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A multimodal brain imaging approach

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A la meua família

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ABSTRACT

Gambling disorder (GD) is characterized by a persistent and repetitive pattern of problematic gambling behavior that results in clinically significant emotional distress or impairment. The prevalence of this disorder is 1.6 - 1.9% of the adult population worldwide. GD is the only disorder recognized as a behavioral addiction in the current diagnostic manuals because of its clinical and neurobiological similarities to substance use disorders (SUDs).

The aim of this thesis was to study the neurobiology of GD, focusing on the fronto-striatal-thalamic circuit, due to its pivotal role in SUDs. Two independent datasets of individuals with GD and healthy controls (HC) were studied: 1) 15 individuals with GD (mean age: 43) and 17 sex- and age-matched HC, with an imaging protocol including structural MRI (gray and white matter measurements), functional MRI (task and resting-state) and PET imaging (with tracers reflecting brain dopamine, opioid, and serotonin function); 2) 20 older adults (mean age: 64) with GD and 40 sex- and age-matched HC. Structural MRI (gray and white matter measurements) from the second dataset was studied in this thesis.

In the first dataset, resting-state fMRI connectivity analysis showed that normal negative connectivity between the right nucleus accumbens and the right dorsolateral prefrontal cortex was lost in the GD group. This abnormal functional connectivity was associated with serotonin, but not with dopamine or opioid function. Task-based fMRI analysis showed an increased BOLD response in the dorsal striatum during gambling compared to neutral cues in individuals with GD compared to HC. The BOLD response in the dorsal striatum was associated with opioid, but not with serotonin or dopamine, function. In the second dataset, individuals with GD showed significantly lower gray matter thickness in the left orbitofrontal cortex and volume in the left thalamus compared to HC. In addition, the brain white matter analyses demonstrated a lower fractional anisotropy and an increased number of white matter lesions in the left anterior corona radiata in GD compared to HC.

The results of this study indicate that GD is associated with converging structural and functional brain abnormalities in the fronto-striatal-thalamic circuit. These findings provide novel information about the neurobiology of GD that can help in the development of new treatment options.

KEYWORDS: Gambling disorder, prefrontal cortex, striatum, thalamus, multimodal

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
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TIIVISTELMÄ

Rahapeliriippuvuus on jatkuvaa ja ongelmallista rahapelikäyttäytymistä, joka aiheuttaa merkittävää henkistä kärsimystä tai toimintakyvyn heikkenemistä. Maailmanlaajuisesti sitä esiintyy 1,6–1,9 %:lla aikuisväestöstä ja se on ainoa toiminnalliseksi riippuvuudeksi luokiteltu häiriö, mikä johtuu sen samankaltaisuuksista päihderiippuvuuksien kanssa.

Tämän väitöskirjan tavoitteena oli tutkia rahapeliriippuvuuden neurobiologiaa keskittyen fronto-striataali-talamus-radastoon, joka on keskeinen myös päihderiippuvuuksissa. Tutkimuksessa analysoitiin kahta riippumatonta aineistoa, jotka sisälsivät rahapeliriippuvaisia sekä terveitä verrokkeja: 1) 15 rahapeliriippuvaista (keski-ikä: 43) ja 17 ikä- ja sukupuolivakioitua tervettä verrokkia. Heiltä kuvattiin rakenteellinen magneettikuvaus, toiminnallinen magneettikuvaus (fMRI; tehtävä- ja lepotilakuvaukset) sekä PET-tutkimus merkkiaineilla, jotka heijastavat dopamiini-, opioidi- ja serotoniinitoimintaa aivoissa; 2) 20 iäkästä rahapeliriippuvaista (keski-ikä: 64) ja 40 ikä- ja sukupuolivakioitua tervettä verrokkia. Tässä aineistossa analysoitiin rakenteellisia magneettikuvia.

Ensimmäisen aineiston lepotilan fMRI-konnektiivisuusanalyysi osoitti, että normaalisti negatiivinen yhteys oikean nucleus accumbensin ja oikean dorsolateraalisen prefrontaalikorteksin välillä oli rahapeliriippuvaisilla kadonnut, mikä liittyi serotoniinitoimintaan. Lisäksi rahapeliaiheiset ärsykkeet suurensivat BOLD-vasteita dorsaalisessa striatumissa, mikä puolestaan liittyi opioiditoimintaan. Jälkimmäisessä aineistossa rahapeliriippuvaisilla havaittiin harmaan aineen olevan merkittävästi ohuempaa vasemmassa orbitofrontaalikorteksissa ja vasemman talamuksen tilavuudeltaan pienempi kuin verrokkeilla. Lisäksi aivojen valkean aineen analyysit osoittivat alempaa fraktionaalista anisotropiaa ja enemmän valkean aineen vaurioita vasemmassa anteriorisessa corona radiatassa rahapeliriippuvaisilla.

Tämän väitöskirjatutkimuksen tulokset osoittavat, että rahapeliriippuvuus liittyy yhteneviin rakenteellisiin ja toiminnallisiin aivopoikkeavuuksiin fronto-striataali-talamus-radastossa. Löydökset tarjoavat uutta tietoa rahapeliriippuvuuden neurobiologiasta, mikä voi tukea uusien hoitomuotojen kehittämistä.

AVAINSANAT: Rahapeliriippuuvuus, prefrontaalikorteksi, striatum, talamus, multimodaalinen

Table of Contents

Abbreviations

^{18}F-FDG	2-deoxy-2-18F-fluoro-β-D glucose
5-HT1B	5-hydroxytryptamine 1B receptor
ACC	Anterior cingulate cortex
ALFF	Amplitude of Low Frequency Fluctuations
ATP	Adenosine triphosphate
AUD	Alcohol use disorder
AUDIT	Alcohol Use Disorders Test
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BIS-11	Barratt Impulsiveness Scale
BMI	Body mass index
BOLD	Blood-oxygenation-level-dependent
CAT12	Computational Anatomy Toolbox 12
CR	Corona radiata
CSF	Cerebrospinal fluid
CUD	Cocaine use disorder
D2/3	Dopamine receptor 2/3
DAT	Dopamine transporters
DLPFC	Dorsolateral prefrontal cortex
DMN	Default mode network
dmPFC	Dorsomedial prefrontal cortex
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DTI	Diffusion tensor imaging
DUD	Drug use disorder
DWI	Diffusion-weighted imaging
EPI	Echo-planar imaging
ER	Event-related
ESEMeD	European Study of the Epidemiology of Mental Disorders
FA	Fractional anisotropy

FDA	Food and Drug Administration
FDOPA	6-[^{18}F]fluoro-L-DOPA
FLAIR	Fluid-attenuated inversion recovery
fMRI	Functional magnetic resonance imaging
FWE	Family-wise error
FWHM	Full Width at Half Maximum
GABA	ɣ-amino butyric acid
GD	Gambling disorder
Hb	Deoxygenated hemoglobin
HbO2	Oxygenated hemoglobin
HC	Healthy controls
HRRT	High-resolution research tomography
ICA	Independent component analysis
ICD-11	International Classification of Diseases, 11th Revision
iRISA	Impaired Response Inhibition and Salience Attribution
MD	Mean diffusivity
MMSE	Mini-Mental State Examination
MNI	Montreal Neurological Institute
MOR	Mu-opioid receptor
MRI	Magnetic ressonance imaging
NAcc	Nucleus accumbens
NESARC-III	National Epidemiologic Survey on Alcohol and Related Conditions-III
NMR	Nuclear magnetic resonance
OFC	Orbitofrontal cortex
PET	Positron emission tomography
PFC	Prefrontal cortex
PG	Pathological gambling
ReHo	Regional homogeneity
rNAcc	Right nucleus accumbens
rs-fMRI	Resting-state functional magnetic resonance imaging
SBM	Surface-based morphometry
SERT	Serotonin transporter
SOGS	South Oaks Gambling Screen
SPM12	Statistical Parametrical Mapping 12
SPSS	Statistical Package for the Social Sciences
SUDs	Substance use disorders
TBSS	Tract-based spatial statistics
TIV	Total intracranial volume
TUD	Tobacco use disorder

VBM	Voxel-based morphometry
vmPFC	Ventromedial prefrontal cortex
VS	Ventral striatum
VTA	Ventral tegmental area
WMH	White matter hyperintensities

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Bellmunt-Gil, A.*, Majuri, J.*, Arponen, E., Kaasinen, V.**, & Joutsa, J.** (2023). Abnormal frontostriatal connectivity and serotonin function in gambling disorder: A preliminary exploratory study. *Journal of Behavioral Addictions*, *12*(3), 670-681.

II Bellmunt-Gil, A., Majuri, J., Nummenmaa, L., Helin, S., Forsback, S., Rajander, J., Kaasinen, V., & Joutsa, J (2025). Striatal cue-reactivity and neurotransmitter function in gambling disorder. *Journal of Behavioral Addictions, 14*(2), 997–1009.

III Bellmunt-Gil, A., Vorobyev, V., Parkkola, R., Lötjönen, J., Joutsa, J.*, & Kaasinen, V.* (2024). Frontal white and gray matter abnormality in gambling disorder: A multimodal MRI study. *Journal of Behavioral Addictions*, *13*(2), 576-586.

*,** Equal contribution

1 Introduction

Addiction is a chronic, relapsing brain disorder characterized by compulsive engagement in substance use or a behavior despite negative consequences (American Psychiatric Association, 2013). Addiction affects millions of people worldwide creating an enormous social and economic burden in our societies (Uhl et al., 2019). Traditionally, addiction has been associated with substance use. However, following cumulative scientific evidence, gambling disorder (GD) has recently been acknowledged as an addiction disorder – a behavioral addiction – in the major diagnostic manuals: the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) and the *International Classification of Diseases, 11th Revision* (ICD-11). The recognition of GD as an addiction disorder is largely based on its clinical and neurobiological similarities to substance use disorders (SUDs) (Weinstock & Rash, 2014).

While these similarities have facilitated GD's classification as an addiction disorder, there are some notable neurobiological differences between GD and SUDs. A key feature of SUDs is blunted dopaminergic function, which contributes to the maladaptive behavior including escalating doses. However, findings in individuals with GD have contradicted those in SUDs by showing normal or even higher dopamine neurotransmission in GD compared to controls (Boileau et al., 2013; Joutsa et al., 2012; Majuri et al., 2017a). However, dopamine is still implicated in the development of GD (J. E. Grant et al., 2016; Linnet, 2020). For example, dopamine release has been shown in individuals with GD during slot machine play (Joutsa et al., 2012) and elevated dopamine release has been linked to gambling severity, impulsivity, or risky behavior (Boileau et al., 2014; Joutsa et al., 2012; Linnet et al., 2010, 2011, 2012). In addition, dopaminergic medications used to treat Parkinson's disease have been shown to induce GD (Wolfschlag & Håkansson, 2023). In addition to dopamine, abnormalities in other neurotransmitters, such as opioids and serotonin, have been reported, but their role in GD remains to be characterized (Kaasinen et al., 2023; Potenza et al., 2019).

The fronto-striatal-thalamic brain circuits are thought to play a crucial role in addiction disorders, as these circuits are important for several brain functions, such as reinforcement, reward anticipation, inhibitory control and craving (Huang et al.,

2018; Koob & Volkow, 2016; Potenza et al., 2019). However, most of the data comes from SUDs and the neurobiology of GD remains less well understood (Balodis & Potenza, 2020). One of the limitations of the currently available literature is that most studies have used only a single neuroimaging modality, thus providing information on only one aspect of GD neurobiology. In addition, practically all studies in GD have investigated young individuals, potentially reducing sensitivity to detect brain structural changes that often become more prominent with age, and also limiting the generalizability of the findings to all individuals with GD.

In this thesis, we adopt a multimodal approach by applying a variety of different brain imaging methods in two independent datasets, focusing on the fronto-striatal-thalamic circuitry. To achieve this, functional magnetic resonance imaging (fMRI) was used in individuals with GD to study fronto-striatal connectivity and striatal cue reactivity, and positron emission tomography (PET) with multiple tracers to study the neurotransmitters associated with the functional abnormalities. In addition, structural changes in gray and white matter were measured in older individuals with GD, while focusing on the fronto-striatal-thalamic areas.

2 Review of the Literature

2.1 Addiction disorders

Behaviors that are necessary for survival, such as eating, socializing, and reproducing, are reinforced by the brain's reward system. However, other behaviors that are not evolutionarily beneficial to survival, such as drug consumption or gambling, also engage this system. Initially, individuals participate in these activities often influenced by social contexts or personal choices. Over time, they learn to associate the behavior with the pleasurable or relieving effects it produces, assigning a hedonic value to the behavior or related stimuli. This reinforcement increases the likelihood of repeating the behavior, to continue experiencing those rewarding sensations (Volkow et al., 2019).

Over time and with repetition, the behavior becomes more automatic, and is heavily influenced by environmental cues associated with the addictive behavior or stimulus (Everitt & Robbins, 2005; Koob & Volkow, 2010). Ultimately, the behavior becomes compulsive, and the individual starts to lose control over their actions and the ability to adapt or change those behaviors.

In SUDs, the DSM-5 lists 10 distinct disorders, including alcohol, caffeine, cannabis, hallucinogen, inhalant, opioid, sedative, hypnotic, or anxiolytic use disorder, stimulant, tobacco, and other (or unknown) substance use disorders. GD is the only behavioural addiction currently recognized in the DSM-5, though the list may expand in the future.

2.1.1 Substance use disorders

It has been estimated that 13% of individuals who use psychoactive drugs with addiction potential will develop a SUD (United Nations Office on Drugs and Crime, 2021). According to the United Nations Office on Drugs and Crime (2024) approximately 1 in 81 people worldwide – about 1.2% of the global population – suffered from a drug use disorder (DUD) in 2022, not including alcohol or tobacco. The same organization reported a significant global increase in drug use over the past decade, estimating that 292 million people (5.6% of the population) aged 15 to 64 used a drug in 2022 (United Nations Office on Drugs and Crime, 2024). This

represents a 20% increase compared to the previous decade, although this is partially attributed to population growth. Cannabis was by far the most widely used drug with an estimated 228 million users, followed by opioids (60 million), amphetamine-type stimulants (30 million), cocaine (23 million) and "ecstasy" (30 million). Although there has been a stabilization of global opioid use since 2019, opioids still cause the most harm and health problems worldwide (United Nations Office on Drugs and Crime, 2024).

According to the US-based National Epidemiologic Survey on Alcohol and Related Conditions-III (NESARC-III) alcohol use disorder (AUD) and tobacco use disorder (TUD) exhibit a higher 12-month prevalence than DUD, accounting for 13.9% and 20%, respectively (Chou et al., 2016; B. F. Grant et al., 2015). However, a cross-national study reported a much lower global prevalence of 2.2% (Glantz et al., 2020), which raises the question of whether the global prevalence of TUD might also change. Studies investigating global prevalence changes over time suggest that smoking rates have decreased substantially. From 1990 to 2015, smoking prevalence dropped by 28.4% for men and 34.4% for women. In contrast, alcohol consumption has increased, with AUD rates rising from 8.5% in 2001-2002 to 12.7% in 2012-2013 (B. F. Grant et al., 2017; Manthey et al., 2019; Reitsma et al., 2017).

SUDs often co-occur with other psychiatric illnesses. The European Study of the Epidemiology of Mental Disorders (ESEMeD) project reported that individuals with a lifetime drug use disorder often exhibit comorbid psychiatric conditions, including mood disorders and schizophrenia, with prevalence rates ranging from 7% to 28% (Alonso et al., 2004). Similar estimates have been seen in other US epidemiological studies (Farrell et al., 2003; Jacobi et al., 2004). Furthermore, the risk for people with any mental illness to develop a SUD has been estimated to be 4 to 5 times higher than in healthy individuals (Simon et al., 2015; Wilens et al., 2011). However, establishing causality between SUDs and psychiatric disorders is challenging. The comorbidity between SUDs and mental illnesses may occur in three different directions (Santucci, 2012): (1) common factors contribute to both disorders, (2) mental illness can contribute to SUDs, and (3) SUDs can contribute to the development of mental illnesses.

The diagnosis of SUDs is commonly based on criteria outlined in diagnostic manuals, such as the DSM-5 (American Psychiatric Association, 2013) and ICD-11 (World Health Organization, 2019). These criteria are designed to identify the various dimensions of substance use, from compulsive behavior to physiological dependence, and categorize the severity of the disorder. SUDs are diagnosed if at least two of the following symptoms are present within a 12-month period. The disorder is considered mild if 2 or 3 symptoms are present, moderate with 4 or 5 symptoms, or severe if the individual presents with 6 or more symptoms (American Psychiatric Association, 2013):

1. The substance is often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control use of the substance.
3. A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects.
4. Craving, or a strong desire or urge to use the substance.
5. Recurrent use of the substance resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued use of the substance despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of its use.
7. Important social, occupational, or recreational activities are given up or reduced because of use of the substance.
8. Recurrent use of the substance in situations in which it is physically hazardous.
9. Use of the substance is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Tolerance, as defined by either of the following:
    a. A need for markedly increased amounts of the substance to achieve intoxication or desired effect.
    b. A markedly diminished effect with continued use of the same amount of the substance.
11. Withdrawal, as manifested by either of the following:
    a. The characteristic withdrawal syndrome for the substance
    b. The substance is taken to relieve or avoid withdrawal symptoms.

2.1.2 Gambling disorder

GD is currently the only behavioral addiction officially recognized in the DSM-5, as it shares more behavioral similarities with SUDs than with impulse-control disorders or obsessive-compulsive disorder (Potenza, 2006; Potenza et al., 2009). However, there is ongoing debate about whether some impulse control disorders should be classified as addictions (Brand et al., 2020). Other behaviors commonly referred to as “sex addiction” or “shopping addiction” are not officially classified as behavioral addictions due to a lack of sufficient empirical evidence (Kraus et al., 2016; Leeman & Potenza, 2013). However, the underlying neurobiological mechanisms are thought to be similar relating to attentional biases and craving (Kraus et al., 2016; Leeman & Potenza, 2013). Similar to SUDs, behavioral addictions are characterized by a failure to resist an impulse, drive, or temptation to conduct a behavior that leads to negative consequences to the person or to others (American Psychiatric Association, 2013).

Gambling is defined as an activity where an individual places something of value at risk hoping to get something of greater value (Potenza et al., 2001). Common gambling activities include lotteries, casino gambling and internet gambling. While most people have participated in some type of gambling activity during their life,

only few engage in compulsive gambling. GD, formerly known as "pathological gambling" in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association, 1994), defines a persistent, recurrent pattern of gambling that causes significant distress or impairment (American Psychiatric Association, 2013).

Epidemiology

Pathological gambling (PG) (meeting criteria for the classification in the DSM-IV) affects 1.6% to 1.9% of the adult population (Shaffer et al., 1999; Shaffer & Hall, 2001; Welte et al., 2002), with similar or slightly lower estimates (0.6-1.5%) in the Nordic countries (Bakken et al., 2009; Ekholm et al., 2014; Ilkas & Turja, 2003; Volberg et al., 2001). In DSM-IV, pathological gambling was diagnosed by meeting 5 out of 10 criteria, but in DSM-5, the threshold was lowered to 4 out of 9 criteria. Therefore, it is possible that this estimated prevalence will increase in future epidemiological studies in GD following the adoption of the DSM-5 criteria. Surprisingly, despite the worldwide increase in gambling availability and social acceptability of gambling over the last decades (Cowlishaw & Hakes, 2015), several studies have reported stable (Abbott, 2020; Kessler et al., 2008; Petry et al., 2005; Welte et al., 2015) or even decreased prevalence estimates of pathological gambling and problem gambling (Williams et al., 2012). The explanation for this phenomenon is not certain, but it could be attributed to a lack of novelty and/or adaptations in most parts of the population (Abbott, 2020). For the sake of clarity and consistency, PG will hereafter be referred to as GD.

Previous studies have investigated the psychiatric comorbidity of GD, showing high prevalence rates in several disorders. Ibáñez et al., (2001) reported that 62% of pathological gamblers seeking treatment had another psychiatric disorder diagnosed, with 42% having a personality disorder and 33% having alcohol abuse or dependence. Another study found similar rates for psychiatric comorbidity, reporting a prevalence of 60% among individuals with pathological gambling (Black & Moyer, 1998). In this dataset, 87% had a personality disorder, and 64% SUDs. Moreover, impulse control disorders, such as compulsive sexual behavior and compulsive buying are common in individuals with pathological gambling, affecting 23% of the gamblers in their dataset (Grant & Kim, 2003). Interestingly, a recent, first nation-wide register study in Finland reported even higher rates of psychiatric comorbidities in individuals with GD, with 88.2% of all registered adults with GD (N=3605) having psychiatric comorbidities (Grönroos et al., 2024).

Diagnostic criteria

According to the DSM-5, GD is diagnosed if there is a persistent and recurrent problematic gambling behavior leading to clinically significant impairment or distress, as indicated by the individual exhibiting four (or more) of the following in a 12-month period. The disorder is considered mild if 4 or 5 symptoms are present, moderate if 6 or 7 are met, and severe if the individual presents with 8 or more symptoms (American Psychiatric Association, 2013):

1. Needs to gamble with increasing amounts of money in order to achieve the desired excitement.
2. Is restless or irritable when attempting to cut down or stop gambling.
3. Has made repeated unsuccessful efforts to control, cut back, or stop gambling.
4. Is often preoccupied with gambling (e.g., having persistent thoughts of reliving past gambling experiences, handicapping or planning the next venture, thinking of ways to get money with which to gamble).
5. Often gambles when feeling distressed (e.g., helpless, guilty, anxious, depressed).
6. After losing money gambling, often returns another day to get even ("chasing" one's losses).
7. Lies to conceal the extent of involvement with gambling.
8. Has jeopardized or lost a significant relationship, job, or educational or career opportunity because of gambling.
9. Relies on others to provide money to relieve desperate financial situations caused by gambling.

There are several criteria in GD that underlie the same mechanisms present in SUDs: withdrawal (criterion 2), lack of cognitive control or inhibition (criteria 3, 4, and 6) and decision-making impairment (criteria 8 and 9). Some argue that criterion 1 refers to tolerance, however, one study suggested that this could be due to a cognitive fallacy, in which the gambler believes that the more that is bet, the more chances of winning (Blaszczynski et al., 2008). These similarities show how these two conditions belong to the same disorder, although there are some differences in the nature of each addiction and the clinical presentation.

2.2 Neurobiology of addiction

2.2.1 Reward processing pathways

The ventral tegmental area (VTA), along with the substantia nigra, is one of the brain's largest and primary sources of dopaminergic neurons. These neurons, especially those originating from the VTA, modulate the reinforcing effects of behaviors by increasing dopamine release in the nucleus accumbens (NAcc), which in turn strengthens the association between behavior and pleasure (Fields et al., 2007; Koob & Volkow, 2010). There are two brain dopaminergic pathways originating in

the VTA that are related to reward: the mesolimbic and the mesocortical pathways (Figure 1). The mesolimbic pathway involves dopaminergic projections from the VTA to the NAcc, while the mesocortical pathway projects dopaminergic neurons from the VTA to the prefrontal cortex (PFC). Although the mesocortical pathway is involved in reward-related processes such as cognitive control, regulation of emotional responses and executive function (Volkow et al., 1993), the mesolimbic pathway is involved in the primary reinforcing effects of substances of abuse (Koob & Volkow, 2010; Volkow et al., 2003). The VTA also interacts with other regions within the limbic system, such as the amygdala, which is involved in emotional processing and can influence the reward-related signaling of the NAcc. Additionally, the thalamus plays a crucial role by relaying sensory and motor information, indirectly modulating reward signaling and helping to coordinate these complex brain circuits (James et al., 2021).

When individuals interact with natural rewards (i.e., food, sex, social interactions), dopamine is released in the NAcc, increasing the likelihood of seeking those rewards again in the future. Besides natural rewards, other activities such as drug consumption or gambling can also be highly rewarding and release large amounts of dopamine in the mesolimbic pathway. Substances like cocaine and methamphetamine are highly addictive due to their ability to rapidly increase dopamine levels in the nucleus accumbens, creating intense feelings of pleasure and reward (Volkow et al., 2019). Substances with fast-onset but short-lasting effects, increase addiction risk by creating a sharp contrast between the initial high and the subsequent crash, encouraging repeated use to maintain the dopamine-driven reward (Koob & Volkow, 2016). The method of drug administration, such as smoking or injecting, can further intensify this effect by delivering rapid increases in dopamine more quickly to the brain (Volkow et al., 2003). Similarly, gambling activities that are fast-paced and provide frequent, unpredictable outcomes, such as slot machines, are associated with a higher potential for addiction (Clark, 2010). These games deliver rapid feedback and near-miss outcomes, which activate brain areas involved in reward processing, reinforcing continued play (Clark, 2010).

Over time, and with repeated exposure to these high-dopamine activities, the brain's reward circuitry in some individuals adapts, resulting in neuroplastic changes in the mesolimbic pathway. These adaptations can be influenced by genetic and environmental factors that affect dopaminergic function, increasing sensitivity to addiction-related cues while diminishing responses to natural rewards such as food or sex (Volkow et al., 2019). This leads to an increased vulnerability to compulsive behaviors and the development of addictive disorders (Koob & Volkow, 2016; Scofield et al., 2016).

In addition to dopaminergic mechanisms, opioid neurotransmission plays a critical modulatory role within the brain’s reward circuitry. Endogenous opioids act

primarily on μ-, δ-, and κ-opioid receptors distributed throughout the mesolimbic system, including the VTA, NAc, and PFC (Le Merrer et al., 2009). It has been shown that the opioidergic and dopaminergic systems interact with each other and are involved in human reward functions. (Colasanti et al., 2012; Le Merrer et al., 2009; Mick et al., 2014; Soderman & Unterwald, 2009). The μ-opioid receptors modulate dopaminergic activity in the VTA primarily by inhibiting local GABAergic interneurons (Jalabert et al., 2011; Kalivas, 1993; Spanagel et al., 1992; Volkow & Wise, 2005). In addition, μ-opioid receptors are expressed postsynaptically on VTA dopamine neurons, where they can directly inhibit these neurons independent of GABAergic input (Margolis et al., 2014). Serotonergic signaling also has a role modulating reward processing. Serotonin influences both reward value and behavioral flexibility through its interactions with dopaminergic pathways, where activation of certain receptor subtypes (e.g., 5-HT_2A, 5-HT_1A) can facilitate dopamine release, while others (e.g., 5-HT_2C) mediate inhibitory control (Di Matteo et al., 2008; Pehek et al., 2006; Seymour et al., 2012).

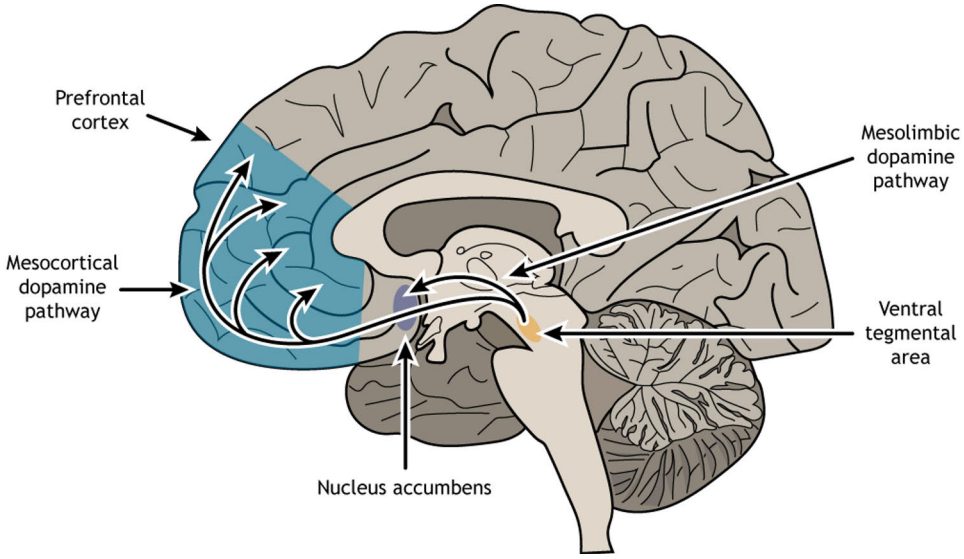

Figure 1. Schematic representation of the mesolimbic and mesocortical pathways. Mesolimbic and Mesocortical Pathways by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

2.2.2 Cue reactivity

Cue reactivity is a critical concept in addiction, promoting the transition from goal-directed actions to automatic responses (Jasinska et al., 2014). Cue reactivity refers to the phenomenon in which individuals exhibit heightened physiological and

psychological responses to stimuli that are associated with a substance or behavior that they are addicted to (Carter & Tiffany, 1999). In substance use, cues that previously predicted drug rewards in specific environments and conditions can evoke stimulus-associated responses such as cravings and drug-seeking behaviors (Volkow et al., 2011). Over time, the reward system becomes sensitized to drug-related cues, leading to automatic drug-seeking behaviors in the presence of those cues, even with the absence of the drug (Koob & Volkow, 2016). This process is closely related to the brain's reward processing pathways, particularly involving fronto-striatal-thalamic circuits, including regions of the PFC such as the ventromedial prefrontal cortex (vmPFC), orbitofrontal cortex (OFC) and the dorsolateral prefrontal cortex (DLPFC), the striatum, and the thalamus (Goldstein & Volkow, 2011). When exposed to drug-related cues, dopamine release in the striatum (particularly the ventral striatum) reinforces the association between the cue and the drug's effects, increasing the intensity of cravings and reinforcing addiction (Phillips et al., 2003; Schultz, 2002; Steinberg et al., 2013).

In the early stages of drug use, the responses to drug cues are primarily goal-directed, with the ventral striatum playing a key role in evaluating the reward potential of the drug. As drug consumption continues, there is a neurobiological shift from the ventral to the dorsal striatum (Belin & Everitt, 2008). Although most of the evidence for this shift comes from animal studies, human research also suggests the involvement of the dorsal striatum in cue-reactivity paradigms (Volkow et al., 2006; Zilverstand et al., 2018). The consequence of this shift is a transition from controlled, reward-driven behavior to automatic responses driven by the associated cues (Everitt & Robbins, 2016). As behavior becomes more automatic, the dorsal striatum and associated motor-related areas become more involved, reducing the need for conscious choices and the anticipation of rewards, which are controlled by the ventral striatum (Koob & Volkow, 2016; Volkow et al., 2006). Changes in how dopamine works and how neurons connect in the dorsal striatum strengthen this habit, making drug-seeking behaviors harder to change, more cue-dependent, and less reliant on external rewards (Everitt & Robbins, 2005).

The PFC is also crucial in modulating cue reactivity, especially in early drug use, where it helps with decision-making and evaluating risks (Goldstein & Volkow, 2011). As drug-seeking becomes more habitual, the influence of the PFC diminishes, and its ability to exert control over the striatum weakens (Koob & Volkow, 2016). This reduced top-down control makes individuals more vulnerable to cue-triggered drug-seeking, leading to compulsive drug use even when the conscious desire to use may be absent.

While much focus is placed on the fronto-striatal regions in cue-reactivity and reward processing, research has also emphasized the thalamus as an integral part of the addiction neurobiology. Animal and human studies suggest that the thalamus

contributes to drug-seeking behaviors by responding to salient cues. In the initial stages of substance use, the thalamus is primarily involved in processing sensory information related to drug cues and relaying this information to brain regions responsible for decision-making and reward evaluation, such as the PFC and ventral striatum. As engagement in addictive behaviors becomes more habitual and automatic, the thalamus transitions from a role focused on integrating sensory and cognitive information to one that supports cue-driven responses. This shift is characterized by altered functional connectivity patterns, particularly between regions involved in reward processing and decision-making, ultimately leading to a reliance on automatic behaviors that are less influenced by conscious thought (Huang et al., 2018).

2.2.3 Prefrontal cognitive control

The PFC plays a crucial role in various cognitive functions essential for everyday life, including attention, working memory, decision-making, and inhibition. These cognitive processes allow individuals to navigate their environment effectively, make reasoned choices, and exercise self-control. In healthy individuals, the PFC enables them to weigh the consequences of their actions and regulate their impulses, preventing engagement in harmful behaviors (Friedman & Robbins, 2022).

An important anatomical and functional distinction can be made between the dorsal and ventral PFC, as described by Goldstein & Volkow. The dorsal PFC, which includes regions such as the DLPFC, anterior cingulate cortex (ACC), and inferior frontal gyrus, is primarily involved in top-down control and meta-cognitive functions. In contrast, the ventral PFC, which encompasses regions like the subgenual ACC and orbitofrontal cortex, is more closely associated with emotion regulation, automatic responses, and impulsivity (Goldstein & Volkow, 2011).

Goldstein and Volkow (2011) proposed the iRISA (Impaired Response Inhibition and Salience Attribution) model to explain how addiction disrupts the balance between these regions (Figure 2). In a healthy state, the dorsal PFC maintains control over ventral PFC regions, allowing for regulation of automatic, emotion-driven responses. This balance ensures that drug-taking behavior is under control or inhibited. However, during addiction, this balance shifts. Drug-related cues gain excessive salience, and the ventral PFC, involved in emotion-driven processes, begins to dominate. As a result, drug-related thoughts and behaviors overshadow non-drug-related functions, weakening self-control and increasing drug-seeking behavior. Impulsivity rises, and cognitive control diminishes, leading to compulsive behaviors. The iRISA model highlights how addiction transforms cognitive control systems into automatic, stimulus-driven behaviors, reinforcing the cycle of addiction.

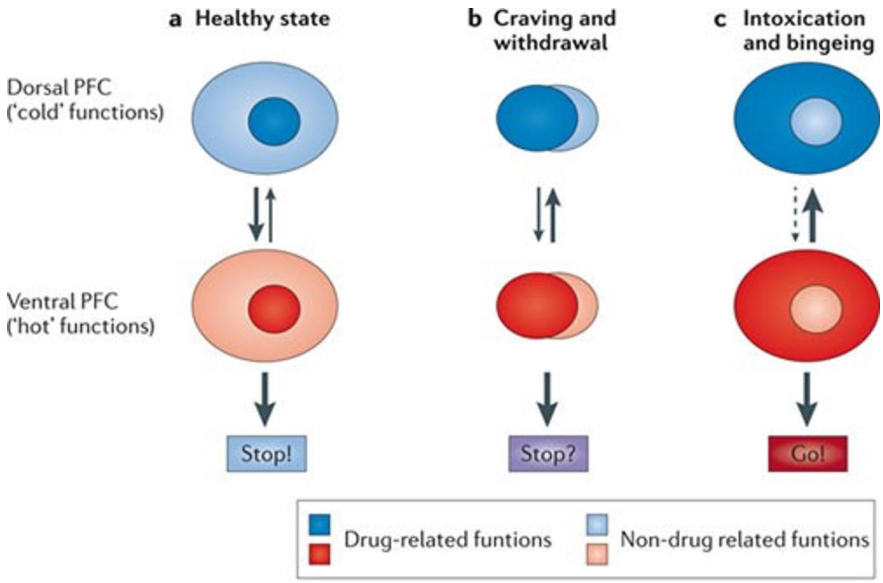

Figure 2. Role of the prefrontal cortex in the iRISA model. Figure 2 is a copy of a figure from an article by R. Z. Goldstein & Volkow, (2011) and has been reprinted with the permission of the copyright holders.

While the iRISA model has been influential in highlighting prefrontal dysfunction in addiction, other models have provided additional insights. Dual-process models, for instance, conceptualize behavior as the outcome of an interaction between a fast, automatic impulsive system and a slower, reflective system mainly controlled by the PFC. Addiction is viewed as a failure of this reflective system to inhibit maladaptive responses triggered by salient drug cues (Wiers et al., 2007). Habit formation models add further information, suggesting that chronic drug use shifts behavior from goal-directed to habitual responding, where processes are increasingly controlled by the dorsal striatum and less influenced by prefrontal executive control (Everitt & Robbins, 2005).

Importantly, the PFC interacts with other brain areas, such as the striatum and the thalamus, to regulate adaptive behaviors (Goulet-Kennedy et al., 2016; Grahn et al., 2008; Haber, 2003, 2016; Parnaudeau et al., 2018). These fronto-striatal-thalamic circuits are integral to various cognitive and behavioral functions, including decision-making, reward processing, and inhibitory control. Dopaminergic signaling within these circuits enhances motivation and reinforces behaviors that lead to rewarding outcomes, thereby supporting goal-directed actions and adaptive learning (Haber, 2016). Individuals with addiction present significant abnormalities in the functioning of fronto-striatal-thalamic circuits. Research has shown that this circuit impairment can lead to deficits in decision-making, increased impulsivity, and alter

the ability to learn from negative outcomes, thereby perpetuating maladaptive behaviors associated with addiction (Morein-Zamir & Robbins, 2015; Park et al., 2010).

2.3 Neuroimaging Gambling Disorder

Having outlined the fundamental neurobiology of addiction, this section will now shift focus to the insights gained from neuroimaging studies in GD. These findings are pivotal for understanding the underlying neural mechanisms of GD and have provided a basis for the research conducted in this thesis.

2.3.1 Structural Neuroimaging Findings

2.3.1.1 Gray matter volume changes

Sixteen studies have investigated gray matter volume and/or surface thickness differences between individuals with GD and HC, mostly in relatively young populations. The study with the oldest GD sample reported a mean age of nearly 48 years (J. E. Grant et al., 2015). Fifteen of these studies conducted voxel-based morphometry (VBM) analyses, while only two studies included surface-based analyses (Bouchard et al., 2021; J. E. Grant et al., 2015). 12 studies performed whole-brain analysis, 10 region-of-interest (ROI)-based analysis, and 6 both whole-brain and ROI-based analyses. The literature search was done on PubMed and Scopus for studies published through July 2025.

Four independent studies using VBM found no significant differences in gray matter volume in individuals with GD or problem gambling compared to HC (Freinhofer et al., 2020; Joutsa et al., 2011; van Holst, de Ruiter, et al., 2012; Yip et al., 2018). The study designs from van Holst et al. (2012) and Yip et al. (2018) also included a third group presenting a SUD (alcohol use disorder and cocaine use disorder, respectively). In both studies, the SUD group showed significant widespread volume reductions in multiple brain regions compared to HCs, indicating morphological abnormalities associated with substance use only.

Contrary to the findings of these studies, 12 out of the 16 studies have reported variable gray matter differences between GD and HC groups. Studies investigating whole-brain abnormalities in individuals with GD show heterogeneous results; however, the most consistently reported abnormalities (mostly volume decreases) are in the frontal lobe (8 studies), particularly in the medial frontal gyrus and OFC. Other studies reported differences in parietal regions, occipital regions, and other well-documented regions to be affected in SUDs such as the striatum, the insula, and the hippocampus (Koob & Volkow, 2010). Only one whole-brain study (Koehler et

al., 2015) has reported increased volumes in the GD group, specifically in the medial frontal gyrus, inferior frontal gyrus, and ventral striatum. These findings may stem from the exploratory nature of the study, which did not use correction for multiple comparisons for the search volume, thereby increasing the risk for false positive findings.

Two studies found significant differences using a surface-based approach. The first study showed thickness decreases in several areas in the frontal lobe and the parietal lobe (J. E. Grant et al., 2015). The second also observed cortical thickness decreases in frontal and parietal regions, alongside increases in visual-related areas (Bouchard et al., 2021). It is worth mentioning that this study used one-sample t-tests to compare the z-scores of GD patients to the normative mean of 0, representing the healthy population. This approach could have biased the results as the normative data might not match the study population.

Studies including ROI analyses have restricted their investigation to cortical and subcortical areas that have demonstrated a role in addiction, such as the insula, frontal cortex, and basal ganglia. By focusing on these predefined areas, these analyses may have enhanced sensitivity, allowing for the detection of subtle gray matter volume changes that otherwise would go unnoticed in whole-brain analyses. These studies have shown volume decreases in the amygdala, hippocampus, putamen and thalamus (Fuentes et al., 2015; Rahman et al., 2014; Takeuchi et al., 2019), but also volume increases in the ventral striatum, medial frontal gyrus and inferior frontal gyrus (Irizar et al., 2020; Koehler et al., 2015). On the other hand, not all studies found significant differences (Freinhofer et al., 2020; J. E. Grant et al., 2015; Yip et al., 2018; Zois et al., 2017).

Overall, findings appear to be heterogeneous, likely reflecting the different study designs and characteristics of each study, such as differences in sample size, scanner resolution, statistical thresholds, or analytic approaches (e.g., whole-brain vs. ROI-based analyses). However, whole-brain analyses highlight more consistent gray matter abnormalities within the frontal lobe, particularly the medial frontal gyrus and OFC, suggesting these regions may play a central role in the neural underpinnings of GD. ROI analyses have complemented whole-brain studies by providing higher sensitivity to smaller areas. These studies have shown gray matter alterations predominantly in subcortical areas, including the striatum, hippocampus, amygdala, and thalamus. However, because ROI studies focus on hypothesis-driven regions, they may not provide a comprehensive picture, and conclusions about the brain regions most involved in GD cannot be drawn based solely on these analyses. Finally, all of these studies have been conducted in relatively young populations, which might make it more challenging to detect pronounced structural differences. In contrast, older populations typically show more brain structural alterations, potentially increasing the sensitivity of analyses to detect changes (Lockhart & DeCarli, 2014).

Table 1. Gray matter studies comparing individuals with GD and HC.

Study	Sample size (F)	Age	MRI	Analysis	Threshold	Findings
Joutsa et al. (2011)	GD: 12 HC: 12	30(22-49) 27(19-55)	1.5T	Whole-brain voxel-wise	p<0.001 uncorrected, cluster threshold:100 voxels	No differences in GM volume between groups
van Holst et al. (2012)	PRG: 40 HC: 54	36.5(10.7) 35.3(10.1)	3T	Whole-brain voxel-wise	p<0.05, FDR corrected; voxel-wise	No differences in GM volume between groups
Rahman et al. (2014)	GD: 32(12) HC: 47(19)	36.5 29.6	3T	ROI	p<0.05	Volume decreases in GD: • right amygdala • left hippocampus
Koehler et al. (2015)	GD: 20 HC: 21	33.7(10.3) 39.2(11.8)	3T	Whole-brain voxel-wise and ROI	p<0.001 uncorrected, cluster threshold:30 voxels; voxel-wise SVC-adjusted alpha error probability p<0.05 FWE corrected	Volume increases in GD: • bilateral medial frontal gyrus • right ventral striatum • left inferior frontal gyrus Volume increases in GD in ROI analysis: • right ventral striatum • right medial frontal gyrus

Grant et al. (2015)	GD: 16(10)
	HC: 17(13)
		47.8(13.7)
		41(14.3)
			3T	Whole-brain voxel-wise and ROI	cluster-forming threshold of $p<0.001$, and $p<0.05$; cluster-wise
					Uncorrected p<0.05; ROI
						Thickness decreases in GD:
						• Right rostral middle frontal
						• Right medial OFC
						• Left inferior parietal
						  • Right post-central gyrus
						  • Right supramarginal gyrus
						  • Right superior frontal gyrus
						No differences in ROI analysis

Study	Sample size (F)	Age	MRI	Analysis	Threshold	Findings
Fuentes et al. (2015)	GD: 37 HC: 30	37.3(9.6) 37.3(9.7)	1.5T	Whole-brain voxel-wise and ROI	p<0.05 FDR corrected; voxel-wise p<0.01, uncorrected; ROI	No differences in GM volume in voxel-wise analysis Volume decreases in GD in ROI analysis: • left putamen • right thalamus • right hippocampus
Mohammadi et al. (2016)	GD: 15 HC: 15	36.7(5.8) 36.8(5.6)	3T	Whole-brain voxel-wise	p<0.05 FWE corrected; voxel-wise	Volume decreases in GD: • right ACC • right OFC • right precentral gyrus • right insula • right hippocampus • right amygdala • bilateral putamen • bilateral supplemental motor area
Zois et al. (2017)	GD: 60 HC: 98	36.7(8.9) 36.1(9.7)	3T	Whole brain voxel-wise and ROI	p<0.05 FWE corrected, cluster threshold:230 2; voxel-wise	Volume decreases in GD: • left superior medial frontal gyrus • right medial orbital frontal gyrus No differences in ROI analysis
Takeuchi et al. (2017)	GD: 36 HC: 36	36.3(10.6)	3T	Whole-brain voxel-wise	p<0.005, uncorrected, cluster threshold=20 0; voxel-wise	Volume decreases in GD: • supramarginal gyrus • bilateral posterior cerebellum
Yip et al. (2018)	GD: 35(9) HC: 37(9)	38.4(11.8) 38(11)	3T	Whole-brain voxel-wise and ROI	p<0.05 FWE corrected: cluster-level	No differences in GM volume between groups
Ruiz de Lara et al. (2018)	GD: 25 HC: 25	31.7(8.2) 31.1(7.1)	3T	Whole-brain voxel-wise	p<0.001 uncorrected; cluster threshold=41 6; voxel-level	Volume decreases in GD: • dmPFC
Takeuchi et al. (2019)	GD: 46 HC: 52	35 (9.5) 35.8(7.8)	3T	ROI	p<0.05 FWE corrected; cluster threshold=20	Volume decreases in GD: • left amygdala

Study	Sample size (F)	Age	MRI	Analysis	Threshold	Findings
Irizar et al. (2020)	GD: 18(2) HC: 21(1)	33.6(8) 31(4.6)	3T	ROI	p<0.05 Bonferroni corrected	Volume increases in GD: • right inferior frontal gyrus
Draps et al. (2020)	GD:26 HC: 25	33.2(7.5) 34.5(6.2)	3T	Whole-brain voxel-wise	p<0.001, uncorrected; voxel-level and FWE, p<0.05; cluster-level	Volume decreases in GD: • left frontopolar cortex
Freinhofer et al. (2020)	GD: 27(4) HC: 22(2)	43.9(11.9) 40.8(14.3)	3T	Whole-brain voxel-wise and ROI	p<0.05 FWE corrected; voxel-level	No differences in GM volume between groups
Bouchard et al. (2021)	GD: 17(8) HC: normative database of 2713 cortical and 2790 subcortical anatomical scans	41.2(16.7) N.A.	3T	ROI	p<0.01 Bonferroni corrected	Volume increases in GD: • Pericalcarine cortex • Lingual gyrus • Entorhinal cortex • Pallidum • Putamen • Thalamus • Nucleus accumbens • Ventral diencephalon • Caudate Thickness decreases in GD: • Middle frontal gyrus • Superior frontal gyrus • Inferior parietal gyrus Thickness increase in GD: • Pericalcarine cortex • Lingual gyrus • Entorhinal cortex

GD: gambling disorder; HC: healthy controls; PRG: problem gambling F: females; FWE: family-wise error; ROI: region-of-interest; TFCE: threshold-free cluster enhancement; FDR: false discovery rate; GM: gray matter; SVC: small volume correction; OFC: orbitofrontal cortex; ACC: anterior cingulate cortex; dmPFC: dorsomedial prefrontal cortex

2.3.1.2 White matter integrity changes

Six studies have conducted research on white matter integrity differences between individuals with GD and HC. Four of these studies performed whole-brain analysis, one conducted ROI analysis, and another one used both whole-brain and ROI

analyses. All six studies reported fractional anisotropy (FA) values and two reported both FA and mean diffusivity (MD) values. The literature search was done on PubMed and Scopus for studies published through July 2025.

Most studies have shown significant findings in white matter integrity differences between both the GD and HC groups. From the whole-brain studies, only one did not find any significant results (van Timmeren et al., 2017). All other whole-brain studies have found abnormal white matter integrity in multiple brain areas, with the superior longitudinal fasciculus being reported in all the studies with significant findings. The corpus callosum was also shown to have lower FA values in 3 studies, although one of them was an ROI study focusing on this area. Yip et al. (2017) compared individuals with GD, Cocaine Use Disorder (CUD), and HC, and found that although GD and CUD groups did not differ from each other, both showed similar disruptions in white matter pathways compared to HC. Interestingly, no differences were found in FA, which is the white matter integrity measure used in all other WM studies reported in Table 2, but group differences were shown in PVE2, a more advanced measure that captures the integrity of crossing fiber pathways.

The studies restricting their analysis to an ROI did so by focusing on the corpus callosum and the tracks between the DLPFC and the basal ganglia. Both studies found significantly lowered FA values in those areas in individuals with GD compared to HC (van Timmeren et al., 2017; Yip et al., 2013).

Studies reporting MD measurements showed higher values in the inferior longitudinal fascicle, the uncinate fascicle, the inferior fronto-occipital fascicle, the corpus callosum (Joutsa et al., 2011), and a white matter tract between the DLPFC and the basal ganglia (van Timmeren et al., 2017). MD reflects the average rate of water diffusion within tissue, while FA indicates the directionality of that diffusion – higher FA typically reflects greater fiber organization and integrity. In contrast, increased MD values suggest reduced structural integrity, often due to increased extracellular space and less restricted water movement.

Overall, although findings might appear heterogeneous, some regions seem to be consistently involved in the pathophysiology of GD, such as the superior longitudinal fasciculus and the corpus callosum. However, only 6 studies have investigated white matter structure in individuals with GD, limiting our understanding of the full extent of white matter abnormalities in GD. The limited number of studies, combined with methodological differences (e.g., variations in MRI scanner strength, analysis techniques, and sample sizes), may contribute to the apparent heterogeneity of the findings.

Table 2. White matter studies comparing individuals with GD and HC.

Study	Sample size (F)	Age	MRI	Analysis	Threshold	Findings
Joutsa et al. (2011)	GD: 12 HC: 12	30(22-49) 27(19-55)	1.5T	Whole-brain	p<0.05 FWE corrected	Lower FA: • bilateral superior longitudinal fasciculus • body/splenium of corpus callosum • right superior longitudinal fasciculus/inferior fronto-occipital fasciculus • splenium of corpus callosum • right corticospinal tract Higher MD: • inferior longitudinal fascicle • Uncinate • inferior fronto-occipital fascicle • corpus callosum
Yip et al. (2013)	GD: 19(7) HC: 19(8)	36.8(11.8) 35.5(11.2)	3T	ROI	p<0.05	Lower FA: • left body of corpus callosum • bilateral genu of corpus callosum
Chamberlain et al. (2016)	GD: 16(10) HC: 15(12)	47.4(13.7) 32.5(14.9)	3T	Whole-brain	p<0.05 FWE corrected	Lower FA: • corpus callosal fibres • superior longitudinal fasciculus/cortico spinal tract • left hippocampus
Mohammadi et al. (2016)	GD: 12 HC: 12	36.7(5.8) 36.8(5.6)	3T	Whole-brain	p<0.05 FWE corrected	Lower FA: • bilateral superior longitudinal fascicle • left inferior longitudinal fascicle • bilateral inferior fronto-occipital fascicle • bilateral anterior thalamic radiation
Yip et al. (2017)	GD: 38(10) HC: 38(10)	38.3(11.8) 38.1(10.9)	3T	Whole-brain	p<0.05 FWE corrected	No FA differences between groups Reductions in PVE2: • bilateral corona radiata • bilateral internal capsule • bilateral superior longitudinal fasciculus

Study	Sample size (F)	Age	MRI	Analysis	Threshold	Findings
						• left posterior thalamic radiation • bilateral peduncle • bilateral external capsule
van Timmeren et al. (2017)	GD: 26 HC: 26	37.1(12.1) 37.9(10.6)	3T	Whole brain and ROI	p<0.05 TFCE corrected	No differences in whole-brain analysis Lower FA and higher MD in ROI: • tract between left DLPFC and left basal ganglia

GD: gambling disorder; HC: healthy controls; F: females; FWE: family-wise error; FA: Fractional anisotropy; MD: mean diffusivity; ROI: region-of-interest; TFCE: threshold-free cluster enhancement; DLPFC: dorsolateral prefrontal cortex

2.3.2 Functional Neuroimaging (BOLD) Findings

2.3.2.1 Task-fMRI studies

Reward

In GD, fMRI research on reward has focused on brain responses to reward anticipation and reward outcome. In individuals with GD compared to HC, reward anticipation studies have shown an increased activity in reward-related areas such as the ventral striatum, putamen, insula, medial prefrontal cortex, and OFC when anticipating gambling-related cues (Brevers D et al., 2015; Choi et al., 2012; Sescousse et al., 2013; Worhunsky et al., 2014). In contrast, decreased activation has been reported in regions including the insula, thalamus, and nucleus caudate (Choi et al., 2012; Tsurumi et al., 2014). These mixed findings could potentially reflect the heterogeneity in study designs. Different tasks were used in these studies, including Monetary Incentive Task, Card-Deck paradigm, simulated slot-machine task, and incentive delay task. In addition, the sample sizes of the GD groups were relatively low, ranging from 12 to 24 individuals.

Studies investigating brain responses to reward and loss processing have shown reduced activity in key brain regions associated with reward processing located in fronto-striatal regions such as the ventral striatum and ventral medial prefrontal cortex, but also in the insula (Balodis et al., 2012, 2018). Finally, a near-miss fMRI paradigm showed that individuals with GD exhibited increased ventral striatal responses to near-miss outcomes compared to controls (Sescousse et al., 2016).

These findings highlight a dual pattern of neural dysfunction in gambling disorder, with heightened sensitivity to rewards and near-miss outcomes alongside impaired reward evaluation and loss processing.

Cue-reactivity

Functional MRI studies investigating cue reactivity in GD consistently demonstrate that gambling-related cues elicit altered neural responses in individuals with GD compared to HC. However, findings vary across studies depending on task design, stimulus modality, and comparison conditions.

For example, Limbrick-Oldfield EH et al. (2017) found that individuals with GD showed increased activation in the left insula and ACC when exposed to personally tailored gambling cues. Similarly, the study by Kober H et al. (2016) found that individuals with GD had significantly increased brain activation in the ACC and vmPFC in response to gambling cues. Crockford et al. (2005) also reported greater activation in brain regions while viewing gambling-related videos, including the right DLPFC, right parahippocampal gyrus, and left occipital cortex. Interestingly, their design included wildlife and nature scenes alternating with the gambling-related videos. This choice of comparison stimuli could be seen as notably different from the gambling cues. Therefore, caution is warranted when interpreting the results, as the significant differences between the stimuli may impact the observed gambling-related brain activity.

In contrast, Potenza & Steinberg, et al., (2003) observed decreased activation in the frontal and orbitofrontal cortices, caudate/basal ganglia, and thalamus during the early phases of gambling cue exposure, relative to both neutral baselines and emotionally charged but non-gambling-related scenarios. This study compared the gambling-related stimuli to emotionally charged stimuli (happy and sad content), which might be of importance when interpreting the results, as no neutral stimuli were used to compare the gambling cues.

Together, these studies highlight the complex and heterogeneous neural responses to gambling-related cues in GD. While some research suggests hyperactivation in reward- and salience-related areas, others indicate hypoactivation in executive and reward circuits. Importantly, based on these prior studies, increased striatal cue-reactivity seen in SUDs does not seem to replicate in GD (Cousijn et al., 2013; Engelmann et al., 2012; Koob & Volkow, 2010; Sjoerds et al., 2014; Zhou et al., 2019). The variability in findings may reflect differences in experimental paradigms, such as passive versus active tasks, image versus video stimuli, and the emotional or cognitive salience of control conditions. This underscores the need for more standardized approaches to studying cue reactivity in GD. To attempt to address these gaps, this thesis uses a naturalistic cue-reactivity paradigm using video

stimuli depicting human behaviors, designed to better capture real-world gambling contexts and to provide comparable stimuli. Furthermore, natural rewarding stimuli are included to differentiate between addiction-related and non-addiction-related rewarding processes. By focusing on striatal responses, this work aims to add to the lacking evidence regarding striatal involvement in cue-reactivity processes in GD.

Impulse control and risk-taking

Impulse control and risk-taking in GD have been explored through various fMRI paradigms. One study using the Stroop task demonstrated that individuals with GD exhibited decreased activity in the left vmPFC when responding to infrequent incongruent stimuli, suggesting deficits in attention and inhibition compared to HC (Potenza, Leung, et al., 2003). This partially aligns with findings from a study investigating risk, where they found that individuals with GD exhibited diminished activity in the DLPFC (Fujimoto A et al., 2017). Interestingly, a study examining unaffected siblings of individuals with GD found no significant differences in neural responses to risk taking and impulsivity (Limbrick-Oldfield et al., 2020), suggesting that vulnerability to gambling disorder may not manifest in neural responses under certain conditions.

Decision-making

Decision-making processes in GD involves impaired cognitive control and heightened reward sensitivity, contributing to maladaptive behaviors. Individuals with GD show increased activation in the orbitofrontal cortex, caudate, and amygdala during the Iowa Gambling Task, linked to a preference for immediate rewards and risky choices (Power et al., 2012). Similarly, extreme gambling scenarios evoke heightened cortico-striatal responses, including in the DLPFC and caudate (Gelskov et al., 2016). In contrast, reduced activation in regions linked to cognitive control have been shown during sunk cost decision-making, particularly in the dorsal medial prefrontal cortex (dmPFC) (Fujino et al., 2018). Additionally, Brevers D et al. (2015) observed decreased activity in the globus pallidus during decision-making under risk.

Together, these findings suggest that decision-making in GD reflects a complex interplay between impaired cognitive control and heightened reward sensitivity. These neural alterations likely underlie the preference for immediate rewards, risk-taking tendencies, and difficulties in regulating behaviors that characterize gambling behaviors.

2.3.2.2 Resting-state fMRI studies

Resting-state fMRI (rs-fMRI) research in GD is scarce and much is yet to be understood on the connectivity patterns of the GD brain. Here I will present functional connectivity findings in GD compared to HC from the currently existing studies.

Piccoli et al. (2020) used independent component analysis (ICA) to identify differential functional brain networks between GD and HC. In this study, individuals with GD showed an increased resting state functional connectivity in a network including the caudate nucleus, the nucleus accumbens and the anterior cingulate, and another network within the cerebellum in comparison with the HC group. In addition, the functional connectivity within the cerebellar network was significantly associated with gambling severity.

Other studies have also investigated functional connectivity, but restricted their analyses to predefined networks (e.g., the default mode network [DMN]). One study found an increase in the strength of connectivity between the insula and DMN regions in patients with GD compared to HC. Moreover, the connectivity strength between the insula and DMN was positively associated with the GD duration (Tsurumi et al., 2020). Another study by Jung et al. (2014) showed that individuals with GD presented decreased DMN connectivity with several regions, including the right middle temporal gyrus, left superior frontal gyrus, and precuneus compared with HC.

Contreras-Rodríguez et al. (2016) investigated functional connectivity differences between brain regions (seed-to-voxel analysis) in individuals with GD and HC, based on a previous global connectivity analysis among individuals with cocaine dependence. The study found that both individuals with GD and with cocaine dependence present overlapping connectivity changes compared to HC, particularly increased connectivity between the orbitofrontal and dorsomedial prefrontal cortices, as well as between the amygdala and insula.

Finally, Koehler et al. (2013) also performed seed-to-voxel analysis and found increased connectivity between regions in the prefrontal cortex and the reward system. In this study, functional connectivity was calculated from two seeds extracted from their results on a previous gray matter volumetric study: the right middle frontal gyrus and the right striatum. Results showed that individuals with GD exhibited an increased connectivity from the frontal seed to the right striatum compared with HC, which correlated positively with an impulsivity aspect – non-planning. In addition, they also found an increased connectivity from the right striatum to the right superior and middle frontal gyrus and left cerebellum in individuals with GD compared to HC.

Based on these findings, individuals with GD exhibit distinct and complex alterations in brain connectivity, particularly in networks related to reward

processing, impulse control, and the DMN. However, it should be noted that 1) the number of rs-fMRI studies in GD is still scarce and individual sample sizes have been low (14-24 GD subjects per study) to draw strong conclusions about the functional connectivity of the GD's brain, and 2) the presented rs-fMRI studies used different approaches to analyze their data, making it challenging to directly compare the findings.

2.3.3 Molecular Imaging Findings

Multiple neurotransmitter systems have been implicated in GD. Prior PET studies have focused on the dopamine, serotonin, opioids and ɣ-amino butyric acid (GABA) systems. Here I will focus on the main neurotransmitters studied in this thesis: dopamine, serotonin, and endogenous opioids.

2.3.3.1 Dopaminergic system

Studies investigating the dopaminergic system in individuals with GD have explored different aspects, including dopamine receptor 2/3 (D2/3) availability (5 studies), presynaptic dopaminergic function (2 studies), striatal dopamine release (5 studies), and dopamine transporter (DAT) binding (2 studies).

All five independent PET studies in GD using a D2/3 receptor radioligand, [^{11}C]-raclopride, found no significant differences in dopamine D2/3 receptor binding compared to HC (Boileau et al., 2013; Clark et al., 2012; Joutsa et al., 2012; Linnet et al., 2011). These findings contrast with studies on individuals with SUDs, such as alcohol, nicotine, cocaine, and opiate use disorders, which have consistently shown decreased binding (particularly in the striatum) of these receptors compared to HC (Volkow et al., 2007).

Research exploring dopamine synthesis capacity with [^{18}F]-fluorodopa has shown contradictory results. Van Holst et al (2018) found that individuals with GD had increased dopamine synthesis in the whole striatum compared to healthy controls, suggesting altered presynaptic dopaminergic function in GD (van Holst et al., 2018). However, Majuri et al. (2017a) found no significant differences between GD and controls.

Research investigating dopamine release in GD has studied this by measuring the displacement of a radioligand (e.g., [^{11}C]-raclopride or [^{11}C]-PHNO) following the administration of a stimulant or during task performance. This line of research has revealed heightened dopaminergic reactivity in response to pharmacological and gambling-related challenges. Boileau et al. found greater amphetamine-induced dopamine release in the dorsal striatum of individuals with GD compared to controls, with dopamine release in the ventral striatum (VS) correlating with gambling

severity (Boileau et al., 2014). Joutsa et al. similarly observed striatal dopamine release during slot machine play, where greater release in the VS was linked to symptom severity and subjective 'high' from high rewards (Joutsa et al., 2012). However, no group differences were found in dopamine release between GD patients and controls. These findings contrast with the blunted dopamine release seen in SUDs. Studies using the Iowa Gambling Task (IGT) further associated increased dopamine release in the left VS with riskier decision-making in GD compared to HC, suggesting that elevated dopamine release in GD is linked to gambling severity, impulsivity, and risky behavior (Linnet et al., 2010, 2011, 2012).

Finally, another line of research has focused on dopamine transporters (DAT), which play a key role in regulating synaptic dopamine levels. Findings have been mixed, with two studies reporting no significant differences in DAT striatal density between individuals with GD and HC (Guerra et al., 2023; Kaasinen et al., 2023), whereas another study found reduced DAT availability in the caudate and putamen in individuals with GD (Pettorruso et al., 2019).

Evidence from patients with Parkinson's disease and associated impulse control disorders and/or GD further supports the role of altered dopaminergic signaling in compulsive and reward-driven behaviors. Individuals with PD who develop ICDs or GD while receiving dopaminergic medication show increased striatal dopamine release during reward-related tasks, as well as increased dopaminergic responsivity to reward cues (O'Sullivan et al., 2011; Steeves et al., 2009). This phasic increase is similar to findings in individuals with GD without PD (Boileau et al., 2014; Joutsa et al., 2012), suggesting a shared pattern of enhanced dopaminergic responsivity to rewards. However, unlike primary GD, PD with GD or impulse control disorders occur in the context of dopaminergic therapy and possible baseline dopaminergic alterations, indicating that the mechanisms leading to similar behavioral outcomes may differ (Potenza, 2013).

Overall, these findings suggest that GD does not exhibit the hallmark reductions in striatal D2/3 receptor availability seen in SUDs. Both at baseline and during reward outcome, SUDs exhibit blunted dopaminergic signalling. However, in GD, findings indicate normal or even increased rather than decreased dopamine function. Increases of dopamine release in response to gambling-related and pharmacological challenges, together with potential alterations in dopamine synthesis and transporter availability, points to potentially altered dopaminergic signalling in GD.

2.3.3.2 Serotonergic system

Serotonin is known for having a role in regulating mood and impulsivity (Pourhamzeh et al., 2022). Alterations in serotonin levels can lead to mood disorders such as depression and anxiety. Reduced levels of serotonin are also associated with

increased impulsivity, making individuals more likely to engage in risky behaviors, including addictions (Fischer & Ullsperger, 2017). In addition, serotonin modulates dopamine transmission, affecting reward and punishment learning, which are crucial to addiction (Fischer & Ullsperger, 2017).

In GD, non-pharmacological studies have investigated the role of the serotonergic system via imaging binding to serotonergic transporters and to serotonergic receptors. Some studies using serotonin receptor or transporter radioligands have found no differences in binding levels between individuals with GD and HC (Majuri et al., 2017b; Potenza et al., 2013). However, Potenza et al. (2013) found that symptom severity in GD was associated with higher 5-HT1B binding in the ventral striatum, putamen, and anterior cingulate. In addition, Kaasinen et al. (2023) found significant group differences in [^{123}I]FP-CIT, likely reflecting serotonin transporter (SERT) binding, within the vmPFC, and this was associated with impulsivity. Importantly, findings from impulse control disorders in Parkinson's disease – conditions with behavioral and neurobiological overlap with GD – also implicate serotonergic dysfunction in altered inhibitory control and compulsivity (Prange et al., 2025).

Overall, studies investigating imaging the serotonergic system in GD have shown mixed results, however it can be inferred that the serotoninergic system is associated with impulsivity and brain areas related to reward processing in GD. Additionally, the only study that reported significant group differences included an older sample, which may be more sensitive to neurotransmitter changes, as these changes tend to be more pronounced with age (Dowling et al., 2008). Due to the low number of studies, we still do not fully know how the serotonergic system is characterized in GD.

2.3.3.3 Opioidergic system

The endogenous opioid system plays a role in mediating pleasurable effects of rewards and drugs of abuse (Baldo & Kelley, 2007; Langleben et al., 2012). Moreover, the opioid and dopaminergic systems seem to modulate each other, as shown by the associations between mu-opioid receptors and dopamine system measures (i.e., dopamine D2 receptor and presynaptic dopamine synthesis capacity) in reward areas of the brain such as the striatum and the ventral tegmental area (Majuri et al., 2018; Tuominen et al., 2015). Additionally, Colasanti et al. (2012) and Mick et al. (2014) demonstrated that amphetamine-induced dopamine release leads to endogenous opioid release in the human brain, further supporting the interaction between these systems.

In GD, baseline brain imaging research has explored the role of the endogenous opioidergic system by studying opioid receptor availability (i.e., mu-receptors). No

significant differences in baseline ^{11}C-carfentanil binding were found between GD participants and HC, although a positive correlation was observed between caudate binding and mood-related impulsivity (Mick et al., 2017). Similarly, no differences in mu-opioid binding were detected between GD and HC in a more recent study (Turton et al., 2024). In contrast, reduced opioid mu-receptor binding was observed in the anterior cingulate cortex of GD participants compared to HC (Majuri et al., 2017a). Similar to studies investigating dopamine release, Mick et al. (2016) investigated opioid release via an amphetamine challenge, finding that opioid release in individuals with GD was decreased in several regions, including the putamen, cerebellum, frontal lobe, anterior cingulate, and insula.

The research on opioid receptor availability in GD shows mixed results. These findings suggest that although group-level differences in opioid receptor availability are not consistently observed, alterations in opioid function may still play a role in GD, particularly in relation to reward-related brain regions and impulsivity. However, given the limited studies and variability in methods, further research is needed to fully understand the role of the opioidergic system in GD.

2.4 Existing interventions in gambling disorder

Non-invasive neuromodulation techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have been tested in individuals with GD in an effort to mitigate key behavioral and cognitive features of the disorder, including impaired decision-making, impulsivity, craving, and gambling severity. In a recent review, Pettorruso et al. show heterogeneity in non-invasive neuromodulation protocols for treating GD, with differences in the type of stimulation applied (excitatory or inhibitory), area of stimulation, and lateralization (Pettorruso et al., 2021). All the TMS studies have targeted a single region, the prefrontal cortex, with most focusing on the left DLPFC, likely motivated by its success in treating depression. On the other hand, tDCS protocols have shown positive effects mainly when targeting the right DLPFC, possibly because tDCS is less anatomically precise and modulates broader cortical areas. These interventions have produced improvements in gambling-related behaviors, including craving, amount gambled, decision-making, and impulsivity. However, most studies have assessed only short-term outcomes, and there is currently limited evidence that these effects are sustained over time or translate into long-term reductions in gambling severity.

Pharmacological treatments for GD have targeted several neurotransmitter systems, including dopaminergic, serotonergic, and opioid pathways. A meta-analysis found that antidepressants, opioid receptor antagonists, and mood stabilizers improved GD symptoms compared with placebo (Pallesen et al., 2007). Among

these, opioid antagonists such as naltrexone and nalmefene have shown the most consistent benefits in reducing gambling urges and behaviors, although results remain mixed and high placebo responses have questioned the efficacy of this treatment (Bartley & Bloch, 2013). Serotonergic and dopaminergic medications, including SSRIs and antipsychotics, have generally failed to demonstrate better outcomes over placebo (Bartley & Bloch, 2013; J. E. Grant et al., 2013). To date, no pharmacological therapy has received formal approval for GD, highlighting the need for further controlled trials and individualized treatment approaches. More extensive evidence on the brain areas and neurotransmitter systems affected in GD is necessary to inform personalized or novel treatments.

2.5 Brain imaging techniques

The basics of the methods that were used in this thesis will be introduced in this section, including structural magnetic resonance imaging (MRI) (gray and white matter measurements), fMRI (task and resting-state), and PET imaging.

2.5.1 Structural MRI – gray matter

MRI is based on the principles of nuclear magnetic resonance (NMR), whereby atomic nuclei with unpaired protons, like hydrogen, behave like tiny magnets due to their spin. When placed in a strong magnetic field, these nuclei align with the field, creating a net magnetization. A radiofrequency pulse then knocks the magnetization out of alignment, causing the nuclei to precess, or rotate, emitting a signal at a frequency specific to the type of nucleus and the strength of the magnetic field (known as the Larmor frequency). The relaxation of these nuclei back to their original alignment produces two distinct types of signals: T1 (spin-lattice) and T2 (spin-spin) relaxation, which decay at different rates based on tissue composition. T1-weighted images provide good contrast between fat and water, with fat showing up bright and water appearing darker. T2-weighted images highlight differences in water content, making fluids (like cerebrospinal fluid) appear bright, while fat tends to appear darker. By controlling the MRI's pulse sequences and timing, we can highlight different properties of tissues, such as their spin density and relaxation times, which help produce detailed images. This variability in signal between different tissues makes MRI a useful tool for distinguishing between various tissue types in the brain, such as the gray matter, white matter and cerebrospinal fluid, offering exceptional contrast compared to other imaging modalities (Wr & Cj, 1984). There are two main types of analyses currently used in the field to study gray matter structure: VBM and surface-based analyses.

2.5.1.1 Voxel-based morphometry (VBM)

VBM is a neuroimaging analysis technique that is used to measure GM volumes voxel-by-voxel in the brain. Unlike region-specific approaches, VBM allows for an unbiased, whole-brain assessment of anatomical variation. Due to the anatomical variation between brains of different subjects, high-resolution MRI or T1-weighted images are first mapped into a common space through spatial normalization, a process where the native space images are warped into a standard template. This allows for meaningful comparisons between individuals by aligning all brains to a common space, where corresponding structures can be directly compared across participants. Once aligned, the images are processed to clean and highlight gray matter signal, which enables researchers to examine subtle differences in its distribution. These data are then analyzed to identify patterns of structural variation that may be related to clinical conditions, cognitive traits, or behavioral outcomes. VBM is a useful tool for mapping how brain structure varies across populations or changes over time, as it focuses on volume differences at the level of individual voxels (Ashburner & Friston, 2000).

2.5.1.2 Surface-based analysis

Surface-based analysis is a neuroimaging measurement that analyzes the cerebral cortex's surface geometry. Surface-based approaches capture important features, such as laminar structures and cortical maps (e.g., retinotopic or somatotopic), that cannot be accurately measured using traditional 3D imaging techniques. Contrary to VBM, which is used to assess brain structure by analyzing gray matter volume in a 3-dimensional space, surface-based analysis examines 2-dimensional cortical features such as thickness, surface area, and gyrification by mapping the cortical surface onto a template. To enable this type of analysis, the cortical surface needs to be reconstructed. First, due to the differences in intensity in the T1-weighted images, a normalized intensity image is created that later facilitates the identification of different structures. Following this, the brain is extracted, removing unnecessary parts of the head that are not of interest for our analysis. Next, we segment the gray-white matter on geometric structures, allowing for the separation of the cerebral hemispheres and the separation of subcortical structures. This segmentation is then refined by performing topological corrections, which ensures that any defects in the surface, like holes, are corrected. Finally, this volume is converted into a mesh of interconnected vertices and adjusted to create a smooth and precise representation of both the boundary between gray and white matter and the outer (pial) surface of the brain (Dale et al., 1999).

2.5.2 Structural MRI – white matter

2.5.2.1 Diffusion tensor imaging (DTI)

DTI is based on diffusion-weighted magnetic resonance imaging (DWI), which estimates water molecule diffusion within tissues. In a completely uniform environment, the molecules diffuse equally in all directions. In the brain, however, cellular structures such as membranes and fibers obstruct and restrict the movement of water, causing it to diffuse more in certain directions than others, known as anisotropic diffusion. DTI uses this principle, applying diffusion-sensitizing gradients in multiple directions, enabling the differentiation of tissue microstructure from water diffusion patterns (Basser & Jones, 2002). Mathematically, this is represented as a tensor, often visualized as an ellipsoid, where the principal axis corresponds to the main direction of diffusion (Figure 3) (Basser & Pierpaoli, 1996). Some of the primary measures derived from DTI include MD, which is the average rate of diffusion within a voxel, giving a sense of tissue density or damage; and FA, which quantifies the degree of directional dependence of diffusion, making it a common measure of fiber orientation (Soares et al., 2013). These metrics provide insights into the microstructural integrity and organization of neural architecture, and are crucial for understanding characteristics of white matter fibers in the brain (Van Hecke et al., 2016).

Before conducting DTI analysis, DWI data goes through a series of preprocessing steps to enhance data quality and reliability. This typically involves correcting for motion and distortions caused by head movements and magnetic field inconsistencies, aligning the data to a standard space, and removing artifacts. These steps help ensure that the measures of water diffusion are reliable. From this processed data, key DTI scalars like FA and MD are then calculated. Lower FA values typically reflect lower white matter integrity, while higher MD values reflect greater diffusivity, often associated with white matter damage, such as demyelination, axonal loss, or increased extracellular space.

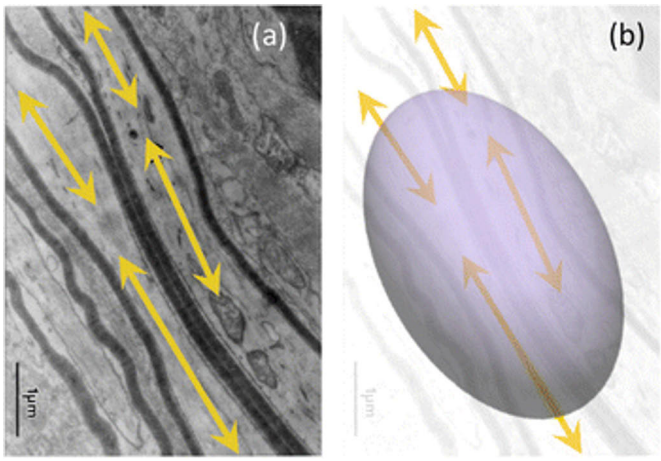

Figure 3. Schematic representation of the relationship between the diffusion tensor and axonal architecture. Figure 3 is a modified version of a figure from an article by Van Hecke et al. (2016) and has been reprinted with the permission of the copyright holders.

2.5.3 Functional MRI

fMRI is a non-invasive brain imaging method developed to measure and map brain activity by detecting changes in blood flow associated with neural activity (Bandettini et al., 1992; Kwong et al., 1992; Ogawa et al., 1990). These changes can be produced either by the resting state activity of the brain, or due to a cognitive state induced by conducting a task.

The central mechanism underlying fMRI is associated with metabolism in the brain: neural signaling requires energy in the form of adenosine triphosphate (ATP) (Roland, 1993). During activation of a brain region, the enhanced energy demand raises the local cerebral metabolic rate of oxygen consumption (Buxton & Frank, 1997). This triggers a vasodilatory response that results in increased blood flow and oxygen delivery, far in excess of metabolic needs.

Two key consequences of increased neural activity that can be detected by an MRI are increases in local cerebral blood flow and changes in the level of blood-oxygenation-level-dependent (BOLD) contrast. BOLD contrast is the generic methodology of most fMRI experiments and relies on the magnetic properties of hemoglobin. Changes in the levels of the two forms of hemoglobin, oxygenated (HbO_2) and deoxygenated (Hb), can be detected using magnetic resonance imaging (Figure 4). HbO_2 is diamagnetic and magnetically similar to tissue, whereas Hb is paramagnetic, which means that it generates local magnetic field gradients that affect the T2 and T2* relaxation times of blood (Thulborn et al., 1982).

Changes in the levels of oxygenated and deoxygenated hemoglobin affect T2* relaxation times, forming the basis of BOLD contrast imaging (Thulborn et al.,

1982). To ensure that these changes accurately reflect neural activity, fMRI data must first undergo preprocessing. This includes correcting for head motion, aligning the images to a standard brain template, and removing distortions from magnetic field irregularities. Depending on whether subjects are performing a task or being imaged at rest, different parameters may need to be considered, such as adjusting for task timing or filtering out non-neuronal signals like those from heartbeats, breathing, or even scanner noise. These steps help ensure that the resulting data accurately reflect the underlying brain activity.

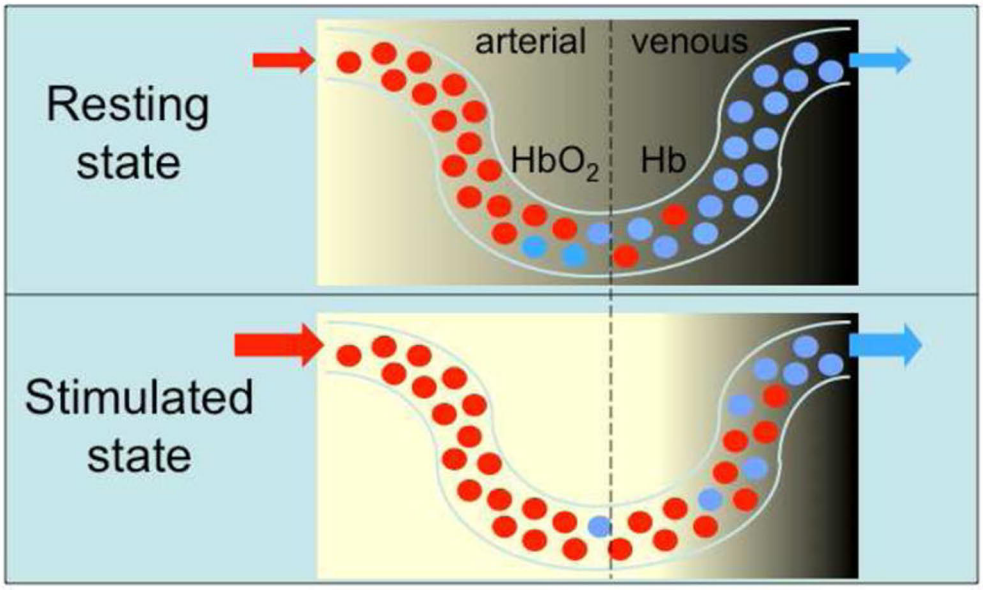

Figure 4. Changes in hemoglobin between resting state and stimulated state. Figure 4 is a copy of a figure from an article by Glover (2011) and has been reprinted with the permission of the copyright holders.

2.5.3.1 Task-functional MRI (task-fMRI)

A traditional task-fMRI experiment presents auditory, visual or other stimuli to induce different cognitive states in the participant, while acquiring MRI volumes through the time of the experiment. In a simple design, we would have two conditions, in which one is the experimental condition, while the other is a control condition. The goal is to observe if differences between these two conditions are significant or not. If a block design is used, the different trials alternate between the experimental and control conditions (Figure 5). This type of design is optimal for detecting activation differences, however, a jittered event-related (ER) design is superior when it comes to characterizing the amplitude or timing of the

hemodynamic response (Buckner et al., 1996; T. T. Liu & Frank, 2004). In the ER design, the tasks presented are brief and have longer periods of control condition. This allows the hemodynamic response to return fully to baseline.

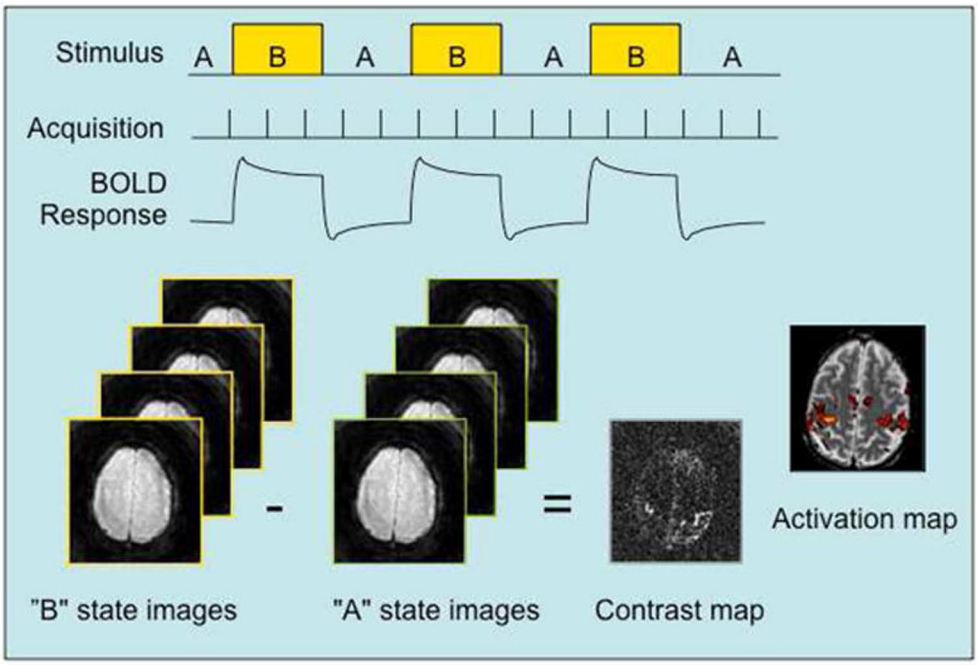

Figure 5. Task-fMRI block design experiment. Figure 5 is a copy of a figure from an article by Glover (2011) and has been reprinted with the permission of the copyright holders.

2.5.3.2 Resting state-functional MRI (rs-fMRI)

Rs-fMRI is a tool for investigating brain function by analyzing spontaneous fluctuations in the BOLD signal. Contrary to task-based fMRI, which requires subjects to participate in a specific activity, rs-fMRI measures brain BOLD responses while subjects are at rest. This technique makes use of low-frequency oscillations within the BOLD signal to capture spontaneous neural activity happening in the default state of the brain (Schölvinck et al., 2010).

There are a number of options available to process data from rs-fMRI studies, all of these giving different information regarding the function of the brain and its regions. The two major approaches are functional segregation and functional integration (Y. Liu et al., 1999; Tononi et al., 1994). Functional segregation methods, such as Amplitude of Low Frequency Fluctuations (ALFF) and regional homogeneity (ReHo), focus on activity confined within specific anatomical regions of the brain. While ALFF measured the total power of the BOLD signal within a

low-frequency range, thus being a regional measure of neural activity, ReHo is a measure of synchrony in the neural activity between adjacent areas. In contrast, functional integration techniques, such as seed-based connectivity analysis (seed-to-seed or seed-to-voxel) and ICA (Figure 6), assess connectivity between different brain regions and show how many areas of the brain communicate with each other and from which networks. While seed-based analysis requires a priori selection of a seed region, and from this reference point identifies all regions showing similar activity, ICA, on the other hand, decomposes the BOLD signal into its basic parts and extracts independent components representing separate neural networks (Lv et al., 2018).

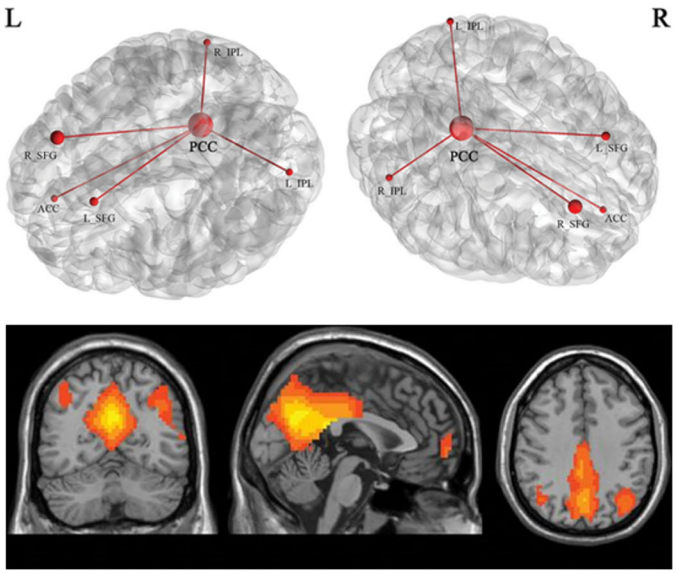

Figure 6. Representation of seed-based connectivity (on top of the figure) and independent component analysis (on the bottom of the figure) which depicts the Default Mode Network. Figure 6 is a modification of a figure from an article by Lv et al. (2018) and has been reprinted with the permission of the copyright holders.

2.5.4 Positron emission tomography (PET)

PET is an imaging technique that offers highly sensitive, non-invasive measurements of regional tissue functions, including neurotransmitter activity, receptor density, enzyme activity, and drug uptake, depending on the radiotracer employed. These radiotracers are injected into the body through a biologically active molecule acting as a carrier. The most commonly used biologically active molecule for PET has been 2-deoxy-2-^{18}F-fluoro-β-D glucose (^{18}F-FDG), which is an analogue of glucose that

enables the imaging of regional brain glucose metabolism (Ido et al., 1978). Neuronal activity is closely associated with energy consumption, therefore, FDG-PET has been extensively applied in studies of neurodegenerative disorders or psychiatric conditions, where alterations in the metabolic activity may reflect dysregulated neural processes. Another example of a radiotracer used in psychiatric research is 6-[^{18}F]fluoro-L-DOPA (FDOPA), used primarily to study a specific neurotransmitter, dopamine, in the brain. It is a labeled form of levodopa (a precursor to dopamine) tagged with the radioactive isotope fluorine-18 (^{18}F) (Garnett et al., 1983).

To study these processes, the study subject is injected with a radiotracer labeled with a positron (β +)-emitting radioisotope — an atom with an excess of protons, which decays to a more stable configuration through β + decay. The radiotracer emits positrons, which interact with electrons in the surrounding tissue, leading to mutual annihilation. This process results in the release of two photons (or gamma rays) emitted in opposite directions, each with a fixed energy of 511 keV. These photons are detected using opposing pairs of detectors in the PET scanner. This process is represented in Figure 7. From the activity distribution of the radioisotope, we can then obtain an image of the tracer distribution. However, to translate these measurements of tracer concentrations into quantitative values of the tissue function we need to apply appropriate tracer kinetic models, as PET only gives accurate measurements of regional tissue concentrations of radioactivity (Belcari et al., 2023; Lammertsma, 2002).

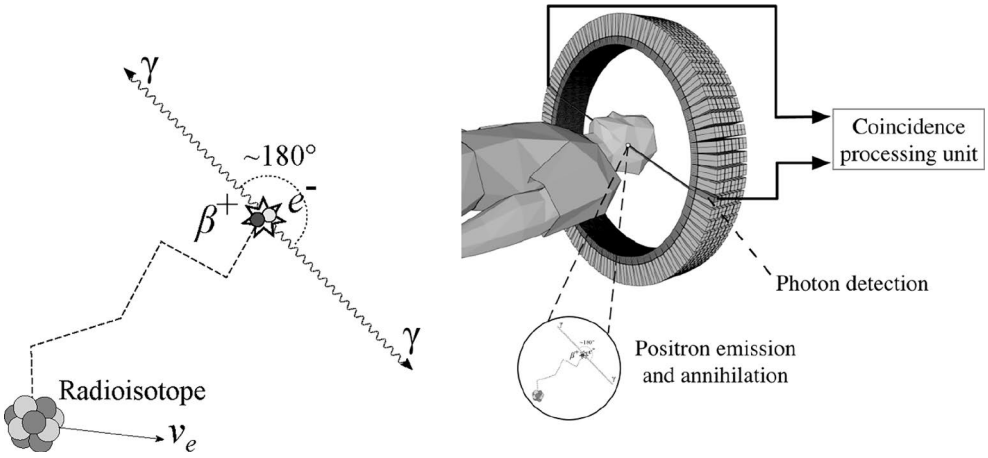

Figure 7. Schematic representation of the PET measurement process. Figure 7 is a copy of a figure from an article by Belcari et al. (2023) which is licensed under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

Tracer kinetics modelling helps distinguish between specific binding, non-specific binding, and free ligand concentrations over time. When the radiotracer is injected intravenously, free, specific, non-specific and intravascular concentrations are not constant, but vary with time. To disentangle these various components, we need to measure cerebral uptake and clearance of the radioligand with the use of dynamic scanning. Here, multiple scans (or frames) are acquired from the first, corresponding to the time of injection, to the last, which can be after 30 to 120 minutes, depending on the kinetics of the radioligand. In addition, brain signal is also dependent on the time course of activity in arterial plasma, making it necessary to measure the arterial plasma curve during the scan. These models enable the extraction of key parameters, such as binding potential, allowing for precise quantification of receptor availability, neurotransmitter activity, or other specific physiological processes (Lammertsma, 2002).

To generate quantitative data from PET scans, the raw imaging data must undergo several steps of analysis. PET scans detect the distribution of the radiotracer in the brain, but the initial data only reflects regional concentrations of radioactivity. To accurately translate this into measurements of tissue function, such as receptor availability or neurotransmitter activity, specialized kinetic models are applied. These models help separate specific binding of the radiotracer from non-specific binding and free ligand concentrations. Additionally, factors such as the time course of radiotracer uptake and clearance, must be accounted for during the analysis to ensure the resulting measurements reflect the true physiological processes that are trying to be measured.

3 Aims

The main objective of this study was to investigate the neurobiology underlying GD using multiple neuroimaging modalities, including structural and functional MRI and PET, focusing on the fronto-striatal-thalamic circuitry. This circuitry is critically involved in reward processing, impulse control, and decision-making processes that are often disrupted in GD. By examining its structure, function, and neurotransmitter systems, we can gain insight into the mechanisms driving the disorder. With the results of this work, we hope to contribute to a better understanding of the neurobiological mechanisms that could inform targeted interventions for this disorder.

The specific aims of this thesis work were:

I. To investigate fronto-striatal connectivity and neurotransmitters (dopamine, serotonin, opioid) associated with connectivity abnormalities in GD (Study I)

II. To examine the striatal hemodynamic responses to cues (gambling, natural rewards, neutral) and neurotransmitter systems associated with cue-reactivity in GD (Study II)

III. To study structural abnormalities in the fronto-striatal-thalamic circuit in older GD individuals. (Study III)

4 Materials and Methods

4.1 Dataset 1

4.1.1 Subjects (study I and II)

Fifteen individuals with GD and 17 HC were enrolled into the study. Individuals with GD were evaluated using a clinical interview based on the DSM-IV criteria. Data collection for this dataset was performed during 2013-2015, therefore, the study protocol was submitted for approval before the publication of the DSM-5 criteria. DSM-IV required meeting at least 5 out of 10 criteria for a diagnosis of pathological gambling, while the DSM-5 reduced this threshold to 4 out of 9 criteria for a diagnosis of GD. All GD subjects fulfilled both of the criteria. Participants matched for sex and age, who were determined to have no gambling problems through a clinical interview, were included in the control group. The exclusion criteria for all subjects in this study were as follows: evidence for current clinically significant medical conditions, neurological disorders and other psychiatric disorders, evidence of current alcohol or substance use disorder, inability to pause medications affecting the central nervous system, body weight more than 180 kg (scanner limit), strong susceptibility to allergic reactions or nausea, current pregnancy, and any contraindications to magnetic resonance imaging.

4.1.2 Clinical and behavioral measures (study I and II)

Clinical and behavioral data was gathered from a clinical interview and validated questionnaires. Information collected from all participants included age, sex, body mass index (BMI), smoking status, and gambling-related measures (gambling hours per week, gambling euros per week and problematic gambling years). In addition, the following questionnaires were given to all subjects: South Oaks Gambling Screen (SOGS) (Lesieur & Blume, 1987), Beck Depression Inventory (BDI) (Beck et al., 1961), the Barratt Impulsiveness Scale (BIS-11) (Barratt, 1985) and the Alcohol Use Disorders Test (AUDIT) (Saunders et al., 1993).

4.1.3 Image acquisition

4.1.3.1 Study I and II

Structural and rs-fMRI, and multiligand PET imaging (^{11}C-MADAM, ^{18}F-FDOPA, ^{11}C-carfentanil) were performed on all subjects.

T1-weighted images and rs-fMRI scans were obtained for all participants using a 3T PET-MRI scanner (Philips Ingenuity, Philips Healthcare, Cleveland, OH, USA) with a 34-channel receiving head coil. In the T1-weighted scanning, we acquired a sagittal 3D T1-weighted turbo field echo (TFE) sense pulse sequence, featuring a repetition time (TR) of 8.1 ms, echo time (TE) of 3.7 ms, flip angle of 7°, matrix size of 256 × 256, and 176 slices, all with isotropic voxels.

PET scans were obtained using a high-resolution research tomography (HRRT) PET scanner (Siemens Medical Solutions, Knoxville, TN, USA). Voxels were nearly isotropic with an intrinsic spatial resolution of 2.5 mm (Jong et al., 2007). Due to scanning three different radiotracers, the scanning time was 231 minutes in total (51 min with ^{11}C-carfentanil, 90 min with ^{18}F-FDOPA and 90 min with ^{11}C-MADAM). All three tracers were scanned during one day for each participant. Details of the full imaging protocol have been described previously (Majuri et al., 2017a; Majuri et al., 2017b).

4.1.3.2 Study I

The rs-fMRI scanning lasted for 6 minutes, where subjects were instructed to remain still in the scanner and with their eyes closed. Scanning protocol used a TR of 2000 msec, TE of 20 msec, flip angle of 75°, 4 mm slice thickness, 35 slices, and parallel multi-slice mode.

4.1.3.3 Study II

For the task-fMRI scanning protocol, we used BOLD echo-planar imaging (EPI). During the stimulus presentations, a whole-brain BOLD-weighted EPI sequence, optimized for BOLD contrast sensitivity, was acquired. This scanning used a TR of 2000 msec, TE of 20 msec, flip angle of 75°, 4 mm slice thickness, 35 slices, and parallel multislice mode. The stimuli followed a block-design format, with each category consisting of 10 blocks lasting 9-14 seconds each, presented twice in a randomized sequence. Brief breaks of 6-9 seconds followed each clip, in which participants viewed a black screen. In total, the task was 17 minutes long. See Figure 8 for a schematic representation of the study design. These stimuli consisted of videos of three different categories including gambling, natural rewards, and neutral.

The gambling videos showed people playing roulette or poker in a casino, where scenes of people placing bets or handling chips were presented. Natural reward videos consisted of "soft porn", in which scenes of nudity and intercourse were shown. The neutral videos featured people carrying out everyday activities (i.e., walking down the street). The videos for each category were extracted from released movies. Two individuals with GD could not undergo fMRI scanning due to scanner malfunction. In addition, one HC participant displayed a lack of occipital BOLD response, probably due to having their eyes closed, and was excluded from the analysis. Moreover, the fMRI task duration varied slightly for three participants: one HC participant watched 59 videos, and two individuals with GD viewed 50 and 33 videos, respectively, out of the total 60 videos.

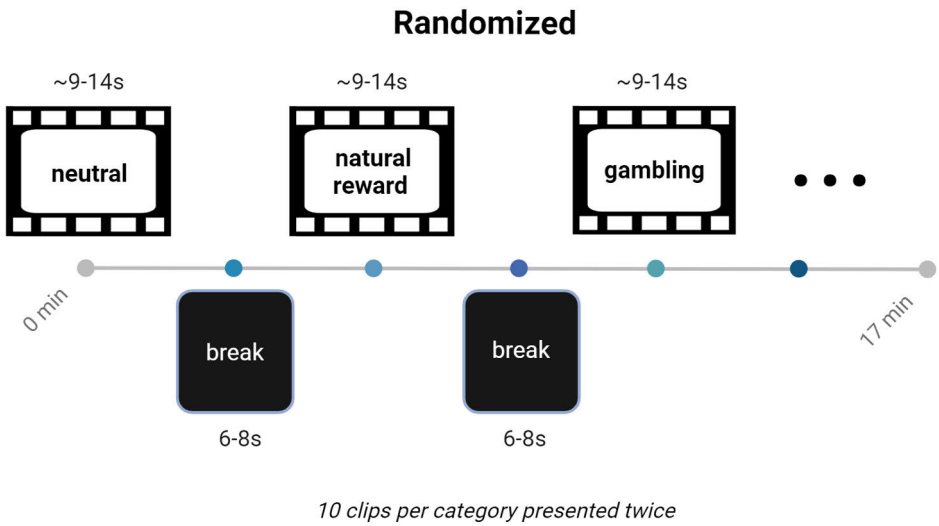

Figure 8. Study design of the task-fMRI block design to study BOLD response in front of gambling, natural reward and neutral cues.

4.1.4 Data preprocessing and analyses

4.1.4.1 Rs-fMRI (Study I)

Preprocessing and analysis of the rs-fMRI data was performed using CONN Toolbox (version 19c, www.nitrc.org/projects/conn, RRID: SCR_009550). The default settings from CONN Toolbox documentation (https://web.conn-toolbox.org/fmri-methods) were applied (Nieto-Castanon, 2020). First, quality assurance of the images was performed. Then, all T1-weighted images were aligned to the anterior and posterior commissures in Statistical Parametric Imaging 12 (SPM12)

(http://www.fil.ion.ucl.ac.uk/spm/, (Friston, 2007)). Finally, we applied the default preprocessing pipeline from CONN Toolbox, which included realignment, slice-timing correction, direct co-registration to structural image, segmentation, normalization to the Montreal Neurological Institute (MNI) template, and functional smoothing using an 8mm Full Width at Half Maximum (FWHM) Gaussian kernel.

Due to scanner equilibration, the first 4 volumes of each subject's scan were removed from the analyses. The denoising of all the preprocessed scans included the following: linear regression of potential confounding effects in the BOLD signal containing WM and cerebrospinal fluid (10 dimensions for WM and 5 for cerebrospinal fluid), motion parameters, outlier volumes, and the effect of rest. A temporal band-pass filtering of 0.008 Hz ~ 0.09 Hz was applied, as recommended by the toolbox developers (Nieto-Castanon, 2020).

The analyses were restricted to the fronto-striatal brain regions. The individual nuclei from the striatum were used as seeds for the seed-to-voxel analyses, with the frontal cortex serving as the target for connectivity analyses. The default CONN-Toolbox striatal masks were used for the seeds, and the FSL's frontal cortex mask from the MNI structural atlas was used for the target (Collins et al., 1995; Mazziotta et al., 2001). A whole-brain mask was used to check for any findings outside the mask to ensure no other results were present. Our results were confirmed with the whole-brain mask. Cluster-level familywise error (FWE) correction was used at a height threshold of $p<0.001$. Clusters were considered significant if the p value was less than 0.05.

4.1.4.2 Task-fMRI (Study II)

For the T1-weighted images, the following pipeline was applied: correction for intensity non-uniformity was performed with ANTs 2.4.4 (Tustison et al., 2010). T1-weighted images were skull-stripped using ANTs. Brains were segmented into cerebrospinal fluid (CSF), white matter (WM) and gray matter (GM) with "fast" from FSL 6.0.6.2 (Zhang et al., 2001). Reconstruction of brain surfaces was performed with Freesurfer 7.3.2 using "recon-all" (Dale et al., 1999). Brains were normalized to MNI space through nonlinear registration with ANTs.

For the functional preprocessing, the following steps were applied: motion correction was performed using "mcflirt" from FSL. Co-registration of BOLD and T1-weighted images was done using "bbregister" from Freesurfer. Confounding time-series were extracted from the preprocessed BOLD data, physiological regressors were extracted for noise correction and motion outliers were identified. Preprocessed BOLD runs were resampled into MNI space.

Subsequent analyses were conducted with SPM12 (http://www.fil.ion.ucl.ac.uk/spm/). First, we regressed out six rigid body

realignment parameters and the motion outlier volumes identified during the preprocessing. Following our hypothesis, we restricted our voxel-wise analyses to the striatum using a mask by Mawlawi et al. (2001). To control for multiple comparisons, peak-level FWE correction was applied ($p<0.05$) and results were considered significant if the corrected p values were less than 0.05. Sex and age were added as covariates. For further exploration of our data we extracted the mean connectivity values from the significant clusters and ROIs from the striatum to study the relationship between these measures, and clinical and PET data.

4.1.4.3 PET (Study I and II)

PET images were preprocessed using SPM8 https://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Realignment and coregistration to T1-weighted images were performed for all individual scans. Each parametric image was normalized to MNI template and smoothed using an 8mm FWHM Gaussian kernel. ROIs from the striatum were obtained with FreeSurfer (version 5.3.0, http://surfer.nmr.mgh.harvard.edu/) (Desikan et al., 2006; Fischl et al., 2002) by using T1-weighted images. Tracer kinetics were measured from the ROIs. Two subjects were excluded from the analyses for the NAcc ^{11}C-MADAM BP_{ND} due to its high standard deviation (>2). Full details of the PET images preprocessing were earlier described (Majuri et al., 2017a; Majuri et al., 2017b).

BPND/Ki values were obtained from the significant connectivity cluster to explore the neurotransmitter activity linked to the observed connectivity abnormalities. Separate general linear models were constructed for each tracer, using the cluster values as the dependent variable to test the Group x right NAcc interaction. Additionally, these ROI analysis results were validated through corresponding voxel-wise analyses in SPM12, also examining the Group x right NAcc interaction. These analyses were conducted with the same frontal mask as with the connectivity analyses. A cluster-level FWE correction was applied with a height threshold of $p < 0.005$. Clusters with FWE-corrected p values less than 0.05 were considered significant.

4.2 Dataset 2 (Study III)

4.2.1 Subjects

Twenty older individuals with GD and 40 HC we enrolled into the study. All participants underwent an evaluation of electronic health records and a clinical interview, where several psychiatric diagnoses were assessed, including GD, current alcohol or other SUDs within the last 6 months, current other Axis I disorders (i.e.

major depressive disorder), ADHD, bipolar disorder or psychotic disorder, current treatment with amphetamine derivatives, methylphenidate, and bupropion or other medications known to interfere with DAT imaging. Diagnoses for the individuals with GD were evaluated using the DSM-5 criteria. Individuals without any gambling problem were included as HC. The exclusion criteria for all subjects included the presence of serious neurological disorders such as neurodegenerative diseases, multiple sclerosis, brain tumors, epilepsy, stroke, and myasthenia gravis, as well as psychiatric disorders other than GD.

4.2.2 Clinical and behavioral measures

Subjects underwent a clinical interview and validated questionnaires to collect clinical and behavioral data. This data included nicotine use, smoking status, alcohol use, and drug use. Questionnaires administered to all participants were the BIS-11, the BDI, the Beck Anxiety Inventory (BAI) and the Mini-Mental State Examination (MMSE). Specific to the GD group, gambling-related information was collected (gambling euros per week, gambling hours per week and problematic gambling years) which included the SOGS.

4.2.3 Image acquisition

A Siemens 3T Skyra Fit system (Siemens Medical Imaging, Erlangen, Germany) was used for MRI scanning. Different sequences were obtained during the scanning: 3D T1, T2, and Fluid-attenuated inversion recovery (FLAIR). T1-weighted images were captured with a TR of 2300 ms and a TE of 2.98 ms. For T2-weighted images, the TR was set to 5000 ms and the TE to 386 ms. FLAIR images had a TR of 3200 ms and a TE of 408 ms. Uniform parameters used in all sequences were a voxel size of 1×1×1 mm, a 256 mm field of view, and a 1 mm slice thickness. For DWI, a single-shot spin-echo echo-planar sequence was used, with TR/TE values of 7600/85 ms, a voxel size of 2 mm^3, a matrix size of 116 × 116 × 80, and 60 gradient directions. Each subject's DWI data included 60 images with a b-value of 1,000 s/mm^2, 9 b = 0 s/mm^2 images, and 8 inverse phase-encoding null images. Due to technical issues, one control subject was excluded, resulting in 39 HC subjects and 20 individuals with GD for the DWI analysis.

4.2.4 Data preprocessing and analyses

4.2.4.1 Diffusion tensor imaging

DWI images were preprocessed using a combination of state of the art tools. Denoising and removal of Gibbs ringing artifacts were performed with MRTrix3 (https://www.mrtrix.org). Corrections for eddy current, head motion, and phase-related distortions within a brain mask were conducted using the FMRIB Software Library (FSL, v.6.0.4) (www.fmrib.ox.ac.uk/fsl). In addition, B1 field inhomogeneity was corrected with the ANTs toolbox (https://www.nitrc.org/projects/ants). FA maps were obtained using "dtifit" from FSL.
We used tract-based spatial statistics (TBSS) implemented in FSL to analyze the FA data. TBSS identifies a common WM skeleton that represents the core of the major WM pathways shared across subjects. Then, it projects into this skeleton the individual FA data. Finally, it normalizes the images to the FMRIB58_FA template in MNI space.

Voxel-wise group analyses were performed using the "randomise" algorithm from FSL with 5000 permutations. Analyses were restricted to the main WM pathways by using a binary mask from the 48 WM tracts of the "JHU ICBM-DTI-81 White-Matter Labels". We included sex, age, and the cerebrospinal fluid volume to total intracranial volume ratio (CSF/TIV) as covariates. The significance of the effects was determined by threshold-free cluster enhancement (TFCE) and familywise error (FWE)-corrected $p<0.05$ threshold. After group analyses, the mean FA values for each significant cluster were extracted for all individuals with GD and analyzed with JMP Pro (SAS Institute Inc., Cary, NC). These analyses comprised regression models with covariates (sex, age, and CSF/TIV) and predictors of interest (duration of problem gambling (in years), SOGS score, BIS score, BDI score, MMSE score, hours of gambling per week and euros lost due to gambling per week). More detailed information about the DTI analyses has been described previously (Bellmunt-Gil, et al., 2024).

4.2.4.2 White matter lesion load

To quantify and localize white matter hyperintensities (WMH), these hyperintensities had to be segmented (Figure 9). To do this, the following steps were carried out. First, WM is segmented in the native T1 image into two classes of hypointense WM and normal bright WM regions. Then, the segmentation results of the previous step are taken as initialization to segment FLAIR image into three classes: CSF, normal brain tissue and hyperintense voxels. Finally, based on the segmentation results from the previous step, the WM and subcortical regions in the

FLAIR image are segmented into two categories, the high intensity and low intensity. Finally, the category having higher intensities is found, which defines the WMH segmentation (Wang et al., 2012).

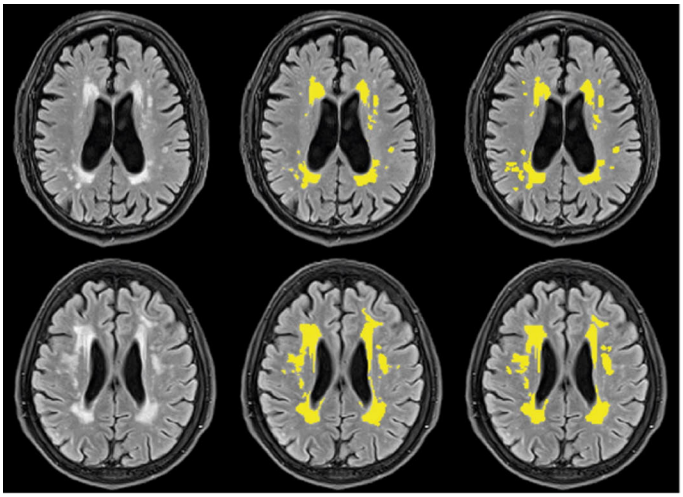

Figure 9. Automated segmentation of white matter hyperintensities (WMH). The first column shows non-segmented WMH. The second column shows automatically segmented WMH. The third column shows manually segmented WMH. Figure 9 is a modified version of a figure from an article by Y. Wang et al. (2012), and has been reprinted with the permission of the copyright holders.

To normalize both the native T1-weighted images and the lesions two steps were taken. First, we normalized the T1-weighted images to the MNI standard space using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/). Then, the transformations derived from this normalization process were applied to the native WM lesions. A voxel-wise comparison of the quantity and distribution of the normalized lesions between groups across the entire brain was performed using NiiStat software (www.nitrc.org/projects/niistat/), where age and sex were included as nuisance covariates. We also controlled for the effect of cardiovascular diseases in both groups, as these are associated with WM hyperintensities and their distribution in the brain (Habes et al., 2018; Pilver & Potenza, 2013). For this between-group comparison, we used the Freedman-Lane method with 2000 permutations and a corrected threshold of $p<0.05$. To verify the findings at tract level, we conducted an ROI analysis with the total lesion volume of the tract where the significant results were located. The tract was extracted from the JHU ICBM-DTI-81 White-Matter atlas. To test the hypothesis that the GD group would have a higher WM lesion load than the control group, a one-tailed Mann-Whitney U test was utilized to compare the WM lesion load between groups within this ROI.

4.2.4.3 Gray matter volume and surface thickness

Preprocessing and analyses for the VBM and surface-based morphometry (SBM) were performed with SPM12's Computational Anatomy Toolbox 12 (CAT12) (http://www.neuro.uni-jena.de/cat/) (Gaser & Dahnke, 2016).

For VBM preprocessing, native T1 weighted images were segmented into GM, WM and CSF files. Subsequently, all images were normalized to a standard space using the DARTEL algorithm. Finally, images were smoothed using an isotropic Gaussian kernel of 8mm FWHM. Between-group volumetric analyses were performed using a subcortical mask created with WFU Pickatlas toolbox (https://www.nitrc.org/projects/wfu_pickatlas/) with x1 dilation. This binary mask contained the caudate, putamen, accumbens, globus pallidus, thalamus, amygdala and hippocampus. The covariates added for the analyses were sex, age, and TIV as indicated by the software's manual. For SBM, the protocol included surface and thickness estimation with a smoothing of 12mm FWHM. The covariates included for the between-group surface analyses were sex and age. Clusters were considered significant for both VBM and SBM analyses if the FWE-corrected p values were less than 0.05. To illustrate how the VBM and SBM results are structurally connected, TrackVis was used (Ruopeng Wang, Van J. Wedeen, TrackVis.org, Martinos Center for Biomedical Imaging, Massachusetts General Hospital).

4.3 Statistical analysis

For all three studies, statistical analyses for demographic, clinical and ROI data were conducted using the Statistical Package for the Social Sciences (IBM SPSS Statistics, version 27, Armonk, NY, USA). Group differences of continuous and categorical variables from the demographic, clinical and imaging data (Study I: connectivity measures; Study II: striatal cue reactivity; Study III: gray and white matter regions) were calculated using different tests, as appropriate: independent samples t-test, chi-square test, Fisher's exact test and Mann-Whitney test. Correlation coefficients between self-reported and brain imaging data were calculated using Pearson and Spearman correlation analyses. In Study II, Fisher's r to z transformation was performed to study significant differences between correlations.

4.4 Ethics

Studies I and II were part of the same research project, while the third study was conducted independently. Both research projects received approval from the Ethics Committee of the Hospital District of Southwest Finland, and all participants provided written informed consent for their participation. The studies were conducted according to the principles of the Declaration of Helsinki.

4.5 Methodological overview from Studies I, II and III

This thesis combined different imaging modalities with two different datasets in a population of individuals with GD and HC: dataset 1 was used in Studies I and II, while Dataset 2 was used in Study III. Table 3 summarizes the basic methodological information of the different studies.

Table 3. Methodological overview from Study I, II, and III

Study	Sample size (F)	Imaging modality	Analysis method	Clinical/Behavioral measures
Study I	GD: 15(7) HC: 17(9)	fMRI & PET	Whole-brain resting-state fMRI (seed-to-voxel) and measurement of dopamine, opioids, and serotonin	• Gambling hours per week • Gambling euros per week • Problem gambling years • PG DSM-IV points • SOGS • AUDIT • Smoking • BIS-11 • BDI
Study II	GD: 13(7) HC: 16(8)	fMRI & PET	Task-fMRI (voxel-based) restricted to striatum and measurement of dopamine, opioids, and serotonin	Same as Study I
Study III	GD: 20(8) HC: 40(19)	Structural and diffusion MRI	Gray matter: VBM and surface-based analysis White matter: DTI and WMH	• Gambling hours per week • Gambling euros per week • Problem gambling years • SOGS • Alcohol use • Nicotine use • Smoking • BIS-11 • BDI • MMSE • Cardiovascular risk factors

GD: gambling disorder; HC: healthy controls; F: females; fMRI: functional magnetic resonance imaging; PET: positron emission tomography; VBM: volume-based morphometry; PG: pathological gambling; DSM-IV: diagnostic and statistical manual of mental disorders 4th edition; SOGS: south oaks gambling screen; AUDIT: alcohol use disorders identification test; BIS: Barrat impulsiveness scale; BDI: Beck depression inventory; MMSE: mini-mental state examination

5 Results

5.1 Findings on fMRI and PET

5.1.1 Fronto-striatal connectivity and implicated neurotransmitters (Study I)

5.1.1.1 Demographics

All the demographic and clinical data of the participants are shown in Table 4. Significant differences were found in all gambling behavior variables and addiction-related variables such as impulsivity (BIS-11 motor and non-planning subscales) and depression (BDI). No significant differences were found in age, sex, AUDIT, smoking, and BIS-11 attention subscale. Although individuals with GD tend to have higher alcohol consumption, the AUDIT scores did not significantly differ compared to HC probably due to the exclusion of any subject with an alcohol use disorder.

Table 4. Demographic and clinical characteristics of all subjects (original publication I)

Category	Variables (mean ± SD)	GD (n=15)	HC (n=17)	P value
Demographics	Age (years)	42.6 ± 11.8	43.3 ± 11.1	0.87
	Sex (male/female)	8/7	8/9	1.00
Gambling Behavior	Gambling hours per week	8.9 ± 7.1	0.5 ± 1.2	<0.001
	Gambling euros per week	164 ± 147	4 ± 7	<0.001
	Problem gambling years	11.6 ± 7.3	0.00 ± 0.00	<0.001
	PG DSM-IV points	7.3 ± 1.4	0.1 ± 0.3	<0.001
	SOGS	13.3 ± 2.3	0.1 ± 0.3	<0.001
Substance Use	AUDIT	5.9 ± 4.0	5.4 ± 3.3	0.69
	Smoking (yes/no)	11/4	7/10	0.07
Impulsivity	BIS-11 (attention)	19.2 ± 3.0	17.7 ± 1.9	0.09
	BIS-11 (motor)	26.5 ± 2.1	22.2 ± 2.4	<0.001
	BIS-11 (non-planning)	28.5 ± 1.8	23.2 ± 4.5	<0.001
Depression	BDI	14.4 ± 7.8	2.8 ± 3.1	<0.001

GD: gambling disorder; HC: healthy controls; SD: standard deviation; PG DSM-IV: pathological gambling Diagnostic and Statistical Manual of Mental Disorders; SOGS: South Oaks Gambling Screen; AUDIT: Alcohol Use Disorders Identification Test; BIS-11: Barratt Impulsiveness Scale – 11; BDI: Beck Depression Inventory

5.1.1.2 Rs-fMRI

Individuals with GD showed a significant difference in connectivity between the right NAcc (rNAcc) (Figure 10A i) and the right DLPFC (Figure 10A iii) compared to the HC group. Specifically, the GD group showed a positive connectivity (positive correlation between timeseries) between these regions, whereas the HC group demonstrated a negative connectivity (negative correlation between timeseries) (Figure 10B). The results did not change when controlling for sex, age, AUDIT or smoking. No other striatal regions had significant connectivity differences between the groups to the frontal cortex. To ensure that there were no other significant connectivities outside of the frontal mask, we repeated the analysis with a whole-brain mask. The findings were consistent with those obtained using the frontal mask, indicating that the observed connectivity patterns were robust and not limited to the predefined regions. The rNAcc-DLPFC connectivity showed no significant correlations with GD and gambling related variables ($p>0.2$), or BDI score ($r = 0.22$, $p = 0.45$).

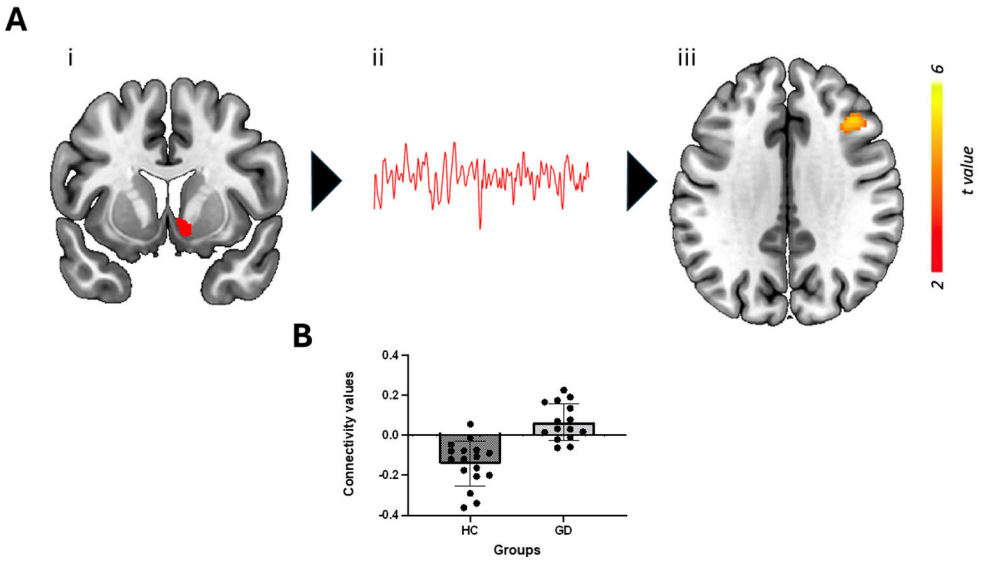

Figure 10. Differential connectivity from rNAcc between individuals with GD and HC group. A. rNAcc seed (i). Graphic representation of the rNAcc timeseries (ii). Connectivity difference between groups to rDLPFC (peak coordinates at 40 26 36, cluster size 187 voxels, $P_{FWE} = 0.01$) (iii) B. Group mean (SD) NAcc-DLPFC connectivity values: HC group −0.14 (0.11) vs. GD group 0.065 (0.093). This figure is a modified version from original publication I which is licensed under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

5.1.1.3 PET

Average PET maps for ^{11}C-MADAM BP_{ND}, ^{18}F-FDOPA K_i and ^{11}C-carfentanil BP_{ND} are shown in Figure 11. A significant Group x right NAcc BP_{ND} interaction in the right DLPFC connectivity cluster was found in ^{11}C-MADAM scans ($F = 5.63$, $p = 0.03$) (Fig. 12A). The voxel-wise analysis also showed a Group x right NAcc BPND interaction in the prefrontal cortex (Figure 12B i), which overlaps with the connectivity difference cluster (Figure 12B ii). This interaction was not found with ^{18}F-FDOPA or ^{11}C-carfentanil. No significant group differences were found in ^{11}C-MADAM BP_{ND} (Majuri, et al., 2017b), and group comparisons for ^{18}F-FDOPA K_i and ^{11}C-carfentanil BP_{ND} have already been reported (Majuri, et al., 2017a).

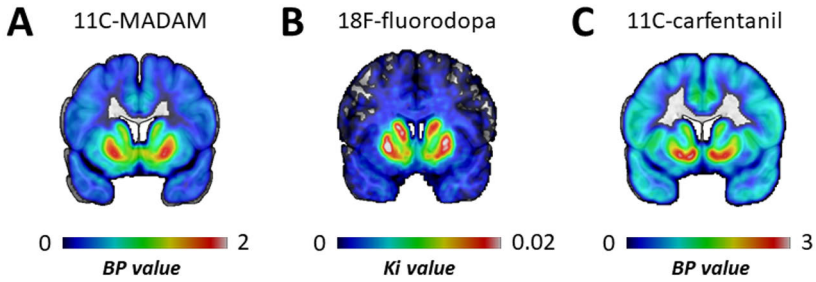

Figure 11. Average whole-brain maps for each tracer (^{11}C-MADAM, ^{18}F-FDOPA and ^{11}C-carfentanil). This figure is a modified version from original publication I which is licensed under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

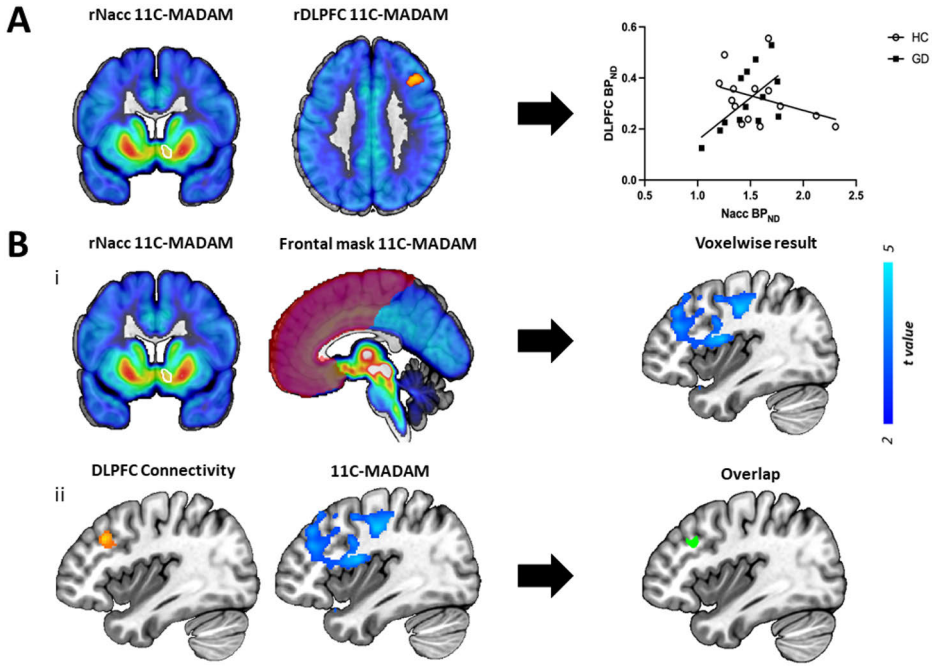

Figure 12. Group x right NAcc interaction in MADAM BP_{ND} and overlap with the DLPFC connectivity difference cluster. A. Masks from the right nucleus accumbens and right dorsolateral prefrontal cortex connectivity cluster overlaid on the average ^{11}C-MADAM BP_{ND} to extract the individual binding values showing a group x NAcc BP_{ND} interaction in the DLPFC BP_{ND}. B. Voxelwise analysis masked to the frontal lobe showing a significant Group x right NAcc interaction (cluster peak at 62-6 40, size 7227 voxels, $P_{FWE} < 0.001$; -48-28 38, 7844 voxels, $P_{FWE} < 0.001$; -9-3 63, 2051 voxels, $P_{FWE} = 0.02$) (i). Overlap between the DLPFC connectivity cluster and the voxelwise result from the Group x right NAcc interaction in MADAM BP_{ND} (center of gravity in MNI 36 24 32). This figure is a modified version from original publication I which is licensed under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

The right NAcc MADAM BPND correlated negatively with attentional impulsivity ($r = -0.73$, $p = 0.005$) in the GD group. Correlations of this binding with other gambling-related variables, BIS total score, AUDIT, smoking or BDI did not reach statistical significance ($p > 0.05$).

5.1.2 Striatal BOLD response and neurotransmitters (Study II)

5.1.2.1 Demographics

The dataset used for this study was the same as with Study I (Table 1). Despite the different numbers of subjects in Study II (13 individuals with GD and 16 HC), the significant differences between the groups in most variables remained unchanged.

However, with this different number of participants included in the study, we found that the GD group had significantly more smokers than the HC group (11 out of 13 in GD, and 6 out of 16 in HC).

5.1.2.2 Task-fMRI

Individuals with GD showed greater BOLD response than HC in the dorsal striatum when watching gambling videos compared to neutral videos (Figure 13). To ensure that this result was not affected by the subjects who had shorter tasks (N=3), we repeated the analysis without them, and the significance of the results did not change.

No significant correlations were found between the dorsal striatum cluster BOLD response and gambling-related variables ($p>0.18$) or other addiction related variables such as AUDIT, smoking, or BDI ($p>0.17$). The HC group showed a significant positive correlation between the BOLD response of the ventral and dorsal striatum ($p=0.003$), while individuals with GD showed a negative non-significant correlation ($p=0.5$). The difference between these two correlations was significant ($p<0.001$) and highlights the disruption in addiction of the neural circuitry involved in reward processing and habit formation.

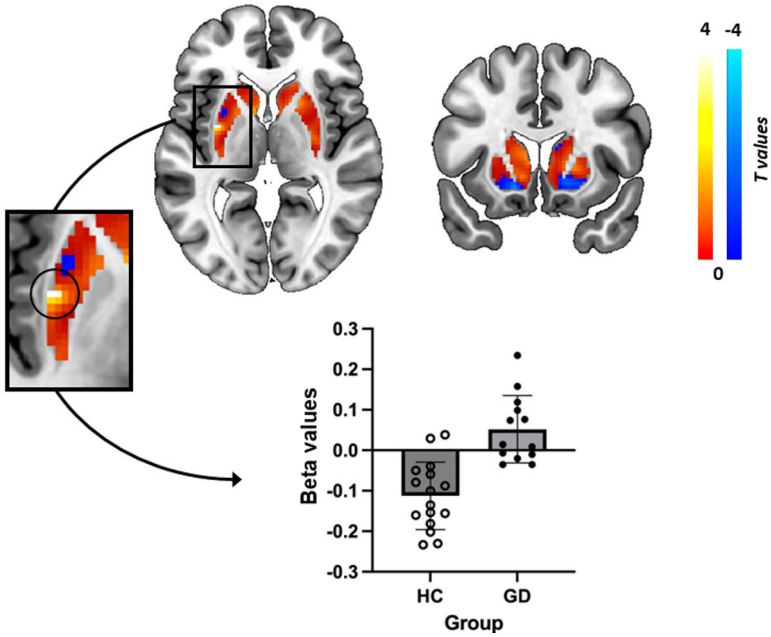

Figure 13. Unthresholded GD>HC BOLD T-map. Significant cluster circled inside the zoomed box (peak coordinates at -32 -2 2, cluster size 2 voxels, PFWE=0.004) B) Plotted beta values within the significant dorsal striatum cluster [HC: -0.11(0.08), GD: 0.05(0.08)]. Figure from original publication II which is licensed under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

5.1.2.3 PET

In an ROI analysis, the BOLD response of the dorsal striatum showed a significant positive correlation with the dorsal striatum ^{11}C-carfentanil BP_{ND} in individuals with GD (r=0.81, p<0.001) (Figure 14C). No other correlations were found in the dorsal striatum between BOLD responses and tracer binding. The HC group did not show any significant correlations. Although we also examined correlations in the ventral striatum, none were significant across any of the groups. In addition, no significant group differences were found in the dorsal and ventral striatum binding for any of the tracers.

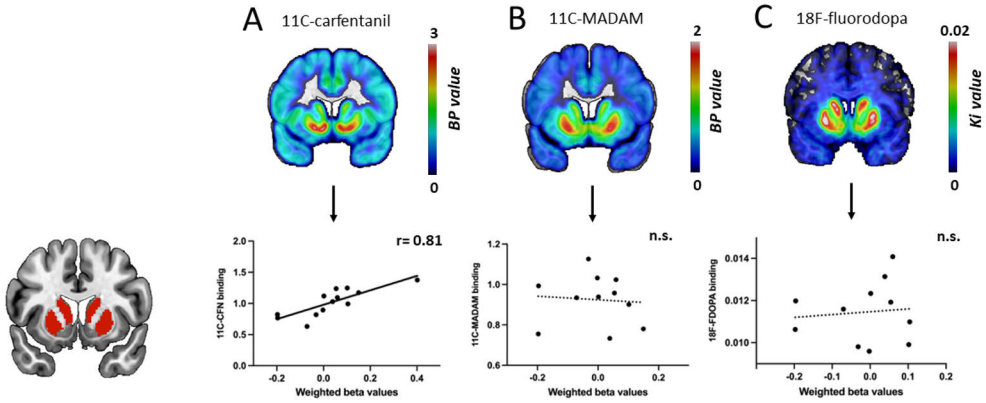

Figure 14. Correlations between BOLD response and tracer binding within the dorsal striatum. A. Significant correlation for ^{11}C-carfentanil *(r=0.81, p<0.001)*. B. Non-significant correlation for ^{11}C-MADAM. C. Non-significant correlation for ^{18}F-FDOPA. This figure is a modified version from original publication II which is licensed under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/). n.s.= non-significant.

5.2 Findings on structural MRI (Study III)

5.2.1 Fronto-striatal-thalamic white and gray matter abnormality in gambling disorder

5.2.1.1 Demographics

Age, sex and MMSE scores did not differ significantly between groups. Significant group differences were found in addiction related variables such as impulsivity, smoking, nicotine use, and alcohol use. In addition, significant differences were also found in the incidence of cardiovascular risk factors (hypertension, type 2 diabetes,

hypercholesterolemia, and coronary heart disease), where individuals with GD had a higher prevalence than HC (p=001) (Table 5).

Table 5. Demographical and clinical characteristics of all subjects (original publication III)

Category	Variables (mean ± SD, median [IQR] or n)	GD (n=20)	HC (n=40)	P value
Demographics	Age (years)	64.0 ± 5.7	66.8 ± 9.0	0.20
	Sex (male/female)	12/8	21/19	0.78
Gambling Behavior	Gambling hours per week	9.5 ± 9.3	n.a.	-
	Gambling euros per week	262 ± 328	n.a.	-
	Problem gambling years	15.7 ± 14.3	n.a.	-
	SOGS	9.2 ± 2.9	n.a.	-
Cognitive function	MMSE	27.7 ± 2.1	28.0 ± 2.1	0.54
Impulsivity	BIS-11 total score	66.8 ± 8.7	57.4 ± 6.4	<0.001
Substance Use	Smoking (yes/no)	5/15	2/38	0.04
	Nicotine use (doses per week)	0 [8]	0 [0]	0.04
	Alcohol use (doses per week)	6.2 ± 9.2	2.8 ± 3.1	0.04
Depression	BDI	7.5 ± 9.3	2.5 ± 3.8	<0.001
Health	Subjects with cardiovascular risk factors	16	18	0.01

GD: gambling disorder; HC: healthy controls; SD: standard deviation; IQR: interquartile range; SOGS: South Oaks Gambling Screen; MMSE: Mini-Mental State Examination; AUDIT: Alcohol Use Disorders Identification Test; BIS-11: Barratt Impulsiveness Scale – 11; BDI: Beck Depression Inventory; n.a.: not applicable

5.2.1.2 Diffusion tensor imaging (DTI)

Lower FA values were found in individuals with GD compared to HC in the genu of the corpus callosum, corona radiata (CR) and the body of the corpus callosum (Table 5, Figure 15). Of the 3 clusters mentioned in Table 3, the FA values in Cluster 2 correlated negatively with SOGS scores (r=0.51, p=0.02) (Figure 15).

Table 5. Significant clusters (GD>HC) (original publication III)

Index	Cluster size (voxels)	Structure	Overlap (voxels)	P-value (TFCE)	Peak coordinates (mm)
1	295	R. Genu of Corpus Callosum	145	0.04	17 24 22
		R. Anterior Corona Radiata	118		
		R. Body of Corpus Callosum	32		
2	219	L. Anterior Corona Radiata	210	0.04	-19 39 5
		L. Genu of Corpus Callosum	9		
3	33	R. Superior Corona Radiata	33	0.05	21 -25 40

R: right; L: left; TFCE: threshold-free cluster enhancement

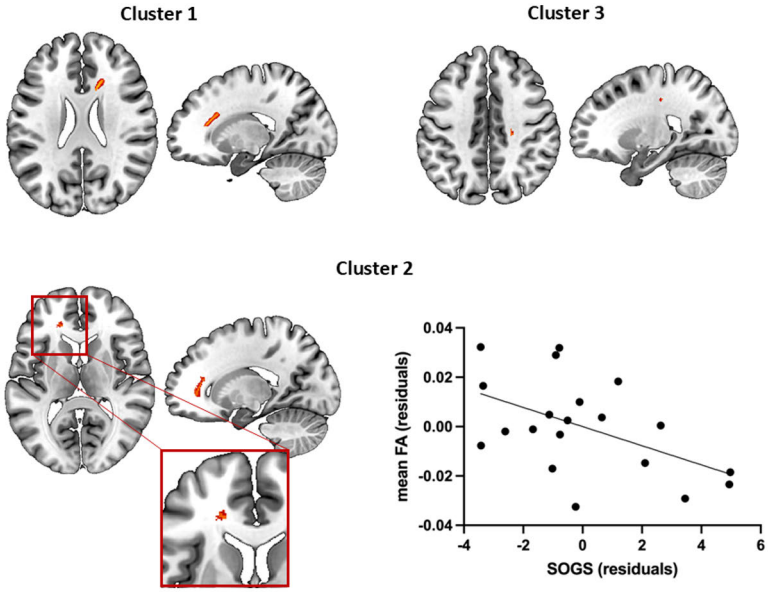

Figure 15. FA differences between groups and correlation with SOGS scores. Location of the clusters with lower FA values in GD group than in the HC group**.** The mean FA from Cluster 2 located in the anterior corona radiata correlated negatively with SOGS scores. FA=fractional anisotropy. Figure from original publication III which is licensed under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

5.2.1.3 Lesion load

Individuals with GD exhibited a cluster with a higher number of WM lesions in the left anterior CR compared to HC when performing whole brain voxel-based lesion-

symptom mapping ($p<0.05$). This cluster remained significant after controlling for cardiovascular diseases. Led by this result, an ROI analysis limited to the anterior CR was performed, and this showed a higher lesion load in the anterior CR in individuals with GD compared to HC ($p<0.05$) (Figure 16). None of these results were significantly correlated with any gambling-related variable or with alcohol use, smoking, or BDI scores.

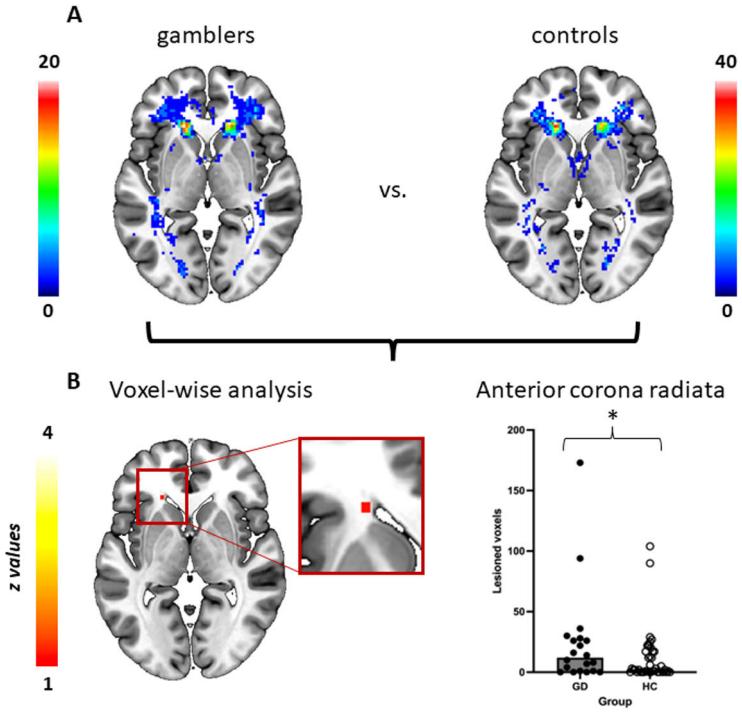

Figure 16. Lesion load voxel-wise and ROI analysis results. A. Whole brain sum of the white matter lesions in gamblers and controls. B. The first figure of the B panel shows the voxel-based lesion-symptom mapping uncorrected map containing the significant cluster located in the left anterior corona radiata (1 significant voxel at -21 30 0). The second figure illustrates the ROI analysis restricted to the left anterior corona radiata, of which the lesioned voxels between groups are plotted. Figure from original publication III which is licensed under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).
*=p<0.05

5.2.1.4 Gray matter

Individuals with GD showed reduced thickness in several brain areas, of which the largest cluster was located in the left OFC ($p<0.001$) (Figure 17A). In addition, the GD group displayed a lower volume in the left thalamus ($p=0.04$) (Figure 17B). The

orbitofrontal and the thalamic cluster did not significantly correlate with smoking, alcohol, BDI scores, or with any gambling-related variable.

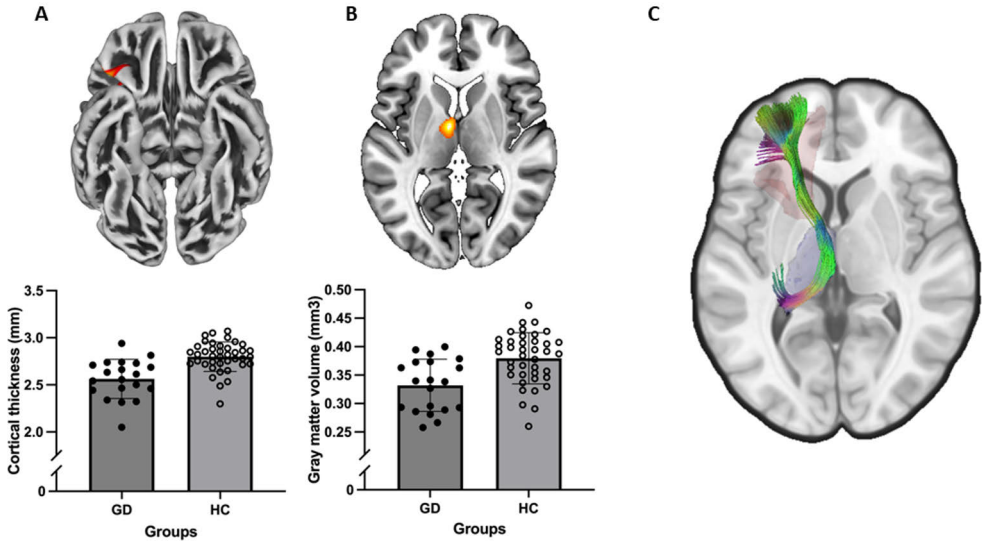

Figure 17. Left orbitofrontal and thalamic results from surface-based and voxel-based morphometry. A. Surface-based morphometry result showing the largest cluster located mostly in the left orbitofrontal cortex (peak coordinates at -39 21 -12, cluster size 169). The other significant clusters: Right medial temporal gyrus (peak coordinates at 48 -15 -13, cluster size 140) / Intracalcarine cortex (peak coordinates at -14 -66 8, cluster size 128) / Left superior temporal gyrus (peak coordinates at -43 -20 1, cluster size 112) / Right temporoparietal junction (peak coordinates at 48 -34 25, cluster size 98) / Right superior temporal gyrus (peak coordinates at 59 7 -15, cluster size 84). B. Voxel-based morphometry result in the left thalamus (peak coordinates at -8 -6 8, cluster size 433, pFWE<0.05. healthy controls (HC) 0.38 (0.045) vs. gamblers (GD) 0.33(0.046), 95% CI [0.023, 0.072]. C. Artistic representation of the left anterior thalamic projection going from the left thalamus to the left orbitofrontal cortex. This figure is a modified version from original publication III which is licensed under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

6 Discussion

6.1 Study I

The findings from Study I show that individuals with GD present a disrupted connectivity between the NAcc and prefrontal cortex. More specifically, the GD group had a loss of negative connectivity between these two areas. In addition, the study showed that the relationship between SERT availability in the right NAcc and DLPFC differed between individuals with GD and HC. Specifically, there was a significant Group x right NAcc BPND interaction in the right DLPFC cluster. Furthermore, the right NAcc MADAM BP_{ND} correlated significantly with attentional impulsivity. These findings indicate that GD is linked to disrupted fronto-striatal connectivity, which is potentially influenced by alterations in serotonin function.

One previous study also examined fronto-striatal connectivity using rs-fMRI, and observed an increased abnormal connection between the DLPFC and the right striatum in the GD group (Koehler et al., 2013). Another study investigated resting-state functional connectivity in individuals with GD using an ICA approach (Piccoli et al., 2020) and reported increased connectivity in a network involving frontal and striatal areas comprised of the anterior cingulate cortex, the caudate, and the NAcc in the GD group compared to HC. Although these studies used different approaches to ours, their findings support the disruption of normal connectivity within fronto-striatal areas in GD and align with our observation of abnormal functional connectivity from the NAcc to the DLPFC.

As for our PET findings, they suggest that serotonin might play a role in modulating both the neural circuitry and behavioral aspects of addiction, as shown by the link with abnormal fronto-striatal connectivity, and the correlation with attentional impulsivity. Supporting this, Potenza et al. (2013) also reported a relationship between serotonergic function and addiction-related behavior, showing that symptom severity in GD was associated with increased 5-HT1B receptor binding in the ventral striatum. Serotonin is critically involved in reward and impulsivity, processes that are central to addictive behaviors (Kirby et al., 2011; Nikolaus et al., 2010). Experimental studies show that increasing 5-HT tone increases reward sensitivity and reduces punishment sensitivity, while depletion has

the opposite effect, highlighting serotonin's role in balancing feedback learning (Bari et al., 2010). Moreover, converging evidence from animal, pharmacological, and imaging studies indicates that serotonin also encodes reward value via interactions with dopamine signaling within fronto-striatal circuits (Kranz et al., 2010; Seymour et al., 2012; Vázquez-Borsetti et al., 2009, 2011). Reduced levels of serotonin in the central nervous system have been associated with increased impulsivity, including impulsive action, and impulsive choice (Cardinal, 2006; Dalley et al., 2011; Pattij & Vanderschuren, 2008). Interestingly, a putative mesocorticostriatal circuit has been proposed in which serotonergic activity mediates impulsivity toward rewards (Miyazaki et al., 2012). This study also shows that the serotonin system is implicated in impulsivity in individuals with GD, which aligns with previous studies showing how serotonin medication decreases impulsivity and urge to gamble in individuals with addiction (Dannon et al., 2005; Fong et al., 2008; Hollander et al., 2000; Kim et al., 2002).

In our study, altered SERT availability in the NAcc could mechanistically influence fronto-striatal connectivity. Higher SERT availability increases serotonin reuptake, reducing extracellular serotonin levels, whereas lower SERT availability enhances synaptic serotonin tone. Changes in serotonin tone can modulate the excitability of striatal neurons and their dopaminergic inputs, influencing fronto-striatal communication and the integration of signals in prefrontal regions. This mechanism could contribute to disrupted NAcc-DLPFC connectivity, affecting functions such as the integration of reward-related signals and inhibition.

6.2 Study II

In Study II, the dorsal striatum showed a higher BOLD response to gambling-related cues in individuals with GD compared to HC. In addition, the data suggest that BOLD responses to gambling cues in the dorsal and ventral striatum are positively correlated in the HC group, but negatively correlated in the GD group. Additionally, the BOLD response of the dorsal striatum was positively associated with opioid, but not with serotonin or dopamine, function within the dorsal striatum among individuals with GD.

Previous studies on cue-reactivity and other reward-related processes in GD have produced mixed results, probably due to the differences in experimental designs and analyses (Balodis et al., 2012; Choi et al., 2012; Crockford et al., 2005; Kober H et al., 2016; Limbrick-Oldfield EH et al., 2017; Potenza, Steinberg, et al., 2003; Sescousse G et al., 2013; van Holst, Veltman, et al., 2012). Some studies have reported reduced ventral striatal activity during reward anticipation or in response to monetary rewards in GD, suggesting a blunted response to extrinsic rewarding stimuli (Balodis et al., 2012; Choi et al., 2012). In contrast, other work has found

increased striatal activity in problem gamblers, with greater ventral striatal activation during the anticipation of monetary gains (van Holst, Veltman, et al., 2012), suggesting increased sensitivity to anticipated rewards. Only a few fMRI studies have used gambling-related video cues to elicit neural responses in GD (Crockford et al., 2005; Kober H et al., 2016; Potenza, Steinberg, et al., 2003; Sescousse G et al., 2013), with only one reporting differential BOLD response in the striatum (Sescousse G et al., 2013). Differences in baseline conditions, comparison stimuli (e.g., gray screens vs. nature videos), and whole-brain vs. ROI-based analyses likely contribute to the lack of convergence across findings.

In addition to group differences in task-evoked BOLD responses, the BOLD signal changes in the ventral and dorsal striatum were significantly and positively correlated during gambling cue exposure in HC, but this was not seen in individuals with GD. The difference in correlation strength between groups was statistically significant, indicating a potential disruption in the coordinated activity between these regions in GD. The VS is a key structure in encoding reward value and prediction, while the dorsal striatum integrates this information to influence action selection and habit formation. The absence of coordinated activity in GD suggests a decoupling of these regions, where the dorsal striatum may operate more independently, potentially driving more automatic, habitual responses. This supports the ventral-to-dorsal shift in control proposed in the habit formation model of addiction (Everitt & Robbins, 2005), where behavior transitions from goal-directed to habitual as addiction progresses.

Regarding the PET findings, it was observed that stronger BOLD responses in the dorsal striatum during gambling cue exposure are positively associated with mu-opioid receptor (MOR) availability in individuals with GD. This positive association supports the hypothesis that the opioidergic system modulates cue-driven activation in reward-related circuits, even in the absence of group differences. Consistent with human pharmacological work, for example by Weber et al. (2016), opioid receptor antagonism reduces cue-induced responding and impulsive reward choice in healthy volunteers, indicating that MOR signalling contributes causally to cue-reactivity. Moreover, PET-fMRI work by Nummenmaa et al. (2018) showed that inter-individual variation in MOR availability predicts BOLD reactivity to appetitive food cues, further highlighting that MOR may modulate neural responsiveness to conditioned reward stimuli. Mechanistically, animal and human data suggest that MOR signalling influences the incentive-salience of reward-predictive cues (i.e., “wanting”), in part via modulation of dopaminergic transmission in the striatum, as shown by enhanced cue-evoked dopamine release in the presence of MOR agonism (DiFeliceantonio & Berridge, 2012; Wassum et al., 2011). Considering this, our findings may reflect increased opioidergic modulation of striatal circuitry in GD, strengthening the neural impact of gambling cues and contributing to the

maintenance of cue-driven motivation. Translationally, these results reinforce the potential of targeting the μ-opioid system (e.g., with antagonists) to diminish cue reactivity in GD.

No evidence of dopaminergic involvement was found in either Study I or Study II. This challenges the traditional view that abnormal dopaminergic signaling underlies all forms of addiction. Studies on SUDs have widely demonstrated that the disorders are characterized by a blunted dopaminergic system both at baseline and at reward processing. However, GD studies have not consistently demonstrated such dopaminergic blunting. Instead, evidence from molecular imaging indicates that individuals with GD show no reductions in striatal D2/3 receptor availability compared to HC (Boileau et al., 2013; Clark et al., 2012; Joutsa et al., 2012; Linnet et al., 2011), in contrast to the decreased receptor binding repeatedly observed in SUDs (Volkow et al., 2007). Furthermore, findings from studies assessing dopamine synthesis capacity and dopamine release suggest that GD may involve normal or even increased dopaminergic responsivity, rather than a deficit. For example, increased dopamine synthesis in the striatum (van Holst et al., 2018) and enhanced dopamine release during gambling-related or pharmacological challenges (Boileau et al., 2014; Joutsa et al., 2012; Linnet et al., 2010, 2011, 2012) have been reported, with dopamine release correlating positively with gambling severity and impulsive or risky decision-making. These findings contrast with SUDs, where chronic drug exposure leads to downregulated dopamine transmission and reduced reactivity to natural rewards (Volkow et al., 2007, 2014). Taken together, the absence of dopamine-related findings in the present studies, combined with previous evidence showing preserved or elevated dopaminergic signaling in GD, supports the notion that behavioral addictions, such as GD, differ from SUDs in their underlying neurochemical profiles. While SUDs are characterized by hypodopaminergic function – potentially reflecting a system affected by the neurotoxic effects of the substances rather than the underlying mechanisms of addiction – GD may instead reflect aberrant regulation of a relatively intact or hyper-responsive dopaminergic system. This could result in maladaptive reinforcement learning and increased cue reactivity, without the dopaminergic downregulation typically associated with SUDs.

6.3 Study III

6.3.1 White matter

In Study III, a reduction in WM integrity was observed in the GD group, predominantly in frontal brain regions, particularly in the anterior corona radiata. In addition, a significant negative correlation was found between SOGS scores and the

FA values in the anterior corona radiata, suggesting that higher gambling severity was associated with greater WM disruption within this tract.

The results of this study, highlighting the anterior CR as the main disrupted area in GD, differ from previous studies that also used FA to examine WM integrity changes in individuals with GD (Chamberlain et al., 2016; Joutsa et al., 2011; Mohammadi et al., 2016; van Timmeren et al., 2017; Yip et al., 2013, 2017). However, this discrepancy may be due to the age difference between our sample and those in other studies. There is a lack of research on older adults with GD (Kaasinen et al., 2023), which may better reflect WM abnormalities due to the normal WM atrophy that occurs over the years. Only one other study has reported white matter abnormalities in the CR in GD, showing reductions in crossing fiber integrity (Yip et al., 2017). Although they used different diffusion metrics to our study, their findings are congruent with our own, and support the involvement of CR microstructure in GD. Although these findings did not specifically replicate those of earlier studies, they add to the evidence suggesting that WM abnormalities are present in individuals with GD, particularly within networks connected to the fronto-striatal-thalamic circuit.

In Study III, voxel-wise whole-brain analysis showed significantly more WMH in the GD group compared to the HC group, specifically in the left anterior CR region of the frontal lobe. Furthermore, the whole anterior CR significantly presented more WMH in individuals with GD than in HC. To date, no previous studies have examined WMH in individuals with GD, making this the first to report such findings. Evidence from SUDs has linked WMH to addiction-related brain pathology, especially in the frontal lobe. Patients with methamphetamine, cocaine, and opioid dependence show greater WMH in frontal regions compared to HC (Alaee et al., 2014; Bae et al., 2006), and similar patterns have been observed in individuals with AUD (Pfefferbaum et al., 2024). The results also align with a recently published circuit that mediates addiction remission and previously reported targets of noninvasive brain stimulation that have demonstrated their effectiveness in treating SUDs (Harel et al., 2022; Joutsa et al., 2022; Zangen et al., 2021).

6.3.2 Gray matter

Study III demonstrated that the GD group had lower cortical thickness in several areas, with the largest cluster covering part of the left OFC and frontal operculum, compared to the HC group. In addition, lower GM volume in the left thalamus was observed in individuals with GD compared to the HC group.

Three previous studies have also reported gray matter abnormalities in the orbitofrontal cortex in individuals with GD compared to HC (J. E. Grant et al., 2015; Mohammadi et al., 2016; Zois et al., 2017), with one using surface-based analysis

(J. E. Grant et al., 2015). That study found thinner cortex in the right OFC in the GD group. There were multiple methodological and sample differences between the latter study and ours (covariates used, imaging analysis pipeline, sample size and mean age), which could account for variations in regional specificity and lateralization. As for the other two studies that found decreased volume in the OFC, the findings were also lateralized to the right hemisphere. Both used VBM, which evaluates regional gray matter volume. In contrast, surface-based analysis (used in Study III and Grant et al.) models the cortex as a surface, allowing for more anatomically precise localization of cortical thinning – a methodological advantage when investigating highly folded regions such as the OFC. However, despite the different techniques used, and the differences in lateralization of the findings, these studies strengthen the evidence implicating the OFC in the neurobiology of GD.

The thalamus has also been reported in previous literature, presenting decreased volume in individuals with GD compared to HC, as in Study III (Bouchard et al., 2021; Fuentes et al., 2015). However, methodological differences across studies warrant careful interpretation. For instance, Fuentes et al. used an ROI-based approach with uncorrected statistical thresholds, which may increase sensitivity but also the risk of false positives. Bouchard et al., on the other hand, employed a normative dataset rather than a demographically matched control group, which, while offering large-scale reference data, may limit direct comparability. In contrast, Study III used whole-brain VBM analysis with statistical significance determined using FWE correction at $p<0.05$, with an age- and sex-matched control group. Overall, despite the methodological differences, the gray matter results of Study III align with previous literature suggesting that GD is characterized by alterations in critical areas of the fronto-striatal-thalamic circuit, a neural network critical in addiction (Koob & Volkow, 2016; Potenza et al., 2019).

6.4 Implications for therapy

The three studies in this thesis demonstrate alterations in individuals with GD compared to HC, primarily within the fronto-striatal-thalamic circuit. In terms of frontal lobe findings, Study I reveals abnormal functional connectivity involving the DLPFC, while Study III shows reduced cortical thickness in the OFC and frontal operculum. Study III also implicates the anterior corona radiata, a white matter tract in the frontal lobe connecting to prefrontal regions including the ventrolateral prefrontal cortex (which overlaps with the OFC and frontal operculum), the DLPFC, and the ACC (Catani et al., 2002; Wakana et al., 2004). Striatal involvement is also demonstrated in Studies I and II, with Study I showing disrupted connectivity between the NAcc and DLPFC, and Study II revealing increased BOLD response to gambling cues in the putamen. Finally, Study III reports reduced thalamic volume in

the GD group compared to HC. While this thalamic finding may seem not related to the other findings, it aligns with the fronto-thalamic component of the circuit, as the anterior corona radiata (found to have disrupted white matter integrity in the same study) includes fibers of the anterior thalamic projection that connect the thalamus with the prefrontal cortex (Catani et al., 2002; Wakana et al., 2004). Taken together, the findings from these studies reflect abnormalities in both the fronto-thalamic and fronto-striatal parts of the fronto-striatal-thalamic circuit, indicating widespread circuit-level disruption in GD.

6.4.1 Neuromodulation treatments

The fronto-striatal circuit alterations identified in this thesis, particularly involving the DLPFC, NAcc, anterior corona radiata, and frontal operculum, have direct relevance for neuromodulation-based treatments of addiction based on previous evidence. The FDA-approved neuromodulation protocol for smoking cessation targets bilateral DLPFC and insula (Dinur-Klein et al., 2014), with emerging evidence highlighting that this protocol using H4 TMS coil can reach deeper regions, preferentially targeting the ACC and insula (Fiocchi et al., 2018). Similarly, studies on alcohol dependence applying TMS with H7 coils targeting medial frontal areas – including the medial prefrontal cortex and ACC – have shown promise in promoting alcohol remission, emphasizing the importance of frontal structures in addiction recovery (Harel et al., 2022). Surgical lesioning approaches, such as cingulotomy and bilateral NAcc lesions, have also shown benefit in refractory addiction cases (Kanaka & Balasubramaniam, 2007; Li et al., 2013; Medvedev et al., 2003). Joutsa et al. have mapped neuroanatomical targets for addiction remission to key regions including the paracingulate gyrus, left frontal operculum, and medial fronto-polar cortex, which align with known lesion- and stimulation-based targets, such as those employed in the smoking and alcohol neuromodulation protocols (Joutsa et al., 2022). Notably, the finding in the left frontal operculum is consistent with the results presented in this thesis. Neuromodulation studies in GD have primarily targeted the left DLPFC, with mixed results (Pettorruso et al., 2021). Only two studies have targeted the right DLPFC using inhibitory rTMS, reporting decreases in gambling urges and reinforcement. These findings in GD, together with the disrupted right DLPFC-NAcc connectivity observed in Study I, suggests that inhibitory stimulation of the right DLPFC may offer a promising alternative – an approach also supported by evidence from SUD studies (Camprodon et al., 2007; Mishra et al., 2010).

While most neuromodulation and surgical interventions to date have targeted cortical (DLPFC, medial prefrontal cortex, ACC, insula) and striatal (NAcc) regions, the thalamus remains an important integrative hub within the fronto-striatal-thalamic circuit. Although direct targeting of the thalamus in addiction treatments is currently

limited, its central role in relaying and modulating fronto-striatal signals suggests it could be a promising focus for future therapeutic interventions. Advances in DBS and deep TMS technologies may enable more precise modulation of thalamic activity, potentially enhancing treatment outcomes in GD and other addictions. However, conventional TMS approaches are constrained by their limited ability to stimulate deep brain structures with spatial precision, as magnetic field strength rapidly decays with distance from the scalp.

6.4.2 Neuropharmacological treatments

This thesis provides evidence associating the opioid and serotonergic system with GD symptomatology. Neuropharmacological treatments targeting the endogenous opioid system have shown the most promising results in treating GD (Bullock & Potenza, 2012). Modulation of the opioid system through antagonists and partial agonists has been effective in reducing gambling urges, severity of GD and gambling behavior (J. E. Grant et al., 2008; Weber et al., 2016). Furthermore, naltrexone, an opiate antagonist, is an approved medication by the FDA to treat opiate use disorders and alcoholism. However, randomized control trials have not provided conclusive evidence supporting the effectiveness of opioid antagonists for the treatment of GD (Alho et al., 2022; Kovanen et al., 2016). While research on the efficacy of serotonergic medications for treating GD is still limited and yields mixed results, selective serotonin reuptake inhibitors (SSRIs) have been suggested as potentially beneficial for helping with symptoms such as impulsivity, gambling urges, and gambling frequency (Black et al., 2007; Dannon et al., 2005; Fong et al., 2008; J. E. Grant & Potenza, 2006; Hollander et al., 2000; Kim et al., 2002). However, due to the lack of robust empirical support, current guidelines recommend the use of SSRIs primarily for individuals with GD who also meet criteria for bipolar spectrum disorders (Bullock & Potenza, 2012). While Study I points to the serotonergic system to be implicated in fronto-striatal function, SSRIs have not shown promising results for the treatment of GD. Based on previous neuropharmacological studies, it is possible that the opioid system is more involved in the pathophysiology of gambling activity. However, this thesis suggests that serotonergic involvement at rest may also be relevant, potentially offering new avenues for targeting fronto-striatal connectivity in treatment.

6.5 Limitations

6.5.1 Dataset 1

There are several limitations that concern Dataset 1 that are common to both Study I and II. First, the sample size of this dataset is relatively small; however, prior fMRI and PET studies in GD have used similar sample sizes. Second, neuroimaging studies involving fMRI and PET are inherently susceptible to multiple sources of noise that might complicate signal interpretation (e.g. head motion, physiological fluctuations, radiotracer-specific factors such as kinetics, binding potential variability, and metabolism). However, state-of-the-art techniques were used to improve the signal-to-noise ratio. Despite these challenges, the findings of Studies I and II were robust across multiple analysis strategies and aligned with previous research.

Third, as both studies are cross-sectional, this restricts the possibility of inferring causality from the neuroimaging findings to behavior. We cannot conclude whether the abnormalities seen at functional, molecular and structural level are due to the disorder per se (GD) or due to other confounding factors such as environmental influences or pre-existing vulnerabilities that might contribute to GD. Longitudinal studies following individuals over time would help understand whether these brain abnormalities precede the onset of the disorder or emerge as a result of chronic gambling behavior. Additionally, studies examining if treatment leads to normalization of these brain measures could further clarify the causal relationships.

Finally, even though not all PET tracers showed significant group-level differences, this does not imply that these neurotransmitter systems are not involved in the connectivity or task-fMRI settings. Each tracer measures only one aspect of the studied neurotransmitter system: for example, [^{18}F]FDOPA measures presynaptic dopamine synthesis capacity, [^{11}C]carfentanil reflects MOR binding potential, and [^{11}C]MADAM measures SERT availability. These markers do not capture the full complexity of neurotransmitter function, such as synaptic neurotransmitter levels, receptor sensitivity, or downstream signaling. Therefore, the absence of significant findings with one tracer or one aspect of a system should not be interpreted as evidence of no involvement.

6.5.1.1 Study I

There are some limitations specific to Study I to be considered. First, no physiological monitoring (e.g., heart rate or respiration) was done during scanning. These physiological signals can influence the BOLD signal and reduce signal-to-noise ratio in functional connectivity measures. Second, the rs-fMRI scan duration

was relatively short (6 minutes). Shorter scan times are associated with reduced reliability and test-retest stability of functional connectivity estimates (Birn et al., 2013). However, these two limitations are common in previous GD rs- fMRI studies. Third, the study focused on fronto-striatal structures, which restricts the ability to find other connectivity alterations in the rest of the brain. However, it is important to note that the main findings were confirmed using a whole-brain mask.

6.5.1.2 Study II

Certain limitations need to be considered when interpreting the results of Study II. First, comparisons between gambling videos and erotic videos, as well as between erotic videos and neutral videos, did not show significant results in the striatum. While this absence of findings may be partly attributed to limited statistical power due to the small sample size, other factors could also contribute. For instance, the neural responses to these categories of stimuli may not be sufficiently distinct, or the erotic videos may have evoked variable responses across participants, reducing sensitivity to detect group differences. Furthermore, unlike previous studies that observed group differences using monetary versus erotic anticipation paradigms (Sescousse et al., 2013), our stimuli involved passive viewing of erotic content, which may elicit a different striatal response profile. Additionally, the gambling video content was not tailored to individuals' preferred gambling types, which could have reduced cue reactivity in the GD group (Limbrick-Oldfield EH et al., 2017). Second, even though subjects with shorter task durations were controlled by repeating the analysis without them, the initial inclusion of these subjects may still add some variability in the BOLD response that could affect the overall findings.

6.5.2 Dataset 2

The following limitations should be considered. First, the sample size of Study III can be considered low for a structural study, although similar studies have recruited a similar number or even fewer participants than ours. Second, the absence of significant correlations with behavioral and clinical variables may be due to limited statistical power. Third, similar to Dataset 1, this study is also cross-sectional, which limits the ability to draw causal inferences. Longitudinal or intervention studies would help clarify whether the observed alterations are antecedents or consequences of GD. Finally, GD has been linked to an increased prevalence of cardiovascular diseases, which is associated with WMH and how they are distributed in the brain (Habes et al., 2018; Pilver & Potenza, 2013). Even though our results remained the same when controlling for the prevalence of cardiovascular risk factors in our study, we could not study how the different vascular risk factors are related to the WMH patterns.

7 Summary/Conclusions

The studies in this thesis provide evidence of an abnormal fronto-striatal-thalamic circuit in individuals with GD, leveraging multiple brain imaging modalities. The results of this thesis show that the fronto-striatal-thalamic circuit in GD is not only altered structurally, but also functionally and molecularly.

In relation to Aim I, Study I demonstrated that there was a loss of connectivity between the right NAcc and the right DLPFC in individuals with GD compared to HC. This alteration was associated with serotonergic binding, suggesting that an abnormal fronto-striatal connectivity in GD is linked to serotonergic dysfunction.

Addressing Aim II, Study II showed that individuals with GD had a stronger brain response to gambling cues in the dorsal striatum, an area involved in habit formation, compared to HC. This response was associated to opioid receptor activity, indicating that dysregulation within the opioidergic system contributes to maladaptive cue-reactivity in GD.

Finally, in line with Aim III, Study III identified structural abnormalities within the fronto-striatal-thalamic circuit in older individuals with GD. Specifically, there was decreased WM integrity and increased WM lesion load in the anterior corona radiata, as well as reduced gray matter density in the OFC and thalamus.

Collectively, these findings provide converging evidence for the involvement of the fronto-striatal-thalamic in the neurobiology of GD. The implications of these findings are significant in terms of understanding the underlying neurobiology of GD from a multimodal approach. By integrating different imaging techniques, this thesis offers a more integrative perspective on GD, complementing previous research that has typically focused on individual imaging modalities.

More research is needed to independently validate these findings and to use longitudinal designs with larger samples for a better understanding of causality in GD. These findings, together with previous literature on neuromodulation suggest that regions such as the DLPFC and NAcc may be promising targets due to their involvement in GD. Pharmacological treatments targetting the opioidergic system show the most promise in treating GD, and this thesis shows alterations in this system in individuals with GD. Additionally, serotonin was shown to be involved in the

abnormal neurobiology of GD at rest in Study I, which further supports the potential benefit of targeting serotonergic pathways for treatment.

This thesis advances our understanding of the neurobiological mechanisms underlying GD. Identifying specific circuits and neurotransmitters involved in GD could inform the development of more targeted and potentially effective interventions in the future.

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List of Figures, Tables and Appendices

Figures

Tables

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