form of the Decay rule, which assumes the expected value for each deck decays towards zero over time (Erev & Roth, 1998).

$$P_j(t+1) = \begin{cases} K \cdot P_j(t) + \varepsilon_{pos}\,, & x(t) \geq 0 \\ K \cdot P_j(t) + \varepsilon_{neg}\,, & x(t) < 0 \end{cases}$$

$P_j(t)$ represents the perseveration value, which decays by K ($0 \leq K \leq 1$) on each trial. The tendency for an individual to perseverate on a deck or switch decks is incremented after each choice by ε_{pos} and ε_{neg}, which may vary between -1 and 1. A positive value indicates the tendency to perseverate by picking the same deck on succeeding trials. Conversely, a negative value is indicative of a tendency to switch.

As stated, the VPP assumes that the expected value and perseveration terms are integrated into a single value signal.

$$V_j(t+1) = \omega \cdot E_j(t+1) + (1-\omega) \cdot P_j(t+1)$$

The weight ω ($0 < \omega < 1$) parameter determines how much weight is given to the expected value and perseveration signals for each option. If ω is above 0.5, greater weight is put on the expected value of each option. Conversely, a value less than 0.5 indicates greater weight based on the perseverance strength. Like the PVL-Delta, these values Vj(t) are entered into a Softmax rule to determine the probability of selecting each option. Altogether, the VPP contains eight free parameters. Four parameters from the PVL-Delta (α, λ, A, c), and four parameters representing the perseverance term (ε_{pos}, ε_{neg}, K, ω).

According to prior work in substance users, the PVL-Delta and VPP models show good generalizability and accurately models the qualitative patterns of IGT data (Steingroever et al., 2013; Worthy et al., 2013). More recently, a novel learning model for the IGT has been proposed that aims to improve model performance, including short- and long-term prediction accuracy and parameter recovery.

Outcome Representation Learning (ORL)

The ORL is a novel reinforcement learning model recently developed by Haines et al., (2018) that has shown to comparably perform or outperform other competing models (including the PVL-Delta and VPP models) in numerous model comparison indices (Haines et al., 2018). The ORL is an accurate and generalizable computational model that optimizes short and long-term prediction accuracy of the IGT in a number of different clinical populations (Haines et al., 2018). Unlike the PVL-Delta and VPP models, which both assume decision-makers value outcomes according to the Prospect

Theory utility function, the ORL differentially captures gains and losses, and thus models separate reward and loss learning rates. This allows the ORL model to account for sensitivity to losses and gains independently. The expected value of a deck is, therefore, updated with separate learning rates for positive and negative outcomes, unlike on the PVL-Delta and VPP models.

$$EV_j(t+1) = \begin{cases} EV_j(t) + A_{rew} \cdot \Big(x(t) - EV_j(t)\Big), & x(t) \geq 0 \\ EV_j(t) + A_{pun} \cdot \Big(x(t) - EV_j(t)\Big), & x(t) < 0 \end{cases}$$

$EV_j(t)$ represents the expected value of deck *j* on trial *t*, while positive A_{rew} $(0 < A_{rew} < 1)$ and negative A_{pun} $(0 < A_{pun} < 1)$ learning rates are used to update expectations after rewards and punishments. The ORL updates the expected values using the objective outcome *x(t)* rather than the subjective utility *u(t)* that is used in the PVL-Delta and VPP models.

The ORL also accounts for win frequency, or the tendency for an individual to select the decks that produce more frequent wins, regardless of long-term value. The phenomenon of individuals preferring frequently winning decks and not accounting for long-term value has been observed regularly in the literature. For example, the 'prominent deck B' phenomenon describes the propensity for individuals in both healthy and clinical populations to prefer the disadvantageous deck B (which provides more frequent wins but worse overall outcomes) to decks C or D, which have better final outcomes (Chiu et al., 2012; Dunn et al., 2006). This is believed to occur because individuals don't accurately account for rare events. Though the PVL-Delta and VPP models implicitly capture win frequency through the Prospect Theory utility function, they do not separate the effect of loss aversion from that of win frequency (Haines et al., 2018). To model win frequency, the ORL separately tracks win frequency in the following equations,

$$EF_j(t+1) = \begin{cases} EF_j(t) + A_{rew} \cdot \Big(sgn(x(t)) - EF_j(t)\Big), & x(t) \geq 0 \\ EF_j(t) + A_{pun} \cdot \Big(sgn(x(t)) - EF_j(t)\Big), & x(t) < 0 \end{cases}$$

where $EF_j(t)$ is the expected outcome frequency and $sgn(x(t))$ has a value of 1, 0, or -1 depending on a positive, zero, or negative outcome on trial *t*. The expected outcome frequency for all unchosen decks $EF_{j'}(t)$ is represented as follows:

$$EF_j(t+1) = \begin{cases} EF_j(t) + A_{rew} \cdot \left(\dfrac{-sgn(x(t))}{C} - EF_{j'}(t) \right), & x(t) < 0 \\ EF_j(t) + A_{pun} \cdot \left(\dfrac{-sgn\big(x(t)\big)}{C} - EF_{j'}(t) \right), & x(t) \geq 0 \end{cases}$$

where *C* is the number of possible alternative choices to the chosen deck. On the IGT, *C* is 3 since there are 3 possible alternative choices to the chosen deck.

To track a participant's tendency to stay or switch decks irrespective of outcome, the ORL uses a choice perseveration model

$$PS_j(t+1) = \begin{cases} \dfrac{1}{1+K'}, & D(t) = j \\ \dfrac{PS_j(t)}{1+K'}, & otherwise \end{cases}$$

where K' is determined by:

$$K = 3^{K'} - 1$$

$PS_j(t)$ is the perseverance weight of deck *j* on trial *t*, while *K* is the decay parameter and represents how quickly decision-makers forget their past choices. Low values of K suggest a decision maker that remembers long history of their own deck selection. The model suggests that the perseverance weight is set to 1 on each trial, and all perseverance weights decay exponentially before the choice is made on the next trial (Haines et al., 2018).

For the final two parameters, the ORL assumes that value, frequency, and perseverance signals integrate in a linear fashion to create a single signal for each of the four decks.

$$V_j(t+1) = EV_j(t+1) + EF_j(t+1) \cdot \beta_F + PS_j(t+1) \cdot \beta_P$$

The effect of outcome frequency β_F $(-\infty < \beta_F < \infty)$ on decision-making is modelled, such that a value of β_F greater than 0 indicates an individual's preference for decks with high win frequency. The perseveration term β_P $(-\infty < \beta_P < \infty)$ is also included in the equation, with a value less than 0 indicating a decision-makers preference for switching from recently chosen decks and a value above 0 indicating their preference to stay on recently chosen decks. Altogether, the ORL contains five parameters: reward learning rate (A_{rew}), loss learning rate (A_{pun}), win frequency (β_F), perseveration (β_P), and decay (K).