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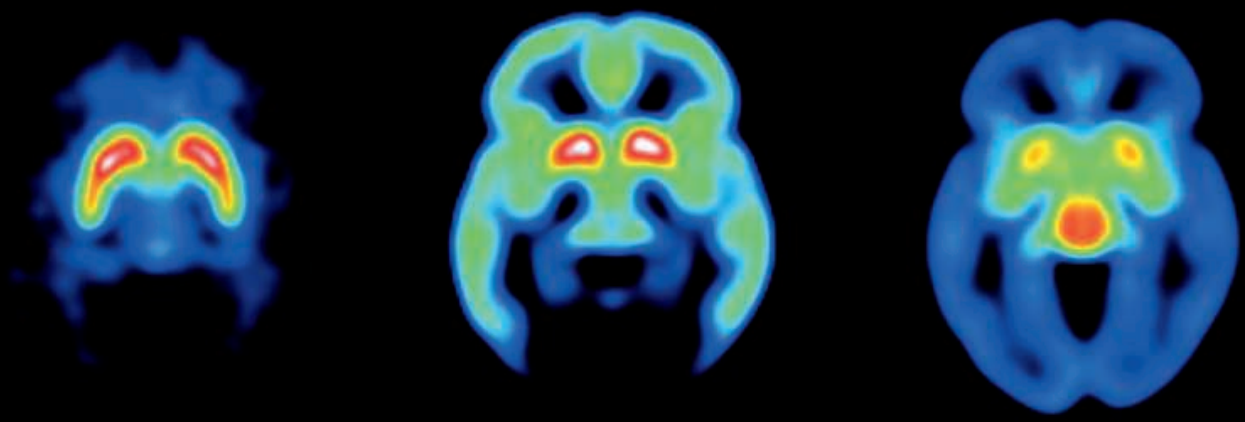

# DOPAMINE, OPIOID AND SEROTONIN NEUROTRANSMISSION IN BEHAVIORAL ADDICTIONS

Joonas Majuri

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
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*To Laura*

# ABSTRACT

Joonas Majuri

**DOPAMINE, OPIOID AND SEROTONIN NEUROTRANSMISSION IN BEHAVIORAL ADDICTIONS**

University of Turku, Faculty of Medicine, Department of Neurology, Doctoral Programme in Clinical Research; Turku PET Centre

Behavioral addictions are psychiatric disorders, in which the object of addiction is not a drug but instead behavior itself, such as gambling or eating. Behavioral addictions share clinical features with substance use disorder, including tolerance against behavior, continued behavior despite negative consequences, withdrawal symptoms and craving. However, little is known about the pathophysiology of these disorders. Behavioral addictions may also serve as a model to investigate the brain reward system at its purest form, without confounding chemical properties of misused drugs.

The aim of this study was to investigate brain neurotransmitter function in behavioral addictions. Brain dopamine, opioid and serotonin systems were investigated in pathological gambling (PG), in binge eating disorder (BED) and in a control group using positron emission tomography (PET). PET scans were performed using [$^{18}$F]fluorodopa to target presynaptic dopamine synthesis rate; [$^{11}$C]carfentanil to label μ-opioid receptors (MORs); and [$^{11}$C]MADAM to label serotonin transporter. Statistical analyses covered between-group comparisons in all three groups, intraregional PET tracer correlations in the PG and the control groups, and correlations between impulsivity and tracer binding in the PG and the control groups.

BED patients showed decreased nucleus accumbens dopamine synthesis, wide-spread decreases in MOR binding, and regionally selective increases and decreases in SERT binding, whereas PG patients failed to show any changes in relation to controls. The changes were independent from possible confounding factors. Dopamine synthesis rate correlated positively with MOR binding in the basal ganglia in both PG and control groups. Impulsivity correlated inversely with SERT binding in the prefrontal cortex in controls. This association was lost in PG, and instead, midbrain MOR binding was related both with impulsivity and nucleus accumbens dopamine synthesis rate.

The results of this study indicate that phenotypically distinct behavioral addictions differ also by their neurobiology. Importantly, the findings contrast with previously published results in substance addictions, indicating individual neurobiology in distinct addiction disorders. Whether the observed neurotransmitter alterations in BED and altered relationship between receptor densities and impulsivity in PG reflect predisposing pathophysiology or a neural adaptation remains to be established.

**Keywords**: addiction, binge eating disorder, dopamine, opioid, pathological gambling, positron emission tomography, serotonin

# TIIVISTELMÄ

Joonas Majuri

**AIVOJEN DOPAMIINI-, OPIOIDI- JA SEROTONIINITOIMINTA TOIMINNALLISISSA RIIPPUVUUKSISSA**

Turun yliopisto, Lääketieteellinen tiedekunta, Neurologian oppiaine, Turun kliininen tohtoriohjelma; Turun valtakunnallinen PET-keskus

Toiminnalliset riippuvuudet ovat psykiatrisia sairauksia, joissa riippuvuuden kohde ei ole kemiallinen aine vaan toiminta tai käytösmalli, kuten esimerkiksi rahapelaaminen tai syöminen. Toiminnallisilla riippuvuuksilla ja päihderiippuvuuksilla on paljon yhteisiä piirteitä, mukaan lukien sietokyvyn nousu, riippuvuuden kohteena olevan toiminnan jatkaminen huolimatta epäedullisista seurauksista, vieroitusoireet ja himo. Kuitenkaan toiminnallisten riippuvuuksien patofysiologiaa ei juurikaan tunneta. Toiminnallisia riippuvuuksia voidaan käyttää myös mallina tutkittaessa aivojen palkkiojärjestelmää puhtaimmillaan ilman päihteiden aiheuttamaa kemiallista sekoittavaa vaikutusta.

Tämän tutkimuksen tarkoituksena oli tarkastella aivojen välittäjäaineiden toimintaa toiminnallisissa riippuvuuksissa. Aivojen dopamiini-, opioidi- ja serotoniinijärjestelmiä tutkittiin peliriippuvuudessa, ahmintahäiriössä ja kontrolliryhmässä positroniemissiotomografialla (PET). PET-kuvauksissa [$^{18}$F]fluorodopa kuvasi presynaptista dopamiinin tuotantokykyä, [$^{11}$C]karfentaniili sitoutui μ-opioidireseptoriin (MOR) ja [$^{11}$C]MADAM puolestaan sitoutui serotoniinin takaisinottajaan (SERT). Tilastollisessa analyysissa tarkasteltiin kaikkien ryhmien välisiä eroja merkkiaineiden sitoutumisessa. Lisäksi peliriippuvuudessa ja kontrolliryhmässä tarkasteltiin eri merkkiaineiden sitoutumisen välisiä riippuvuussuhteita ja impulsiivisuuden ja merkkiaineiden sitoutumisen riippuvuussuhteita.

Ahmintahäiriössä dopamiinin tuotantokyky oli alentunut accumbens-tumakkeessa, MOR-sitoutuminen oli alentunut laaja-alaisesti aivojen eri osissa ja SERT-sitoutumisessa nähtiin alueellisesti vaihtelevia sitoutumisen nousuja ja laskuja, kun taas peliriippuvuus ei eronnut kontrolleista minkään merkkiaineen osalta. Muutokset eivät johtuneet mahdollisista sekoittavista tekijöistä. Dopamiinin tuotantokyky korreloi tyvitumakkeiden MOR-sitoutumisen kanssa sekä peliriippuvuudessa että kontrolleilla. Impulsiivisuus korreloi otsalohkon SERT-sitoutumisen kanssa kontrolliryhmässä, mutta tämä riippuvuussuhde ei ilmennyt peliriippuvuudessa, jossa sen sijaan keskiaivojen MOR-sitoutuminen korreloi sekä impulsiivisuuden että accumbens-tumakkeen dopamiinin tuotantokyvyn kanssa.

Tämän tutkimuksen tulokset osoittavat, että ilmiasultaan erilaiset toiminnalliset riippuvuudet eroavat myös neurobiologisesti toisistaan. Lisäksi tulokset poikkeavat aiemmin julkaistuista tuloksista päihderiippuvuuksissa, mikä tarkoittaa yksilöllisen neurobiologisen taustan ilmenemistä eri riippuvuussairauksissa. Edelleen jää selvitettäväksi, heijastavatko hermovälittäjäaineiden muutokset ahmintahäiriössä sekä hermovälittäjäaineiden ja impulsiivisuuden riippuvuussuhteiden muutokset peliriippuvuudessa altistavaa patofysiologiaa vai hermostollista mukautumista.

**Avainsanat:** riippuvuus, ahmintahäiriö, dopamiini, opioidi, peliriippuvuus, positroniemissiotomografia, serotoniini

# TABLE OF CONTENTS

# ABBREVIATIONS

| | |
|---|---|
| ANOVA | Analysis of variance |
| AUDIT | Alcohol Use Disorders Identification Test |
| ADHD | Attention-deficit/hyperactivity disorder |
| BED | Binge eating disorder |
| BES | Binge eating scale |
| BIS-11 | Barratt Impulsiveness Scale, 11$^{th}$ version |
| BMI | Body mass index |
| $BP_{ND}$ | A ratio of specific binding relative to the nondisplaceable binding |
| DAT | Dopamine transporter |
| DEBQ | The Dutch Eating Behavior Questionnaire |
| DSM | The Diagnostic and Statistical Manual of Mental Disorders |
| $p_{FWE}$ | Familywise error corrected p-value |
| GABA | $\gamma$-aminobutyric acid |
| GLM | General linear model |
| GP | Globus pallidus |
| HRRT | High Resolution Research Tool |
| ICD | Impulse control disorder |
| $K_i$ | Influx constant rate |
| MDMA | 3,4-Methylenedioxymethamphetamine |
| MOR | μ-opioid receptor |
| NAcc | Nucleus accumbens |
| OCC | Occipital cortex |
| OFCPET | Orbitofrontal cortexPositron emission tomography |
| PFC | Prefrontal cortex |
| PG | Pathological gambling |
| ROI | Region of interest |
| SERT | Serotonin transporter |
| SOGS | South Oaks Gambling Screen |
| SPECT | Single-photon emission computed tomography |
| SRTM | Simplified reference tissue model |
| SSRI | Selective serotonin reuptake inhibitor |
| VTA | Ventral tegmental area |

# LIST OF ORIGINAL PUBLICATIONS

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I. Majuri J, Joutsa J, Johansson J, Voon V, Alakurtti K, Parkkola R, Lahti T, Alho H, Hirvonen J, Arponen E, Forsback S, Kaasinen V: Dopamine and opioid neurotransmission in behavioral addictions: A comparative PET study in pathological gambling and binge eating. *Neuropsychopharmacology 2017;42(5):1169–1177* (E-pub 2016 Nov 24). DOI: *10.1038/npp.2016.265*

II. Majuri J, Joutsa J, Johansson J, Voon V, Parkkola R, Alho H, Arponen E, Kaasinen V: Serotonin transporter density in binge eating disorder and pathological gambling: A PET study with [$^{11}$C]MADAM. *European Neuropsychopharmacology 2017;27:1281–1288* (E-pub 2017 Oct 9). DOI: *10.1016/j.euroneuro.2017.09.007*

III. Majuri J, Joutsa J, Arponen E, Forsback S, Kaasinen V: Dopamine synthesis capacity correlates with mu-opioid receptor availability in the human basal ganglia: a triple-tracer PET study. *NeuroImage 2018; 183:1–6* (E-pub 2018 Aug 2). DOI: *10.1016/j.neuroimage.2018.07.069*

IV. Majuri J, Joutsa J, Arponen E, Forsback S, Kaasinen V: Distinct serotonergic and opioidergic regulation of impulsivity in healthy individuals and pathological gamblers. *[submitted]*

# 1 INTRODUCTION

Different drug addictions share clinical characteristics that are not directly linked to the pharmacological effects of the particular drug that is being abused. According to the 10th edition of the World Health Organization's International Classification of Diseases (ICD-10) criteria, substance addictions are characterized by a strong urge or compulsion to use drugs, loss of self-control over substance-taking behavior, withdrawal symptoms when the substance use pauses, tolerance, excessive time using the drug (i.e., drug use becoming a central function of one's life) and continuing the drug-related behavior despite the evident negative consequences. These characteristics may also be present in conditions that do not involve excessive use of a pharmacological substance (Yau & Potenza, 2015). A behavior itself can be addictive and can lead to compulsive engagement in the behavior, withdrawal symptoms, loss of self-control over a particular behavior and marked negative consequences. These conditions are referred to as behavioral addictions.

Behavioral addictions provide a unique opportunity to investigate addicted brains without the confounding chemical effects of misused drugs. Gambling disorder was the first behavioral addiction finally classified as an addictive disorder in the 5th version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Other disorders commonly regarded as behavioral addictions are binge eating disorder (eating addiction), Internet gaming disorder, compulsive shopping and compulsive pornography use or compulsive sexual behavior. As the concept of behavioral addictions is a relatively new topic in the field of neuroscience, little is known about the neurobiology of these disorders. Gaining knowledge of the neurobiological framework of behavioral addictions is also needed to guide future pharmacological interventions against these disorders, which mostly lack efficacious treatments at the moment.

Brain reward processing is altered in substance addictions. Previously, altered mesolimbic dopamine neurotransmission has been considered critical in substance addiction (Koob & Volkow, 2016). There is also evidence of the involvement of other neurotransmitters in brain reward processing and addictions, in particular, the endogenous opioid system and serotonergic system are involved (Daw *et al.*, 2002; Kranz *et al.*, 2010; Darcq & Kieffer, 2018). Whether alterations in neurotransmission in the addicted brain are neurochemical adaptations to continuous drug intake or predisposing traits to addictions remains elusive. Here, behavioral addictions can help us understand the direction of causality of previously observed neurobiological differences in substance use disorders. Furthermore, brain dopamine, opioid and serotonin systems have never previously been studied at the same time in different behavioral addictions.

The purpose of this thesis was to investigate brain neurotransmitters known to participate in reward processing in addicted brains. This study focused on the neurobiology of two distinct behavioral addictions, gambling disorder and binge eating disorder. Specifically,

brain dopamine, opioid and serotonin transmission was observed using positron emission tomography (PET) with the radioligands [$^{18}$F]fluorodopa, [$^{11}$C]carfentanil and [$^{11}$C]MADAM, respectively, in both patient groups and in a control group. Approaching two distinct behavioral addiction disorders with multiple PET scans was a unique basis for this study.

# 2 REVIEW OF THE LITERATURE

## 2.1 Substance addictions

Substance addictions share common clinical signs and symptoms regardless of the particular misused drug. The core of all substance addictions is compulsory drug use despite marked negative social, economic and health consequences. Drug addictions are associated with loss of control over drug use, developing tolerance and increasing doses to obtain the desired psychopharmacological response and displaying withdrawal symptoms when the drug is removed (WHO, 2018). In the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), substance use is considered disordered if two or more following symptoms are met during the past 12 months and substance use leads to significant impairment or distress (APA, 2013). Mild substance use disorder is indicated if two or three symptoms are fulfilled; if four or five criteria are met, a diagnosis of moderate substance use disorder can be made, and six points or more means severe substance use disorder:

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 effort to cut down or control the 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 substance use results in a failure to fulfill major role obligations at work, school, or home.
6. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance.
7. Important social, occupational, or recreational activities are given up or reduced because of the use of the substance.
8. Recurrent substance use in situations in which it is physically hazardous.
9. The substance use 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 use of the substance.
10. Tolerance, as defined by either a need for markedly increased amounts of the substance to achieve intoxication or desired effect, and/or a markedly diminished effect with continued use of the same amount of the substance.
11. Withdrawal, as manifested by either the characteristic withdrawal syndrome for the substance, and/or the substance is taken to relieve or avoid withdrawal symptoms.

The most commonly misused drugs are alcohol, tobacco, cannabis, different stimulants and opiates. Globally, heavy binge drinking prevalence was 18% in 2015, and the prevalence rate was 15% for daily tobacco smoking (Peacock *et al.*, 2018). The past-year prevalence rates were 3.8% for cannabis, 0.77% for amphetamine, 0.37% for opiate and 0.35% for cocaine use (Peacock *et al.*, 2018). In Finland, the most commonly used illegal drugs are cannabis, stimulants and opiates. In 2010, 17% of people aged 15–69 tried cannabis,

and their respective values were 2.1% for amphetamine, 1.7% for MDMA, 1.5% for cocaine and 1.0% for opiates (Varjonen, 2015). It has been approximated that in Finland, 18000–30000 inhabitants are problem users of amphetamine or opiates (0.55–0.9%) (Varjonen, 2015). The prevalence of hazardous drinking in Finland is approximately 5.8% in people aged 30–64 (Halme *et al.*, 2008).

The concept and dangers of addiction are catching fire and being recognized around the world: for example, public interest towards opiates has risen in the last few years in the USA as overdose-related deaths have increased, and the situation has been named an opioid epidemic (Rudd *et al.*, 2016). The global mortality rate due to smoking is 111/100000, due to alcohol (33/100000) and due to illegal drugs (6.9/100000) (Peacock *et al.*, 2018). In Finland, 1730 alcohol-related deaths were counted in 2016, which corresponded to 3.2% of all deaths in Finland in that year (THL, 2017). According to Finland's Cause of Death Register, 141 drug poisoning deaths were registered in 2016, and the death rate had stayed quite stable over the past years (THL, 2017).

It has been approximated that substance addictions lead to costs of billions every year (Thavorncharoensap *et al.*, 2009; Kranzler & Soyka, 2018). Thus, effective treatment strategies are demanded, not only to reduce individual distress and health risks but also for nationwide economic reasons. Psychotherapy and peer support may be advantageous for some patients (Bassuk *et al.*, 2016; Carroll & Kiluk, 2017). Alcohol dependency may be treated with disulfiram, acamprosate and opioid antagonists (Kranzler & Soyka, 2018). Methadone, buprenorphine and opioid antagonists may be used to treat opioid addiction, and methadone and buprenorphine may also be used as maintenance therapy (Dugosh *et al.*, 2016). Nicotine addiction may also be treated with replacement therapy but also with varenicline and bupropion (Gómez-Coronado *et al.*, 2018). Nevertheless, amphetamine, cocaine and cannabis addictions lack efficacious pharmacological treatment (Phillips *et al.*, 2014; Lévesque & Le Foll, 2018).

## 2.2 Behavioral addictions

### *2.2.1 Gambling disorder*

Gambling disorder (previously pathological gambling (PG) in DSM-IV) has been described as a prototype of behavioral addictions because it is characterized by typical addictive symptoms (e.g., tolerance, withdrawal syndromes), but there is no drug modulating brain neurobiology, thereby demonstrating the underlying addictive neurocircuits at their purest form (Robbins & Clark, 2015). PG is the only behavioral addiction currently classified under the section "Substance-Related and Addictive Disorders" in DSM-5 (Bechara, 2003). In DSM-IV, PG was included in the section "Impulse-Control Disorders

Not Elsewhere Classified". According to DSM-5, gambling disorder can be diagnosed if at least four out of nine symptom criteria are fulfilled during the past 12 months, and the gambling behavior is not explained by a manic episode (APA, 2013). The exact diagnostic criteria in DSM-5 are as follows:

1. Need to gamble with increasing amount of money to achieve the desired excitement
2. Restless or irritable when trying to cut down or stop gambling
3. Repeated unsuccessful efforts to control, cut back on or stop gambling
4. Frequent thoughts about gambling (such as reliving past gambling experiences, planning the next gambling venture, thinking of ways to get money to gamble)
5. Often, gambling when feeling distressed
6. After losing money gambling, often returning to get even (referred to as "chasing" one's losses)
7. Lying to conceal gambling activity
8. Jeopardizing or losing a significant relationship, job or educational/career opportunity because of gambling
9. Relying on others to help with money problems caused by gambling

In comparison to DSM-IV, the diagnostic criteria for gambling disorder are now somewhat more liberal. Previously, five out of ten symptoms were needed for a diagnosis of PG. The tenth symptom no longer included in DSM-5 was a commitment of illegal acts to obtain money for gambling or paying gambling debts (Stinchfield, 2003; Stinchfield *et al.*, 2005; Jiménez-Murcia *et al.*, 2009).

The estimates of the prevalence of PG and gambling disorder vary according to the methodology used. In addition to the DSM criteria, the South Oaks Gambling Screen (SOGS) and Problem Gambling Severity Index are commonly used to diagnose PG (Lesieur & Blume, 1987; Ferris & Wynne, 2001). SOGS scores of 3 or 4 are considered an indicator of problem gambling, whereas scores of 5 or greater are considered to reflect the actual probable gambling disorder (Calado & Griffiths, 2016). Additionally, Problem Gambling Severity Index scores of 8 or more are considered to reflect problem gambling, and a score of 3–8 indicates moderate risk gambling (Ferris & Wynne, 2001). The worldwide lifetime prevalence of PG varies between 0.3%–3.4%, whereas the past-year prevalence of PG is 0.02%–2.2% (Calado & Griffiths, 2016). The worldwide lifetime prevalence of problem gambling, considered a risk factor for developing PG, is 0.7%–6.5%, whereas past-year problem gambling is evident in 0.1–5.8% of the population (Calado & Griffiths, 2016). Several factors, including cultural aspects, access to different gambling opportunities and the instrument used to screen PG, contribute to the highly variable prevalence rates (Calado & Griffiths, 2016). In Finland, national gambling surveys have been performed at four-year intervals since 2003. The survey was last conducted in 2015, when 4515 inhabitants participated. Among these subjects, past-year problematic gambling (SOGS score of 3 or more) was evident in 3.3% of subjects. The prevalence of probable gambling disorder (SOGS score of 5 or more) was 1.3% (Salonen & Raisamo, 2015). In a previous Finnish gambling survey in 2011, the past-year prevalence of problem gambling and probable gambling disorder were 2.7% and 1.0%, respectively (Salonen &

Raisamo, 2015). The prevalence rates have remained quite stable in Finland over the past years (Calado & Griffiths, 2016). Gambling disorder affects males more often than females (Kessler *et al.*, 2008).

Comorbid psychiatric diseases commonly occur in PG patients. Substance use disorders are frequent in PG patients, and a previous meta-analysis suggested a comorbidity rate of 58% (Lorains *et al.*, 2011). Mood disorders are present in 38% and anxiety spectrum disorders in 37% of PG patients (Lorains *et al.*, 2011). A recent study found that lowering the PG DSM-5 criteria cutoff points did not change the prevalence of comorbid psychiatric disorders (Nicholson *et al.*, 2018). From a psychological perspective, PG subjects often have impairments in inhibitory control, planning, decision-making, compulsivity and cognitive flexibility (Grant *et al.*, 2016). One of the key characteristics of PG patients is increased decisional impulsivity and delay discounting, indicating that they prefer immediate or short-term rewards instead of long-term benefits (Grant *et al.*, 2016). Typical psychological features in PG are gamblers' fallacy (e.g., a bias in processing random effects during gambling where gamblers often fail to predict future random events based on previous gambling events), "chasing one's losses" (e.g., continuing to gamble after a monetary loss to win back the losses), overestimation of gambling skills and enhanced motivation to gamble after near-miss outcomes (APA, 2013; Clark *et al.*, 2014).

Currently, the treatment options for PG are limited. Cognitive behavioral therapy, brief motivational interviewing and peer support, such as those provided by Gamblers Anonymous, may all be beneficial (Yau & Potenza, 2015). However, there is no officially approved pharmacotherapy or neuromodulation for PG (Yau & Potenza, 2015). Most promising medications have been opioid antagonists, but the data remain controversial (Kim *et al.*, 2001; Grant *et al.*, 2006; Grant *et al.*, 2008; Toneatto *et al.*, 2009; Grant *et al.*, 2010; Kovanen *et al.*, 2016). Previous studies have concentrated on naltrexone and nalmefene, and intranasal naloxone is currently under investigation (Johansson *et al.*, 2018). Selective serotonin reuptake inhibitors (SSRIs) have also been widely investigated, but the data are mixed at best (Hollander *et al.*, 2000; Blanco *et al.*, 2002; Kim *et al.*, 2002; Grant *et al.*, 2003). Several other agents have been tested in different trials, mostly with small sample sizes. N-acetylcysteine has shown preliminary efficacy in a relatively small open-label trial, (Grant *et al.*, 2007), but there are no randomized controlled trials. Sertraline, topiramate, bupropion and olanzapine have failed to show efficacy (Saiz-Ruiz *et al.*, 2005; Black *et al.*, 2007; McElroy *et al.*, 2008; Berlin *et al.*, 2013).

### *2.2.2 Binge eating disorder*

Binge eating disorder (BED) is the most common eating disorder (Hutson *et al.*, 2018). Epidemiological data exist mostly from Western countries (Kessler *et al.*, 2013). The worldwide lifetime prevalence of BED is 0.2%–4.7% depending on country of origin,

with the highest prevalence rates in Brazil (Kessler *et al.*, 2013). BED affects females more commonly than males (Hudson *et al.*, 2007; Kessler *et al.*, 2013). BED is characterized by repeated periods of eating large amounts of food, a loss of control over eating behavior and, importantly, the absence of compensatory behaviors trying to minimize the weight gain (Hutson *et al.*, 2018). Previously, in DSM-IV, BED was not classified in a chapter of "Eating disorders", but described in the section "Eating Disorder Not Otherwise Specified". In DSM-5, it has been included in the category "Feeding and Eating Disorders" (APA, 2013). In relation to DSM-IV, the diagnostic criteria remained as they were, except for the duration of the symptoms. In DSM-IV, BED was diagnosed if binge eating occurred, on average, at least two days a week for a period of six months. DSM-5 diagnostic criteria are listed below:

1. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:
    a. Eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances.
    b. A sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating).
2. The binge eating episodes are associated with three or more of the following:
    a. eating much more rapidly than normal
    b. eating until feeling uncomfortably full
    c. eating large amounts of food when not feeling physically hungry
    d. eating alone because of feeling embarrassed by how much one is eating
    e. feeling disgusted with oneself, depressed or very guilty afterward
3. Marked distress regarding binge eating is present
4. Binge eating occurs, on average, at least once a week for three months
5. The binge eating is not associated with the regular use of inappropriate compensatory behavior (e.g., purging, fasting, excessive exercise) and does not occur exclusively during the course of anorexia nervosa or bulimia nervosa.

BED share many features with substance addictions, including diminished control over behavior, craving and continued behavior despite obvious negative consequences (Gearhardt *et al.*, 2011). Binge eating has been associated with emotional dysregulation, impairments in cognitive flexibility, motivational processes and reward processing, and impulsivity (Whiteside *et al.*, 2007; Hutson *et al.*, 2018). BED patients also tend to express habitual learning strategies rather than goal-directed strategies in habitual learning tasks, a pattern that is also detected in substance use disorders (Voon *et al.*, 2015). Thus, it has been suggested that BED could be a form of behavioral addiction. Term "food addiction" has also been used (Gearhardt *et al.*, 2011). Some scientists prefer the term "eating addiction" rather than "food addiction" (Hebebrand *et al.*, 2014). However, BED and food addiction criteria are not entirely overlapping and may reflect distinct entities (Gearhardt *et al.*, 2012).Similar to PG, BED also commonly occurs together with other psychiatric disorders. Anxiety spectrum disorders are evident in 56–65% of BED patients, and mood disorders are found in 46% of BED patients (Hudson *et al.*, 2007; Kessler *et al.*, 2013). Drug addictions are not as common in BED patients as in the PG population,

as the prevalence of comorbid substance use disorder is 23%–24% in BED compared to 58% in PG (Hudson *et al.*, 2007; Lorains *et al.*, 2011). Due to excessive calorie intake, BED is associated with obesity, increasing the risk for other diseases, such as hypertension, diabetes, and cardiovascular diseases (Hudson *et al.*, 2007; Kessler *et al.*, 2013). Interestingly, even when compared to BMI-matched controls in a five-year follow-up study, binge eating patients were more likely to develop components of metabolic syndrome (Hudson *et al.*, 2010).

As in PG, nonpharmacological treatment options, such as cognitive behavioral therapy, have shown some efficacy (Brownley *et al.*, 2016). Lisdexamphetamine, a prodrug of dextroamphetamine, is the only officially approved medication for the treatment of BED (McElroy, 2017). It has been shown to both reduce binge eating episodes and lower weight (Brownley *et al.*, 2016; McElroy *et al.*, 2016; McElroy, 2017). Lisdexamphetamine acts by blocking dopamine and norepinephrine reuptake, enhancing the synaptic concentrations of these neurotransmitters (McElroy, 2017). SSRI medications reduce binge-eating behavior but not weight, and these drugs are an option for patients with comorbid major depression (Guerdjikova *et al.*, 2012; Brownley *et al.*, 2016). Orlistat may be combined with treatment to support weight reduction (Grilo *et al.*, 2005). Topiramate is also effective in reducing binge eating and weight, but its side effects limit its use (McElroy *et al.*, 2007; Brownley *et al.*, 2016; McElroy, 2017). Lastly, acamprosate, atomoxetine, baclofen, naloxone, the novel MOR antagonist ALKS-33, liraglutide and bupropion have been investigated in single studies with mixed results (McElroy, 2017).

### *2.2.3 Other behavioral addictions*

Beyond PG and BED, several other behaviors may be considered behavioral addictions due to their addictive-like characteristics. Internet gaming disorder, compulsive shopping and compulsive sexual behavior are disorders typically grouped as behavioral addictions. Common to these disorders are high psychiatric comorbidity (Black *et al.*, 1997; Mueller *et al.*, 2010; VAN Rooij *et al.*, 2014; Derbyshire & Grant, 2015; Cheng *et al.*, 2018) as well as lack of efficacious treatments, with cognitive behavioral therapy showing the most promising results (Derbyshire & Grant, 2015; Müller *et al.*, 2015; Soares *et al.*, 2016; Zajac *et al.*, 2017). In China and South Korea, treatment camps for Internet addicted children exist, highlighting the burden of the disorder, but the knowledge of the efficacy of the camps is limited (Petry *et al.*, 2015).

Internet gaming disorder is currently classified in Section III as a disorder requiring more study in DSM-5 (Petry & O'Brien, 2013). As the Internet may be used in several ways, it is noteworthy that online gambling is better conceptualized as gambling than Internet gaming disorder, but online gaming is among other online behaviors most strongly associated with problematic Internet use, warranting an individual diagnose (Zajac *et al.*,

2017). Compulsive shopping is another behavioral addiction that is characterized by overpowering urges against buying and shopping and a loss of control over spending, which can lead to financial problems, distress and social and marital problems (McElroy *et al.*, 1994; Müller *et al.*, 2015). For compulsive shoppers, the buying process itself is the perpetuating feature, not the bought items, which often are hidden or otherwise never used (Lejoyeux & Weinstein, 2010). Most previous studies have adapted diagnostic criteria for compulsive buying suggested by McElroy *et al*. (McElroy *et al.*, 1994). Compulsive sexual behavior is characterized by compulsive and repeated sexual fantasies, urges or behaviors causing distress, feelings of guilt, or other negative consequences (Derbyshire & Grant, 2015). Typical forms of repeated sexual behavior are inter alia excessive masturbation and compulsive pornography use (Derbyshire & Grant, 2015).

According to a recent meta-analysis, the prevalence of compulsive shopping is 4.9% and is more common in young and female subjects (Maraz *et al.*, 2016). The prevalence rates of compulsive sexual behavior in general populations vary between 1–5% (Derbyshire & Grant, 2015). Additionally, prevalence rates of Internet gaming disorder are highly variable, being approximately 0.5–6% (Petry *et al.*, 2015). Internet gaming disorder affects males more commonly than females, and young age is also a recognized risk factor for Internet gaming disorder (Petry *et al.*, 2015). Behavioral addictions also cooccur. Twenty-three percent of 96 PG patients had another ICD, and the existence of ICDs in addition to PG behavior was related to worse symptoms of PG (Grant & Kim, 2003). In a sample of 171 patients with compulsive shopping, BED co-occurred with 14% of patients and PG with 5.5% of patients (Mueller *et al.*, 2010). Patients with treated Parkinson's disease had some impulse control disorder in a likelihood of 13.6%, and 3.9% had two or more impulse control disorders (Weintraub *et al.*, 2010). Although there is overlap in the existence of different ICDs in Parkinson's disease, individual susceptibility may lead to the expression of different phenotypes (Voon *et al.*, 2017). Parkinson's disease patients with ICDs express wide symptoms for other psychiatric disorders, and those who have multiple ICDs had more depression and obsessive-compulsive symptoms than those with only one ICD (Jaakkola *et al.*, 2014).

Taken together, behavioral addictions are an evolving concept touching a remarkable number of patients, their family members and other social contacts. Different ICDs may occur at the same time, but distinct neurobiological circuits may lay behind different phenotypes and subtypes of behavioral addictions (Voon *et al.*, 2017). As some of the behavioral addictions are not already classified as addictions in the DSM-5 due to lack of proper neurobiological data, neuroimaging of different behavioral addictions are highly needed for conceptualizing these diseases and to target possible psychopharmacological treatments.

## 2.3 Neurobiology of substance addictions

### *2.3.1 Dopamine*

Major dopaminergic pathways include the nigrostriatal, mesolimbic and mesocortical pathways (Dalley & Roiser, 2012). The mesolimbic pathway originates from the ventral tegmental area and projects to the ventral striatum, e.g., to the NAcc. It has long been suggested that a key mechanism of reward and addiction is dopamine release in the NAcc. Several drugs, including methamphetamine, cocaine, alcohol and opiates, enhance dopamine neurotransmission in the NAcc either directly increasing extracellular dopamine levels or indirectly via regulatory neurotransmitter systems. For example, cocaine blocks dopamine reuptake from the synaptic cleft, whereas opiates inhibit GABAergic inhibition of VTA dopaminergic cells, leading to enhanced dopamine release in the NAcc (Volkow *et al.*, 2011). Similarly, reductions in the NAcc extracellular dopamine levels during drug withdrawal are common for stimulants, ethanol and opiates (Rossetti *et al.*, 1992).

NAcc dopamine release may be either tonic or phasic. In particular, phasic dopamine release (burst firing) has been linked to the addictive effects of drugs (Floresco *et al.*, 2003; Koob & Volkow, 2016). Phasic dopamine release in the NAcc quickly increases the local dopamine concentration in the synaptic cleft. There are micromolar concentrations in the synaptic cleft, and dopamine is removed efficiently from the synaptic cleft by dopamine transporters (Grace, 2000). In contrast, the effects of tonic dopamine release are more spatially distributed (Floresco *et al.*, 2003). The extracellular dopamine concentration consists not only of tonically released dopamine but also from the overflow from the synaptic cleft (Grace, 2000). Tonic firing releases dopamine into the extrasynaptic space, where dopamine concentration is so low that the dopamine does not activate postsynaptic cells but can get high enough to act via presynaptic D2R autoreceptors to attenuate phasic dopamine neurotransmission (Grace, 2000; Floresco *et al.*, 2003). Therefore, tonic dopamine levels are an important modulator of phasic, reward-related dopamine release (Grace, 2000).

Several dysfunctions in the mesolimbic dopamine system have been identified in drug addictions. Reduced striatal D2/D3 receptor binding is a hallmark of substance addictions, including alcohol (Hietala *et al.*, 1994; Volkow *et al.*, 1996; Martinez *et al.*, 2005), opiate (Wang *et al.*, 1997a; Martinez *et al.*, 2012), cocaine (Volkow *et al.*, 1993; Martinez *et al.*, 2004) and methamphetamine (Volkow *et al.*, 2001; Lee *et al.*, 2009) addiction. Addicted individuals also show blunted dopamine release in the striatum following pharmacological challenges compared to non-addicted controls (Martinez *et al.*, 2005; Martinez *et al.*, 2007; Martinez *et al.*, 2012). Some scientists have proposed that especially hyperactivity of the dopamine D3-type receptors is behind addiction neurocircuits (Payer *et al.*, 2014). Based on preclinical data, it has been suggested that repeated drug

exposure increases extracellular dopamine concentration, which leads to a decrease in phasic dopamine release via activation of presynaptic autoreceptors on dopaminergic nerves (Grace, 2000). Interestingly, healthy subjects with a family history of substance use disorders show similarly blunted responses to amphetamine compared to controls matched for substance use (Casey *et al.*, 2014). However, the findings regarding presynaptic dopamine synthesis capacity are somewhat mixed, as [$^{18}$F]fluorodopa PET studies have found decreased synthesis capacity in cocaine but not in alcohol dependence (Wu *et al.*, 1997; Heinz *et al.*, 2005b; Kienast *et al.*, 2013) (Table 1, page 23). Finally, addicted individuals show enhanced dopamine release following drug-related cues (Volkow *et al.*, 2006; Wong *et al.*, 2006). It has been hypothesized that this dopamine release following exposure to cues is due to conditioning: phasic dopamine release strengthens the selected synaptic connections (Floresco *et al.*, 2003). The discrepancy between the expected reward and the actual blunted response to the drug may be the key mechanism that leads to compulsory drug seeking (Volkow *et al.*, 2011). However, even though dopamine systems seem crucial for addictions, treatments targeting dopaminergic neurons have generally failed to show efficacy in substance addictions (Kishi *et al.*, 2013a; Kishi *et al.*, 2013b).

### *2.3.2 Opioid*

The brain opioid system has been considered a key modulator of hedonic balance, enhancing reward-based learning and reducing aversion (Darcq & Kieffer, 2018). The interactions between brain dopamine and opioid systems are robust. One of the brain areas where dopamine-opioid interactions occur is the VTA. MOR-expressing GABAergic interneurons project to NAcc dopaminergic afferents in the VTA, and GABA release attenuates dopamine release in the NAcc. MOR activation in the VTA leads to inhibition of GABAergic attenuation, which enhances dopaminergic neurotransmission in the mesolimbic pathway (Johnson & North, 1992; Spanagel *et al.*, 1992; Madhavan *et al.*, 2010; Jalabert *et al.*, 2011). Similar activation of the mesolimbic dopamine system is observed if MOR-mediated inhibition of GABAergic neurotransmission occurs in the ventral globus pallidus, which seems to specifically enhance tonic dopamine release (Kalivas *et al.*, 1993; Wu *et al.*, 1996; Floresco *et al.*, 2003; Hjelmstad *et al.*, 2013). However, dopamine antagonist treatment has a minor effect on opiate self-administration in animal models, which supports the idea that the rewarding effects of opiates are partially independent from dopamine system (Hnasko *et al.*, 2005; Badiani *et al.*, 2011; Darcq & Kieffer, 2018).

Opioid receptors have distinct roles in reward processing. MORs mainly mediate natural rewards, and MOR agonists induce feelings of pleasure and euphoria, whereas κ-opioid receptor (KOR) activation mediates aversion and dysphoria and affects mood (Darcq &

Kieffer, 2018). Previous PET studies labeling MORs have rather coherently shown increased MOR binding irrespective of the drug of abuse in alcohol (Heinz *et al.*, 2005a; Williams *et al.*, 2009; Weerts *et al.*, 2011) cocaine (Zubieta *et al.*, 1996; Gorelick *et al.*, 2005) and opiate dependency in early abstinence (Williams *et al.*, 2007) (Table 1). Interestingly, a recent postmortem study found reduced MOR expression in alcohol-dependent subjects (Hermann *et al.*, 2017). The authors hypothesized that the previously observed increased MOR binding in [$^{11}$C]carfentanil PET scans in early abstinent alcoholics could have been due to acutely reduced levels of endogenous opioids rather than increased MOR expression. MOR expression was suggested to be reduced as a neuroadaptive consequence of increased endogenous opioid levels following alcohol consumption (Hermann *et al.*, 2017).

In healthy humans, pharmacological challenges using opioid agonists have led to reduced striatal D2R binding in [$^{11}$C]raclopride studies, reflecting dopamine release (Hagelberg *et al.*, 2002; Spreckelmeyer *et al.*, 2011). However, opioid agonist-induced dopamine release is lost in opiate-dependent subjects, which could play a role in the neurobiology of addiction (Daglish *et al.*, 2008; Watson *et al.*, 2014). This confirms the preclinical findings suggesting dopamine-independent neurocircuits in opioid-related rewards (Badiani *et al.*, 2011). There is also some evidence suggesting that alcohol-dependent subjects have blunted endogenous opioid responses to orally administered dextroamphetamine (Turton *et al.*, 2018), but the evidence supporting dopamine-induced opioid release in healthy controls is still mixed (Colasanti *et al.*, 2012; Guterstam *et al.*, 2013; Mick *et al.*, 2014). Naltrexone, an MOR antagonist, has been accepted as a treatment of alcohol dependence, but it has also been studied in the context of other substance addictions, and there are some promising results, for example, in stimulant-dependent patients (Aboujaoude & Salame, 2016). Whether the opioid system acts mainly via mesolimbic dopamine neurons or other neurocircuits remains to be established.

### *2.3.3 Serotonin*

In addition to dopamine and opioid systems, serotonin is also involved in reward processing (Daw *et al.*, 2002; Kranz *et al.*, 2010). Ventral and dorsal raphe nuclei are the main loci for brain serotonergic neurons. Efferent fibers from the raphe nuclei project to the NAcc, VTA, substantia nigra, hippocampus, amygdala and prefrontal cortex, among others (Dalley & Roiser, 2012). The connection between dorsal raphe nuclei and VTA is well established, and it has been reported that serotonergic neurons directly synapse onto VTA dopamine cells (Hervé *et al.*, 1987; Van Bockstaele *et al.*, 1994). Recent data have suggested that glutamate and serotonin coact in the projections from the raphe nuclei to the VTA (Liu *et al.*, 2014; McDevitt *et al.*, 2014; Qi *et al.*, 2014). Whether serotonin acts on reward processing throughout the mesolimbic dopamine system or mainly on its own

remains somewhat unclear. One interesting [$^{11}$C]raclopride PET study indicated decreased dopamine release in the putamen and parallel increased cocaine craving in non-dependent cocaine users following tryptophan depletion (Cox *et al.*, 2011).

In general, all drugs of abuse increase extracellular serotonergic levels after acute administration (Kirby *et al.*, 2011). Furthermore, stimulants and ethanol inhibit serotonergic neuronal activity by activating presynaptic inhibitory autoreceptors (Kirby *et al.*, 2011). Only acutely administered opioids seem to increase serotonin neuronal activity by inhibiting regulatory GABAergic interneurons and thus indirectly facilitating serotonin release (Jolas & Aghajanian, 1997; Tao & Auerbach, 2002). Extracellular serotonin levels decrease after withdrawal of cocaine, ethanol and opioids (Kirby *et al.*, 2011). Interestingly, animal models revealed increased impulsivity after cocaine withdrawal, highlighting the role of serotonergic balance in impulsivity (Winstanley *et al.*, 2009).

As there are over 10 distinct serotonin receptors, simple conclusions about the role of the single serotonin receptors in the functioning serotonin system are not easy to draw (Kirby *et al.*, 2011). 5-$HT_{1A}$ receptor binding has been found to be increased in prefrontal and anterior cingulate cortices in impulsive and aggressive subjects (Witte *et al.*, 2009) but is not altered in alcohol dependence (Martinez *et al.*, 2009). 5-$HT_{1B}$ receptor binding has been found to be reduced in alcohol-dependent subjects and in cocaine-dependent subjects (Hu *et al.*, 2010; Matuskey *et al.*, 2014). Further, studies targeting 5-$HT_{2A}$ and 5-$HT_{2C}$ receptors have shown opposing roles mediating impulsivity in animal models. A 5-$HT_{2A}$ antagonist infused into the NAcc appeared to decrease impulsivity, whereas a 5-$HT_{2C}$ antagonist increased impulsivity (Robinson *et al.*, 2008). Similarly, the ratio of these two receptors in the prefrontal cortex seems to correlate with motor impulsivity in animals (Anastasio *et al.*, 2015), but in healthy humans, self-reported impulsivity did not correlate with 5-$HT_{2A}$ binding (da Cunha-Bang *et al.*, 2013). MDMA and hallucinogen users show slightly decreased 5- $HT_{2A}$ binding in cortical regions (Erritzoe *et al.*, 2011).

SERT binding has been reported to be either increased, unchanged or decreased in different drug addictions. 3,4-methylenedioxymethamphetamine (MDMA) binds to monoamine transporters, especially SERT, and inhibits serotonin reuptake (Kirby *et al.*, 2011). Vast decreases in SERT binding have been reported in patients with MDMA addiction (McCann *et al.*, 2005; Erritzoe *et al.*, 2011; Roberts *et al.*, 2016). A postmortem study with methamphetamine users also found decreased SERT density in cortical regions (Kish *et al.*, 2009). However, both methamphetamine and MDMA have toxic effects on serotonergic neurons, so the reduced SERT density might reflect either a decreased number of serotonergic nerve terminals or a downregulation of SERT (Gross *et al.*, 2011; Kirby *et al.*, 2011; Vegting *et al.*, 2016). On the other hand, cocaine has been shown to increase SERT density in animal and human studies (Jacobsen *et al.*, 2000; Banks *et al.*, 2008). The role of SERT is particularly unclear in alcohol dependence, where one study has reported reduced SERT binding and others found no differences (Szabo *et al.*, 2004;

Brown *et al.*, 2007; Martinez *et al.*, 2009) (Table 1). Drugs targeting SERT have shown only modest effects in the treatment of alcohol dependence with comorbid depression, but no evidence of benefit in opioid dependence or cocaine dependence (Pani *et al.*, 2010; Pani *et al.*, 2011; Agabio *et al.*, 2018).

**Table 1.** Presynaptic dopamine synthesis, μ-opioid receptor (MOR) binding and serotonin transporter (SERT) binding in different drug addictions in human PET studies as compared to healthy controls. Only PET studies including alcohol, cocaine or opioid dependent subjects are presented.

| Target | Drug | Study | Tracer | Binding |
|---|---|---|---|---|
| **Presynaptic dopamine synthesis** | Cocaine | Wu *et al.*, 1997 | [$^{18}$F]fluorodopa | Decreased in the striatum |
| | Alcohol | Heinz *et al.*, 2005b | [$^{18}$F]fluorodopa | No differences |
| | Alcohol | Kienast *et al.*, 2013 | [$^{18}$F]fluorodopa | No differences |
| **MOR** | Cocaine | Zubieta *et al.*, 1996 | [$^{11}$C]carfentanil | Increased in the caudate nucleus, thalamus and anterior cingulate, frontal and temporal cortices |
| | Cocaine | Gorelick *et al.*, 2005 | [$^{11}$C]carfentanil | Increased in the anterior cingulate, frontal and temporal cortices |
| | Alcohol | Heinz *et al.*, 2005a | [$^{11}$C]carfentanil | Increased in the ventral striatum |
| | Alcohol | Williams *et al.*, 2009 | [$^{11}$C]diprenorphine | No differences, a trend towards increased binding in several regions |
| | Alcohol | Weerts *et al.*, 2011 | [$^{11}$C]carfentanil | Increased in the the cingulate cortex , insula and basal ganglia including the ventral striatum |
| | Opioids | Williams *et al.*, 2009 | [$^{11}$C]diprenorphine | Increased in the orbitofrontal cortex, a trend towards increased binding in several regions |
| **SERT** | Alcohol | Szabo *et al.*, 2004 | [$^{11}$C]McN5652 | Decreased in the midbrain |
| | Alcohol | Brown *et al.*, 2007 | [$^{11}$C]DASB | No differences |
| | Alcohol | Martinez *et al.*, 2009 | [$^{11}$C]DASB | No differences |

### *2.3.4 Other neurotransmitters*

Glutamate is the main excitatory neurotransmitter of the brain. It is thought to be involved in impulsive and addictive neurocircuits. Prefrontal glutamatergic neurons project to the VTA GABAergic neurons, and thus glutamatergic signaling from the PFC facilitates mesolimbic dopamine release (Gariano & Groves, 1988; Karreman & Moghaddam, 1996;

Carr & Sesack, 2000). It has been hypothesized that the impaired glutamatergic neurotransmission from the prefrontal cortex to the NAcc reduces one's ability to behaviorally adapt to new environmental stimuli, which in addiction models facilitates previously learned drug-seeking strategies (Kalivas, 2009). Indeed, cocaine administration has been shown to affect glutamate receptor densities in the striatum and midbrain (Pomierny-Chamiolo *et al.*, 2017). A study with [$^{11}$C]ABP688 PET targeting metabotropic glutamate type 5 receptors found increased receptor binding in multiple cortical regions and in the amygdala in cocaine users, whereas nicotine dependency was associated with globally decreased uptake (Akkus *et al.*, 2013; Akkus *et al.*, 2018).

Noradrenaline is a monoaminergic transmitter; thus, stimulants and cocaine also affect the brain noradrenaline system (Zaniewska *et al.*, 2015). Main noradrenergic nuclei are the locus coeruleus and lateral tegmental nuclei, and noradrenergic fibers innervate the forebrain, hippocampus, midbrain, amygdala and hypothalamus, among other regions (Weinshenker & Schroeder, 2007; Zaniewska *et al.*, 2015). In animal models, noradrenaline has been linked to several addiction-related behaviors, and further, the noradrenaline system is known to link to mesolimbic dopamine as locus coeruleus electrical stimulation leads to VTA dopamine burst firing (Weinshenker & Schroeder, 2007). Prazosin, an alpha-1 adrenergic receptor antagonist, administration resulted in elevated dorsal caudate D3 receptor binding, as measured with [$^{11}$C]PHNO PET, indicating reduced dopamine release after blockage of adrenergic receptors (Le Foll *et al.*, 2017). Prazosin also showed promising results for alcohol dependence in a randomized pilot study (Simpson *et al.*, 2009).

GABA is mainly an inhibitory neurotransmitter and interacts with various other neurotransmitter systems (Jolas & Aghajanian, 1997; Tao & Auerbach, 2002; Jalabert *et al.*, 2011). The role of GABAergic inhibition of mesolimbic dopamine neurons is robust and discussed above. In alcohol dependence, [$^{11}$C]Ro154513 PET may be used to image GABA-benzodiazepine receptors with special selectivity for GABA receptor subtype α5 (Lingford-Hughes *et al.*, 2012). Uptake of this tracer in the NAcc was reduced in alcohol-dependent subjects (Lingford-Hughes *et al.*, 2012). Additionally, benzodiazepine dependence has been shown to be associated with disinhibition of VTA dopaminergic neurons, which leads to dopamine release in the NAcc (Tan *et al.*, 2010). This dopaminergic effect is mediated by $GABA_A$ receptors: benzodiazepine-mediated activation of $GABA_A$ receptor-expressing VTA interneurons triggers drug-evoked synaptic plasticity (Tan *et al.*, 2010).

## 2.4 Neurobiology of behavioral addictions

As behavioral addictions are a relatively new concept, neuroimaging research is needed to confirm the similarities between substance addictions and behavioral addictions and to

compare the different phenotypes of behavioral addictions. Modern neuroimaging techniques have increased our understanding of neurobiological underpinnings in addiction disorders. As it is necessary to understand the basis of the molecular imaging techniques, I will briefly introduce the physical basis of positron emission tomography before continuing to review the current knowledge of the neurobiology of behavioral addictions, concentrating on molecular imaging findings.

### *2.4.1 Principles of positron emission tomography*

Positron emission tomography (PET) is a fine imaging technique to evaluate various physiologic processes *in vivo*. PET is noninvasive and thus enables detailed neuroreceptor and metabolic mapping of the living human brain. In PET imaging, biologically active molecules, termed ligands or tracers, are labeled with specific kinds of radioactive nuclei. These ligands are administered intravenously before PET imaging. The PET scanner measures radioactivity from the decaying nuclei of the PET ligands as a function of time, termed the time-activity curve (Lammertsma, 2002). The time-activity curve is then mathematically modeled to obtain quantitative values representing biological properties of the tissue.

The radioactive nuclei needed for PET imaging are produced using a cyclotron. Negative hydride ions are accelerated to a spiral path in a magnetic field of a cyclotron and then directed through a graphite foil, which captures electrons of accelerated ions. Graphite foil allows protons to pass to a target where they collide with stable isotopes, producing desired radioisotopes (Pichler *et al.*, 2018). Typical radioisotopes used in PET imaging include $^{11}$C and $^{18}$F. The half-life, i.e., the time needed for that half of the radioactive nuclides to decay, is 20.3 min for $^{11}$C and 110 min for $^{18}$F (Turkington, 2001). The desired radionuclides are then chemically bound to biological ligands to synthesize the desired radiotracer, traditionally using conventional heaters (Pichler *et al.*, 2018). Common ligands are glucose, different amino acids, ammonia and more complex biologically active molecules that target, for example, neuronal receptors (Pichler *et al.*, 2018).

The physical basis of positron emission relies on beta plus ($\beta^+$) decay. Inside the nucleus of the labile radioactive isotope, a proton (p) decays to a neutron (n), a positron ($e^+$) and an electron neutrino ($\upsilon$). Below, a schematic illustration where X is a parent nucleus, Y represents the daughter nucleus after decay, A represents the number of protons and neutrons together and Z is a number of protons in the nucleus is represented:

(1) $$p \rightarrow n + e^+ + \upsilon,$$

which is equivalent to

(2) $$^{A}_{Z}X \rightarrow {}^{A}_{Z-1}Y + e^+ + \upsilon.$$

After $\beta^+$ decay, an emitted positron loses its kinetic energy quickly in tissue medium and finally collides with an electron ($e^-$). As a result of the annihilation, two gamma photons ( $\gamma$ ) with 511 keV energy each are emitted in approximately opposite directions. This event is called annihilation (Figure 1). This can be shown schematically as follows:

(3) $e^+ + e^- \rightarrow \gamma + \gamma.$

PET scanners can detect annihilated gamma photons. PET scanners have multiple detectors organized in a rim shape. When a pair of photons with approximately 511 keV energy are detected almost simultaneously at any of two detectors in the detector ring, a coincidence event (true count) is registered. A line between these two detectors forms a line of response, as it is known that the radionuclide decay has occurred between these two detectors. Detection of a single photon without a simultaneous opposite photon is filtered as a false count. All coincidence events from all possible lines of response are collected either as a list mode or as a sinogram and then reconstructed to form a quantitative PET image.

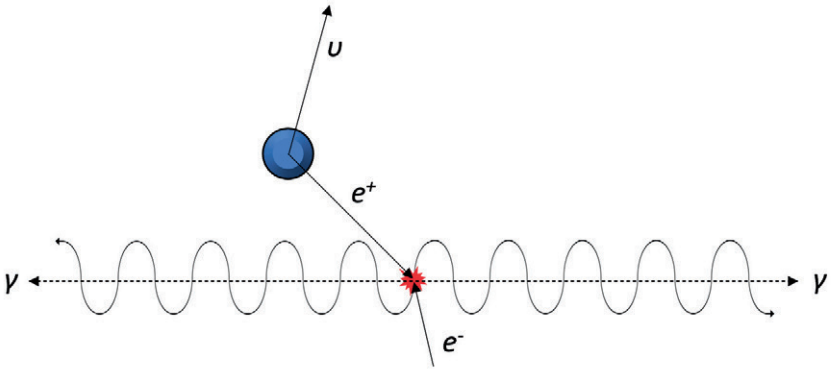


**Figure 1:** Annihilation. As a $\beta^+$ radioactive nucleus (blue) decays, it emits an electron neutrino (υ) and a positron ($e^+$). Collision between positron and tissue electron ($e^-$) is called an annihilation (red), and the energy of these two particles is freed as two gamma photons (γ) are emitted in opposite directions. Artwork by Joonas Majuri.

Mathematical models are needed to form and compare quantitative PET images. Compartmental models allow us to model tracer kinetics *in vivo.* Typically, a two-tissue compartmental model is used in PET pharmacokinetic modeling (Figure 2). Tracers administered intravenously are delivered within blood throughout the body and tissues, and a proportion of the tracer reaches its specific target receptors. In a particular tissue, total tracer concentration ($C_T$) consists partly of free tracer in the extracellular fluid ($C_F$), partly of specifically bound tracer to the specific molecular targets ($C_S$) and partly of nonspecifically bound tracer to the tissue matrix ($C_{NS}$). Nonspecifically bound and free fraction of

the radionuclides may be expressed together as nondisplaceable tracer concentration $C_{NB}$. This can be shown schematically as follows:

(4) $C_T = C_F + C_{NS} + C_S = C_{NB} + C_S$.

Radioligand concentration is often expressed as a ratio of plasma radiotracer levels and volumes of distribution (V). This can be shown as follows:

(5) $V_T = V_{NB} + V_S$.

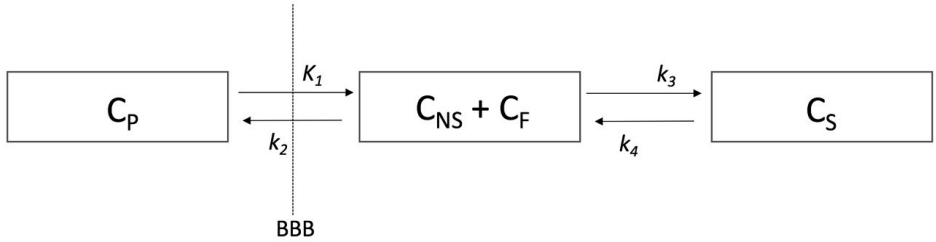


**Figure 2:** Schematic drawing representing the two-tissue compartmental model. At equilibrium, the rate constants $K_1$, $k_2$, $k_3$ and $k_4$ are stable, and the tracer concentrations in plasma ($C_P$), extracellular fluid ($C_F$), specific molecular targets ($C_S$) and tissue matrix ($C_{NS}$) are constant. BBB = blood-brain barrier. Modified from (Innis *et al.*, 2007)

At equilibrium, the radionuclide plasma concentrations, the nondisplaceable fraction of tracer concentration and the specifically bound tracer fraction are at steady state, where the rate constants $K_1$, $k_2$, $k_3$ and $k_4$ are stable. Importantly, these constant ratios equal equilibrium volumes (Innis *et al.*, 2007). In a two-compartmental model, this may be written as follows:

(6) $V_T = \frac{K_1}{k_2}\left(1 + \frac{k_3}{k_4}\right) = \frac{K_1}{k_2}\left(1 + \frac{B_{max}}{K_D}\right) = \frac{K_1}{k_2}(1 + BP_{ND})$,

where $B_{max}$ reflects the specific receptor density, $K_D$ dissociation constant and $BP_{ND}$ is the ratio of specific radiotracer binding relative to the nondisplaceable binding. If the tracer accumulates to the specific target tissue ($k_4$=0), the accumulation may be described using the net influx constant rate ($K_i$):

(7) $K_i = \frac{K_1 k_3}{k_2 + k_3}$.

Basically, PET imaging measures target tissue radioconcentration. Arterial plasma samples are often taken during PET imaging to determine plasma radiotracer concentrations, i.e., the input function. These variables are then applied to compute relevant distribution

volumes (Lammertsma, 2002). Computational reference region models allow the noninvasive estimations of nondisplaceable binding without measuring plasma radiotracer and radiometabolite concentrations (Lammertsma, 2002). In this thesis, the Patlak plot is used to estimate $K_i$ values and simplifies the reference tissue model (SRTM) to calculate $BP_{ND}$ values (Patlak & Blasberg, 1985; Gunn *et al.*, 1997).

PET is not the only way to investigate the human brain *in vivo*. Single-photon emission computed tomography (SPECT) is a method where radioactive tracers are also used, but unlike the PET tracer, SPECT tracers decay by sending only one γ photon. The SPECT scanner includes a collimator, which filters out indirectly radiating photons and allows only photons travelling almost directly through channels of the collimator. Photons passing through collimators are collected in scanner detectors. Both the collimator and detector rotate, allowing object examination and data collection from multiple directions. Generally, the signal-to-noise ratio and resolution are better in PET than in SPECT, and it is possible to obtain quantitative values from PET scanning, but SPECT has tracers with longer half-lives and less expensive scanning systems, making it more widely available (Lammertsma, 2002; Wernick & Aarsvold, 2004; Hutton, 2014).

### *2.4.2 Molecular imaging in gambling disorder*

Although dopamine D2/D3 deficits have been consistently observed across all substance addictions, several baseline PET studies have failed to replicate this finding in PG using either [$^{11}$C]raclopride or [$^{11}$C](+)PHNO (Linnet *et al.*, 2010; Clark *et al.*, 2012; Joutsa *et al.*, 2012a; Boileau *et al.*, 2013). In addition, some studies have suggested enhanced dopamine release in the striatum after exposure to a pharmacological or gambling stimulus (Joutsa *et al.*, 2012a; Boileau *et al.*, 2014). This again is in direct contrast to substance use disorders, which are associated with dramatically reduced striatal dopamine release (Martinez *et al.*, 2005; Martinez *et al.*, 2007; Martinez *et al.*, 2012).

Further evidence for the central model of dopamine in gambling disorder is provided by impulse control disorders in Parkinson's disease where dopaminergic medications can trigger behavioral addictions (Weintraub *et al.*, 2010). Acute dopamine agonist treatment has been shown to decrease both tonic and phasic dopamine firing in the dopaminergic neurons of VTA, possibly by activating D2R autoreceptors (Voon *et al.*, 2017). However, tonic firing normalizes during chronic dopamine agonist treatment, but phasic dopaminergic activity remains at a lower level, which is hypothesized to be a consequence of desensitization of D2R autoreceptors (Voon *et al.*, 2017). As novel rewarding stimuli, conditioned cues, positive prediction error and reward anticipation release striatal dopamine, dopaminergic medications may change the ability to learn from these stimuli-driven reactions and from negative prediction errors, predisposing Parkinson's disease patients to ICDs (Voon *et al.*, 2017). PET imaging studies have revealed that patients with ICDs

related to Parkinson's disease show decreased NAcc D2/3 receptor binding and enhanced striatal dopamine release after reward-related cues or during a gambling task (Steeves *et al.*, 2009; O'Sullivan *et al.*, 2011; Payer *et al.*, 2015; Stark *et al.*, 2018). Another vulnerable factor for ICDs may be reduced dopamine transporter concentration, which has been detected in SPECT studies in Parkinson's disease patients with ICDs, suggesting decreased dopamine uptake from the synaptic cleft (Cilia *et al.*, 2010; Voon *et al.*, 2014). Additionally, the presynaptic dopamine synthesis rate was normal in the striatum but increased in the medial OFC in Parkinson's disease patients with ICDs (Joutsa *et al.*, 2012b).

Opioid antagonists have shown some efficacy in treating PG (Kim *et al.*, 2001; Grant *et al.*, 2006). Therefore, it is somewhat surprising that only one previous PET study has investigated the brain opioid system in PG. Mick *et al*. found no difference in baseline MOR binding in a [$^{11}$C]carfentanil study but reported a blunted endogenous opioid release following oral amphetamine administration when compared to controls (Mick *et al.*, 2016). Similar blunted endogenous opioid release was found in subjects with alcohol dependence (Turton *et al.*, 2018).

Studies investigating brain neurotransmitter function in PG are relatively scarce. Single studies have probed serotonin and GABA systems in PG. Potenza *et al*. conducted a [$^{11}$C]P943 PET study and found that gambling symptom severity correlated with tracer accumulation in the ventral striatum and anterior cingulate cortex, even though no difference in the baseline serotonin 1B receptor binding was evident (Potenza *et al.*, 2013). Increased $GABA_A$ receptor binding has been reported in PG patients in the hippocampus using [$^{11}$C]Ro154513 PET (Mick *et al.*, 2017). In this study, impulsivity scores correlated with tracer uptake in the nucleus accumbens, hippocampus and amygdala in the PG group but not in healthy controls. The glucose metabolic rate, as measured with [$^{18}$F]FDG, has been reported to be elevated in the orbitofrontal and medial frontal cortices and decreased in the ventral segments of the striatum, but all subjects included in this trial had a history of bipolar disorder, which confounded the results (Hollander *et al.*, 2008; Pallanti *et al.*, 2010).

In conclusion, previous PET imaging studies in PG have found that mesolimbic dopamine release, blunted endogenous opioid release after dopaminergic stimulation, and increased $GABA_A$ binding are related to gambling disorder. Previous studies have concentrated mostly on postsynaptic dopamine function, and little is known about presynaptic dopamine function as well as other neurotransmitters, for example, the role of different serotonin receptors and serotonin transporters.

### *2.4.3 Molecular imaging in other behavioral addictions*

An important feature links binge eating disorder to gambling disorder: both may be expressed as a side effect of dopamine agonist treatment for Parkinson's disease (together with hypersexuality and compulsive shopping) (Weintraub *et al.*, 2010). To date, only one study has investigated the dopamine system in BED using PET. In this study, BED was associated with greater dopamine release in the caudate nucleus after exposure to food stimuli and oral methylphenidate (Wang *et al.*, 2011). Dopamine D2/D3 receptor binding did not differ significantly between BED patients and obese control subjects at baseline, although BED patients had higher trend-level $BP_{ND}$ values in the striatum (Wang *et al.*, 2011). This is in line with PET studies with PG where enhanced dopaminergic responses are reported, but interestingly, contrasts with bulimia nervosa, where amphetamine challenge leads to blunted dopamine responses in the putamen without significant baseline differences in D2R density (Broft *et al.*, 2012). Animal studies in BED have found increased MOR density and decreased D1R density in the striatum (Heal *et al.*, 2017).

SPECT studies targeting SERT have shown conflicting results: an [$^{123}$I]β-CIT study found reduced SERT binding in the midbrain and that this downregulation recovered after a group psychotherapy and fluoxetine treatment, whereas an [$^{123}$I]ADAM study with six patients with night eating syndrome found increased uptake in the midbrain (Kuikka *et al.*, 2001; Tammela *et al.*, 2003; Lundgren *et al.*, 2008). A [99mTc]ethyl-cysteine-dimer SPECT study found elevated prefrontal responses to food cues compared to obese and nonobese controls (Karhunen *et al.*, 2000).

Molecular imaging studies of other behavioral addictions are scarce. There are discrepancies in diagnostic criteria applied, and as relatively new disorders, only few studies have concentrated on molecular imaging of these conditions. Similar to eating and gambling, computer game playing has also been demonstrated to release dopamine in the striatum (Weinstein, 2010). This particular study was performed with [$^{123}$I]IBZM SPECT at baseline and after computer game playing. Another study with [$^{11}$C]raclopride found that subjects with Internet use disorders have reduced tracer uptake in the dorsal caudate; however, the study included only five subjects with Internet use disorder (Kim *et al.*, 2011). Furthermore, reduced glucose metabolism in the orbitofrontal regions has been linked to reduced D2R and 5HT2A ligand [$^{11}$C]NMSP uptake in the striatum in a dual-tracer PET study (Tian *et al.*, 2014). There are no published studies investigating compulsive sexual behavior using PET or SPECT (Kraus *et al.*, 2016) or in compulsive shopping.

### 2.4.4 Overview of fMRI studies in addictions

Functional magnetic resonance imaging (fMRI) is another method that is used to study the human brain *in vivo*. fMRI measures cerebral blood oxygenation levels and thus activation and deactivation patterns in the brain during different stimuli (Cacace *et al.*, 2000). The temporal resolution of fMRI is superior to molecular imaging techniques, but unlike PET and SPECT, fMRI does not recognize the underlying neurotransmitters. As fMRI does not require exposing subjects to radiation and is a less expensive method, it has been more widely used to investigate the human brain. Thus, the literature concerning fMRI studies in addictions and relationships between molecular and fMRI neuroimaging studies should be discussed briefly.

In general, substance addictions are related to decreased striatal activation during reward anticipation but increased ventral striatal activity during reward outcomes (Luijten *et al.*, 2017). Similar to substance addictions, the PG patients also showed decreased striatal activity related to reward anticipation, but in contrast to people with substance addictions, they showed decreased striatal responses during the reward outcomes (Reuter *et al.*, 2005; Balodis *et al.*, 2012; Luijten *et al.*, 2017). Luijten *et al*. found that the blunted response to reward outcomes was related to activity in the dorsal striatum and proposed that the difference between people with substance addictions and PG in monetary fMRI tasks may partially arise from the fact that monetary gambling is the core feature in PG, while substance-addicted individuals have other drivers of addictive behavior.

Further evidence about the role of the striatum was provided by a slot-machine fMRI study that showed enhanced NAcc responses to near misses in PG (Sescousse *et al.*, 2016). However, altered striatal responses are not only observed in PG fMRI studies. Hypoactivation of ventrolateral PFC has been observed in probabilistic reversal-learning task experiments in which PG patients had been compared to nicotine-dependent and cocaine-dependent subjects (de Ruiter *et al.*, 2009; Verdejo-Garcia *et al.*, 2015). Insular activity was also reduced in a monetary fMRI task in people with PG (Balodis *et al.*, 2012), and interestingly, PG patients with insular damage had a reduced tendency to engage in the gambler's fallacy and reduced motivational responsiveness to near misses, whereas subjects with lesions in the amygdala or ventromedial PFC did not show this pattern (Clark *et al.*, 2014).

Similar to substance addictions, alterations in reward processing networks have been established in BED. Enhanced OFC and ventral striatal responses to food pictures are detected in BED patients compared to responses in normal-weighted controls, obese controls and subjects with bulimia nervosa (Schienle *et al.*, 2009; Weygandt *et al.*, 2012; Lee *et al.*, 2017). BED patients showed decreased ventral activity during anticipatory phases

in a monetary reward/loss task compared to activity in obese controls, whereas no differences were detected between BED subjects and lean control subjects (Balodis *et al.*, 2013). After recovery, this activation pattern appeared to normalize (Balodis *et al.*, 2014).

As fMRI measures changes in cerebral blood oxygenation levels, the neurotransmitters associated with detected hemodynamic responses remain elusive. One study found a relationship between midbrain fMRI signals and NAcc dopamine release during reward anticipation and outcome phases in a sample of healthy subjects who completed a delayed monetary incentive task during both [$^{11}$C]raclopride PET and fMRI scans (Schott *et al.*, 2008). Dopamine-related drugs have been shown to modulate fMRI reward prediction error signals in the striatum in healthy subjects (Pessiglione *et al.*, 2006), but sulpiride, a dopamine receptor antagonist, did not modulate ventral striatal responses to near misses either in healthy subjects or in PG patients (Sescousse *et al.*, 2016). Molecular imaging studies are thus needed to further investigate the underlying neurotransmitters in behavioral addictions.

# 3 AIMS OF THE STUDY

The main objective of this study was to investigate brain opioid, dopamine and serotonin neurotransmission in people with two different behavioral addictions: in patients with gambling disorder and patients with binge eating disorder. The principal analysis method was positron emission tomography targeting these three neurotransmitters. The specific aims for each substudy were as follows:

I: To compare [$^{11}$C]carfentanil binding to brain μ-opioid receptors and dopamine synthesis rate, measured with [$^{18}$F]fluorodopa, between patients with pathological gambling, binge eating disorder and healthy controls

II: To compare [$^{11}$C]MADAM binding to brain serotonin transporter between patients with pathological gambling, binge eating disorder and healthy controls

III: To investigate links between brain dopamine and opioid systems in healthy individuals and to characterize whether this interaction is altered in pathological gambling

IV: To investigate the relationships between impulsivity and brain μ-opioid receptor binding, dopamine synthesis rate and serotonin transporter density in healthy individuals and to characterize whether these interactions are altered in pathological gambling.

# 4 MATERIALS AND METHODS

All studies were conducted according to the principles of the Declaration of Helsinki. The local ethics committee reviewed and approved the study protocols. All subjects signed an informed written consent form.

## 4.1 Subjects

An overview of the practical steps of the study is presented in a Figure 3 on page 37. The subjects were partly recruited from a previous study performed at the Finnish National Institute of Health and Welfare and partly using advertisements in newspapers and websites related to gambling or binge eating. The exclusion criteria are listed below:

- Evidence of clinically significant cardiovascular, renal, hepatic, hematological, gastrointestinal, pulmonary, endocrinological or neurological disease
- Evidence of alcohol or substance use disorder within the last 6 months
- Intoxication or recent (less than 36 hours) drug or alcohol usage
- Body weight > 180 kg (scanner limit)
- Strong susceptibility to allergic reactions or nausea
- Blood donation within 60 days prior to the study
- Prior PET study exposure
- Any contraindication to magnetic resonance imaging
- Coffee or tea consumption within the last 12 hours prior to the study
- Current pregnancy
- Other current psychiatric DSM-IV Axis-I disorder

The screening protocol included clinical interviews, blood samples (blood count, liver function, blood sugar values, creatinine, qualitative urine drug screen and an additional qualitative pregnancy test for women), Alcohol Use Disorders Identification Test (AUDIT) questionnaire, Binge Eating Scale (BES), South Oaks Gambling Screening (SOGS) and an anamnestic form for MR imaging (Gormally *et al.*, 1982; Lesieur & Blume, 1987; Babor *et al.*, 2001). During the clinical interview, the diagnosis of BED/PG, according to the DSM-IV, was confirmed, and for the healthy controls, the absence of symptoms related to gambling problems or binge eating was confirmed. A total of 67 subjects were screened for the study. Timing problems excluded thirteen subjects for participating in the study. Four subjects did not fulfill the diagnostic criteria for PG or BED, three showed evidence of current alcohol abuse, and two subjects met criteria for a current DSM IV axis I psychiatric disorder. Six subjects were excluded due to other reasons. Therefore, our final sample consisted of 39 subjects (17 healthy controls, 15 PG, and 7 BED patients). None of these subjects used medications targeting brain dopamine or opioid systems. One PG patient used citalopram for mild anxiety symptoms but was allowed to enter the study after a five-day period of abstinence. This particular subject was excluded from the [$^{11}$C]MADAM analysis.

All subjects were asked to complete the following questionnaires: Beck Depression Inventory (BDI), Yale Food Addiction Scale, The Dutch Eating Behavior Questionnaire (DEBQ) and 11th version of Barratt Impulsiveness Scale (BIS-11) (BECK *et al.*, 1961; Wardle, 1987; Patton *et al.*, 1995; Beck *et al.*, 1996; Gearhardt *et al.*, 2009; Stanford *et al.*, 2009). Additionally, subjects' eating, gambling and smoking habits were asked about in detail.

## 4.2 Radiochemistry

The tracers [$^{11}$C]carfentanil, [$^{11}$C]MADAM and [$^{18}$F]fluorodopa were applied in this study. [$^{11}$C]carfentanil is a selective MOR agonist. MORs are found throughout various brain regions (Pfeiffer *et al.*, 1982), with the highest levels of [$^{11}$C]carfentanil binding in the basal ganglia and thalamus and intermediate levels of binding in the frontal and parietal cortices (Frost *et al.*, 1985). As an agonist, internalization of a ligand-MOR complex may occur with [$^{11}$C]carfentanil administration (Sternini *et al.*, 1996). A recent animal study showed that 92–94% of the [$^{11}$C]carfentanil signal arises from plasma membrane MORs, but the signal is partly affected by endocytosis of ligand-receptor complexes and a reduced affinity of internalized MORs (Quelch *et al.*, 2014). [$^{11}$C]MADAM is a selective SERT inhibitor with high uptake in the raphe nuclei, striatum, hippocampus and cingulate gyri (Lundberg *et al.*, 2005). The distribution of these high-affinity binding sites are in line with postmortem data (Laruelle *et al.*, 1988; Bäckström *et al.*, 1989). [$^{18}$F]fluorodopa (6-[$^{18}$F]fluoro-$_{L}$-dopa) is a radiolabeled precursor of endogenous dopamine, analogous to levodopa, which is transported into neural cells by membrane transporters, converted into active dopamine by aromatic $_{L}$-amino acid decarboxylase and stored in the synaptic vesicles (Brown *et al.*, 1999). Thus, [$^{18}$F]fluorodopa may be used to illustrate dopamine synthesis capacity, and for example, reduced binding is observed in Parkinson's disease following a loss of nigrostriatal dopamine fibers (Kaasinen & Vahlberg, 2017). [$^{18}$F]fluorodopa accumulates mainly in the striatal regions with a high density of dopamine neurons, but the signal may arise from other monoaminergic neurons from extrastriatal regions because [$^{18}$F]fluorodopa uptake may also occur in noradrenergic and serotonergic neurons (Brown *et al.*, 1999).

The production of all three radioligands has been described in detail previously (Halldin *et al.*, 2005; Forsback *et al.*, 2009; Hirvonen *et al.*, 2009). Tracer production was performed in the Turku PET Centre and followed the EU GMP regulations. [$^{11}$C]Methane was produced with the cyclotron and used as a precursor for [$^{11}$C]methyl triflate. Methylation of desmethyl carfentanil and desmethyl MADAM was performed with [$^{11}$C]methyl triflate to produce [$^{11}$C]carfentanil and [$^{11}$C]MADAM. [$^{18}$F]fluorodopa was produced via the electrophilic radiofluorination technique. Radiochemical purity was over 95% in all production runs. At the time of injection, the mean specific activity of [$^{11}$C]carfentanil

was 590 GBq/μmol (SD 290 GBq/μmol). For [$^{18}$F]fluorodopa, the mean specific activity exceeded 5 GBq/μmol. For [$^{11}$C]MADAM, the mean specific activity was 395 GBq/μmol (SD 130 GBq/μmol).

## 4.3 PET protocol

We used the High Resolution Research Tool (HRRT; Siemens Medical Solutions, Knoxville, TN, USA) for PET imaging. HRRT reaches almost isotropic 2.5 mm intrinsic spatial resolution (de Jong *et al.*, 2007). The scans were performed in 3D mode with scatter correction. For attenuation corrections, a transmission scan with a rotating 137-Cs rotating point source was performed before each dynamic scan. To reduce head movements during scanning, individually shaped thermoplastic masks were applied. Furthermore, a stereotaxic infrared camera (Polaris Vicra, Northern Digital, Waterloo, Canada) registered head movements during scanning. Four [$^{18}$F]fluorodopa scans and three [$^{11}$C]MADAM scans were carried out using a Velcro strap instead of the thermoplastic mask.

All three PET scans were conducted in the same day. Scans were performed at fixed intervals, and regular hospital lunch was served between the [$^{11}$C]carfentanil and [$^{11}$C]MADAM scans ([$^{11}$C]carfentanil scan at 0900–1000 hours, lunch at 1100–1200 hours, [$^{11}$C]MADAM scan at 1200–1300 hours and [$^{18}$F]fluorodopa scan at 1430–1530 hours). Due to scanner malfunction or tracer production failure, one [$^{11}$C]carfentanil scan and three [$^{18}$F]fluorodopa scans were performed on a separate day. The [$^{11}$C]carfentanil scans consisted of 13 frames (3 x 1 min, 4 x 3 min, 6 x 6 min), [$^{18}$F]fluorodopa scans were divided into 22 frames (4 x 1.5 min, 2 x 2 min, 16 x 5 min) and [$^{11}$C]MADAM included 19 frames (3 x 1 min, 4 x 3 min, 10 x 6 min and 2 x 7.5 min). The subjects were not allowed to sleep during [$^{11}$C]carfentanil scanning (Li & van den Pol, 2008).

T1-weighted MR images were registered on a separate day using a PET-MRI scanner (Philips Ingenuity; Philips Healthcare, Cleveland, OH, USA). MRI scanning was performed using both a 34-channel receiving head coil and a sagittal 3D T1-weighted TFE sense pulse sequence (TR 8.1 ms, TE 3.7 ms, flip angle 7°, matrix 256 × 256, 176 slices) with an isotropic voxel.

## 4.4 Image preprocessing

Image preprocessing steps are briefly summarized in Figure 3. At first, dynamic DICOM files were converted to Nifti format using Statistical Parametric Mapping (SPM8) program run on MATLAB R2012a (MathWorks, Natick, MA, USA). Motion correction was also performed using SPM8. Parametric PET images were realigned frame to frame, and the fourth frame of the [$^{11}$C]carfentanil dynamic image was used as a reference frame.

For one HC subject who lacked an appropriate [$^{11}$C]carfentanil scan, a fourth frame of [$^{11}$C]MADAM scanning was used as a reference frame. According to motion data during scanning, there were a total of ten scans in which the intraframe head movement was excessive. For these ten scans and 5 subjects, individual reconstructions were made using an in-house method (Johansson *et al.*, 2016).

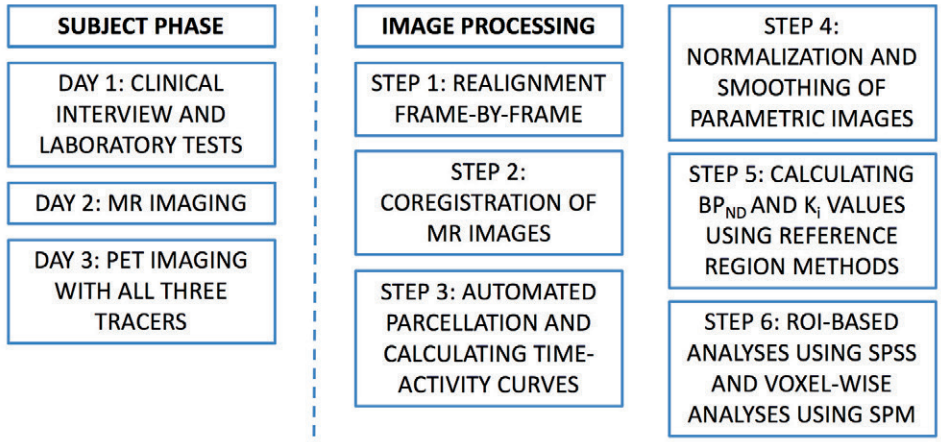


**Figure 3:** an overview of the study's subject phase and data preprocessing steps. Artwork by Joonas Majuri.

The dynamic PET image frames were realigned and coregistered to the individual T1-weighted MR images as reference images. Modeling of the voxelwise time-activity curves to calculate the parametric PET images was performed in the native space. Individual T1-weighted images were segmented and normalized to MNI 152 space using SPM default tissue probability maps (TPMs). Normalization of the parametric PET images was performed using the deformation fields obtained from the normalization of the T1-weighted MR images. The final voxel size in the parametric images was 1.5 x 1.5 x 1.5 mm. Normalized parametric images were smoothed with 8 mm Gaussian kernel with full width at half maximum.

Parallel to the voxel-by-voxel analysis, anatomical regions of interest (ROIs) analyses were also carried out. ROIs were defined for each individual using automated parcellation implemented in FreeSurfer software (version 5.3.0, http://surfer.nmr.mgh. harvard.edu/) using T1-weighted MR images (Fischl *et al.*, 2002; Desikan *et al.*, 2006). Seven subcortical regions included in the analysis were the thalamus, caudate nucleus, globus pallidus, putamen, nucleus accumbens, amygdala and hippocampus. We also included all cortical regions described by software developers (Desikan *et al.*, 2006). Each ROI time-activity curve was determined by calculating an average time-activity curve from all the voxels included in a single ROI. A simplified reference tissue model (SRTM) was applied to calculate $BP_{ND}$ values for the tracers [$^{11}$C]carfentanil and [$^{11}$C]MADAM, whereas

[$^{18}$F]fluorodopa influx constant rates ($K_i$ values) were calculated using a Patlak plot (Patlak & Blasberg, 1985; Gunn *et al.*, 1997). The occipital cortex (OCC) was used as a reference region for [$^{11}$C]carfentanil and [$^{18}$F]fluorodopa because there is negligible or no specific tracer binding for these tracers in that region (Hoshi *et al.*, 1993; Takikawa *et al.*, 1994; Vingerhoets *et al.*, 1996; Endres *et al.*, 2003). Similarly, the cerebellar cortex was designated as the reference region for [$^{11}$C]MADAM (Lundberg *et al.*, 2005).

## 4.5 Statistics

### *4.5.1 Demographic data*

The demographic data and questionnaire data were analyzed with SPSS software (IBM SPSS Statistics, version 22, Armonk, NY, USA). Group differences were investigated using a one-way analysis of variance (ANOVA) model for continuous variables and $\chi 2$ tests for categorical variables. Within-group correlations between gambling behavior symptom severity (SOGS, DSM-IV symptoms, gambling euros per week, gambling hours per week, and BDI) and different dimensions of trait impulsivity were calculated with Spearman rank correlation coefficients.

### *4.5.2 Studies I and II*

In Studies I and II, PET radioligand uptake was compared across all three groups. Both an anatomical ROI-based approach and a voxel-by-voxel approach were performed. ROI-based analyses were calculated with SPSS software (IBM SPSS Statistics, version 22, Armonk, NY, USA). [$^{11}$C]carfentanil and [$^{11}$C]MADAM $BP_{ND}$ values and [$^{18}$F]fluorodopa $K_i$ values were compared between groups using a one-way ANOVA model. With [$^{18}$F]fluorodopa, analyses were restricted to the subcortical nuclei (thalamus, caudate nucleus, globus pallidus, putamen, nucleus accumbens, amygdala and hippocampus) because the cortical binding of this tracer is low (Martin *et al.*, 1989). For the [$^{11}$C]-labeled tracers, analyses were also run in all cortical ROIs. To account for problems with multiple comparisons, p-values less than 0.01 were considered statistically significant, and Bonferroni correction was applied for *post hoc* analyses. To account for the possible confounding factors, analyses were replicated separately for female and nonsmokers only. The relationship between tracer binding and questionnaire data was investigated using Spearman rank order correlation coefficients for each group separately. These analyses were repeated with GLM to account for confounding factors, such as BMI and depression.

Similar analyses were also run voxel-by-voxel using SPM8. The between-group differences were approached using a general linear model, and analyses were performed across the whole brain volume. For multiple comparisons, cluster-level familywise error p-values ($p_{FWE}$) were applied with a cluster-forming threshold of $p<0.01$, and statistical significance was reached at the level of $p_{FWE}$ less than 0.05.

### *4.5.3 Study III*

In study III, we investigated whether [$^{18}$F]fluorodopa uptake may be intraregionally related to [$^{11}$C]carfentanil binding. Fifteen healthy controls and 13 PG patients were included, as they had successfully completed both scans. We also investigated the intraregional correlations between [$^{18}$F]fluorodopa and [$^{11}$C]MADAM to test the specificity of the possible dopamine-opioid interaction. [$^{11}$C]MADAM data were missing from one PG patient. BED patients were not included because of the small sample size. The results were calculated using both ROI and voxelwise methods. The analyses were restricted to only subcortical brain regions, including the amygdala, caudate nucleus, globus pallidus, hippocampus, nucleus accumbens, putamen, and thalamus, because of the poor signal-to-noise ratio of cortical [$^{18}$F]fluorodopa uptake (Martin *et al.*, 1989). ROI-based results were calculated using SPSS, version 22, as in Studies I and II. General linear model (GLM) was applied, [$^{18}$F]fluorodopa uptake was used as a dependent variable, and group status, [$^{11}$C]carfentanil $BP_{ND}$ values were included as covariates. The model assumptions were investigated by visually inspecting the normality of the variables and model residuals and by Levene's test, which was significant in the putamen ($p=0.03$) and caudate nucleus ($p=0.04$). The results were confirmed by adding Beck Depression Inventory scores and smoking status to the model as covariates. Additionally, within-group correlations were calculated using Spearman rank correlation coefficients. Bonferroni-corrected p-values less than 0.05 were considered significant. The correlations between [$^{18}$F]fluorodopa and [$^{11}$C]MADAM were investigated using identical analyses.

The intraregional correlations were also calculated voxel-by-voxel. VoxelStats MATLAB package (Mathotaarachchi *et al.*, 2016) was used to define the voxel-by-voxel comparison of two independent parametric data sets. That is, correlations were calculated independently within each voxel using GLM, and correction for multiple comparisons was based on random field theory with a cluster-forming threshold at $p < 0.001$. Search volume was restricted using a mask created using the Human Atlas AAL library in WFU Pick Atlas toolbox (Maldjian *et al.*, 2003). Analyses were restricted to the basal ganglia, amygdala, hippocampus and thalamus, as well as all brain areas showing [$^{18}$F]fluorodopa $K_i$ values greater than 0.005. The GLM model was identical to the ROI-based approach, with [$^{18}$F]fluorodopa $K_i$ as the dependent variable and group status and [$^{11}$C]carfentanil

$BP_{ND}$ as the independent variables. FWE-corrected p-values less than 0.05 were considered significant.

### *4.5.4 Study IV*

In study IV, correlations between self-reported impulsivity, as measured with the BIS-11, and [$^{18}$F]fluorodopa, [$^{11}$C]MADAM and [$^{11}$C]carfentanil uptake were calculated (Patton *et al.*, 1995). In this study, only PG patients and healthy controls were included, as the group size for BED was too small to make reliable conclusions about the correlations. BIS-11 measures three different traits of impulsivity: attention (inability to focus attention or concentrate), motor (acting without thinking) and nonplanning (lack of futuring or forethought) impulsivity (Patton *et al.*, 1995; Stanford *et al.*, 2009). A BIS-11 total score of 72 or more is generally considered impulsive (Stanford *et al.*, 2009). As one PG patient did not complete the BIS-11 questionnaire at all, this particular subject was removed from this analysis. One PG subject had one missing answer in the BIS-11 nonplanning section, and this answer was replaced with an average value. Considering that there were PET scans failures, the final sample in this analysis consisted of 14 PG patients for the [$^{11}$C]carfentanil analyses, 13 PG patients for the [$^{11}$C]MADAM and [$^{18}$F]fluorodopa analyses and 16 HC subjects for all tracers.

Statistical analyses were run on updated versions of SPM and SPSS. SPM12 was run on MATLAB R2016a (MathWorks, Natick, MA, USA), and SPSS version 25 was applied (IBM SPSS Statistics, Armonk, NY, USA). The primary statistical method in study IV was the voxel-by-voxel approach. Analyses were restricted to the basal ganglia, midbrain, cingulate cortex, orbitofrontal cortex and prefrontal cortex for their relevance in impulsivity (Korponay *et al.*, 2017) except in the case of [$^{18}$F]fluorodopa, where the analyses were restricted to subcortical regions (Martin *et al.*, 1989). The associations between dimensions of impulsivity and tracer uptake were investigated using multiple regression separately in both groups, with cluster-level FWE-corrected p-values less than 0.05 considered statistically significant. Parallel ROI-based analyses were performed in predefined anatomical regions where the voxel-by-voxel analysis revealed significant correlations between tracer uptake and impulsivity. Spearman correlation coefficients were calculated separately for both groups. Furthermore, GLM with group and impulsivity as covariates and tracer uptake as the dependent variable was performed, and the interaction term group x impulsivity score was included in the model. Additionally, considering the importance of the striatal dopamine system in impulsivity, the same predefined ROIs where the voxelwise analysis revealed differences were used to calculate possible associations between [$^{18}$F]fluorodopa binding in the NAcc, caudate nucleus and putamen. Striatal [$^{18}$F]fluorodopa uptake was explained with a model including tracer uptake in a

particular predefined ROI, group status and their interaction. P-values less than 0.05 were considered statistically significant.

As predefined FreeSurfer ROIs did not include VTA ROIs, the Marsbar toolbox was used to extract VTA [$^{11}$C]carfentanil $BP_{ND}$ values from unsmoothed parametric images using a previously published VTA binary mask (Brett *et al.*, 2002; Pauli *et al.*, 2018). One PG patient showed no specific VTA MOR binding, and therefore ROI analyses were confirmed by excluding this subject. Further, [$^{11}$C]carfentanil $BP_{ND}$ values were extracted also from the substantia nigra to investigate the specificity of the midbrain [$^{11}$C]carfentanil binding.

### *4.5.5 Considerations of statistical methods*

As described above, both ROI-based analyses and voxel-by-voxel analyses were performed in each study. These methods were complementary to each other. Considering the small sample sizes, the use of two distinct methods strengthens the liability of the results. The ROI-based approach has been widely used in previous molecular imaging studies and thus warranted. However, a total of 41 cortical and subcortical ROIs were defined, thus increasing the possibility of false positive findings. Another limitation was the predefined borders of the ROIs. The utility of the voxel-by-voxel approach lies in the capability to detect signals anywhere in the limits of search volume, which also enables cluster detection between distinct ROIs. Additionally, conservative FWE corrections were used to minimize the risk of false positives in the voxel-by-voxel analyses.

Spearman rank correlation coefficients were used in each study instead of Pearson correlation coefficients as Pearson correlations are more prone to single deviant values in small samples.

# 5 RESULTS

## 5.1 Demographic data

The main demographic features of the studied subjects are presented in Table 2. The studied groups did not differ in terms of age and alcohol consumption. The BED group had a higher proportion of women, but there were no differences in the sex ratio between the PG patients and controls (Table 2). The BED patients weighed more than the PG patients and controls, but the PG patients weighed as much as the controls (Bonferroni-corrected *post hoc* p = 1.00). Smoking appeared to be more common in the PG group than in the other subgroups (Table 2). Both patient groups were more depressed compared to controls, but the PG and BED patients did not show differences in BDI scores (Table 2).

**Table 2.** The demographic characteristics of the subjects. Values are means (SD) or n. [1]One-way ANOVA or chi-square test. BMI= body mass index, BDI= Beck Depression Inventory, AUDIT= Alcohol Use Disorders Identification Test. For *post hoc* tests, a Bonferroni correction was applied to continuous variables, whereas independent Fisher's exact test analyses were applied in the case of sex and smoking. Modified from study I.

| | **HC** | **PG** | **BED** | **P-value[1]** | ***Post hoc* tests** | | |
|---|---|---|---|---|---|---|---|
| | | | | | C vs PG | C vs BED | PG vs BED |
| **N** | 17 | 15 | 7 | | | | |
| **Age (years)** | 43.3 (11.1) | 42.6 (11.8) | 49.4 (5.1) | 0.35 | 1.00 | 0.62 | 0.51 |
| **Sex (m/f)** | 8/9 | 8/7 | 0/7 | 0.048 | 1.00 | 0.05 | 0.022 |
| **BMI (kg/m$^2$)** | 24.8 (2.1) | 25.4 (3.6) | 30.9 (6.6) | 0.003 | 1.00 | 0.003 | 0.01 |
| **Smoking (y/n)** | 7/10 | 11/4 | 2/5 | 0.08 | 0.09 | 0.67 | 0.07 |
| **BDI** | 2.8 (3.1) | 14.4 (7.8) | 15.4 (9.6) | <0.001 | <0.001 | <0.001 | 1.00 |
| **AUDIT** | 5.4 (3.3) | 5.9 (4.0) | 3.3 (1.1) | 0.23 | 1.00 | 0.51 | 0.29 |

As expected, the PG patients scored high on gambling-related questionnaires, whereas the BED patients scored higher on eating-related questionnaires (Table 3). Five PG subjects (33%) reported that their favorite gambling form was slot machines, whereas three PG subjects (20%) preferred poker, another three subjects preferred lottery and four subjects (26%) preferred other forms of gambling or said that they do not have a favorite gambling form. However, 8 out of 15 subjects (53%) reported that their last played game was on a slot machine. Interestingly, the PG patients scored higher on the motor and nonplanning subscales of the Barratt Impulsiveness Scale compared to the controls (Bonferroni-corrected *post hoc* p-values $\leq 0.001$), whereas self-reported impulsivity was similar in the HC and BED groups (Table 3). There were no group differences in the atten-

tional impulsivity subscale. *Post hoc* analysis revealed that the PG patients and BED patients differed in terms of motor impulsivity (p = 0.004), whereas there was no group difference in terms of nonplanning impulsivity (p = 0.45). Nonplanning impulsivity score and SOGS scores correlated in the PG group (r=0.74, p=0.002). No other correlations with PG symptom severity and self-reported impulsivity were detected.

**Table 3.** Differences between participant groups in gambling, eating and impulsivity. Questionnaire data from the Yale Food Addition Scale, DEBQ and BIS-11 are missing for one PG patient. [1]One-way ANOVA. PG DSM-IV = DSM-IV diagnostic criteria for pathological gambling, SOGS = South Oaks Gambling Screen, DEBQ = The Dutch Eating Behavior Questionnaire. Modified from Studies I and IV.

| Behavior | Item | Control | PG | BED | P-value[1] |
|---|---|---|---|---|---|
| **Gambling** | PG DSM-IV | 0.1 (0.3) | 7.3 (1.4) | 0 (0) | <0.001 |
| | SOGS | 0.1 (0.3) | 13.3 (2.3) | 0.4 (0.5) | <0.001 |
| | Duration of problem gambling (years) | 0 (0) | 11.6 (7.3) | 0 (0) | <0.001 |
| | Gambling per week (€) | 3.9 (7.4) | 152 (149) | 2.9 (4.6) | <0.001 |
| | Gambling per week (hours) | 0.5 (1.2) | 8.7 (7.2) | 0.5 (1.2) | <0.001 |
| | Gambling debt (€) | 0 (0) | 18000 (15600) | 0 (0) | <0.001 |
| **Eating** | Binge Eating Scale | 2.1 (2.1) | 4.4 (4.4) | 30.9 (4.6) | <0.001 |
| | Yale food addiction scale | 5.4 (3.4) | 9.1 (9.5) | 42.3 (6.5) | <0.001 |
| | DEBQ emotional | 20.5 (5.0) | 21.2 (8.7) | 50.0 (8.3) | <0.001 |
| | DEBQ external | 23.7 (5.3) | 26.1 (7.3) | 37.5 (6.3) | <0.001 |
| | DEBQ restrained | 24.8 (6.8) | 20.9 (10.6) | 35.3 (3.4) | 0.002 |
| | Duration of problem eating (yrs) | 0 (0) | 0 (0) | 18.1 (14.9) | <0.001 |
| **Impulsivity** | BIS-11 Attentional | 17.7 (1.9) | 19.2 (3.0) | 17.1 (3.2) | 0.15 |
| | BIS-11 Motor | 22.2 (2.4) | 26.5 (2.1) | 22.6 (3.0) | <0.001 |
| | BIS-11 Nonplanning | 23.2 (4.4) | 28.6 (2.0) | 26.0 (5.2) | 0.002 |
| | BIS-11 total score | 63.1 (6.4) | 74.2 (5.0) | 65.7 (9.4) | <0.001 |

## 5.2 Group differences in tracer binding (Studies I and II)

Seventeen healthy controls, 15 PG and 7 BED patients entered the study, as described in the Methods section. However, due to scanner malfunction, one HC lacked [$^{11}$C]carfentanil data. One HC declined [$^{11}$C]MADAM and [$^{18}$F]fluorodopa scanning. During [$^{11}$C]MADAM scanning, two PG patients showed excessive head motion that could not be corrected with individual reconstructions, and these patients were excluded from the [$^{11}$C]MADAM analysis. One of these two PG patients was the same subject using citalopram, and thus, all of the subjects included in the final [$^{11}$C]MADAM sample did not use medications targeting the serotonin system. Additionally, two PG patients were not available for [$^{18}$F]fluorodopa scanning. Altogether, the final PET sample size consisted

of 38 [$^{11}$C]carfentanil scans, 36 [$^{18}$F]fluorodopa scans and 36 [$^{11}$C]MADAM scans. The groups did not differ in injected tracer doses or tracer masses (Table 4).

**Table 4:** Number of PET scans included in the analysis, injected tracer doses and injected tracer masses. [1]One-way ANOVA. Modified from Studies I and II.

| | HC | PG | BED | P-value[1] |
|---|---|---|---|---|
| **Number of [$^{11}$C]carfentanil scans** | 16 | 15 | 7 | |
| **Dose of [$^{11}$C]carfentanil (MBq)** | 495 (17) | 483 (49) | 504 (13) | 0.35 |
| **Mass of [$^{11}$C]carfentanil (µg)** | 0.428 (0.307) | 0.569 (0.542) | 0.422 (0.197) | 0.56 |
| **Number of [$^{18}$F]fluorodopa scans** | 16 | 13 | 7 | |
| **Dose of [$^{18}$F]fluorodopa (MBq)** | 228 (4) | 229 (12) | 225 (6) | 0.67 |
| **Mass of [$^{18}$F]fluorodopa (µg)** | 9.30 (3.31) | 11.28 (3.59) | 10.54 (5.88) | 0.40 |
| **Number of [$^{11}$C]MADAM scans** | 16 | 13 | 7 | |
| **Dose of [$^{11}$C]MADAM (MBq)** | 499 (16) | 485 (24) | 501 (13) | 0.081 |
| **Mass of [$^{11}$C]MADAM (µg)** | 0.444 (0.257) | 0.357 (0.088) | 0.315 (0.114) | 0.26 |

### *5.2.1 [$^{11}$C]carfentanil*

[$^{11}$C]carfentanil binding differed significantly across the groups in the thalamus, the nucleus accumbens, the hippocampus, the posterior cingulate gyrus, the isthmus of the posterior cingulate gyrus, the parahippocampal gyrus, the frontal pole, the pars orbitalis of the ventrolateral prefrontal cortex, the lateral orbitofrontal cortex, and the ventrolateral prefrontal cortex (Table 5, page 48). *Post hoc* analyses clarified that BED patients had significantly lower $BP_{ND}$ values in these regions when compared to controls and PG patients (Table 5). [$^{11}$C]carfentanil $BP_{ND}$ values did not differ between the PG patients and controls in any of the studied ROIs.

Possible confounding effects of sex and smoking were investigated. The primary results remained in all ten regions when only nonsmokers were analyzed. Similarly, the significance of lower $BP_{ND}$ values was also evident in all the regions when data from only women were used in the analyses. Lastly, the GLM model revealed that the significance of the lower $BP_{ND}$ values in the BED group remained even though BMI was added as a covariate (for example, in the NAcc, $p=0.003$), except in the thalamus (group effect, $p=0.090$) and in the hippocampus ($p=0.11$).

Correlations between BED symptom severity (DEBQ, BES, Yale food addiction scale scores) and [$^{11}$C]carfentanil binding were investigated in the regions showing the greatest decrease in MOR binding in the BED group, namely, the isthmus of the cingulate, the nucleus accumbens, the frontal pole, and the pars orbitalis of the ventrolateral prefrontal cortex. The questionnaire data did not correlate with tracer uptake in any of these regions.

Voxel-based analyses confirmed the decreased MOR binding in the BED group. A large significant cluster covered multiple brain regions, including the posterior cingulate gyrus, the thalamus, the anterior cingulate gyrus and the midbrain (cluster size 248.8 cm3, peak voxel at −66, −51, −6 mm, $T_{max}$=6.15, $p_{FWE} < 0.001$), when the BED patients were compared to the controls (Figure 4). Additionally, the BED patients showed decreased [$^{11}$C]carfentanil binding in the frontal cortex compared to the PG patients (cluster size 59.9 cm3, peak voxel at − 9, 63, 33 mm, $T_{max} = 6.18$, $p_{FWE} < 0.001$). Interestingly, the PG patients showed lower [$^{11}$C]carfentanil uptake in the anterior and posterior cingulate cortex (cluster size 45.6 cm3, peak voxel at 20 − 24, 34 mm, $T_{max}$= 6.04, $p_{FWE} = 0.001$) compared to the controls (Figure 4). There were no regions where [$^{11}$C]carfentanil binding was greater in the BED or PG groups than in the control group.

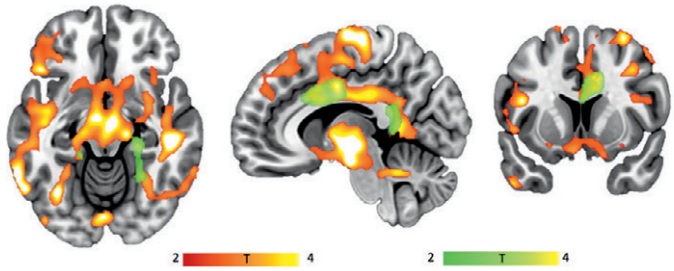


**Figure 4:** Regions with significant decreases in [$^{11}$C]carfentanil binding in voxel-by-voxel analysis. Decreased MOR binding was restricted to anterior and posterior cingulate gyri in pathological gambling (PG) whereas wide-spread losses were detected in binge eating disorder (BED). Red-yellow clusters: BED patients, green clusters: PG patients. The left panel is modified from Study I, other panels are original artwork by Joonas Majuri.

### *5.2.2 [$^{18}$F]fluorodopa*

[$^{18}$F]fluorodopa binding differed significantly between groups in the nucleus accumbens by one-way ANOVA ($p < 0.001$). *Post hoc* analysis revealed that the BED patients had significantly lower [$^{18}$F]fluorodopa $K_i$ values compared to the controls (20% lower; $p < 0.001$) and the PG patients (20% lower $K_i$ values; $p = 0.001$). [$^{18}$F]fluorodopa $K_i$ values in the nucleus accumbens did not differ between the PG and control groups. In other ROIs, one-way ANOVA did not show significant group differences.

When only nonsmokers were included in the analyses, the BED patients still showed lower $K_i$ values in the nucleus accumbens compared to the controls (*post hoc* p=0.001). Similarly, the results remained when only women were analyzed (*post hoc* p=0.001 for

BED vs HC and p<0.001 for BED vs PG). Adding BMI as a covariate to the ANOVA model did not change the results (effect of group p=0.01). In the BED patients, binge eating symptom severity (e.g., DEBQ, BES, Yale food addiction scale scores) did not correlate with [$^{18}$F]fluorodopa binding in the nucleus accumbens when investigated with Spearman correlation coefficients.

Voxel-by-voxel analyses confirmed the ROI-based findings. The BED patients showed decreased [$^{18}$F]fluorodopa uptake bilaterally in the nucleus accumbens (cluster size of 16.5 cm3, peak voxel at − 6, 11, − 12 mm, $T_{max}$= 5.16, $p_{FWE}$ < 0.001, Figure 5). The cluster also partly covered the caudate nucleus and the putamen. There were no regions showing increased [$^{18}$F]fluorodopa binding in the BED patients when compared to the controls. No differences were detected between the PG patients and controls or between the BED and PG patients.

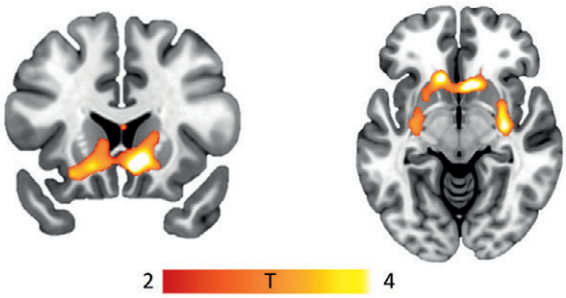


**Figure 5:** Regions with significant decreases in [$^{18}$F]fluorodopa binding in voxel-by-voxel analysis in binge eating group. The cluster covered bilaterally nucleus accumbens and extended to caudate nuclei and putamen. Artwork by Joonas Majuri.

### *5.2.3 [$^{11}$C]MADAM*

Again, no differences were detected between [$^{11}$C]MADAM binding between the PG patients and controls. Instead, SERT binding was regionally either increased or decreased in the BED group depending on the ROI. Increased SERT binding was detected in the superior and inferior parietal cortices and the lateral OCC when compared to the HC and PG groups (Table 5). The findings were not lateralized in the inferior parietal cortex, but only right hemisphere $BP_{ND}$ values were significantly different in the lateral occipital and superior parietal cortices, even though the $BP_{ND}$ values of these regions also approached significance in the left hemisphere (left lateral OCC: p=0.088, right: p<0.001; left superior parietal cortex: p=0.061, right: p<0.001). [$^{11}$C]MADAM binding was decreased in the nucleus accumbens, inferior temporal gyrus and lateral orbitofrontal cortex when the BED patients were compared to the controls. The differences were statistically significant

in the inferior temporal gyrus and lateral orbitofrontal cortex in the *post hoc* comparisons of the PG and BED patients but was not evident in the nucleus accumbens (Table 5).

The analyses were performed again by exploring the confounding effects of sex and smoking. The results remained significant in all the investigated regions when only women were included in the model. When only nonsmokers were analyzed, the group differences between the BED patients and controls remained only in the areas where the BED patients had increased SERT binding. In the nucleus accumbens, inferior temporal gyrus and lateral orbitofrontal cortex, the results became nonsignificant ($p = 0.13$ in the nucleus accumbens). When body mass index and BDI score were used as covariates in a general linear model along with the group status, the statistical significance of the group difference remained again in the regions showing elevated SERT binding in the BED group and in the inferior temporal gyrus (for the effect of group, $p=0.002$ in the inferior parietal cortex, $p=0.003$ in the superior parietal cortex, $p<0.001$ in the lateral OCC, $p=0.029$ in the inferior temporal gyrus, $p=0.094$ in the lateral OFC, and $p=0.12$ in the NAcc).

The correlation between [$^{11}$C]MADAM $BP_{ND}$ values and BED symptom severity, BDI score and BMI was investigated in all six ROIs showing group differences in the primary one-way ANOVA model. None of these variables correlated with tracer uptake in the BED group.

Voxel-based results confirmed the increased SERT binding in the BED group compared to the PG group. Two statistically significant clusters appeared in the right OCC (cluster size 44.4 cm3, peak voxel at 18, -51, 4 mm, $T_{max}=5.68$, $p_{FWE}=0.001$) and in the left parietal cortex (cluster size 31.7 cm3, peak voxel at -51, -57, 19 mm, $T_{max}=5.36$, $p_{FWE} = 0.009$) (Figure 6). There was no detectable decrease in SERT binding in the BED group when compared to the controls or PG patients. SERT binding appeared similar between the PG and HC groups also in the voxel-by-voxel analysis.

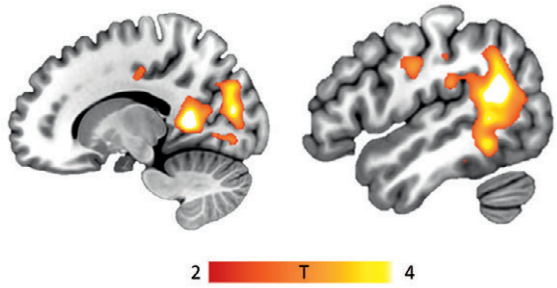


**Figure 6**: Regions with significant decreases in [$^{11}$C]MADAM binding in voxel-by-voxel analysis in binge eating group. The clusters covered the right occipital cortex and left parietal cortex. Artwork by Joonas Majuri.

**Table 5.** Group differences in [$^{11}$C]carfentanil and [$^{11}$C]MADAM $BP_{ND}$ and [$^{18}$F]fluorodopa $K_i$ values. Regions with a significance level of P<0.01 in one-way ANOVA are presented here, and regions with not statistically significant differences in the Supplementary Table 1. PCC = posterior cingulate gyrus, PFC = prefrontal cortex, OFC = orbitofrontal cortex. Ventrolateral PFC is formed by fusing three primary Free-Surfer ROIs, the pars opercularis, pars orbitalis and pars triangularis. Modified from studies I and II.

| Tracer | Region | HC | PG | BED | *F*-value | *P*-value | *P*-value *Post hoc* Bonferroni | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | One-way ANOVA | One-way ANOVA | C vs PG | C vs BED | PG vs BED |
| [$^{11}$C]carfentanil | Isthmus of PCC | 0.469 (0.092) | 0.416 (0.113) | 0.191 (0.089) | 18.9 | <0.001 | 0.468 | <0.001 | <0.001 |
| | Nucleus accumbens | 2.27 (0.26) | 2.12 (0.33) | 1.49 (0.29) | 17.5 | <0.001 | 0.502 | <0.001 | <0.001 |
| | Frontal pole | 0.765 (0.206) | 0.803 (0.244) | 0.350 (0.177) | 11.4 | <0.001 | 1.000 | 0.001 | <0.001 |
| | Pars orbitalis of ventrolateral PFC | 0.809 (0.152) | 0.777 (0.181) | 0.495 (0.087) | 10.6 | <0.001 | 1.000 | <0.001 | 0.001 |
| | Parahippocampal gyrus | 0.296 (0.086) | 0.259 (0.086) | 0.142 (0.100) | 7.5 | 0.002 | 0.755 | 0.001 | 0.019 |
| | PCC | 0.874 (0.166) | 0.856 (0.144) | 0.630 (0.159) | 6.5 | 0.004 | 1.000 | 0.005 | 0.010 |
| | Thalamus | 1.41 (0.18) | 1.33 (0.25) | 1.07 (0.17) | 6.5 | 0.004 | 0.981 | 0.003 | 0.027 |
| | Hippocampus | 0.211 (0.089) | 0.218 (0.107) | 0.0736 (0.108) | 5.7 | 0.007 | 1.000 | 0.013 | 0.010 |
| | Lateral OFC | 0.868 (0.126) | 0.853 (0.181) | 0.650 (0.119) | 5.7 | 0.007 | 1.000 | 0.008 | 0.016 |
| | Ventrolateral PFC | 0.830 (0.142) | 0.797 (0.182) | 0.605 (0.092) | 5.5 | 0.008 | 1.000 | 0.008 | 0.028 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **[$^{18}$F]fluorodopa** | Nucleus accumbens | 0.0115 (0.0011) | 0.0114 (0.0014) | 0.00915 (0.00104) | 10.4 | <0.001 | 1.000 | <0.001 | 0.001 |
| **[$^{11}$C]MADAM** | Superior parietal cortex | 0.222 (0.090) | 0.237 (0.072) | 0.492 (0.203) | 14.99 | <0.001 | 1.00 | <0.001 | <0.001 |
| | Inferior parietal cortex | 0.298 (0.082) | 0.318 (0.084) | 0.477 (0.071) | 12.86 | <0.001 | 1.00 | <0.001 | 0.001 |
| | Lateral occipital cortex | 0.231 (0.060) | 0.216 (0.080) | 0.372 (0.090) | 11.51 | <0.001 | 1.00 | 0.001 | <0.001 |
| | Inferior temporal gyrus | 0.286 (0.055) | 0.263 (0.039) | 0.196 (0.045) | 8.643 | 0.001 | 0.591 | 0.001 | 0.017 |
| | Lateral OFC | 0.410 (0.083) | 0.395 (0.091) | 0.280 (0.067) | 6.245 | 0.005 | 1.00 | 0.005 | 0.018 |
| | Nucleus accumbens | 1.656 (0.394) | 1.500 (0.225) | 1.193 (0.141) | 5.642 | 0.008 | 0.536 | 0.006 | 0.117 |

## 5.3 Tracer intercorrelations (Study III)

[$^{11}$C]MADAM binding did not correlate with [$^{18}$F]fluorodopa data in any of the studied ROIs. Instead, [$^{18}$F]fluorodopa $K_i$ values correlated with [$^{11}$C]carfentanil $BP_{ND}$ values in the caudate nucleus (p=0.002, Bonferroni-corrected *post hoc* p=0.013), putamen (p=0.001, *post hoc* p=0.005) and globus pallidus (p<0.001, *post hoc* p=0.002). Importantly, there was no group x [$^{11}$C]carfentanil interaction or an effect of group on [$^{18}$F]fluorodopa binding. Adding smoking status as a covariate to the model did not change the results (caudate nucleus p=0.007, Bonferroni-corrected *post hoc* p=0.022, putamen p=0.004, *post hoc* p=0.011, globus pallidus p<0.001, *post hoc* p=0.001). Similarly, the results remained significant after controlling for depression scores (caudate nucleus p=0.003, Bonferroni-corrected *post hoc* p=0.010, putamen p=0.003, *post hoc* p=0.008 and globus pallidus p<0.001, *post hoc* p=0.001). Spearman correlations confirmed the GLM findings by showing the intraregional correlation of [$^{18}$F]fluorodopa $K_i$ and [$^{11}$C]carfentanil $BP_{ND}$ values in the caudate nucleus, putamen and globus pallidus in the HC group and in the putamen and globus pallidus in the PG group (Table 6). Voxel-by-voxel analysis corroborated that [$^{18}$F]fluorodopa and [$^{11}$C]carfentanil uptake values correlated in both caudate nuclei (cluster size 8.16 cm3, peak voxel at 9, 13.5, 15 mm, $T_{max}$=7.79) and in the left putamen (cluster size 0.45 cm3, peak voxel at -31.5, -3, 7.5 mm, $T_{max}$=4.61) (Figure 7). There was no significant group x [$^{11}$C]carfentanil $BP_{ND}$ interaction or group effect in the voxelwise results.

**Table 6**: Intraregional correlations between [$^{18}$F]fluorodopa $K_i$ and [$^{11}$C]carfentanil $BP_{ND}$. Reprinted with permission from Study III.

| | **Healthy controls** | | **PG patients** | | **All subjects (N=28)** | | |
|---|---|---|---|---|---|---|---|
| **Region of interest** | Spearman *r* | *p* | Spearman *r* | *p* | Spearman *r* | *p* | Bonferroni corrected *p* |
| **Putamen** | 0.705 | 0.003 | 0.591 | 0.033 | 0.556 | 0.002 | 0.015 |
| **Caudate nucleus** | 0.580 | 0.024 | 0.267 | 0.38 | 0.461 | 0.014 | 0.095 |
| **Globus pallidus** | 0.550 | 0.034 | 0.715 | 0.006 | 0.610 | 0.001 | 0.004 |
| **Nucleus accumbens** | 0.355 | 0.19 | 0.011 | 0.97 | 0.107 | 0.59 | |
| **Amygdala** | 0.232 | 0.41 | 0.055 | 0.86 | 0.137 | 0.49 | |
| **Thalamus** | 0.114 | 0.69 | 0.544 | 0.055 | 0.323 | 0.094 | |
| **Hippocampus** | –0.145 | 0.61 | 0.308 | 0.31 | 0.031 | 0.88 | |

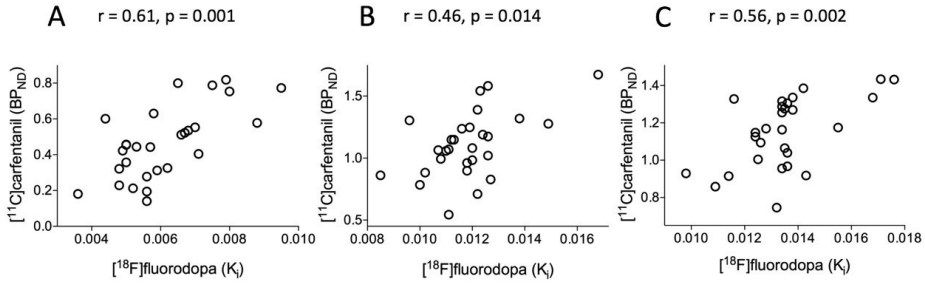


**Figure 7:** Intraregional correlations between [$^{18}$F]fluorodopa and [$^{11}$C]carfentanil binding together in healthy controls and pathological gamblers. The r and p values are obtained using Spearman rank correlation coefficients. A: globus pallidus B: caudate nucleus C: putamen. Modified from Study III.

## 5.4 Correlations with impulsivity (Study IV)

Nonplanning impulsivity correlated negatively with [$^{11}$C]MADAM binding in the left prefrontal cortex in the HC group (size 20.4 cm$^3$ and $p_{FWE}$ = 0.001 with cluster-forming threshold p<0.01, $T_{max}$ = 5.30, peak voxel at -12 34 -8 mm) but not in the PG group. The ROI-based approach was limited to ventrolateral PFC, and the voxel-based findings were confirmed: in the ventrolateral PFC, the HC group showed a negative correlation between nonplanning impulsivity and [$^{11}$C]MADAM uptake (r=-0.52, p=0.04), whereas PG patients failed to show this correlation (r=0.08, p=0.80). The correlation was found only in the left ventrolateral PFC (right VLPFC, r= -0.24, p=0.38; left VLPFC, r=-0.57, p=0.02). Using GLM, the group x nonplanning impulsivity interaction was significant in the ventrolateral PFC (p = 0.03), also after including BDI and smoking status as covariates (p=0.02). [$^{11}$C]MADAM binding in the ventrolateral PFC did not correlate with striatal dopamine synthesis rate in either group.

Nonplanning impulsivity correlated positively [$^{11}$C]carfentanil binding in the midbrain including VTA and bilaterally in the globus pallidus in the PG group (cluster size 13.5 cm$^3$ with cluster-forming threshold p < 0.005, $p_{FWE}$ = 0.03, $T_{max}$ = 6.92 and peak voxel at -12 -6 -9 mm) but not in the HC group. For the ROI analysis, VTA and substantia nigra [$^{11}$C]carfentanil values were extracted and analyzed together with [$^{11}$C]carfentanil $BP_{ND}$ values in the globus pallidus. ROI analyses confirmed the association in the PG group (in VTA, r=0.61, p=0.02; in GP, r=0.58, p=0.03; in substantia nigra, r=0.54, p=0.05) and the independency in the HC group (in VTA, r=0.23 p=0.39; in GP, r=-0.22 p=0.42; in nigra, r=0.27, p=0.30). The correlations in the left and right GP and left and right substantia nigra were not hemisphere-dependent in the PG patients (right GP, r=0.52, p=0.05 and

left GP, r=0.53, p=0.05; right nigra, r=0.54, p=0.05 and left nigra, r=0.55, p=0.04). Excluding the one outlier subject did not change the results. However, the group x nonplanning interaction did not reach significance in the GLM model (VTA, p=0.06; GP, p=0.10; nigra, p=0.13). Instead, VTA [$^{11}$C]carfentanil $BP_{ND}$ in the PG group correlated negatively with NAcc [$^{18}$F]fluorodopa uptake (r=-0.56, p=0.05) but did not correlate in other striatal ROIs (r=-0.10 and p=0.75 in the putamen and r=0.06 and p=0.85 in the caudate nucleus). Using a GLM model and NAcc [$^{18}$F]fluorodopa ~ group x VTA [$^{11}$C]carfentanil, the interaction term was significant (p=0.03). The significant modulatory effect of group on impulsivity remained after excluding one outlier subject (p=0.04), or including BDI and smoking as covariates (p=0.02). VTA [$^{11}$C]carfentanil $BP_{ND}$ values in the HC group and GP and substantia nigra [$^{11}$C]carfentanil $BP_{ND}$ values in either group did not correlate with NAcc dopamine synthesis capacity.

Motor impulsiveness or attentional impulsiveness did not correlate with MOR or SERT binding in either group. Additionally, any dimensions of self-reported impulsivity and [$^{18}$F]fluorodopa binding did not correlate with each other in either group.

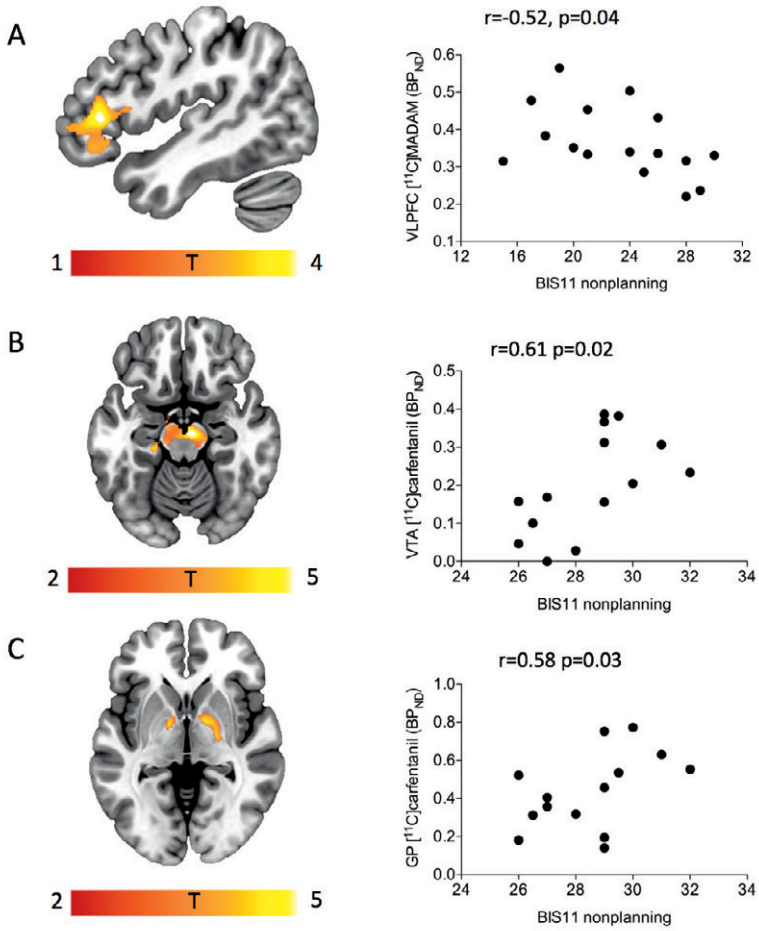


**Figure 8:** Correlations between non-planning impulsivity and tracer uptake. Left panels show results of multiple regression in voxel-by-voxel analysis, whereas scatter plots on the right originate from ROI-based results. The r and p values are obtained using Spearman rank correlation coefficients. A: relationship with [$^{11}$C]MADAM binding in control group in the ventrolateral prefrontal cortex (VLPFC). B: relationship with [$^{11}$C]carfentanil binding in pathological gamblers (PG) in the ventral tegmental area (VTA). C: relationship with [$^{11}$C]carfentanil binding in pathological gamblers (PG) in the globus pallidus (GP). Artwork by Joonas Majuri.

# 6 DISCUSSION

The main findings of this study were the clear neurobiological differences between different types of behavioral addictions and between behavioral and substance addictions. Binge eating disorder was associated with widespread lower MOR binding, lower striatal dopamine synthesis capacity, and regionally altered patterns in SERT binding. However, pathological gamblers did not show differences in the measured dopamine or serotonin neurotransmission compared to controls (Studies I and II). In the PG group, decreased MOR binding was detected in a very limited region in the cingulate cortex and only in the voxel-by-voxel analysis (Study I). The results did not support a common neurobiological framework for these two disorders, although both have been conceptualized as behavioral addictions. The results of this study also provided evidence of the interaction between brain opioid and dopamine neurotransmission (Study III). In addition, the results demonstrated that altered MOR function may mediate impulsivity, which is a common characteristic for addiction disorders, through its interactions in the mesolimbic dopamine system (Study IV).

## 6.1 Group differences

### *6.1.1 Opioid*

In substance addictions, MOR binding has been found to be increased irrespective of the drug of abuse. Elevations in MOR binding have been reported at least in opiate, alcohol and cocaine addictions (Zubieta *et al.*, 1996; Gorelick *et al.*, 2005; Heinz *et al.*, 2005a; Williams *et al.*, 2007; Williams *et al.*, 2009; Weerts *et al.*, 2011). In Study I, widespread decreases in MOR binding in the BED patients were detected, which stands in marked contrast to substance addictions. Decreases in MOR binding were also observed in the PG patients but in many fewer brain regions. Together, these findings pointed to not only a distinct neurobiological framework of behavioral addictions compared to substance addictions but also underlined differences between different types of behavioral addictions. Our BED patients were advised not to binge eat, and similarly, the PG patients were not allowed to gamble 48 hours prior to scanning. Thus, these results may be comparable to previous PET studies in early abstinent substance-dependent patients, if binge eating is considered as ‘substance abuse’.

Previous studies have indicated that MORs play a role in hedonic processing and incentive motivation in addition to reward processing (Berridge *et al.*, 2009; Haber & Knutson, 2010; Cambridge *et al.*, 2013; Ziauddeen *et al.*, 2013). Patients with BED show blunted motivational responses and increased hedonic responses to salient food cues when treated

with the MOR antagonist GSK1521498 but, interestingly, also decreased hedonic responses to palatable food consumption (Cambridge *et al.*, 2013; Ziauddeen *et al.*, 2013). Thus, it appears that the decreased MOR binding can enhance hedonic responses to food cues that may facilitate eating behavior; however, this does not provide the expected pleasure, and this discrepancy leads to overconsumption of food products. However, Study I cannot address whether the observed decreases in MOR binding served as a predisposing trait or were secondary to continued eating behavior. Drugs targeting MORs have not clinically meaningfully altered BED (McElroy *et al.*, 2013; Ziauddeen *et al.*, 2013; McElroy, 2017). The findings of lower [$^{11}$C]carfentanil uptake in BED do not support the idea of opioid antagonists as an effective treatment for BED, compared to findings in alcohol dependence. In alcohol dependence, opioid antagonists are an approved therapy, and increased MOR binding has been observed (Heinz *et al.*, 2005a; Williams *et al.*, 2009; Weerts *et al.*, 2011; Kranzler & Soyka, 2018).

The findings in BED are highly interesting in terms of other eating disorders and obesity. Similar to BED, bulimia nervosa (BN) is an eating disorder characterized by excessive food intake, but unlike patient with BED, BN patients try to control their weight gain, for example, by vomiting after binge eating, engaging in excessive amounts of exercise, or using laxatives (APA, 2013). Obesity is characterized by chronic overeating, whereas BED is characterized by eating excessive amounts of food in a discrete period of time (APA, 2013; Joutsa *et al.*, 2018). Obesity is common in patients with BED, but only a minority of all obese people suffer from BED (Yanovski, 2003). Both BN patients and morbidly obese subjects have shown reduced MOR binding: bulimic patients in the frontoinsular regions and obese subjects more generally throughout the brain (Bencherif *et al.*, 2005; Karlsson *et al.*, 2015a). In this sample, BMI was included as a confounding factor, and it did not affect the robust decreases in the MOR binding in the BED patients. In a recent analysis, morbidly obese subjects without BED and obese subjects with BED showed similar reductions in MOR density despite the different eating disorder phenotypes (Joutsa *et al.*, 2018). Moreover, a longitudinal PET study found that bariatric surgery elevated brain MOR binding by 23%, back to normal levels (Karlsson *et al.*, 2015b). Karlsson *et al*. hypothesized that excessive food intake, rather than elevated weight, downregulates brain MOR density in response to continuous opioid release following food intake, as patients who underwent bariatric surgery were still overweight after surgery but showed normalized opioid function in relation to decreased food intake. Indeed, feeding appears to release opioids independently from the hedonic responses to food (Tuulari *et al.*, 2017).

In Study I, the PG patients showed decreased MOR density in the dorsal cingulate cortex in a voxel-by-voxel analysis, which contrasts with the findings in substance addictions with increased MOR binding. However, the difference between the PG patients and controls did not reach significance in the ROI analysis. It is possible that the discrepancy between the ROI and voxel-by-voxel results were caused by the fact that anatomically

determined ROIs do not match functional MOR distribution, making ROI-based analyses less sensitive. Our findings are in line with a previous [$^{11}$C]carfentanil PET study in pathological gambling that did not find any differences in baseline MOR binding, including in the cingulate cortex (Mick *et al.*, 2016). As there appears to be no clear differences in MOR binding in the PG subjects compared to healthy individuals, the pharmacological role of opioid antagonists in treating PG can be questioned on the basis of these results.

### *6.1.2 Dopamine*

In Study I, decreased dopamine synthesis capacity in the NAcc, a key region in reward processing, was observed. Group differences between the PG patients and controls were not detected. These findings highlight the neurobiological differences between different behavioral addictions. Lisdexamphetamine, which increases synaptic concentrations of brain monoamines including dopamine, has been shown to be efficacious in the treatment of BED (McElroy, 2017). The finding of a lowered dopamine synthesis rate in BED may be an underlying mechanism behind the therapeutic efficacy of lisdexamphetamine.

The results of [$^{18}$F]fluorodopa studies in substance addictions are scarce. No baseline differences in alcohol or nicotine dependence have been observed, whereas [$^{18}$F]fluorodopa uptake has been reported to be decreased in cocaine dependence (Wu *et al.*, 1997; Heinz *et al.*, 2005b; Kienast *et al.*, 2013; Bloomfield *et al.*, 2014). The decreases observed in [$^{18}$F]fluorodopa uptake in BED resemble the findings in cocaine addiction (Wu *et al.*, 1997), whereas PG resembles alcohol and nicotine addictions in terms of dopamine synthesis capacity (Heinz *et al.*, 2005b; Kienast *et al.*, 2013; Bloomfield *et al.*, 2014). The combined results suggest syndrome-specific patterns of dopamine synthesis in different addiction disorders.

Our BED patients were more obese than the PG patients and controls. Eating is known to release dopamine in the reward circuit (Norgren *et al.*, 2006; de Araujo *et al.*, 2008), and PET studies in obesity have found trends towards an inverse relationship between BMI and dopamine synthesis capacity in the caudate nucleus (Wilcox *et al.*, 2010; Wallace *et al.*, 2014). Our obese BED subjects showed decreased dopamine synthesis rates, especially in the key structure of the brain reward system, the ventral striatum. The results were independent of BMI, indicating that the finding was specific for BED and not associated with body weight in general.

A recent independent [$^{18}$F]fluorodopa study suggested an increased dopamine synthesis rate in the putamen in people with a gambling disorder (van Holst *et al*., 2018). Although van Holst *et al*. reported elevations in dopamine synthesis that were not replicated in Study I, their results can be considered to support the idea of opposite dopaminergic levels in people with BED and PG observed in Study I. It should be noted that the subjects in

that particular study had relatively mild gambling symptoms (past 3-month SOGS mean scores of 3.23), whereas all our subjects had current gambling symptoms. Another difference in our study subjects was the frequency of smoking, which was more common in our PG subjects. Van Holst *et al*. also speculated that the difference between their results and our results may have been caused by a history of drug use in our subjects, as the drug history of our subjects in the original publication of Study I was not separately reported,. Our subjects did not have drug dependence six months prior to the study, and urine drug screens needed to be negative to enter the study, so this theory is unlikely. Furthermore, the preferred gambling forms appeared somewhat similar in Study I and in the study by van Holst *et al*., at least in terms of slot machine gambling prevalence.

Previous PET studies targeting postsynaptic striatal D2 receptor binding have suggested that the receptor binding is not altered in PG or BED at baseline (Linnet *et al.*, 2010; Wang *et al.*, 2011; Clark *et al.*, 2012; Joutsa *et al.*, 2012a; Boileau *et al.*, 2013), whereas different substance addictions have been related to reduced receptor binding (Volkow *et al.*, 1993; Hietala *et al.*, 1994; Volkow *et al.*, 1996; Wang *et al.*, 1997a; Volkow *et al.*, 2001; Martinez *et al.*, 2004; Martinez *et al.*, 2005; Lee *et al.*, 2009; Martinez *et al.*, 2012), as discussed in detail in the Introduction. Similarly, substance addictions have been associated with blunted dopamine release in the striatum, whereas gambling, food cues or amphetamine challenge has been associated with enhanced striatal dopamine release in behavioral addictions (Martinez *et al.*, 2005; Martinez *et al.*, 2007; Wang *et al.*, 2011; Joutsa *et al.*, 2012a; Martinez *et al.*, 2012; Boileau *et al.*, 2014). In addition, a study investigating dopamine transporter (DAT) with [$^{123}$I]FP-CIT found decreased dopamine transporter density in PG patients compared to healthy volunteers, suggesting reduced reuptake of dopamine (Pettorruso *et al.*, 2018). Thus, behavioral addictions have been linked to hyperdopaminergic brain function. Current findings were in line with previous reports in PG, as no baseline differences in dopamine neurotransmission were observed, but contrasts with BED were observed by showing reduced dopamine synthesis. BED may share similar features with substance use disorders in dopamine neurotransmission, but apparently PG does not.

### *6.1.3 Serotonin*

Study II also showed that, similar to opioid and dopamine neurotransmission, SERT density was abnormal in BED but unaltered in PG. SERT upregulation in BED was observed in the parietal and occipital cortices and downregulation in the nucleus accumbens and orbitofrontal cortex. These findings again highlighted the differences in the neurobiology of these two addiction phenotypes. As the PG and BED patients did not differ in BDI scores, depression is an unlikely explanation for the observed changes.

Previous molecular imaging studies investigating SERT in substance addictions have been inconclusive. MDMA and methamphetamine addictions are associated with down-regulation and cocaine addiction with upregulation of SERT, but the results are mixed in alcohol dependence (Jacobsen *et al.*, 2000; Szabo *et al.*, 2004; McCann *et al.*, 2005; Brown *et al.*, 2007; Banks *et al.*, 2008; Kish *et al.*, 2009; Martinez *et al.*, 2009; Erritzoe *et al.*, 2011; Roberts *et al.*, 2016). Interestingly, reduced SERT binding has been observed in the OCC in MDMA addiction, an area that showed elevations in BED in Study II (Kish *et al.*, 2009). The results of Study II add inconclusive data on the role of SERT in addictive disorders.

The brain areas that showed decreases in SERT density are involved in reward processing, delay discounting, reversal learning and goal-directed control, which are cognitive processes that are impaired in BED (Mole *et al.*, 2015; Voon, 2015; Banca *et al.*, 2016; Voon & Dalley, 2016). The lateral OCC is needed to analyze visual and haptic representations of objects, whereas the parietal cortex guides goal-directed actions and acts as an integrative area for sensory information collected by visual and auditory cortices (Erdogan *et al.*, 2016; Rohe & Noppeney, 2016). The impairments in serotonin transmission in these regions in BED may represent deficits in the interpretation and integration of sensory food cues and feeding sensations, but the differences in SERT binding may be based on compensatory neural adaptations to continuous feeding as well, and this hypothesis needs to be confirmed in future studies.

In BN, an [$^{123}$I]ADAM SPECT study found no difference in SERT density between patients with bulimia, their healthy twin sisters or in healthy controls, whereas an [$^{123}$I]β-CIT study found reduced uptake in the thalamus and hypothalamus (Tauscher *et al.*, 2001; Koskela *et al.*, 2007). However, [$^{11}$C]McN5652 and [$^{11}$C]DASB PET studies found no significant alterations in SERT binding in BN (Bailer *et al.*, 2007; Pichika *et al.*, 2012). Thus, the increases in SERT binding observed in Study II are in contrast to previous studies in BN. Although [$^{11}$C]MADAM $BP_{ND}$ values were rather low in cortical regions in Study II, a previous test-retest study indicated good reproducibility in [$^{11}$C]MADAM uptake (Lundberg *et al.*, 2006). Notably, previous PET studies targeting SERT in BN were performed in recovered BN patients, whereas the BED patients in Study II had current BED symptoms; thus, it is also possible that similar SERT patterns may also be observed in BN in the active phase.

High BMI, another possible confounding factor in this study, has previously been investigated in relation to SERT, but SPECT studies investigating SERT have shown conflicting results, as one study reported a positive correlation with BMI in the thalamus, but another study found no correlation between BMI and SERT binding (Koskela *et al.*, 2008; Hesse *et al.*, 2014). In contrast, a negative relationship between SERT binding, measured with [$^{11}$C]DASB, and BMI has been reported in subcortical regions and in cortical re-

gions, including the parietal cortex, in healthy controls (Erritzoe *et al.*, 2010). Furthermore, obese subjects had similar [$^{11}$C]DASB uptake both before and after a gastric bypass procedure compared to controls (Haahr *et al.*, 2015). Taken together, previous data support the assumption that the findings reported in Study II are independent of body weight.

## 6.2 Tracer intercorrelations

In Study III, dopamine synthesis capacity correlated with MOR density in the caudate nucleus, putamen and globus pallidus. Two previous multitracer PET studies have investigated the relationships in opioid and dopamine systems: D2R density, measured with [$^{11}$C]raclopride, correlated positively with MOR binding in the NAcc and the caudate nucleus (Tuominen *et al.*, 2015). Another study found a positive correlation with [$^{11}$C]raclopride uptake and dopamine synthesis rate, measured with [$^{18}$F]FMT, in all the striatal regions at baseline (Berry *et al.*, 2018). Interestingly, dopamine release following amphetamine administration was not related to baseline dopamine synthesis rate (Berry *et al.*, 2018). In conclusion, striatal MORs, D2 receptors and dopamine synthesis capacity appear to be in tight connection with each other in the basal ganglia in healthy brain. In Study III, the PG patients showed similar correlations between [$^{18}$F]fluorodopa and [$^{11}$C]carfentanil binding than controls, indicating intact dopamine-opioid interactions in PG. This leads to a suggestion that in PG, pharmacotherapies targeting opioid system may be used to modify dopamine neurotransmission in the basal ganglia.

D2 receptors in the striatum are expressed on postsynaptic medium spiny neurons, which project to the globus pallidus externa and subthalamic nucleus. This neuronal pathway is considered to be the indirect pathway (Gerfen *et al.*, 1990; Yager *et al.*, 2015). In contrast, the striatal direct pathway consists of D1R-expressing neurons that innervate the internal GP and the substantia nigra pars reticulata (Gerfen *et al.*, 1990; Yager *et al.*, 2015). Interestingly, striatal areas rich with MORs are innervated by dopaminergic neurons rising from the substantia nigra, and dopamine afferents seem to modulate MOR distribution in postnatal rats (Gerfen *et al.*, 1987; Caboche *et al.*, 1991). Furthermore, MORs and D2Rs coexist in the same striatal cells (Ambrose *et al.*, 2004), and dopaminergic nerve terminals form asymmetric excitatory synapses with MORs (Wang *et al.*, 1997b). Based on current findings and previous data, it is postulated that the relationship between [$^{18}$F]fluorodopa and [$^{11}$C]carfentanil found in Study III represents a relationship between the dopaminergic system and MORs, mainly in the indirect striatal pathway. However, this assumption needs to be verified, as presynaptic MORs may also have an effect on the [$^{11}$C]carfentanil signal (Arvidsson *et al.*, 1995; Gracy *et al.*, 1997; Henderson, 2015).

SERT density was not correlated in Study III with [$^{18}$F]fluorodopa uptake, which served as a negative control. Previous studies have indicated that each monoamine cell expresses only its specific monoamine transporter (Amara & Kuhar, 1993; Glatt & Reus, 2003;

Rothman & Baumann, 2003). Therefore, it was assumed that [$^{11}$C]MADAM binding would not correlate with dopamine synthesis capacity, as was shown. The independency of dopamine synthesis from serotonin reuptake highlighted the specificity of the intraregional dopamine-opioid interaction. The lack of correlations between [$^{18}$]fluorodopa and [$^{11}$C]MADAM also confirmed that the observed association between dopamine and opioid systems was not due to general factors affecting all tracers.

Only intraregional correlations between tracer uptake profiles were investigated in Study III. Studying interregional correlations may provide more insights into the functional neurotransmitter networks, as the intraregional approach is restricted to local neurotransmitter connections. This kind of experiment requires adequate sample sizes to provide reliable outcomes, but future studies with larger sample sizes or data sharing may help to address this issue.

## 6.3 Impulsivity and tracer binding

Impulsivity is a personality trait that predisposes individuals to the development of addictive disorders and increases the risk for relapse during abstinence in people with drug addictions (Zilberman *et al.*, 2003; Verdejo-García *et al.*, 2008). As dopamine, opioid and serotonin neurotransmitters have all previously been linked to impulsivity (Dalley & Roiser, 2012; Weber *et al.*, 2016), we sought to determine whether impulsivity would be related to these neurotransmitters. PG patients have previously shown elevated scores on several self-reported impulsivity questionnaires (Verdejo-García *et al.*, 2008), and among these questionnaires, the BIS-11 was applied to evaluate trait impulsivity in Study IV. The results of the study showed that nonplanning impulsivity correlated with SERT density in healthy individuals but not PG patients. In the PG patients, midbrain and pallidal MOR binding correlated with nonplanning impulsivity. Similar correlations were not detected in the HC group, but the group difference between the correlations remained slightly nonsignificant. Furthermore, binding to ventral tegmental MORs also correlated with nucleus accumbens [$^{18}$F]fluorodopa uptake, which linked the MOR-mediated impulsivity to the mesolimbic dopamine system.

### *6.3.1 Serotonin*

Serotonin has been considered one of the key neurotransmitters in impulsivity (Dalley & Roiser, 2012). Both clinical and preclinical studies have found an inverse relationship between impulsivity and brain serotonin levels using tryptophan depletion (Dalley & Roiser, 2012). PET studies have investigated possible serotonergic deficits in conditions

related to impulsivity. Serotonin transporter (SERT) density has been reported to be reduced in the anterior cingulate cortex in patients with impulsive aggression, in the striatum and midbrain in patients with conduct disorder, and nonsignificantly in various brain regions, including the striatum, anterior cingulate cortex, thalamus and insula (Frankle *et al.*, 2005; Karlsson *et al.*, 2013; Chang *et al.*, 2017; Vanicek *et al.*, 2017). None of these studies investigated the association between SERT density and impulsivity, except Chang *et al*., who did not find a correlation between SERT binding and BIS-11 scores in patients with conduct disorder (Chang *et al.*, 2017).

In Study IV, nonplanning impulsivity was inversely related to [$^{11}$C]MADAM binding in the ventrolateral PFC in the healthy controls. As increased brain serotonergic tone has been previously linked to decreased impulsivity (Dalley & Roiser, 2012), the association between decreased [$^{11}$C]MADAM uptake and higher impulsivity was due to reduced SERT density rather than elevated baseline serotonergic tone. The healthy prefrontal cortex is needed to inhibit premature responses and to enhance one's ability to make nonimpulsive choices (Bari & Robbins, 2013). Prefrontal lesions and diseases related to prefrontal cortical damage, such as frontotemporal dementia, have been associated with increased impulsivity and disinhibited behavior (Piguet *et al.*, 2011; McDonald *et al.*, 2017). Specifically, left ventrolateral PFC cortical thickness has been reported to be inversely related to self-reported impulsivity in healthy volunteers (Schilling *et al.*, 2012). Thus, it can be hypothesized that serotonergic neurotransmission in the ventrolateral PFC is needed to guide normal impulsivity-related behaviors in the healthy brain.

### *6.3.2 Opioid*

The opioid system is also involved in impulsivity. One previous PET study with 19 healthy subjects found elevated [$^{11}$C]carfentanil binding potentials in the anterior cingulate cortex, ventral globus pallidus, nucleus accumbens and amygdala compared to subjects with lower impulsivity (Love *et al.*, 2009). In Study IV, similar associations were not detected in a heathy control group with comparable sample size but instead, positive correlations between BIS-11 scores and [$^{11}$C]carfentanil $BP_{ND}$ values were observed in more impulsive PG patients, thus partially supporting previous findings by Love *et al*. Some differences do exist between the studies: in Study IV, a high-resolution HRRT scanner was used while Love *et al*. had Siemens HR+, and further, Love *et al*. applied a revised version of the NEO Personality Inventory as a behavioral measurement.

SERT density did not correlate with any of the studied impulsivity measures in the PG group. Instead, MOR binding correlated positively with nonplanning impulsivity in the VTA, substantia nigra and bilateral GP. These findings supported the idea that serotonergic neurotransmission in the ventrolateral PFC is needed for the normal modulation

of impulsive behaviors, whereas this system is absent in people with PG, where impulsivity is mainly modulated by the midbrain and pallidal MORs. This hypothesis needs to be confirmed in future studies. It should be noted that the differentiation of the VTA and substantia nigra [$^{11}$C]carfentanil signal from the midbrain was inconclusive as their volumes were very small and their [$^{11}$C]carfentanil $BP_{ND}$ levels were relatively low. Additionally, the relationship between SOGS scores and nonplanning impulsivity scores raises the question of whether the observed associations with [$^{11}$C]carfentanil binding reflect symptom severity or impulsivity in people with PG.

The importance of the VTA and GP MORs regulating the brain dopamine system simultaneously with the brain reward system is apparent in any case. Ventral GP neurons densely innervate the VTA, and opioid administration to the ventral GP decreased GABAergic inhibitory influence on mesolimbic dopamine nerves and facilitated dopaminergic signaling (Kalivas *et al.*, 1993; Wu *et al.*, 1996; Floresco *et al.*, 2003; Hjelmstad *et al.*, 2013). Similarly, MOR-dependent inhibition of local GABAergic interneurons in the VTA led to enhanced dopaminergic neurotransmission (Johnson & North, 1992; Hjelmstad *et al.*, 2013). Further evidence about the role of the GP in addiction disorders has been published in a report where bilateral lesions in the GP led to remission of alcohol and opiate addictions (Moussawi *et al.*, 2016). Indeed, other studies have confirmed the role of GP in reward processing and cue-induced drug seeking (Smith *et al.*, 2009; Mahler *et al.*, 2014).

Pharmacological modulation of the opioid system, however, has produced mixed results in animal studies (Weber *et al.*, 2016). Naltrexone reduced cue reactivity but not reward impulsivity compared to placebo, even though there is a trend towards reduced reward impulsivity after naltrexone treatment (Weber *et al.*, 2016). Another study confirmed that acutely administered naltrexone did not affect impulsivity either in the control group or in a group of alcohol-dependent subjects (Mitchell *et al.*, 2007). Again, opioid antagonists have shown mixed results in the treatment of PG (Kim *et al.*, 2001; Grant *et al.*, 2006; Grant *et al.*, 2008; Toneatto *et al.*, 2009; Grant *et al.*, 2010; Kovanen *et al.*, 2016). Thus, work towards a more complete understanding of the neurobiological pathways behind PG is needed.

### *6.3.3 Dopamine*

Previous PET studies have found that impulsive individuals have reduced D2/3 receptor binding in the ventral striatum and VTA, similar to the findings in individuals with drug addictions (Dalley *et al.*, 2007; Volkow *et al.*, 2009; Buckholtz *et al.*, 2010; Anderson *et al.*, 2017). Buckholtz *et al*. demonstrated that trait impulsivity correlated negatively with VTA D2 autoreceptor binding and positively with striatal dopamine release after amphetamine challenge, together with an inverse relationship between striatal dopamine release

and VTA autoreceptor binding (Buckholtz *et al.*, 2010). Additionally, in methamphetamine users, impulsivity correlated negatively with D2/D3 receptor binding (Lee *et al.*, 2009). Furthermore, dopamine transporter density is also reduced in patients with ADHD, a disorder linked to increased impulsivity (Volkow *et al.*, 2009). Amisulpride, a dopamine antagonist, has been shown to reduce cue reactivity and reward impulsivity in humans (Weber *et al.*, 2016). In Study IV, no correlations between BIS-11 scores and [$^{18}$F]fluorodopa uptake were observed in either healthy volunteers or impulsive PG patients. However, VTA MOR binding was related to the nucleus accumbens dopamine synthesis capacity and thus linked MOR-mediated pathological nonplanning impulsivity to the mesolimbic dopamine system.

Interestingly, previous animal studies have found that increased tonic dopaminergic levels have been shown to attenuate PFC-originating neural inputs in the NAcc (Grace, 2000; Goto & Grace, 2005). The attenuation of glutamatergic neurotransmission from the PFC to NAcc is thought to cause a reduced ability to adapt to new environmental stimuli, strengthening previously learned drug-seeking behavior in addicted individuals (Kalivas, 2009). In Study IV, the normal serotonergic function in the ventrolateral PFC was lost in the PG patients. Questions regarding the interplay between glutamate and serotonin systems in the PFC have been raised and need to be investigated in the future.

## 6.4 Limitations

Several factors need to be considered when interpreting these findings. The main weakness of this study was the small group size in the BED group. However, the BED group showed robust differences in the neurotransmitter function compared to the other groups, indicating that the sample size was sufficient to investigate differences between behavioral addictions. The recruitment of BED patients was more challenging than expected. In addition, the BED group consisted of only women and the BED patients weighed more than the controls and PG patients. However, conducting the analyses in subgroups or adding these factors as confounding variables did not change the main results. The HC and PG groups were matched by age, sex, BMI and alcohol consumption, but the groups differed in smoking, which was taken into account in the confirmatory analyses and did not change the results. Finally, both the PG and BED patients were more depressed than the control subjects, although this difference makes depression an unlikely explanation for the robust group differences between BED and PG.

An important notion regarding PET studies, especially regarding [$^{11}$C]carfentanil scans, is that a single baseline PET study cannot determine if differences in tracer uptake are due to, for example, changes in protein expression, receptor affinity or alterations in the levels of endogenous receptor ligands competing for the binding sites. Another important consideration is the direction of causality, which remains unclear, as changes in receptor

binding may either be the consequence of the behavior (e.g., excessive food intake) or a predisposing neurobiological feature leading to the behavior. In addition, [$^{18}$F]fluorodopa may also be taken up by other monoaminergic cells and converted to dopamine; thus, part of the signal may arise from other monoaminergic cells (Brown *et al.*, 1999). However, the [$^{18}$F]fluorodopa signal in the striatum can be considered mainly an indicator of dopaminergic function (Lloyd & Hornykiewicz, 1970; Martin *et al.*, 1989).

Several limitations regarding the performed analyses should also be discussed. In Studies I and II, group differences in [$^{11}$C]carfentanil and [$^{11}$C]MADAM were calculated in a total of 41 cortical and subcortical brain regions. Even though p-values were adjusted to minimize the risk for false positive findings, there is a risk for type I error in the ROI data. However, complementary voxel-by-voxel analyses with conservative FWE corrections confirmed the significance of the group differences. In Studies III and IV, correlational methods were applied. It should be pointed out that our sample size is rather small for correlational methods. Correlation coefficients start to stabilize if the sample size is increased to over 150 subjects, and smaller samples may overestimate the true correlation coefficients (Schönbrodt & Perugini, 2013). However, these sample sizes are rarely feasible for PET studies due to imaging costs and irradiation. Thus, the findings from correlational analyses should be considered with caution and warrant independent replication.

# 7 CONCLUSIONS

The aim of this thesis was to investigate brain dopamine, opioid and serotonin neurotransmission in different behavioral addictions, namely, pathological gambling and binge eating disorder. This revealed that different behavioral addictions differ by their neurobiology as measured with [$^{18}$F]fluorodopa, [$^{11}$C]carfentanil and [$^{11}$C]MADAM PET. The findings contrast with previously published results in substance addictions, indicating the independent neurobiological framework of behavioral addictions. Furthermore, this study showed that dopamine and opioid systems are tightly connected in the basal ganglia, in both healthy persons and pathological gamblers. Lastly, this study revealed that normal serotonergic modulation of impulsivity is diminished in pathological gambling, and instead, opioidergic modulation appears to have a central role.

The findings do not support the idea of neurobiologically similar behavioral addictions. The findings in binge eating disorder, especially regarding the opioid system, resemble obesity and bulimia nervosa and warrant the classification as an eating disorder, but findings regarding dopamine synthesis resemble substance addictions. Although PET imaging has widened our understanding of substance addictions, the addiction neurocircuit in pathological gambling remains elusive. In the absence of confounding drugs of abuse, the baseline changes in gambling may be so diminutive or restricted that current molecular imaging techniques are too coarse to detect the changes.

The differences between behavioral addictions and substance addictions highlight that an individual understanding of each addiction disorder is needed. The discrepancy between the neurobiology of addictive disorders may have an impact in the future, for example, with individual drug development for distinct disorders. Beyond pathological gambling, other behavioral addictions are still very poorly understood conditions. Whether we see other behavioral addictions recognized in future diagnostic manuals depends on the future research effort to understand these disorders. The development of potentially efficacious pharmacotherapies and classifying behavioral addictions may be guided by neuroimaging studies, and hopefully we will see new studies in the coming years. Patients suffering from these disorders have a right to get the proper diagnosis, to be treated and faced without prejudices, and a chance to get efficacious treatment.

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Joonas Majuri

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# APPENDICES

**Supplementary Table 1:** Group differences in [$^{11}$C]carfentanil $BP_{ND}$ and [$^{18}$F]fluorodopa $K_i$ values. Regions with a significant group differences ($p<0.01$ in one-way ANOVA) are presented in Table 5. All regions-of-interest (ROIs) analyzed in study I are shown here. ANOVA = analysis of variances, VPC = ventrolateral prefrontal cortex. Modified from study I. Modified from study I.

| Tracer | Region | HC | PG | BED | *F*-value One-way ANOVA | *P*-value One-way ANOVA |
|---|---|---|---|---|---|---|
| **[$^{11}$C]carfentanil** | Fusiform gyrus | 0.499 (0.099) | 0.464 (0.103) | 0.361 (0.073) | 5.0 | 0.012 |
| | Caudal anterior cingulate cortex | 1.16 (0.19) | 1.08 (0.20) | 0.884 (0.176) | 5.0 | 0.012 |
| | Rostral middle frontal gyrus | 0.858 (0.158) | 0.874 (0.195) | 0.649 (0.145) | 4.6 | 0.017 |
| | Pars triangularis of VPC | 0.783 (0.140) | 0.765 (0.199) | 0.579 (0.090) | 4.3 | 0.022 |
| | Medial temporal lobe[1] | 0.490 (0.093) | 0.463 (0.109) | 0.359 (0.092) | 4.3 | 0.022 |
| | Temporal pole | 0.799 (0.140) | 0.817 (0.168) | 0.617 (0.173) | 4.2 | 0.023 |
| | Pars opercularis of VPC | 0.884 (0.154) | 0.837 (0.182) | 0.685 (0.111) | 3.8 | 0.031 |
| | Inferior temporal gyrus | 0.768 (0.108) | 0.737 (0.144) | 0.614 (0.123) | 3.7 | 0.035 |
| | Orbitofrontal cortex[2] | 0.860 (0.142) | 0.863 (0.189) | 0.681 (0.129) | 3.6 | 0.038 |
| | Lateral temporal lobe[3] | 0.726 (0.095) | 0.709 (0.133) | 0.590 (0.108) | 3.6 | 0.037 |
| | Insula | 0.904 (0.126) | 0.850 (0.144) | 0.760 (0.097) | 3.1 | 0.060 |
| | Middle temporal gyrus | 0.791 (0.108) | 0.774 (0.146) | 0.656 (0.129) | 2.9 | 0.070 |
| | Superior temporal gyrus | 0.655 (0.099) | 0.654 (0.128) | 0.545 (0.109) | 2.7 | 0.084 |
| | Precuneus | 0.507 (0.100) | 0.490 (0.108) | 0.401 (0.103) | 2.6 | 0.085 |
| | Superior frontal gyrus | 0.828 (0.175) | 0.836 (0.196) | 0.658 (0.162) | 2.6 | 0.087 |
| | Transverse temporal cortex | 0.354 (0.147) | 0.327 (0.137) | 1.06 (2.24) | 1.7 | 0.20 |
| | Medial orbitofrontal cortex | 0.847 (0.174) | 0.880 (0.205) | 0.731 (0.148) | 1.6 | 0.22 |
| | Precentral gyrus | 0.543 (0.107) | 0.538 (0.129) | 0.452 (0.109) | 1.6 | 0.21 |
| | Rostral anterior cingulate cortex | 1.05 (0.22) | 1.03 (0.19) | 0.887 (0.208) | 1.6 | 0.21 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Banks of superior temporal sulcus | 0.721 (0.0965) | 0.714 (0.141) | 0.628 (0.114) | 1.6 | 0.21 |
| | Putamen | 1.19 (0.15) | 1.15 (0.23) | 1.05 (0.17) | 1.4 | 0.25 |
| | Amygdala | 1.34 (0.32) | 1.32 (0.29) | 1.16 (0.17) | 1.1 | 0.35 |
| | Nucleus caudatus | 1.17 (0.21) | 1.05 (0.29) | 1.12 (0.21) | 1.0 | 0.38 |
| | Caudal middle frontal gyrus | 0.733 (0.135) | 0.738 (0.172) | 0.657 (0.155) | 0.74 | 0.48 |
| | Postcentral gyrus | 0.334 (0.097) | 0.339 (0.109) | 0.288 (0.055) | 0.74 | 0.49 |
| | Globus pallidus | 0.517 (0.240) | 0.469 (0.229) | 0.588 (0.109) | 0.72 | 0.49 |
| | Paracentral gyrus | 0.423 (0.116) | 0.427 (0.115) | 0.378 (0.126) | 0.45 | 0.64 |
| | Supramarginal gyrus | 0.740 (0.111) | 0.747 (0.156) | 0.697 (0.144) | 0.35 | 0.71 |
| | Superior parietal cortex | 0.288 (0.084) | 0.311 (0.106) | 0.291 (0.086) | 0.26 | 0.77 |
| | Entorhinal cortex | 0.371 (0.157) | 0.359 (0.185) | 0.375 (0.192) | 0.029 | 0.97 |
| | Inferior parietal cortex | 0.553 (0.080) | 0.561 (0.127) | 0.554 (0.135) | 0.021 | 0.98 |
| **[$^{18}$F]fluorodopa** | Putamen | 0.0133 (0.0015) | 0.0137 (0.0019) | 0.0113 (0.0032) | 3.4 | 0.044 |
| | Nucleus caudatus | 0.0119 (0.0013) | 0.0120 (0.0020) | 0.0102 (0.0032) | 2.0 | 0.15 |
| | Globus pallidus | 0.00601 (0.0013) | 0.00630 (0.0015) | 0.00537 (0.0011) | 1.0 | 0.36 |
| | Thalamus | 0.00180 (0.00038) | 0.00162 (0.00041) | 0.00167 (0.00027) | 0.9 | 0.42 |
| | Hippocampus | 0.00264 (0.00081) | 0.00277 (0.00045) | 0.00238 (0.00053) | 0.79 | 0.46 |
| | Amygdala | 0.00510 (0.00088) | 0.00501 (0.00090) | 0.00486 (0.00134) | 0.14 | 0.87 |

[1]ROI formed by fusing entorhinal cortex, fusiform gyrus, parahippocampal gyrus and temporal pole

[2]ROI formed by fusing lateral orbitofrontal cortex and medial orbitofrontal cortex

[3]ROI formed by fusing banks of superior temporal sulcus, inferior temporal gyrus, middle temporal gyrus, superior temporal gyrus and transverse temporal cortex.

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