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NEUROBIOLOGY OF PATHOLOGICAL GAMBLING

Brain imaging and epidemiological studies

by

Juho Joutsa

TURUN YLIOPISTO
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From Department of Neurology and Turku PET Centre, University of Turku and Turku University Hospital

Supervised by

Adjunct Professor Valtteri Kaasinen
Department of Neurology and Turku PET Centre
University of Turku
Turku, Finland

and

Professor Juha O. Rinne
Turku PET Centre
University of Turku
Turku, Finland

Reviewed by

Professor Seppo Kaakkola
Department of Neurology
University of Helsinki
Helsinki, Finland

and

Professor Paola Piccini
Centre of Neuroscience
Division of Experimental Medicine
Imperial College London
London, UK

Dissertation Opponent

Professor Tapani Keränen
Clinical Pharmacology and Therapeutics
Department of Pharmacy
University of Eastern Finland
Kuopio, Finland

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ABSTRACT

Juho Joutsa

NEUROBIOLOGY OF PATHOLOGICAL GAMBLING

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From Department of Neurology and Turku PET Centre, University of Turku and Turku University Hospital, Turku, Finland

Pathological gambling, a form of behavioral addiction, refers to maladaptive, compulsive gambling behavior severely interfering with an individual's normal life. The prevalence of pathological gambling has been estimated to be 1–2% in western societies. The reward deficiency hypothesis of addiction assumes that individuals that have, or are prone, to addictions have blunted mesolimbic dopamine reward signaling, which leads to compulsive reward seeking in an attempt to compensate for the malfunctioning brain reward network.

In this research project, the effects of gambling were measured using brain [^{11}C] raclopride PET during slot machine gambling and possible brain structural changes associated with pathological gambling using MRI. The subjects included pathological gamblers and healthy volunteers. In addition, impulse control disorders associated with Parkinson's disease were investigated by using brain [^{18}F]fluorodopa PET and conducting an epidemiological survey.

The results demonstrate mesolimbic dopamine release during gambling in both pathological gamblers and healthy volunteers. Striatal dopamine was released irrespective of the gambling outcome, whether the subjects won or not. There was no difference in gambling induced dopamine release between pathological gamblers and control subjects, although the magnitude of the dopamine release correlated with gambling related symptom severity in pathological gamblers. The results also show that pathological gambling is associated with extensive abnormality of brain white matter integrity, as measured with diffusion tensor imaging, similar to substance-addictions.

In Parkinson's disease patients with impulse control disorders, enhanced brain [^{18}F] fluorodopa uptake in the medial orbitofrontal cortex was observed, indicating increased presynaptic monoamine function in this region, which is known to influence signaling in the mesolimbic system and reward processing. Finally, a large epidemiological survey in Finnish Parkinson's disease patients showed that compulsive behaviors are very common in Parkinson disease and they are strongly associated with depression.

These findings demonstrate the role of dopamine in pathological gambling, without support for the concept of reward deficiency syndrome.

Key words: Pathological gambling, dopamine, Parkinson's disease, Impulse control disorders, PET, MRI, DTI

TIIVISTELMÄ

Juho Joutsa

PELIHIMON NEUROBIOLOGIA

Aivokuvantamis- ja epidemiologiset tutkimukset

Neurologian oppiaine ja Valtakunnallinen PET-keskus, Turun yliopisto ja Turun yliopistollinen keskussairaala

Pelihimo on toiminnallisen riippuvuuden muoto ja tarkoittaa pakonomaista rahapelaamista, joka haittaa merkittävästi yksilön elämää. Pelihimon esiintyvyydeksi on länsimaisessa väestössä arvioitu 1–2 %. Addiktion reward deficiency -hypoteesin mukaan mesolimbinen dopamiinivälitteinen palkkiojärjestelmä toimii vajaasti yksilöillä, jotka kärsivät addiktioista tai ovat taipuvaisia addiktion kehittymiseen. Hypoteesin mukaan tämä johtaa pakonomaiseen palkkiohakuisuuteen, joka on yritys kompensoida vajaasti toimivaa aivojen palkkiojärjestelmää.

Tässä tutkimuksessa rahapelaamisen vaikutuksia aivoihin mitattiin [^{11}C]-raklopridi-PET-kuvauksella raha-automaattipelaamisen aikana ja pelihimoon mahdollisesti liittyviä aivojen rakenteellisia muutoksia magneettikuvantamisella. Tutkittavina olivat pelihimosta kärsivät henkilöt sekä terveet verrokit. Lisäksi tutkimuksessa selviteltiin Parkinsonin tautiin liittyvien impulssikontrollihäiriöiden neurobiologiaa aivojen [^{18}F]-fluorodopa-PET-kuvauksella sekä epidemiologiaa laajalla poikkileikkaus-tutkimuksella.

Rahapelaamisen aikana dopamiinia vapautui mesolimbisessä järjestelmässä sekä peliriippuvaisilla henkilöillä että terveillä vapaaehtoisilla. Dopamiinia vapautui riippumatta pelaamisen tuloksista (voitto tai ei voittoa). Vaikka dopamiinin vapautumisessa ei havaittu eroja ryhmien välillä, pelihimosta kärsivillä dopamiinin vapautuminen korreloi pelihimon oireiden vaikeusasteeseen. Toisaalta aivojen diffuusiotensorikuvauksella saadut tulokset osoittivat, että pelihimoon liittyy laaja-alaisia aivojen valkean aineen muutoksia, joita on aiemmin havaittu päihderiippuvuuksien yhteydessä.

Parkinsonin tautia sairastavista potilaista impulssikontrollihäiriöistä kärsivillä havaittiin mediaalisella orbitofrontaalisella kuorikerroksella [^{18}F]fluorodopan kertymän lisääntyminen, mikä viittaa monoamiinitoiminnan lisääntymiseen tällä alueella. Aivojen orbitofrontaalisen kuorikerroksen tiedetään vaikuttavan mesolimbisen järjestelmän toimintaan ja palkkiosignaalien käsittelyyn. Laajan epidemiologisen tutkimuksen mukaan impulssikontrollihäiriöt olivat erittäin yleisiä suomalaisilla Parkinsonin tautia sairastavilla henkilöillä, ja nämä häiriöt olivat voimakkaasti yhteydessä masennukseen.

Löydösten perusteella dopamiini-välittäjäaine on merkittävä tekijä pelihimon taudinkuvassa, mutta tulokset eivät tue hypoteesia reward deficiency -syndroomasta.

Avainsanat: Pelihimo, dopamiini, Parkinsonin tauti, impulssikontrollihäiriöt, PET, MRI, DTI

TABLE OF CONTENTS

ABBREVIATIONS

AADC = aromatic amino acid decarboxylase

BDI = Beck depression inventory

BP_{ND} = non-displaceable binding potential

BR = behavioral rating

DAT = dopamine transporter

DRD2 = dopamine D2 receptor

DSM-IV = Diagnostic and statistical manual of mental disorders, fourth edition

DTI = diffusion tensor imaging

FA = fractional anisotropy

(f)MRI = (functional) magnetic resonanse imaging

ICD = impulse control disorder

K_i = net influx rate

LEDD = levodopa equivalent daily dose

MD = mean diffusivity

mOFC = medial orbitofrontal cortex

PD = Parkinson's disease

PET = positron emission tomography

PG = pathological gambling

QUIP = the questionnaire for impulsive-compulsive behaviors in Parkinson's disease

RDS = reward deficiency syndrome

ROI = Region of interest

S(n)PM = Statistical (non-)Parametric Mapping

SOGS = South Oaks Gambling Screen

SPECT = single-photon emission computed tomography

TBSS = tract-based spatial statistics

UPDRS = Unified Parkinson's disease rating scale

VBM = voxel-based morphometry

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which will be referred to by corresponding Roman numerals:

I Joutsa J, Johansson J, Niemelä S, Ollikainen A, Hirvonen MM, Piepponen P, Arponen E, Alho H, Voon V, Rinne JO, Hietala J, Kaasinen V. Mesolimbic dopamine release is linked to symptom severity in pathological gambling. *NeuroImage. 2012;60(4):1992-9.*

II Joutsa J, Saunavaara J, Parkkola R, Niemelä S, Kaasinen V. Extensive abnormality of brain white matter integrity in pathological gambling. *Psychiatry Res. 2011;194(3):340-6.*

III Joutsa J, Martikainen K, Niemelä S, Johansson J, Forsback S, Rinne JO, Kaasinen V. Increased medial orbitofrontal [^{18}F]fluorodopa uptake in Parkinsonian impulse control disorders. *Mov Disord. 2012;27(6):778-82.*

IV Joutsa J, Martikainen K, Vahlberg T, Voon V, Kaasinen V. Impulse control disorders and depression in Finnish patients with Parkinson's disease. *Parkinsonism Relat Disord. 2012;18(2):155-60.*

1. INTRODUCTION

Gambling has been present in mankind for thousands of years (Arnold, 1977). The wide attraction to gambling could be explained by the capability of gambling to activate the phylogenetically ancient brain mesolimbic reward network, thus mimicking the effects of natural rewards needed for survival of the individual, survival of the genes, and reproduction of the organism (Durrant *et al.*, 2009; Olsen, 2011). For most people, gambling is a form of entertainment with few adverse effects. However, for some people gambling becomes seriously maladaptive, interfering with their finances, work, and relationships causing significant subjective suffering. This situation is referred to as pathological gambling (PG). PG shares clinical features with substance addictions and can be considered as a behavioral addiction (Olsen, 2011). It has been shown that substance addicted individuals have an abnormally functioning brain reward network, but it is not clear whether similar abnormality exists in behavioral addictions without the direct pharmacological abuse of the brain (Volkow *et al.*, 2009).

PG is relatively common in western societies affecting approximately 1-2% of the population at some point of their life (Schaffer *et al.*, 1999). In individuals suffering from Parkinson's disease (PD), a chronic neurogenerative disorder affecting the brain nigrotriatal dopamine neurons, the prevalence of pathological gambling and other compulsive behaviors seems to be even higher compared to the general population (Ambermoon *et al.*, 2011). However, only a few studies have compared the prevalence rates directly. The risk of developing behavioral compulsions in PD seems to relate especially to dopaminomimetic medication (Weintraub *et al.*, 2010a). To date, neurobiology of PG is largely unknown and no specific pharmacological treatment exists. Therefore, research on the neurobiological mechanisms of PG is required.

This work aims to investigate the neurobiology of pathological gambling with positron emission tomography (PET) and structural MRI. The primary objective was to explore the mesolimbic dopaminergic neurotransmission with [^{11}C]raclopride PET during slot machine gambling in pathological gamblers and compare them to healthy individuals. The possible abnormalities in brain structure related to PG were investigated with brain MRI using voxel-based morphometry (VBM) and diffusion tensor imaging (DTI) with tract-based spatial statistics (TBSS). Furthermore, presynaptic dopaminergic activity was investigated with [^{18}F]fluorodopa PET in individuals suffering from PD with and without PG or other impulse control disorders (ICDs). Finally, to get a comprehensive view of the prevalence, characteristics, and association to depression of impulsive-compulsive behaviors in PD, a survey including 575 Finnish Parkinson patients was conducted.

2. REVIEW OF THE LITERATURE

2.1 Addiction disorders

2.1.1 Evolutionary aspects

Sufficient nutrition and breeding are crucial for life. Thus, evolution has favored qualities that ensure adequate nutrition and production of offspring. One of the key mechanisms ensuring this behavior is the brain reward circuitry. The functions, beneficial for the survival of the specie, activate the brain reward circuitry and are experienced as pleasurable, thus promoting goal-oriented behavior relevant to the survival and reproduction of the organism (Durrant *et al.*, 2009). Interestingly, the use of psychoactive substances has been part of human lives for thousands of years, and is present in every culture (Durrant *et al.*, 2009). Substance use, however, seems to have little benefits and can be harmful in terms of survival. Why has evolution preserved such a behavior that is unbeneficial to the individual, although, intuitively, it seems that it should have been eradicated by the natural selection process?

Substances of abuse directly activate via pharmacological mechanisms the brain reward signaling, thus mimicking (and exceeding in magnitude) the signals of natural rewards. Hence, the brain reward system falsely interprets the signals of the drugs as highly beneficial for the survival/reproduction of the individual. Therefore, human predilection to the substances of abuse might be caused by misfiring of the brain reward circuitry. Moreover, the predilection does not only concern humans, but also animals, indicating that the brain reward system has developed early in the course of evolution (Nesse & Berridge, 1997; Berridge & Kringelbach, 2008).

Like substance use, gambling has also been very widespread, both timely and culturally, in the history of the humankind (Arnold, 1977). Clearly, there is something in gambling that abuses the brain systems developed in the needs for survival and reproduction. Life is full of choices in the environment of limited resources, and each choice includes a risk. Risky choices could be considered as gambling – weighing the different options according to their probability. With limited resources and challenged long-term survival (which drives the evolution), more risk prone behavior aiming for short-term benefits might provide the niche for survival (Petry, 2005; Durrant *et al.*, 2009).

2.1.2 Substance addiction

Humans are vulnerable to the addicting effects of various pharmacological substances. The substances causing addiction are the substances whose effects are experienced to be pleasurable (or alleviate negative emotions), and include a large variety of different types

of molecule groups, such as stimulants, opioids, marijuana, alcohol, nicotine etc. (Nesse & Berridge, 1997). The degree of substance use can be divided into three categories: use (recreational or harmless), abuse (causing some degree of harm), and addiction (dependence according to the criteria in DSM-IV) (Koob & Le Moal, 1997). Substance dependence is characterized by the excess urge or compulsion to take the drug despite the adverse consequences, and dysphoric mood when abstinent of the drug of being abused (Koob & Le Moal, 1997). The estimates, derived from a very large population survey (n = 43,093) conducted in the US, of the current substance dependence rates are <1% for illicit drugs, 4% for alcohol, and 13% for nicotine, and the lifetime rates of substance dependence are far greater (Grant *et al.*, 2004a; Grant *et al.*, 2004b; Compton *et al.*, 2007). Substance dependence and excess substance use in general is a major public health problem and can cause significant subjective suffering for the affected individuals and people close to them.

2.1.3 Behavioral addictions

All addictions do not necessarily involve pharmacological substances. Historically, the only disorders that have been considered addictions are those involving alcohol or other centrally acting agents. The non-drug addictions, however, share many characteristics of drug addictions. Like substance addictions, non-drug addictions manifest in similar psychological and behavioral patterns including cravings, impaired control over the behavior, tolerance, withdrawal, and high rates of relapse (Olsen, 2011). Non-drug addictions have thus been termed "behavioral addictions". The concept of non-drug addictions or behavioral addictions is relatively new, and is included for the first time in the proposed revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (Holden, 2010). There are several compulsive activities that could be considered as non-drug addictions (Olsen, 2011). To date, the most extensively studied form of behavioral addiction is pathological gambling (PG), which is also the focus of this thesis and will be reviewed in detail in the next section (*2.1.4*). However, other behavioral addictions apart from PG have also received growing research attention during recent years. Sexual addiction (termed also as hypersexuality or compulsive sexual behavior etc.) seems to share the characteristic features of addiction (craving, compulsive nature of the behavior, and continuing of the behavior despite even devastating consequences), and has thus been suggested to be included to the category of behavioral addictions (Garcia & Thibaut, 2010). In addition, there is a range of compulsive behaviors with possibly similar symptomatology and background neurobiology, such as addictions to eating (Parylak *et al.*, 2011), shopping (Black, 2007), internet use (Bergmark *et al.*, 2011), work (Andreassen *et al.*, 2012), physical exercise (Berczik *et al.*, 2012), and possibly many more. Behavioral addictions recognized in the context of Parkinson's disease (PD) [often referred to as impulse control disorders (ICDs)] include compulsive gambling, sexual behavior, shopping, and eating (reviewed in section *2.1.4.2*). The term impulsive-compulsive behaviors (ICBs) in PD refers to ICDs, dopamine dysregulation syndrome (DDS, addiction to antiparkinsonian medication) and compulsive repetitive stereotyped actions, such as punding, hobbyism, and walkabout.

2.1.4 Pathological gambling

2.1.4.1 Epidemiology and characteristics

For many persons, gambling is a common form of entertainment with no or minimal adverse effects on their lives. However, for some people, gambling becomes severely maladaptive, interfering with their finance, work, relationships and mental health. This kind of maladaptive behavior is referred to as pathological gambling (PG). The gambling behavior of the affected individuals is characterized with the need to gamble with increasing amounts of money, chasing losses, excess time consumed in gambling or thinking of it, unsuccessful attempts to cut down gambling, attempts of concealing the gambling involvement, and financial problems due gambling losses.

Currently, the diagnosis of PG (or level 3 gambling) in Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) is based on the criteria, which are presented in Table 1. However, gambling involvement and related problems are often considered as a continuum, and in the scientific literature, several different nomenclatures have been used for describing different stages of this continuum. In addition to PG, the term 'problem gambling' has also been used to describe pathological and also milder forms of disordered gambling (3-4 affirmative answer in DSM-IV criteria, also termed as at-risk or level 2 gambling). Level 1 and level 0 gambling refer to gambling behavior without any adverse effects and not gambling at all, respectively (Petry, 2005).

Table 1. DSM-IV Pathological Gambling Diagnostic Form

1.	Have you often found yourself thinking about gambling [e.g., reliving past gambling experiences, planning the next time you will play or thinking of ways to get money to gamble]?
2.	Have you needed to gamble with more and more money to get the amount of excitement you are looking for?
3.	Have you become restless or irritable when trying to cut down on or stop gambling?
4.	Have you gambled to escape from problems or when you are feeling depressed, anxious or bad about yourself?
5.	After losing money gambling, have you returned another day in order to get even?
6.	Have you lied to your family or others to hide the extent of your gambling?
7.	Have you made repeated unsuccessful attempts to control, cut back or stop gambling?
8.	Have you been forced to go beyond what is strictly legal in order to finance gambling or to pay gambling debts?
9.	Have you risked or lost a significant relationship, job, educational, or career opportunity because of gambling?
10.	Have you sought help from others to provide the money to relieve a desperate financial situation caused by gambling?

Five or more affirmative answers indicate pathological gambling. Adapted from the American Psychiatric Association Diagnostic Criteria from the DSM-IV (1994)

PG is a common disorder affecting approximately 1-2% of the adult population at some point of their life (Schaffer *et al.*, 1999). When also taking into account individuals with less severe gambling problems (level 2), the lifetime prevalence is approximately 5% (Schaffer *et al.*, 1999). The current diagnostic procedure is a diagnosis made by a psychiatrist in a face-to-face interview according to the DSM-IV. However, several self-report screening and diagnostic tools have also been developed. Currently, the most widely used screening tool is South Oaks Gambling Screen (SOGS), a 20-item self-report tool, developed more than 20 years ago (Lesieur & Blume, 1987).

Slot machines are the most common form of gambling for pathological gamblers, and they have been referred to as the "crack-cocaine" of gambling due to their assumed high addiction potential (Petry, 2003; Dowling *et al.*, 2005). However, the scientific evidence regarding the especially high addiction potential of slot machine gambling is somewhat inconclusive (Dowling *et al.*, 2005). At the moment, there is no specific pharmacologic treatment for problem gambling. Antidepressive medications, opioid antagonists and possibly mood stabilizers have been indicated to be beneficial (and superior compared to placebo), but are probably still inferior treatment options compared to non-pharmacological therapies (Pallesen *et al.*, 2007; Leung & Cottler, 2009; Hodgins *et al.*, 2011).

Problem gambling is often associated with several psychiatric comorbidities. Not surprisingly, the most common comorbidities are substance use disorders followed by mood and anxiety disorders (Lorains *et al.*, 2011). Also various personality traits, such as impulsivity and antisocial personality, seem to be more prevalent in pathological gamblers than in the general population [reviewed in (Petry *et al.*, 2005)]. However, the directionality of problem gambling and comorbid psychiatric disorders remains to be clarified. In addition, an emerging body of evidence has linked problem gambling, not just to psychiatric conditions, but also to neurological conditions such as PD, an association first reported by Molina et al. a decade ago (Molina *et al.*, 2000; Ambermoon *et al.*, 2011).

2.1.4.2 Pathological gambling and other ICDs in patients with Parkinson's disease

Parkinson's disease (PD) is a chronic neurodegenerative disorder characterized by resting tremor, rigidity, and slowness of movement. The key motor symptoms of PD are a result of a progressive loss of nigrostriatal dopaminergic neurons (i.e. neurons originating from the substantia nigra to the striatum). Initially, as in the famous essay by Dr. James Parkinson (Parkinson, 1817), PD was thought to manifest only as a motor disorder, but subsequently has been shown to affect mental functions as well. The current pharmacological treatment aims mainly to increase the brain dopamine function.

The point prevalence of ICDs (problem gambling, hypersexuality, compulsive shopping, and compulsive eating) is approximately 14% in patients with PD according to the

largest epidemiological study to date (n = 3,090) (Weintraub *et al.*, 2010a). PG is thought to be much more prevalent in PD patients compared to the general population, occurring at the rate of 3.4 to 6% [reviewed in (Djamshidian *et al.*, 2011)], but there are only a few studies directly comparing the prevalence rates to the prevalence rate of the general population. In fact, two case-control studies published recently did not find any differences in problem or pathological gambling rates between PD patients and the general population (Antonini *et al.*, 2011; de Chazeron *et al.*, 2011), although some studies have demonstrated a clearly increased prevalence in PD patients compared to non-PD subjects (Avanzi *et al.*, 2006; Crockford *et al.*, 2008). In addition, the methods used to estimate PG, and the terminology describing the degree of severity of disordered gambling, vary from study to study further confusing the estimates. Recently, a self-report tool, questionnaire for impulsive-compulsive behaviors in Parkinson's disease (QUIP), has been developed and validated for screening purposes of Parkinsonian ICDs (Weintraub *et al.*, 2009), and it has been shown to be equally useful as patient and/or informant reported (Papay *et al.*, 2011).

Although it can be argued if the prevalence of PG (or other ICDs) is higher in PD patients compared to the general population, there is a substantial amount of evidence linking PD ICDs to dopamine replacement therapy (DRT) (Grosset *et al.*, 2006; Gallagher *et al.*, 2007; Singh *et al.*, 2007; Weintraub *et al.*, 2010a). For instance, practically all types of dopaminomimetic medication, commonly used in the treatment of PD, have been linked to the context of ICDs. The most convincing evidence demonstrates the role of dopamine agonists in the development of ICDs [reviewed in (Ambermoon *et al.*, 2011)]. Dopamine agonist use has been demonstrated to increase the ICD risk by almost three-fold (Weintraub *et al.*, 2010a), and some studies have suggested a dose-dependent effect, but the evidence concerning the issue is not clear [reviewed in (Ambermoon *et al.*, 2011)]. Furthermore, there are some anecdotal reports demonstrating the disappearance of ICDs after discontinuation of these medications (Singh *et al.*, 2007; Mamikonyan *et al.*, 2008; Macphee *et al.*, 2009; Bharmal *et al.*, 2010; Sohtaoğlu *et al.*, 2010). ICDs are most likely a class-side-effect of dopamine agonists, since there has been no evidence of differences between dopamine agonists in the ICD risk [reviewed in (Ambermoon *et al.*, 2011)]. Also levodopa has been shown to be associated with ICDs in a dose-dependent fashion (Weintraub *et al.*, 2010a). Interestingly, amantadine was initially suggested as a possible treatment for ICD problems (Thomas *et al.*, 2010), but has subsequently been shown to be associated with ICDs in a much larger population (Weintraub *et al.*, 2010b). Anticholinergic medication, which is also used in the treatment of PD, has not been reported to be associated with ICDs. However, to date, there are no prospective, controlled studies with a sufficient sample population investigating medical interventions or treatment modifications on ICD problems. Dopaminergic treatment has been associated with ICDs in non-PD populations, for example in restless legs syndrome (RLS), as well (Voon *et al.*, 2011b)2011b. However, the connection between dopaminergic medication and ICDs in RLS is less clear than in PD, which could relate to the smaller doses used in the treatment of RLS.

Also, other factors such as the male sex, younger age, not being married, younger age at PD onset, earlier or family history of ICD problems, and substance use have been associated with PG and other ICDs in PD [for reviews, see (Ceravolo *et al.*, 2009; Ambermoon *et al.*, 2011)]. PD patients with ICDs are characterized by impulsiveness and novelty seeking; and suffer more from depression, anxiety, obsessive-compulsive symptoms, and greater functional impairment compared to patients without ICDs; according to a large multicenter case-control study (Voon *et al.*, 2011c). However, the patients with different ICD subtypes (PG, hypersexuality, shopping, eating) might differ in subject characteristics and psychiatric symptoms. More specifically, patients with PG and compulsive shopping seem to resemble each other more than patients with hypersexuality and compulsive eating (Voon *et al.*, 2011c). Slot machine gambling may be the most common form of gambling also in PD patients with problem gambling (Gallagher *et al.*, 2007).

2.2 Neurobiology of pathological gambling

2.2.1 Brain reward system and dopamine neurotransmission

Human dopaminergic systems consist of several pathways (Figure 1). The mesolimbic pathway, originating from the ventral tegmental area (VTA) to the basal ganglia [nucleus accumbens (NAcc), which is located in the ventral striatum], is thought to be the essential part of the brain reward system, although also the mesocortical pathway and other neurotransmitter systems participate in the reward and reward-related stimuli processing (Koob & Nestler, 1997). Anatomically speaking, the striatum is comprised of the NAcc, caudate, and putamen. Functionally, the striatum can be divided to the ventral, associative, and sensorimotor parts (Haber & McFarland, 1999; Kegeles *et al.*, 2010). The ventral striatum includes not only NAcc, but also the ventral parts of the caudate and putamen, which also connect to the limbic system. Therefore, the ventral striatum has no definitive anatomical boundaries, and thus, the anatomical delineation of the structure is somewhat challenging. Widely accepted criteria for delineating the ventral striatum neuroimaging studies are described in detail by Mawlawi and colleagues (Mawlawi *et al.*, 2001). The functional division and connections of the striatum are presented in Figure 2.

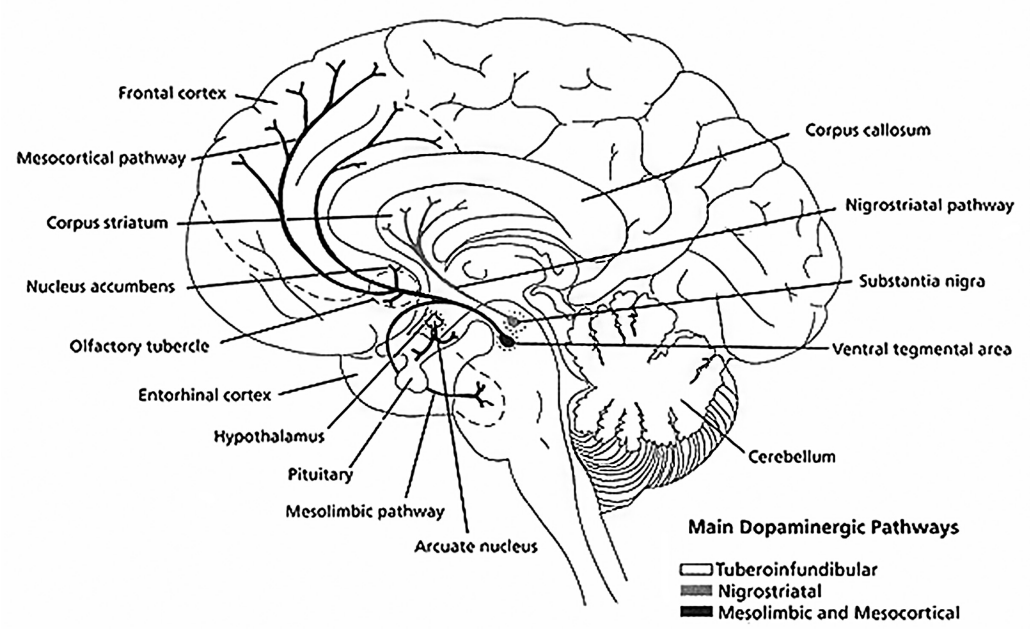

Figure 1. Brain dopaminergic pathways
A schematic representation of the main human brain dopaminergic pathways. Adapted from (Crocker, 1994).

Studies in rhesus monkeys have shown that rewarding stimuli (fruit juice in this case) evoke phasic signaling bursts in VTA dopamine neurons projecting to NAcc (Schultz *et al.*, 1997). Interestingly, not just reward, but after learning, also conditioned stimulus predicting the future reward evoke signal transmission of the dopamine neurons, and the proportion of the signaling seems to shift towards coding the conditioned stimulus and not the reward (Schultz *et al.*, 1997). However, if the expected reward is not received, the signaling of the dopamine neurons slows down, therefore coding for reward prediction error (Schultz *et al.*, 1997). Furthermore, Fiorillo et al. have shown that the magnitude of the signal evoked by conditioned reward predicting stimulus is dependent on the probability of the expected reward, the effect being maximal when the uncertainty is the greatest (Fiorillo *et al.*, 2003), which is likely to be relevant in the context of gambling. The reward coding of the VTA dopamine neurons are depicted in Figure 3. Furthermore, practically all pharmacological substances of abuse have been shown to activate the mesolimbic dopaminergic pathway projecting to NAcc (Koob, 1992).

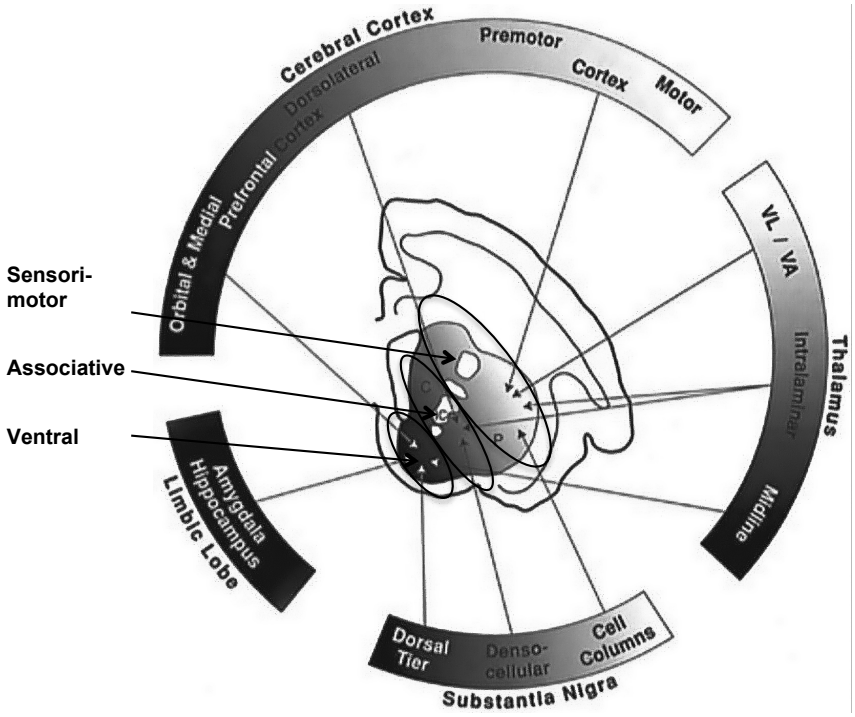

Figure 2. Functional division of the striatum
A schematic representation of the striatal connections and functional division separating the sensorimotor, associative, and ventral striatum. According to Mawlawi *et al.*, the ventral striatum lays anteriorily to the anterior commissure. The border between the ventral and dorsal striatum (the associative and sensorimotor striatum) is defined by a line joining 1) the intersection between the outer edge of the putamen with a vertical line going through the most superior and lateral point of the internal capsule; and 2) the centre of the portion of the anterior commissure transaxial plane overlying the striatum; and 3) extended to the internal edge of the caudate (Mawlawi *et al.*, 2001). C = caudate. P = putamen. VA = ventral anterior nucleus. VL = ventral lateral nucleus. Adapted from (Haber & McFarland, 1999; Kegeles *et al.*, 2010).

Functional neuroimaging studies have provided us *in vivo* evidence of the neurobiological processes of normal and abnormal functions of the brain reward-related networks in humans. *In vivo* PET studies in humans have confirmed the observations of reward-related dopamine signaling in rhesus monkeys of non-pharmacological rewards, such as monetary reward during various tasks (Koepp *et al.*, 1998; Zald *et al.*, 2004; Schott *et al.*, 2008; Steeves *et al.*, 2009), food after fasting (Small *et al.*, 2003), and pleasurable music (in individuals who respond exceptionally strongly to music) (Salimpoor *et al.*, 2011); and pharmacological rewards, such as stimulants, alcohol, nicotine, and cannabis [reviewed in (Volkow *et al.*, 2009)].

2.2.2 Addiction theories

Substances of abuse release striatal dopamine, and the magnitude of the dopamine release is correlated positively with the subjective euphoria induced by the drug (Koob

& Bloom, 1988; Volkow *et al.*, 1999; Drevets *et al.*, 2001). Given the role of dopamine in brain reward-related signal processing, PET imaging studies of addiction disorders have mainly focused on the brain dopaminergic system. Consistent evidence shows attenuated baseline striatal dopamine D2 receptor availability and dopamine release in response to acute administration of a drug in substance addicted individuals [reviewed in (Volkow *et al.*, 2009)]. In addition to the impairment of the mesolimbic dopaminergic pathway, also altered frontal cortical function has been linked to the addiction disorders (Volkow *et al.*, 2005). Furthermore, there is a convincing body of evidence of the brain structural abnormalities related to long-term excessive substance use (Sullivan & Pfefferbaum, 2005; Berman *et al.*, 2008; Lim *et al.*, 2008; Azizian *et al.*, 2009).

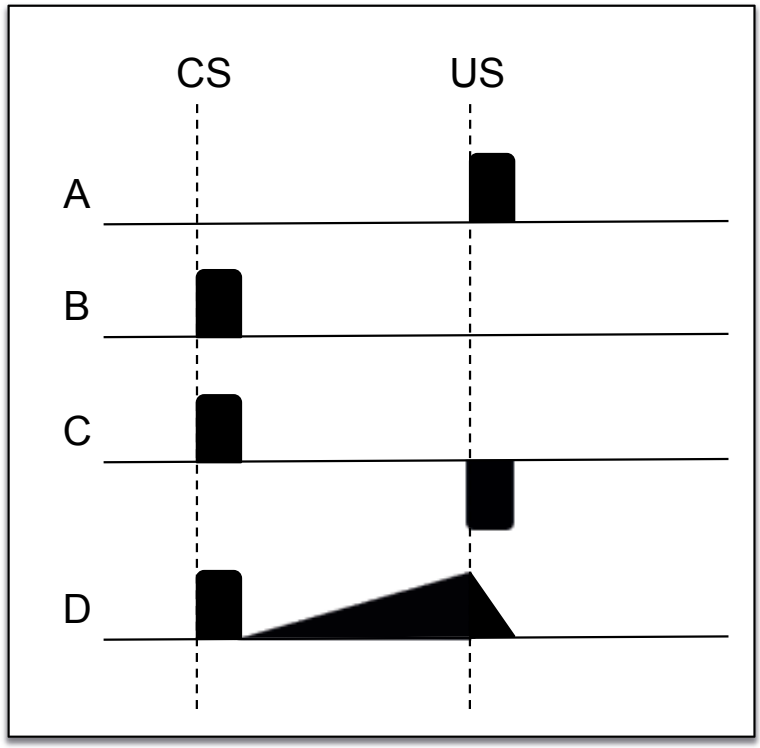

Figure 3. Reward-related stimuli coding in the mesolimbic dopamine neurons
CS = conditioned stimulus. US = unconditioned stimulus (reward). A. The mesolimbic dopamine neurons response with increasing phasic firing to surprising rewards (US). B. After learning with repeated exposure to the CS – US pairs, the activation of the dopamine neurons move towards conditioned reward-predicting stimulus (CS) and not the US anymore. C. Phasic firing pattern to reward predicting stimulus when reward is surprisingly omitted, demonstrating the reduction in neuronal activity at the time of the expected reward. D. Firing patterns to conditioned stimulus predicting reward with maximal uncertainty of reward delivery demonstrating the tonic activation of the dopamine neurons in response to uncertainty of the receipt of the reward. The upward activation bars indicate increase and downward decrease in neuronal firing. The figure is based on several sources of previous literature (Schultz *et al.*, 1997; Fiorillo *et al.*, 2003; Kaasinen *et al.*, 2009).

At the moment, there are a few prominent theories of the neurobiological mechanism of addiction disorders: the reward deficiency syndrome (RDS) hypothesis (Blum *et al.*, 2000; Comings & Blum, 2000), the impulsivity hypothesis (Bechara, 2005), and the incentive sensitization theory (Robinson & Berridge, 1993). The RDS hypothesis has been developed from the basis of genetic studies connecting certain alleles of dopamine-related genes to addiction disorders. The RDS hypothesis predicts that individuals with RDS have diminished brain reward responses to the natural rewarding stimuli, and hence, develop addiction in attempting to compensate for the non-hedonic state by the use of pharmacological substances, which have a stronger capability to directly activate the mesolimbic reward circuitry (Blum *et al.*, 2000). Contradicting the RDS hypothesis, the impulsivity hypothesis assumes addiction to be caused by an imbalance between two neural systems controlling the decision-making: Increased reward signaling and impaired reflective system for controlling the impulses (Bechara, 2005). Partly in parallel with the latter assuming more of a hyper- than hypodopaminergic state, the incentive sensitization theory postulates that addiction results from the hypersensitized brain reward system resulting from repeated drug exposure causing incentive salience for drug use (Robinson & Berridge, 1993; 2008). Positron emission tomography (PET) imaging results have mainly supported the principle of the RDS hypothesis, whereas fMRI studies have provided inconclusive results [for a review, see (Hommer *et al.*, 2011)]. However, the neurobiology of addiction is a complex process involving multiple neural systems, and thus cannot be explained solely with the altered mesolimbic function. Recently, Volkow et al. have proposed a refined model of addiction based on neuroimaging (mainly PET) findings from the grounds of the RDS hypothesis, but also include aspects from the other theories (Volkow *et al.*, 2010). The model addiction neurobiology of Volkow and colleagues assumes decreased reward sensitivity, enhanced conditioned cue responses, negative mood, and impaired brain control circuits (Volkow *et al.*, 2010). Of the above-mentioned theories, the present project and the study design focused mainly on testing the principles of the RDS hypothesis in PG, because it has been supported by a recent fMRI study (Reuter *et al.*, 2005), and the available methodology was comparable to prior PET studies, which have provided evidence supporting the dopaminergic reward deficiency state in the context of substance addictions.

2.2.3 Neuroimaging studies in pathological gambling

In the following sections, the findings of the studies in PG, and also other ICDs associated with PD, are reviewed. Neuroimaging studies with PD patients are presented separately as behavioral addictions in PD might constitute a distinct entity from these disorders in the general population.

It has been estimated that in PG, genetic factors contribute to approximately of 50-60% of the variance (Lobo & Kennedy, 2009). Dopamine-related genes have been under especial attention, given the crucial role of dopamine in the brain reward circuits. Pathological gamblers have been shown to have some differences in dopamine D1, D2 and D4

receptor, and dopamine transporter (DAT) genes compared to non-gamblers (Blum *et al.*, 1995; Comings *et al.*, 1997; Comings *et al.*, 1999; Comings *et al.*, 2001). Human *in vivo* PET studies investigating the dopamine system have indicated, for example, dopamine D2 receptor (*DRD2)*-related *TaqIA* genotype having effect on the striatal *DRD2* receptor availability (Pohjalainen *et al.*, 1998; Jönsson *et al.*, 1999). In addition to the dopamine-related genes, other neurotransmitters have been connected to PG, but the evidence is less clear, and they are beyond the scope of this thesis (Pérez de Castro *et al.*, 1999; Ibañez *et al.*, 2000; Comings *et al.*, 2001; Pérez de Castro *et al.*, 2002). Early studies investigating the neurobiology of PG, have investigated cerebrospinal fluid (CSF) neurotransmitters and their precursors/metabolites, and suggested increased dopamine and noradrenaline, but decreased serotonin, neurotransmission in PG patients (Roy *et al.*, 1988; Bergh *et al.*, 1997; Nordin & Eklundh, 1999). However, the evidence is inconclusive and limited by the small sample sizes and robustness of the methods.

2.2.3.1 Neuroimaging in pathological gambling

PET and SPECT. There are only a relatively small number of published neuroimaging studies on PG. By using PET, pathological gamblers (without PD) have been investigated by two separate groups, with [^{18}F]fluorodeoxyglucose or with [^{11}C]raclopride. The baseline studies showed higher [^{18}F]fluorodeoxyglucose metabolic rates in the dorsal parts of the striatum and the thalamus, and orbitofrontal and medial frontal cortices; and decreased metabolic rates were found in the ventral parts of the striatum and the thalamus [but not in the regions of interest (ROIs) as a whole] in PG (Hollander *et al.*, 2008; Pallanti *et al.*, 2010). Baseline striatal dopamine D2(D3) receptor binding potentials, as measured with [^{11}C]raclopride, did not differ between pathological gamblers and healthy volunteers (Linnet *et al.*, 2010). Hollander et al. investigated seven pathological gamblers without a control group using [^{18}F]fluorodeoxyglucose during black jack gambling, with and without monetary rewards, and found that monetary rewards were associated with increased metabolic rates in the primary visual cortex, the cingulate gyrus, the putamen, and prefrontal areas (Hollander *et al.*, 2005). Linnet et al. studied 16 PG patients and 15 volunteers using [^{11}C]raclopride during Iowa Gambling Task (IGT), but did not find overall differences in the striatal dopamine release between the groups, but noticed that PG patients losing money released more dopamine in the left ventral striatum compared to controls (n=8 vs n=5) (Linnet *et al.*, 2010). Furthermore, Linnet and colleagues found that the PG patients experienced higher excitement levels during IGT performance, the dopamine release correlated to excitement levels (in PG patients only), and patients who released dopamine experienced higher excitement levels, but showed poorer IGT performance, than the healthy volunteers (Linnet *et al.*, 2011a; Linnet *et al.,* 2011b). A [^{18}F]fluorodeoxyglucose PET study in PG patients with lifetime comorbid bipolar disorder with lithium intervention PG-bipolar patients found an increased metabolic rate in the dorsal parts of the striatum and the thalamus, and orbitofrontal and medial frontal cortices; and decreased metabolic rates in the ventral parts of the striatum and the thalamus (but not in the ROIs as a whole) (Hollander *et al.*,

2008; Pallanti *et al.*, 2010). Lithium seemed superior to placebo in treatment effects, and normalized the ventral striatal metabolic rate, while increasing the orbitofrontal metabolism further (Hollander *et al.*, 2008; Pallanti *et al.*, 2010). In addition, there is also a single PET study investigating availability of brain serotonine 1B receptors in pathological gamblers, which found no differences between PG patients and healthy volunteers (Potenza *et al.*, 2011).

fMRI. fMRI studies in pathological gamblers have shown diminished responses to winning and losing gambling in the ventral striatum and the ventral prefrontal cortical regions; although the data is not completely uniform (Reuter *et al.*, 2005; de Ruiter *et al.*, 2009; Miedl *et al.*, 2010). Gambling cues instead have resulted in increased activation of multiple brain regions including prefrontal cortical, parahippocampal and occipital cortical areas in pathological gamblers compared to healthy volunteers (Crockford *et al.*, 2005; Goudriaan *et al.*, 2010; Miedl *et al.*, 2010), although there are also contradicting results (Potenza, 2008). There is also data indicating decreased sensitivity coupled with lower ventrolateral prefrontal activation to monetary losses during gambling in pathological gamblers (de Ruiter *et al.*, 2009). In addition, there is also evidence pointing to increased frontal risk responsiveness in pathological gamblers during gambling (Miedl *et al.*, 2010). Furthermore, pathological gamblers have been shown to express diminished ventromedial prefrontal cortical activity during response inhibition in the Stroop task (Potenza *et al.*, 2003).

Structural. To date, there is only a single study investigating the brain structure in PG (Yip *et al.*, 2011). The study focused only on the white matter integrity in three subsections of corpus callosum, and found bilaterally reduced fractional anisotropy of the genu of corpus callosum. There are no studies investigating the brain white or gray matter morphometry in PG.

2.2.3.2 Neuroimaging in Parkinson's disease with pathological gambling and other ICDs

PET and SPECT. The results of PET imaging studies using [^{11}C]raclopride have indicated an enhanced dopaminergic ventral striatal response to winning gambling in PD patients with PG, and also to reward-related cues in PD patients with ICDs (Steeves *et al.*, 2009; O'Sullivan *et al.*, 2011b). Also PD patients with dopamine dysregulation syndrome (DDS) have been shown to have greater ventral striatal dopamine release with levodopa administration than patients without DDS, and the amount of dopamine release correlated with a subjective rating of wanting the drug (Evans *et al.*, 2006). However, the enhanced ventral striatal dopamine release in response to levodopa administration has not been demonstrated with PD ICDs (O'Sullivan *et al*., 2011b). In addition, one study found lower dopamine D2(D3) receptor availability in the ventral striatum in PD patients with behavioral addictions (Steeves *et al.*, 2009), but there are negative findings as well (Evans *et al.*, 2006; O'Sullivan *et al.*, 2011b). Cilia et al. reported lower DAT binding in the ventral striatum in PD patients with ICDs compared to control PD patients (Cilia *et al.*, 2010). A single-photon emission computed tomography (SPECT) study

using technetium TC 99m ethylcysteinate dimer bicisate has shown increased resting perfusion in the right hemisphere including the orbitofrontal cortex, the hippocampus, the amygdala, the insula, and the ventral pallidum in PD patients with PG. Furthermore, an H_2O PET study during a card game with and without apomorphine injection revealed the opposite (decrease in patients with, and increase in patients without PG) patterns of cerebral blood flow change in the lateral orbitofrontal cortex, the cingulated, the amygdala, and the external globus pallidus (van Eimeren *et al.*, 2010).

fMRI. Functional MRI studies have shown that dopaminergic medication used in the treatment of PD patients increases the reward-related activity of the ventral striatum, orbitofrontal cortex, and related structures; which could relate to the excess reward-seeking behavior of PD patients suffering from ICDs [reviewed in (Kassubek *et al.*, 2011)]. Dopamine agonists have been demonstrated to influence the reward prediction error signaling in the human ventral striatum (Abler *et al.*, 2009), and to promote risk-prone choices (Riba *et al.*, 2008; Ye *et al.*, 2010). Indeed, Voon et al. demonstrated an increased reward-related ventral striatal blood-oxygen-level-dependent (BOLD) activity and a greater parallel positive prediction error in PD-ICD vs PD-control patients in response to a dopamine agonist administration (Voon *et al.*, 2010). Similarly, another study group demonstrated increased fMRI BOLD response to gambling-related cues in PD patients with PG in the ventral striatum, the anterior cingulated cortex, and the frontal cortical areas compared to PD patients without PG (Frosini *et al.*, 2010). It has been demonstrated that, normally, the ventral striatum responds hemodynamically to risk (Preuschoff *et al.*, 2006). However, PD-ICD patients have been shown to express a bias towards risky choices along with low orbitofrontal and anterior cingulate cortex activity and the risk sensitivity is further enhanced by dopaminergic medication together with a simultaneous decrease in the ventral striatal activity (Rao *et al.*, 2010; Voon *et al.*, 2011a).

Structural. The only study investigating brain structural changes in PD ICDs found no focal gray matter volume alterations (Biundo *et al.*, 2011). There are no studies investigating the white matter morphometry or structure in PD ICDs.

2.2.3.3 Summary of the previous findings based on literature

In summary, fMRI data has suggested blunted mesolimbic reward signaling and enhanced cue-reactivity in PG, similar to the findings with substance-addicted individuals (Crockford *et al.*, 2005; Goudriaan *et al.*, 2010; Miedl *et al.*, 2010). However, the only PET studies directly investigating the mesolimbic dopamine neurotransmission provided inconclusive results (Linnet *et al.*, 2010; Linnet *et al.,* 2011b). It should be noted, though, that the study by Linnet et al. also failed to show a significant dopaminergic response to gambling in the whole study sample, and hence, the methods might not have been sensitive to detect possible group differences. fMRI studies have revealed dopaminergic stimulation to enhance mesolimbic reactions in reward-related stimuli processing, and demonstrated changes in these functions in PD patients suffering from

ICDs [reviewed in (Kassubek *et al.*, 2011)]. Furthermore, PET studies have indicated enhanced mesolimbic dopamine function in PD patients with ICDs (Steeves *et al.*, 2009; O'Sullivan *et al.*, 2011b). However, it should be noted, that these studies often suffer from small and heterogeneous samples. Therefore, the role of the mesolimbic dopaminergic neurotransmission in PG and other behavioral addictions still remains somewhat unclear, and the brain structural changes associated with these conditions are largely unknown. Moreover, a growing body of evidence points out also to the significance of other (for example prefrontal cortical) regions apart from the mesolimbic dopamine network in the pathophysiology of behavioral addictions.

2.3 Neuroimaging methodology

2.3.1 Positron emission tomography (PET)

Positron emission tomography (PET) imaging is a non-invasive method that enables *in vivo* molecular imaging. In PET, radiolabeled ligands are used to investigate the passage and functions of the ligand molecule in a living organ, such as the brain.

2.3.1.1 Physical basis

The physical basis of PET imaging lies in biologically active molecules labeled with short-lived positron emitting radio nuclei, which are produced in cyclotrons. These nuclei undergo *beta plus decay*, or positron emission, converting a proton (p) to a neutron (n) while emitting a positron (e^+) and an electron neutrino (υ):

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

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

Commonly used PET radioisotopes include ^{11}C, ^{15}O, and ^{18}F, with respective half-lives of approximately 20.3 min, 2.07 min, and 110 min. The emitted positron has a large amount of energy and while passing through the matter, the positron loses energy, and finally, when enough energy is lost, it collides with an electron. This process is called *annihilation*. In annihilation, two photons with energy of 511 keV are emitted in opposite directions:

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

[for a review, see (Turkington, 2001)]

2.3.1.2 PET scanner

The annihilated photons, or gamma rays, are detected by the PET scanner. The PET scanner has a ring (or multiple rings) of radiation detectors. The detection of the

annihilated 511 keV photon pair in the opposite sides of the detector rim is termed as a coincidence event (true count), which is registered by the PET scanner unlike the single events (false counts). The direct line drawn between the detectors of a true count is referred to as the line of response (LOR). Any combination of two detectors of the detector rim forms a LOR. Collected data is recorded in sinograms, where parallel LORs are grouped together, and presented in a sinogram matrix with the angle of LORs on the vertical axis and the single LORs in that angle on the horizontal axis. The sinograms are collected in frames representing the temporal distribution of the coincidence events. The data in the sinograms is then used to reconstruct the spatial images, which reflect the radioactivity-concentration within the matter inside the PET scanner in a function of time. The schematic illustration of the annihilation event inside of the PET detector rim is depicted in Figure 4 [reviewed in (Turkington, 2001; Saha, 2005)].

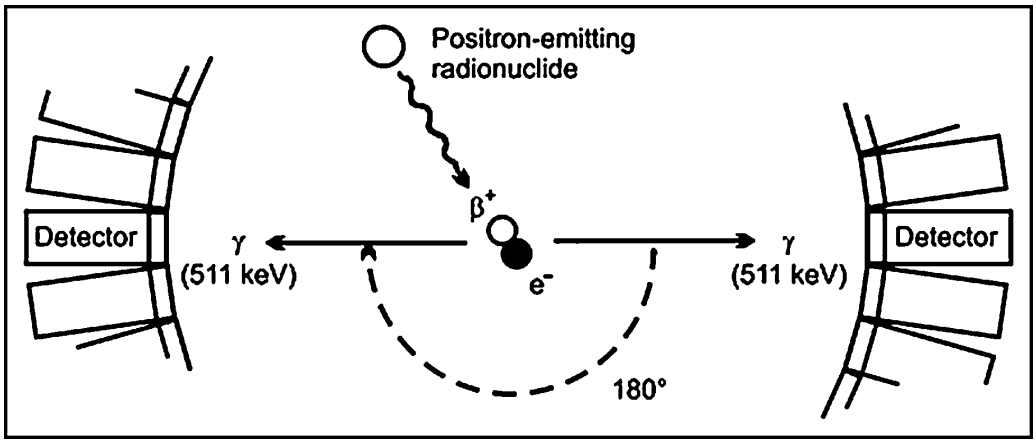

Figure 4. Coincidence event inside the PET scanner
A schematic illustration of a coincidence event inside the PET scanner detector rim. First, a positron is emitted from a nucleus undergoing beta plus decay. Then, the positron collides with an electron resulting in two gamma quants emitted in opposite directions (annihilation). The two (near) simultaneous counts on opposite sides of the PET detector rim form a true count (Verel *et al.*, 2005).

There are several sources of error in PET measurements, such as scatter, attenuation, random events, detector dead time, noise, and spatial resolution, which I will briefly introduce. Scattering of the photons occur while penetrating the surrounding tissue, and thus, the photons are not detected in the original LOR, but instead in a different LOR leading to false localization of the event. Attenuation is also caused by the photon-matter interactions, as the photons might get absorbed or scattered resulting in reduced signal registered by the scanner. Random events refer to simultaneous single events, which are interpreted as coincidence events by the PET scanner. After each event, there is a latent time in the detector, when it is unable to detect another event, thus leading to signal attenuation. The problem of latent time enhances with increasing rate of events (radioactivity). However, the increased event rate improves the data quality by reducing

the proportion of the random noise of the signal. The spatial resolution is restricted by the displacement of the positron from the decayed nucleus to the location of the annihilation, which is dependent on the positron energy, which varies according to the decaying nuclei [positron range full width at half maximum (FWHM) 1.1 mm for ^{11}C and 1.0 mm for ^{18}F in water (Cho *et al.*, 1975)]. Moreover, the noncollinearity (the angle between the annihilation photons differs slightly from 180 degrees) and detector characteristics such as size and depth of the detectors affect the spatial resolution. There are several techniques developed to cope with these problems, except for the displacement of the positron between emission and annihilation events, but they are beyond the scope of this thesis [reviewed in (Turkington, 2001; Saha, 2005)].

2.3.1.3 Receptor binding

In brain PET imaging, we are interested in the characteristics of neurotransmitter systems, which are measured indirectly using various ligands. According to the Michaelis-Menten equation, ligand-receptor interactions can be described as follows:

$$[L]+[R]\underset{k_{off}}{\overset{k_{on}}{\Leftrightarrow}}[LR]$$

k_{on}/k_{off} can be marked with K_d, which is the inverse of the receptor affinity. Receptor availability (B_{max}) * affinity ($1/K_d$) is termed as binding potential (BP). From the equation above, we can derive a linear representation of the saturation binding curve, referred to as the Scatchard's plot:

$$\frac{[LR]}{[L]} = -\frac{1}{K_d}B + \frac{B_{\max}}{K_d}$$

From the Scatchard's equation, the parameters of interest are easily defined: The slope ($1/K_d$) equals to the affinity, the y-intercept ([LR] = 0) to BP, and the x-intercept ([LR]/[L] = 0) to B_{max}.

2.3.1.4 Pharmacokinetic modeling

Radioactivity per volume is easily converted to tracer concentration using the specific activity (Bq/mol) corrected for physical decay. A straightforward and simple method for evaluating the tracer uptake from PET images (though providing information of only the relative tracer accumulation to the tissue) is calculating the standardized uptake value (SUV, which is the tracer concentration normalized for the injected dose per body mass) ratio with the following formula:

$$SUV_{ratio} = \frac{SUV_{tissue}}{SUV_{ref}} = \frac{C_{tissue}}{C_{ref}}$$

However, to achieve more meaningful biological data (pharmacokinetics of the ligand), mathematical modeling of the tissue time-activity data is needed. The aim is to characterize the pharmacokinetics (transport through blood-brain barrier and/or specific interactions with the brain tissue) of the tracer ligand. Arterial blood (or actually the concentration free fraction of the unmetabolized ligand in the plasma) sampling is used to obtain the information of the supply of the tracer to the tissue ("system input"), and the PET scanner is used to obtain the radioactivity per volume in the tissue of interest ("system output").

In vitro receptor quantification methods often take advantage of the equilibrium state, where there is no net change of the substrate between the compartments, thus allowing the direct measurements of the stable concentrations. However, achieving the equilibrium state in PET studies can be problematic, and thus instead of directly measuring the equilibrium state, the pharmacokinetic parameters of the tracer are estimated indirectly using rate constants (k's) between kinetic compartments. Compartmental models illustrate the tracer kinetics and in the following paragraphs, I will briefly introduce the models used in this project.

The two-tissue-compartmental model, generally used in PET brain receptor studies, is depicted in Figure 5A. We are interested in the non-displaceable binding potential (BP_{ND}) of the tracer (specific binding, k_3/k_4 in Figure 5A). BP_{ND} could be estimated directly from the kinetic rate constants (k's) or indirectly, as done in study I, using a simplified reference tissue model (SRTM, Figure 5B) (Lammertsma & Hume, 1996). The BP_{ND} resulting from this model is described by the following equation:

$$BP_{ND} = \frac{k_3}{k_4} = f_{ND}\frac{B_{\max}}{K_d} = f_{ND}\frac{1}{K_d}B_{\max}$$

In the equation, f_{ND} is the free fraction of the ligand in non-displaceable tissue compartment, B_{max} is the receptor availability, and $1/K_d$ is the affinity.

Calculating the tracer kinetics using kinetic compartment models involve non-linear fitting requiring time-consuming heavy computing. Thus, alternative data evaluation methods, namely linearized graphical methods, have been developed. A common method, which was also used in study III, for irreversible binding (i.e. when $k_4=0$) is the Patlak plot (Gjedde, 1982; Patlak *et al.*, 1983). The Patlak plot is based on model function transformations, which enables a linear-fitting process, and thus, reduces markedly the computational processing. The slope of the linear phase of the plot is used for estimation of the radioligand kinetics [the net influx rate (K_i), which reflects the trapping rate of the tracer in the steady state condition]:

$$K_i = \frac{K_1 k_3}{k_2 + k_3}$$

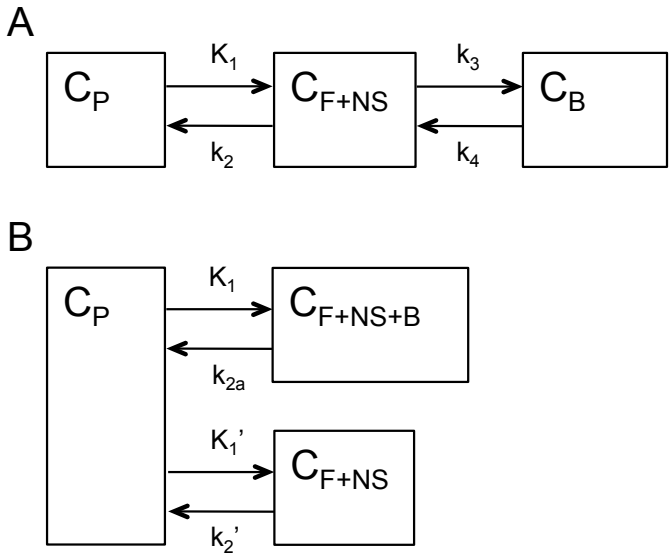

Figure 5. Compartmental models
Schematic presentation of the principle A. of the standard two tissue-compartmental model assuming that the free (C_F) and non-specific (C_{NS}) bound compartments reach equilibrium rapidly, and B. of the simplified reference tissue model. C_P = free plasma concentration. C_B = specifically bound concentration. K_1, k_2, k_3, k_4 = rate constants. k_{2a} = overall rate constant. The figure is depicted in several sources of literature, see for example (Lammertsma, 2010).

2.3.1.5 Imaging dopamine neurotransmission

The dopaminergic synapse is depicted in Figure 6. Two commonly used tracers in imaging dopamine neurotransmission are [^{11}C]raclopride ([^{11}C]-(S)-(-)-3,5-dichloro-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2-hydroxy-6-methoxybenzamide) and [^{18}F]fluorodopa (6-[^{18}F]fluoro-3,4-dihydroxy-L-phenylalanine) tracers. [^{11}C]raclopride is a dopamine D2(D3) receptor antagonist that competes for the binding with endogenous dopamine. Since [^{11}C]raclopride competes with endogenous dopamine in a manner consistent with the occupancy model (i.e. increase in synaptic dopamine concentration results in increased occupancy of the receptors by dopamine, thus, reducing the available binding sites for the radiotracer), it is used in displacement paradigms to estimate endogenous dopamine release after pharmacological or non-pharmacological stimuli (Laruelle, 2000). In the displacement paradigm, the subjects undergo a control scan first without the stimulus of interest, and then with the stimulus. BP_{ND} is then calculated for each condition separately. The release of endogenous dopamine competing for the dopamine D2(D3) receptor (for brevity, referred to as *DRD2* in this thesis) binding sites results in decrease in measured raclopride BP_{ND}. Respectively, reduction in the synaptic concentration of endogenous dopamine results in an increase of [^{11}C]raclopride BP_{ND}. [^{11}C]raclopride is administered in tracer (minute) concentrations, and thus, has no significant effect on receptor availability, which could be a potential confounder in the measurement of

synaptic dopamine fluctuations. For clarity, the decrease in raclopride BP_{ND} is referred to as endogenous dopamine release in this thesis. However, there are also alternative explanations for the decrease in BP_{ND} and this issue will be discussed later (*6.1.1.6*) (Laruelle, 2000). For [^{11}C]raclopride, the cerebellum can be used as a reference tissue for SRTM, since the cerebellum is void of *DRD2*s (Lammertsma *et al.*, 1996).

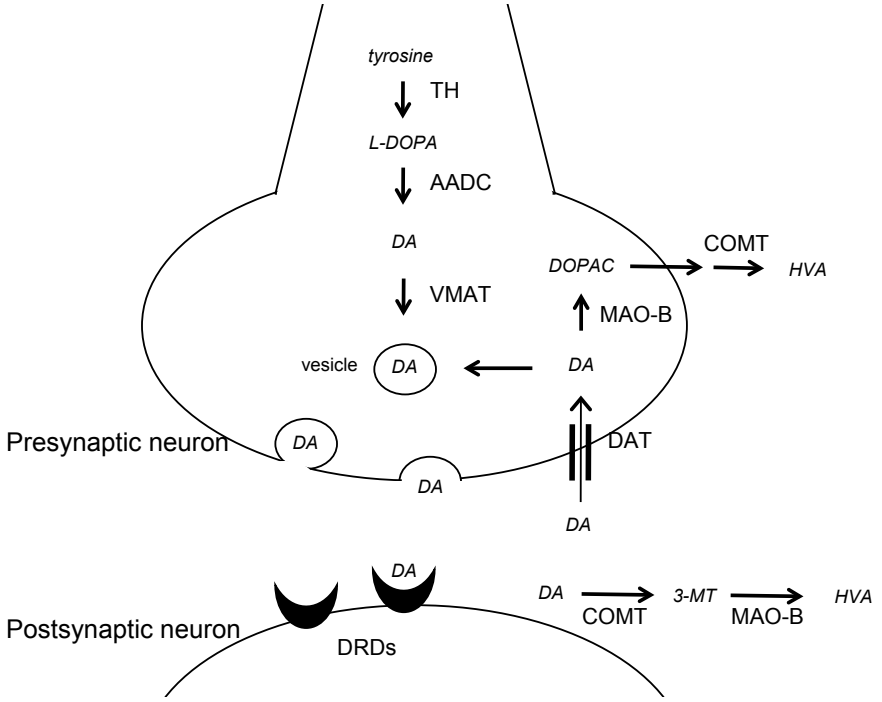

Figure 6. Dopaminergic synapse
Schematic illustration of the synaptic dopamine transmission demonstrating the production of dopamine (DA) from its precursors and release to / removal from the synaptic cleft. AADC = aromatic amino acid decarboxylase. COMT = catechol-O-methyl transferase. DAT = dopamine transporter. DRDs = dopamine receptors. HVA = Homovanillic acid. L-DOPA = L-3,4-dihydroxyphenylalanine. MAO-B = monoamine oxidase B. TH = tyrosine hydroxylase. VMAT = vesicular monoamine transporter. 3-MT = 3-methoxytyramine. Note that the figure is simplified for clarity and is not intended as a comprehensive representation of the synaptic dopamine transmission. The figure is based on several sources of previous literature; see for example (Blackstone, 2009; Iversen *et al.*, 2009).

The displacement method has been used in numerous experiments investigating challenges, which manipulate synaptic dopamine concentration in animals [reviewed in (Laruelle, 2000)]. The usefulness of [^{11}C]raclopride displacement method in humans was first demonstrated using acute amphetamine administration, which resulted in a 10-23% decrease in [^{11}C]raclopride BP_{ND} (Farde *et al.*, 1992; Volkow *et al.*, 1994). Subsequently, an *in vivo* increase in synaptic dopamine concentration has been demonstrated using the displacement method in response to various other pharmacological agents, such as cocaine, metamphetamine, methylphenidate, ketamine, psilocybin, nicotine, alcohol,

and marijuana (Laruelle, 2000; Bossong *et al.*, 2009; Volkow *et al.*, 2009). Also, it has been shown that the route of administration of the drug (and consequently the speed of entry into the brain) seems to have an effect on the kinetics of dopamine release, which relates to the experienced euphoria [reviewed in (Volkow *et al.*, 2011)]. Recently, an increase in synaptic dopamine concentration using [^{11}C]raclopride PET displacement method has been shown also in association with several behavioral stimuli, which will be reviewed in more detail in the discussion (section *6.1.1.2*).

[^{18}F]Fluorodopa uptake assesses the presynaptic decarboxylation rate of levodopa in the nerve cells. After decarboxylation, fluorodopamine becomes trapped inside the cell, and thus, can be considered as a case of irreversible binding and can be calculated using the Patlak plot. [^{18}F]fluorodopa uptake depends on the aromatic amino acid decarboxylase (AADC) activity in the brain (Brown *et al.*, 1999). AADC participates to the processing of L-DOPA, which is a precursor for all monoamines (dopamine, serotonine, and noradrenaline). Thus increased fluorodopa uptake signifies increased turnover of dopamine alone or monoamines in general depending on the relative activities of monoamines in different brain regions. In the dopamine-rich striatum the [^{18}F] fluorodopa uptake (AADC activity) is considered to reflect mainly dopamine functions, whereas in extrastriatal regions the uptake can be considered to reflect a sum effect of monoaminergic activity (Brown *et al.*, 1999). [^{18}F]Fluorodopa PET has been shown to be useful in demonstrating the striatal dopamine deficiency, which is a hallmark of PD, and thus, has a well-established role as a diagnostic tool in clinically uncertain cases of early PD [reviewed in (Brooks, 2010)].

2.3.2 Structural MRI and voxel-based morphometry (VBM)

Structural MRI. The nuclei of atoms behave like microscopic magnets. MRI scanner applies a powerful magnetic field making the magnetic moments of the nuclei of atoms align in a parallel or anti-parallel direction. This alignment induces a net magnetization, which is termed as the magnetic moment. The nucleus of the hydrogen atom (H^1) has the highest energy and is abundant in the human body [mainly located in water molecules (H_2O)], and thus is the nucleus used in almost all clinical MR imaging. The time to return (relaxation time) to the original state differs according to the proton density and the molecular structures of the tissue. Differences in the relaxation times (for example T1- and T2-relaxation times) form the basis of tissue contrast in the MR images. T1-weighted images are the most used ones in clinical settings, with excellent discrimination of fat and water, shown bright and dark, respectively. T2 weighted images are also widely used in clinical settings, similarly differentiating fat from water, but with opposite tissue intensity coding as in T1-weighed images (fat is shown dark and water bright) [For a review, see (Hendee & Morgan, 1984a; b)].

Voxel-based morphometry (VBM). VBM is a method developed for analyzing local brain volumes or densities in a voxel-based manner across the entire brain using the information of T1-weighted images. The shape and size of human brain are variable, and

thus the T1-weighted images are first spatially normalized to the same stereotactic space using mutual information algorithm to enable the voxel-wise analysis between different subjects. The gray and white matter are segmented to different images, and analyzed separately. For the statistical voxel-wise analysis, the images are smoothed to improve the signal-to-noise ratio, and general linear model (GLM) is applied to identify regions with statistically significant effects of interest (Ashburner & Friston, 2000).

2.3.3 Diffusion tensor imaging (DTI)

Diffusion. Diffusion describes the random motion, or Brownian motion, of particles resulting from the thermal energy carried by the molecules. DTI focuses on how free or isotropic the diffusion (i.e. is the diffusion mechanically restricted in some way) is in a given location. In the example of the brain, diffusion of the white matter is generally more restricted (axons allow diffusion mainly along with longitudinal axis of the axon) than in the gray matter, and cerebrospinal fluid has almost isotropic diffusion [for reviews, see (Le Bihan, 2003; Mukherjee *et al.*, 2008)].

DTI principle. As described above (*2.3.2*), conventional T1- or T2-weighted MRI measures signal intensities, which are dominated by water concentration of the given tissue. In DTI, field gradients are applied to achieve location dependent frequencies using water molecules as microscopic probes (or intuitively described, as tagging location information to the protons of the water molecules). In order to measure diffusion, a pulsed magnetic field gradient is used, which means applying linear inhomogeneous magnetic fields (gradients), which can be switched on and off (hence called pulsed). Each gradient direction includes a pair of dephasing and rephrasing gradients, opposing to each other. If no movement of the protons has occurred between the dephasing and rephrasing gradients, the net magnetization returns to the original level. When movement occurs, this leads to signal loss since the rephasing gradient does not restore the original phase for all protons, if the location of the proton has changed, and is thus not exposed to exactly opposing gradient. This signal loss is what is measured with DTI. One dephasing-rephasing gradient pair provides information of the motion in the single gradient direction in question only (motion perpendicular to the gradient direction does not affect the signal intensity). Hence, in DTI, multiple different gradient encoding directions are needed to define the diffusion ellipsoid which reflects the water diffusion within the three dimensional space (Figure 7). An important issue in DTI is to differentiate diffusion and other ways of water motion, such as flow and bulk motion. In theory however, flow and bulk motion lead to a different outcome than diffusion. Flow and bulk motion do not lead to signal loss, since the moving "unit" of water is larger than the voxel size leading to shift of signal phase [reviewed in (Le Bihan *et al.*, 2001; Le Bihan, 2003; Mori, 2007)].

Diffusion parameters. The mathematics behind the diffusion parameters is beyond the scope of this thesis, so I will only briefly introduce the parameters relevant to this study. There are several ways of describing diffusion data. The mean diffusivity (MD)

describes the mean squared displacement of the water molecules; diffusion anisotropy describes how directional the displacement of the water molecules is; and the main direction of diffusivities (eigenvalues and -vectors) describes the orientation of the diffusion direction in three-dimensional space. MD is completely insensitive to the direction of the diffusion with higher values reflecting less restricted diffusion. There are several parameters to describe the diffusion anisotropy, but the most commonly used is fractional anisotropy (FA), which ranges from zero to one. An FA value 1 indicates that the diffusion occurs only along a single axis and value 0 indicates completely undirectional (isotropic) diffusion. Generally, within the brain, the highest FA values can be found from large bundles of coherent axons, such as the corpus callosum, and the lowest from the CSF (Figure 7C). The information about the direction of diffusion can be used for fiber tracking, given the assumption that the direction of fibers is collinear with the direction of the eigen-vector with the largest eigen-diffusivity (Le Bihan *et al.*, 2001).

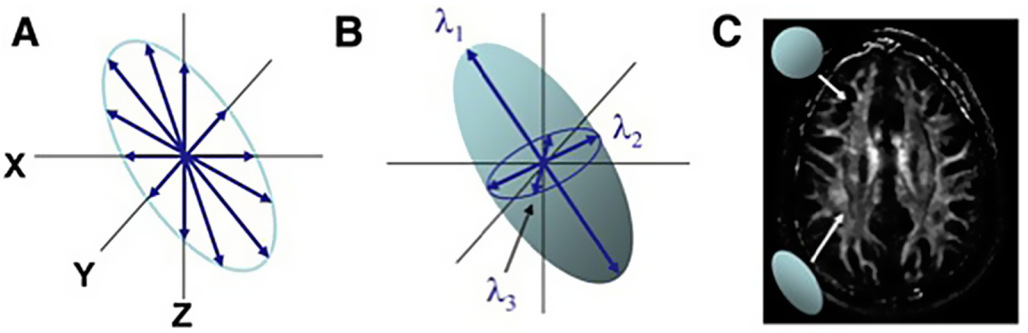

Figure 7 Diffusion tensor imaging (DTI)
A. Diffusion measurements along with six gradient encoding directions, and B. the estimated diffusion ellipsoid together with the eigen-vectors. C. Fractional anisotropy (FA) map of the brain. Dark regions indicate low FA (spherical diffusion ellipsoids) reflecting free diffusion, and bright regions indicate high FA values (elongated diffusion ellipsoids) reflecting anisotropic diffusion. Adapted from (Mori & Zhang, 2006).

3. OBJECTIVES OF THE STUDY

The principal aim of the study was to investigate dopaminergic neurotransmission during gambling and, to find out whether the short-term and long-term effects of gambling are similar to those of the administration of dopaminergic psychostimulants. Another aim of the study was to investigate brain structure in pathological gambling. Furthermore, to get a comprehensive view of pathological gambling and other impulsive-compulsive disorders, a survey investigating the prevalence and associated factors of these disorders was conducted among Finnish Parkinson's disease patients. Therefore, the specific objectives of this study were:

I To demonstrate the short-term and the long-term effects of gambling on basal ganglia dopaminergic neurotransmission in pathological gambling

II To demonstrate possible structural brain abnormalities in pathological gambling

III To demonstrate the possible differences in presynaptic monoaminergic baseline activity in Parkinson's disease patients with and without impulse control disorders

IV To demonstrate the epidemiology and associated factors of pathological gambling and other impulse control disorders in Finnish patients with Parkinson's disease

Note: The roman numerals refer to the original publications

4. MATERIALS AND METHODS

4.1 Overall study design

The project was conducted during the years 2009 – 2011 under the project name of 'Dopamiergic reward mechanisms in patholigical gambling' (DOPGAM). The study protocol was approved by the local ethical committee (Ethics committee of the Hospital District of Southwest Finland, permission number 15721) and conducted according to the Declaration of Helsinki. Written informed consent was obtained prior to the study after explaining the study protocol to the subjects. The study flow chart is presented in Figure 8.

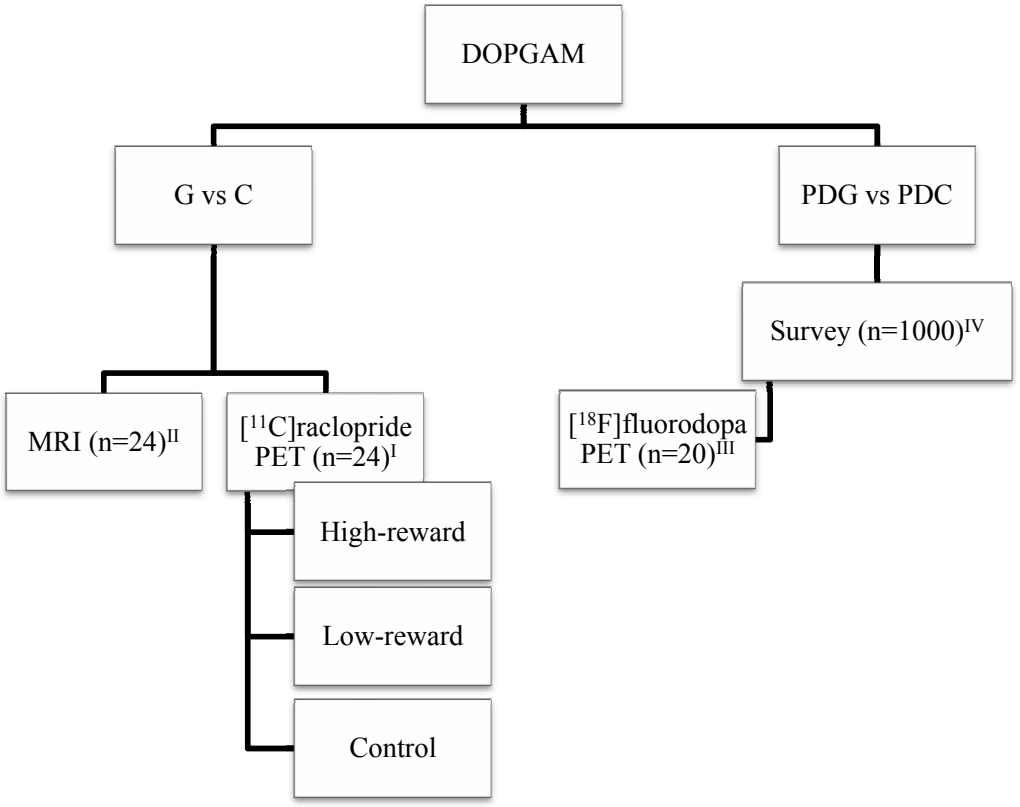

Figure 8 Study flow chart.
G = pathological gamblers. C = healthy controls. PDG = Parkinson's disease patients with impulse control disorders. PDC = Parkinson's disease patient controls. Corresponding study numbers (original publications) are indicated with superscript Roman numerals.

4.2 Subjects

4.2.1 Neuroimaging studies (studies I - III)

Four groups of subjects were included in neuroimaging studies:
Group G: 12 pathological gamblers (studies I and II)
Group C: 12 healthy volunteers (studies I and II)
Group PDG: 10 PD patients with ICDs (study III)
Group PDC: 10 PD patients without ICDs (study III)

The group G subjects were recruited from the subjects of a prior study (Lahti *et al.*, 2010) and via online advertisements in a national gambling helpline (www.peluuri.fi). Subjects of group C were recruited via email and online advertisements to the students of University of Turku and Turku University of Applied Sciences. The subjects for groups PDG and PDC were recruited from the responders of the epidemiological survey (study IV, described in *4.2.2*).

Subjects were first interviewed via telephone by a clinical investigator to evaluate their suitability to participate in the study. A consultant psychiatrist confirmed/excluded pathological gambling (PG) diagnoses according to DSM-IV (groups G and C) or ICDs according to previously described criteria (Weintraub *et al.*, 2009) (groups PDG and PDC) and assessed psychiatric axis I disorders using SCID-I (First *et al.*, 1996) in a face-to-face interview (except for one subject, who was interviewed via telephone). All subjects underwent an extensive laboratory blood test and urine drug screens, an interview by a physician, and a brain MRI scan, which was evaluated by an experienced neuroradiologist. In addition, the Unified Parkinson's Disease Rating Scale (UPDRS I-V, Finnish version 1.0, http://www.parkinson.fi/sairausryhmät/parkinsonin-tauti/updrs) scores were recorded for groups PDG and PDC. The subjects provided information for Finnish versions of South Oaks Gambling Screen (SOGS, http://www.paihdelinkki.fi/testaa/rahapelitesti) (Lesieur & Blume, 1987) and Beck Depression Inventory (BDI, translation by the research department of the Social Insurance Institution of Finland) (Beck *et al.*, 1961), and their current gambling behavior was inquired in detail.

<u>General inclusion criteria for neuroimaging studies:</u>
Male, age 18-75 years
Cooperative and willing to complete all aspects of the study
Will provide written informed consent prior to their participation in the study

<u>General exclusion criteria for neuroimaging studies:</u>
Insufficient health status to complete the study
Evidence of previous or current substance use disorder within last 6 months
Body weight > 180 kg (scanner limit)
Any contraindication to MRI
Clinically significant abnormalities in the brain MRI scan

Strong susceptibility to allergic reactions or nausea
Blood donation within 60 days prior to the study
Intoxicated or recent (less than 36 h) drug or alcohol usage
Consumption of coffee or tea within the last 12 hours prior to the study
Chronic medical condition or medication known to have an effect on central dopamine function, except for PD and antiparkinsonian medication in groups PDG and PDC
Not able to stop antiparkinsonian medication for 12 hours (groups PDG and PDC)

Four group G subjects (two with major depression, one with alcohol dependence and bipolar type II, and one with alcohol dependence and major depression), one group PDG (ischemic lesions in the brain MRI) and two group PDC subjects (unable to stop dopaminergic medication) were excluded from the study at the screening visit.

4.2.2 Epidemiological survey (study IV)

A postal survey of a PD patient population was performed between October 2009 and June 2010. To get a comprehensive view of the prevalence of risk for ICDs, a stratified random sample (n=1000) was obtained from the patient register of the Finnish Parkinson Association, which includes about half of a total of approximately 10 000 Finnish PD patients. The sample was obtained in four blocks: by gender [men and women in proportion 3:2 according to the approximation of the gender distribution in PD in Finland (Kuopio *et al.*, 1999)] and by age (above and below 65 years in proportion 1:1). Furthermore, the sample was weighted according to the distribution of population density in Finland.

4.3 Methods

4.3.1 [^{11}C]raclopride PET (study I)

In study I, the healthy volunteers and pathological gamblers (groups C and G) were scanned three times with [^{11}C]raclopride PET under different conditions to investigate striatal dopamine neurotransmission during gambling. The striatal dopamine neurotransmission in PD patients with PG has been investigated previously using comparable methodology (Steeves *et al.*, 2009), and therefore, the groups PDC and PDG were not investigated with [^{11}C]raclopride in the present project.

4.3.1.1 Radiotracer synthesis and scanner

[^{11}C]Raclopride was synthesized by a previously described method (Langer *et al.*, 1999), with minor modifications. The radiochemical purity of the product exceeded 99 % in all syntheses (n=71), except for one failed synthesis (low-reward scan of a pathological gambler). PET imaging was performed using GE Advance PET scanner (General Electric Medical Systems, Milwaukee, WI, USA), with 35 slices of 4.25 mm

thickness covering the whole brain [axial field of view (FOV) 15.2 cm] in the 3D-mode. The basic performance characteristics tests of this camera indicate transaxial and axial spatial resolution full with at half maximum (FWHM) of 4.3 and 4.3 mm, respectively (Lewellen *et al.*, 1996). The scanning time was 54 min consisting of 15x1 min, 7x2 min, and 5x5 min frames.

4.3.1.2 Scanning protocol

Before each experiment a transmission scan for attenuation correction was performed using Ge-68 rod sources. An antecubital vein was cannulated and a rapid bolus injection of [^{11}C]raclopride [mean (SD) dose = 207 (9.6) MBq, injected mass ranging from 0.2 to 2.3 μg], was given at the beginning of the scanning. A Velcro strap was used to minimize the head movement, and head motion tracking (Polaris, Northern Digital Inc., Canada) was applied during the scans. A plastic cap with infrared light reflectors for a Polaris tracking tool was attached on the top of the head with rubber bands. The motion tracking data was used for determining the optimal reference frames for frame-by-frame motion correction, image quality control, and exclusion of differences in motion between groups or scans.

The subjects were instructed to fast overnight and they received a small breakfast and a lunch, after arriving at the PET centre and after the second scanning, respectively. The subjects lay supine in the scanner and performed the gambling/control tasks during the entire 54 min scanning, controlling the task functions with a computer mouse with the dominant hand. Each subject underwent three [^{11}C]raclopride PET scans on the same day under three different conditions: CONTROL, HIGH-REWARD, and LOW-REWARD task, which are described in the next section (*4.3.1.3*). The interval of the [^{11}C]raclopride injections was approximately three hours (clearly more than five times the half time of ^{11}C, which is 20.3 min) to allow sufficient decay of the previous bolus before the next scan. The order of the conditions was fully counterbalanced and the subjects were blinded to the predetermined outcomes of the gambling tasks.

4.3.1.3 Tasks

The CONTROL task was to select button A or B when lit on the screen together with sound signals, providing visual, auditory, and motor activation without gambling (Figure 9B).

The act of gambling involves not only winning and losing, but also elements such as reward prediction, risk, and near misses. Therefore, to separate the neurobiological effects of winning gambling from gambling in general, two different gambling tasks were used in this study – HIGH-REWARD and LOW-REWARD. Both tasks had similar basic elements of gambling, but HIGH-REWARD included also winning, while there was no net win or loss during the LOW-REWARD scan. For HIGH-REWARD and LOW-REWARD scans, a commercial slot machine software was used including original

sound effects (“Double pot” or “Tuplapotti”, Finnish Slot Machine Association, Figure 9A). The gambling tasks were executed with an Adobe Flash (Adobe Systems Inc, San Jose, CA, USA) version of the game. Instead of using randomness, the outcomes of the gambling tasks were determined by creating specific C programs, which were interpreted by Adobe Flash. Gambling with a “double pot” requires very little or no skill at all. Three spinning wheels with symbols with five win lines determine the wins, and a “coin flip” button (choosing from heads or tails) can be used to double the wins with the risk of losing the win. The duration of a single game (from spinning the wheels to the outcome) is approximately four seconds. Wins are associated with a particular win tune (common with the slot machines of the Finnish Slot Machine Association) and sound of coins dropping into a container. The software was modified so that only a 1 € bet (selecting all five win lines) was possible and doubling was limited to wins less than 2 € to reduce the variability of the gambling outcomes. The maximum win in a single game was 20 €.

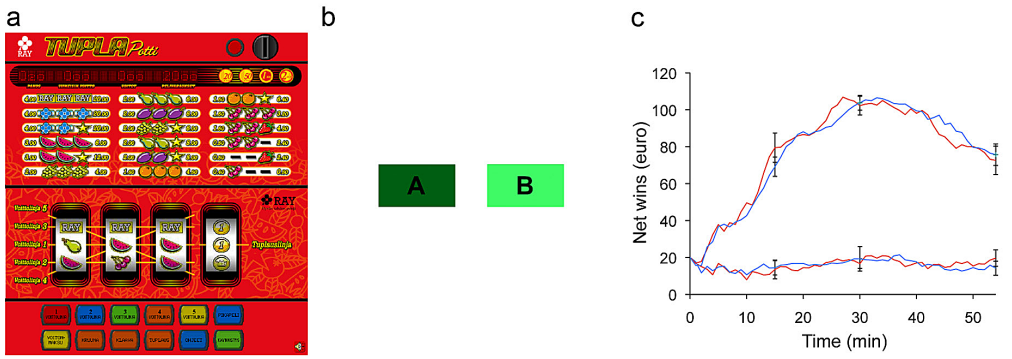

Figure 9 Tasks
A. Screen view of the gambling task (Double pot -slot machine), which was used for the high-reward and the low-reward tasks. B. Screen view of the sensorimotor control task. C. Mean net win curves of the high-reward task (upper two curves) and the low-reward task (lower two curves). Error bars indicate 95 % confidence intervals at corresponding time-points. Blue = controls. Red = pathological gamblers. Note: the groups did not differ in net wins (rmANOVA group x time interaction $F_{1,3} = 1.69$, $P = 0.21$, and $F_{1,3} = 1.77$, $P = 0.16$, for the high-reward and the low-reward tasks, respectively). The figure has previously been published in the original publication I.

Each participant was given 20 € as their starting bankroll, and they were instructed that, if they should lose the initial amount, it would be automatically reloaded by the slot machine, and that they could keep the possible winnings without having to pay for the possible losses. According to the Finnish Slot Machine Association, the normal payback rate of the commercial slot machine version is approximately 93%. For the present study, the software was programmed differently for the two gambling tasks: 1) HIGH-REWARD - impossible to lose, certain winning, corresponding to a mean payback rate of 371 %, and 2) LOW-REWARD – no marked net wins or losses, the net win curve remained around the initial amount during the whole task. For the HIGH-REWARD scan, the aim of the programming was to maximize the gambling “high” and

dopamine release, and the program gave big wins especially during the first 25 minutes of gambling/scanning (Figure 9C).

4.3.1.4 Physiological measures

During the gambling tasks, heart rate, blood pressure, and subjective emotions on a behavioral rating scale were measured at time points 0 min (just before beginning of the gambling task), 15 min, and 30 min after the tracer injection. Behavioral ratings (BRs) included urge to gamble, high, positive mood, excitement, and alertness on a scale from zero to ten, ten meaning the strongest possible feeling of the emotion in question.

4.3.1.5 Image analysis

Preprocessing. External motion tracking data was used 1) to examine the data quality, 2) to exclude possible group or condition related differences in the subject's motion that could affect the outcome of the PET measurements, and 3) for determining suitable reference frames for correcting the misalignments between the frames due to subject motion. Over 97% of the frames had within-frame motion less than the resolution of the scanner indicating good image quality and there were no statistically significant differences between the groups or conditions in the subject motion. Misalignments between PET sessions and between frames in each session were compensated for using a mutual information algorithm in Statistical Parametric Mapping (SPM, Wellcome Department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm/). More detailed information about the motion tracking is available as online supplementary material of the original publication I.

Regions of interest (ROIs). For ROI analysis, subjects' PET and T1-weighted MR images were coregistered and MR image was used as a structural reference for delineating the ROIs. A common ROI set including the cerebellar cortex, and the striatal subregions (the venral striatum, caudate, and putamen) was drawn bilaterally using Imadeus (version 1.20, Forima Inc., Turku, Finland) on transaxial planes. ROIs were then used to obtain time-activity curves (TACs) for kinetic analyses.

Kinetic analysis and SPM. The simplified reference tissue model (SRTM) with the cerebellum as the reference tissue was applied in the quantification of non-displaceable [^{11}C]raclopride binding potential (BP_{ND}) (Lammertsma & Hume, 1996). For the voxel-wise SPM analysis, determining parameters for spatial normalization of the movement corrected images to Montreal Neurological Institute (MNI) space was carried out using a [^{11}C]raclopride template created from a data set of healthy volunteers (Haltia *et al.*, 2007). These parameters were used for normalizing individual voxel-wise BP_{ND} images to the MNI space, and were then smoothed with a 10 mm FWHM isotropic Gaussian kernel (voxel size 2x2x2 mm^3). An average smoothed BP_{ND} image of the whole sample was calculated, and a binary mask with a threshold of $BP_{ND} > 0.75$ was created to confine the analyses to the basal ganglia area. The peak voxels are presented in MNI coordinates.

4.3.2 Structural MRI and DTI (study II)

4.3.2.1 Scanner and sequences

MRI was performed on a Philips Gyroscan Intera 1.5 T CV Nova Dual scanner (Philips Healthcare, Best, The Netherlands) equipped with a SENSE head coil. T1- and T2-weighted, DT, and FLAIR sequences were obtained. Whole-brain T1-weighted three-dimensional fast field echo (FFE) data set with 1 mm isotropic voxel was acquired in transverse plane [parameters of acquisition: time of repetition (TR) 25 msec, echo time (TE) 4.6 msec, flip angle 30 degrees, number of excitations (NEX) 1, field of view (FOV) 256 x 256 mm] yielding at least 160 contiguous slices in order to cover the whole head.

Spin-echo EPI sequence was used for DTI acquisition [3 mm slices with 1 mm gap, repetition time (TR) = 5616-6277 ms (with one exception where TR was 7046 ms), TE 89, NEX = 2, FOV 240 mm, acquisition matrix 112 x 111, interpolated reconstruction matrix 256 x 256, b-values for diffusion weighting 0 and 1000 s/mm^2, 32 gradient-encoding directions, spectral presaturation inversion recovery (SPIR) technique was used for fat suppression].

4.3.2.2 Voxel-based morphometry (VBM)

The preprosessing was performed using SPM8 (Wellcome Department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm/), with VBM8 toolbox (Christian Gaser, University of Jena, Department of Psychiatry, http://dbm.neuro.uni-jena.de/vbm8/) executed in Matlab R2008b (MathWorks, Natick, MA) using the default options (Ashburner & Friston, 2000; 2005; Cuadra *et al.*, 2005). To improve the quality of spatial normalization, the anterior commissure was first identified in each individual T1 image and manually marked as the origin for high-dimensional Diffeomorphic Anatomiacal Registration Through Exponential Lie Algebra (DARTEL) normalization to achieve optimal normalization (Ashburner, 2007). Jacobian determinants derived from the spatial normalization were used for voxel value modulation (Ashburner & Friston, 2000; 2005). T1-weighted images were segmented into gray matter, white matter, and cerebrospinal fluid compartments. The normalized, images (modulated and unmodulated) were smoothed with a 12 mm FWHM Gaussian kernel. Global volumes of each segment were computed using native-space tissue maps of each subject.

4.3.2.3 Diffusion tensor imaging (DTI)

Voxel-wise statistical analysis of the diffusion data was carried out using the tract-based spatial statistics (TBSS) tool (Smith *et al.*, 2006). Data was analyzed using the Oxford Centre for Functional MRI of the Brain (FMRIB) software library (FSL) of analysis tools (version 4.1.7, http://www.fmrib.ox.ac.uk/fsl/) (Smith *et al.*, 2004). First, FA images were created by fitting a tensor model to the raw DTI data using FMRIB's Diffusion Toolbox (FDT), and then the brain tissue was extracted using the Brain

Extraction Tool (BET) (Smith, 2002). FA images were then aligned to a 1x1x1 mm standard space [using FMRIB58_FA template, which is a high-resolution average of 58 well-aligned healthy subjects aged between 20-50 in the Montreal Neurological Institute/ International Consortium for Brain Mapping space (MNI/ICBM152), implemented in FSL] using the FMRIB's Nonlinear Registration Tool (FNIRT) (Andersson *et al.*, 2007), which uses a b-spline representation of the registration warp field (Rueckert *et al.*, 1999). Then aligned dataset was affine-transformed into the 1x1x1mm standard space (MNI/ ICBM152). The accuracy of spatial normalization was visually inspected. Next, the mean FA image was created and thinned to create a mean FA skeleton, which represents the centers of major white matter bundles common to the sample. The threshold of the FA skeleton was set to FA values of 0.20 or higher to include the major white matter pathways, but avoiding the peripheral parts of the brain where good tract correspondence across subjects is not likely. Each subject's aligned FA data was then projected onto this skeleton. The nonlinear registration parameters from the FA images were also applied to the MD images. As ROIs, the entire white matter tract skeleton and areas under respective significant regions in TBSS analysis were used, to calculate global diffusion parameters and estimate the effect sizes of the diffusion abnormality in PG patients, respectively. For quality control, the ROIs were deprojected back to the native diffusion space and the correspondence to the white matter tracts was visually inspected.

Localization and labeling of tracts with abnormal diffusion (the analysis is described in *4.5.4*) in pathological gamblers were confirmed and identified with Johns Hopkins University (JHU) white-matter tractography atlas (Wakana *et al.*, 2004; Mori *et al.*, 2005). In addition, the involvement of the subregions of the corpus callosum was identified visually by an experienced neuroradiologist.

4.3.3 [^{18}F]fluorodopa PET (study III)

In study III, the PD patients (groups PDC and PDG) were scanned with [^{18}F]fluorodopa PET to investigate the presynaptic dopamine (or monoamine) function. PD is known to affect the brain [^{18}F]fluorodopa accumulation, particularly in striatal areas, but it is not known whether the presynaptic dopamine (monoamine) function has a role in the patophysiology of ICDs. The subjects in groups C and G were not investigated with [^{18}F]fluorodopa in addition to the three [^{11}C]raclopride to control the total radiation dose.

4.3.3.1 Radiotracer synthesis and scanner

[^{18}F]fluorodopa was synthesized as described previously (Forsback *et al.*, 2009). The radiochemical purity of the product exceeded 96% in all syntheses. The scanning was performed with ECAT EXACT HR+ PET (Siemens/CTI, Knoxville, TN, USA) with 63 imaging planes of 2.45 mm thickness and 15.5 cm axial FOV running in 3D mode. The basic performance characteristic tests indicate transaxial and axial spatial resolution

(FWHM) of 4.3 mm and 4.1 mm, respectively (Adam *et al.*, 1997) . The 90 min scan consisted of 15x1 min, 5x3 min, and 12x5 min frames.

4.3.3.2 Scanning protocol

The subjects were scanned once while in resting condition. Subjects were instructed to discontinue all antiparkinsonian medications for at least 12 hours (≥24 h for slow release medications) prior to the tracer injection. The subjects fasted at least four hours and were given 150 mg carbidopa orally one hour prior to the [^{18}F]fluorodopa injection to prevent the peripheral decarboxylation of [^{18}F]fluorodopa. Antecubital vein was cannulated and a rapid bolus of [^{18}F]fluorodopa [mean (SD) = 188 (6.6) MBq] was given at the beginning of the PET scan. A vacuum hood was used to reduce head movement during the scans.

4.3.3.3 Image analysis

Preprosessing. Misalignments due to head movement were compensated for using a mutual information algorithm implemented in Statistical Parametric Mapping (SPM8, Wellcome Department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm/) in two steps. First, the frames were coregistered to an investigator-selected frame with little visible motion artifact. Second, the coregistered frames were summed and each coregistered frame was coregistered to the summed image. The spatial normalization was carried out in two steps. First, a study specific PET template was created using the parameters of the normalization of T1-weighted MR images. Second, PET images were normalized to the MNI space using the template for ROI and Statistical non-Parametric Mapping (SnPM) analyses. In order to investigate and correct for possible partial volume effect (PVE) caused by the signal from adjacent white matter (Cropley *et al.*, 2008), images were analyzed both with and without PVE correction. The PVE correction was performed using PVElab software (http://nru.dk/downloads/software) according to the principles of the method proposed by Rousset et al (Rousset *et al.*, 1998).

Regions of interest (ROIs). A common automated ROI set (bilaterally to the ventral striatum, the dorsal caudate, the anterior putamen, the posterior putamen, the medial orbitofrontal cortex and the occipital cortex) was drawn using Imadeus software (Version 1.20, Forima Inc., Turku, Finland). ROIs were used to obtain TACs for kinetic analyses.

Kinetic analysis and SnPM. K_i^{ref} values representing the uptake of [^{18}F]fluorodopa were calculated with the graphical analysis method using data from 15 to 90 min from the injection and the occipital cortex as the reference region (Patlak & Blasberg, 1985). The parametric images were then smoothed using 8 mm FWHM Gaussian kernel. The analysis mask was created using WFU PickAtlas (version 3.0.3, Neuroimaging Informatics Tools and Resources Clearinghouse, http://www.nitrc.org/projects/wfu_pickatlas/), and included striatal regions, all frontal cortical regions, gyrus rectus, and anterior cingulum. The non-parametric voxel-wise analysis approach was selected based on the distributions of the variables in the ROI data.

4.3.4 Epidemiological survey (study IV)

The survey questionnaire consisted of three subsections. Part I included demographic data, such as sex, age, year of PD diagnosis, information about working and education, place of living, smoking, alcohol consumption, medical conditions, and used medications. Antiparkinsonian medication including dosing, possible treatment changes because of ICDs or other side effects, motor fluctuations, and PD-related neurosurgical procedures were asked about in detail. To assess the dopaminergic load of the antiparkinsonian medications, the total levodopa equivalent daily doses (LEDDs) were calculated as described previously (Tomlinson *et al.*, 2010)2010.

In part II of the survey, current (within the last four weeks) ICDs (gambling, sexual behavior, shopping, and eating) along with other compulsive behaviors (hobbyism, punding, walkabout, and compulsive medication use) were inquired about using a direct Finnish translation of QUIP (Weintraub *et al.*, 2009), because a validated Finnish version was not available at the time of the study. The prevalence of disordered gambling was estimated using SOGS (Lesieur & Blume, 1987), inquiring about the symptoms within the last three months.

In part III, current depressive symptoms were assessed with BDI (Beck *et al.*, 1961), which has been shown to be valid for screening and severity assessment of depression in PD patients (Schrag *et al.*, 2007).

With QUIP, the cut-off points proposed by the authors of the original validation study were used (Weintraub *et al.*, 2009). With SOGS, five or more points was considered to indicate PG (Lesieur & Blume, 1987). In BDI, the severity of depressive symptoms was assessed using common cut-off values (Beck *et al.*, 1988). To estimate the prevalence of clinically significant depression in this sample, the BDI score with a cut-off of 17 points was used, since the symptoms of PD and depression partly overlap and thus higher cut-offs are needed for assessing depression in PD patients (Schrag *et al.*, 2007). A questionnaire with more than 20% of missing answers was considered as a missing value. A more detailed description of the analysis of the study IV can be found from the original publication IV.

4.4 Statistical analyses

All statistical analyses, except for voxel-by-voxel analyses, were performed using PASW statistics (version 18, SPSS Inc., Chicago, Illinois). The normality of the distributions was evaluated using Shapiro-Wilks or Kolmogorov-Smirnov test and visual inspections of the histograms. P values less than 0.05 were considered significant.

4.5.1 Demographic data and psychometric measures (studies I-IV)

Group differences in continuous demographic data were tested using Student's t-test, one-way ANOVA, Mann-Whitney U-test, or Kruskall-Wallis ANOVA, when appropriate.

Categorical demographic data was analyzed with Pearson's Chi-Square, or Fischer's Exact test when the assumptions of Pearson's Chi-Square were not met. Correlation analyses between demographic and neuroimaging data were performed with Pearson's correlation coefficient (r) or Spearman's rank order correlation coefficient (rho), when appropriate.

4.5.2 Physiological data, behavioral ratings and gambling outcomes (study I)

Physiological measures and behavioral ratings were analyzed with 2 x 3 repeated measures ANOVA (rmANOVA) with high-reward and low-reward scan analyzed separately (two groups, three time-points). For correlation analyses, a delta value for the behavioral ratings was calculated, which describes the change between the ratings during and before the gambling task, using the following formula:

$$\Delta BR = \frac{BR_{30\,\mathrm{min}} + BR_{15\,\mathrm{min}}}{2} - BR_{0\,\mathrm{min}}$$

The gambling outcomes were also investigated with 2 x 3 rmANOVA using the net wins at 15min, 30min, and 54min after injection. The values from one low-reward scan of a pathological gambler are missing due to a failed radiotracer synthesis (n = 24 for the high-reward task and n = 23 for the low-reward task).

4.5.3 [^{11}C]raclopride PET (study I)

SPM analysis. One control subject was excluded from the SPM analysis because of partially missing cortical data due scanner malfunction, and thus, the data set consisted of 68 scans. The voxel-by-voxel analyses were performed with SPM5 running in Matlab R2008b for Windows (Math Works, Natick, MA, USA). In the comparison of pathological gamblers and controls, a 2 x 3 rmANOVA model was used (68 scans, n = 23; two groups, three conditions). Dopamine release (condition effects) and differences in dopamine release between the groups (group x condition interactions) were tested with a height threshold of $T_{1,41} = 3.30$ (uncorrected $P < 0.001$), with cluster level FWE-corrected $P < 0.05$ considered significant. The highest peak of statistical significance of the dopamine release during the high-reward scan was defined with a two-sided F-contrast with a height threshold of $F_{1,41} = 8.80$, FWE-corrected $P < 0.05$ at voxel level.

ROI analysis. After identifying the region where dopamine release occurred, BP_{ND}s from the cluster of the highest peak of statistical significance [52 voxels, peak at (-10 4 2)] were extracted with MarsBar toolbox (Brett *et al.*, 2002) implemented in SPM5, and used for subsequent analyses. A 2 x 3 rmANOVA model was also used for the ROI-data (71 scans).

Dopamine release was estimated by calculating relative (%) delta values ($r\Delta BP_{ND}$) of the BP_{ND}s with the formula:

$$r\Delta BP_{ND} = \frac{BP_{ND(High-reward/Low-reward)} - BP_{ND(Control)}}{BP_{ND(control)}}$$

The decrease in raclopride binding (by the release of endogeneous dopamine) is therefore reflected as negative $r\Delta BP_{ND}$ values. Correlation analyses with $r\Delta BP_{ND}$ were performed using Spearman's rho or Pearson's r, when appropriate.

4.5.4 VBM and DTI (study II)

VBM. In VBM, the smoothed, modulated data was analyzed using statistical parametric mapping (SPM8) using the general linear model. For the statistical analysis, voxels with a gray or white matter value less than 0.1 were excluded to avoid possible edge effects around the border between gray and white matter. In the analysis of regional gray or white matter volumes, global gray or white matter volumes, respectively, were entered as confounders in ANCOVA. The analyses were performed with both, modulated and unmodulated images. The level of statistical significance was set at $P < 0.001$, uncorrected for multiple comparisons ($t_{22} = 3.53$), 100 or more contiguous voxels (>100 mm^3).

DTI. In DTI, the projected data was analyzed using a non-parametric approach built into TBSS. Randomize tool (v.2.8 in FSL 4.1.7), a simple permutation program enabling modeling and inference (thresholding) using the standard general linear model design setup (Nichols & Holmes, 2002), was used for a two-regressor analysis (equivalent to the unpaired t-test) to test differences in FA and MD images between the PG patient group and the control group (Smith & Nichols, 2009). Ten thousand permutations of the data were generated to build up the null distribution, and the Threshold-Free Cluster Enhancement (TFCE) option was applied with default parameters to enhance cluster-like structures (Smith & Nichols, 2009). To control for type I errors, family-wise error (FWE)-correction at voxel-level was applied. The peak voxels are presented in MNI coordinates.

Global volumes and DTI measurements were compared between PG patients and healthy controls using Student's t-test or Mann-Whitney U-test, when appropriate. Correlation analyses between structural and diffusion parameters, BMI, and age were analyzed using Pearson's r or Spearman's rho. Correlation analyses between diffusion parameters and psychometric measures were performed with partial correlation coefficient controlling for age. Effect sizes were calculated with Cohen's d:s.

4.5.5 [^{18}F]fluorodopa PET (study III)

SnPM analysis. As non-parametric approach was selected, voxel-wise analyses were performed with SnPM5 using independent samples t-test (Nichols & Holmes, 2002). Ten mm variance smoothing was applied. The results were examined at cluster level with a threshold of pseudo-T value of 2.75 with a search volume equivalent to 47,039 voxels

= 376,312 mm^3. FWE-corrected P values less than 0.05 were considered statistically significant.

ROI analysis. The ROI data was analyzed separating the left and right side of the brain, but also according to the side (ipsilateral/contralateral) of predominant side of motor symptoms, as the nigrostriatal impairment is often asymmetrical in PD. Group differences in the ROI-based data were investigated with the Mann-Whitney U-test, and correlation analyses were performed with Spearman's rho. Differences in the [^{18}F]fluorodopa uptake between different regions were tested using Friedman's ANOVA and post-hoc tests using Wilcoxon's signed-rank test with Bonferroni correction. The correlation between K_i^{ref} values with and without PVE correction was studied using Pearson's r.

4.5.6 Factors associated with impulse control disorders (ICDs) and depression (study IV)

The association of factors with ICDs (binary dependent variables) was studied using binary logistic regression analyses, and with depression (ordinal dependent variable) using cumulative logistic regression analyses. ICDs and depression were both used as dependent and factor variables, since the causal relationships between them are not clear. Statistically significantly associated factors in univariate logistic regression analyses were included in the corresponding multivariate analyses. The results of logistic regression were quantified by calculating odds ratios (ORs) and cumulative odd ratios (CORs) with their 95% confidence interval (CI).

5. RESULTS

5.1 Demographic data in neuroimaging studies (studies I-III)

The demographic data of the groups C and G (studies I and II) are presented in Table 2.

Table 2. Demographic data of groups controls (C) and pathological gamblers (G) (studies I and II)

	Controls (n=12)		Gamblers (n=12)		
	median/n	(range/%)	median/n	(range/%)	P
Age (years)	27.0	(19 – 55)	30.0	(22 – 49)	0.62
BMI (kg/m^2)	27.5	(25 – 35)	27.5	(21 – 36)	0.75
Income per month(€)	1000	(400–3500)	2425	(250–3600)	0.30
BDI score	0	(0 – 2)	6.0	(1 – 19)	<0.001*
Education (n)					
..Comprehensive school	0	(0)	1	(8)	0.64[1]
..Vocational / high school	10	(83)	8	(67)	
..University	2	(17)	3	(25)	
Daily nicotine use (n)	3	(25)	6	(50)	0.40[1]
Age of PG onset (a)	na		17	(10 – 39)	na
PG duration (years)	na		12	(1 – 20)	na
Gambling debts (€)	0	(0)	20000	(0–75000)	<0.001*
SOGS score	0.5	(0 – 1)	14.0	(10 – 18)	<0.001*
Weekly gambling activity: [2]					
..Electronic machines (h)	0.1	(0 – 1)	4.0	(1 – 14)	<0.001*
..Electronic machines (€)	1	(0 – 5)	100	(20 – 500)	<0.001*
..Electronic machines (%)[3]	na		60	(0 – 95)	na
..Slot machines (%)[3]	na		27.5	(5 – 70)	na

Median (range) values or number (relative number) of subjects are presented, when appropriate. Statistical significance was tested using Mann-Whitney U test, unless otherwise stated. [1]Fischer's Exact test. [2]Self-estimated gambling activity during the last three months prior to the study. [3]Relative proportion of all gambling activity. BDI = Beck depression inventory. BMI = body mass index. PG = pathological gambling. SOGS = South Oaks gambling screen. na = not applicable. *Statistically significant.

Demographic data of the groups PDC and PDG (study III) is presented in Table 3. All subjects had Hoehn & Yahr stage 2 – 3. In both groups, four subjects had right side predominant motor symptoms. Levodopa medication was used by nine subjects in each group, and dopamine agonist medication was also used by nine subjects in each group.

Table 3. Demographic data of PD controls (PDC) and PD patients with ICDs (PDG) (study III)

	PD controls (n=10)		PDs with ICDs (n=10)		
	median	(range)	median	(range)	P
Age (years)	61.5	(53 – 70)	61.5	(45 – 71)	0.76
BMI (kg/m^2)	29.5	(24 – 38)	25.5	(21 – 32)	0.24
MMSE	27.5	(22 – 30)	27.5	(24 – 30)	
Age of PD onset	57.0	(47 – 63)	53.0	(40 – 65)	0.51
PD duration (years)	5.0	(1 – 8)	7.0	(3 – 9)	0.09
UPDRS I	2	(0 – 4)	3	(0 – 6)	0.11
UPDRS II	6	(1 – 31)	12	(8 – 19)	0.05*
UPDRS III					
..medicated	32	(19 – 49)	31	(24 – 41)	0.88
..unmedicated	42.5	(25 – 52)	39	(28 – 48)	0.57
UPDRS IV	3	(0 – 10)	5	(2 – 9)	0.09
LEDD (mg/d)	826	(210 – 1127)	635	(250 – 876)	0.06
LEDD DA (mg/d)	200	(0 – 320)	171.5	(0 – 280)	0.38

Median (range) values, or number of subjects, are presented. P values were calculated using Mann-Whitney U test. DA = dopamine agonist. ICD = impulse control disorder. LEDD = levodopa equivalent daily dose. MMSE = Minimental state examination. PD = Parkinson's disease. UPDRS = Unified Parkinson's Disease Rating Scale. *Statistically significant.

5.2 Mesolimbic dopamine function in pathological gambling (study I)

5.2.1 Gambling task outcome

The net win curves of the gambling tasks are presented in Figure 9C. The high-reward task produced a mean (SD) peak net monetary win of 93.70 (4.50) € around 30 min of scanning, 54.20 (11.90) € end-point, and 0 to 20 € range of individual game (spin) payouts. The low-reward task produced -3.20 (8.10) € end-point net win with 0 to 16 € individual game payouts.

Pathological gamblers played faster, and thus resulted in a greater number of played games than controls [mean (SD) 483 (39) and 437 (39), respectively, $P < 0.001$]. However, there were no differences between the groups in net wins [rmANOVA group x time interaction $F = 1.69$, $P = 0.21$ (high-reward), and $F = 1.77$, $P = 0.16$ (low-reward)] due to programming (Figure 9C).

5.2.2 Physiological and behavioral measures

The changes in mood ratings during the tasks are presented in Table 4. The high-reward task increased (rmANOVA time effects) subjective feelings of "urge to gamble" ($F = 9.55$, $P < 0.001$), "high" ($F = 21.91$, $P < 0.001$), "excitement ($F = 10.29$, $P = 0.001$), and "alertness ($F = 5.10$, $P = 0.02$). Pathological gamblers experienced more "urge to gamble"

(F = 7.65, P = 0.01), but there was no group x time interaction indicating that the groups did not differ in reactions to the high-reward task (Table 4). In the low-reward task the ratings of "positive mood" decreased (F = 3.97, P = 0.03) and pathological gamblers rated higher "urge to gamble" (F = 5.95, P = 0.02) and "excitement" (F = 4.93, P = 0.04) (Table 4). In addition, there was a significant group x time effect in "urge to gamble" (F = 3.37, P = 0.04) indicating that the "urge to gamble" increased in pathological gamblers while it decreased in healthy volunteers (Table 4).

Table 4. Change in behavioral ratings. Positive values indicate increased rating.

High-reward					
	Controls (n=12)	**Gamblers (n=12)**		**$P_{rmANOVA}$**	
	mean (SD)	mean (SD)	Group	Time	G x T
High	2.75 (2.45)	3.17 (3.27)	ns	***	ns
Positive mood	0.79 (2.31)	0.58 (1.90)	ns	ns	ns
Alertness	0.67 (1.79)	1.46 (2.24)	ns	*	ns
Excitement	1.75 (1.73)	1.58 (2.68)	ns	**	ns
Urge to gamble	1.08 (1.86)	1.50 (1.31)	*	***	ns
Low-reward					
	Controls (n=12)	**Gamblers (n=11[a])**		**$P_{rmANOVA}$**	
	mean (SD)	mean (SD)	Group	Time	G x T
High	0.71 (2.00)	0.77 (1.92)	ns	ns	ns
Positive mood	-0.42 (0.90)	-0.82 (1.06)	ns	*	ns
Alertness	0.50 (1.78)	0.32 (1.45)	ns	ns	ns
Excitement	0.08 (1.94)	0.82 (2.05)	*	ns	ns
Urge to gamble	-0.50 (1.00)	0.86 (2.25)	*	ns	*

Behavioral rating delta values [$(BR_{15min} + BR_{30min}) / 2 – BP_{0min}$], representing the change from the level prior to the task. G x T = group x time interaction in rmANOVA. [a]One missing value due to a failed radiotracer synthesis. *P<0.05, **P<0.01, ***P<0.001.

The heart rates increased during the high-reward scan for a while, but decreased during the low-reward scan (task x time interaction effect, F = 10.78, P < 0.001). However, there were no differences between the groups. Blood pressure levels remained unaffected by the gambling tasks and did not differ between the groups.

5.2.3 Dopamine neurotransmission

Dopamine release during gambling. SPM analyses revealed that gambling induced dopamine release during both the high-reward scan and the low-reward scan. Dopamine was released in the associative part of the caudate nucleus during the low-reward scan, extending to the ventral striatum during the high-reward scan (Figure 10). There was a correlation in the magnitude of the dopamine release between the high-reward and low-reward scan (Figure 11A). The magnitude of dopamine release did not differ between the groups (no significant group x task interaction) and there were no areas with significant increase in raclopride binding.

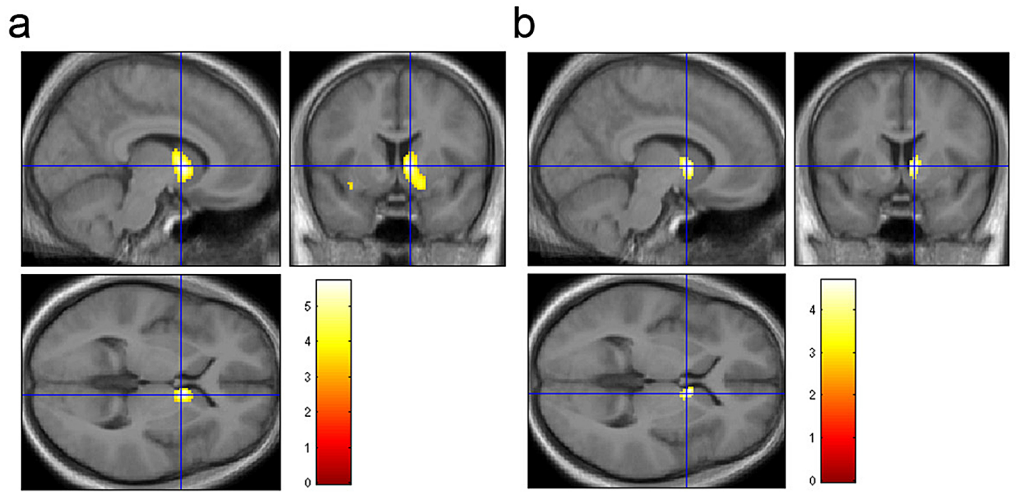

Figure 10. Dopamine release during gambling
The results of SPM repeated measures ANOVA analysis overlaid on the average T1 weighted MRI image of the studied sample. A, B. Areas of decreased [^{11}C]raclopride BP_{ND} with height threshold $T_{1,41} = 3.30$. Yellow scale bars indicate the corresponding T values. A. Condition effect, high-reward versus control scan, statistical peak voxel at (-10 4 2), $T_{max} = 5.71$, cluster of 322 voxels = 2576 mm^3, FWE-corrected P = 0.002. B. Condition effect (low-reward versus control scan), statistical peak voxel at (-10 4 2), Tmax = 4.68, cluster of 95 voxels = 760 mm^3, FWE-corrected P = 0.043. The figure has been previously published in original publication I.

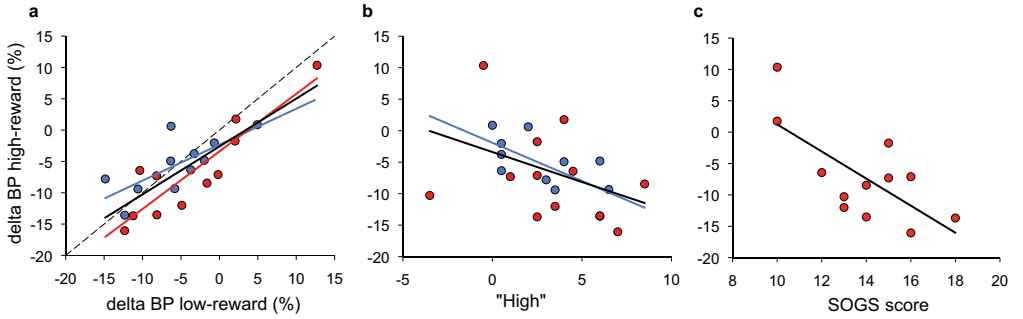

Figure 11. Correlations of dopamine release during the high-reward scan
A. Correlation of dopamine release (as indicated by negative $r\Delta BP_{ND}$) between high-reward and low-reward scans, $rho_{22} = 0.76$, P < 0.001 in the whole sample; $rho_{11} = 0.74$, P = 0.01 in controls; $rho_{11} = 0.81$, P = 0.003 in pathological gamblers. B. Correlation between $r\Delta BP_{ND}$ and change in the rating of "high" ΔBR in the reward scan, $rho_{23} = -0.47$, P = 0.02 in the whole sample; $rho_{11} = -0.68$, P = 0.02 in controls. C. Correlation between SOGS score and $r\Delta BP_{ND}$ during the high-reward scan in pathological gamblers, $rho_{12} = -0.59$ P = 0.04. Black line = regression line of the whole sample. Blue = controls. Red = pathological gamblers. Dashed line = line of equivalent dopamine release during reward and no-reward (area under the line = greater dopamine release during reward than no-reward). SOGS = South Oaks gambling screen. $r\Delta BP_{ND}$ = relative [^{11}C] raclopride non-displaceable binding potential delta value. ΔBR = behavioral rating delta value. The figure has been previously published in the original publication I.

However, there was no significant dopamine release as measured from ROI data (Table 5).

Table 5. [^{11}C]raclopride binding potentials

Region	Group	Task			$P_{rmANOVA}$		
		Control mean (SD)	Low-reward mean (SD)	High-reward mean (SD)	Group	Task	G x T
Vstr L	C	2.33 (.32)	2.31 (.31)	2.23 (.25)	0.22	0.31	0.36
	G	2.15 (.31)	2.15 (.25)	2.17 (.21)			
Vstr R	C	2.35 (.33)	2.42 (.35)	2.29 (.30)	0.32	0.19	0.16
	G	2.25 (.42)	2.20 (.27)	2.22 (.23)			
Cau L	C	2.07 (.31)	2.03 (.34)	2.04 (.32)	0.33	0.37	0.57
	G	1.95 (.28)	1.95 (.21)	1.91 (.22)			
Cau R	C	2.12 (.36)	2.05 (.31)	2.07 (.32)	0.32	0.12	0.38
	G	1.99 (.30)	1.97 (.23)	1.90 (.22)			
Put L	C	2.70 (.30)	2.72 (.27)	2.71 (.29)	0.28	0.32	0.19
	G	2.63 (.33)	2.60 (.26)	2.54 (.24)			
Put R	C	2.65 (.34)	2.67 (.30)	2.67 (.29)	0.37	0.56	0.47
	G	2.59 (.30)	2.57 (.27)	2.52 (.24)			
Dstr L	C	2.47 (.30)	2.45 (.28)	2.47 (.29)	0.26	0.28	0.29
	G	2.37 (.30)	2.35 (.22)	2.29 (.21)			
Dstr R	C	2.46 (.34)	2.43 (.29)	2.44 (.30)	0.27	0.33	0.44
	G	2.34 (.29)	2.32 (.24)	2.26 (.21)			

C = control group (n=12). G = pathological gambler group (n=12 in the control and high-reward tasks, n=11 in the low-reward task). G x T = group x task interaction effect. Vstr = ventral striatum. Cau = dorsal caudate. Put = dorsal putamen. Dstr = dorsal striatum (dorsal caudate + dorsal putamen). L = left. R = right. $P_{rmANOVA}$ = repeated measures ANOVA P value.

Effect of behavioral responses. The magnitudes of the dopamine release during the high-reward scan correlated with the change in subjective ratings (negative correlation between $r\Delta BP_{ND}$ and ΔBR) of "high" (rho_{23} = -0.47, P = 0.02; Figure 11B), "positive mood" (rho_{23} = -0.52, P = 0.01), and "alertness" (rho_{23} = -0.43, P = 0.04). When separating the groups, dopamine release correlated with "high" (negative correlation between $r\Delta BP_{ND}$ and ΔBR, rho_{11} = -0.68, P = 0.02, Figure 11B) and "positive mood" (rho_{11} = -0.68, P = 0.01) in healthy controls, but not in gamblers. The dopamine release during the low-reward scan was not correlated with any of the behavioral ratings groups analyzed together, or separately.

Effect of addiction severity and type. Higher SOGS score predicted higher dopamine release in the high-reward scan (SOGS vs $r\Delta BP_{ND}$ r_{12} = -0.59, P = 0.04; Figure 11C), but not in the low-reward scan, although there was a trend towards the same direction (r_{11} = -0.56, P = 0.08). The preference for slot machine gambling correlated with ratings of "high" during the high-reward scan (r_{12} = 0.61, P = 0.04), but not during the low-

reward scan (r_{11} = -0.21 to 0.13, P > 0.54). Furthermore, the preference for slot machine gambling was associated with greater dopamine release in the high-reward scan (slot machine gambling vs rΔBP_{ND} r_{12} = -0.61, P = 0.03), and also in the low-reward scan (slot machine gambling vs rΔBP_{ND} r_{11} = -0.60, P = 0.05).

5.2.4 Dopamine D2 (D3) receptor availability

The control task D2 receptors BP_{ND} did not differ between pathological gamblers and controls in voxel-wise analysis or when using ROI data. However, the average BP_{ND}s in striatal subregions were consistently lower in pathological gamblers than in controls, but the difference did not reach statistical significance (ROI data is presented in Table 5, section *5.2.3*). There were no correlations between baseline [^{11}C]raclopride BP_{ND} and gambling related parameters, such as SOGS score, DSM-IV item score, duration/age of onset of gambling problems, nor BDI score in pathological gamblers.

5.3 Brain structure in pathological gambling (study II)

Global volumes. The global volumes of gray matter, white matter and CSF with global white matter mean FA and MD values are presented in Table 6. Global white matter volume correlated with global mean FA (rho_{24} = 0.44, P = 0.03), but not with global mean MD (rho_{24} = -0.30, P = 0.16). Global mean FA correlated negatively with global mean MD (r_{24} = 0.81, P < 0.001). Age correlated negatively with global gray matter volume (rho_{24} = 0.78, P < 0.001) and global mean FA (rho_{24} = -0.55, P = 0.005), and positively with global mean MD (rho_{24} = 0.43, P = 0.04) and CSF volume (rho_{24} = 0.46, P = 0.03), but not with global white matter volume (rho_{24} = -0.07, P = 0.74).

Table 6. Global volumes and mean diffusion parameters

	Controls (n=12) mean (SD)	**Gamblers (n=12)** mean (SD)	P
Gray matter volume (cm^3)	929 (68)	936 (64)	0.78
White matter volume (cm^3)	623 (37)	624 (36)	0.96
Total brain volume (cm^3)	1552 (71)	1560 (62)	0.77
CSF volume (cm^3)	417 (76)	454 (86)	0.26
Global mean FA	0.417 (0.012)	0.404 (0.012)	0.01*
Global mean MD ($x10^{-6}$ mm/s^2)	772 (19)	786 (22)	0.09

Statistical testing was performed using Student's t-test. Total brain volume = gray + white matter. CSF = cerebrospinal fluid. Global mean diffusion parameters [fractional anisotropy (FA) and mean diffusivity (MD)] represent mean values of the entire white matter tract skeleton created with TBSS. *Statistically significant.

Regional diffusion analysis revealed extensive lower white matter integrity (lower FA and higher MD) in pathological gamblers compared to control subjects (Figure 12). Lower FA was found bilaterally in the corpus callosum, the cingulum, the superior longitudinal fascicle, the inferior fronto-occipital fascicle, the anterior limb of internal capsule, and the anterior thalamic radiation; and on the left side of the brain in the inferior longitudinal fascicle and uncinate/inferior fronto-occipital fascicle. Higher MD was discovered in the corresponding white matter tracts, though the changes were more extensive than seen with FA, also including the right inferior longitudinal fascicle and the right uncinate/inferior fronto-occipital fascicle. Pathological gamblers had 8.1% lower mean FA and 4.6% higher mean MD in the respective areas when

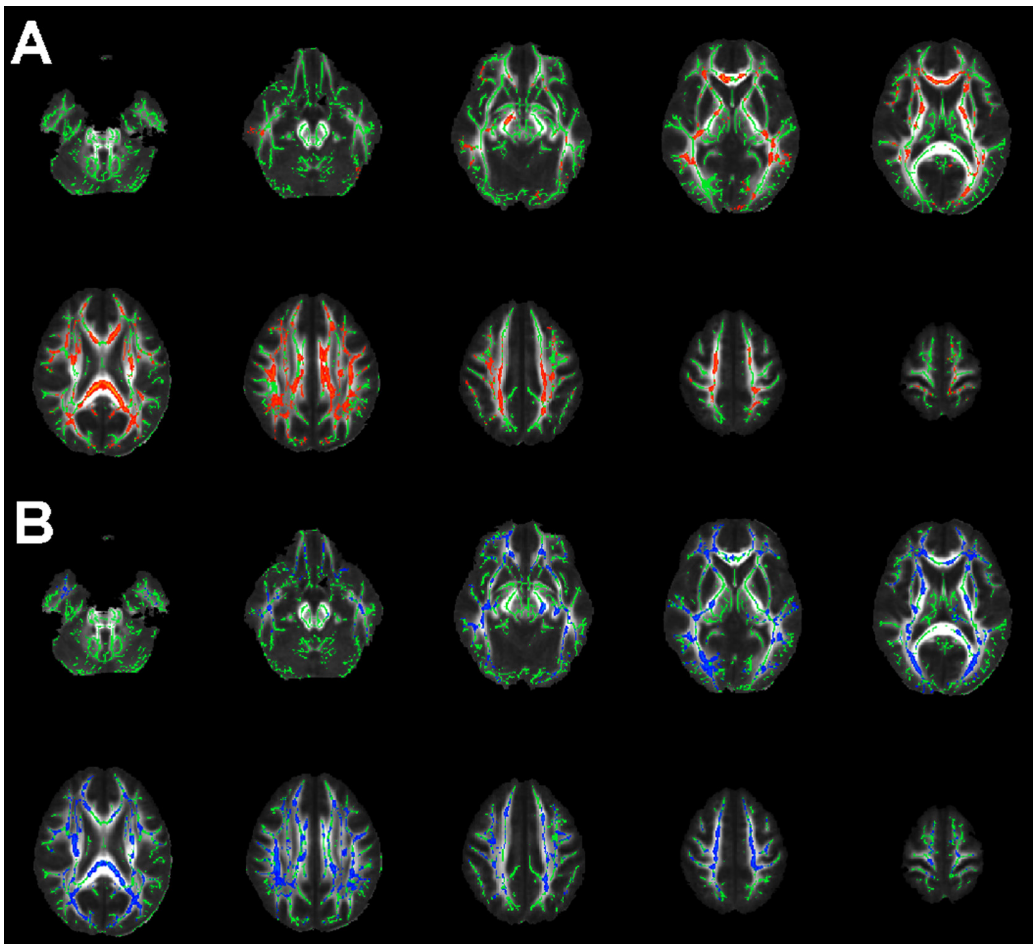

Figure 12. Group differences in regional diffusion parameters
Brain white matter tract skeleton (shown in green) of the studied sample superimposed on the mean fractional anisotropy (FA) image. Statistically significant group differences of A. FA values lower and B. mean diffusivity (MD) values higher in pathological gamblers (n=12) compared to controls (n=12). Red-yellow scale in A. represents P values 0.05 – 0.005 and blue-light blue scale in B. represents P values 0.05 – 0.006. All P values are FWE-corrected for multiple comparisons. The figure has been published previously in the original publication II.

compared to the control subjects, P < 0.001 (Figure 13). The results remained significant after controlling individually for age, current nicotine use status, skeleton mean MD/FA, antidepressive medication use, and TR values. Furthermore, the results remained significant removing subjects with prior alcohol addiction (n = 3) from the analysis with P < 0.001 for both FA and MD. There was no correlation between altered FA or MD and gambling related parameters (SOGS score or disease onset/duration) or BDI scores in pathological gamblers.

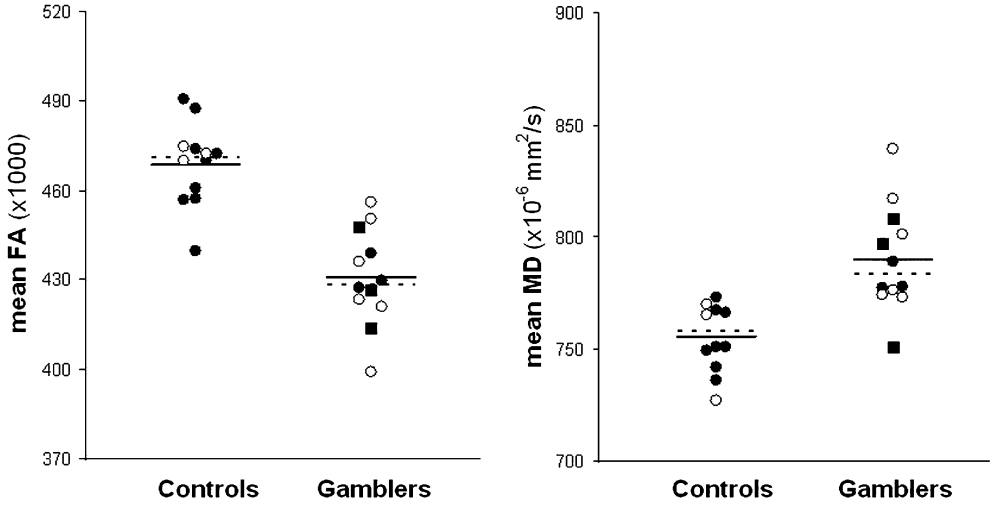

Figure 13. Regional fractional anisotropy (FA) and mean diffusivity (MD) values
A. Mean FA and B. mean MD values obtained from areas of significant group differences (FWE-corrected P<0.05. shown in red-yellow or in blue in Figure 12A and B, respectively). n=24. Solid circles = subjects without nicotine addiction. Open circles = subjects with nicotine addiction. Solid square = subjects with previous alcohol dependence. Solid line = mean. Dotted line = median. Note that the individuals with nicotine addiction or the individuals with previous alcohol dependence do not markedly differ in FA or MD compared to other subjects. The figure has been published previously in the original publication II.

There were no differences between the groups in the regional gray or white matter volume or density. Thus, correlation analyses with regional gray or white matter volumes were not performed.

5.4 Presynaptic monoamine function in Parkinsonian ICDs (study III)

PD patients with ICDs had 35% greater median fluorodopa uptake in the left medial orbitofrontal cortex (mOFC), but no differences in striatal subregions (Table 7, Figure 14). The result of the left mOFC remained significant after excluding subjects with any current psychiatric Axis-I disorder (n = 5) [48% difference in K_i^{ref} ($10^{-3}min^{-1}$), median (range) 2.16 (1.95 – 3.14) for the ICD group and 1.46 (0.41 – 2.48) for the control group, P = 0.008]. When separating pathological gamblers (n = 5) from other ICDs,

patients with PG had higher left mOFC uptake than control patients [48% difference in K_i^{ref} ($10^{-3}min^{-1}$), median (range) 2.36 (2.12 – 3.14) and 1.59 (0.41 – 2.48), respectively, P = 0.01], but patients with other ICDs did not differ from control subjects. Voxel-wise analysis confirmed the higher mOFC uptake revealing a 382 voxel (3056 mm^3) cluster, with FWE-corrected P = 0.03, extending bilaterally (Figure 14B). The uptake ratio mOFC:putamen was higher in the ICD patients compared to controls [40% difference, median (range) 0.60 (0.44 – 1.24) and 0.43 (0.06 – 0.75), respectively, P = 0.05] When dividing brain hemispheres according to the laterality of the motor symptoms, higher mOFC uptake was seen on the ipsilateral side to the predominant symptoms [31% difference, median (range) 2.24 (1.57 – 3.14) and 1.71 (0.00 – 2.82), for patients with and without ICDs, respectively, P = 0.04], and no differences in striatal subregions. The results remained the same when PVE corrected images were used, as the left mOFC uptake was higher in patients with ICDs compared to control patients [median (range) 2.17 (1.54 – 3.32) and 1.56 (0.35 – 2.39), respectively, P = 0.02]. Furthermore, there was a strong correlation between K_i^{ref} values with and without PVE correction ($r_{20} > 0.82$, P < 0.001 in all examined regions).

Table 7. [^{18}F]fluorodopa uptake K_i^{ref} ($10^{-3}min^{-1}$) in PD patients with and without ICDs

	PD controls (n=10)		PDs with ICDs (n=10)		
Region	median	(range)	median	(range)	P
mOfc L	1.59	(0.41 – 2.48)	2.14	(1.57 – 3.14)	0.02*
mOfc R	1.99	(0.00 – 2.82)	2.25	(1.12 – 3.07)	0.11
Vstr L	8.23	(6.46 – 10.60)	8.92	(6.77 – 10.40)	0.41
Vstr R	8.79	(7.77 – 10.20)	8.75	(7.31 – 10.10)	0.76
Cau L	7.31	(5.71 – 11.45)	7.49	(4.87 – 9.35)	0.60
Cau R	7.63	(4.53 – 9.90)	7.22	(5.42 – 9.20)	0.71
Ant. Put L	4.50	(2.94 – 7.88)	4.61	(3.24 – 5.86)	0.60
Ant. Put R	4.53	(2.58 – 6.82)	3.64	(2.87 – 6.63)	0.08
Post Put L	2.55	(1.14 – 5.04)	1.98	(0.87 – 4.04)	0.29
Post Put R	2.39	(1.01 – 5.52)	1.83	(0.72 – 5.82)	0.71

Statistical significance was tested using the Mann-Whitney U test. Ant Put = anterior putamen. Cau = caudate nucleus. ICD = impulse control disorder. mOFC = medial orbitofrontal cortex. PD = Parkinson's disease. Post Put = posterior putamen. Vstr = ventral striatum. L = left. R = right. *Statistically significant.

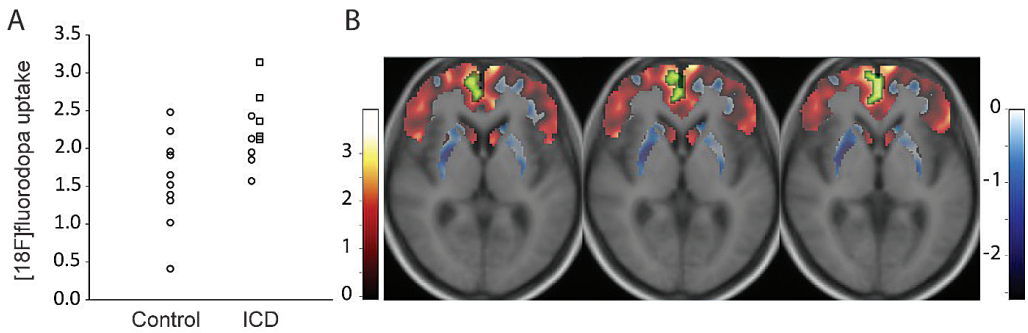

Figure 14. [^{18}F]fluorodopa uptake
A. [^{18}F]fluorodopa uptake [K_i^{ref} (x10^{-3} min^{-1})] in the left medial orbitofrontal cortex. Square = pathological gambler. B. Statistical pseudo-T map of the voxel-wise group comparison (unpaired t-test, impulse control disorder (ICD) group > control group) of the [^{18}F]fluorodopa uptake (n=10 vs. n=10). The statistically significant cluster is marked in green. The figure has been published previously in the original publication III.

5.5 Epidemiological survey (study IV)

5.5.1 Demographic data

Six-hundred-and-five (60.5%) of the 1000 questionnaires were returned. Thirty patients were excluded from the statistical analyses because of insufficient data or no evidence of PD diagnosis, leaving 575 patients for the final analyses. Men (63.5%) and young patients (57.4% ≤65 years) were more over-represented in the final sample compared to the selected study population (60% male and 50% young patients), $P < 0.01$.

The most commonly used combination of antiparkinsonian medication was levodopa and dopamine agonist (311 patients, 54% of the total sample), with almost half of them using additionally a monoamine oxidase B (MAO-B) inhibitor (148 patients, 26%). A combination of dopmine agonist and MAO-B inhibitor without levodopa was used by 64 (11%) of the patients. Monotherapy was used by 141 (25%) patients [89 (15%) for levodopa, 38 (7%) for dopamine agonist, and 13 (2%) for MAO-B inhibitor alone]. Approximately half of the patients reported motor fluctuations (281 patients, 49%). Forty-six patients (8%) were taking antidepressive medication. The demographic data according to ICDs is presented in Table 8.

Table 8. Demographics of patients with Parkinson's disease (PD) in Study IV

	All (n = 575)		**ICD-negative** (n=360)		**ICD-positive** (n = 192)		
	n (%)	n[1]	n(%)	n[1]	n (%)	n[1]	P
Male sex	365 (63.5)	575	209 (58.1)	360	144 (75.0)	192	<0.001*
Age ≤ 65 years	330 (54.7)	575	190 (52.8)	357	130 (67.7)	192	0.001*
Age of PD onset		558		350		187	0.01*
..≤ 50 years	109 (19.5)		60 (17.1)		43 (23.0)		
..51 - 59 years	220 (39.4)		131 (37.4)		84 (44.9)		
..≥ 60 years	229 (41.0)		159 (45.2)		60 (32.1)		
PD duration < 5 years	227 (40.7)	558	148 (41.1)	350	116 (60.4)	187	0.33
Rural	173 (30.1)	572	99 (27.7)	357	59 (30.7)	192	0.46
Education		518		326		172	0.94
..compulsory school	145 (28)		89 (27.3)		49 (28.5)		
..vocational or high school	268 (51.7)		170 (52.1)		87 (50.6)		
..university (of applied sciences)	105 (20.3)		67 (20.6)		36 (20.9)		
Working		575		360		192	0.07
..full-time	25 (4.3)		12 (3.3)		13 (6.8)		
..part-time	20 (3.5)		16 (4.4)		4 (2.1)		
Current smoking	40 (7.1)	562	21 (6.0)	350	18 (9.4)	191	0.14
Current alcohol use	425 (75.8)	561	260 (74.1)	351	156 (81.7)	191	0.05*
Family history of PG	43 (7.5)	575	22 (6.1)	360	20 (10.4)	192	0.07
Levodopa medication	451 (78.7)	573	282 (78.3)	360	151 (79.1)	191	0.84
Dopamine agonist medication	430 (74.9)	574	273 (75.8)	360	142 (74.0)	192	0.63
..pramipexole	267 (46.5)		162 (45.1)		94 (49.2)		
..ropinorole	155 (27.0)		104 (29)		45 (23.6)		
..other	9 (1.6)		6 (1.7)		2 (1.0)		
MAO-B medication	282 (49.1)	574	168 (46.7)	360	101 (52.9)	191	0.17
..selegiline	226 (39.5)		134 (37.2)		83 (43.5)		
..rasagiline	55 (9.6)		34 (9.4)		18 (9.4)		
LEDD		548		347		184	0.37
..0 - 300 mg	126 (23)		82 (23.6)		39 (21.2)		
..301 - 600 mg	172 (31.4)		113 (32.6)		54 (29.3)		
..601 - 900 mg	136 (24.8)		86 (24.8)		44 (23.9)		
..> 900 mg	114 (20.8)		66 (19.0)		47 (25.5)		
BDI score		549		346		186	<0.001*
..0 – 9	287 (52.3)		216 (62.4)		62 (33.3)		
..10 – 18	161 (29.3)		90 (26.0)		65 (34.9)		
..19 – 29	85 (15.5)		37 (10.7)		47 (25.3)		
..≥ 30	16 (2.9)		3 (0.9)		12 (6.5)		

BDI = Beck depression inventory. ICD = impulse control disorder. LEDD = levodopa-equivalent daily dose. MAO-B = monoamine oxidase B. PG = pathological gambling. [1]number of patients included in the analysis. Note: The relative values (%) are calculated relative to the number of patients providing the information to the particular question and not relative to all responders of the survey. *Statistically significant.

5.5.2 Prevalence rates

The prevalence of probable PG (SOGS ≥ 5 points) was 7.0% and of probable problem gambling (SOGS ≥ 3 points) was 9.1%. For any ICD, 34.8% of the subjects were screened positive with QUIP (12.5% screened positive for multiple ICDs). The prevalence rates for positive screens in ICDs separately were 8.8% for gambling, 22.8% for sexual, 10.1% for shopping, and 11.8% for eating behaviors. More information about the prevalence rates is available in Table 2 of the original publication IV.

A conservative estimation of the prevalence rate of clinically significant depression (BDI ≥17 points) was 18.4% in this sample. Using lower BDI cut-offs, the prevalence rose to 29.5% with BDI ≥ 14 points and to 47.6% with BDI ≥ 10 points.

5.5.3 Factors associated with ICDs

Depressive symptoms (as measured with BDI) were independently associated with ICDs in general and all individual ICDs separately with ORs ranging from 2.58 to 62.95 depending on the depression symptom severity and ICD in question (for more details, see Table 3 of the original publication III). In addition, the male sex was associated [multivariate analysis, OR (95% CI)] with ICDs in general [2.20 (1.20 – 3.66), P < 0.001], gambling problems [3.43 (1.54 – 7.65), P = 0.003] and hypersexuality [7.03 (3.61 – 13.71), P < 0.001]. Age 65 years or less was independently associated with ICDs in general [OR 2.09 (95% CI 1.20 – 3.66), P = 0.009], and also with gambling, hypersexuality and shopping although the association was not independent of the other factors. Current smoking was independently associated with compulsive shopping [OR 2.54 (95% CI 1.04 – 6.18), P = 0.04]. In addition, several factors, such as high LEDDs, young age of PD onset, and current alcohol use were more common in patients screened positive for ICDs, but were not independently associated with positive screens. The results of the univariate and multivariate binary regression analyses are presented in Table 3 of the original publication III.

Eighty-two patients reported some withdrawn PD medication due to side effects. For 13 patients the reason to abandon/reduce a medication was an ICD, but 11 of them still screened positive for ICDs in this study.

Of the total 59 patients screened positive with SOGS and/or QUIP for PG, gambling in general had begun in 27 patients (45.8%) before PD diagnosis, in 21 (35.6%) patients after the diagnosis and in 10 (16.9%) after the initiation of PD medication. Seven of the patients reported pramipexole, one ropinirole and one bromocriptine as the cause of the gambling behavior. Seven (11.9%) of the gamblers reported having relatives with gambling problems. The most common form of gambling was slot machine gambling [38 (64.4%) of the 59 patients who screened positive for gambling]. Twenty (33.9%) of the 59 patients with problem gambling reported loneliness, 17 (28.8%) mental stress, 18 (30.5%) depression, and 22 (37.3%) boredom as factors that provoke gambling behavior. Nine (15.3%) reported gambling while under the influence of alcohol.

5.5.4 Factors associated with depression

Positive screen for ICDs was the most important factor predicting depressive symptoms [cumulative odds ratio, COR 3.9 (95% CI 2.6-5.8), P < 0.001]. Furthermore, median BDI scores increased linearly with the number of ICDs screened positive (Figure 15). Factors, independently associated with higher BDI scores, also included not using dopamine agonist medication [COR 1.93 (95% CI 1.27 – 2.94), P = 0.002] and high (> 900 mg) LEDDs [COR 1.88 (95% CI 1.00 – 3.52), P = 0.05]. In addition, lower education, current alcohol use, and short PD duration were associated with higher BDI scores in univariate, but not in multivariate analyses. The detailed description of the results can be found in Table 4 of the original publication III. There was no difference in BDI scores between users of pramipexole (n=267) and ropinirole (n=155), which were the most commonly used dopamine agonist medications in this sample (P = 0.59).

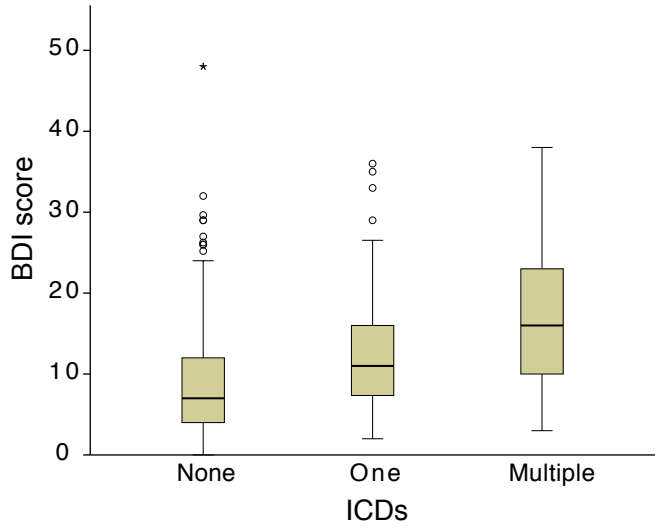

Figure 15. Depressive symptoms according to the ICD risk
None (n=348), One (n=121), and Multiple (n=69) refer to the number of ICDs screened positive with the questionnaire for impulsive-compulsive behaviors in Parkinson's disease (QUIP). Kruskall-Wallis one-way ANOVA P < 0.001, all contrasts P < 0.001 (Bonferroni corrected for multiple comparisons). BDI = Beck Depression Inventory. ICD = impulse control disorder. Thick line = median. Brown box = interquartile range (IQR). Whiskers = 1.5 x IQR. The figure has been published previously in the original publication IV.

6. DISCUSSION

6.1 Brain dopaminergic neurotransmission in pathological gambling

6.1.1 Mesolimbic dopamine function

Study I was the first study directly investigating *in vivo* human dopamine neurotransmission during slot machine gambling, and further separating gambling with and without monetary winning. The results show that basal ganglia dopamine is released during winning slot machine gambling and that the magnitude of dopamine release is associated with parallel subjective feelings of "high". However, non-hedonic gambling without winning also released dopamine, which correlated strongly with the magnitude of dopamine release during hedonic gambling, irrespective of the subjective feelings. The gambling induced dopamine release does not differ between a heterogeneous group of pathological gamblers and healthy volunteers, but the gamblers with the most severe gambling-related symptoms or preference to the slot machine gambling released the most dopamine while being the most euphoric.

6.1.1.1 Behavioral responses to gambling

Pathological gamblers experienced a higher "urge to gamble" in study I, which is in concordance with the increased incentive salience towards gambling actions in pathological gamblers as has been described in the literature (Grant *et al.*, 2010; Sodano & Wulfert, 2010). In addition, during the monotonous hour-long non-rewarding gambling pathological gamblers experienced an increasing "urge to gamble" while control subjects expressed less of an "urge to gamble" in the course of the low-reward task possibly reflecting the impaired stimulus-outcome based learning in PG (van Holst *et al.*, 2010). However, there were no signs of attenuated (nor enhanced) gambling induced euphoria in addicted individuals as could be expected based on the RDS hypothesis (Blum *et al.*, 2000).

6.1.1.2 Gambling releases striatal dopamine

Several pharmacological [reviewed in (Volkow *et al.*, 2009)] and non-pharmacological [reviewed in (Egerton *et al.*, 2009)] rewards have been shown to activate the mesolimbic dopamine neurotransmission in humans. Furthermore, it has been shown that the magnitude of the dopamine release by pharmacological rewarding agents, such as stimulants, relates to the experienced euphoria induced by the drug (Volkow *et al.*, 1999). The evidence of human *in vivo* mesolimbic dopamine release associated with pharmacological rewards, however, is somewhat less clear (Egerton *et al.*, 2009). When applying similar methods (namely [^{11}C]raclopride PET with displacement method)

with the non-pharmacological rewards as has been done with pharmacological agents, monetary reward during a video game (although without sensorimotor control task or movement correction) (Koepp *et al.*, 1998), a gambling task (in PD patients) (Steeves *et al.*, 2009), a delayed monetary incentive task (Schott *et al.*, 2008), or an active card selection task (Zald *et al.*, 2004); food (after fasting) (Small *et al.*, 2003); and music (in individuals with exceptionally strong emotional responses to the particular music) (Salimpoor *et al.*, 2011) have shown a statistically significant reduction in [^{11}C]raclopride non-displaceable binding potential (BP_{ND}) indicating endogenous dopamine release. Interestingly, several studies with acute non-pharmacological rewards have produced only trend-line effects, or significant effects only in subpopulations of the study's sample in respect to dopamine release (Egerton *et al.*, 2009). This was also the case in the only previous study investigating the dopamine release in gamblers and healthy volunteers using the Iowa Gambling Task (Linnet *et al.*, 2010; Linnet *et al.,* 2011b). The previous findings together with the results of study I suggest that non-pharmacological rewarding stimuli do release mesolimbic dopamine, but the effect sizes are of lesser magnitude compared to pharmacological rewarding stimuli.

Mesolimbic dopamine neurons originating from the VTA to the basal ganglia have been shown to encode not only reward value, but also reward risk, in non-human primates (Schultz *et al.*, 1997; Fiorillo *et al.*, 2003), and comparable hemodynamical responses in humans have been seen as well (Preuschoff *et al.*, 2006). Furthermore, non-human primate studies have demonstrated the selective role of dopamine in the form of stimulus-reward learning in which incentive salience is assigned to cues predicting the reward (Flagel *et al.*, 2011). Human neuroimaging studies with substance addictions have confirmed existing conditioned striatal dopamine release in response to reward predicting cues (Volkow *et al.*, 2006).

Study I replicates the previously reported mesolimbic dopamine release in response to monetary rewards (Zald *et al.*, 2004; Schott *et al.*, 2008; Steeves *et al.*, 2009), but also shows that mere slot machine gambling without winning money is sufficient to induce mesolimbic dopamine transmission. Moreover, the dopamine release during non-rewarding gambling runs parallel with the dopamine release during rewarding gambling, although the dopamine release was associated with hedonia (as captured by the terms 'positive mood' and 'high') only during winning gambling. The slot machine gambling session of this study involved over 400 repetitions of unrelated events, which had the elements of reward prediction, risk and high-reward (win) or low-reward (no win). The difference in dopamine release between the two tasks could be explained by the low-reward task represented as a powerful conditioned stimulus (spinning the wheels), and the high-reward task as quite similar conditioned stimulus accompanied with greater unconditioned stimulus (wins). This view is supported by the fact that the dopamine release during high-reward, but not during low-reward, correlated with hedonia. Moreover, also consistent with this idea, during non-rewarding gambling, the dopamine release occurred in the associative striatum, known to participate in cue-reactivity, also

extending to the ventral striatum, which is a key region in the brain reward signaling, during the rewarding gambling [see Figures 2 and 10, (Kegeles *et al.*, 2010)]. However, dopamine release capacity seems to also show a marked inter-individual variability, irrespective of the challenge (Scott *et al.*, 2007; Buckholtz *et al.*, 2010b), which could also explain the strong correlation between high-reward and low-reward dopamine release. There are some studies supporting this view as the ventral striatal fMRI response to reward cues correlates, not only with the magnitude of dopamine release in the corresponding task (Schott *et al.*, 2008), but also with pharmacologically or placebo-induced dopamine release (Scott *et al.*, 2007; Buckholtz *et al.*, 2010a). Interestingly, dopamine was released only on the right side of the striatum, which could relate to hemispheric differences in dopaminergic reward processing as has been suggested in the case of incentive motivation (Tomer *et al.*, 2008). It is also possible that the captured effect is only the peak of broader dopamine release, but this explanation seems unlikely, since there was not even near-significant effect on the left striatum. Moreover, a recent [^{11}C]raclopride PET study has suggested that dopaminergic reward processing during gambling may indeed be lateralized to the right ventral striatum (Martin-Soelch *et al.*, 2011).

6.1.1.3 Is there blunted dopamine reward signaling in pathological gambling?

The RDS hypothesis predicts that most addicted individuals would express the lowest dopaminergic and hedonic responses to rewarding gambling (Blum *et al.*, 2000). There is a substantial body of evidence from human neuroimaging studies supporting the blunted responses to drugs in substance addictions (Volkow *et al.*, 2011). However, the studies have been conducted with substances and individuals addicted to substances that are known to pharmacologically directly increase synaptic brain dopamine levels. Importantly, [^{11}C] raclopride PET studies in humans addicted to heroin did not reveal corresponding blunting of the dopaminergic neurotransmission, although the drugs were capable of inducing euphoria, thus questioning the role of dopamine in substance addictions, at least with substances whose effects are not mediated primarily by dopamine (Daglish *et al.*, 2008). There are also several other lines of evidence contradicting the RDS theory. For instance, personality traits commonly associated with PG, such as impulsivity and antisociality (Steel & Blaszczynski, 1998), are associated with increased mesolimbic dopamine responses to various stimuli (Forbes *et al.*, 2009; Buckholtz *et al.*, 2010a; Buckholtz *et al.*, 2010b). Moreover, pathological gamblers have been shown to have increased midbrain reactions to near-misses during slot machine gambling (Chase & Clark, 2010). As stated above, the results of this study confirm the previous reports that gambling with monetary rewards releases dopamine in the mesolimbic system. However, despite the induced hedonia and striatal dopamine release, there were no differences between pathological gamblers and healthy volunteers in subjective feelings or dopamine release, and no difference in baseline dopamine D2(D3) receptor binding either. These results are in concordance with the previous study investigating pathological gamblers and matched controls with [^{11}C]raclopride displacement method during Iowa Gambling Task

(IGT) performance (Linnet *et al.*, 2010; Linnet *et al.*, 2011b). Furthermore, the addiction severity and slot machine gambling preference in pathological gamblers were linked to a greater dopamine release and experienced a "high" during rewarding gambling. Concordant findings have been reported with Parkinson patients with PG (Steeves *et al.*, 2009). These findings could be interpreted to be in contradiction with RDS behind the neuropathology of PG.

However, fMRI studies have demonstrated contradictory results showing blunted ventral striatal hemodynamic response to gambling in pathological gamblers (Reuter *et al.*, 2005). The difference in findings by Reuter et al. and this study might relate to the temporal scale difference between fMRI (capable to separate individual events in gambling) and [^{11}C]raclopride PET displacement method (averaging the effects during the whole scanning time), or by the fact that, in this study, an ecologically valid gambling stimulus was used, to which part of the gamblers were specifically addicted to, instead of a task just mimicking gambling. It is intriguing to speculate that if we had investigated only gamblers who prefer slot machines, would we have also seen the enhanced dopaminergic responses to gambling as was seen in the study by Steeves and colleagues investigating PD patients with PG (Steeves *et al.*, 2009). One possible explanation behind the contradicting results could be that conditioned stimulus during gambling drives the overall dopaminergic response magnitude seen in PET imaging. However, this doesn't seem plausible since there were no differences between the groups in gambling without wins either, despite differing responses in "urge to gamble", but the dopamine release was linked to slot machine preference in gamblers. It is important to acknowledge that study I, like other previous studies, was done at a single time point, year(s) after the emergence of gambling problems in pathological gamblers. Therefore, the results reflect only the present state of dopamine signaling and causal relationships can only be speculated.

6.1.1.4 Dopamine D2(D3) receptor availability in pathological gambling

Chronic substance abuse (e.g. cocaine, amphetamine, alcohol, heroine, nicotine) has been shown to be associated with reduced striatal dopamine D2(D3) receptor (*DRD2*) binding (Volkow *et al.*, 1993; Hietala *et al.*, 1994; Wang *et al.*, 1997; Volkow *et al.*, 2001; Fehr *et al.*, 2008). It has been speculated that the reduced D2 receptor availability would result from a reduced number of receptors (Volkow *et al.*, 2009). It should be noted, that these studies have investigated individuals with addiction to substances that via direct pharmacological mechanisms affect the brain dopamine neurotransmission and therefore, it might be complicated to interpret these findings relate to addiction *per se*. If these changes in neurotransmission were the main neurobiological mechanism of addiction disorders in general, one would expect comparable findings in patients with behavioral addictions. Indeed, there is some evidence of reduced striatal *DRD2* binding in obesity (Haltia *et al.*, 2007; Volkow *et al.*, 2008), but the previous study by Linnet et al. did not find altered *DRD2* binding in pathological gamblers, which is in line with the

results of the present study (Linnet *et al.*, 2011a). However, obesity might not fulfill the criteria for behavioral addiction and thus might have different background neurobiology than PG (Holden, 2010). Although the results of both of these studies oppose the findings with substance addicted individuals, the number of subjects were relatively low (study I included 12 and the study by Linnet and colleagues 16 to 18 pathological gamblers), and thus the negative results are susceptible to type II errors. Therefore, larger studies are still needed to verify whether there truly is no alteration of the baseline *DRD2* availability in PG and in other forms of behavioral addictions.

6.1.1.5 Alternatives to the reward deficiency syndrome in pathological gambling

To date, it is still not clear, whether pathological gamblers have altered dopaminergic responses to gambling, but the current evidence does not support blunted dopamine release, which would be assumed if the RDS would be the principal mechanism behind PG. The competing theories of addiction – namely the impulsivity hypothesis and incentive sensitization theory – offer alternative explanations, including more like enhanced than reduced mesolimbic reactivity, behind PG (Bechara, 2005; Robinson & Berridge, 2008). Although there are results supporting the RDS hypothesis instead of these theories, there are also several lines of evidence supporting the alternative hypotheses (Hommer *et al.*, 2011). For example, the previously observed effect of impulsivity to the mesolimbic dopamine release capacity (Buckholtz *et al.*, 2010b) and enhanced striatal dopaminergic cue reactivity (reactions to conditioned stimuli) in addicted individuals, which seem to correlate with "wanting" of the drug or the particular behavioral stimulus (Volkow *et al.*, 2006; O'Sullivan *et al.*, 2011b), could be interpreted to favor the principles of the alternative hypotheses (Robinson & Berridge, 2008). One possible explanation of the current findings is that individuals, who develop PG, initially have higher dopaminergic responses to gambling [as could be speculated based on the association between personality traits associated with PG and mesolimbic dopamine release capacity (Buckholtz *et al.*, 2010a; Buckholtz *et al.*, 2010b)] and therefore have a predilection for gambling. Then slowly, the response attenuates as "tolerance" develops, similarly to repeated use of pharmacological substances, leading to reduced reward signaling (Reuter *et al.*, 2005) and gambling with increasing amounts of money. To directly test this hypothesis, neuroimaging with long-term follow-up beginning from pre-morbid time would be required. However, the neurobiological mechanisms of PG are likely to include, not only the mesolimbic system and the dopaminergic system, but also changes, for instance, in the frontal cortical areas participating to the reward processing and addiction neuropathology (Volkow *et al.*, 2010). Developing addiction, then, probably involves even more complex neurobiological mechanisms involving the brain memory and inhibitory networks among others as has been speculated in the context of substance addictions (Volkow *et al.*, 2010). Furthermore, it is noteworthy that there might be several "paths" to PG, and possibly different brain mechanisms as well, as might be considered on the basis of different subtypes of PG (Milosevic & Ledgerwood, 2010). The subtypes and gambling preferences may have a substantial effect on the

results of functional neuroimaging studies of PG, which should be considered when conducting research on this topic.

6.1.1.6 Methodological considerations

The voxel-wise SPM analysis revealed statistically significant dopamine release in the right associative striatum (in the dorsal caudate nucleus) during the non-hedonic gambling, extending to the right ventral striatum during hedonic gambling. However, the ROI analysis was negative with respect to dopamine release, which could be explained by the fact that dopamine release was seen only in part of the caudate nucleus and the peak of dopamine release was found on the border of the dorsal caudate nucleus and the ventral striatum, and thus not covered by any single anatomical ROI. Furthermore, limitations caused by the scanner resolution and 4.25 mm slice thickness together with different orientation of the slices in different individuals showing the ventral striatum can be considered suboptimal for delineating ROI to a small region, such as the ventral striatum, thus provoking excess variation to the data. In addition, the ROIs were drawn to transaxial slices, which cannot be considered ideal for delineating the ventral striatum (Mawlawi *et al.*, 2001). However, the SPM results remained significant even when using the most stringent statistical criteria (FWE-corrected two-sided F-test with threshold of $P < 0.05$ at voxel-level) indicating a highly significant effect despite the negative findings in the ROI data. Furthermore, the greater dopamine release in pathological gamblers with predominant slot machine gambling addiction highlights the importance of the use of carefully selected stimulus in behavioral addiction research. Moreover, the behavioral ratings (increasing euphoria during the high-reward task, but no change during the low-reward task) indicated adequate design and stimulus "strength" separating the hedonic gambling from non-hedonic. As mentioned earlier in this thesis (*2.3.1.5*), the [^{11}C]raclopride displacement paradigm can be used to indirectly measure endogenous dopamine release via competition of the receptor binding, but it should be acknowledged that there are also other factors affecting the [^{11}C]raclopride binding, which are discussed in the comprehensive review by Marc Laruelle (Laruelle, 2000). Decrease in [^{11}C] raclopride binding results from reduced receptor availability (B_{max}) and/or affinity. There is a vast number of studies that have provided evidence supporting the occupancy model for [^{11}C]raclopride, and issues, such as, the receptor internalization and changes in receptor affinity states probably not affect to the binding of the antagonist tracer [^{11}C] raclopride (Laruelle, 2000). Therefore, the reduction in [^{11}C]raclopride in study I is interpreted to reflect mainly endogenous dopamine release. It should also be noted that motor activation or head movement during the scans can also cause a reduction in [^{11}C] raclopride binding (Badgaiyan *et al.*, 2003). However, in this study, the subject motion did not differ between the conditions as measured with an external motion detector. In addition, the reduction in [^{11}C]raclopride BP_{ND} was seen on the side ipsilateral of the hand controlling the task (except in one subject). Therefore, the alternative explanations to the changes raclopride binding seem unlikely and the reduction of BP_{ND} can be considered to indicate endogeneous dopamine release. Moreover, the baseline [^{11}C]raclopride BP_{ND}

reported in this study should be interpreted with caution, since the subjects were not scanned in resting state, but while performing a control task. Therefore, the control task having effect on striatal dopamine transmission and subsequent changes to measured BP_{ND} cannot be excluded.

6.1.2 Dopamine neurotransmission in Parkinsonian ICDs

Parkinson's disease (PD) patients suffering from impulse control disorders (ICDs) show enhanced mesolimbic dopaminergic response, demonstrated by greater dopamine release in the ventral striatum, to gambling with monetary wins and to reward predicting cues compared to PD patients without ICDs (Steeves *et al.*, 2009; O'Sullivan *et al.*, 2011b). In addition, previous studies have shown PD patients with ICDs to have reduced dopamine transporter (DAT) and DRD2 availability in the ventral striatum in the resting state (Steeves *et al.*, 2009; Cilia *et al.*, 2010). Study III investigated resting-state dopamine function using [^{18}F]fluorodopa measuring the trapping rate and decarboxylation activity in the presynaptic axonal terminals. There was no evidence of altered striatal uptake in this study, but the results demonstrate markedly increased the uptake of [^{18}F]fluorodopa in the medial orbitofrontal cortex (mOFC). The negative results concerning the ventral striatum (not even a trend-level difference between the groups, see Table 7) in this study could be interpreted to suggest comparable dopamine production in presynaptic nerve terminals in PD with and without ICDs. When intact dopamine production is combined with the observation of reduced DAT binding indicating slower removal from the synaptic cleft (Cilia *et al.*, 2010), the findings of this study suggest that the reported lower DRD2 availability (Steeves *et al.*, 2009) results from increased amounts of dopamine in the synaptic cleft, and not reduced number of D2 receptors in PD patients suffering from ICDs, as speculated by the authors. In summary, the current evidence points towards increased mesolimbic dopamine function in PD ICDs. However, Parkinson ICD neuroimaging studies, including this study, commonly suffer from relatively small and heterogeneous samples, which may explain the partly contradictory results between studies (Steeves *et al.*, 2009; Cilia *et al.*, 2010; van Eimeren *et al.*, 2010; O'Sullivan *et al.*, 2011b). With the current rather limited knowledge, it is diffucult to evaluate, whether the behavioral addictions in the context of medicated PD patients have comparable neurobiological mechanism as these disorders in the general population, or whether they form a distinct entity. Therefore, the role striatal dopamine function in PD ICDs still needs further investigation.

Studies in rhesus monkeys have demonstrated that neurons in the mOFC activate in response to rewards and reward-predicting stimuli, and during the reward expectation (Tremblay & Schultz, 1999; 2000). The mOFC is also directly connected to the ventral striatum (Lehéricy *et al.*, 2004). Substance addicted individuals seem to have lower baseline metabolism in the prefrontal cortical areas and the orbitofrontal cortex has been shown to participate in reward processing, salience attribution and inhibitory control (Volkow *et al.*, 2011). Interestingly, the metabolism of the mOFC increases after the

administration of drugs or drug-predicting cues in addicted individuals, and is associated with substance craving (Heinz *et al.*, 2004; Volkow *et al.*, 2005). Thus, the stronger medial orbitofrontal cortical AADC function in PD patients with ICDs in study III suggests the area also has a role in Parkinsonian ICDs. The imbalance between better-preserved mOFC function relative to the striatal areas, contributing to the motor symptoms, might lead to an overstimulation of the mOFC by dopamine replacement therapy. Thus, the resulting sensitivity of the mOFC function might disrupt the normal reward processing, enhancing the incentive salience towards addicting stimuli in susceptible individuals. Indeed, supporting this view, PD patients with ICDs seem express enhanced reward-related responses in the orbitofrontal cortex by administration of dopaminergic medication [reviewed in (Kassubek *et al.*, 2011)]. Prospective and functional brain imaging studies are required for clarifying the role of mOFC in pathogenesis of ICDs in PD.

6.1.2.1 Methodological considerations.

Study III was the first study investigating the presynaptic dopamine function in Parkinsonian ICDs with [^{18}F]fluorodopa PET, which is a widely used method with a well-established role as a diagnostic tool in early PD (Brooks, 2010; Tatsch, 2010). However, the validity of the cortical [^{18}F]fluorodopa signal has raised some concerns (Cropley *et al.*, 2008). Therefore, to address these concerns, the analyses were also performed using images with partial volume effect (PVE) correction, which did not change the results indicating the validity of the signal. In addition, there are also earlier studies which demonstrated the usefulness of the [^{18}F]fluorodopa signal in several selected extrastriatal regions (Moore *et al.*, 2008; Klein *et al.*, 2010). It should be noted that the changes in the [^{18}F]fluorodopa uptake do not necessarily indicate increased dopamine turnover alone, but also other monoamines such as serotonin and noradrenaline, depending on the relative activity of these neurotransmitters in the brain region in question, as explained in the section *2.3.1.5*. Comorbidities are a common problem in PG as they are in other addiction disorders as well (Lorains *et al.*, 2011). In addition, PD, as a progressively disabling neurodegenerative disease, compromises the capability of the patient to manage through the 90 min neuroimaging sessions. These issues make the recruitment of the subjects more difficult, and therefore, we were forced to include some PD patients with other psychiatric conditions apart from behavioral addictions and not only "pure" PD patients with and without ICDs. However, the groups did not markedly differ in the presence of comorbidities and excluding the subjects with any comorbid psychiatric disorder did not change the interpretation of the results indicating that the noted difference in the mOFC monoamine function genuinely relates to the neurobiology ICDs and not to any confounding factors. There was no correlation between the mOFC function and ICD duration, which could signify the altered mOFC function to precede behavioral problems, or be a false negative caused by the relatively small and heterogeneous sample. The ICDs in this study included a variety of different problems (PG, hypersexuality and compulsive eating), which might not be totally alike in terms of behavioral or neurobiological issues (Voon *et al.*, 2011c). This idea is further

supported by the results of this study showing that, when separating patients with PG from other ICDs, PG patients still differed from the control group, whereas the patients with other ICDs did not. Therefore, it is possible that the findings of study III could relate specifically to PG and not ICDs in general.

6.2 Brain structure in pathological gambling

6.2.1 Brain white matter abnormality in pathological gambling

The diffusion tensor imaging (DTI) analysis (Study II) revealed extensive lower brain white matter integrity involving multiple tracts in pathological gamblers compared to healthy volunteers. The results demonstrate widespread white matter abnormality in an addiction disorder in the absence of toxic effects of substances of abuse, although the changes are comparable to white matter abnormalities in substance-addicted individuals. However, there were no differences in brain regional gray or white matter volumes between the groups. The discrepancy in the results of the two methods could reflect differences in sensitivity of the methods and/or differences in underlying biological aspects these methods are able to detect (microscopic axonal diffusion with DTI and brain tissue volume changes with VBM). It is also possible that the abnormalities in axonal diffusion precede volumetric changes, and thus, would have been seen in more severe cases or longer durations of PG. The more severe disordered gambling is associated with more comorbid psychiatric disorders (Crockford & el-Guebaly, 1998), and would have led to exclusion from this study, and subsequently to the underestimation of the volumetric changes. In addition, the relatively small sample size for a volumetric study may have led to false negative findings in brain regional volumetry.

In parallel with the negative VBM results of this study, a previous study investigating PD patients with (n=33) and without (n=24) ICDs did not find group differences in focal gray matter volumes (Biundo *et al.*, 2011). However, Biundo *et al.* did not investigate brain white matter integrity in their patients. It should also be noted that PD ICDs might constitute a distinct entity and have a different neurobiological background compared to the behavioral addictions in the general population. Also, alterations in the brain structure might be more difficult to detect in older individuals suffering from a neurological disorder, because of the variation in focal brain structures due to age- or disease-related confounding effects to the possible structural changes associated with the addiction disorder.

Based on the results of this study, several white matter tracts were affected in PG, including tracts with limbic connections (the cingulum, the anterior thalamic radiation, the uncinate/inferior longitudinal fascicle), the superior longitudinal fascicle, the inferior fronto-occipital fascicle, and the anterior limb of internal capsule; which have all been shown to be affected also by substance abuse at least in one study (Lim *et al.*, 2008; Liu *et al.*, 2008; Ashtari *et al.*, 2009; Jacobus *et al.*, 2009; Pfefferbaum *et al.*, 2009; Yeh

et al., 2009; Lane *et al.*, 2010; Romero *et al.*, 2010; Xu *et al.*, 2010). In addition, there are convincing number of studies demonstrating altered diffusion in corpus callosum in substance addictions (Moeller *et al.*, 2007a; Lim *et al.*, 2008; Yeh *et al.*, 2009; Lane *et al.*, 2010; Xu *et al.*, 2010) and in PG (Yip *et al.*, 2011). Yip et al. limited their investigations to only the subsections of the corpus callosum finding low white matter integrity in the genu, whereas the present study demonstrated extensive low white matter integrity also including the genu, the body and the splenium of corpus callosum. Together, these results suggest that the white matter disruption might be related to addiction and not to direct toxic effects of the pharmacological substances. In addition, the integrity of the uncinate/inferior longitudinal fascicle has been shown to modify the ventral striatal hemodynamical response of loss versus gain in a gambling task in healthy volunteers (Camara *et al.*, 2010), and further, altered hemodynamical reward processing has been demonstrated in PG (Reuter *et al.*, 2005). The results of study II combined with the results by earlier studies suggest a role for dysfunctional white matter with limbic connections in the neurobiology of PG.

It is not clear if the white matter changes predispose individuals for developing addiction disorders or whether the changes are a consequence of the disorder. This was a cross-sectional study in a single time-point, and thus, it is impossible to determine when the white matter abnormality has developed. Only part of the previous studies have found correlations (but mostly rather modest) with white matter integrity abnormality and addiction severity or duration (Chung *et al.*, 2007; Lim *et al.*, 2008; Liu *et al.*, 2008; Alicata *et al.*, 2009; Pfefferbaum *et al.*, 2009; Yeh *et al.*, 2009; Xu *et al.*, 2010) and there are several negative results (Moeller *et al.*, 2007a; Moeller *et al.*, 2007b; de Win *et al.*, 2008; Salo *et al.*, 2009; Lane *et al.*, 2010; Martín-Santos *et al.*, 2010). In study II, there was no correlation between gambling-related parameters and white matter integrity impairment, which could be interpreted to suggest premorbid white matter abnormality. However, the lack of correlations in this, or previous studies could also be false negatives due to small sample sizes, heterogeneity of the studied samples, and/or insensitivity of the methods.

6.2.1.1 Methodological considerations

Study II was the first to explore brain structure and axonal integrity across the whole brain in PG. The study was performed using a fairly recently developed method for DTI analysis (TBSS), which has been designed to avoid problems in spatial coregistration of white matter tracts, and hence, to minimize the possibility of false negative/positive findings caused by misalignments between the subjects (Smith *et al.*, 2006). In addition, an adequate number (32) of gradient encoding directions were used to ensure reliable estimates of the diffusion parameters. However, there are some limitations that ought to be pointed out. First, the number of subjects for brain regional structural analysis is somewhat low, which might contribute to the negative findings in VBM and lack of correlation between gambling-related behavioral measures and DTI parameters. Second,

there are some psychiatric disorders in the PG group that could bias the results, but could not be avoided since psychiatric comorbidity is very common in PG (Lorains *et al.*, 2011). However, current axis I psychiatric diagnoses were carefully excluded by a consultant psychiatrist, and the analyses were conducted also controlling for previous disorders, which did not change the results. Third, the DT sequence with gaps and varying repetition time (TR) values could be considered suboptimal for DTI analyses. However, the normalization results and the localization of deprojected ROIs, which in theory could be compromised by the gaps, were carefully inspected and found to be successful. In addition, the imaging parameters were the same for both groups and the analyses were performed also controlling for TR values.

6.3 Pathological gambling and other ICDs in Parkinson's disease

6.3.1 Prevalence

Pathological gambling. In study IV, the prevalence rates of PG and ICDs were investigated in a large (n = 575), non-selected sample of Finnish patients with PD. This was the first study in northern Europe that assessed impulsive-compulsive behaviors in PD. The prevalence of PG using SOGS was 7.0%, which is very high compared to the rate (1.0%) of the earlier survey in general population by Finnish Ministry of Health and Social Welfare (Aho & Turja, 2007). Although Aho and Turja conducted a telephone survey, the results are likely to be comparable as both studies used SOGS with the same cut-off. Therefore, in Finland, PG seems to be clearly (up to seven times) more common in PD patients than in the general population. These results are supported by previous studies conducted in Italy and Canada (Avanzi *et al.*, 2006; Crockford *et al.*, 2008), but opposed by a French study directly comparing the prevalence of gambling problems between medicated PD patients and general population (de Chazeron *et al.*, 2011). However, de Chazeron et al. had only 115 healthy subjects in their control group, which could lead to a false negative finding, as the prevalence of PG is quite low. The rates of gambling related problems are culturally affected, which could be caused by restrictions of, or general attitudes towards gambling (Ambermoon *et al.*, 2011). In Finland, there is a high concentration of electronic gaming machines, which are present for example even in every medium-sized supermarket, providing easy access to gambling activities, and thus, provides lot of opportunities to gamble as well as cues provoking the gambling behavior. The prevalence of PG in among Finnish PD patients seemed to be in similar level or even somewhat higher compared to previous studies using SOGS with PD patients in Italy (2.0-6.1%) and Canada (3.4%) (Avanzi *et al.*, 2006; Voon *et al.*, 2006; Isaias *et al.*, 2008). However, there are methological differences between the studies despite the use of the same questionnaire (SOGS), and thus, direct comparison of the prevalence rates is not possible. The largest study with 3090 PD patients from U.S. and Canada estimated the rate of problem gambling (including also at-risk gamblers) to be 5.0% (Weintraub *et al.*, 2010a), which is lower than in study IV (9.1%). However, it is known that SOGS

tends to overestimate the prevalence rates of disordered gambling compared to DSM-IV diagnoses in general population surveys, but the issue has not been investigated in PD patients (Petry, 2005). It should also be noted that the sample in this study may not be completely representative of the PD patients in the general population, even though we used weighted sampling, since the sample was obtained from the patient registry and 39.5% of the selected patients did not respond to the survey. Thus, some level of selection bias cannot be ruled out.

ICD screening. In the sample of study IV, 34.8% of the patients were screened positive for ICDs using QUIP. The rate of patients screening positive remains high even if all non-responders would have been completely void of ICDs (19.2% screened positive of the total 1000 patients included in the survey). The individual rates of positive screens for ICDs in QUIP were 22.8% for hypersexuality, 11.8% for compulsive eating, 10.8% for compulsive shopping, and 8.8% for problem gambling. However, these numbers should not be interpreted as actual prevalence rates of ICDs or indicative of relative prevalence between different ICDs, because QUIP was designed as a screening instrument, and thus has high negative predictive values and relatively low positive predictive values, which vary according to the ICD (Weintraub *et al.*, 2009). Despite the fact that ICDs (especially problem gambling) seem to be less common in Asian PD patients (Fan *et al.*, 2009; Lee *et al.*, 2010), similarly to the results of Study IV, a recent study in Malaysian PD patients found approximately every third patient having a positive screen with QUIP (Lim *et al.*, 2011).

6.3.2 Factors associated with ICDs

Medication. Several independent studies, including the largest study, have provided evidence of the role of dopaminergic medications in the development of ICDs (Weintraub *et al.*, 2010a; Ambermoon *et al.*, 2011). However, in study IV, the dopaminergic medication was not associated with increased risk for ICDs. There are several possible explanations for the lack of medication effect in this study. Firstly, study IV was conducted several years after the role of antiparkinsonian medication in ICDs had emerged in the scientific literature. In fact, several patients reported medication withdrawal because of ICDs. Secondly, the dopamine agonist doses in the sample of Study IV were relatively small compared, for example, to the study by Weintraub et al. (Weintraub *et al.*, 2010a). This is relevant especially if the effect of dopamine agonists on ICD behaviors would prove as dose-dependent (Ondo & Lai, 2008). Therefore, these results should not be interpreted as disfavoring the role of dopaminergic medication in Parkinsonian ICDs.

Depression. The severity of depressive symptoms was the single most important factor associated with all ICDs, individually or together, in this sample. With an opposite approach, ICDs were the most important predictor of presence of depression. Depression was also associated with high total LEDDs, probably reflecting more advanced disease, and not using dopamine agonists, but the effects were smaller compared to the effect of ICDs. The findings of recent case-control studies support the results of this study in

the respect that PD patients with ICDs suffer more depressive symptoms compared to PD patients without ICDs (O'Sullivan *et al.*, 2011a; Voon *et al.*, 2011c). Furthermore, behavioral addictions in the non-PD population are often comorbid with depression and have also been shown to have overlapping genetic variance (Potenza *et al.*, 2005). Thus, depression clearly runs parallel with behavioral addiction disorders. However, the direction of causality between ICDs and depression is not yet known: behavioral addiction might lead to secondary depression or depression could be a predisposing factor for developing ICDs. Further studies exploring the causality between depression and behavioral addictions are needed.

Other. In accordance with previous studies, young age (≤ 65 years) was a risk factor for ICDs in general, but also for hypersexuality alone, which has not been reported previously (Grosset *et al.*, 2006; Singh *et al.*, 2007; Ondo & Lai, 2008; Bostwick *et al.*, 2009; Lee *et al.*, 2010; Weintraub *et al.*, 2010a). The male sex increased the odds for compulsive gambling and hypersexuality comparable to previous studies (Isaias *et al.*, 2008; Fan *et al.*, 2009; Weintraub *et al.*, 2010a). Current smoking, which has been shown to be associated with ICDs (Bostwick *et al.*, 2009; Weintraub *et al.*, 2010a), was an independent predictor for compulsive shopping alone. Earlier studies have found a younger age at the PD onset, being unmarried, and family history of gambling problems to relate to ICDs, but the data of study IV did not support these issues as independent predictors of ICDs (Ambermoon *et al.*, 2011). However, a younger age of onset was associated with ICDs in general and all ICDs individually, but the association was not significant in multivariate analysis indicating that the association could be explained through other variables.

6.4 Summary

In summary, studies I and II investigated striatal brain dopaminergic and structural changes, respectively, in the same population of pathological gamblers. The results of the present project show that gambling releases striatal dopamine, irrespective of the gambling outcome (study I). However, study I further demonstrates that there were no differences between pathological gamblers and healthy volunteers, but the gambling related symptoms' severity correlated with the magnitude of the gambling induced dopamine release, thus questioning the presence of the hypodopaminergic state, and subsequently, the validity of the dopamine RDS hypothesis in PG. It is of interest to note that although no baseline group differences were seen using PET and a dopamine tracer, widespread group-differences between pathological gamblers and healthy subjects were seen using modern DTI methodology (study II). Future studies will determine whether the impairment in brain white matter integrity is a predisposing factor for developing conditions like PG, or a consequence of the addiction and long-term abuse of the brain reward network. Studies III and IV were performed with a population of PD patients. The results of the study III revealed that the presynaptic mOFC monoamine function is altered in PD patients with ICDs indicating a role for this brain region in

the pathophysiology of these disorders. The results of study IV demonstrate that PG, and other ICDs, are not only very common in PD, but also are strongly associated with depression. These observations highlight the importance of acknowledging these issues in the clinical management of PD patients.

In conclusion, mesolimbic dopamine is likely to play a role in the neurobiology of PG as evident from neuroimaging studies and observations with Parkinson patients. However, the involvement of other neurotransmitter systems and other brain circuits apart from the mesolimbic system also seems plausible based on frequent psychiatric co-morbidity and partial effects of pharmacological substances (opioid antagonists and selective serotonin uptake inhibitors) for targeting non-dopamine systems in the treatment of PG (Hodgins *et al.*, 2011).

7. CONCLUSIONS

The following main conclusions can be drawn on the basis of this study:

I Slot machine gambling releases dopamine in the human brain mesolimbic reward system irrespective of the gambling outcome, but does not differ between pathological gamblers and healthy individuals. Furthermore, gamblers with a preference for slot machine gambling or more severe gambling disorders released the most dopamine. Thus, the results question the validity of the reward deficiency hypothesis as a causative factor in pathological gambling.

II Pathological gambling is associated with extensive lower brain white matter integrity resembling the previous findings with substance-addicted individuals. Thus, this observation demonstrates brain white matter abnormality in the context of addiction disorders in the absence of chronic use of pharmacological substances directly affecting the brain.

III Parkinson's disease patients with impulse control disorders have a higher presynaptic monoaminergic function in the medial orbitofrontal cortex when measured with [^{18}F]fluorodopa PET. Better-preserved medial orbitofrontal cortex monoamine function influencing the reward-related processing might contribute to the medication induced behavioral disturbances in Parkinson's disease.

IV The prevalence of pathological gambling is approximately seven times higher in patients with Parkinson's disease compared to the general population. The high numbers of those who screened positive for impulse control disorders – together with the strong association of these disorders with depression – encourages clinicians to perform routine testing of impulse control disorders and co-morbid depression.

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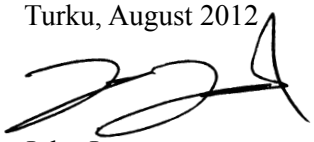

Juho Joutsa

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