Clinical and Functional Neuroimaging Studies on Impulse Control Disorders and Related Behaviours in Parkinson's Disease

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Abstract

In this thesis, I use clinical assessments and neuroimaging modalities to investigate the pathophysiology underlying impulse control disorders (ICDs) and related addictive behaviours in Parkinson's disease (PD).

Using PET with ^{11}C-raclopride, I found that PD patients with a range of ICDs showed an increase in dopamine release in their ventral striatum on exposure to reward-related visual cues compared to PD controls. Further, the amount of increased dopamine release in patients with single ICD was similar to those with comorbid ICDs, suggesting the sensitisation of ventral striatum of PD ICD patients, regardless of their disease load. I also found that PD ICD patients with punding, characterised by stereotypical behaviours with similarities to obsessive compulsive disorders, had lower baseline dopamine D2 receptor binding in the dorsal, but not ventral, striatum at rest compared to controls.

In the fMRI imaging study with a block design paradigm, PD patients with compulsive sexual behaviours (CSB) showed increase in sexual desire on exposure to sexual visual cues compared to controls with a corresponding change in blood oxygen level-dependent signal in brain regions corresponding to emotional, cognitive, autonomic, visual and motivational processes. When OFF medication, CSB patients showed decreases in activation during the presentation of sexual cues relative to rest, which was not seen when ON medication. This provides evidence that passive visual cues can act as motivational cues for vulnerable individuals.

In the final data chapter, I show that the Internet use habits of PD ICD patients had greater interference (increased time spent, obsessive thoughts) with life functioning compared to PD and healthy subjects, suggesting that PD ICD patients have an increased tendency towards excessive Internet use, which may coexist as an addictive behaviour.

These studies show that PD patients on dopaminergic medication have a propensity toward impulse control disorders and related behaviours via sensitisation of the dorsal and ventral striatum. There is also an increased tendency to excessive Internet use in PD ICD subjects. These findings contribute to our understanding of the mechanisms through which a subset of PD patients choose to pursue aberrant rewarding behaviours despite negative consequences, with direct implication for clinicians managing this patient group.

Declaration of Originality

The work presented herein was carried out in the Centre for Neuroscience of the Division of Experimental Medicine of the Department of Medicine at Imperial College London from April 2008.

This thesis is the result of my own work, and any quotation from or description of the work of others is acknowledged herein by reference to their sources. This thesis is not the same as any that I have submitted for any other degree, diploma or qualification at any other university. No part of this thesis has been or is being concurrently submitted for any such degree, diploma or other qualification.

The thesis is 43,000 words long, excluding references, and contains 17 tables, 20 figures, 3 equations and 1 box.

Kit Wu
08/09/2014

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Publications Contributing to This Thesis

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1. **Wu K**, Politis M, Piccini P. Parkinson disease and impulse control disorders: A review of clinical features, pathophysiology and management. *Postgrad Med J*. 2010: 85; 590–6.
2. O'Sullivan SS, **Wu K**, Politis M, Lawrence AD, Evans AH, Bose SK, Djamshidian A, Lees AJ, Piccini P. Cue-induced striatal dopamine release in Parkinson's disease-associated impulsive-compulsive behaviours. *Brain*. 2011: 134; 969–978.
3. **Wu K,** Politis M, Piccini P. Impulse control disorders in Parkinson's disease: A review. *Current Psychiatry Reviews*. 2012: 8; 3: 235–246.
4. Politis M, Loane C*, **Wu K***, O'Sullivan SS, Woodhead Z, Kiferle L, Lawrence AD, Lees AJ, Piccini P. Neural response to visual sexual cues in dopamine treatment linked hypersexuality in Parkinson's disease. *Brain* 2013: 136; 398–409. (*These authors contributed equally.)
5. **Wu K**, Politis M, O'Sullivan SS, Lawrence AD, Warsi S, Lees AJ, Piccini P. Problematic Internet Use in Parkinson's disease. Parkinsonism and Related Disorders. 2014, epub ahead of print.
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List of Abbreviations

2D	Two-dimensional
3D	Three-dimensional
11C	Carbon-11
18F	Fluorine-18
AADC	Aromatic Amino Acid Decarboxylase
ACC	Anterior Cingulate Cortex
AC	Anterior Commissure
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
B_{avail}	Density of receptors available to bind radioligand *in vivo*
B_{max}	Density of receptors *in vivo*
BBB	Blood Brain Barrier
BDI-II	Beck Depression Inventory – Version II
BE	Binge Eating
BP	Binding Potential
BP_{ND}	Non-displaceable Binding Potential
C_{max}	Peak Plasma Concentration
CB	Compulsive Buying
CNS	Central Nervous System
COMT	Catechol-O-Methyltransferase
CSB	Compulsive Sexual Behaviour
CT	Computed Tomography

D2 receptor	Dopamine Type 2 receptor
D3 receptor	Dopamine Type 3 receptor
DA	Dopamine Agonist
DAT	Dopamine Transporter
DBS	Deep Brain Stimulation
DDS	Dopamine Dysregulation Syndrome
DRT	Dopaminergic Replacement Therapy
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders IV
fMRI	Functional Magnetic Resonance Imaging
FOV	Field of View
H&Y	Hoehn and Yahr
ICD	Impulse Control Disorder(s)
in vitro	Within the glass
in vivo	Within the living
IV	Intravenous
K_D	Radioligand equilibrium dissociation constant
Ki	Influx Constant
L-Dopa	Levodopa
LED	Levodopa Equivalent Dose
MBq	MegaBecquerel
mg	Milligram
min(s)	Minute(s)
mm	Millimetre
MMSE	Mini-Mental State Examination
MNI	Montreal Neurological Institute

MRI	Magnetic Resonance Imaging
mSV	Millisievert
MTGA	Multiple Time Graphical Analysis
NIH	National Institute of Health
PD	Parkinson's disease
PG	Pathological Gambling
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
post hoc	After this
RAC	11C-raclopride
ROI	Region-of-Interest
sec(s)	Second (s)
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error (of Mean)
SI	International System of Units
SPECT	Single Photon Emission Computed Tomography
SPM	Statistical Parametric Mapping
SRTM	Simplified Reference Tissue Model
T	Tesla
$t_{1/2}$	Half-life
T_{max}	Time to peak plasma drug concentration
TAC	Time Activity Curve
UPDRS	Unified Parkinson's Disease Rating Scale
UK	United Kingdom

USA	United States of America
CDR	Volume of Distribution Ratio
VMAT2	Vesicular Monoamine Transporter
VTA	Ventral Tegmental Area

Chapter 1
Introduction

1.1 Parkinson's disease: A brief overview

Parkinson's disease (idiopathic Parkinson's disease; PD) is a neurodegenerative disorder, which causes a significant decline in quality of life for both the patients and their carers and contributes to substantial economic and health costs.

In the UK, the prevalence of PD ranges from 105 to 178 persons per 100,000, adjusted for age, with an estimated total of 150,000 people affected (Parkinson'sUK, 2009). The incidence of PD rapidly increases with increasing age, with the average onset at about 60 years. In Europe, the prevalence and incidence is similar to that of the UK (von Campenhausen et al., 2005). One systematic review of studies published from 1965 to 2008 on Asian populations yielded 21 studies, and found a prevalence of 51.3-176.9 per 100,000, and an incidence rate of 6.7 to 8.7 per 100,000 (Muangpaisan, Hori, & Brayne, 2009). Subsequently, the same research group have published a systematic review of the worldwide prevalence and incidence of Parkinson's disease, and noted a wide variation between different regions and study groups, concluding that the main reasons for such variations are due to differences in survival across countries and sampling techniques (Muangpaisan, Mathews, Hori, & Seidel, 2011)

1.1.1 Clinical features of PD

Clinically, Parkinson's disease is characterised by the cardinal triad of bradykinesia, rigidity and tremor. Bradykinesia (or akinesia in advanced disease) refers to slowness (or absence) of movement, which can sometimes be presented by patients as micrographia (small handwriting). Rigidity (stiffness, increased muscle tone) refers to an increase in resistance to passive movement around a joint. The resting tremor is usually seen in the upper arms with a frequency of 4-6Hz, which is maximal when the limb is at rest and is reduced with voluntary movement. The tremor is described as a pill-rolling motion of the hand and is typically unilateral at onset. An estimated 30% of patients have little or no perceptible tremor, and these cases are described as 'akinetic-rigid' type. The combination of tremor and rigidity felt by an examiner at the wrist of the upper limb is described as 'cogwheeling'. Other features noted in PD include hypomimia (decreased facial expression), decrease blink rate, and hypophonia (soft speech). Finally, postural instability, usually appearing in advanced PD, denotes failure of postural reflexes, which leads to impaired balance and falls (Jankovic, 2008).

A range of non-motor features have also been observed, which, in the last decade or so, have been increasingly recognised. Their clinical presentations are wide-ranging and affect almost every aspect of the body. For example, autonomic failure can be presented as orthostatic hypotension and abnormalities of sweating, sphincter control, and erectile dysfunctions (Jankovic, 2008). Cognitive and neurobehavioural abnormalities are commonly reported – the Sydney Multicenter Study of PD found

that 84% of patients with PD were found to have slow cognitive decline and that 48% met the criteria for dementia after 15 years of follow-up (Hely, Morris, Reid, & Trafficante, 2005). Depression affects about 40% of patients before, at, or after diagnosis, and has been shown to be the most important factor correlating with impaired quality of life. Other commonly reported non-motor features include late onset hypo-osmia, REM sleep behaviour disorder, apathy, anxiety, hallucinations, and pain. In some cases, these features have been reported to predate the motor features of PD described above. Reported features of PD are summarised in Box 1.

More recently, a group of neuropsychiatric behaviours has been increasingly reported in PD patients in association with dopaminergic medication use. These include features of obsessive-compulsive and impulsive disorders, such as craving (especially for sweets), binge eating, compulsive foraging, compulsive sexual behaviour, pathological gambling, compulsive shopping, dopamine dysregulation syndrome (an addiction-like behaviour to dopaminergic medication) and punding (Weintraub et al., 2006). These conditions are the focus of the projects in this PhD thesis.

Throughout research literature, 'Impulse Control Disorders' have been used interchangeably with other terms such as 'Impulse Control Behaviours', 'addictive behaviours', 'behavioural addictions', and 'Reward seeking behaviours' (to name just a few). Further, subtypes of ICDs have been coined 'behaviours' (e.g. compulsive sexual *behaviour* is a type of Impulse Control *Disorder),* and the same type of pathological behaviour have been given different names, e.g. 'compulsive sexual behaviour' and 'hypersexuality'. To minimise confusion, I have used the same terms as that of the Diagnostic and Statistical Manual of Psychiatric Disorders

(American_Psychiatric_Association, 2000), and used the same term to describe each type of pathological behaviour throughout this thesis.

Box 1. Motor and non-motor features of Parkinson's disease.

Motor disturbances	Resting tremor, bradykinesia, rigidity, postural and gait instability
Autonomic dysfunction	Orthostatic hypotension, constipation, urinary and sexual dysfunction, weight loss
Sensory disturbanes	Pain and paresthesia, anosmia, visual discrimination defects, ageusia
Mood disturbances	Depression, anxiety and panic attacks, apathy
Sleep disturbances	Sleep fragmentation, excess daytime somnolence, vivid dreaming, insomnia, REM behaviour disorder, restless leg syndrome and periodic limb movements, sleep apnoea
Neuropsychiatric disorders	Impulse control disorders, hallucinations, illusions, delusions
Cognitive disturbances	Cognitive impairment, dementia
Others	Seborrhoea, dry eyes, fatigue, diplopia, blurred vision, weight loss

1.1.2 Neuropathology features of PD

PD has traditionally been defined as a clinico-pathological entity, in which progressive levodopa-responsive parkinsonism without atypical features is associated, at autopsy, with neuronal loss and the presence of eosinophilic intracytoplasmic Lewy bodies in specific central and autonomic nervous structures. These include the pigmented brainstem monaminergic nuclei, the substantia nigra (dopaminergic) and locus coeruleus (noradrenergic). However, the pathology is thought to be much more widespread and reported to also involve serotonergic raphe nuclei, dopaminergic mesolimbic, mesocortical and tubero-infudibular pathways, the cholinergic nucleus basalis of Meynert, the cerebral cortex, the hypothalamus, the dorsal motor nucleus of vagus, the olfactory tract and sympathetic ganglia (Quinn et al., 2009). In 2003, Braak and colleagues reported a staging system to classify the neuropathology of Parkinson's disease, in which Lewy bodies first appear in the olfactory bulb, medulla oblongata and pontine tegmentum – individuals at this stage being asymptomatic. As the disease progresses, Lewy bodies appear in the substantia nigra and the areas of midbrain and forebrain to finally reach the neocortex (Braak et al., 2003). However, others have argued that although this system reflects the topographical sequence of Lewy body distribution, there has not been an attempt to correlate Lewy body and neuronal density with loss of neurons and synaptic connections, as well as the lack of clinical correlation with clinical severity of PD (Burke, Dauer, & Vonsattel, 2008).

1.1.3 Diagnosis of Parkinson's disease

Diagnosis of PD is based on clinical criteria as there is yet no definitive investigation. The presence of rest tremor, bradykinesia, rigidity and loss of postural reflexes are

generally considered the cardinal signs of PD. Furthermore, clinicians rely on the clinical presentation of these features to differentiate PD from other parkinsonism disorders (Parkinson's plus syndromes). Features that suggest a diagnosis other than idiopathic PD include: absence of rest tremor, early occurrence of gait abnormality, postural instability, dementia, hallucinations and the presence of dysautonomic, ophthalmoparesis, ataxia and other atypical features, in addition to poor or no response to levodopa.

Commonly used diagnostic criteria for idiopathic PD include the 'UK Parkinson's Disease Society Brain Bank's clinical criteria for diagnosis of probable Parkinson's disease' (Hughes, Daniel, Kilford, & Lees, 1992) – which is used for the studies in this thesis project (see Appendix 1) – and the 'National Institute of Neurological Disorders and Stroke (NINDS) diagnostic criteria for Parkinson's disease (Gelb, Oliver, & Gilman, 1999). Rapid developments in neuroimaging, such as the use of single photon emission computed tomography with the radioligand ^{123}I-FP-CIT to assess striatal presynaptic dopamine transporter density have also helped to confirm the diagnosis, whilst other neuroimaging techniques have been employed to advance research in PD (Piccini & Brooks, 2006).

1.2 Impulse control disorders and addictive behaviours in Parkinson's disease

1.2.1 Introduction

Impulse Control Disorders (ICDs) are described in the Diagnostic Statistical Manual, version 4 (DSM-IV) as a group of psychiatric disorders characterised by a failure to

resist an impulse, drive or temptation to perform an act that is harmful to the individual or to others (American_Psychiatric_Association, 2000, 2013). They comprise a wide range of neuro-behavioural disorders, including pathological gambling (PG), compulsive buying (CB), binge eating (BE), compulsive sexual behaviour (CSB), aggression, jealousy and phobias. As ICDs are a group of heterogenous conditions, some (for example, pathological Internet use or Internet addiction) have not yet been formally categorised. Conceptually, ICDs have been thought of as 'behavioural addictions' and lie within a spectrum of disorders with ICDs at one end and obsessive-compulsive disorders at the other (Brewer & Potenza, 2008).

In the last decade, ICDs have become a well-recognised clinical phenomenon with their neuro-psychiatric features often being associated with dopaminergic medication. This phenomenon has not only been widely reported in patients with PD, but also in other conditions, such as restless leg syndrome, for which dopaminergic medications is a treatment option (Evans, Lawrence, Potts, Appel, & Lees, 2005; A. D. Lawrence, Evans, & Lees, 2003; Voon et al., 2007; Weintraub et al., 2006) . The four most common ICDs reported in PD patients include binge eating (Molina et al., 2000), pathological gambling (the most recent edition of DSM-V has renamed this as Gambling Disorder) (Gschwandtner, Aston, Renaud, & Fuhr, 2001; Molina et al., 2000), compulsive buying (also known as compulsive shopping) (Dodd et al., 2005) and compulsive sexual behaviour (also known as Hypersexuality) (Wingo, Evatt, Scott, Freeman, & Stacy, 2009). A study of over 3,000 PD patients reported an increased risk of CSB and PG in males, and of BE and CB in females. PD patients with ICDs were generally younger than those without ICDs and there is a higher

prevalence of ICDs in younger PD patients, even when taking into account the higher use of dopamine agonists (DA) in these patients (Weintraub, Koester, et al., 2010).

1.2.2 Clinical phenomenology of Impulse Control Disorders in Parkinson's disease

The reported prevalence of ICDs in PD varies from 5.9% to 13.7% (Voon et al., 2006). Such a wide disparity between results from different studies is thought to be due to variation in clinical practice and assessment criteria. Recently, a large cross-sectional study on 3,090 PD patients from 46 movement disorder centres in North America (The DOMINION study) provided a more definitive insight into the clinical facets of four commonly occurring ICDs in PD. Subject recruitment was standardised, where inclusion criteria required subjects to be between the age of 30 and 75, to have the diagnosis of idiopathic PD and dopaminergic agent treatment for at least one year with no dosage changes for six months. This study identified an overall prevalence of ICDs in 13.6% of its PD cohort treated with dopaminergic medication (Weintraub, Koester, et al., 2010). It also found that ICDs were more common in patients treated with a dopamine agonist than in those not taking a dopamine agonist (17.1% vs. 6.9%). The frequency of ICDs was similar for pramipexole (a partial DA receptor agonist) and ropinirole (mainly D2 DA receptors but also has affinities for D_3 and D_4 DA receptors). In another multicentred study involving 1233 medicated PD patients, it was found that oral DA treatment (pramipexole and ropinirole) was associated with higher risk of ICDs compared with transdermal DA (rotigotine): 42% patients treated with oral DA developed ICD, versus 19% patients treated with rotigotine. In univariate analysis, a younger age, treatment with rasagiline, and especially treatment with an oral DA (pramipexole or ropinirole) were significantly associated with ICD. The researchers concluded that since pramipexole, ropinirole and rotigotine are non-

ergolinic DAs with very similar pharmacodynamic profiles, it is likely that other factors including route of administration (transdermal vs oral) explain the difference in risk of ICD development (Garcia-Ruiz et al., 2014). However, a review of case reports and cohort studies on the published literature has not found an increase in incidence of ICDs in patients receiving intrajejunal levodopa or subcutaneous apomorphine compared to oral dopaminergic medications (Todorova & Ray Chaudhuri, 2013).

Although recent research evidence indicates that dopaminergic medications are thought to influence the development of ICDs in PD, it is notable that a study of a drug-naïve cohort using the Minnesota Impulsive Disorders Interview (MIDI) – a screening tool for a range of ICDs – found that 17.5% of their 103 consecutive PD patients screened positive for at least one impulse control disorder, with CSB most commonly recorded at 10.7%. However, in a clinical interview based on DSM-IV diagnostic criteria, none of these patients satisfied clinical diagnostic criteria for an impulse control disorder. In addition, the PD cohort as a whole had similar frequency of impulse control disorders compared to a group of healthy non-PD subjects, where 20% reported at least one abnormal behaviour in the MIDI screening tool (Antonini et al., 2011). The results of this study suggest that subclinical behavioural abnormalities are common in PD even before initiation of dopamine replacement therapy (DRT), and that these patients may be more prone to developing a clinically apparent ICD after initiation of DRT.

1.2.3 Pathological gambling

Pathological gambling is characterised by: (i) a preoccupation with gambling, (ii) betting increasing amounts of money, (iii) persistence of these behaviours despite negative outcomes and (iv) unsuccessful attempts to stop this behaviour. Clinically, the diagnosis of pathological gambling as a behavioural disorder benefits from a well-defined criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM). Version IV of the DSM list a set of 10 criteria to aid diagnosis of pathological gambling: When an individual satisfies three out of 10 criteria, it is suggestive of problem gambling, whilst satisfying five out of the 10 criteria suggests a diagnosis of PG (American_Psychiatric_Association, 2000). In the most recent, Version V of the DSM, published in 2013, pathological gambling has been renamed Gambling Disorder (American_Psychiatric_Association, 2013). However, as the studies carried out in this thesis project were conducted between 2008 and 2011, the DSM-IV criteria for pathological gambling were used (see Appendix 2).

The lifetime prevalence of PG in patients with PD ranges from 3% to 8%, in contrast to a lower prevalence estimates of 0.42% to 2.5% for the general North American population (Lu, Bharmal, & Suchowersky, 2006; Petry, Stinson, & Grant, 2005; Voon et al., 2007; Weintraub et al., 2006). One study reports a prevalence of 8% for patients on DA agonists (Grosset et al., 2007). In addition, it seems that cultural differences and reporting criteria have an impact. For example, in a Chinese cohort of 400 patients, PG was reported to have a prevalence of 0.32% and problem gambling up to 1.7% (Fan, Ding, Ma, & Chan, 2009). It was speculated that this relatively lower rate might be due to the collection of responses through self-reported questionnaires and telephone interviews, as well the limited availability of DA agonists in China since 2007, leading to lower usage of DA agonists such as

pramipexole (46%) compared to Western countries (50–68%) (Pontone, Williams, Bassett, & Marsh, 2006; Weintraub et al., 2006). In a study conducted on 225 non-PD subjects with PG, 44 (19.6%) had co-occurring compulsive sexual behaviour (J. Grant & steinberg, 2005). Other psychiatric disorders such as depression and alcohol abuse have also been reported (J. Y. Lee et al., 2010; Shaffer, Hall, & Vander Bilt, 1999; Voon, Sohr, et al., 2011).

1.2.4 Compulsive sexual behaviour

Sexual content in the media has become more explicit and accessible to the general public, and such material is readily and freely available on the Internet. Compulsive sexual behaviour is a cause of significant morbidity for patients with Parkinson's disease receiving dopamine replacement therapies (Voon & Fox, 2007; Weintraub et al., 2006). However, little is known about its underlying neurobiology in PD, or how visual sexual stimuli, similar to the portrayals of sexuality in the mainstream mass media, affect the brain and behaviour in such vulnerable individuals.

Reports of CSB in Parkinson's subjects include excessive request for sex from a spouse or partner, increased pornographic interest, compulsive masturbation and sexual promiscuity (Voon et al., 2006). Individuals may resort to Internet-based pornographic sites as an outlet for their maladaptive behaviour (Wu et al., 2014). Although the prevalence of CSB in PD was estimated to be 3.5% in a large study of patients receiving dopamine agonist therapy, with men being more likely than women to have a diagnosis of CSB (Weintraub, Koester, et al., 2010), a newer but smaller study gives an estimated prevalence of 7%, with a link to levodopa therapy (Hassan et al., 2011).

It has been shown that continuous exposure to sexual material can stimulate excessive and socially unacceptable preoccupations with sex in some constitutionally vulnerable individuals (Rees & Noyes, 2007). Dopamine agonists have been highlighted as the culprit in causing CSB in several studies on PD patients (Weintraub, Koester, et al., 2010), although other studies have linked CSB with levodopa therapy (Ballivet, Marin, & Gisselmann, 1973; Hassan et al., 2011; Uitti et al., 1989). Studies in monkeys indicate that a synergistic interaction between dopamine drugs and sexual cues markedly enhances excessive sexual activity (Pomerantz, 1990). The importance of cues being highly associated with reward is consistent with incentive salience theory, where 'wanting' is produced by a synergistic interaction between the current state of the mesolimbic dopamine system and the presence of rewards or their cues (Berridge, 2012; Zhang, Berridge, Tindell, Smith, & Aldridge, 2009).

The criteria used for diagnosis of compulsive sexual behaviour for the studies in this thesis are detailed in Appendix 3.

1.2.5 Binge eating

Binge eating is defined as recurring episodes of eating significantly more food in a short period of time than most people would eat under similar circumstances, with episodes marked by feelings of lack of control. The foods consumed tend to be carbohydrates, fat-rich foods or sugar-rich foods such as chocolate and candies. Patients tend to eat much more quickly during binging episodes than when they are taking their normal meals and continue to do so when not really hungry. They may experience rapid weight gain. The person may feel guilty, embarrassed or disgusted

by their behaviour and may binge alone to hide their behaviour. BE differs from the common phenomenon of overeating. While overeating may be a challenge for many people, binge eating episodes are much less common, far more severe and are associated with marked stress and negatively impact on the sufferer's quality of life (American_Psychiatric_Association, 2013). BE was reported in 4.3% of PD patients in the DOMINION study (Weintraub, Koester, et al., 2010) .

The studies in this thesis project used the DSM-IV criteria for binge eating (see Appendix 4) where it was classifed as an 'eating disorder not otherwise specified'. In DSM-V, BE has been classified as a distinct entity althought the definitions have not changed.

1.2.6 Compulsive buying

CB is defined as an uncontrollable and excessive buying of goods that can lead to psychological distress and substantial debt. In patients with PD who manifest this behaviour, purchases tend to be very narrow and focused, such as buying one sort of item (e.g. gold fish tanks, laptop computers) repetitively and far in excess of their needs. It is not currently listed as a specific disorder in the current DSM-V, but researchers have proposed that CB lies within a spectrum of impulsive-compulsive disorders (Weintraub & Potenza, 2006) The DOMINION study estimates the prevalence to be 5.7% (Weintraub, Koester, et al., 2010), and in other studies it has been reported to range from 0.4% to 5.7%, with the overall prevalence being 7.2% for patients on dopamine agonists (Weintraub et al., 2006).

The diagnostic criteria used for CB are detailed in Appendix 5.

1.2.7 Other impulsive-compulsive behaviours in Parkinson's disease patients

1.2.7.1 Dopamine dysregulation syndrome

Dopamine dysregulation syndrome (DDS) is defined as the co-occurrence of ICDs and PD in the context of compulsive medication use (Evans et al., 2004; Giovannoni, O'Sullivan, Turner, Manson, & Lees, 2000). Patients develop an addictive pattern of dopaminergic medication use where they request larger doses of dopaminergic medication inappropriate for the severity of PD symptoms or self-escalate these medications against their physician's advice. They tend to hoard more medication than required. Patients may also describe a perceived ineffectiveness of medications and typically exhibit avoidance of the Parkinsonian OFF periods. As treatment continues, severe drug-induced dyskinesias occur along with socially harmful behaviours. Patients with DDS devote a great deal of time to maintaining a complex and frequent drug regime, and any attempt by the physician to reduce the overall antiparkinsonian medication dose is met with resistance. The pattern of inappropriate dopaminergic medication use in patients with ICDs often resembles that of addiction to psychostimulants. Patients may develop a range of psychiatric syndromes, such as mood disorders, hypomania and manic or cyclothymic affective syndromes in relation to DRT. When the level of DRT is reduced, they may develop a withdrawal state characterised by dysphoria, depression, irritability and anxiety. These symptoms must persist for at least six months to satisfy the criteria of DDS (Appendix 6). The prevalence of DDS in patients attending specialist PD centres is about 3–4% (Evans et al., 2004). Patients with ICDs in the context of compulsive medication use are observed to be taking greater levodopa equivalent daily doses (LEDDs) of

dopaminergic medications compared to their counterparts who do not have DDS (Evans et al., 2004).

1.2.7.2 Punding

Punding is a peculiar stereotyped behaviour characterised by an intense fascination with complex, excessive, non-goal-oriented, repetitive activities such as manipulation of technical equipment like televisions, computers etc.; handling, examining or sorting through common objects; grooming; tidying; aimless wandering/driving; artistic occupations such as drawing, painting, carpentry, singling, writing or playing an instrument; or engagement in extended monologues devoid of content (Evans et al., 2004). Punding seems to entail activities that the person is used to or likes to do. If interrupted, individuals with punding feel uneasy and irritated and want to go back to the same task. There appears to be a gender-related component, with men typically tinkering with, for example, electronics and women more often grooming. Punders often dedicate many hours at a time to their chosen activities, even in the face of negative consequences (for example polishing nails to the point of bleeding). As such, these behaviour become very troublesome and lead to profound social withdrawal. Most patients describe punding as a meaningless activity in which they get stuck or 'hung-up' in and cannot give up (A. J. Lawrence et al., 2007).

Punding was first described in cocaine and amphetamine addicts (Rylander, 1972), and later reported with the use of levodopa in Parkinson's disease (Friedman, 1994). The prevalence of punding in Parkinson's patients on dopaminergic medication has been estimated to vary from 1.4% (Miyasaki, Al Hassan, Lang, & Voon, 2007) to 14% (Evans et al., 2004), with such disparity due to different treatment options and

sampling methods. Little is known about its underlying pathophysiology, but earlier studies by Rylander highlighted similarities of punding behaviours to some of the features seen in obsessive-compulsive disorder (OCD) such as the repetitive and restricted nature of the behaviours (Rylander, 1972). However, punding also clearly differs from OCD by the lack of obsessive thoughts and punding being associated with feelings of calmness and intense curiosity, rather than negative affect.

1.2.7.3 Pathological Internet use

The popularity of the Internet has grown immensely over the last decade, so much so that it has become an important tool in our daily lives. Its benefits have given people with limited mobility, such as those with Parkinson's disease (PD), greater independence and better quality of life (Houlihan et al., 2003).

More recently, there has been mounting interest in the concept of Problematic Internet Use (PIU), also known as Internet addiction disorder, or pathological computer use. PIU is conceptually thought of as a behavioural addiction, similar to gambling disorder (K. Young, 1996, 2004) . Its commonly used working diagnostic criteria have been adapted from the Diagnostic and Statistical Manual – version IV (DSM-IV) criteria for PG (K. Young, 1996). The prevalence of PIU in the general population in North America and Europe has been estimated as 1.5% to 8.2%, with such a variance due to different populations and assessment tools used (Weinstein & Lejoyeux, 2010).

Similar to PG, people with PIU spend excessive amounts of time on the Internet at the expense of and to the detriment of other aspects of their lives. The behaviour tends to target particular activities, for example online gambling, multi-user gaming, cybersex

or viewing online pornography. Anyone with Internet access can become dependent upon it regardless of gender and age, but most research conducted on it in the general population targets young people and college students. In the ICD population, pathological gambling and compulsive sexual behaviour have been mostly linked to PIU, compared to other types of ICDs, such as compulsive buying or binge eating (Cash, Rae, Steel, & Winkler, 2012).

PIU in Parkinson's disease has not been systematically studied. To date in the literature, there are only a handful of reported cases of compulsive Internet use, and mainly in association with PG. Fan and colleagues reported one case of compulsive Internet browsing in a group of 400 Chinese PD patients (Fan et al., 2009); Larner reported another of using the Internet for gambling purposes (Larner, 2006) and a case series of eight patients with PG, four of whom were reported to use the Internet as a medium to propagate their aberrant behaviour (Wong, Cowen, Allen, & Newman, 2007). A further case documented a patient who compulsively spends time on his computer building word games as a form of punding behaviour (Fasano, Elia, Soleti, Guidubaldi, & Bentivoglio, 2006). These cases are all associated with dopaminergic medication use and suggest that compulsive Internet or computer use is a form of addictive behaviour in PD. Currently there is no study specifically comparing Internet use in PD with ICDs to a PD control group, nor to the general population.

1.2.8 Clinical factors associated with Impulse Control Disorders in PD

The occurrence of ICDs in only a subset of PD patients suggests that specific groups of individuals with PD are susceptible to developing ICDs during the course of disease, particularly during treatment with a dopamine agonist. As such, identifying

clinical factors associated with development of ICDs in PD patients may allow us to distinguish patients at increased risk, prompting specific screening and monitoring of at-risk individuals.

Evidence from case series and larger studies has pointed towards several common clinico-psychiatric traits associated with ICDs in PD patients. These include a younger age, being unmarried, having a current cigarette smoking habit and having a family history of gambling problems. The personality traits of novelty seeking and disinhibition have been associated with increased rate of ICDs in PD patients on DRT. Furthermore, dopamine agonist treatment in PD is associated with a 2–3.5 fold increase in the odds of having an ICD. This represents a drug class relationship across ICDs (Weintraub, Koester, et al., 2010). Early PD onset was correlated with a higher rate of ICDs, and the association persisted after adjusting for confounders. No significant association has been found between severity of PD and ICDs.

A case-control study using a subset of patients from the DOMINION trial also found that ICD patients with PD tend to have a higher L-Dopa intake compared to PD patients without ICDs, but no difference in dopamine agonist dose (Voon, Sohr, et al., 2011). PD ICD patients had reduced motivation, higher depression scores (15-item Geriatric Depression Scale), state and trait anxieties (State-trait anxiety inventory) and OCD behaviours (Obsessive-compulsive inventory). Also, PD ICD patients differed from PD patients without ICDs in having higher novelty seeking and impulsivity. In addition, PD ICD patients were more likely to be current or ex-smokers, but did not differ in their alcohol intake from PD patients without ICDs (Voon, Sohr, et al., 2011).

These individual factors will be explored in turn below.

1.2.8.1 Dopaminergic medication

Early case reports and case series noted the onset of ICD behaviours co-occurring with onset or dose increase of dopamine agonists and a remission of symptoms with reduction or cessation of dopaminergic medication (Gschwandtner et al., 2001; Molina et al., 2000). However, these earlier studies did not take into account the differences in prescribing practice, such as dosing and alternative types of DRT (levodopa vs. dopamine agonists). More recently, this observation has been confirmed by larger cross-sectional, multi-centre studies that systematically assessed the association of medication with ICDs in PD patients. It was shown that PG, CSB and CB were strongly associated with the use of dopamine agonists as a class, but not with any specific agonists (Voon et al., 2006; Voon, Sohr, et al., 2011; Weintraub, Koester, et al., 2010; Weintraub et al., 2006). In addition, PD patients with ICDs were shown to take larger amounts of total LEDDs (calculated for dopamine agonists and levodopa) compared to patients without ICDs. However, this trend was not seen when different types of ICDs were analysed individually, and an increased total LEDD dose has not been shown to predict the presence of an ICD (Weintraub et al., 2006).

ICDs have also been reported in other patient groups where dopamine agonists are employed as treatment options – for example, in Parkinsonian-plus disorders such as multi-systems atrophy (MSA) and progressive supranuclear palsy (PSP), where use of pramipexole or ropinirole have been associated with the onset of compulsive gambling, increased sexual behaviour, CB or BE (Klos, Bower, Josephs, Matsumoto,

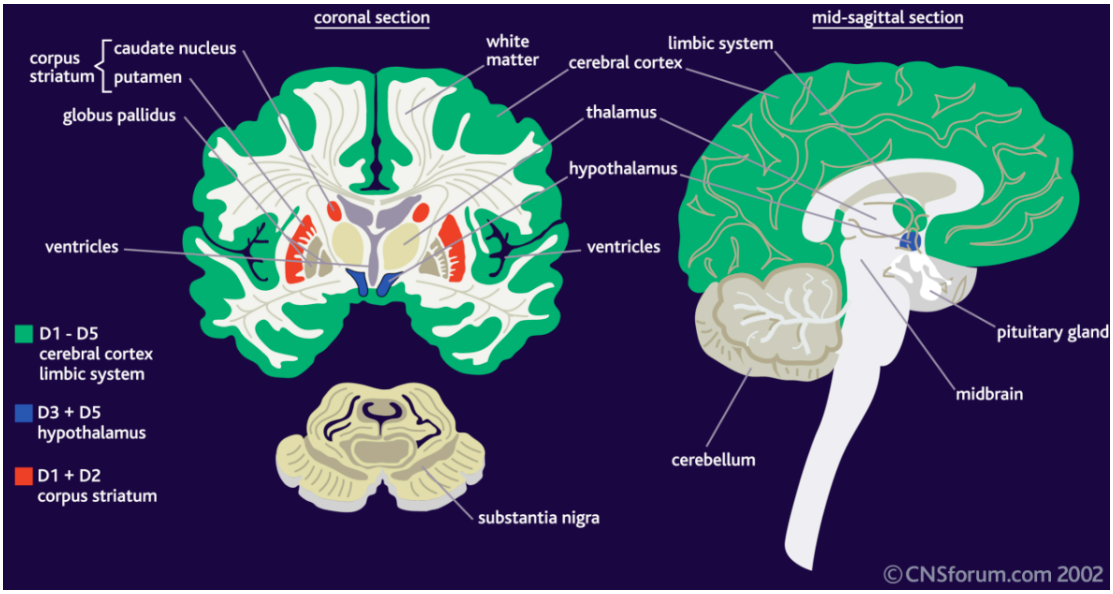
& Ahlskog, 2005; McKeon et al., 2007; O'Sullivan et al., 2010). Similar behaviours have been reported for fibromyalgia (Holman, 2009) and restless leg syndrome (Evans & Butzkueven, 2007; Quickfall & Suchowersky, 2007; Tippmann-Peikert, Park, Boeve, Shepard, & Silber, 2007). For example, a survey of 70 patients with idiopathic restless legs syndrome treated with one or more dopaminergic medications found that 7% of patients noted a change in gambling behaviour, and 6% reported an increased urge and time spent in gambling after the use of dopaminergic medication (Driver-Dunckley et al., 2007). These findings suggest that it is the medication, rather than the pathogenesis of PD, that causes the development of ICDs. Furthermore, these behaviours are not limited to an oral mode of administration as rotigotine, a dopamine agonist with transdermal preparation, was also shown to be connected with PG and CSB in three PD patients (Wingo et al., 2009).

The use of dopaminergic medications may contribute to the development of ICDs via several mechanisms. Firstly, they may interfere with the endogenous physiological pattern of dopamine release and cause excessive stimulation of dopamine receptors, resulting in aberrant activity in the implicated neuroanatomical regions. Secondly, exogenous dopaminergic stimulation may enhance the shift from goal-directed behaviours to stimulus response or habit formation, and chronic stimulation may result in neuronal sensitisation of ventral or dorsal striatal areas, leading to behavioural sensitisation.

In addition, specific dopamine receptor subtypes may be implicated. Dopamine D3 receptors (D3) are predominantly expressed in ventral areas of the striatum involved in reward, emotional and cognitive processes (Benninger & Banasikowski, 2008;

Gurevich & Joyce, 1999). The relative binding affinities of D3 to D1 or D2 receptors differ between dopamine agonists, and interaction between anti-Parkinsonian medication and dopamine receptors may lead to the development of ICDs in PD patients (Pontone et al., 2006). This finding was replicated in an animal study where related levodopa administration resulted in ectopic induction of Dopamine D3 Receptors in dorsal striatum, a process that could be responsible for development of behavioural sensitisation (Bordet et al., 1997). Moreover, pramipexole and ropinirole are two non-ergot dopamine agonists widely used in PD patients and which have tropism for D3 receptors found in the nucleus accumbens and the olfactory tubercle (Gerlach et al., 2003). Their affinities for D3 receptors are at least 100-fold greater than for D2 receptors; neither pramipexole nor ropinirole has any affinity for D1 receptors. A diagram with distribution of dopamine D1-D5 receptors in normal brain is illustrated in Figure 1. PG and compulsive behaviours are associated with dysfunction of these frontal subcortical regions, suggesting a link between specific dopamine receptors and development of aberrant behaviours (Singh, Kandimala, Dewey, & O'Suilleabhain, 2007). However, the observation of withdrawal symptoms when stopping levodopa treatment in non-parkinsonian patients, such as those who received the wrong diagnosis, further supports the view that it is the drug rather than the underlying dopaminergic state that leads to the symptoms of ICDs (Merims, Galili-Mosberg, & Melamed, 2000). Conversely, the fact that withdrawing from D3-preferring agonists results in a resolution or reduction of the aberrant behaviour suggests that they are related. A minority of affected PD patients, however, experience withdrawal symptoms when reducing the dose of dopamine agonists, with symptoms such as panic, dysphoria, depression, agitation and autonomic symptoms.

Figure 1. Distrubution of dopamine D1-D5 receptors in normal brain.



(Reproduced from www.cnsforum.com/educationalresources/imagebank/dopaminergic/hrl_rcpt_sys_da_dist)

There is less evidence for the possible association between monoamine oxidase inhibitors type B (MAO-B) and the development of ICD. Rasagiline is a second generation MAO-B inhibitor, inducing moderate symptomatic and possibly disease modifying benefits with apparently good tolerability and safety profile in PD patients. However there has been single case reports of PD patients developing ICDs when treated de novo with MAO-B inhibitors (Reyes, Kurako, & Galvez-Jimenez, 2014) (Vitale et al., 2013).

Interestingly, a recent study has also linked amantadine with the presence of ICDs. The mode of action of amantadine has yet to be elucidated, but it is a medication commonly used to treat dyskineisas in patients with PD, and is believed to have both glutamatergic and pro-dopaminergic properties. Amantadine was shown to be associated with the presence of one or more ICDs, and after controlling for confounding clinical variables, it was found to be specifically associated with PG,

CSB and CB (Weintraub, Koester, et al., 2010). However, in this large-scale study, amantadine patients were also found to be on higher levodopa dosages (since amantadine is typically used to treat dyskinesias associated with high levodopa dosages), and higher levodopa dosages were also associated with ICDs, suggesting a possible confounding issue. In contrast, in a smaller study (n=17), amantadine use was reported to be efficacious for treatment of PG in patients with PD (Thomas, Bonanni, Gambi, Di Iorio, & Onofrj, 2010). The authors hypothesised that the antiglutamatergic properties of amantadine may have caused such an effect, and this is supported by another positive study of N-acetylcsyteine (NAC), an amino acid that modulates glutamatergic activity in the treatment of PG in the general population (J. E. Grant, Kim, & Odlaug, 2007). It may also be that the properties of amantadine are twofold and not fully understood at present. The authors state that chronic dopaminergic stimulation has been linked with both ICDs and dyskinesias but hypothesise that amantadine appears to have dyskinetic effects, which may be related to its antiglutamatergic properties. Thus the pro-dopaminergic activity of amantadine may contribute to ICD development in at-risk PD patients, whilst its antiglutamatergic properties may have beneficial effects when introduced in patients already suffering from ICDs. A prospective randomised and blinded study would be of use in elucidating the precise link between amantadine and the onset of ICD.

1.2.8.2 Personality traits

Novelty-seeking personality traits are characterised by exploratory approach behaviours, excitement with novel situations, impulsivity and rapid decision-making, and a number of these have been associated with development of ICDs in patients with PD. However, PD patients generally have lower measures of novelty seeking

compared to healthy volunteers, and it has been suggested that this reflects underlying mesolimbic dopaminergic neurodegeneration in PD patients (Menza, 2000). Interestingly, the lower frequency of smoking and caffeine use in PD patients has been associated with lower measures of sensation-seeking traits (Allam, Campbell, Hofman, Del Castillo, & Fernandez-Crehuet Navajas, 2004; Evans et al., 2006). This is in contrast to patients who take dopaminergic medication, as illustrated in two separate case-control studies where PD patients with PG, CSB and/or compulsive medication use were found to have higher measures of novelty seeking compared to matched healthy controls and PD control patients (Evans et al., 2005; Voon et al., 2007). In addition, novelty-seeking personality traits were found to be significant predictors for the development of DDS (Evans et al., 2005) and for the development of PG in PD patients (Voon et al., 2007).

PD patients with CB have been found to prefer smaller immediate rewards to larger delayed ones (Voon et al., 2010). They make more impulsive choices relative to PD controls. However, the range of ICD behaviours are heterogenous – for example, patients with CB are more likely to choose small short-term gains compared to larger longer-term rewards (Eagle & Baunez, 2010; Voon et al., 2010). Furthermore, in PD populations with ICDs, it has been observed that their motivation is focused on the particular ICD(s), rather than general motivation being increased (Voon, Sohr, et al., 2011).

It has also been observed that CSB has a male predominance whereas CB and BE have a female predominance; in the case of PG, however, there was no difference in gender although in the non-PD general population PG has a male predominance

(Voon, Sohr, et al., 2011). These features suggest a potential role for biological or social influences in the development of particular ICDs. In addition, subjects with PG and CS have more overlapping features when compared to those with CSB and BE, specifically in terms of greater anxiety, obsessive-compulsive features and novelty seeking. Compulsive shoppers, in particular, received higher levodopa doses and had greater exploratory excitability and impulsive choice measures relative to matched controls (Voon, Sohr, et al., 2011). These variations may reflect differences in the type of reward, such as consumable (e.g. food or sex) and non-consumable (e.g. monetary, gambling or shopping) rewards, degree of social interaction, or the level of arousal associated with these behaviours.

1.2.8.3 Comorbid psychiatric history

PD patients with a history of psychiatric disorders are thought to be more susceptible to the development of ICDs, especially in the context of DRT. This is supported by a study of PD patients with ICDs where the rates of comorbid psychiatric diagnosis were found to be higher in the ICD group (Pontone et al., 2006) and also by the observation that higher rates of psychiatric comorbidity and depression are to be found in individuals with PG in non-PD populations (Dell'Osso, Allen, & Hollander, 2005). Anxiety disorders and PG frequently coexist, and treatments approved for anxiety disorders appear to target both anxiety and gambling measures (J. E. Grant, Potenza, et al., 2006). Compared to PD patients without an ICD, those with an ICD scored higher on measures of depression, anxiety, obsessive-compulsive features, novelty seeking, impulsivity and current and former smoking habits. The greater association between ICDs and psychiatric rather than neurological features raises the possibility that psychiatric comorbidity may contribute to the development of ICDs in

PD. In comparison to the non-PD general population, depression occurs as a frequent comorbidity with gambling, and genetic factors also contribute substantially (Potenza, Xian, Shah, Scherrer, & Eisen, 2005).

In addition, both PD patients and non-PD individuals with ICDs have higher Geriatric Depression Scale values, although the precise relationship to the occurrence of abnormal behaviour is still unclear. Furthermore, antidepressants are frequently used in the treatment of ICDs, and there is increasing evidence that impulsivity and depression may be associated with low serotonin (5-HT) function, resulting in an imbalance between dopamine and 5-HT neurotransmission. Although no clinical studies have shown that antidepressants are effective treatment options for this group of patients (Frankle et al., 2005), subtle symptoms of depressed mood, appetite changes, irritability and disinhibition are more likely to be present in the group of patients with ICDs (Pontone et al., 2006).

There is a further suggestion that a family history of psychiatric illness may also be associated with the development of ICDs in patients with PD. This is illustrated by a study of PG and medication association in PD which found that three out of 10 PD patients with ICDs had a psychiatric history in their first-degree relatives, compared to 286 PD patients without PG where none of them had this feature (Voon et al., 2006). However, data on clinical features has come from case series and case-control studies with small numbers of patients, and more objective methods are necessary to determine a precise relationship between the development of ICDs and a comorbid psychiatric history in PD patients.

1.2.8.4 Early onset PD

Patients who develop PD at a younger age are more likely to develop ICDs, particularly if they are treated with a dopamine agonist (Voon et al., 2006; Weintraub, Koester, et al., 2010). PD patients who developed PG were found to be nine years younger at the onset of their parkinsonian symptoms (49 years old on average) compared with the mean age of 58 years at onset observed in a group of 286 patients without PG (Evans et al., 2005).

1.2.8.5 History of alcoholism or substance use

Compulsive medication use in PD and PG has been associated with a personal or immediate family history of alcohol use, which was found to be an independent predictive factor for the development of PG with dopamine agonists (Dodd et al., 2005; Stamey & Jankovic, 2008). However, observational studies on adult twins (in the non-PD population) suggested that there may be some common genetic ground between PG and alcohol dependence, as it was observed that up to 42% of gamblers also manifest symptoms of alcohol dependence (Lobo & Kennedy, 2006; Slutske et al., 2001), but the precise relationship between alcohol use and the development of PG has not been fully elucidated.

1.2.8.6 Deep brain stimulation (DBS)

Whilst electrical stimulation to the subthalamic nucleus has been shown to markedly improve the motor symptoms of PD, its relationship to the development of ICDs in PD patients is unclear. ICDs have been reported to occur following DBS (Lim, Evans, & Miyasaki, 2008; Volkmann, Daniels, & Witt, 2010) although it has been argued that this may be due to a reduction of dopaminergic medication use associated with successful surgery (Ardouin et al., 2006; Bandini, Primavera, Pizzorno, & Cocito,

2007; Witjas et al., 2005). Another study found that following DBS of the subthalamic nucleus there was no association between the use of dopamine agonists and impulsivity in DBS patients, though ICDs were observed in three of the 16 patients (Halbig et al., 2009).

It has been suggested that the use of electrical stimulation may block the direct pathway of the basal ganglia and in turn produce another type of impulsivity (Frank, Samanta, Moustafa, & Sherman, 2007). In a cohort of 96 PD patients, it was found that more PD patients with BE had a history of DBS (44% vs. 14%) and that a history of DBS was the only independent predictor of overeating (Zahodne et al., 2011).

1.2.8.7 Dyskinesias

The recent observation that dyskinesias are associated with multiple ICDs, but not single ICDs, suggests potential overlapping mechanisms across a range of excessive, repetitive motoric behaviours, perhaps linked to dopaminergic modulation. Relative to controls, PD patients with multiple ICDs had higher dyskinesia measures (Voon et al., 2009; Weintraub, Sohr, et al., 2010). Overall, ICD patients had greater functional impairment in routine daily activities compared with PD controls, despite exhibiting a similar severity in motor signs. This may be due to an increased severity of depression or other psychiatric symptoms adversely impacting on functional abilities. Given the association of ICDs with higher levodopa use, these effects may be mediated by levodopa rather than dopamine agonists *per se*. Further supporting evidence for this comes from local electric field potentials from deep brain stimulation of PD patients who either have ICDs or dyskinesias. It was found that both these groups have greater subthalamic nucleus activity in the theta-alpha band, with different corticosubthalamic

coherence suggestive of associative-limbic and motor corticostriatal activity, compared to post-DBS patients with neither dyskinesias nor ICDs (Rodriguez-Oroz et al., 2011). This suggests a potential similar underlying pathophysiology between behavioural and motor symptoms that may implicate specific dopamine receptor subtypes, or serotonergic, glutamatergic or sensitisation mechanisms, although further studies are warranted.

1.2.8.8 Genetic influences

Studies in genetic influences on the development of ICDs in patients with PD are limited. However, in the non-PD population, observational studies have supported genetic influences on the development of ICD, particularly for PG. For example, the Vietnam Era Twin (Registry) reports that genetic factors account for 34–54% of predisposition to PG (Eisen et al., 1998). This degree of heritability is similar to those of other psychiatric disorders, such as drug addiction (Tsuang et al., 1996).

One of the few studies on PD patients focusing on genetic traits was conducted by Lee and colleagues (2009), who found an association of ICDs with patients carrying the AA genotype of a dopamine receptor D3 variant (DRD3 p.S9G) and the CC genotype of the GRIN2B (c.366C>G) in 404 PD patients. Of this cohort, 14.4% of subjects had impulse control-related behaviours, and the study suggested that carrying either of these genotypes was an independent risk factor for the development of impulse control and related behaviours.

As dopamine plays a key role in reward mechanisms, it follows that genetic polymorphisms which affect dopamine neurotransmission may influence an

individual's response in anticipation of reward. Genetic polymorphisms to key enzymes in the degradation of dopamine will cause a flux in the intrasynaptic availability of dopamine. For example, healthy subjects who possess the dopamine D2 receptor A1 allelic gene have reduced dopamine function and were less effective at gaining money in an anticipation paradigm compared to their A2 counterparts (Jonsson et al., 1999; Kirsch et al., 2006). Interestingly, the presence of the D2 receptor A1 allele was twice as high in PG subjects compared to controls (Comings et al., 1996). Evidence also supports its predilection in alcohol dependence (Ritchie & Noble, 2003), compulsive eating and smoking (Blum et al., 1995; Haile, Kosten, & Kosten, 2007).

Other genetic polymorphisms include the exon 3 variable number of tandem repeats (VNTR) polymorphism for the dopamine D4 receptor, where the 7 repeat polymorphism results in a reduced or suboptimal response to dopamine (Swanson et al., 2000). Adults with the L allelic variant have increased cravings for food, cigarettes, alcohol and heroin in response to cues (Hutchison, LaChance, Niaura, Bryan, & Smolen, 2002; Hutchison, McGeary, Smolen, Bryan, & Swift, 2002; Shao et al., 2006; Sobik, Hutchison, & Craighead, 2005). Similarly, the dopamine transporter is responsible for removing dopamine from the extracellular space, so variations to its function as a result of allelic differences will have an influence on the available dopamine level in the synapse (Bannon, Michelhaugh, Wang, & Sacchetti, 2001). A functional VNTR polymorphism in the 3' untranslated region of the DAT gene has been found, where the 10/10 repeat geneotype has excessive amounts of the transporter and therefore low extracellular dopamine levels.

Catechol-O-methyltransferase (COMT) is an enzyme abundant in the frontal cortices responsible for the breakdown of dopamine due to the lack of dopamine transporter (DAT) in this region. The functional polymorphism val158met leads to reduced function of the met/met alleles, with reduced breakdown of dopamine, and therefore higher levels in the frontal regions is thought to influence reward responsivity and decision-making (Marco-Pallares et al., 2009; Roussos, Giakoumaki, Pavlakis, & Bitsios, 2008; van den Bos, Homberg, Gijsbers, den Heijer, & Cuppen, 2009). Other genetic variants involving MAO-A (Ibanez, Perez de Castro, Fernandez-Piqueras, Blanco, & Saiz-Ruiz, 2000), serotonin transporter and dopamine receptors D_1, D_2, and D_3 (Comings et al., 1996; Perez de Castro, Ibanez, Saiz-Ruiz, & Fernandez-Piqueras, 1999; Swanson et al., 2000) have also been studied in the healthy population, but few studies have focused on PD subgroups of patients.

1.3 The role of functional neuroimaging in understanding the neurobiology of ICDs

1.3.1 Studies investigating impulsivity personality traits

It has been postulated that behavioural addictions, such as gambling, are caused by dysregulation of the dopaminergic pathways, much like that for drug addiction. These changes, as manifested by neurochemical fluxes, may exist in addicted individuals even before they begin taking drugs (i.e. individual susceptibility). Using a reversible D2/3 receptor binding ligand 11C-raclopride, Volkow and colleagues found that differences in dopamine D2 and D3 receptors binding in the striatum of healthy invididuals without previous drug exposure predicted the degree of 'liking' of a single dose of methylphenidate (Volkow, Fowler, Wang, Ding, & Gatley, 2002). Those with low binding indicating higher engdogenous DA levels or low D2/3 receptor

availability were more likely to report the drug as pleasurable than those with high binding. In addicted individuals, low binding of 11C-raclopride in the striatum correlated with reduced glucose metabolism in the orbitofrontal and anterior cingulate cortex, areas associated with reward processing an inhibitory control (Volkow et al., 2001).

In healthy, non-PD, individuals without addiction, a PET study with 18F-fallypride (a a radioligand that binds to extrastriatal D2/D3 receptors) has found that amphetamine-induced DA release was greater in those with greater impulsivity traits (Buckholtz et al., 2010). The prefrontal cortex has also been implicated in contributing to the propensity for individuals' impulsive behaviours. i.e. poor inhibitory control mediated by frontal under-activity may represent a risk factor for addiction. In the motor domain, impulsivity is measured using response inhibition paradigms in which a subject is required to inhibit a well-practised or automatic action (e.g. stop-signal and go/no-go tasks). Chemical addictions have been associated with poor performance on these tasks, and mixed results have been found in behavioural addictions (N. S. Lawrence, Jollant, O'Daly, Zelaya, & Phillips, 2009). Using a Stroop task in which an automatic spoken response must be limited, Potenza and colleagues found hypoactivation of the left ventromedial prefrontal cortex for those trials requiring inhibition in pathological gamblers compared with controls, but similar performance was observed in both groups (Potenza et al., 2003). These studies suggest that impulsivity in chemical addictions reflects hypoactivation of frontal brain areas sub-serving response inhibition in the healthy brain.

1.3.2 Studies investigated the role of dopamine agonist in altering learning from reward and punishment

In the non-PD population, it has been shown that DA agonists trigger behavioural changes and that these changes are associated with DA agonist-dependent changes in the frontstriatal activity measured with fMRI (Cools, Lewis, Clark, Barker, & Robbins, 2007). This corroborates with a study showing that those PD individuals with high trait impulsivity that are on dopaminergic medications are more susceptible to development of ICDs (Voon et al 2011), suggesting that dopaminergic medications are implicated in the development of ICDs in PD. Given the involvement of ventral striatum in drug and behavioural addictions, it might be predicted that excessive limbic dopaminergic stimulation via dopamine agonists might increase addictive behaviours. Thus PD patients with preserved ventral striatal DA projects at the time of initial treatment maybe particularly susceptible of developing ICDs. Tonic occupation of postsynaptic receptors may also impair ability to learn from reward and/or punishment. Van Eimeren and colleagues have shown that, in PD patients without ICDs, both dopamine agonist and L-Dopa diminished ventral striatal reward processing. Further, dopamine agonist, but not L-dopa, increased activity in the orbitofrontal cortex during the receipt of the reward (van Eimeren et al., 2009). In a different study on patients with restless legs treated with dopamine agonists, Abler and colleagues showed that fMRI activation of the ventral striatum in response to reward expectation only occurred when subjects were on dopamine agonists (Abler, Hahlbrock, Unrath, Gron, & Kassubek, 2009). Upon receipt or omission of rewards, agonists were associated with abnormal processing of errors. On the other hand, Voon et al observed greater learning from positive feedback in a group of PD patients with ICDs compared with control PD patients when on DA agonists, associated with greater ventral striatal activity (Voon, Gao, et

al., 2011). Thus, in patients without ICDs, DA agonists led to markedly changed neural processing of negative consequences, and that positive reinforcement may be augmented by agonists due to tonic occupation of postsynaptic receptors during positive feedback that may signal that a response gave greater than expected reward, and therefore, should be repeated.

Further, the idea that intact impulse control may protect patients from development of ICDs during agonist exposure is supported by a recent $^{15}H_2O$ PET study where PD patients were scanned before and after administration of DA agonists to measure changes in regional cerebral blood flow during a card selection game with feedback (van Eimeren et al., 2010). The authors observed that DA agonists increased activity in brain areas associated with impulse control in patients without pathological gambling. The PD gamblers however showed a significant DA agonist induced reduction of activity. These findings indicate that DA agonists may interact with underlying differences in dopaminergic modulation of prefrontal cortex to induce ICDs in susceptible individuals, potentially linked with poor inhibitory control and therefore increased impulsivity.

1.3.3 Studies investigating different mechanism through which dopaminergic medication promotes pathological impulsive behaviour

1.3.3.1 Increased response to rewards due to sensitization of ventral striatum

An early PET study with 11C-raclopride by colleagues from my research group found that PD patients with DDS showed an enhanced dopamine release in the ventral striatum in response to levodopa. Further, such change correlated with increased motivation to take the drug (Evans et al., 2006). These findings corroborated with

those of drug addiction in the general population where individuals with drug addictions show enhanced ventral striatal dopamine release. On this front, Volkow and colleagues have shown that chronic drug abuse in substance-addicted individuals causes ventral striatal dopaminergic abnormalities (Volkow et al., 2001; Volkow et al., 1993). The results support the incentive sensitisation theory, which posits that compulsive drug use arises from the excessive attribution of incentive salience or 'wanting' for drug rewards and their cues due to progressive neuroadaptation in striatal neurocircuitry (Robinson & Berridge, 1993). Applied to behavioural addictions, it is therefore feasible that compulsive reward-seeking behaviours arise from excessive attribution of incentive salience for rewards and their associated cues (Berridge, 2012). In a study of PD individuals with PG, using ^{11}C-raclopride with PET, following dopamine agonists, patients with pathological gambling demonstrated greater decreases in binding potential in the ventral striatum during gambling than control patients, likely reflecting greater dopaminergic release (Steeves et al., 2009).

Results from studies on compulsive sexual behaviour in animal models and non-PD individuals have also supported that excessive dopaminergic stimulation increases addictive behaviours. In animals, sexual-related cues enhance sexual motivation and pursuit in the dopaminergic neural circuits involving the VS, hypothalamus, amygdala and the medial prefrontal cortex (PFC) (Pfaus et al., 2010; Stolzenberg & Numan, 2011). Further, sensitisation by dopaminergic drugs has been shown to enhance the pursuit of natural rewards (including sexual incentives) as a result of excessive incentive salience attribution to reward-related cues (Afonso, Mueller, Stewart, & Pfaus, 2009; Fiorino & Phillips, 1999b; Nocjar & Panksepp, 2002). Moreover, dopaminergic drugs and sexual behaviours have been shown to co-activate a

population of neurons in the VS, amygdala, hypothalamus and anterior cingulate cortex (ACC), identifying potential sites where drugs can influence sexual behaviour (Frohmader, Wiskerke, Wise, Lehman, & Coolen, 2010; Holder et al., 2010). In line with the incentive sensitisation theory, CSB in patients with PD could be associated with increased processing in brain regions linked to sexual motivation and cue reactivity and that these activations could be potentiated by dopaminergic medication.

In the general population, it has been shown that visual cues related to different rewards elicit increased dopamine release in the striatum (Koepp et al., 1998; Sescousse, Redoute, & Dreher, 2010) - this has not been investigated in patients with Parkinson's disease. Reward-related visual cues are particularly pertinent in today's society where we are bombarded with visual imageries from advertising campaigns centred on food (supermarket adverts), gambling activities (lotteries, online gambling sites), store promotions and portrayals of sexuality in everyday media. The effects of these on vulnerable individuals, such as patients with ICDs, are not known.

1.3.3.2. Reduced ventral striatal D2 receptor availability related to reward deficiency syndrome

The reward deficiency syndrome, first coined by Blum et al refers to an insufficiency of 'usual feelings of satisfaction', as a result of dysfunction in the brain reward cascade caused by reduced striatal D2 receptor availability (Blum et al., 1996). It has been found that individuals with alcohol dependence and other drug addictions have reduced basal striatal dopamine levels.

In this regard, Steeves et al observed reduced binding in 11C-raclopride during a control task involving no reward in PD individuals, and the authors concluded that

this indicated lower D2/3 receptor availability. Further, they showed an increased release of DA in the ventral striatum during a gambling task involving real monetary reward, indicating abnormalities in DA binding in patients with pathological gambling similar to those reported for chemical and behavioural addictions in the general population, implying that PD patients who develop an ICD may represent a susceptible group of individuals whose ICDs has been unmasked via the application of agonists.

1.3.3.3. Downregulation of midbrain dopamine autoreceptor function

A lack of homeostatic control over striatal dopamine release causes increased sensitivity to rewards and propensity for impulsive action. This is demonstrated in a PET study by Ray and colleagues, who found that, changes in 11C FLB-457 (a PET radiotracer with high affinity for extrastriatal DA D2/3 receptors) binding potential during gambling was reduced in PD patients with pathological gambling in the midbrain (Ray et al., 2012). The degree of occupation of the DA D2/3 receptors during gambling was also correlated with impulsivity.

In summary, neuroimaging studies have provided insight into the link between ICDs and chemical addictions, showing similar changes in fronto-striatal brain activity and neurotransmitter release. In PD, dopamine agonists may induce changes in brain function that impair patients' ability to learn from both reward and punishment. Recent studies have also suggested that increased susceptibility for ICD and addiction associated with impulsive personality trait may be dependent on normal variations in brain function that, in PD, exposure to dopamine agonist may lead to pathological behaviours. However, it should be noted that the latter studies have employed

hypothetical experimental design paradigms that simulate, but do not represent, real-life circumstances.

1.4 Comorbidity of impulse control disorders in Parkinson's disease patients

Impulse control disorders (ICDs) on the whole occur in about 14% of patients with Parkinson's disease treated with dopaminergic medication (Weintraub, Koester, et al., 2010), but over a quarter (28%) of these patients have been shown to have co-morbid ICDs (i.e. more than one ICD) (Weintraub, Koester, et al., 2010).

Evidence from epidemiology studies in the general population have also shown that 23% of pathological gamblers report a comorbid impulse control disorder, most commonly compulsive sexual behaviour and compulsive buying (J. E. Grant & Kim, 2003), and 61% of pathological gamblers satisfy diagnostic criteria for personality disorders and have increased frequency of other ICDs (Kruedelbach et al., 2006).

A clinical case-control study noted that PD patients with comorbid ICDs had greater functional impairment in activities of daily living compared to those without, despite having similar severity of motor signs (Voon, Sohr, et al., 2011). These findings reverberate evidence from the general (non-PD) population, where comorbidity of diseases has been linked to worse clinical severity, more functional impairment, poorer prognosis and more resistance to treatment compared with uncomplicated symptom presentations (i.e. those with a single diagnosis), (Krueger & Bezdjian, 2009; Krueger, Caspi, Moffitt, Silva, & McGee, 1996; Verhulst & van der Ende, 1993).

Furthermore, PD patients with comorbid ICDs have greater functional impairment in activities of daily living compared to those with a single ICD, despite having similar severity of motor signs (Voon, Sohr, et al., 2011). The underlying neurobiology in PD-ICDs is thought to involve drug-induced neuroplasticity in the dopaminergic mesolimbic reward circuitry, such that reward-related stimuli acquire excessive salience, triggering impulsive pursuit ('wanting') (Robinson & Berridge, 1993). Existing neuroimaging studies have supported this by showing increased ventral striatal dopamine release to reward-related cues in PD patients with pathological gambling compared to PD controls (Joutsa, Johansson, et al., 2012). In animal models, incentive salience 'wanting' can be very narrowly focused on a single preferred type of reward cue, or more broadly focused such that multiple incentives become more 'wanted' together (Berridge, 2012). For example, amphetamine sensitisation in rats can amplify the incentive value of drug-associated stimuli (but not food or sex) for some individuals, but it can also enhance 'wanting' of both food and sex rewards (but not drugs) in others (Nocjar & Panksepp, 2002). Such broad motivational 'wanting' may underlie the development of comorbid ICDs in PD patients, where an individual develops several different ICDs simultaneously. The extent to which the breadth of incentive salience attribution is linked to alterations in striatal dopaminergic neurotransmission is unknown (Berridge, 2012).

There are currently no neuroimaging studies on comorbidity of ICDs in PD; however, in non-PD subjects, exposure to reward-related cues triggers both the excessive 'wanting' for that particular type of reward (e.g. pathological gambling or cocaine) and also enhances the pursuit of other reward types (food and sex) (Fiorino &

Phillips, 1999a; Nocjar & Panksepp, 2002). Such a 'cross-sensitisation' phenomenon may therefore underlie the neurobiology for development of comorbid ICDs in PD patients where an individual develops two or more clinically different ICDs.

1.5 Overview of chapters

Chapter 2 contains the methodologies used for the studies in this thesis and is divided into three subsections. The first part details patient recruitment and clinical assessments relating to PD patients with and without ICDs and matched healthy volunteers. The second part explores the general methodological principles of PET. In the last subsection, the methodological basis of functional magnetic imaging is discussed. Specific methodologies related to each study are detailed within the respective chapter.

In Chapter 3, using positron emission tomography with 11C-RAC, I investigate whether passive viewing of rewarding visual cues has an effect in striatal dopamine neurotransmission in PD patients with and without impulse control disorders.

Chapter 4 examines punding behaviour in PD patients, and its associated striatal dopamine D_2 receptor binding compared to a PD control group using PET with 11C-RAC.

In Chapter 5, I use functional MRI to explore changes in striatal BOLD signal in PD patients with compulsive sexual behaviour compared to a control group and discuss their associated clinico-behavioural differences.

Chapter 6 examines excessive Internet use in PD patients with ICDs and assesses their severity against a group of PD controls and healthy volunteers using the Yale-Brown Obsessive Compulsive Scale, adapted for Internet use.

In Chapter 7, I discuss the main findings from my studies and suggest recommendations for future research for PD patients with impulse control disorders and related addictive behaviours.

Chapter 2
Methodology

2.1 Patient recruitment and clinical assessments

2.1.1 Ethical approval

All studies received ethical approval from the Hammersmith and Queen Charlotte's and Chelsea Hospitals Research Ethics Committee. Permission to administer radioactive substances was obtained from the Administration of Radioactive Substances Advisory Committee (ARSAC) of the Department of Health, UK. The radioactive tracers were fully supplied by Hammersmith Imanet plc, London, UK.

2.1.2 Subject recruitment and clinical assessment of participants with Parkinson's disease

Participants with PD were recruited from specialist Movement Disorder Clinics at Imperial College NHS Healthcare Trust and at the National Hospital for Neurology and Neurosurgery, Queen Square. Healthy volunteers were recruited through advertisement in London newspapers, PD society UK, local PD newsletters and magazines and publicity posters.

Each potential participant who showed an interest in the research project was invited to attend a brief meeting in a clinic room at the Cyclotron Building at Hammersmith Hospital. The purpose of this was to allow for an opportunity to ask questions that they may have had after reading about the research project (from the patient

information leaflet given previously) and to obtain written consent. Those who were interested in participating in studies involving PET imaging were given a tour of the scanning facilities.

All subjects gave informed written consent in accordance with the Declaration of Helsinki (International Committee of Medical Journal Editors, 1991).

All participants who consented to participate in the research study were then scheduled for a detailed, face-to-face semi-structured interview. This clinical interview lasted approximately one hour and consisted of a review of their history of Parkinson's disease, their medications, a physical examination and the completion of a battery of clinico-behavioural questionnaires. The name and dose of each anti-parkinsonian medication was recorded and calculated into 'levodopa equivalent daily dose (Evans et al., 2004) (see equation 1).

Patients were also asked if they wanted to have their carer or spouse present during these research sessions to help with completion of questionnaires or collateral history. I also talked with the carers regarding the confidentiality of these sessions and that they may be asked to leave the room at the patient's request.

2.1.3 Diagnosis of Parkinson's disease

A full medical history was taken where participants were asked to provide chronological details of their symptoms similar to attending a first consultation with a neurologist in a clinical setting. For each symptom related to their Parkinson's disease, they were asked to give further information as appropriate, such as time of onset and details related to severity. Following this, each patient was asked about other aspects of his or her medical history such as past medical illnesses, systems review, drug history, social history and any other relevant information.

The parkinsonian symptoms reported by the patient were checked to ensure that they satisfied the clinical diagnostic criteria given by the UK Parkinson's Disease Society Brain Bank's clinical criteria (Hughes et al., 1992).

2.1.4 Assessment for evidence of impulse control disorders

During the face-to-face interview, using open-ended questions, patients were asked if they had ever experienced impulse control disorders in their lifetime and particularly since they have been diagnosed with PD. Following this, patients were asked specifically about particular impulse control disorders such as gambling, binge eating, shopping and compulsive sexual behaviour. Patients were also asked specific questions related to their medication intake, punding behaviour and Internet use. Patients were subsequently assessed for ICD and related behaviours using the diagnostic criteria detailed in Appendices 2–8.

2.1.5 Medication review

Patients were asked to provide a list of their anti-parkinsonian medication and the length of time they had been on that specific medication. Those who were assessed to have evidence of any ICDs and related behaviours were asked to provide details of any medications when the behaviour started and any subsequent medication changes. Patients were also asked to provide the names and doses of all medications for treatment of other medical conditions (if any).

2.1.5.1 Calculation of L-Dopa equivalent daily dose

Calculation of an L-Dopa equivalent daily dose (LEDD) for each patient was based on theoretical equivalence to L-Dopa as described in Evans et al. (2004).

Equation 1. Calculation of L-dopa equivalent daily dose

LEDD = L-Dopa dose + L-Dopa dose x 1/3 if on entacapone + bromocriptine (mg) x 10 + cabergoline or pramipexole (mg) x 67 + ropinirole (mg) x 20 + pergolide (mg) x100 + apomorphine (mg) x 8.

2.1.6 Evaluation of motor symptoms

Clinical evaluation of motor symptoms severity was performed using the United Parkinson's Disease Rating Scale (UPDRS) – part III (Goetz et al., 2007) and a modified version of the Hoehn &Yahr scale (Hoehn & Yahr, 1967).

During the semi-structured interview, subjects were assessed whilst on their own medications. In studies detailed in subsequent chapters, subjects were assessed with

UPDRS Part III and H&Y staging in an OFF medication condition and in an ON medication condition after administration of L-Dopa 250/carbidopa 25.

2.1.6.1 Unified Parkinson's Disease Rating Scale (UPDRS)

The UPDRS is currently the most established scale for assessing disability and impairment (Goetz et al., 2007; Ramaker, Marinus, Stiggelbout, & Van Hilten, 2002). It was developed in an attempt to combine elements of a number of scales to produce an efficient and flexible tool to monitor the impact of PD and the degree of disability caused. The scale has three sections that evaluate the key areas of disability, together with a fourth section that evaluates any complications of treatment. Part I assesses cognition, behaviour and mood. Part II is intended for the patient to evaluate their ability to carry out activities of daily life and includes tasks such as swallowing, handwriting and cutting food. Part III of the UPDRS is used in the studies of this thesis to record the motor function of patients when ON and OFF medication (see Appendix 9). It provides a comprehensive coverage of the cardinal motor symptoms in patients with PD (e.g. tremor, rigidity, bradykinesia, postural instability) and contains 27 questions (for 14 subitems) for the different body regions, scored from 0 (normal) to 4 (maximal severity) with a maximum (worst) total score of 108. Finally, Part IV assesses complications of antiparkinsonian therapy, such as dyskinesias, dystonia and symptomatic orthostasis.

2.1.6.2 Hoehn and Yahr scale

The Hoehn and Yahr scale (H&Y) is commonly used in clinical studies to compare groups of patients and to provide gross assessment of disease progression (Hoehn & Yahr, 1967). The modified H&Y staging assesses the relative level of disability as

follows: stage 0 = no signs of disease; stage 1= unilateral disease; stage 1.5 = unilateral plus axial involvement; stage 2= bilateral disease without impairment of balance; stage 2.5 = mild bilateral disease with recovery on pull test; stage 3 = mild to moderate bilateral disease with some postural instability, but physically independent stage 4 = severe disability but still able to walk or stand unassisted and stage 5 = wheelchair-bound or bedridden unless aided (Goetz et al., 2004).

2.1.7 Other clinical assessments

All participants also underwent the following assessments.

2.1.7.1 Mini-mental state examination

Introduced in 1975 by Folstein and colleagues, the Mini-Mental State Examination (MMSE) is a 30-point questionnaire test that is used to screen for cognitive impairment (Folstein, Folstein, & McHugh, 1975). It tests for different facets of cognition such as orientation in time and place of the test, repeating lists of words, arithmetic, language use and comprehension, short-term memory and basic motor skills. It can also be used as a guide to evaluate the severity of the impairment. The maximum score is 30; a score greater than or equal to 25 points indicates normal cognition. Attainment of 21 to 24 points indicates mild cognitive impairment, 10 to 20 points indicates moderate impairment, and any score less than 9 points indicates severe impairment.

In the study for this PhD, patients scoring below 26 were excluded because of the requirement to complete self-administered questionnaires.

2.1.7.2 Beck Depression Inventory version II

The Beck Depression Inventory-II (BDI-II) created by Dr Aaron T Beck is one of the most widely used instruments for measuring the severity of depression. The revision in 1996 (Beck, Steer, Ball, & Ranieri, 1996) made the questionnaire more consistent with the Diagnostic and Statistical Manual – IV (DSM-IV) criteria for depression. The scale consists of 21 multiple-choice questions, where each statement ranges from zero to three with a maximum total score of 63. Subjects pick one statement in each group that best describes the way they have been feeling during the past two weeks (including the day of the test). A score of 0–13 refers to minimal depression, 14–19 indicates mild depression, 20–28 refers to moderate depression and 29 and above denotes severe depression (i.e. the higher the total score, the more severe the depressive symptoms). The BDI-II is shown to have a high one-week test-retest reliability (Pearson r=0.93), suggesting that it was not overly sensitive to daily variations in mood. This self-reporting depression screening tool has been validated in patients with PD, with the optimal cut-off for discriminating between depressed and non-depressed PD patients set at 16–17 for BDI II (Leetjens et al 2000; Silberman et al 2006). BDI-II was used for all subjects during their semi-structured clinical interview for screening of depression.

2.1.7.3 Alcohol Use Disorder Identification Test (AUDIT)

This questionnaire was developed by WHO and consists of 10 questions to determine if an individual's alcohol consumption may be harmful (Saunders, Aasland, Babor, de la Fuente, & Grant, 1993). Questions 1 to 3 ask about alcohol consumption, 4 to 6 relate to alcohol dependence and 7 to 10 consider alcohol-related problems. A score of 8 or more in men and 7 or more in women indicates that the individual is likely to

be consuming harmful levels of alcohol. A score of 20 or above suggests alcohol dependence (Babor, Higgins-Biddle, Saunders, & Monteiro, 2006).

2.1.7.4 The Fagerstrom Test for Nicotine Dependence (FTND)

This six-item questionnaire was designed to screen for nicotine dependence (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1993). A score of 1–2 indicates low dependence, 3–4 indicates low to moderate dependence, 5–7 moderate dependence and 8 or above high dependence.

2.1.8 Clinical assessment of non-PD participants (healthy volunteers)

Similar to PD participants, healthy volunteers attended an initial brief interview. The purpose of this was to obtain written consent and to allow for an opportunity to ask questions that they may have after reading about the research project (from the patient information leaflet sent to them previously). Those that were interested in participating in studies involving PET imaging were given a tour of the scanning facilities.

They were subsequently scheduled for a face-to-face assessment where a detailed medical history and physical examination were performed. Anyone with major psychiatric comorbidity was excluded from the research. The healthy volunteers also underwent self-completed questionnaires to assess for different types of ICDs (Appendices 2–8).

All normal controls recruited were in good healthy and did not have any history of neurological or psychiatric illnesses, and were not taking any medication.

2.1.9 Diagnostic criteria used for evaluating impulsive-compulsive disorders and related behaviours

During the semi-structured interview, I assessed each patient against the diagnostic criteria for the four most commonly reported ICDs and related addictive behaviours in Parkinson's disease patients.

2.1.9.1 Gambling

See Appendix 2.

2.1.9.2 Compulsive sexual behaviour

See Appendix 3.

2.1.9.3 Compulsive buying

See Appendix 4.

2.1.9.4 Binge eating

See Appendix 5.

2.1.9.5 Dopamine Dysregulation Syndrome (DDS)

See Appendix 6.

2.1.9.6 Punding

See Appendix 7.

2.1.10 Questionnaires used for assessment of impulse control and related disorders

2.1.10.1 Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP)

The questionnaire was designed and validated as a screening instrument and consists of three sections: Section 1 assesses for four commonly occurring ICDs (compulsive gambling, sexual, buying and eating behaviours) and consists of five questions including an introductory question that defines and gives examples of problem behaviours; section 2 assesses for other compulsive behaviours (punding, hobbyism, and walkabout) through three distinct introductory questions and two common additional questions; and section 3 assesses for compulsive medication use using five questions. The QUIP was tested on a sample of 157 patients with idiopathic PD. The ICD section of the QUIP has at least 80% sensitivity and specificity for each of the four ICDs. The sensitivity and specificity for the hobbyism subsection was >90% (Weintraub et al., 2009).

This questionnaire acted as a screening test, taken at the beginning of the semi-structured interview, and any positive answer was followed up to verify whether the patient had a clinically significant ICD or other compulsive behaviour.

2.1.10.2 Brief Sensation Seeking Scale (BSSS-4)

Sensation seeking is a personality trait with a biological basis defined by the 'seeking of varied, novel, complex and intense sensations and experiences, and the willingness to take physical, social, legal and financial risks for the sake of such experience' (Zuckerman & Neeb, 1979). Sensation seeking has been associated in a number of risky behaviours such as heavy drinking and drug abuse. High sensation seekers tend

to go for activities that provide greater arousal. Various sensation seeking scales exist to test for personality traits of thrill and adventure seeking, experience seeking, disinhibition and boredom susceptibility. These characteristics have been found to be potential endophenotypes for ICDs. The four-item index (BSSS-4) has been shown to perform similarly to longer measures (Stephenson, Hoyle, Palmgreen, & Slater, 2003).

2.1.10.3 Yale-Brown Obsessive Compulsive Scale, adapted for Internet

The original Yale-Brown Obsessive Compulsive Scale (Y-BOCS) is a 10-item questionnaire which measures obsessive and compulsive elements separately (Goodman, Price, Rasmussen, Mazure, Fleischmann, et al., 1989). This questionnaire has been widely used and adapted for screening and evaluation of various impulsive-compulsive behaviours, such as gambling (J. E. Grant et al., 2003), compulsive sexual behaviour (Coleman et al., 2010), and compulsive shopping (Monahan, Black, & Gabel, 1996). The Y-BOCS has been widely used in the general population among those with OCD and/or ICD with good validity and reliability (Deacon & Abramowitz, 2005; Goodman, Price, Rasmussen, Mazure, Delgado, et al., 1989; J. E. Grant, Mancebo, Eisen, & Rasmussen, 2010) (J. E. Grant, Mancebo, Pinto, Eisen, & Rasmussen, 2006) (Stengler-Wenzke, Kroll, Riedel-Heller, Matschinger, & Angermeyer, 2007). The questionnaire has an equal number of questions on obsessions and compulsions without giving bias to either component. It has also been successfully adapted for use on ICDs, showing good reliability and validity for pathological gambling (J. E. Grant et al., 2003; Pallanti, DeCaria, Grant, Urpe, & Hollander, 2005) and compulsive shopping (Black, Gabel, Hansen, & Schlosser, 2000; Monahan et al., 1996; Mueller et al., 2008).

The Y-BOCS has been adapted for Internet use (Appendix 8) and applied in the study of pathological Internet use in Parkinson's disease patients (Chapter 6). Only non-essential Internet usage (non-business or non-academic use) was evaluated, in line with recommendations for assessing PIU (K. Young, 2004). Participants were advised that 'Internet use' denotes access to the Internet via an electronic medium, to include laptop and desktop computers, tablet computers, smartphones and any other media through which Internet can be accessed.

2.1.11 Statistics

For the studies included in this thesis, SPSS (SPSS version 20 statistical software for Mac, SPSS Inc., IL, USA) software packages were used.

For between-group comparisons regarding the clinical data, one-way ANOVA assumptions were tested with the Bartlett and Kolmogorov and Smirnov methods. Where a successful normality test was obtained and SDs were not different among groups tested, one-way ANOVA was used and multiple comparisons were checked with the Bonferroni *post hoc* test. Where normality tests failed and SDs were different among groups tested, the nonparametric Kruskal-Wallis test was used and multiple comparisons were checked with Dunn's test. The significance (alpha level) was set at $p<0.05$ corrected, and all significance levels reported in two-group comparisons in this thesis are two-tailed.

Additional statistical studies employed in each study are documented in the methods section of each chapter.

2.2 Positron Emission Tomography (PET) methodology

2.2.1 Introduction on Positron Emission Tomography

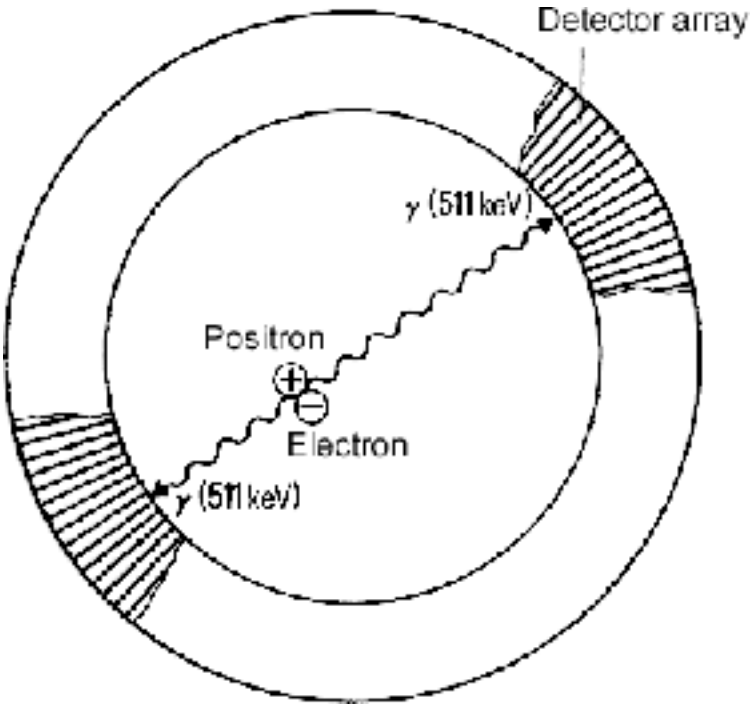
Positron Emission Tomography (PET) is a nuclear medicine imaging technique that measures biological processes of a given tissue by mapping the functional activity through short-lived radionuclides (A. Paans & van Waarde, 2002). The PET technique is unique in that it detects metabolism within living tissue (*in vivo*), where as other types of nuclear medicine detects the amount of radioactive substance collected in a body tissue at a certain location. Positrons were first discovered in the 1930s. They are particles of equal mass but have an opposite charge to electrons and are their anti-matter equivalent. When emitted from an unstable nucleus, a positron travels one to three millimetres before colliding with an electron in the outer shell of an atom. This results in annihilation, and the energy is emitted as two 511keV gamma rays, released at 180 degrees to each other. The first positron imaging device was used in the early 1950s at Massachusetts General Hospital in Boston to detect brain tumours and other brain diseases. The development of reconstruction algorithms associated with Computed Tomography (CT) imaging induced a widespread interest in PET technology. Since the mid 1980s, PET has become a tool for medical diagnosis, dynamic studies of human metabolism and studies of brain activation (A. M. Paans, van Waarde, Elsinga, Willemsen, & Vaalburg, 2002). Subsequently, one of its major applications has been in furthering our understanding of complex neurological disorders like PD.

PET imaging starts with the injection of an active tracer (for example, raclopride or flurodopa), a biological molecule which carries a positron emitting isotope such as

carbon-11 (half life, $t_{1/2}$=20 minutes) and fluorine 18 ($t_{1/2}$=110 minutes). The half life, $t_{1/2}$, for radioisotopes is the amount of time it takes for half of the label to decay; the faster the decay, the less time between injection and scanning.

Within minutes, the molecule accumulates in an area of the body for which it has an affinity. These positrons collide with free electrons, usually no farther away than 1mm from point of emission. The collision results in a conversion from matter to energy and emits two high-energy gamma rays in opposite directions (Figure 2). These, after administration, can be recorded simultaneously by a pair of detectors and the annihilation processed that occurred along the line connecting the detectors. The exact position of the annihilation can be computed by measuring the time difference between the arrivals of the two rays. The information is recorded in real time to obtain structural and kinetic information, such as the distribution of receptors in the brain or areas of increased blood flow stimulation.

Figure 2. Principle of PET imaging - the collision of a positron with an electron results in two gamma rays emitted in opposite directions



(Reproduced from

http://www.cs.uni-magdeburg.de/~nroeber/english/intern/node15.html#122)

2.2.1.1 Advantages of PET imaging

PET has high sensitivity and provides good spatial and temporal resolution by accurately determining the activity concentration of the radiotracer within a volume. The resolution of images from a PET scan is two to three fold higer than Single Photon Emission Computerised Tomography (SPECT), another imaging technique that also uses gamma rays - commonly used to help with the clinical diagnosis of PD [also known as a DaT (dopamine transporter) scan]. The unique advantage of PET over other modalities is its ability to determine tissue metabolism *in vivo* by measuring the activity concentration of a radiotracer within a volume. Using different radiotracers, it is possible to measure blood flow, oxygen concentration and glucose metabolism. In a research context, this allows for measurement of different compounds to further our understanding of the underlying biology of different tissue states. Applied clinically, PET is useful for diagnosis of different conditions and is excellent at differentiating between benign and malignant tissue; as such, it is also useful to monitor for response to treatment (e.g. chemotherapy).

2.2.1.2 Disadvantages of PET imaging

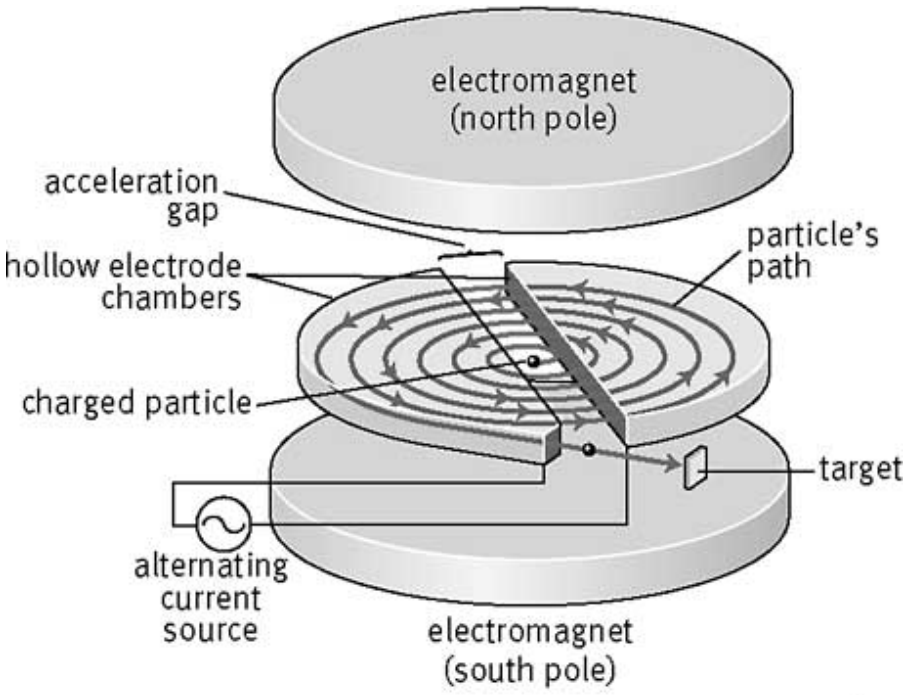
PET is limited by the high costs involved in producing the radioisotopes and the specialised on-site chemical synthesis apparatus. In addition, it involves exposure to ionising radiation. The total dose of radiation is small, however – usually around 7mSv. This can be compared to 2.2mSv average background radiation in the UK, 0.02mSv for a chest x-ray, up to 8mSv for a CT scan of the chest and 2-6mSv per annum for aircrews.

2.2.2 The cyclotron

The process of isotope production begins with the production of negatively charged hydrogen ions in a particle accelerator called a cyclotron. The particle is usually produced from an ion source, either a proton or deuteron. These particles are injected into the cyclotron through a beam. The cyclotron accelerates charged particle beams using a high frequency alternating voltage applied between two 'D'-shaped electrodes (the 'dees'). An additional static magnetic field is applied in a perpendicular direction to the electrode plane, enabling particles to re-encounter the accelerating voltage many times at the same phase (Figure 3). These negatively charged hydrogen ions are converted into positively charged protons. The interaction of protons with the stable forms of elements such as oxygen, nitrogen or carbon converts them to a radioactive condition. The radioactive condition is largely unstable because it possesses too many protons and is called radioisotope.

As the particle gains energy, it follows a spiral path from the centre of the cyclotron as a maximum radius from where it is then focused by an electrostatic deflecting beam to bombard a target. Through computer software, the radioisotopes are then made to attach to the synthetic molecule of interest, such as raclopride, DASB or flurodopa in a biosynthesiser unit called a hot cell.

Figure 3. Principles of the cyclotron.



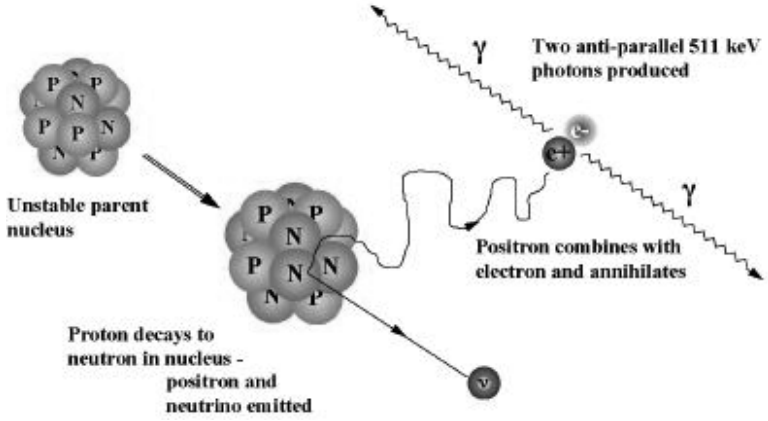
The accelerating electric field reverses just at the time the electrons finish their half circle so that it accelerates them across the gap. With a higher speed, they move in a larger semicircle. After repeating this process several times, they come out the exit port at a high speed.

(Reproduced from http://hyperphysics.phy-astr.gsu.edu/hbase/magnetic/cyclot.html)

2.2.3 Coincidence detection

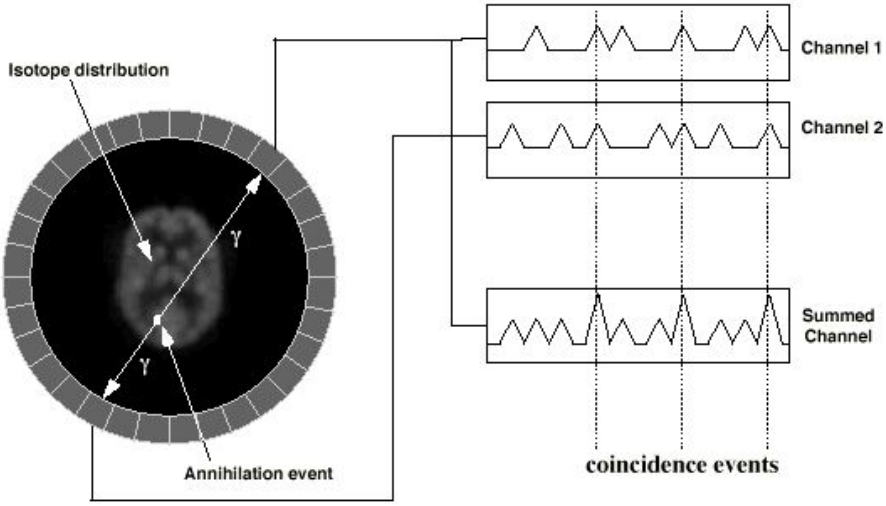
The radionuclide in the radiotracer decays, and the resulting positrons subsequently annihilate on contact with electrons after travelling a short distance of several millimetres within the body. Each annihilation produces two gamma rays (511 keV photons) travelling in opposite directions (Figure 4). The gamma rays can be detected by a detector made from a scintillation bismuth germanate crystal connected to a photomultiplier tube. The detector electronics are linked so that two detection events unambiguously occurring within a certain time window (a coincident) is determined to have come from the same annihilation. The scintillation crystal emits low-energy photons (visible light) after interaction with high-energy photons (gamma rays). The photomuliplier tube then converts the scintillation events into electrical pulses (Figure 5).

Figure 4. Positron annihilation to produce two gamma rays (511keV)



(Reproduced from http://depts.washington.edu/nucmed/IRL/pet_intro/intro_src/section2.html)

Figure 5. Coincident detection.



(Reproduced from http://depts.washington.edu/nucmed/IRL/pet_intro/intro_src/section2.html)

The size of the crystal detection system is a major factor in the resolution of the PET camera, and the maximal physical image resolution is approximately 1.1 to 1.2 times greater than the width of the individual detector crystals. In current PET scanners, the detector is made of multiple rings stacked on top of each other to detect volumetric data from a wide field of view (FOV). In two-dimensional scanning, the coincidences within the same ring define an intra-ring image, and coincidences between adjacent rings form independent inter-ring images (cross-planes). In a three-dimensional scanning, coincidence detected between all rings are counted, which results in a six-fold increase in signal but also an increase in count due to scatter (Cherry, Woods, Hoffman, & Mazziotta, 1993). When scattered events are subtracted, the efficiency of coincidence detection at the centre of the FOV increases by a factor of 4.8 (Spinks et al., 1992). The advantage of 3D acquisition over 2D is that scans of comparable quality can be obtained by using four times less radiation.

2.2.3.1 Types of coincidence events

PET radiotracers emit positrons. The PET tracers produce positively charged positrons that travel a short distance in the brain before colliding with a negatively charged electron. The positron and the electron annihilate each other and, in the process, emit two gamma ray photons (511 KeV) at 180 degrees to each other. The photons are detected as 'pairs in coincidence' by a series of specialised detectors arranged in a ring around the subject. A coincidence event is assigned to a line of response (LOR) joining the two relevant detectors, which gives positional information on the detected radiation.

'True' coincidences occur when both photons from an annihilation event are detected by detectors in coincidence, neither photon undergoes any form of interaction prior to detection and no other event is detected within the coincidence time-window.

'Random' coincidences occur when two photons from separate annihilation events are detected simultaneously at opposing detectors. These are identified by introducing a delay into one side of the coincidence detection circuit by 48nsecs, and coincidences resulting from a single annihilation event are not detected under these circumstances.

Annihilation events in which one of the photons is deflected ('scattered') but in which the two photons are nevertheless detected simultaneously at opposing detectors can still constitute a proportion of the true rate. However, scattered photons tend to have lower energy, and so the scatter fraction may be minimised by energy windowing. Scattered coincidences can add statistical noise to the signal.

'Multiple' coincidences occur when more than two photons are detected in different detectors within the coincidence resolving time. In this situation, it is not possible to determine the LOR to which the event should be assigned, and the event is rejected.

2.2.4 Image reconstruction and attenuation correction

True coincidence events detected are recorded in real time as a series of histograms by a computer system and sorted into sinograms. The computer then generates 3-dimensional images through the application of a 'filtered back projection' reconstruction algorithm similar to that used in computed tomography (CT) (Phelps, 1977). The algorithm consists of the projection of a series of radiation profiles

(sinograms) recorded at different angles to produce a cross-sectional image of the original distribution of radioactivity. The sinograms used in image reconstruction in PET represent the distribution of activity in the scanned tissue, reduced by tissue attenuation. It is, therefore, necessary to correct for this attenuation in order to allow for true quantitative reconstruction.

The tissue attenuation is measured by performing transmission and blank emission scans. A 5- to 10-minute transmission scan is performed prior to injection of the tracer to correct for tissue attenuation of gamma radiation. The radioisotopes (known as PET tracers) are injected as IV bolus in the bloodstream where they migrate to the regions of interest (ROI). The injection is followed by a phase called 'time lag', where the scanner records the concentration and distribution of the tracer.

In a transmission scan, the tissue attenuation of 511keV photons along all coincidence lines is calculated by exposing the subject to be imaged to an external ring or rotating point positron source emitting 511keV gamma radiation, usually ^{68}Ge-^{68}Ga. The blank emission scan is performed with no tissue between the detector rings to detect levels of background radiation. The ratio of the blank and transmission scan data provides attenuation coefficients for 511keV gamma rays on a voxel basis for the object to be studied.

2.2.5 PET scanner

PET scans for the studies in this PhD thesis were performed with a CTI/Siemens 962 ECAT HR+ (Siemens; Munich, Germany) 3D PET camera with a total axial field of view (FOV) of 15.5 cm. This camera has a mean image trans-axial resolution (3D

mode) over a 10 cm radius FOV (from the centre) of 6.0±0.5 mm and an axial resolution of 5.0±0.8 mm (Brix et al., 1997).

2.2.6 PET Radioligand: 11C-raclopride

The radioisotope 11C-raclopride (RAC) was used for the studies in this thesis project RAC is a synthetic compound of the salicylamide series that has been used over the last two decades in PET imaging as a marker for dopamine D2 and D3 receptor binding by acting as a reversible antagonist (Farde, Hall, Ehrin, & Sedvall, 1986). This has allowed scientists to directly assess the availability of D2 receptors and, indirectly, the levels of pre-synaptic dopamine release and has been used in a number of studies on PD (Antonini, Schwarz, Oertel, Pogarell, & Leenders, 1997; Rinne et al., 1993).

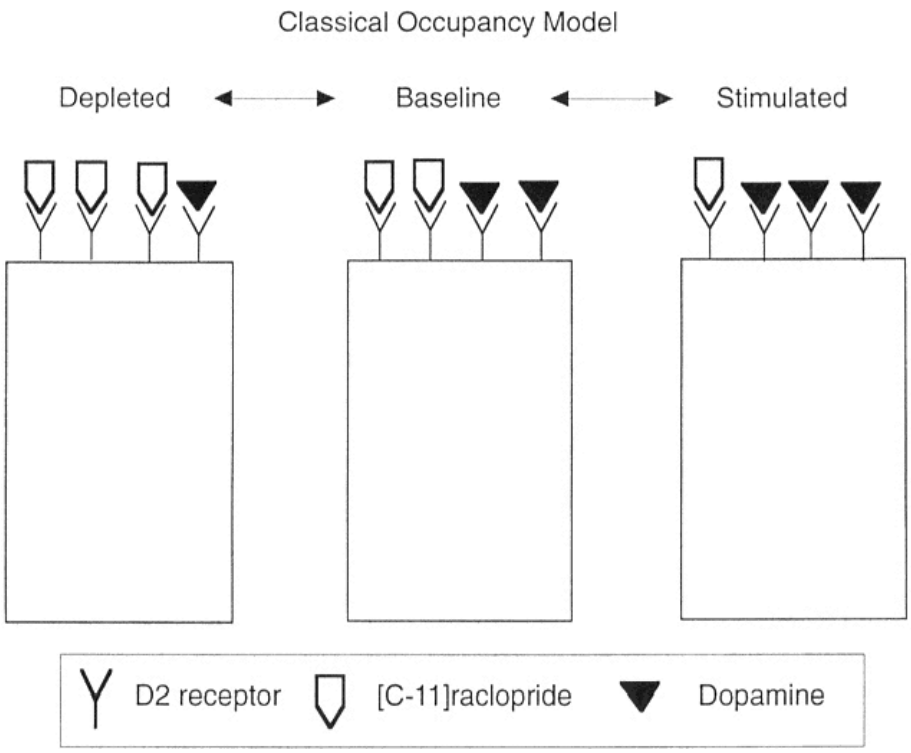
Several pharmacological aspects of RAC make it a suitable radioligand for PET. It has a low nanomolar affinity for D2 and D3 receptors and a low lipophilicity such that the tracer reaches equilibrium between brain and plasma after IV administration within the time course of a PET scan (Farde et al., 1986). Being a reversible antagonist of D2 receptors, its uptake in the brain is influenced by endogenous dopamine and competes for D2 receptor binding with endogenous dopamine. Early studies reported a rapid uptake of ligand by the brain, with striatal radioactivity reaching a peak at 25 minutes post IV injection and then slowly declining as dissociation from binding sites occurred. Cerebellar activity peaked rapidly and then declined throughout the time course of the scan (Farde et al., 1986).

RAC also has a good safety and tolerability profile, with the majority of the tracer being rapidly excreted through the renal system (Ribeiro et al., 2005). The mean effective dose of RAC for normal adults was estimated to be 6.7 +/- 0.4μSv/MBq (mean +/- SD). It was also shown that by using 222 MBq for each injection, subjects may be able to undergo two to three PET scans per year for adequate cerebral D2 receptor imaging and for the evaluation of neuroprotective drugs (Ribeiro et al., 2005). The authors of another study have also found that the doses of RAC commonly used in PET research (270-555MBq) were much lower than the acceptable maximum single radiation dose under the USA federal regulations for studies performed under the Radiation Drug Research Committee (Slifstein et al., 2006).

2.2.6.1 Displacement studies

Neurotransmitter fluxes can be indirectly measured with PET imaging in the living human brain. When endogenous dopamine binds to D2 receptors, it competes with the reversible antagonists Raclopride (Figure 6). This phenomenon allows synaptic dopamine levels to be estimated indirectly from changes in the tracer's D2 receptor binding (Laruelle, 2000; Ross & Jackson, 1989).

Figure 6. Classic occupancy model of ^{11}C-raclopride binding to dopamine D2 receptors



Schematic representation of the Classic Occupancy Model adopted to explain the increase and decrease of ^{11}C -raclopride binding following depletion or stimulation, respectively, of dopamine concentration in the vicinity of D2 receptors by dopamine. At a tracer dose, ^{11}C-raclopride occupies a fraction of the available receptors. As such, the effective binding of ^{11}C-raclopride is related to its binding potential, which in turn is affected by the presence of dopamine in a complex manner since dopamine affects both the number and affinity of the available sites. Reproduced from Laruelle (2000).

Typically D2 binding of RAC is computed from regional brain Time Activity Curves (TACs) using the Simple Reference Tissue Model (SRTM), which assumes that the cerebellum is devoid of dopamine receptors, and so its TAC reflects non-specific binding levels in other brain regions. Following challenges that increase synaptic dopamine concentrations, reductions in radiotracer BP_{ND} are assumed to directly reflect changes in the availability of D2 receptors due to occupancy by endogenous dopamine (Laruelle, 2000).

In reality, this theory is probably more complex as binding of dopamine leads to internalisation of D2 receptors (Ginovart, 2005). However this does not invalidate the Classic Occupancy Model as RAC can only bind to D2 receptors on the cell surface due to its low lipophilicity, preventing diffusion through plasma membranes into the cell cytoplasm (Laruelle, 2000). Increase in dopamine synaptic concentrations can be achieved *in vivo* by administering inhibitors of the Dopamine Transporter (DAT) such as methylphenidate (Volkow et al., 1994) and cocaine (Schlaepfer, Pearlson, Wong, Marenco, & Dannals, 1997) or with dopamine releasers such as amphetamines (Ginovart, Farde, Halldin, & Swahn, 1999; Laruelle, 2000).

2.2.7 PET scanning procedures

A schematic diagram of the PET scanning procedure is illustrated in Figure 7.

Figure 7. Overview schematic flow chart of the PET imaging process.

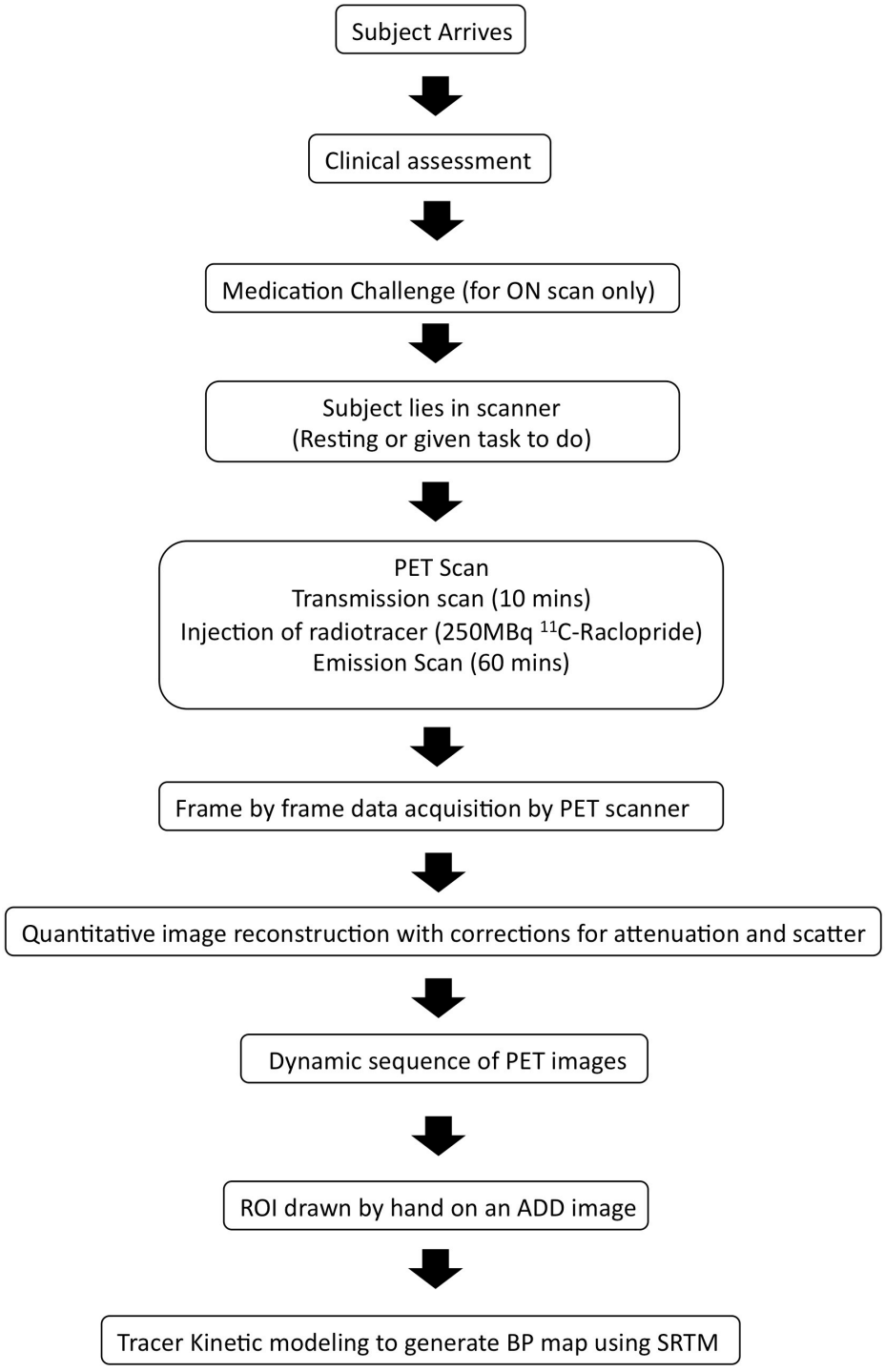


Figure legend: ON scan denotes PET scan following 250 mg levodopa challenge taken 60 minutes prior to start of scan.

All participants underwent RAC scans on a weekday morning (1100–1300) after a 12-hour withdrawal of their medications for PD. Patients were instructed to fast from 10 PM the evening before each scan and to avoid alcohol, smoking, and caffeinated beverages for at least 12 hours before scanning.

PET scans were performed with a CTI/Siemens 962 ECAT HR+ (Siemens; Munich, Germany) 3D PET camera with a total axial field of view (FOV) of 15.5 cm. This camera has a mean image trans-axial resolution (3D mode) over a 10 cm radius FOV (from the centre) of 6.0±0.5 mm and an axial resolution of 5.0±0.8 mm (Brix et al., 1997). A mean dose of 250 MBq ^{11}C -RAC was administered as an intravenous bolus over 10 seconds. Dynamic data were collected over 60 minutes as 20 time frames. The patient's head movement was minimised using a soft head-strap, and position was monitored using a laser system to ensure that the detectors and orbito-meatal line were parallel throughout the scan.

2.2.8 Tracer kinetic modelling

For RAC data analysis, the estimation of binding potential (BP) was performed using quantitative tracer kinetic modelling. Based on *in vitro* radioligand, BP is defined as the ration of Bmax (receptor density) to K_D (radioligand equilibrium dissociation constant). See Equation 2. As the affinity of ligand binding is the inverse of K_D, BP can be equivalently viewed as the product of Bmax and affinity (Mintun, Raichle, Kilbourn, Wooten, & Welch, 1984) .

Equation 2. Estimation of binding potential

$$BP = \frac{B_{\max}}{K_D} = B_{\max} \times \frac{1}{K_D} = B_{\max} \times \text{affinity}$$

In vivo BP measures target receptors in terms of specific radioligand binding. Specific binding is defined as that associated with the target and distinct from radioligand which is free in solutions or nonspecifically associated with other macromolecular components. BP quantifies the equilibrium concentration of specific binding as a ratio to some other reference concentration (Innis et al., 2007).

BP_{ND} refers to the ratio at equilibrium of specifically bound radioligand to that of non-displacable radioligand in tissue. The BP_{ND} measurement compares the concentration of radioligand in receptor-rich to receptor-free regions, and forms the basis of Simplified Reference Tissue Compartmental Model (SRTM) (Gunn, Lammertsma, Hume, & Cunningham, 1997; Lammertsma & Hume, 1996) that uses cerebellum as the reference tissue. The BP_{ND} reflects but not typically equals B_{max}/KD, which is true for *in vitro* measurements (Mintun et al., 1984). BP_{ND} does not require blood sampling, and therefore it is relatively easy to implement. However, use of BP_{ND} as an outcome measure relies on the assumption that non-displaceable uptake is independent of subject groups or treatment effects.

2.2.9 Region of Interest (ROI) analysis

The most common way to determine what the local activity concentration is in a PET image (or volume) is to define a region of interest (ROI) on an image using an analysis software package. The average voxel value within the region is calculated. This value is then converted to an activity concentration in becquerels per millimetre. Because PET data sets are usually made up of a stack of images that form a volume, a volume of interest (VOI) can be defined by connecting several ROIs defined on

multiple contiguous planes into a single VOI. If a dynamic sequence of images has been acquired, the ROI that has been defined can be applied to the same region on all images to generate a time activity curve (TAC) that shows the radiotracer concentration in a specific region of the body over time. This time-dependent data set can then be used with a compartmental model to determine biologically meaningful parameters and to construct parametric images.

Analysis of PET data in this thesis project was performed using a region-of-interest (ROI) approach. Each scan generated 20 frames of dynamic images over 60 minutes. The dynamic images were calibrated and then summed to produce an 'ADD image'. This consisted of the integrated total emission data for the whole brain during the scan. The subdivisions and 'ADD image' were then normalised to an RAC template on Montreal Neurological Institute space using Statistical Parametric Mapping (SPM) software (SPM2; Wellcome Department of Cognitive Neurology, London). The normalisation process allowed for the standardisation of the brain position and shape and facilitated the tracing of the ROIs, which were drawn manually with guidance from a well-established probabilistic brain atlas developed in-house (Duvernoy, 1999; Gousias et al., 2008). The ROIs traced were left and right caudate, putamen and ventral striatum (Figure 8). These striatal regions have an abundance of D2 receptors for the binding of the radioligand raclopride. Each object map was applied to the dynamic images to generate time activity curves of brain uptake of ^{11}C -RAC using ANALYZE 8.1 software (Mayo Clinic). For each patient, the average left and right caudate, putamen and ventral striatum regional binding potential (BP_{ND}) was calculated for statistical analysis using the SRTM, with the cerebellum as a reference region (Gunn et al., 1997; Lammertsma & Hume, 1996). The cerebellum is relatively

devoid of D2/3 receptors, and this method has been proven to be superior to kinetic modelling using arterial data.

Figure 8. Striatal Region-of-Interests on an MRI T2 image

Figure 8a. Caudate and Putamen (demonstrated by anatomical areas outlined in red and annotated in white letters on an MRI T2 image in the axial plane)

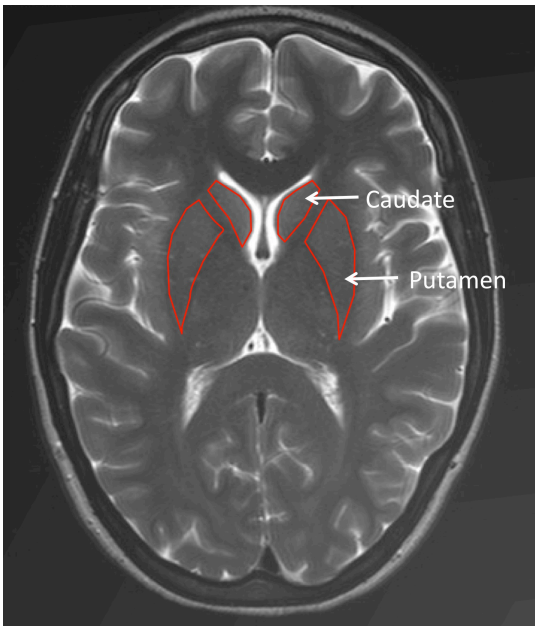
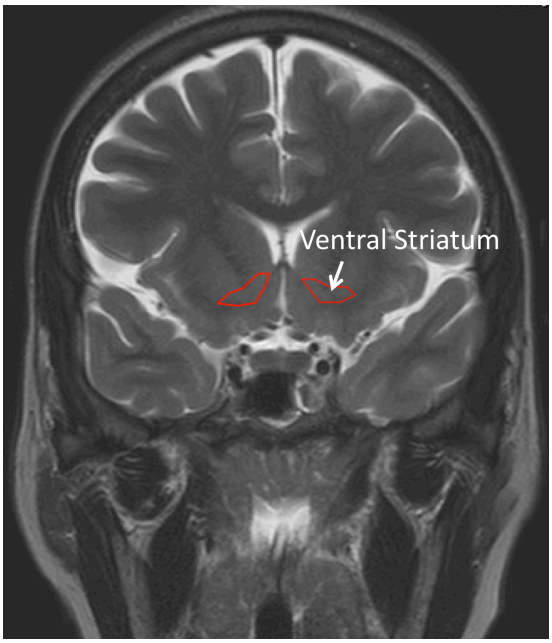


Figure 8b. Ventral striatum (demonstrated by anatomical areas outlined in red and annotated in white letters on an MRI T2 image in the coronal plane)



2.3 Functional magnetic imaging methodology

2.3.1 Introduction to functional magnetic imaging

This section provides a brief account of the general principles of functional magnetic resonance imaging (fMRI) and the methodologies used in analysis of fMRI data.

Functional magnetic resonance imaging is one of the most exciting methodologies to evolve in the last century and has capitalised on the physical principles discovered from nuclear magnetic resonance (NMR) and magnetic resonance imaging (MRI). Whereas MRI is used to produce structural images for anatomical and clinical studies, the functional component of fMRI allows for an indirect measure of activity of a particular tissue by measuring changes in oxygen levels of the blood. This has proved to be invaluable to clinicians and scientists investigating the cognitive and behavioural aspects of the nervous system.

2.3.2 Physiological principles of fMRI

The fMRI method capitalises on magnetic differences between oxygenated and deoxygenated blood. In short, haemoglobin in the blood becomes strongly paramagnetic in its deoxygenated state. Deoxygenated haemoglobin can therefore be used as a naturally occurring contrast agent, with highly oxygenated brain regions producing a larger magnetic resonance (MR) signal than less oxygenated areas. Thus, during brain activation, localised increases in blood flow will increase blood oxygenation and consequently reduce deoxygenated haemoglobin, causing the MR signal to increase. It is assumed that these localised increases in blood oxygenation reflect increases in neuronal activity. This method, blood-oxygenation-level dependent (BOLD) imaging, eliminates the need for exogenous contrast agents

(Kwong et al., 1992; Ogawa, Lee, Kay, & Tank, 1990; Turner, Le Bihan, & Chesnick, 1991).

2.3.2.1 Spin and radiofrequency pulse

Atomic particles possess a property called spin. In nuclei with an even number of protons and neutrons, the pairing of atomic particles leaves a net magnetic moment of zero. In nuclei with an odd number of protons and neutrons, such as the hydrogen nucleus (^{1}H), the unpaired particle has a net magnetic field. They behave like tiny rotating magnets. MRI uses signals from nuclei with an odd number of protons or neutrons. The signal from ^{1}H, the most abundant atom in the brain, is the most commonly used signal for MRI. In the presence of a magnetic field, the hydrogen atoms, which are present in the water molecules of the brain, align themselves with the magnetic field and reach an equilibrium state. Exchange of energy between two systems at a specific frequency is called resonance.

2.3.2.2 BOLD signal

The BOLD fMRI technique is designed to measure changes in the inhomogeneity of the magnetic field that result from changes in blood oxygenation (Roy & Sherrington, 1890). However, the exact relationship between the MR signal and physiological mechanism underlying this signal is unclear. The BOLD signal correlates best with the local field potential (LFP) rather than neuronal firing rates based on studies of simultaneous electrophysiological and fMRI BOLD recordings in non-human primates (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001), suggesting that the BOLD signal reflects synaptic process rather than axonal spiking. However, a separate study in humans using the same paradigm showed equal correlations between

local field potentials and BOLD compared to spike activity (action potential) and BOLD (Mukamel et al., 2005).

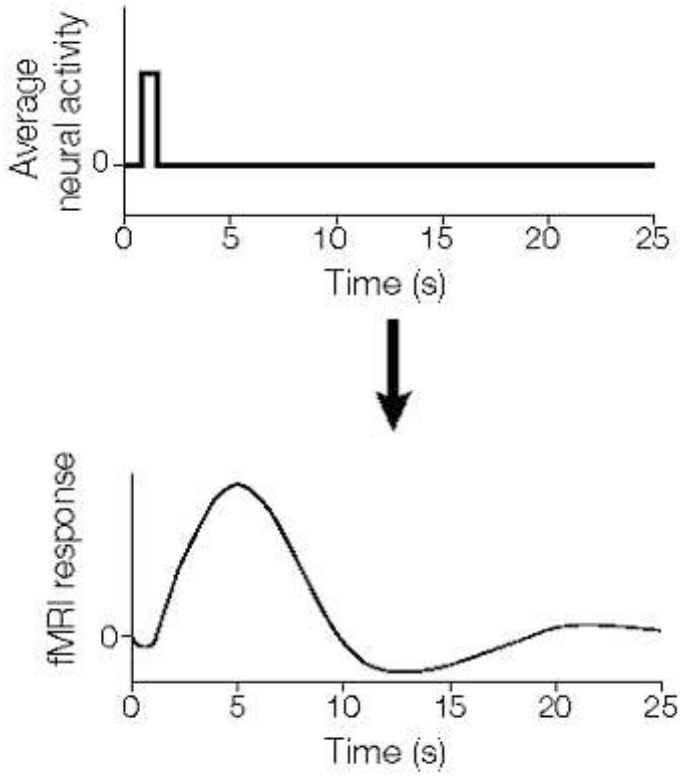
Current data from the literature supports the theory that the BOLD signal correlates better with local field potential (reflecting inputs and intrinsic activity) than neuronal firing rates (reflecting outputs). This is in keeping with the organisation of the cerebral cortex. The vast majority of excitatory and inhibitory neurons terminating on a cell in the cerebral cortex originate from neighbouring cells in close vicinity to the synapse (Sillito & Jones, 2002). Given that the BOLD signal likely has a positive relationship with both synaptic activity and action potentials, the BOLD signal may be interpreted as reflecting increased activation in that region for a specific experimental condition. It is worthy to note that the BOLD signal does not distinguish between inhibitory or excitatory synaptic activity. Local field potentials can be excitatory (70–80% of cortex) or inhibitory (20% of cortex). However, in theory, since the BOLD signal reflects both synaptic activity and action potentials, inhibitory synaptic activity may decrease BOLD signals by reducing net spiking potential.

To date, most studies have relied on the phasic changes in the BOLD signal to indicate neural activations. These changes occur over several seconds. Following the presentation of a stimulus, the fMRI signal begins to increase after a few seconds and does not peak until approximately 5 to 6 seconds after the stimulus. Subsequently, when the stimulus is turned off, or activity ends, the signal takes approximately 10 to 12 seconds to return to baseline (Figure 8). However, rather than settling directly back to baseline, the BOLD signal decreases below baseline for a short period; this is

referred to as the post-undershoot (Buxton, Wong, & Frank, 1998), and is called the Haemodynamic Response Function (HRF). This relatively long haemodynamic response was originally considered as a limitation for the temporal resolution of fMRI studies. However, this has been overcome by the development of event-related designs and selective trial averaging so that it is now possible to measure activation over events just two seconds apart (Dale & Buckner, 1997).

The HRF profile shows some variability both between subjects and between different brain regions. When repetitive transient neural activations occur in close temporal succession, the resulting HRFs sum non-linearly (Glover, 1999). Furthermore, this non-linear summation also varies between cortical regions. To limit the effects of closely temporally related stimuli, the following measures were employed for the fMRI study conducted in Chapter 5: the experiment was a block-design paradigm, with each block of stimuli lasting 14.7s. Within each block, seven images were displayed consecutively, each pictorial image was displayed for 2100ms and each thematic block was followed by a 4000ms rating slide, followed by 1000ms interstimulus interval of a fixation cross. In addition stimulus times were staggered relative to scan times by ensuring that trials and TR were non-integer multiples of one another to ensure a higher effective sampling rate.

Figure 9. The haemodynamic response function of fMRI (reproduced from Heeger and Rees, 2002).



There are several characteristics of the BOLD fMRI signal that affect the design of imaging studies and the interpretation of their results. These include stimulus characteristics such as duration, presentation rate and stimulus intensity. Most importantly, these effects vary as a function of the stimulus type (e.g. visual vs. affective) and brain region of interest (e.g. visual cortex vs. amygdala).

2.3.3 Block vs. event-related designs

Two types of fMRI study designs are commonly employed: block design and event-related design. Block design is an epoch-based design using blocks of stimulation and

event-related design is where data are recorded to monitor the BOLD response following a marked (pre-determined) event such as a single stimulus or task.

Block design experiments (Bandettini, Wong, Jesmanowicz, Hinks, & Hyde, 1994) are used to average across many trials to obtain sufficient signal-to-ratios to generate functional activation images.

The disadvantages of Block designs are that they do not allow separate trials within the task blocks to be distinguished. Block designs are not feasible if we want to consider trials that depend on a subject's performance (e.g. correct or wrong; choosing among different alternatives) or need to present trials in a non-blocked fashion (e.g. the oddball paradigm). In contrast, Dale and Buckner (1997) demonstrated the possibility of using fMRI for selective averaging of rapidly presented individual trial events – a technique that was used in event-related potential (ERP) studies such as EEG/MEG. It is shown that the haemodynamic response is delayed and lasts for several seconds even for brief stimulations. As the haemodynamic response to individual trials extends temporally, the responses to successive trials may overlap. Hence, the inter-trial interval between successive trials needs to last for about 15 seconds. However, this severely limits the number of trials, which can be averaged per unit time, thus limiting the achievable signal-to-noise ratio. Dale and Buckner (1997) demonstrated that the haemodynamic response to successive events summates in an approximately linear fashion even at relatively short inter-trial intervals (2 and 5 seconds), and hence selective averaging of rapidly presented individual trials is feasible. These finding support the Linear Time Invariant Model for the haemodynamic response function (Boynton, Engel, Glover, & Heeger, 1996).

Dale has shown that the statistical efficiency of rapid event-related designs when the inter-trial interval is appropriately jittered can be up to 10 times greater than fixed inter-trial interval designs (Dale, 1999). Further, random intermixing of trial types eliminates strategy effects that might otherwise confound the results in blocked task paradigms.

2.3.4 fMRI data pre-processing

Pre-processing is a necessary step to transform raw fMRI data into a format that is suitable to be statistically analysed. This process involves correcting the slice time, spatial realignment to the first volume to account for movement, and then spatially normalisation. The image analysis for the fMRI study (Chapter 5) was conducted using Statistical Parametric Mapping, SPM 5 (Wellcome Department of Imaging Neuroscience, UCL, UK).

2.3.4.1 Spatial and temporal realignment

Despite the liberal use of foam support and head restraints during scanning, subjects commonly show several millimetres of displacement and several degrees of rotation during a scan, leading to voxel misalignment and additional variance. Spatial realignment is crucial given that we use such a small voxel size in fMRI practice (3x3x3 mm). Spatial preprocessing involves a rigid body (6 degrees of freedom) transformation to minimise the sum of squared difference of voxel intensity between successive scans and a reference scan (T1 structural scan). A rigid body can have a linear translational movement or a rotational movement in each of the three directions (X, Y and Z). Correspondingly, there are six parameters that need to be estimated (X, Y, Z translations, pitch, roll and yaw). For multi-session data, realignment works in

two steps. First, the first functional images from each session are realigned to each other, taking the first session as reference. Second, the remaining images within each session are realigned to the first image. As a consequence, all images are realigned to the first image from the first session. The echo planar images are then re-sampled and a mean echo planar image volume is generated.

The EPI time series are then normalised and spatially smoothed. Each individual subject's data were pre-processed independently.

2.3.4.2 Spatial normalisation

The process of normalisation refers to transformation of fMRI data into a standardised anatomical space. In the fMRI study in this thesis project, all echoplanar data were spatially normalised to a standard brain using Montreal Neurological Institute standard stereotactic space using parameters from the segmented T1 structural image.

2.3.4.3 Spatial smoothing

In an fMRI study involving multiple subjects, echo-planar images for each subject are smoothed prior to statistical analysis so that corresponding sites of activation can be superimposed. Smoothing has the effect of increasing signal to noise ratio. The idea of smoothing is to replace the intensity value within each voxel with a weighted average (as determined by a Gaussian kernel centred on that particular voxel) that incorporates the intensity values of the neighbouring voxels. From the matched filter theorem, a filter that is matched to the signal should be employed to achieve optimum resolution of signal from noise, and since haemodynamic responses are modelled to have a Gaussian shape, a Gaussian kernel of the size of at least twice the voxel size

should be used for smoothing of the functional images (Full Width Half Maximum [FWHM] of 6 to 8 mm). In the study in Chapter 5, a FWHM of 8 mm was used. Smoothing is performed to compensate for residual between-subject variability after normalisation. Smoothing also permits the application of Gaussian random field theory at the statistics inference stage.

The resultant advantages of spatial smoothing are therefore several fold: smoothing will make errors more normally distributed and ensure that subsequent parametric statistics are valid, and spatial smoothing can accommodate inter-subject differences in anatomical variability at homologous brain regions.

2.3.5 Basic principles of fMRI analysis

Functional specialisation and integration are important principles central to the science of neuroimaging. Function specialisation refers to the anatomically distinct neural areas specialised to perform specific cognitive or motor function. This is in contrast to functional integration, which relates to the interaction between these functionally segregated areas. fMRI uses the haemodynamic responses accompanying mental processes to investigate the localisation and integration of these functions in the brain, for which one of the most common methods is statistic parametric mapping (SPM), which uses mass univariate statistical tests (one of each voxel in the image volume).

SPM links the measured BOLD response and task components using a design matrix allowing incorporation of a wide range of task-related and task-unrelated factors within the same model. The General Linear Model (GLM) is a statistical model

which provides a framework for parameter estimation for each factor at each image voxel. This results in statistical parameters which form an image – the statistical parametric map (SPM).

The design matrix is separated into effects of interest and confounders, such as residual variance associated with head movement and error. The main effects of different psychological inputs can then be modelled as stick functions or blocks of stimulation in separate columns of the design matrix. To approximate the haemodynamic response, each stick function, block of activity, parametric modulator and confound is convolved with a canonical HRF (Friston, 2004). Session effects, covariates, and low frequency drift of the magnetic field are treated as confounds. The GLM is applied with the null hypothesis of no significant activation between event trials and baseline. The design matrix is applied independently to all voxels and allows perturbing inputs (trial events) to be connected to all regions while discounting interactions between regions. However, as the neuronal response of neighbouring voxels is often related and not truly dependent, correction for multiple corrections is applied, the most conservative of which is the Bonferroni corrector or Family-Wise error.

One of the most commonly used tools to localise neural activities is the technique of cognitive subtraction. If two or more closely related factors differ by only a single construct, calculating the net activity difference between the two tasks will identify neuronal activity specifically related to that factor. Alternatively, two or more orthogonal factors can be modulated, and the interaction between these factors can be identified.

In fMRI analyses, because of short range serial temporal correlation, data rarely conform to the assumptions of independent and identical distribution used in standard statistical tests. To account for the temporal correlation, the error structure is modelled with a first-degree auto-regressive process and solved using Restricted Maximum Likelihood, producing corrected degrees of freedom. This technique is employed in first-level analysis, together with the application of random field theory, to produce a SPM for each subject. Once completed for each subject for the study, second-level random effects analysis is performed to allow for generalisation of results to the whole cohort. Summary statistics for each contrast of interest are concatenated across subjects with the associated error terms reflecting between subject variability.

A random effects analysis can be carried out to find the areas that are activated in much the same way across all subjects, as opposed to a fixed-effects model, which gives areas that are activated on the average across the subjects. The difference between fixed and random effects is crucial since a fixed effects analysis may yield significant results when one or a couple of subjects has a large activation whilst the other subjects do not show much activation. The random effects analysis incorporates both within-subject variance as well as between-subject variance. This allows generalisation of the results to the population from which the subjects were drawn.

Chapter 3

PET imaging of impulse control disorders in Parkinson's disease patients

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3.1 Introduction

In this study, I use ^{11}C-RAC with PET to investigate dopamine neurotransmission in PD patients with and without ICDs in response to reward-related visual cues. Exploration of this would be particularly pertinent to (1) elucidate the neurobiology underlying this group of patients and (2) to inform clinical management of these patients as they are more challenging to treat.

3.2 Aims and hypotheses

The aims of this study are:

1. To investigate striatal dopamine neurotransmission across a broad spectrum of Parkinson's disease-associated ICDs in relation to L-Dopa and reward cues.
2. To compare dopamine neurotransmission between PD patients with comorbid ICDs, a single ICD and PD control patients in response to viewing of passive reward-related cues and neutral cues.
3. To explore clinical and neuroimaging correlates between PD ICD patients as a group and controls, and to further examine these correlations between those

with comorbid ICDs, a single ICD and controls.

I hypothesise that patients with ICDs would demonstrate sensitisation of their ventral striatal circuitry in response to reward-related cues compared to PD controls. PD patients with comorbid ICDs will have greater ventral striatal dopamine release in response to reward-related cues compared to those with single ICDs and to controls. I also hypothesise that PD patients with comorbid ICDs will also have characteristic traits showing greater risk-taking behaviour and greater clinical impairment compared to those with a single ICD and controls.

3.3 Methods

3.3.1 Participants

A total of 17 patients with ICDs and nine control patients free from any symptoms of ICDs or other neurological and psychological comorbidities were studied. All patients satisfied the Queen Square Brain Bank for Neurological Disorders clinical criteria for Parkinson's disease (Hughes et al., 1992).

3.3.2 Evaluation of clinical and behavioural characteristics

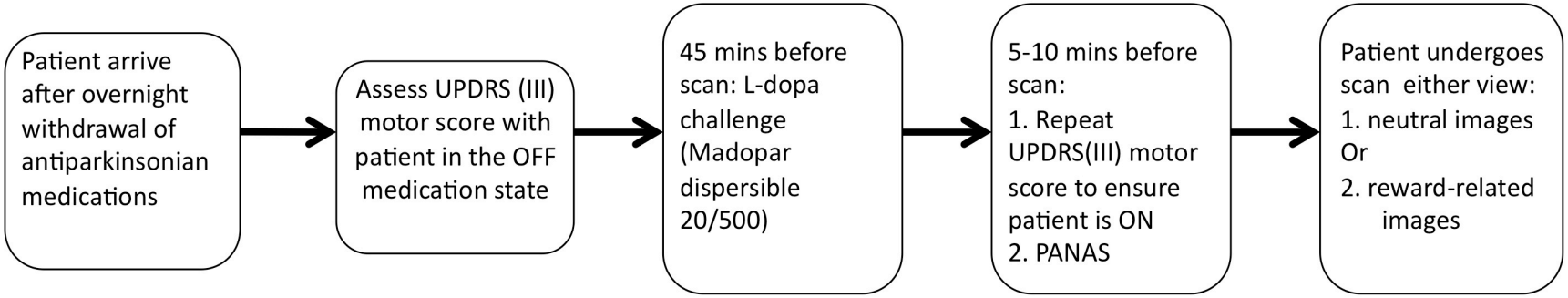
All participants were assessed as detailed in Chapter 2, section 2.1.

3.3.3 PET scanning procedures

All participants underwent two ^{11}C-RAC scans on separate weekday mornings after a 12-hour withdrawal of their medications for PD. Patients were instructed to fast from 10 PM the evening before each scan to control for the state of hunger and to avoid alcohol, smoking and caffeinated beverages for at least 12 hours before scanning.

An overview of the procedures on the day of each scan is illustrated in Figure 9, and each of the components is described below.

Figure 10. Schematic diagram to illustrate the procedure on the day of the PET scan



Abbreviations: UPDRS (III) = Unified Parkinson's Disease Rating Scale (Part III); PANAS = Positive And Negative Affect Schedule: a two 10-item mood scales that reliably measures positive and negative affect.

3.3.3.1 Medication (Levodopa) challenge

All participants in this study were given an oral dose of Levodopa (Madopar dispersible 50/200) 45 minutes prior to scanning.

Levodopa (L-dopa; L-3,4-dihydroxyphenylalanine) is a natural chemical synthesised from the amino acid L-tyrosine. L-Dopa is the precursor to the neurotransmitter dopamine, norepinephrine and epinephrine. As a drug, it has a half life of 0.7 to 1.5 hours and is excreted through the renal system.

L-Dopa 200/Benserazide base 50 mg (Madopar Dispersible 250®) is a combination of levodopa and the peripheral decarboxylase inhibitor benserazide for the treatment of PD. Current evidence shows that symptoms of PD are related to depletion of dopamine in the corpus striatum. Administration of dopamine is ineffective in the treatment of PD as it does not cross the blood-brain barrier (BBB). However, L-Dopa, the metabolic precursor of dopamine, does cross the BBB and presumably is converted to dopamine in the brain. This is thought to be the mechanism whereby L-Dopa relieves symptoms of PD.

When L-Dopa is administered orally, it is rapidly decarboxylated to dopamine in extracerebral tissues so that only a small portion of a given dose is transported unchanged to the central nervous system (CNS). For this reason, large doses of L-Dopa are required for adequate therapeutic effect, and these may often be accompanied by nausea and other adverse reactions, some of which are attributed to dopamine formed in extracerebral tissue. Since L-Dopa competes with certain amino

acids for transport across the gut wall, the absorption of L-Dopa may be impaired in some patients on a high protein diet. Benserazide inhibits decarboxylation of peripheral L-Dopa. It does not cross the BBB and does not affect the metabolism of L-Dopa within the CNS. Since its decarboxylase-inhibiting activity is limited to extracerebral tissues, administration of benserazide with L-Dopa makes more L-Dopa available for transport to the brain. In a clinical study, the latency to 'ON' was significantly faster with Madopar 250 dispersible compared to standard (non-dispersible) forms of L-Dopa preparation (Sinemet 200/50), with an equal amount of duration of 'ON' (Steiger, Stocchi, Bramante, Ruggieri, & Quinn, 1992). As such, using Madopar dispersible can reduce the total time involved per scanning procedure.

3.3.3.2 Assessments before and after each PET scan

Each patient arrives at the research centre in an OFF medication state on the morning of a scanning session (after withdrawal of their usual anti-parkinsonian medication from 10 PM the evening before). I then assess them on the motor score of the UPDRS (Part III). Following this the patient is given a single dose of Madopar 250-mg dispersible 45 minutes before the injection of ^{11}C-RAC.

Immediately prior to the patient entering the scanner, I re-examined the patients on the motor score of UPDRS (Part III) to ensure that they were in an ON medication state (Stebbins & Goetz, 1998), and asked to completed the Positive and Negative Affect Schedule (PANAS). PANAS is composed of two 10-item mood scales that reliably measure positive and negative affect (Watson, Clark, & Tellegen, 1988); (Crawford & Henry, 2004).

3.3.3.3 Visual task during PET scan

During one scan, patients were asked to view neutral cues throughout the scanning period (the neutral scan). During the other scan, patients were shown a series of reward-related visual cues (the reward scan). These images of similar resolution consisted in equal proportion of pictures of appetising foods, pictures with sexual themes, and depictions of gambling/money or shopping-related activities. A sample of neutral and reward-related visual cues is illustrated in Figure 10. Most of these pictures were obtained from the International Affective Picture System (IAPS) (Lang, Bradley, & Cuthbert, 2008). The order of scanning conditions was randomised for each patient.

Figure 11. A sample selection of neutral and reward-related images shown to patients during PET scanning

I decided to use passive visual cues as they require minimal motor demands. Furthermore, excessive reward pursuit following drug-induced sensitisation is thought to result from excessive incentive salience attribution to reward cues (Wyvell & Berridge, 2001). In addition, heightened cue reactivity has been reported in drug addiction (Carter & Tiffany, 1999) and in a number of ICDs in the non-PD population, including pathological gambling (Sodano & Wulfert, 2010), compulsive shopping (Starcke, Schlereth, Domass, Scholer, & Brand, 2012) and binge eating (Sobik et al., 2005).

The images were presented as a PowerPoint ™ (Microsoft; Redmond, WA, USA) presentation on a computer screen placed in front of the patient's full field of view while the patient was prone in the scanner. The picture presentation started two minutes prior to a bolus injection of ^{11}C-RAC and ran continuously until the end of the scan. Each image was shown for 10 seconds, and patients were exposed to 360 images in total for the duration of each scan without repetition.

Please refer to section 2.2.7 (PET scanning procedures) for details of PET scanner and PET radiochemistry.

3.3.4 Positron Emission Tomography data analysis

Please refer to section 2.2.9 (Region of Interest analysis) for PET data analysis.

For each patient, RAC BPND values of the striatal regions during the reward scan were compared to the RAC BPND during the neutral scan and expressed as a percentage change. This is calculated using equation 3.

Equation 3. Calculation of percentage change in RAC BPND comparing reward scan to neutral scan.

$$\text{Percentage change in RAC } BP_{ND} \text{ comparing reward scan to neutral scan} = 100\% \times \left\{ \frac{[(BP_{ND} \text{ value in neutral scan}) - (BP_{ND} \text{ value in reward scan})]}{[(BP_{ND} \text{ value in neutral scan})} \right\}$$

3.3.5 Statistical analysis

Please see Chapter 2, section 2.1.11.

Group comparisons for differences in percentage change in ^{11}C-RAC BP_{ND} in the striatal regions (caudate, putamen and ventral striatum) between different groups were tested with one-way analysis of variance (ANOVA) and Fisher's Least significant difference. Univariate correlations between percentage change in RAC BP_{ND} and variables such as percentage change in PANAS scores or craving scores were made using Spearman's rho correlation tests separately on each group. The alpha level was set at $p<0.05$, corrected for multiple comparisons.

3.4 Results

3.4.1 Comparison of PD ICD group vs. PD control group

3.4.1.1 Clinical data

Patients were matched for sex, age, PD duration and medication intake (Table 1). Patients with PD and ICD behaviours as a group had higher UPDRS (III) motor scores when OFF medication (p=0.0392), higher depression scores from BDI (II) (p=0.0288) and higher Brief Sensation Seeking Score (p=0.0357) compared to non-ICD controls.

Table 1. Clinical and psychological data of PD ICD group and PD control group (for PET study of PD ICD subjects)

	PD ICD patients	**Non-ICD patients**	**Mean difference**	**p**
Sample size	17 (14M: 3F)	9 (7M: 2F)		
Age (yrs)	59.8 (2.3)	60.2 (3.2)	-0.40 [-8.67 to 7.87]	0.9199
Age at PD onset (yrs)	47.1 (2.7)	50.3 (3.4)	-3.28 [-12.37 to 5.82]	0.4580
Disease duration (yrs)	12.8 (2.2)	9.9 (2.1)	2.88 [-3.41 to 9.17]	0.3532
UPDRS (III) OFF medication	41.47 (2.50)	32.78 (3.00)	8.693 [0.48 to 16.91]	0.0392**
LEU DA (mg/day)	244.11 (37.74)	165.56 (48.85)	78.56 [-51.68 to 208.8]	0.2203
Percentage of patients on DA (%)	16 (94.1%)	7 (77.8%)		0.2677[&]
L-Dopa (mg/day)	515.65 (59.00)	666.33 (129.00)	-150.7 [-462.8 to 161.4]	0.3108
Total LEDD (mg/day)	748.00 (66.10)	831.89 (119.20)	-83.89 [-342.1 to 174.3]	0.5089
MMSE	29.29 (0.27)	29.56 (0.24)		0.7501[a]
BDI (II)	16.41 (1.90)	10.44 (1.70)	5.967 [0.679 to 11.260]	0.0288**
BSS	7.47 (0.89)	4.78 (0.81)	2.693 [0.197 to 5.189]	0.0357**
Alcohol Use Disorder Identification Test: self-report version	2.12 (0.50)	1.44 (0.72)		0.2680[a]
Fagerstrom Test for Nicotine Addiction	0 (0)	0 (0)		1.0000

All values are given as mean (SEM). LEU DA, L-Dopa and total LEDD reported as at time of recruitment. Mean difference reported with [95% confidence interval]. Abbreviations: LEU DA = Levodopa Equivalent Units of Dopamine Agonists; LEDD = L-Dopa Equivalent Daily Dose; MMSE =

Mini Mental State Examination; BDI(II) = Beck Depression Inventory, version II; BSS = Brief Sensation Seeking. Statistical analysis conducted using two-sampled t test with Welch's correction where statistical significance is considered as alpha<0.05. ** denotes statistical significance; [a] Mann Whitney U test; [&] Fisher's exact test.

Details of individual patients with PD and their ICDs are listed in Table 2. Seven patients reported single 'pure' ICDs; of these, four patients had compulsive sexual behaviour (57.1%) and three had pathological gambling (42.9%). Ten patients reported more than one ICD—one had four ICDs (10%), two patients had three ICDs (20%), and the remaining seven patients had two ICDs (70%). Notably, all patients with single ICDs were male; binge eating and especially compulsive buying only occurred in conjunction with other ICDs and were never present as isolated, 'pure' conditions.

Table 2. Details of ICD behaviours in PD ICD subjects

Number	Sex	CSB	BE	PG	CB	Comments
1	M	+	+	+	+	CSB: Pestered wife for sex, several sexual affairs, internet pornography PG: visiting betting shops, Internet gambling, slot machines, horses, sports BE: Predilection for ice-cream, chocolate, 15 kg weight gain CB: Compulsively buys clothes, bags, shoes.
2	M	+	+	+		CSB: Internet pornography, pesters wife for sex, solicited prostitutes BE: Predilection for sweet foods and cakes, e.g. eating several bars of chocolates at once. Increased in weight of 8–10 kg in several months PG: Attends betting shops, sports and slot machines at every opportunity possible, thinks about gambling 'all the time'.
3	F	+	+		+	CSB: Pesters partner for sex, visiting pornography sites, using sex toys BE: Sweets, chocolates CB: Compulsively buys handbags and shoes, several copies of same items
4	M	+			+	CSB: Online pornography sites CB: Compulsively buys gadgets, computer equipment

5	M	+			+	CSB: Multiple affairs, compulsive sexual thoughts CB: Repetitively buying several of the same items of equipment excessive for needs
6	M	+	+			CSB: Internet pornography, obsessive thoughts about sex BE: Carbohydrate rich foods, weight gain 10 kg in a few months
7	M	+			+	CSB: Pestering friends for sexual favours, Internet pornography sites CB: Buying clothes and shoes to excess on credit card, excessive buying for family members
8	M	+				CSB: solicited prostitutes, watched Internet pornography
9	M	+				CSB: Visiting online pornography sites, pestering wife for sex
10	M	+				CSB: Internet pornography, solicited prostitutes, sexual promiscuity
11	F		+		+	BE: Liking for sweets, eats several large packets per day CB: Compulsively buys toiletries such as deodorants and perfumes. Compulsive buying of sweet foods.
12	M		+	+		PG: Internet gambling websites late into night, lied to family about money lost BE: Biscuits and sweets to replace main meals, weight gain.
13	F			+	+	PG: Internet bingo at worst all day and into night CB: Buys haberdashery, online bidding

14	M		+			BE: Compulsively eats sweets, carbohydrate rich food. Increased weight.
15	M			+		PG: Visiting betting shops, horses, sports, slot machines
16	M			+		PG: Stays in betting shop most of the day, betting on horses, scratch cards
17	M			+		PG: Bingo 5–6 times per week, 4–5 hours at a time.
	Total	10	7	7	7	
	>1 ICD	70%	85.7%	57.1%	100%	

3.4.1.2 PET data: Comparison of ICD vs. PD controls

Using the a priori defined striatal regions of interest, I found no significant differences at baseline in RAC BP_{ND} between the two groups during the PET scan showing neutral images . However, on comparing RAC BP_{ND} percentage differences between the reward and neutral scans, I found increased ventral striatal dopamine release to reward cues in the ICD group compared to PD controls as demonstrated by a reduction in ^{11}C-raclopride BP_{ND} ($p=0.0018$) (Table 3; Figures 11 and 12).

Table 3. Percentage reduction in regional RAC BPND comparing reward scan to neutral scan in PD ICD and PD control groups

Regions-of-interest	PD ICD group (n=17)	PD controls (n=9)	Mean difference [95% Confidence Interval]	P value
Caudate	6.701 (2.641)	3.827 (2.687)	2.874 [-7.267 to 13.01]	0.4541
Putamen	8.125 (2.606)	4.247 (1.877)	3.878 [-6.23 to 14.02]	0.2395
Ventral Striatum	18.00 (3.053)	5.647 (1.669)	12.35 [2.211 to 2.49]	0.0018**

Values given are % change (SEM) in BP_{ND} values comparing scan with reward cues to scan with neutral cues. Comparisons made with one-way ANOVA corrected with Fisher's Least Significant Difference. Statistical analysis conducted using two-sampled t test with Welch's correction where statistical significance is considered as alpha<0.05. ** denotes statistical significance.

Figure 12. Percentage change in regional RAC BP_{ND} values comparing reward scan to neutral scan in PD ICD and PD control groups

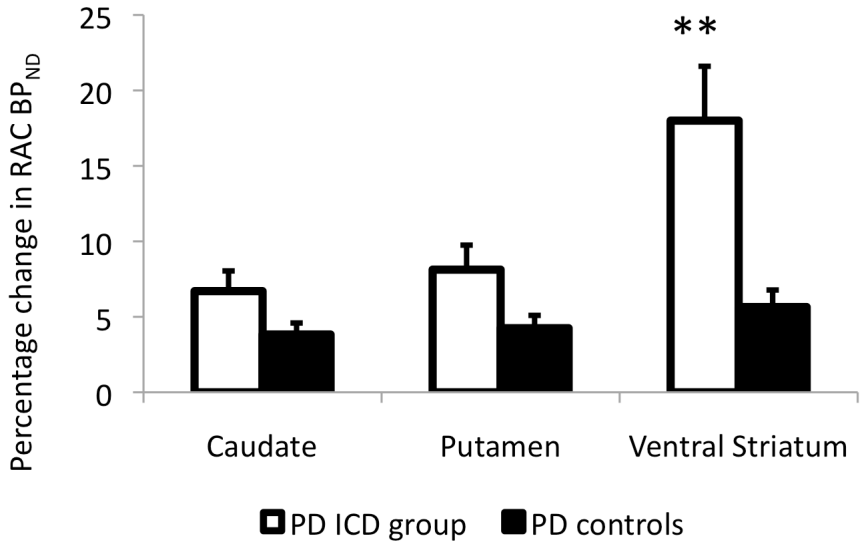


Figure legend: ** denotes statistical significance, where alpha level is set at <0.05.

Figure 13. Representative PET scan images of PD ICD and PD control groups during scans with neutral and reward-related visual cues.

The top two scans represent PET images from the neutral scans. The lower two scans represent PET images from the scans showing reward-related images.

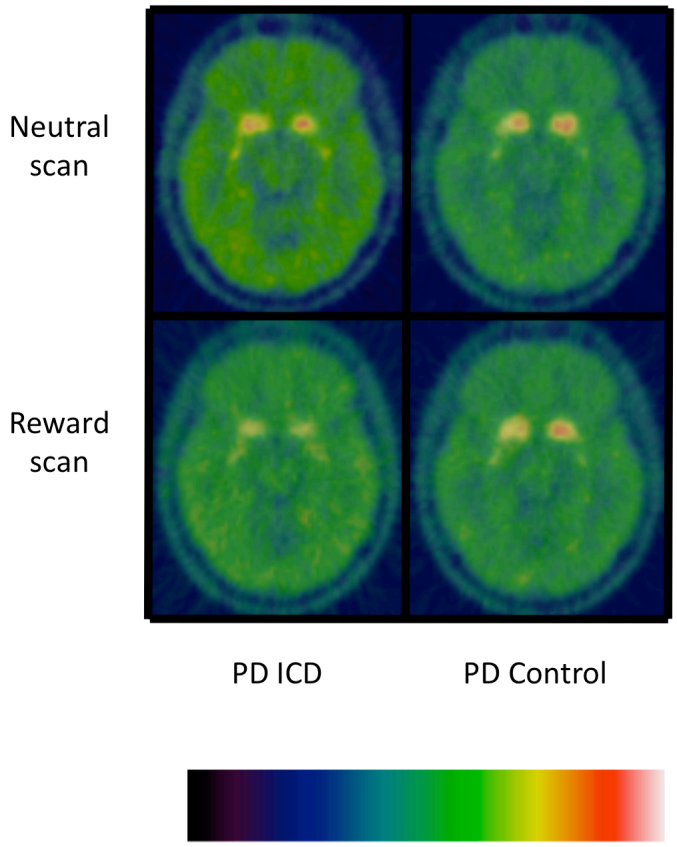


Figure legend: PD ICD patient has reduced RAC BP_{ND} binding most marked in the ventral striatum as demonstrated by reduced colour intensity on the reward-related scan compared to the neutral scan. The difference is much less prominent in the PD control patient.

Results of the PANAS showed that during the neutral scan, there was no difference in percentage change in the positive or negative score in both PD ICD and non-ICD control groups (Table 4). However, during the reward scan, there was a significant increase (p=0.0187) in the positive score in the PD ICD group compared to the control group.

Table 4. PANAS scores for PD ICD and PD control groups

		PD ICD group	**PD controls**	**Mean difference**	**P =**
Neutral cues scan:	Percentage change in PANAS positive score	4.62 (5.538)	-21.58 (13.48)	26.20 [6.260 to 58.660]	0.1023
	Percentage change in PANAS negative score	-15.94 (9.196)	-32.01 (16.90)	16.07 [-25.85 to 58.00]	0.4199
Reward cues scan:	Percentage change in PANAS positive score	17.80 (3.576)	-27.20 (14.87)	45.00 [9.73 to 80.20]	0.0187**
	Percentage change in PANAS negative score	-30.41 (8.878)	-41.84 (15.65)	11.44 [=22.90 to 45.77]	0.4984

Values given are % change (SEM). Comparisons made with *t* test (two-tailed, unequal variance), ** denotes statistical significance, where alpha level is set at $p<0.05$.

3.4.1.3 Clinical correlations

I did not find any correlations between sensation seeking measures and the percentage change in RAC BP_{ND} of the three-striatal regions in the PD ICD group nor in the PD control group.

3.4.2 Comparison of PD patients with comorbid ICDs, single ICD and PD control groups

3.4.2.1 Clinical and psychological data

Patients were matched for sex, age, PD duration and medication intake (Table 5). Levels of depression, as evidenced by BDI (II) scores were significantly higher in the ICD groups compared to controls, and greatest in the comorbid ICD group. Scores for BSS were also higher for patients with ICDs, particularly the comorbid cases, but the overall group effect failed to reach statistical significance (p=0.097, table 5).

Table 5. Clinical and psychological data for PD patients with comorbid ICDs, single ICD and PD control group.

	Comorbid ICD group	**Single ICD group**	**Non-ICD controls**	[a]***p***
Frequency	10	7	9	
Age (yrs)	58.10 (2.78)	62.29 (3.88)	60.22 (3.18)	0.668
Age at PD onset (yrs)	43.80 (3.42)	51.71 (3.97)	50.33 (3.37)	0.254
Disease duration (yrs)	14.33 (11.19)	10.57 (1.99)	9.89 (2.06)	0.478
UPDRS (III) 'off' medication	41.00 (3.46)	42.14 (3.84)	32.78 (3.00)	0.133
LEU DA (mg/day)	244.00 (55.44)	244.29 (51.36)	165.56 (48.85)	0.485
L-dopa (mg/day)	268.53 (84.92)	538.00 (83.36)	666.33 (128.96)	0.483
Total LEDD (mg/day)	724.00 (98.99)	782.29 (83.45)	831.89 (119.16)	0.751
BDI (II)	19.30 (2.35)[bc]	12.29 (2.60)[§c]	10.44 (1.70)[§b]	0.018** [§]0.583 [b]0.007** [c]0.040**

BSS	5.00 (0.91)	6.14 (1.10)		0.097
MMSE	29.6 (0.7)	29.3 (1.0)		[±]0.890
AUDIT	2.12 (0.50)	1.44 (2.22)		0.268
FTND	0	0		1.000

All values are given as mean (SEM). [a]Omnibus comparisons made with one-way ANOVA, where statistical significance is considered as alpha<0.05. Abbreviations: LEU DA = Levodopa Equivalent Units of Dopamine Agonists; LEDD = L-Dopa Equivalent Daily Dose; BSS = Brief Sensation seeking scale; MMSE = Mini Mental State Examination; BDI(II) = Beck Depression Inventory, version II; AUDIT = alcohol use disorder identification test; FTND = The Fagerstrom test for nicotine dependence. ** Statistically significant. [±]Kruskal-Wallis test. [§]Post-hoc comparison (Fisher's Least Significant Difference t-test) between controls and single ICD groups. [b]Post-hoc comparison between controls and >1 ICD group. [c]Post-hoc comparison between single and >1ICD group.

3.4.2.2 PET data

The RAC BP_{ND} raw values for the scan with neutral cues were similar for all three groups of patients for each striatal region (Figures 13 a, b and c).

By contrast, the percentage reduction in ventral striatal (but not caudate or putamen) regional RAC BP_{ND} during reward vs. neutral scans were significantly different between groups, and was significantly larger in both of the ICD groups compared to control patients, indicating a significantly elevated endogenous ventral striatal dopamine release in response to reward-related visual cues in both ICD groups relative to controls (figures 13d, e, and f). The levels of reward-related ventral striatal dopamine release were, however, comparable in both the single and comorbid ICD cases. (Table 6).

Figure 14. Scatterplot of regional RAC BP_{ND} during the scan showing neutral cues.

Figure 13a. Caudate (PD controls: 1.542±0.243; single ICD: 1.684±0.417; >1 ICD: 1.860±0.354; p=0.134). Figure 13b. Putamen (PD controls: 11.998±0.242; single ICD: 2.087±0.413; >1 ICD: 2.335±0.436; p=0.0854). Figure 13c. Ventral striatum (PD controls: 1.502±0.300; single ICD: 1.606±0.314; >1 ICD: 1.779±0.331; p=0.164).
Figures 13d-f. Percentage reduction in regional RAC BPND comparing scan with reward cues to scan with neutral cues (please see Table 6 for values). Fig 13d. Caudate. Figure 13e. Putamen. Figure 13f. Ventral Striatum. ** Denotes statistical significance.

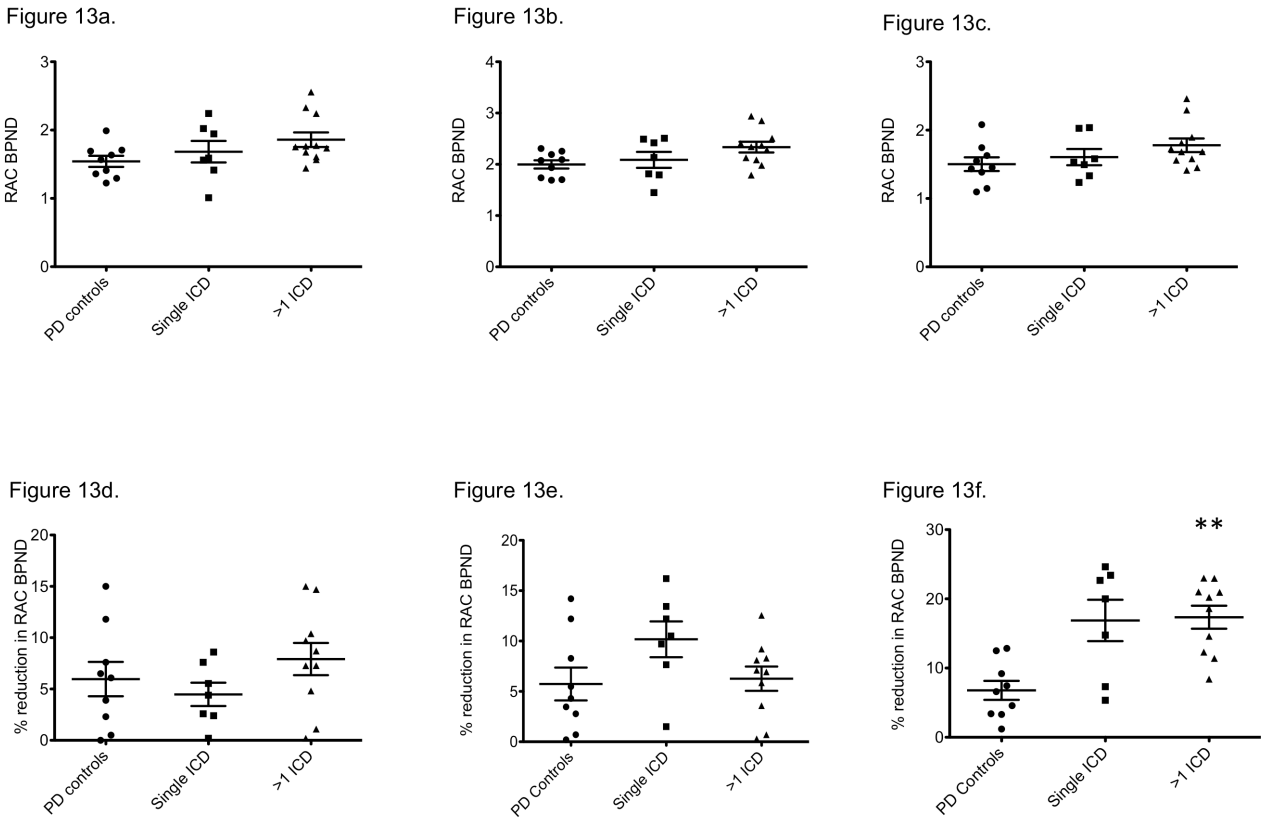


Table 6. Percentage reduction in regional RAC BP_{ND} values comparing reward scan to neutral scan in comorbid ICDs, single ICD and PD control groups

Regions-of-interest	Comorbid ICD group (n=10)	Single ICD group (n=7)	Non-ICD controls (n=9)	F (2, 23)	*p* value
Caudate	7.88 (2.74)[bc]	4.03 (4.85)[ac]	5.96 (3.37)[ab]	0.285	0.754 [a]0.716 [b]0.692 [c]0.460
Putamen	5.97 (2.86) [bc]	10.47 (4.75) [ac]	5.77 (2.44) [ab]	0.590	0.563 [a]0.340 [b]0.965 [c]0.350
Ventral Striatum	17.51 (2.77)[bc]	17.19 (6.82)[ac]	6.74 (2.15)[ab]	3.306	0.050** [a]0.051 [b]0.028** [c]0.920

Omnibus comparisons made with one-way ANOVA. Values given are % change (SEM) in BP_{ND} values comparing scan with reward cues to scan with neutral cues. [a]Post-hoc comparison (Least Significant Difference) between controls and single ICD groups. [b]Post-hoc comparison between controls and >1 ICD group. [c]Post-hoc comparison between single and >1ICD group. ** denotes statistical significance.

3.4.2.3 Subjective cue reactivity

Subjective cue-reactivity (as measured by pre-post scan change in PA and NA on the PANAS) did not differ between groups in the neutral condition (data available on request). In contrast, in the reward cue condition, there was significant change in PA, but not NA between groups (Table 7), with both ICD groups showing relative increases in PA compared to controls (who reported a decrease in PA over time). The two ICD groups showed comparable increase in PA.

Table 7. Subjective cue-reactivity (PANAS) scores for comorbid ICDs, single ICD and PD control groups.

		Comorbid ICD group (n=10)	**Single ICD group (n=7)**	**Non ICD control group (n=10)**	**F value (2, 23)**	***p* =**
Reward cues scan:	Percentage change in PA (post-pre)	15.47 (5.37)[bc]	18.91 (5.00)[ac]	-27.20 (13.87)[ab]	6.746	0.005** [a]0.005 [b]0.004 [c]0.813
	Percentage change in NA (post-pre)	-38.69 (13.86)	-14.30 (0.78)	-41.84 (15.65)		0.361

Values given are % change (SEM). All comparisons made with one-way ANOVA, followed by post-hoc testing with Fisher's Least Significance t-test where appropriate. ** denotes statistical significance, where alpha level is set at $p<0.05$. a = Comorbid ICD group vs controls; b = Single ICD group vs controls; c = Comorbid ICD group vs single ICD group. PA = positive affect (e.g. 'alert'); NA = negative affect (e.g. 'nervous').

3.4.2.4 Relationship between ventral striatal dopamine release and behavioural data

I did not find any significant correlations between changes in ventral striatal dopamine neurotransmission during reward vs. neutral cue scans and trait sensation seeking, depression severity or subjective cue-reactivity (PA) in the ICD or control groups (all $p>0.05$).

3.5 Summary of findings

In this PET study, I investigated dopamine neurotransmission in PD patients with a range of ICDs (PD ICD group) and PD controls. I exposed subjects to a range of visual cues during two ^{11}C-RAC PET scans, where during one scan I showed them reward-related passive visual cues; and during the other I showed them neutral visual cues. On the whole, I observed a greater reduction in RAC BP_{ND} in the ventral striatum of subjects with ICDs compared to controls following exposure to reward-related visual cues. These changes indicate an increase in dopamine release in the PD ICD group in response to viewing of reward-related cues.

I then performed a secondary analysis where I divided the PD ICD group into those with comorbid ICDs and those with a single 'pure' ICD and compared their dopamine release to the PD control group. I found that both comorbid and single ICD groups showed greater dopamine release in the ventral striatum to heterogenous reward-related images compared to the control group, but dopamine release was comparable between those with comorbid and those with a single ICD.

This study explored the range of chosen activities pursued for each impulse control disorder. Nine out of ten patients with compulsive sexual behaviour have admitted to watching pornography, whilst four reportedly pestered their partner or friend for sex. Patients with binge eating have a predilection for sugary foods such as chocolate, sweets and ice cream, and foods rich in carbohydrates (cakes and biscuits), which invariably led to marked weight gain. Those with pathological gambling preferred slot machines, horse and sports betting and bingo. Three of seven patients pursued their gambling in betting shops, two used online gambling sites, whilst one patient used both mediums to gamble and one did not disclose location. Females with compulsive buying prefer to buy fashion items such as clothes, bags and shoes, whilst males tend to go for electronic items as well as clothing. The precise motivational mechanisms underpinning the various behavioural symptoms manifested in ICDs are important topics for future investigation. It was notable that binge eating and compulsive shopping, unlike pathological gambling and compulsive sexual behaviour, never occurred in isolation.

Subjects with ICDs had higher levels of depression (a finding that extended itself when the group was dissected into those with comorbid ICDs and single ICD). Those with comorbid ICDs also had marginally increased sensation seeking scores compared to subjects with a single ICD and control group, despite having similar disease duration and motor disability.

Chapter 4

PET imaging of punding behaviour in Parkinson's disease patients

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4.1 Introduction

In this chapter, I investigate resting baseline dopamine level in PD patients with punding behaviour (PD punders) compared to PD control patients. I also explore whether PD punders display characteristic traits similar to that observed in subjects with OCD.

4.2 Aims and hypotheses

The aims of this study are:

1. To invesetigate baseline resting dopamine state in PD patients with and without punding behaviour.

2. To compare clinico-behavioural characteristics in these two patient groups, including obsessive compulsive traits using the Padua Inventory for obsessive compulsive traits.

I hypothesise that Parkinson's disease patients with punding will have lower D2/3 binding in the dorsal striatum compare to controls, similar to that found in non-PD OCD subjects, and that they will also demonstrate a higher level of obsessive-compulsive characteristics as measured using the Padua Inventory.

4.3 Methods

4.3.1 Participants

Thirteen PD patients with punding behaviours and 15 participants with PD who were free from symptoms of punding, ICD or DDS were studied. All patients satisfied the Queen Square Brain Bank for Neurological Disorders clinical criteria for Parkinson's disease (Hughes et al., 1992).

4.3.2 Evaluation of clinical and behavioural characteristics

All participants were assessed as detailed in Chapter 2, section 2.1. In addition, they were also asked to complete *PADUA Inventory – Washington State University Revision (PI-WSUR):* a self-reporting measure to assess symptoms of OCD (Burns, 1996). It consists of five subscales: contamination obsessions and washing compulsion, dressing / grooming compulsions, checking compulsions, obsessional thoughts of harm and obsessional impulses to harm. Punding is thought to share similarities with OCD as the repetitive and complex behaviours in punding may be considered a form of compulsion.

4.3.3 PET scanning procedures

All participants for this study underwent one ^{11}C-RAC scan in an OFF medication state on a weekday morning as per protocol detailed in section 2.2.7.

4.3.4 Positron Emission Tomography data analysis

Please refer to section 2.2.9 (Region of Interest analysis) for PET data analysis.

4.3.5 Statistical analysis

Statistical analysis was carried out as detailed in Chpater 2, section 2.11. Group comparisons for differences in ^{11}C-RAC BP_{ND} in the striatal regions (caudate, putamen and ventral striatum) between the two different patient groups were tested with independent t test. The alpha level was set at $p<0.05$.

4.4 Results

4.4.1 Demographics and clinical behaviour

Punders and control subjects were matched for age, disease duration and disease severity (Table 8). Total daily Levodopa equivalent units and amount of dopamine agonist were similar in both groups (punders: 727.54 ± 421.58; controls: 686.57± 283.97; p=0.840). Seven patients from each group were on dopamine agonists: ropinirole (punders n=3; controls n= 2), ropinirole XL (punders n=1; controls n= 2), pramipexole (punders n=3; controls n=1); rotigotine (punders n=1; controls n= 2). Regarding rescue medications, one punder and one control participant were prescribed fast-acting dispersible levodopa, whilst another punder was prescribed apomorphine bolus injections. Punders scored marginally higher on the Beck Depression Inventory (II) and the Padua Inventory although differences between the two groups were not significant on either of these measures [BDI(II): PD punders 15.16 (8.17); PD controls 12.77 (6.00); p=0.41, Padua Inventory total score: PD punders 12.69 (16.56); PD controls 12.77 (6.00); p=0.27]. However, I observed a

significantly higher score for the dressing/grooming subscale in the PD punders compared to controls [PD punders 2.62 (2.69); PD controls 0.73 (1.67); p=0.042].

Table 8.Clinical and behavioural characteristics of PD punders and PD control groups.

	Punders	**Controls**	**p value**
Number of participants	13	15	
Gender	11M: 2F	10M:5F	
Age in years	61.15 (10.72)	66.55 (7.29)	0.23
Disease duration	10.04 (4.01)	8.68 (4.80)	0.43
H&Y score	2.66 (0.88)	2.39 (0.65)	0.39
UPDRS III (OFF medication)	41.17 (14.38)	39.29 (9.98)	0.71
Dyskinesias	7	4	0.25[§]
Total LEDD in mg/d	727.54 (421.58)	686.57 (283.97)	0.84
Dopamine agonist (LEDD) in mg/d	160.67 (161.15)	170.00 (175.89)	0.89
No. on dopamine agonist	7	7	0.70[§]
BDI (II)	15.16 (8.17)	12.77 (6.00)	0.41
Padua Inventory	12.69 (16.56)	7.06 (6.12)	0.27
Contamination obsession and washing compulsions subscale	5.38 (7.70)	3.06 (3.59)	0.33
Dressing / grooming compulsions subscale	2.62 (2.69)	0.73 (1.67)	0.042 **
Checking compulsions subscale	2.85 (4.91)	2.26 (2.58)	0.71
Obsessional thoughts of harm to self/others subscale	1.46 (2.99)	0.73 (1.10)	0.42
Obsessional impulses to harm self/others subscale	0.38 (1.39)	0.20 (0.56)	0.66

Abbreviations: H&Y: Hohn & Yhar; UPDRS: United Parkinson's Disease Rating Scale; LEDD: Levodopa Equivalent Daily Dose; BDI: Beck's Depression Inventory. [§] Chi-square test. **denotes statistical significance, two tailed student t test.

The stereotyped behaviours reported are detailed in Table 9. Behaviours were often influenced by their previous occupation, whilst others were related to their hobbies. Three patients satisfied criteria for dopamine dysregulation syndrome. Other concomitant impulse control disorders reported were CSB (n=8), PG (n=2), CB (n=5), and BE (n=2).

Table 9. Punding behaviours of PD participants diagnosed with punding.

Age (yrs), gender	**Previous occupation**	**Punding behaviour**	**Concomittant ICD, DDS**
66M	Academic	Intense writing of monologues with no real content	CSB
54M	Builder	Sorting tools, dismantling computers and reassembling without success	CSB, PG
41M	Banker	Obsession with sorting and organising media collection (CDs/DVDs)	DDS, CSB
63M	Banker	Walking with no intended goal, often at night and for several hours at a time, despite medication wearing off and freezing	DDS
69M	Labourer	Repetitively sorting and resorting household objects	PG, CB
72M	Self-employed Businessman	Sorting and re-sorting receipts, papers.	CSB
56F	Housewife	Jewellery making but disassembling and reassembling >5 hours/day, pointless driving, arranging kitchen cupboards	CB

69F	Housewife	Sorting and rearranging items in kitchen cupboard, household objects	BE, CB
47M	Engineer	Dismantling and reassembling electrical items, old computers, laptops	CSB, BE
62M	Engineer	Dismantling and reassembling machinery	CB
78M	Self-employed businessman	Repetitive actions of sorting, examining, arranging and resorting objects, obsession with sorting meds into dosset boxes	CSB, DDS
66M	Self-employed businessman	Writing blogs with no specific content, repetitively sorting emails and files on computer	CSB
51M	Academic	Repetitive editing of video clips, labelling media files	CSB, CB

Abbreviations: ICD: Impulse Control Disorder; DDS: Dopamine Dysregulation Syndrome; CSB: compulsive sexual behaviour; PG: pathological gambling; CB: compulsive buying; BE: binge eating.

4.4.2 PET with ^{11}C-RAC (punders vs controls)

Compared to controls, punders had lower RAC BP_{ND} levels in caudate (punders: 1.718 ± 0.2033; controls: 2.067 ± 0.2661; p=0.0006) (Figure 14a), indicating higher resting endogenous dopamine level in this group. RAC BP_{ND} values for putamen were also lower in punder compared to control but this was not statistically significant (punders: 2.548 ± 0.3763; controls: 2.824 ± 0.3765; p=0.0641). RAC BP_{ND} values in the ventral striatum were similar between the two groups (punders: 1.342 ± 0.248; controls: 1.348 ± 0.268; p=0.9499) (Figures 14b and c).

4.4.3 Correlations

I did not find any significant correlation between caudate RAC BP_{ND} and depression score (p=0.6320), nor to the Padua Inventory (p=0.475) or its subscales.

Figure 15. Scatterplots showing RAC BP_{ND} values (y-axis) for the three striatal regions for PD punders and PD control groups

Figure 14a. Caudate

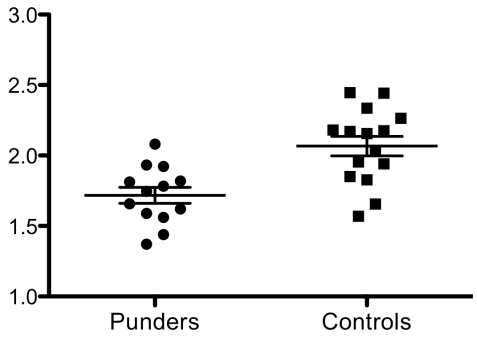


Figure 14b. Putamen

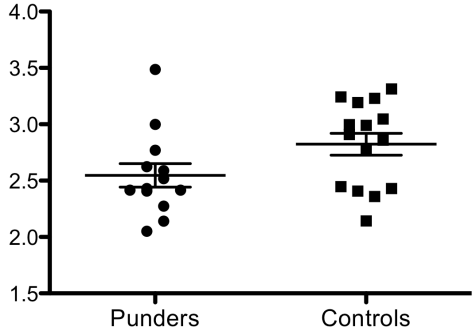
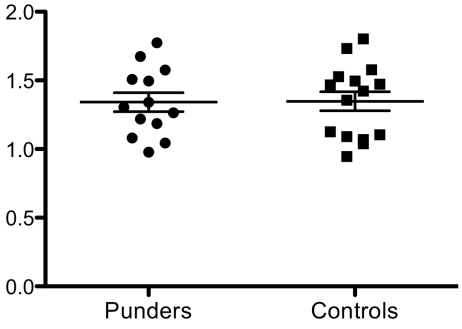


Figure 14c. Ventral striatum



4.5 Summary of findings

I studied dopamine D2 binding in PD participants with punding and compared them to PD control participants using positron emission tomography with ^{11}C-RAC. I observed lower values of RAC BP_{ND}) in the caudate of punders compared to controls when participants were scanned under resting condition in an OFF medication state.

In looking at the clinical aspects between the punding and control groups, I did not find any discernable pattern to the dopamine receptor stimulation profile of the medications used by the punders compared with the nonpunders. More punders reported dyskinesias (n=7) than controls (n=4) but the difference was not statistically significant. Punders scored higher in the Padua inventory but the scores remain within the non-OCD range and did not differ significantly from PD controls, suggesting that punding behaviour does not have the characteristics, nor is it driven by the anxiety of obsessions.

I also observed a higher percentage (100%) of comorbid ICDs in the punding group than previously reported (59%) (Fasano & Petrovic, 2010). Similar to other reports of punding, I did not find any difference in depression scores between punders and controls (Fasano et al), suggesting that punding does not correlate with mood or anxiety disorders.

Chapter 5

Neural response to visual sexual cues in Parkinson's disease patients with compulsive sexual behaviour: A study using fMRI

5.1 Introduction

Very little is known about the underlying neurobiology of CSB, or how visual sexual stimuli, similar to the portrayals of sexuality in the mainstream mass media, may affect the brain and behaviour in such vulnerable individuals. In this study, I employ fMRI to investigate the neural response of PD patients with and without CSB on exposure of sexual-related stimuli.

5.2. Aims and hypotheses

The aims of this study are:

1. to investigate blood-oxygen-level depdendence (BOLD) signal alterations in PD subjects with CSB (PD-CSB) and PD controls in response to passive sexual-related vs neutral visual cues.

2. to correlate the above imaging results with behavioural assessments of sexual motivation.

I hypothesise that PD patients with CSB would show aberrant sexual cue-related activity in regions linked to sexual motivation, which would be modulated by dopaminergic medication, and linked to enhanced sexual motivation.

5.3 Methods

5.3.1 Participants

Twenty-four non-demented patients with idiopathic Parkinson's disease were studied. Twelve of these patients fulfilled the proposed operational diagnostic criteria for CSB (Voon et al., 2006). The other 12 patients had no history of CSB or other ICDs and served as a control group.

5.3.2 Clinical and behavioural assessments

All patients attended a semi-structured interview with the author (KW) to complete an assessment battery as detailed in Chapter 2, section 2.1.

5.3.3 fMRI scanning procedures

Participants were scanned on two separate mornings (between 11:00 and 13:00) seven days apart in a cross-over randomised design after skipping breakfast and stopping medication at least 12 hours prior to scanning.

5.3.3.1 Medication (Levodopa) challenge

Participants were scanned in the practically defined OFF medication condition in one scan and in ON medication condition after receiving an oral dose of levodopa (Madopar dispersible 50/200) 45 minutes prior to the scan starting (see section 3.3.3.1 for biochemistry of levodopa). The use of L-Dopa was chosen because all Parkinson's disease patients were previously taking this, whereas not all were on the same dopamine agonist. Moreover, L-Dopa can increase sexual motivation in PD, and CSB has been observed in combination with concurrent L-Dopa treatment, not just dopamine agonist treatment (Ballivet et al., 1973; Hassan et al., 2011).

5.3.3.2 Assessments before and after each fMRI scan

Motor performance was assessed with the UPDRS motor scores at baseline and immediately before scanning to ensure patient has responded to the medication (defined as > 25% improvements in UPDRS-III motor scores).

Before and after scanning, participants were asked to rate their libido and sexual desire on a visual analogue scale (10 cm), anchored between 'the lowest ever' (0 cm = 0 points) and 'the most ever' (10 cm = 10 points). Both scales were self-reported and related to how the participants felt within the past hour only. Single-item desire scales have been shown to be as reliable as longer multi-item questionnaires (West & Ussher, 2010). Since most of the Parkinson's disease patients with CSB had additional ICDs, similar self-reported desire scales for gambling, drugs and food were also administered.

5.3.3.3 Scanning procedures

Participants were placed in the scanner with headphones and padding round the head, the shoulders and arms to ensure as little area for movement as possible. Movements were monitored throughout the scans and, in case of excessive movements, the scan was either restarted or the relevant volumes were removed from the analysis (5.2% of runs were restarted due to tremor or dyskinesias). Imaging acquisition was conducted on a 3T Philips Intera whole-body scanner. Whole-brain data were acquired with 199 volumes of T2*-weighted gradient-echo-planar imaging in ascending order with an automated higher-order shim procedure [slice thickness 3.25mm; repetition time (TR) 3000ms; echo (TE) 30ms; 90° flip angle; field of view (FOV) 190 x 219; matrix 112 x 112]. The slice acquisition angle was set at -30° from the anterior-posterior (AC-PC) line to reduce frontal lobe signal dropout due to the air sinuses, with a z-shim gradient correction to compensate for through-plane susceptibility gradients (Deichmann, Gottfried, Hutton, & Turner, 2003; Goldstone et al., 2009). One high-resolution T1-weighted turbo field echo structural scan was also collected (TE 4.6ms; TR 9.7ms, 8° flip angle; FOV 240 mm).

5.3.4 fMRI paradigm

During the fMRI scan, five types of colour images were presented in a block design: (i) dopaminergic drugs cues, (ii) appetising food cues, (iii) money and gambling cues, (iv) sexual cues and (v) neutral cues. The vast majority of reward-related and neutral visual cues were obtained from the International Affective Picture System (IAPS) (Lang et al., 2008) and were supplemented by freely available images obtained from websites. A visual sexual cue was defined as including depictions of intimate touching, passionate kissing, physical flirting, and provocative images of women or men (gender based: men saw women and women saw men) with their bodies partly

clothed. Neutral visual cues included landscapes and nature scenes, household objects, and random patterns. The IAPS sexual visual stimuli has been previously validated and have been shown to induce significant levels of sexual arousal in previous fMRI / psychophysiological studies (Bradley, Codispoti, Sabatinelli, & Lang, 2001; Walter et al., 2008).

Images of similar resolution were presented in 14.7s blocks in two runs lasting 9 min 56s each. Each block contained seven different images from the same category, with a total of six blocks of each type shown in a pseudorandom block order with a randomised image order in each block. Run order was counterbalanced across participants and visits. Each image was displayed for 2,100 ms and each thematic block was followed by a 4,000 ms rating slide whereby the participant had to rate from one to five how much they liked the block of images they saw (with one being 'I hated it' and five being 'I loved it'). These ratings were made by voice and they were recorded in a computer. The rating slide was followed by a 1,000 ms inter-stimulus interval of a fixation cross. Images were viewed via a mirror mounted above an eight-channel RF head coil, which displayed images from a projector using the IFIS-SA image presentation system (In Vivo, Wurzburg, Germany) and E-Prime software (Psychology Software Tools Inc., Pittsburgh, PA, USA).

5.3.5 fMRI data analysis

Imaging data were analysed using Statistical Parametric Mapping version 5 (SPM5, Wellcome Department of Imaging Neuroscience, UCL, UK). The first five volumes of each fMRI run were discarded to allow for equilibrium effects, and all functional scans were realigned to the first scan of the run and then again to the mean of all of

the volumes for motion and slice-timing correction. All scans included in the final analysis consisted of less than 2 mm of movement in each direction. I explored the data for residual artifacts using the TSDiffAna utility implemented in SPM5, which produces mean and variance images for each functional volume (http://imaging.mrc-cbu.cam.ac.uk/imaging/DataDiagnostics). An artifact is defined as the co-occurrence of a variance spike and a mean intensity drop uncorrelated with experimental design. I did not detect any artifacts that needed more detailed inspection. The mean functional image was co-registered to the T1 structural image. The echo-planar images were then normalised into Montreal Neurological Institute (MNI) standard stereotactic space using parameters from the segmented T1 structural image and smoothed using an 8 mm full-width at half-maximum (FWHM) Gaussian filter.

5.3.5.1 First-level analysis

First-level analysis was performed at the single participant level where individual contrasts were created in a general linear model for each reward condition minus baseline (neutral pictures) and for sex minus other rewards (sex vs. other rewards). The general linear model included six motion and nuisance parameters, accounting for movement and other nuisance artifacts occurring in three directions of translation (displacement) and three axes of rotation (x, y, z translation and x, y, z rotation) for each run. Contrasts of interest produced as this stage (e.g. sex vs. neutral) were used in the second-level, group random effects analysis. A statistical threshold of $p < 0.001$ uncorrected and cluster extent over 10 voxels (2 x 2 x 2 mm) was used for activation using whole-brain analysis with correction for multiple comparisons using the false discovery rate (FDR) at $p < 0.05$ (Genovese et al., 2002). Coordinates of peak voxel activation within the brain were determined at the group level for ON and OFF scans

in Parkinson's disease patients with and without CSB. I also performed an additional between-group (Parkinson's disease controls vs. Parkinson's disease CSB) and between-condition (OFF vs. ON medication) analysis in order to investigate whether motion parameters were larger in one patient group or condition group than the other and found that movement did not vary between groups and conditions ($p > 0.1$ in both cases).

5.3.5.2 Second-level analysis

Since a regional a priori hypothesis existed, additional second-level random effects analyses (sex vs. neutral and sex vs. other rewards contrasts in ON and OFF medication conditions) were carried out for specific regions-of-interest (ROIs) using MarsBar (Brett *et al*., 2002) using the same statistical threshold (FDR at $p < 0.05$). These regions were OFC, ACC, posterior cingulate cortex (PCC), amygdala, VS and the hypothalamus. The models of OFC, ACC, PCC and amygdala were taken from the 'Automated Anatomic Labeling' (AAL) library that accompanies MarsBar. The VS and hypothalamus object maps were constructed by drawing these ROIs in ANALYZE medical imaging software (version 8.1, Mayo Foundation). These object maps were then used to mask out the rest of the brain, allowing comparisons within specific volumes (1850 mm^3 in each hemisphere for VS and 1380 mm^3 in each hemisphere for the hypothalamus). Individual participants' contrast (e.g. sex vs. neutral) values of each ROI for both ON and OFF medication scans were extracted for correlation with the behavioural data.

5.3.6 Statistical analysis

Statistical analyses were performed as detailed in Chapter 2, section 2.2.9. Comparisons within groups (e.g. Parkinson's disease CSB OFF scan sex vs. neutral) were performed using paired *t* tests and comparisons between groups (e.g. Parkinson's disease CSB OFF sexual vs. neutral – vs. – Parkinson's disease controls sexual vs. neutral) were performed using two sample *t* tests. For the clinical and behavioural analysis, variance homogeneity and Gaussianity were tested with Bartlett and Kolmogorov-Smirnov tests. Parametric and non-parametric tests were used appropriately. Pearson correlation coefficient *r* and Spearman's rho (ρ) (when variables were not normally distributed) were used to examine the relationship between individual sexual desire scores after exposure to sexual visual cues and individual bilateral BOLD ROI contrast values for sexual vs. neutral contrast in the ON and OFF medication states. The Bonferroni correction was used to counteract the problem of multiple comparisons.

5.4 Results

5.4.1 Participants' clinical and behavioural characteristics

PD-CSB subjects were taking significantly more dopamine agonists and significantly less L-Dopa compared to controls. The two groups did not statistically differ in any of the other clinical characteristics (age, sex, disease duration, UPDRS part III OFF, ON and response after L-Dopa, MMSE, and daily LED_{TOTAL}). Eight out of 12 PD-CSB patients exhibited at least one additional ICD (Tables 10 and 11).

Table 10. Clinical characteristics of participants (in fMRI study of PD patients with CSB)

	PD CSB	PD controls	*p* value
Number of subjects	12	12	-
Age (years ± SD)	55.2 ± 9.2	62.3 ± 9.7	0.077[b]
Sex	11M/1F	10M/2F	-
Disease duration (years ± SD)	9.6 ± 5.2	10.1 ± 6.4	0.85[b]
UPDRS OFF motor (Part III) score (mean ± SD)[a]	40.2 ± 10.1	34.9 ± 9.9	0.21[b]
UPDRS ON motor (Part III) score and % improvement (mean ± SD)[a]	23.1 ± 8.2 (43.8 ± 9.7%)	20.0 ± 5.5 (41.4 ± 11.7%)	0.29 (0.59)[b]
MMSE (mean ± SD)	29.8 ± 0.4	28.9 ± 2.2	0.30[c]
Daily LED_{TOTAL} (mg ± SD)	600 ± 327	778 ± 278	0.17[b]
Daily $LED_{L\text{-}DOPA}$ (mg ± SD)	288 ± 326	646 ± 264	< 0.05[c]
Daily LED_{DA} (mg ± SD)	311 ± 183	132 ± 143	< 0.01[c]

[a] The average of five evaluations on five different days; [b] Unpaired t test; [c] Mann-Whitney test; PD CSB: Parkinson's disease patients with compulsive sexual behaviour; PD controls: Parkinson's disease patients without compulsive sexual behaviour or other impulsive-compulsive behaviours; M=male; F=female; SD=standard deviation; UPDRS=Unified Parkinson's Disease Rating Scale; LED=Levodopa Equivalent – the dose is calculated similarly to a previous report (Politis et al., 2010) LED (mg) = (1 X Levodopa) + (0.77 X Levodopa CR) + (1.43 X Levodopa + Entacapone) + (1.11 X Levodopa CR + Entacapone) + (20 X Ropinirole) + (20 X Ropinirole ER) + (100 X Pramipexole) + (30 X Rotigotine) + (10 X Bromocriptine) + (8 X Apomorphine) + (100 X Pergolide) + (67 X Cabergoline); LED formula, In Levodopa/Carbidopa or Benserazide hydrochloride: Only Levodopa is calculated; MMSE=Mini-Mental State Examination.

Table 11. Details of PD participants with compulsive sexual behaviours

Subjects	Sex	Age	Type of CSB behaviour	Other ICBs	Dopaminergic therapy	Daily LED_{DA}	Daily $LED_{L\text{-}Dopa}$
1	M	46	Pornography / Repetitively engaging in sexual fantasies and urges	CB	Cabergoline	280	0
2	M	65	Sex with people with whom he normally would not associate / Spend excessive time obsessing about sex or engaged in sexual activity	-	Pramipexole	267	0
3	M	72	Sex with people with whom he normally would not associate	-	Ropinerole, Levodopa	180	700
4	M	65	Empty affairs / Involvement with Internet pornography	-	Pramipexole	200	0
5	M	50	Patient refused to disclose	BE, CB	Ropinerole, Levodopa	180	800
6	F	55	Increased sexual activity	CB	Pramipexole	200	0
7	M	53	Pornography	-	Pramipexole, Levodopa	240	260
8	M	53	Empty affairs / Obsessive sexual thoughts	PG, BE, CB	Ropinerole	360	0
9	M	60	Patient refused to disclose	BE, CB	Ropinerole, Levodopa	300	600
10	M	41	Pornography / Frequent visits to prostitutes	DDS	Cabergoline, Levodopa	530	500
11	M	45	Video Pornography / Involvement with Internet pornography	DDS	Pramipexole, Levodopa	200	600
12	M	57	Involvement with Internet pornography	DDS, PG, BE	Ropinerole	800	0

CB=Compulsive Buying; BE=Binge Eating; PG=Pathological Gambling; DDS=Dopamine Dysregulation Syndrome

Before the OFF and the ON scans, PD-CSB and PD control patients did not differ on sexual desire scores (Table 12). After the OFF and the ON scans where participants had been exposed to sexual cues, PD–CSB patients showed a significant increase in their sexual desire compared to their rating before scan and also showed a significant increase compared to the sexual desire of the PD controls, the latter remaining relatively stable pre and post scan. PD CSB patients had higher increases in their sexual desire in the ON compared to the OFF scan (Table 12). The PD-CSB and PD control groups did not show any within or between group differences in food, gambling and drug desire before and after the ON and OFF scans.

Table 12. Sex cravings before and after exposure to common sexual visual stimuli.

OFF scan	*Before* sexual visual stimuli	*After* sexual visual stimuli	*P* value
PD controls (mean ± SE)	1.98 ± 0.59	2.25 ± 0.45	0.31[a]
PD CSB (mean ± SE)	2.67 ± 0.56	3.70 ± 0.50	< 0.01[a]
P value	0.40[b]	< 0.05[b]	
ON scan	*Before* sexual visual stimuli	*After* sexual visual stimuli	*P* value
PD controls (mean ± SE)	1.32 ± 0.28	2.12 ± 0.60	0.18[d]
PD CSB (mean ± SE)	2.01 ± 0.39	5.24 ± 0.41	< 0.001[a]
P value	0.15[c]	< 0.001[b]	

[a] Paired t test; [b] Unpaired t test; [c] Mann-Whitney test; [d] Wilcoxon matched pairs test

PD-CSB patients liked the sexual visual cues presented during the fMRI significantly more than controls (quality of data = 85.2%; 3.4 ± 1.2 vs. 2.1 ± 0.6, mean ± SD; $P < 0.05$, unpaired t test with Welch correction) but there was no difference in their ratings for reward cues related to drugs, money and gambling or food ($p > 0.1$ in all cases, unpaired t test with Welch corrections). No differences were found between ON and OFF scans.

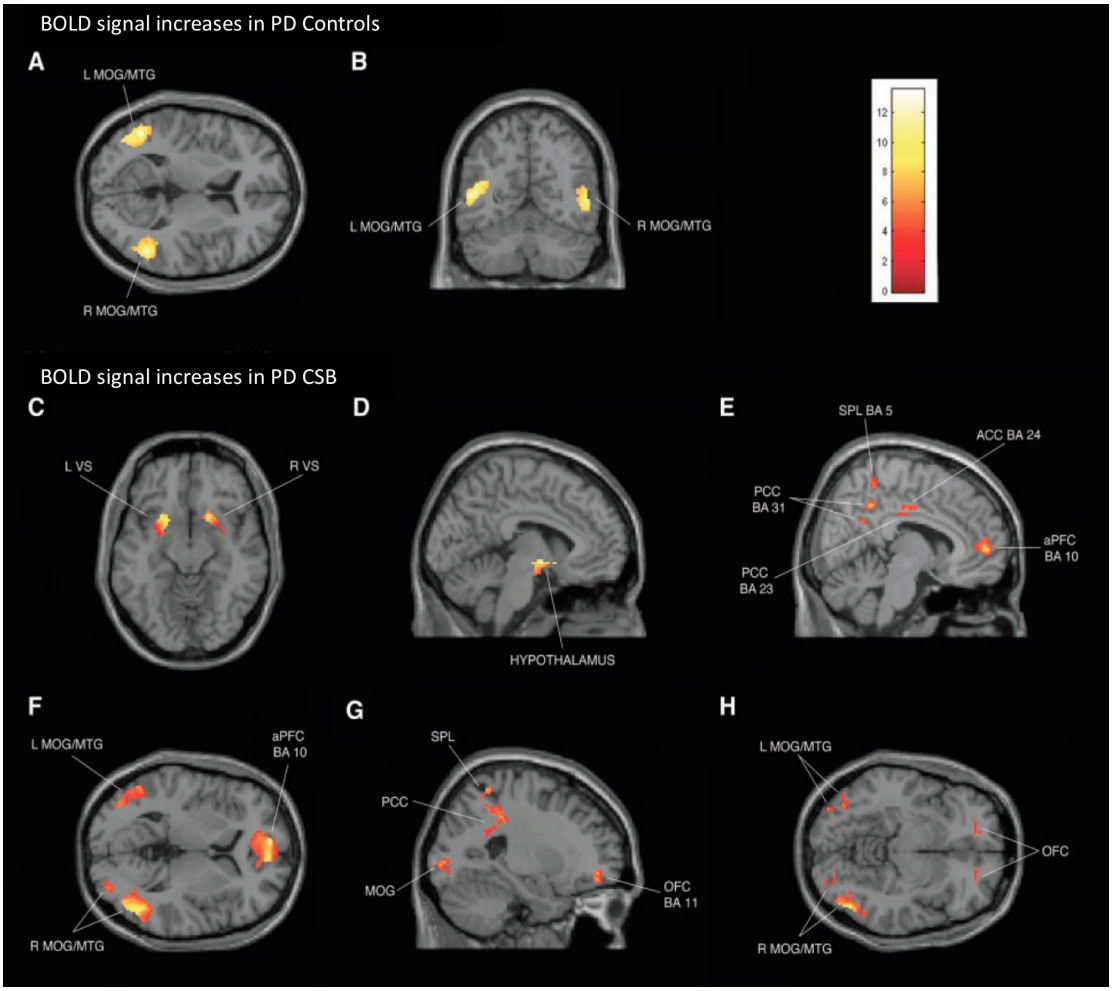
5.4.2 Region-of-interest fMRI analysis

The ROI analysis showed that the PD-CSB patients had stronger activity (increased BOLD signal) than the PD controls during exposure to sexual vs. neutral visual cues in the OFF medication states in the following regions: OFC (L: $p < 0.001$, R: $p < 0.005$), ACC (L: $p < 0.005$, R: $P < 0.001$), PCC (L: $p < 0.001$, R: $p < 0.001$), left amygdala ($p < 0.05$), VS (L: $p < 0.05$, R: $p < 0.05$), and hypothalamus (L: $p < 0.005$, R: $p < 0.01$) (Figures 15C–H). For the same contrast in the ON medication state, a similar set of regional brain activations was observed, and there were no significant differences in activations between ON and OFF scans. When I compared the effect of OFF vs. ON medication state just in the group of PD-CSB patients, I found no differences in activation.

The ROI analysis showed that the PD-CSB patients had stronger activity during exposure to sexual compared to other rewards visual cues in the OFF medication states in the following regions: OFC (L: $p < 0.001$, R: $p < 0.001$), ACC (L: $p < 0.001$, R: $p < 0.001$), PCC (L: $p < 0.001$, R: $p < 0.001$), VS (L: $p < 0.001$, R: $p < 0.001$), and hypothalamus (L: $p < 0.001$, R: $p < 0.001$). Similar activations were observed during the ON medication state, and there were no significant differences in activations between OFF and ON scans.

Figure 16. Projections of statistical parametric maps showing significant BOLD signal increases associated with exposure to common sexual visual cues (compared to neutral visual cues) in PD control participants and PD-CSB participants..

PD control patients (Figures A and B) and PD-CSB patients (Figures C–H). Sagittal (left) and axial (right) views showing activation in anterior prefrontal cortex (aPFC) (BA 10), anterior cingulate cortex (ACC) (BA 24), superior parietal lobule (SPL) (BA 5), posterior cingulate cortex (PCC) (BA 23 and 31), left and right middle temporal gyrus (MTG) and middle occipital gyrus (MOG). Bilateral activation in MTG and MOG is also present in the PD control group. The colour bar indicates T-values.



5.4.3 Whole-brain fMRI analysis

5.4.3.1 Common brain activity between Parkinson's disease compulsive sexual behaviour and Parkinson's disease controls patients

PD-CSB and PD controls showed similar significant BOLD signal increases during exposure to sexual vs. neutral visual cues in both ON and OFF medication states bilaterally in middle temporal gyrus (MTG) and middle occipital gyrus (MOG) (Figures 15A and 15B; Tables 13 and 14). For the same contrast in the OFF state, PD-CSB and PD controls showed similar significant BOLD signal decreases bilaterally in isthmus of cingulate gyrus (ICG) (BA 29 and 30), parahippocampal gyrus (PHG), and cuneus (BA 17) (Figures 16A and 16B; Tables 13 and 14).

Figure 17. Projections of statistical parametric maps showing significant BOLD signal decreases associated with exposure to common sexual visual cues compared to neutral visual cues in PD control and PD CSB participants during OFF medication state.

PD controls (Figures A and B) and PD-CSB patients (PD CSB, Figures C and D) during OFF medication state. Axial views (left and right) showing bilateral deactivation in parahippocampal gyrus (PHG), cuneus (BA 17), isthmus of cingulate gyrus (ICG) (BA 30), insula and right claustrum. Deactivation in insula and claustrum are only specific to the group of PD-CSB patients compared to controls. The colour bar indicates T-values.

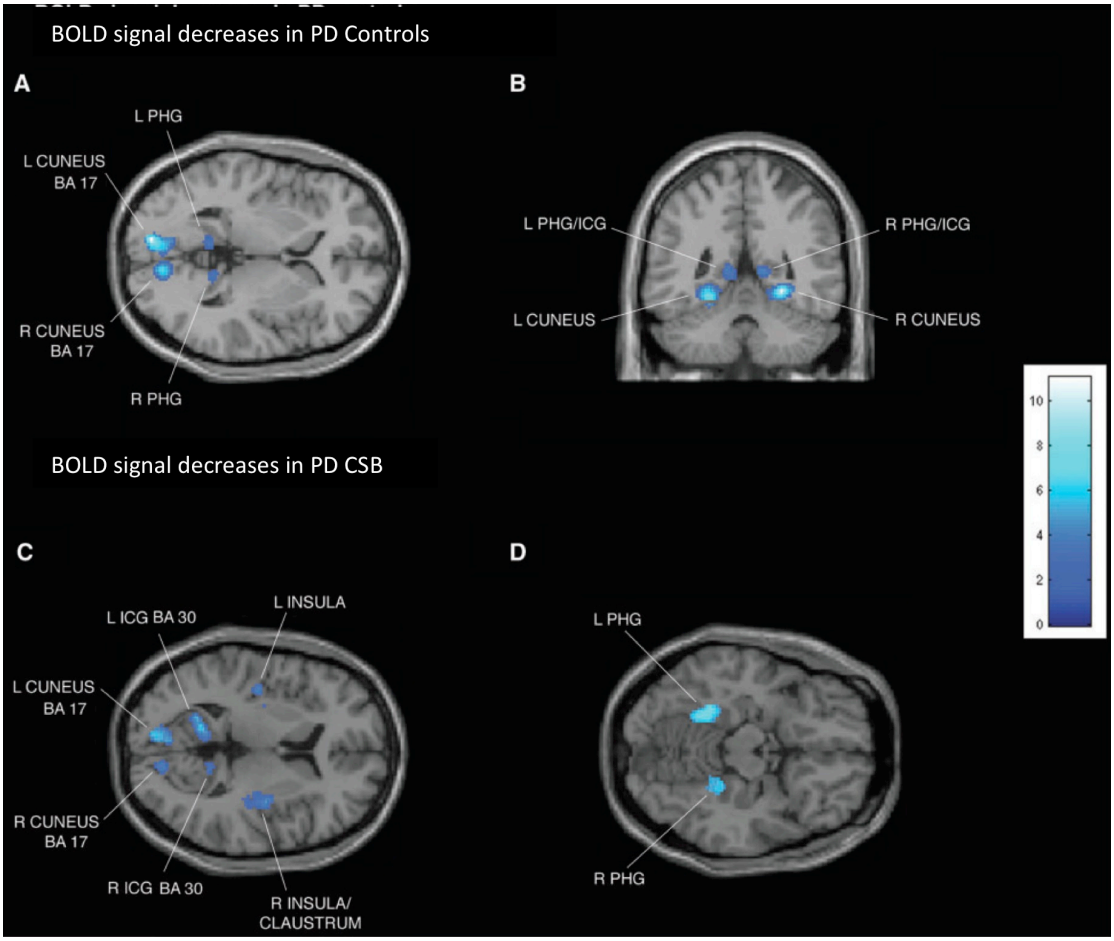


Table 13. SPM analysis: areas of significant BOLD signal increases and decreases in Parkinson's disease patients with CSB during exposure to sexual visual cues compared to neutral visual cues.

A. OFF phase – BOLD increases during sexual visual stimuli								
Anatomical region	Brodmann Area	MNI coordinates			Z-score	T-score	No of voxels	*p* value FDR corrected
		x	y	z				
Left anterior prefrontal cortex (aPFC) / medial frontal gyrus (frontal lobe)	10	-8	56	4	5.44	12.94	520	0.000
Right anterior prefrontal cortex (aPFC) / medial frontal gyrus (frontal lobe)	10	7	53	4	4.89	9.68	520	0.000
Left superior parietal lobule (parietal lobe)	7	-30	-58	54	3.51	4.92	68	0.000
Right superior parietal lobule (parietal lobe)	5	24	-46	62	4.11	6.59	441	0.000
Right inferior parietal lobule (parietal lobe)	40	62	-36	26	3.89	5.93	97	0.000
Left middle temporal gyrus (temporal lobe)	-	-54	-64	8	6.61	4.12	760	0.000
Right middle temporal gyrus (temporal lobe)	-	50	-66	8	5.52	13.52	1298	0.000
Left middle occipital gyrus (occipital lobe)	-	-40	-64	-14	6.64	4.13	760	0.000
Right middle occipital gyrus (occipital lobe)	-	48	-70	0	4.63	8.48	1298	0.000
Left ventral anterior cingulate cortex (limbic lobe)	24	-14	-18	40	3.85	5.80	99	0.000
Right ventral anterior cingulate cortex (limbic lobe)	24	6	-15	38	3.83	5.76	99	0.000
Right dorsal posterior cingulate cortex (limbic lobe)	31	8	-48	42	4.37	7.48	52	0.000
Right ventral posterior cingulate cortex (limbic lobe)	23	4	-16	33	3.04	3.93	25	0.000
Left hypothalamus (sub-lobar)	-	-8	-6	-8	3.39	4.66	11	0.001
B. OFF phase – BOLD decreases during sexual visual stimuli								
Left isthmus of cingulate gyrus (limbic lobe)	30	-17	-58	8	3.77	5.59	34	0.000
Right isthmus of cingulate gyrus (limbic lobe)	29	12	-46	6	3.24	4.34	40	0.000
Left parahippocampal gyrus (limbic lobe)	36	-27	-41	-14	4.63	8.48	213	0.000

Left parahippocampal gyrus (limbic lobe)	37	-30	-44	-14	4.63	8.48	213	0.000
Right parahippocampal gyrus (limbic lobe)	36	22	-39	-14	4.70	8.82	74	0.000
Right claustrum (sub-lobar)	-	36	-11	8	3.28	4.42	243	0.000
Left insula (sub-lobar)	13	-42	-14	8	3.10	4.04	40	0.001
Right insula	13	38	-17	14	3.05	3.94	243	0.000
Left cuneus	17	-10	-86	4	4.54	8.13	226	0.000
Right cuneus	17	11	-80	8	3.88	5.88	857	0.000
C. Differences between ON and OFF phase increases								
No significant differences								
D. Differences between ON and OFF phase decreases								
In ON phase no significant decreases in any region								

Table 14. SPM analysis: areas of significant BOLD signal increases and decreaes in PD controls during exposure to reward visual cues compared to neutral visual cues.

A. OFF phase – BOLD increases during sexual visual stimuli								
Anatomical region	Brodmann Area	MNI coordinates			Z-score	T-score	No of voxels	*p*-value FDR corrected
		x	y	z				
Left middle temporal gyrus (temporal lobe)	-	-48	-60	10	4.48	7.87	435	0.000
Right middle temporal gyrus (temporal lobe)	-	52	-58	2	5.00	10.27	624	0.000
Left middle occipital gyrus (occipital lobe)	-	-46	-70	12	5.40	12.63	435	0.000
Right middle occipital gyrus (occipital lobe)	-	46	-72	0	5.15	11.07	624	0.000
B. OFF phase – BOLD decreases during sexual visual stimuli								
Left isthmus of cingulate gyrus (limbic lobe)	29	-6	-50	6	4.57	8.24	393	0.000
Right isthmus of cingulate gyrus (limbic lobe)	30	14	-50	12	5.15	11.08	162	0.000
Left parahippocampal gyrus (limbic lobe)	37	-26	-42	-8	4.57	8.24	136	0.000
Right parahippocampal gyrus (limbic lobe)	30	12	-47	-0	3.29	4.43	446	0.000
Left cuneus (occipital lobe)	17	-6	-86	2	4.15	6.71	83	0.000
Right cuneus (occipital lobe)	17	10	-78	4	5.00	10.28	136	0.000
C. Differences between ON and OFF phase increases								
No significant differences								
D. Differences between ON and OFF phase decreases								
In ON phase no significant decreases in any region								

5.4.3.2 Brain activity specific to Parkinson's disease compulsive sexual behaviour patients

Whole-brain analysis confirmed the ROI results and showed additional significant BOLD signal increases in the group of PD-CSB compared to PD controls during exposure to sexual vs. neutral visual cues in the OFF and ON medication states in the following regions: bilateral anterior PFC (aPFC) (BA 10) and superior parietal lobule (SPL) (BA 5 and 7), and right lateralised activation in the inferior parietal lobule (IPL) (BA 40) (Figures 15C–H; Tables 13, 14). For the same contrast in the OFF state, PD-CSB compared to PD controls showed significant BOLD signal decreases bilaterally in insula and right claustrum (Figures 16C and 16D; Tables 13 and 14). There were no different BOLD signal increases during exposure to sexual vs. neutral visual cues in PD-CSB patients between the OFF and ON medication states.

Whole-brain analysis also confirmed the ROI results in PD-CSB patients when compared sexual vs. other rewards visual cues and showed additional significant BOLD signal increases in the OFF and ON medication states in bilateral dorsolateral PFC (BA 9) and right lateralised activation in aPFC (BA 10) and PHG.

5.4.4 Effect of L-Dopa medication in brain activity in Parkinson's disease compulsive sexual behaviour patients

In the group of PD-CSB patients in ON medication state, the decreases observed in the OFF state and in the OFF and ON states in PD controls (reduced BOLD signal during exposure to sexual vs. neutral visual cues in ICG, PHG, cuneus, insula and claustrum) were eliminated (Tables 13 and 14).

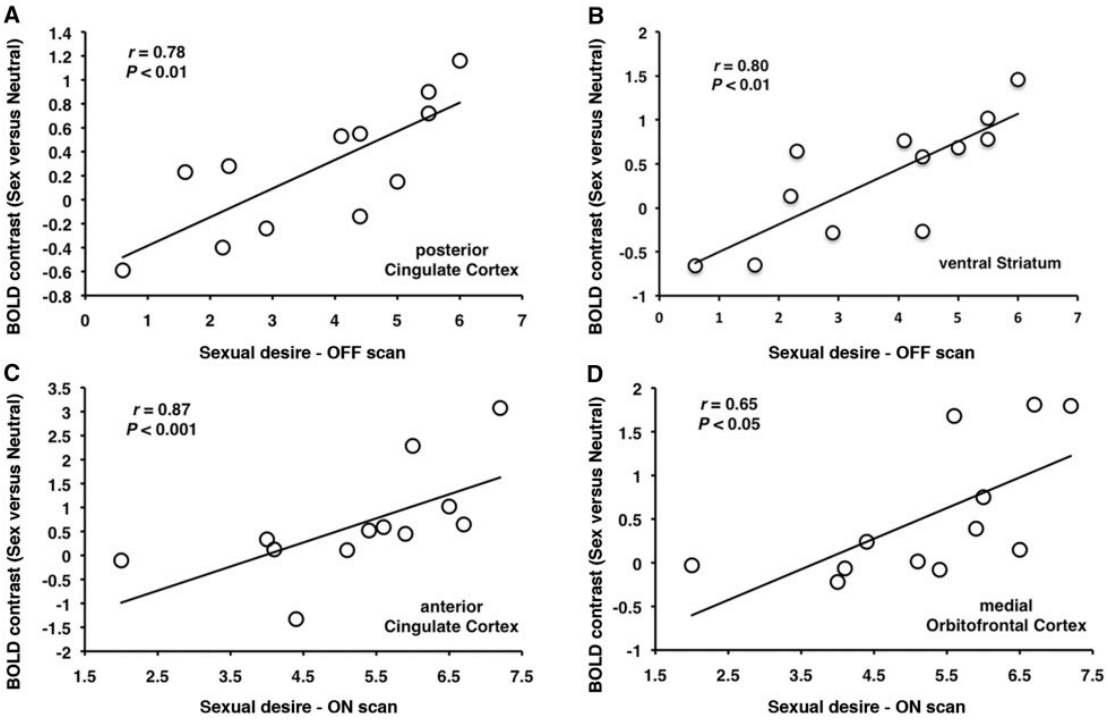
5.4.5 Brain activity related to other reward visual cues in Parkinson's disease compulsive sexual behaviour patients

I found no significant differences within or between PD-CSB and PD controls in any other reward condition minus baseline (neutral pictures) (e.g. dopaminergic drugs vs. neutral) in either ON or OFF scans.

5.4.6 Correlations

In the group of PD-CSB patients, sexual desire post-exposure to sexual visual cues correlated in OFF medication state with the activity contrast (sex vs. neutral) in PCC ($r = 0.78$, $p < 0.01$) and VS ($r = 0.80$, $p < 0.01$) (Figures 17A and 16B), and in ON medication state with the activity in ACC ($r = 0.87$, $p < 0.001$) and medial OFC ($r = 0.65$, $p < 0.05$) (Figures 17C and 17D). No correlations were found in the PD-CSB group between 'liking' the sexual cues and brain activity during exposure to sexual vs. neutral visual cues in both ON and OFF medication states. No correlations were found between desire scores and activity contrasts in the PD control group in both ON and OFF medication states ($p > 0.1$ in all cases).

Figure 18. In PD-CSB individuals, sex cravings post-exposure to erotic visual cues correlate with increases in PCC activation during OFF medication (A), with increases in ACC (B), medial OFC (C), and acitvation during ON medication.



5.5 Summary of findings

This study explored the mechanisms underpinning dopaminergic medication linked compulsive sexual behaviours in patients with PD. By employing behavioural assessments of sexual motivation and using an fMRI paradigm with common portrayals of sexuality (similar to those projected by mass media) as visual cues, this study confirmed that exposure to such cues was sufficient to increase the sexual desire of PD CSB patients by activating brain regions linked to sexual motivation.

In agreement with functional imaging studies of visual sexual stimulation in healthy individuals (Arnow et al., 2002; Redoute et al., 2000; Walter et al., 2008), exposure to visual sexual cues activated parieto-temporal-occipital visual processing regions such

as the MOG and MTG in the PD CSB group and PD controls. In PD-CSB patients, exposure to sexual visual cues in both ON and OFF medication conditions showed increased activation in OFC, ACC, PCC, VS, aPFC, SPL, amygdala and the hypothalamus compared to controls. PD-CSB patients showed significantly increased sexual desire and liking of the sexual content following exposure to sexual cues. Their sexual desire was increased more when they were ON L-Dopa compared to OFF medication after exposure to sexual content. The crucial role of ACC, PCC, VS and OFC in sexual motivation was highlighted by the fact that increased activation in these regions correlated with increased sexual desire.

Since the majority (8/12) of PD CSB patients had at least one additional ICD (e.g. pathological gambling, binge eating, etc.), I wanted to test whether the changes in behavioural assessments and brain activation following reward cue exposure were specific to sex or extended to other rewards. Self-reported desire and liking for gambling, drugs and food were not different within or between the groups of PD CSB and PD controls before and after the ON and OFF scans. Similarly, there were no differences between PD CSB and PD controls in neural response to other rewarding visual cues in the fMRI analysis, indicating that the imaging results were also specific to CSB. However, I also wanted to explore the specific brain activity related to sexual visual cues compared to other rewards. The findings revealed strong activation in both ON and OFF state scans in OFC, ACC, PCC, VS, aPFC, dorsolateral PFC, PHG and hypothalamus, confirming the specific importance of these regions in sexual motivation and desire, at least in the context of CSB.

The enhanced brain activity after exposure to sexual cues was not influenced by the administration of L-Dopa as suggested by the similar BOLD signal increases in ON and OFF medication scans. However, the absence of acute L-Dopa effect does not eliminate the effect of synergistic interaction of mesolimbic dopamine state and the presence of sexual cues in stimulating enhanced 'wanting' for sexual reward in the PD CSB group (Berridge, 2012; Oei, Rombouts, Soeter, van Gerven, & Both, 2012).

In the PD-CSB group of patients, after acute L-Dopa challenge, the decreases observed when OFF their drugs and in the OFF and ON states in PD controls (reduced BOLD signal during exposure to sexual vs. neutral visual cues in ICG, PHG, cuneus, insula and claustrum) were eliminated (for a similar effect of dopaminergic drug challenge in cocaine addiction, see Volkow et al, 2010).

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Chapter 6

Problematic Internet use in Parkinson's disease patients

6.1 Introduction

In this chapter, I examine patients with PD and healthy controls for excessive Internet use, and adapt the 10-item Y-BOCS (Goodman, Price, Rasmussen, Mazure, Fleischmann, et al., 1989; Shapira et al., 2003) as a tool to explore problematic levels of Internet use in PD patients with and without ICDs and healthy controls, adapting the questions for Internet use (Appendix 8).

6.2 Aims and hyptheses

The aims of this study are:

1. To explore non-essential Internet use in PD ICD patients, PD control patients and healthy volunteers to see the range of online activities these three groups engage in.
2. Using the Y-BOCS, to subjectively explore possible Internet use in these three groups of patients.

I hypothesised that the PD–ICD group will spend more time on the Internet, particularly accessing websites related to their ICDs (e.g. gambling, pornography) relative to both the PD control and healthy volunteer (HV) groups.

6.3 Methods

6.3.1 Participants

Twenty-nine patients were identified as having problematic Internet use based on their report of maladaptive behaviour that causes functional impairment according to proposed diagnostic criteria (Shapira, Goldsmith, Keck, Khosla, & McElroy, 2000; Shapira et al., 2003). These patients also satisfied the diagnostic criteria for one of the four major ICDs (CSB, PG, CB and BE) reported in PD using the following: (1) DSM-IV diagnostic criteria for pathological gambling (American_Psychiatric_Association, 2000); (2) DSM-IV proposed criteria for binge eating (American_Psychiatric_Association, 2000); (3) proposed criteria for compulsive sexual behaviour (Voon & Fox, 2007); and (4) compulsive buying (Voon & Fox, 2007). Nineteen patients with PD free from any symptoms of ICDs or other neurological and psychological comorbidities were recruited as controls. All patients with PD satisfied the Queen Square Brain Bank for Neurological Disorders clinical criteria (Hughes et al., 1992). None of the participants in this study has been diagnosed with PIU prior to the use of PD medication, and none had a diagnosis of obsessive-compulsive disorder. Twenty non-PD healthy volunteers matched for age and sex were recruited from individuals who responded to a local newspaper advert and acted as a comparison group. All participants endorsed using the Internet for 'non-essential' purposes.

6.3.2 Additional measures

All participants underwent a semi-structured face-to-face interview with the myself as detailed in Chapter 2, section 2.1.

In addition, they were asked to complete the Yale-Brown Obsessive Compulsive Scale – a 10-item questionnaire which measures obsessions and compulsive elements separately (Goodman, Price, Rasmussen, Mazure, Fleischmann, et al., 1989), adapted for Internet use (Shapira et al., 2000). The Y-BOCS is a suitable tool for our target group as it is used widely in the general population among those with OCD and/or ICD with good validity and reliability (J. E. Grant, Mancebo, et al., 2006). The questionnaire has an equal number of questions on obsessions and compulsions, without giving bias to either component. It has also been successfully adapted for use in non-PD cases with PIU (Shapira et al., 2000) as well as for use in ICDs, showing good reliability and validity for pathological gambling (J. E. Grant et al., 2003) and compulsive shopping (Black et al., 2000). Only non-essential Internet usage (non-business or non-academic use) was evaluated, based on recommendations for assessing PIU (K. S. Young, 1998). Participants were advised that 'Internet use' denotes access to the Internet via an electronic medium, including laptop and desktop computers, tablet computers, smart phones and any other media through which Internet can be accessed.

The scores for Internet-related compulsions and obsessions in the PD–ICD group were evaluated for internal consistency with a Cronbach's Alpha coefficient (Cronbach, 1951).

PD ICDs were also asked to document what types of websites they spend most time on whilst online.

6.3.3 Statistical analysis

Statistical analysis was performed as detailed in Chapter 2, section 2.2.9. Group comparisons for groups of PD–ICD, PD controls and non-PD controls were tested with one-way analysis of variance (ANOVA) with Bonferroni *post hoc* test or its non-parametric equivalent: the Kruskal-Wallis test with Dunn's *post hoc* test. The alpha level was set at $p<0.05$ and corrected in instances for which multiple comparisons were indicated.

6.4 Results

6.4.1. Participant demographics and clinical details

The PD–ICD and PD control groups were matched for medication intake. Both PD groups had similar BDI (II) scores and BSS scores, but these were significantly higher when compared to healthy volunteers. See Table 15.

Table 15. Clinical and behavioural details of participants in study investigating Internet use in Parkinson's disease.

	PD ICD	PD controls	Healthy volunteers	p value
Frequency	29 (4F: 25M)	19 (6F: 13M)	20 (3F: 17M)	-
Age (yrs)	63.25 (9.28)	62.32 (9.06)	60.25 (10.33)	0.5802[a]
Disease duration (yrs)	12.44 (8.01)	10.37 (6.26)	-	0.3637[b]
UPDRS (III) OFF medication	38.44 (11.34)	34.40 (11.13)	-	0.2825[b]
Total LEDD (mg/day)	673.20 (309.82)	768.83 (321.67)	-	0.5576[b]
L-Dopa (mg/day)	324.31 (202.94)	231.70 (84.72)	-	0.1800[b]
LEU DA (mg/day)	348.89 (307.72)	537.13 (329.28)	-	0.3702[b]
Percentage of patients on DA (%)	82	90	-	-
BDI (II)	15.48 (8.80)**	14.32 (9.76)**	6.35 (8.88)	**<0.0001**
BIS/BAS	56.89 (8.06)	55.37 (7.47)	55.80 (7.48)	0.0786[a]
BSS	6.96 (3.12)	7.211 (3.38)	10.35 (3.96)	**0.0033**

Values represent mean (standard deviation); § Kruskal-Wallis statistic; ns = non-significant; ** significant on PD ICD vs. HV and PD control vs. HV; [a] one way analysis of variance with Bonferroni correction; [b] unpaired t test with Welch's correction.

6.4.2 Distribution of ICDs and types of websites frequented

Of the 29 PD patients with ICD, 15 had a single ICD, eight had two ICDs, four had three ICDs and two patients had four ICDs. There were 19 patients with CSB, 10 patients with binge eating, 13 patients with PG and nine patients with CB. All patients with binge eating had a coexisting ICD. All patients with CSB and/or PG use the Internet for sexual-related activities and online gambling, respectively, whilst only four out of nine patients with CB admitted to carrying out shopping-related activities online – two (50%) of these patients reported the use of online auction websites. See Table 16.

Table 16. Details of Internet use behavioural for PD participants with ICDs.

Subject number	CSB	BE	PG	CB	Types of websites commonly frequented
1	+			+	Shopping portals: various
2	+	+	+	+	Gambling (various); online shopping websites of department stores for daily goods and supermarkets for food; Internet pornography
3	+		+		Internet pornography; online gambling (various)
4	+				Internet pornography
5			+		Horse betting, shares and stocks
6			+		Gambling (various)
7			+		Roulette and bingo
8	+	+	+	+	Internet pornography, gambling (various)
9	+		+		Horse and sports betting
10			+		Gambling sites (mainly black jack and roulette)
11	+	+			Online bingo, fruit machines; Internet pornography sites and chat rooms

12	+				Internet pornography sites
13			+		Gambling sites (various)
14		+	+		Gambling sites (various)
15	+		+	+	Horse and sports betting; online shopping; Internet pornography
16	+	+	+		Betting (various), Internet pornography (various)
17		+	+	+	Online slot machines, bingo; shopping portals (various)
18	+				Internet pornography (various)
19	+	+			Internet pornography, online chat rooms on pornography sites
20	+	+		+	Internet pornography (various)
21				+	Online auction website
22	+	+			Internet pornography (various)
23	+	+			Internet pornography (various)
24				+	Shopping portals (various)
25	+				Internet pornography (various)
26	+				Internet pornography (various)
27				+	Online auction website and shopping portals (various)

28	+				Internet pornography (various)
29	+				Internet pornography (various)
Frequency	**19**	**10**	**13**	**9**	

6.4.3 Yale-Brown Obsessive Compulsive Score, adapated for Internet (Y-BOCS-Internet)

PD–ICD patients scored significantly higher in the total score on the Y-BOCS-Internet questionnaire compared to their PD counterparts ($p<0.0001$) and to healthy volunteers ($p<0.0001$) [PD–ICD mean (±SD) : 13.69 (±8.49); PD controls: 5.42 (±3.56); HV: 4.70 (±1.12)] (Figure 18). This was the case for both the obsessive and compulsive features [obsessive component subscores: PD–ICD: 6.17 (±4.34); PD controls: 2.16 (±1.83); HV: 1.85 (±2.60); $p<0.0001$ for both group comparisons, compulsive subscores PD–ICD: 7.55 (±4.62); PD controls: 3.26 (±1.99); HV: 2.90 (±2.57); $p<0.0001$ for both group comparisons] (Figure 19). They scored significantly higher on seven out of a total of 10 questions within both the compulsive and the obsessive elements (Table 17). This is particularly true for the following: the larger amounts of time they spent on the Internet (Q6); their effort to resist (Q4) and their drive to use the Internet (Q10); thoughts about Internet use (Q1) and its interference with participants' social, work or role functioning (Q2); the increased amounts of effort to resist thoughts of Internet use (Q9) and the feeling of a lack of control over thoughts of Internet use (Q5).

The Cronbach's Alpha coefficient for the total Y-BOCS-Internet scale for the PD–ICD group is 0.879, showing good internal consistency.

Table 17. Breakdown of Y-BOCS-Internet scores

Scores breakdown	**PD ICD**	**PD controls**	**Healthy Volunteers**	**p value**
Total score	13.69 (8.49)*	5.42 (3.56)	4.70 (1.12)	**<0.0001**
Q1: How much of your time is occupied by thoughts about Internet use, whether it be for a specific task or generally browsing on the Internet?	2.07 (1.03)*	1.05 (0.71)	0.85 (0.75)	**<0.0001**
Q2: How much do your thoughts about Internet use interfere with your social, work or role functioning?	1.07 (1.10)*	0.32 (0.48)	0.25 (0.55)	**0.0025**
Q3: How much distress do your thoughts about Internet use cause you?	0.79 (1.77)	0.16 (0.37)	0.20 (0.52)	ns
Q4: How much effort do you make to resist thoughts about using the Internet?	1.17 (1.37)*	0.42 (1.07)	0.20 (0.52)	**0.0030**
Q5: How much control do you have over your thoughts about Internet use?	1.07 (1.22)~	0.21 (0.54)	0.35 (0.67)	**0.0092**
Q6: How much time do you spend on the Internet (per	2.38 (0.86)*	1.53 (0.51)	1.50 (0.76)	**0.0001**

day)?				
Q7: How much does your Internet use interfere with your social, work or role functioning?	0.72 (0.92)	0.32 (0.48)	0.30 (0.57)	ns
Q8: How would you feel if you were prevented from using the Internet?	1.41 (1.30)	0.63 (0.68)	0.60 (0.75)	ns
Q9: How much of an effort do you make to resist using the Internet?	1.69 (1.53)*	0.58 (1.22)	0.25 (0.64)	**0.0002**
Q10: How strong is your drive to use the Internet?	1.35 (1.30)*	0.21 (0.42)	0.25 (0.44)	**0.0002**
Obsessive component (Sum of Q1 to Q5)	6.17 (4.34)*	2.16 (1.83)	1.85 (2.60)	**<0.0001**
Compulsive component (Sum of Q6 to Q10)	7.55 (4.62)*	3.26 (1.99)	2.90 (2.57)	**<0.0001**

Figure 19. Total score for Y-BOCS-INternet for PD ICD, PD control and healthy volunteers groups.

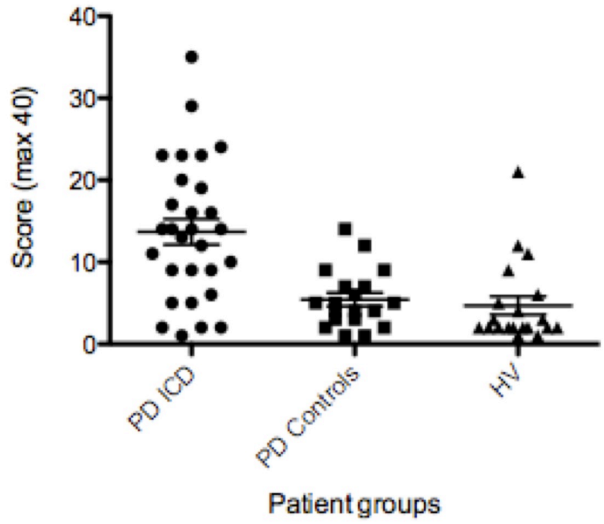
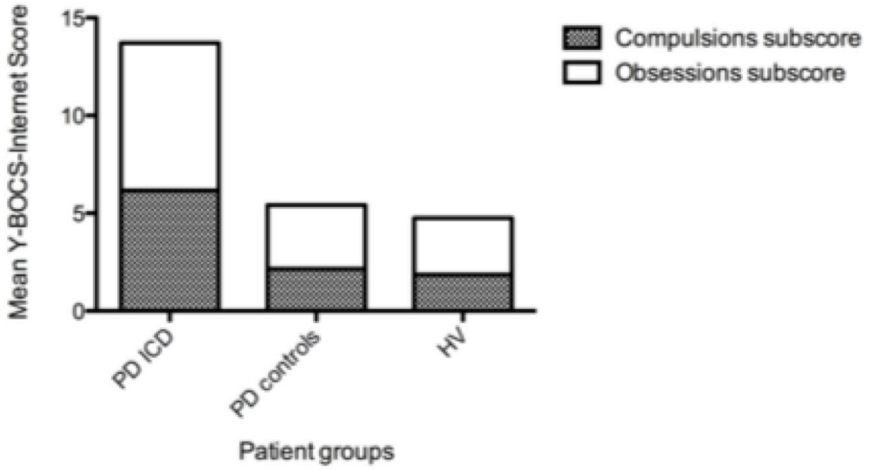


Figure 20. Mean obsessive and compulsive sub-scores for the Y-BOCS-Internet for PD ICD, PD control and healthy volunteers groups.



6.4.4. Correlation of clinical data

I found that the PD–ICD subjects that scored high in obsessive features on the Y-BOCS also scored high in the compulsive features (Spearman's rank correlation coefficient=0.756, $p<0.0001$). I did not find any statistically significant correlation between the Y-BOCS and number of ICDs present, BDI scores nor the BSS-4 questionnaire.

6.4 Summary of findings

Using Y-BOCS adapted for Internet use, I observed that PD patients (without ICDs) had similar scores to HV, but those with PD and ICD scored significantly higher compared to the other two groups. In the breakdown of questionnaires, PD patients with ICDs scored significantly higher regarding their time occupied by thoughts about Internet use (Q1) and time actually spent on the Internet, their drive to use the Internet and the amount of effort exerted to resist thoughts of the Internet. By comparing the ICD subtypes within the PD–ICD group, I found that those who utilise the Internet to facilitate activities related to their ICD are mainly patients with CSB and PG, and approximately half of the patients for CB. The results suggest that Parkinson's patients with impulsive-compulsive disorders have increased tendencies towards excessive, maladaptive Internet use, particularly those displaying pathological gambling or compulsive sexual behaviours.

Chapter 7

Conclusions and reviews of major findings

A range of impulse control disorders and related addictive behaviours such as punding and problematic Internet use have been reported in Parkinson's disease. The central role of dopaminergic drug therapy in these disorders (Weintraub, Koester, et al., 2010) suggests that they may be different manifestations of the same underlying causal mechanism, but what this mechanism is remains unclear. In this thesis project, I conducted studies investigating the role of dopamine underlying pathophysiology of impulse control disorders and related behaviours in Parkinson's disease patients using clinical assessments, PET and fMRI neuroimaging techniques.

7.1 Dopamine neurotransmission of impulse control disorders in Parkinson's disease

In Chapter 3, using PET with ^{11}C-raclopride, I investigated dopamine neurotransmission in PD patients with a range of ICDs on exposure to reward-related and neutral visual cues. I observed a greater reduction in RAC BP_{ND} in the ventral, but not dorsal striatum, of PD subjects with ICDs compared to PD controls following exposure to non-specific reward-related vs. neutral visual stimuli. The radioligand

^{11}C-racloride binds irreversibly to $D_{2/3}$ post-synaptic receptors, and is sensitive to competition from endogenously released dopamine in response to drugs or tasks that induce dopamine release. In this study, the observed decreases in binding potential are, therefore, likely to reflect dopamine release in response to viewing of reward-related cues.

Both comorbid and single ICD groups showed greater dopamine release in the ventral striatum to heterogenous reward-related images compared to the control group, but dopamine release was comparable between those with comorbid and those with a single ICD, and was not related to levels of depression. Previous studies on PD patients focusing on a single ICD, such as pathological gambling, have shown a greater reduction in RAC BP_{ND} in response to gambling cues (Joutsa, Johansson, et al., 2012; Steeves et al., 2009). However, this is the first study to compare PD subjects with comorbid ICDs to subjects diagnosed with only one ICD. This study adds a further layer of evidence in suggesting that the magnitude of ventral striatal dopamine release is not directly related to the presence of comorbidity, nor to levels of depression severity (J. E. Grant & Kim, 2003; Joutsa, Johansson, et al., 2012; Voon, Sohr, et al., 2011).

According to the Incentive Sensitisation Theory of Robinson and Berridge, repeated use of psychostimulant drugs produces progressive neuroadaptations in ventral striatal reward circuitry rendering it hypersensitive to drugs and their associated cues, enable these stimuli to elicit intense drug seeking (Berridge & Robinson, 1998). It is therefore feasible that dopaminergic medication in vulnerable PD individuals causes a similar augmentation of striatal dopamine neurotransmission. An earlier PET study

with ^{11}C-Raclopride on PD patients with dopamine dysregulation (addiction-like excessive use of dopamine replacement therapy) revealed that they release more dopamine in ventral striatum in response to levodopa challenge compared to controls (Evans et al., 2006).

Notably, animal models of incentive sensitization show that repeated exposure to psychostimulants, such as amphetamine, can increases the salience not just of drugs and their associated cues, but also for other 'natural' rewards such as food and sexual stimuli (Engber, Susel, Juncos, & Chase, 1989; Nocjar & Panksepp, 2002; Robinson & Berridge, 2003). Likewise, amphetamine has been shown to increase motivation for gambling in a manner that is predicted by the severity of the subject's gambling (Zack & Poulos, 2004), and in our earlier study of DDS, elevated levels of levodopa evoked ventral striatal dopamine release were correlated with enhanced motivation for money in a simple card sorting task (Evans et al., 2006). Taken together the evidence suggest that mechanisms for induction of ICD by dopaminergic medications could potentially operate on multiple levels: by preferentially activating dopamine receptor subtypes, sensitizing receptors or by providing excessive dopaminergic stimulation to circuits regulating individual components of the addiction process, including 'wanting' motivation, but also potentially other mechanisms such as reward learning; habit formation and stress regulation (A. D. Lawrence et al., 2003).

This study also explored the range of chosen activities pursued for each impulse control disorder, and is found to be similar to that reported in the non-PD ICD population. Subjects with compulsive sexual behaviour admitted to watching pornography and pestering their partner or friend for sex; those with binge eating tend

to eat sweet, calorie-rich foods; those with pathological gambling preferred slot machines, horse and sports betting and bingo; and subjects with compulsive buying had a narrow range of focus in their purchase products. The precise motivational mechanisms underpinning the various behavioural symptoms manifested in ICDs are important topics for future investigation.

Subjects with comorbid ICDs had higher levels of depression and marginally increased sensation seeking scores compared to those with a single ICD and control group, despite having similar disease duration and motor disability. These observations are similar to those in larger populations of PD patients (Joutsa, Martikainen, Vahlberg, Voon, & Kaasinen, 2012; Voon, Sohr, et al., 2011) as well as from the general psychiatric populations where comorbidity is associated with more severe psychopathology, and greater psychosocial functioning impairments(Krueger & Bezdjian, 2009; Verhulst & van der Ende, 1993). Black and Moyer found a high rate of comorbid ICDs in a cohort of pathological gamblers, with a concurrent diagnosis of compulsive buying (23%), compulsive sexual behaviour (17%), and intermittent explosive disorder (13%)(Black & Moyer, 1998). They also had higher rates of lifetime mood (60-76%), anxiety (16-40%), and substance use (33-63%) disorders (Black & Moyer, 1998; Bondolfi, Osiek, & Ferrero, 2000; el-Guebaly, 1995; Ibanez et al., 2000). Similarly, binge eaters who display gambling behaviour have reduced self-esteem compared to those with binge eating alone (Yip, White, Grilo, & Potenza, 2011).

Individuals with comorbid ICDs did not, however, show greater elevations of ventral striatal dopamine release during exposure to a broad range of reward-related stimuli

(e.g. food, sex, gambling cues) relative to those with a single ICD, and the magnitude of ventral striatal dopamine release was unrelated to levels of sensation seeking or depression. In animal models, there is large individual variation in the 'breadth' of reward 'wanting' resulting from incentive sensitization (Berridge, 2012). Thus, amphetamine sensitization in rats can amplify the incentive value of drug-associated stimuli (but not food or sex) in some individuals, but enhance 'wanting' of both food and sex rewards (but not drugs) in others (Nocjar & Panksepp, 2002). Thus, individuals with comorbid (vs. single) ICDs might have a broader focus of 'wanting' across several types of incentive (e.g. food, sex, money), which, as demonstrated in this study, is not reflected in greater elevations of evoked ventral striatal release to heterogenous reward cues per se. In animal models, the 'focus' of incentive salience wanting onto particular reward cues has been shown to be regulated by opioid mechanisms in central amygdala and neostriatum (Berridge, 2012).

It was notable that binge eating and compulsive shopping, unlike pathological gambling and compulsive sexual behaviour, never occurred in isolation. Whilst the high levels of comorbidity between different ICDs in PD suggest that they result from a shared vulnerability, it is also possible that the pathophysiology of binge eating and compulsive shopping is somewhat different to pathological gambling and compulsive sexual behaviour. For example, it is now clear that there are multiple forms of impulsivity and compulsivity, some of which may be mediated by dopaminergic function, and others which may be mediated by serotonergic functioning (Dalley & Roiser, 2012). It was also notable that all single ICD cases were men, and sex differences in ventral striatal dopamine release have been previously reported where

men show greater ventral striatal dopamine release following amphetamine (Munro et al., 2006).

Overall, this study identified a number of new clinical and neuroimaging findings between Parkinson's patients with comorbid ICDs compared to those with a single ICD and control PD subjects who were matched for age, disease severity and dopaminergic medication. Translated clinically, patient with comorbid ICDs can pose more challenges for their physicians and carers, in particular in managing mood disorders and sensation seeking behaviours.

7.2 Dopaminergic basis of punding behaviour in Parkinson's disease

In Chapter 4, I compared basal striatal dopamine D2 binding in PD patients with punding behaviour and PD control patients using PET with ^{11}C-raclopride. Although dorsal striatal dopaminergic pathways have previously been implicated in punding behaviors in non-PD OCD subjects (Denys, van der Wee, Janssen, De Geus, & Westenberg, 2004), this study is the first to specifically study punding in Parkinson's disease using ^{11}C-raclopride PET. I found lower RAC BP_{ND} values in the dorsal striatum (caudate and putamen) of punders compared to controls when subjects were scanned under resting condition. This indicates that there are higher endogenous dopamine levels in punders at rest compared to controls. The neuroimaging results from this study draw parallels to those seen in the OCD populations. Denys and colleagues found low D2 receptor binding in the caudate of patients with OCD compared to healthy controls (Denys et al., 2004), whilst another study demonstrated

impairment in both the serotonergic system in the frontal regions and dopaminergic system in the striatum. Further, it is interesting that low D2 receptor binding in the striatum is linked to increased social withdrawal in OCD, which is a typical feature of punding and other forms of stereotypy (Schneier et al., 2008).

One of the reasons that punder had lower levels of caudate D2 binding at baseline compared to controls, as reflected by RAC BP_{ND}, may be due to a higher level of endogenous dopamine as result of chronic exposure to dopaminergic medication. Dopamine, whose function is enhanced by cocaine and amphetamine, is a monoamine neurotransmitter with a central role in reward seeking behaviors. Striatal dopamine is thought to play a determinant role in psychomotor induced stereotypies. This has been argued to occur through incentive salience where punding may represent a form of psychomotor sensitization phenomenon with chronic dopaminergic medication use (Berridge, 2012; Berridge, Robinson, & Aldridge, 2009), as well as a process of habit formation through cue-conditioned learning (Everitt & Robbins, 2005). Several lines of evidence from animal studies support these views. Repeated dosing of amphetamines in rats results in behavioral sensitization, manifested as increased locomotion and stereotypic behavior with each subsequent dose of amphetamine (Lundh & Tunving, 1981; Rhee, Albertson, & Douglas, 1988). Thus, the punding behaviors seen in PD individuals resembles some of the complex streotypies seem in these animal studies treated with chronic or large doses of amphetamines (Schiorring, 1981) and levodopa (Randrup & Munkvad, 1966), with the underlying neurobiology has been linked to the dorsal striatum and its dopaminergic irrigation.

An alternative explanation for the difference in caudate D2 receptor binding may be a decreased level of dopamine D2 receptors in punders compared to controls. Indeed, both genetic studies of mice with D2 receptor knockout genes and chronic studies suggest that reduced D2 receptors could be a contributing factor (either as a result of postsynaptic D2 receptors or presynaptic D2 autoreceptors). Rosengarten and colleagues found that genetically based reductions in D2 receptors were linked to enhanced stimulant induced stereotypies in different strains of rodents (Rosengarten, Schweitzer, & Friedhoff, 1986). Further, another study found increased stereotyped grooming in D2 knockout mice by administration of a D1 agonist, and concluded that cocaine intake result in an exaggerated striatal increase in extracellular dopamine levels due to the loss of D2 receptor-mediated presynaptic autoreceptor functions, in turn causing D1 receptor overstimulation in D2 receptor knockout mice (Welter et al., 2007). These studies support other models of stereotypy that emphasize greater D1 relative to D2 stimulation in the dorsal striatum in the pathogenesis of stimulant-induced stereotypy, for example, that of the 'complex superstereotypy' in rodents being linked to excessive D2 stimulation in the dorsal striatum (Berridge & Aldridge, 2000a, 2000b). Given that levodopa acts on both D1 and D2 receptors, lower D2 receptors could lead to a relative increased D1 stimulation by levodopa in the striatum, possibly causing an increase in punding behavior. Notably, hypodopaminergic DAT knockout mice display this superstereotypy characterized by excessively strong and rigid manifestations of complex and fixed action patterns (Berridge, Aldridge, Houchard, & Zhuang, 2005). Interestingly, a recent neuroimaging study has shown reduced DAT binding in the striatum of patients with PD and a range of impulse control disorders, where the authors postulate that greater dopaminergic striatal activity in PD patients with ICDs (in comparison to PD patients

without ICDs) may be related to reduced uptake and clearance of dopamine from the synaptic cleft (Voon et al., 2013). Punding in association with dopaminergic medication intake in Parkinson's patients may therefore represent the culmination of a continuous process of psychomotor stimulation (mediated by ventral striatal structures) and behavioral competition (mediated by dorsal striatal structures). These findings lend parallels to the results of this study showing lower baseline dopamine D2 receptor binding, indirectly observed by lower RAC BP_{ND} in the dorsal striatum of punders with Parkinson's disease.

The frequent co-existence between punding behavior, impulse control disorders and addiction raises the broader notion of 'impulsivity' and 'compulsivity' as originating from the same neurobiological entity (Robbins, Gillan, Smith, de Wit, & Ersche, 2012). For example, reduced basal striatal D2 receptor binding on ^{11}C-raclopride has been seen in both cocaine and amphetamine abusers (Martinez et al., 2004; Volkow et al., 2001), where these addicted populations have high levels of punding behaviors. In a monkey model, Groman and colleagues found that D2 receptors in caudate and putamen were reduced in methamphetamine treated moneys, and such reductions correlated with perseverative behavior of previously rewarded actions (Groman et al., 2012). In Parkinson's disease, patients with punding have been observed to share similar traits with individuals with ICDs, such as male gender, young age, a history of psychiatric problems and depression, suggesting that these two clinical phenomena may share common neurobiological footing (Evans et al., 2004; A. J. Lawrence et al., 2007; Voon & Fox, 2007; Voon et al., 2007). Their frequent co-occurrence may also explain the increased presence of ICD and/or DDS in the cohort of patients in this study. Further, recent neuroimaging studies using ^{11}C-raclopride PET in patients with

PD and ICD showed enhanced ventral striatal dopamine release in response to reward-related cues (O'Sullivan et al., 2011; Steeves et al., 2009). Another study of PD patients with addiction to dopaminergic medication demonstrated enhanced striatal dopamine release in response to levodopa challenge (Evans et al., 2006). Such similar pathophysiological findings in individuals with different phenotypes beg the question whether these behaviors should be grouped together.

The subjects of this study did not have any discernable pattern to the dopamine receptor stimulation profile of the medications used by the punders compared with the nonpunders. More punders reported dyskinesias (n=7) than controls (n=4) but the difference was not statistically significant. Evans and colleagues (2006) found that dyskinesias were present in all but one patient in the DDS group and most complained of distressing motor fluctuations, suggesting that dyskinesias were associated with medication overuse nature of DDS rather than punding (Evans et al., 2006). Similar to previous reports (A. J. Lawrence et al., 2007), punders scored higher in the Padua inventory but the scores remain within the non-OCD range and did not differ significantly from PD controls, suggesting that punding behavior does not have the characteristics or driven by the anxiety of obsessions.

In this study, I reported a higher percentage (100%) of co-morbid ICDs in the punding group than previously reported (59%) (Fasano & Petrovic, 2010). This difference may be due to sampling techniques (face-to-face interview by trained neurologist) compared to other studies (postal questionnaires). Furthermore, patients with punding are reported to have enhanced appetitive behaviors (Evans et al., 2004). Similar to other reports of punding, I did not find any difference in depression scores between

punders and controls (Fasano et al), suggesting that punding does not correlate with mood or anxiety disorders.

In summary, I showed that Parkinson's disease with punding have increased basal dopamine level in the dorsal striatum compared to controls. Increased basal dorsal striatal dopamine level may therefore contribute to the habit formation in stereotypic behaviours of punding.

7.3 Neural response of reward-related visual cues in compulsive sexual behaviour

Compulsive sexual behaviour is a relatively common unwanted effect of dopaminergic medication, which can result in devastating social consequences. In Chapter 5, I explored the mechanisms underpinning dopaminergic medication linked CSB in patients with PD using behavioural assessments of sexual motivation and an fMRI paradigm. I found that passive viewing of sex-related cues caused an increase in the sexual desire of PD CSB patients by activating brain regions linked to sexual motivation.

In agreement with functional imaging studies of visual sexual stimulation in healthy individuals (Arnow et al., 2002; Redoute et al., 2000; Walter et al., 2008), exposure to visual sexual cues activated parieto-temporal-occipital visual processing regions such as the MOG and MTG in the PD CSB group and PD controls. In PD CSB patients, exposure to sexual visual cues in both ON and OFF medication conditions showed increased activation in OFC, ACC, PCC, VS, aPFC, SPL,

amygdala and the hypothalamus compared to Parkinson's disease controls. Parkinson's disease CSB patients showed significantly increased sexual desire and liking of the sexual content following exposure to sexual cues. Their sexual desire was accentuated when they were ON L-Dopa compared to OFF medication after exposure to sexual content. The crucial role of ACC, PCC, VS and OFC in sexual motivation was underscored by the fact that increased activation in these regions correlated with increased sexual desire.

Animal studies have shown that dopamine is involved in sexual motivation and urge triggered by sexual cues in areas including VS, the hypothalamus, medial PFC, amygdala and ACC and that a sensitising regime of dopaminergic drugs can lead to exaggerated sexual pursuit and predation (Afonso et al., 2009; Fiorino & Phillips, 1999b; Nocjar & Panksepp, 2002; Pfaus et al., 2010; Stolzenberg & Numan, 2011). Concurrent experience with dopaminergic drugs and sexual activity is required for development of compulsive sexual behaviour (Frohmader, Lehman, Laviolette, & Coolen, 2011), mirroring the delayed onset of CSB in Parkinson's disease following treatment with dopaminergic drugs (Giladi, Weitzman, Schreiber, Shabtai, & Peretz, 2007). Moreover, recent work has shown that drugs of abuse can activate the same neuronal systems as a sexual reward, with overlap occurring in regions including the hypothalamus and ACC (Frohmader et al., 2010). These findings, taken together with those from previous studies conducted with animals, support the incentive sensitisation theory as a framework for understanding the mechanisms of dopaminergic drug-induced CSB in Parkinson's disease. The incentive sensitisation theory holds that dopamine motivates the pursuit of rewards by attributing incentive salience to reward-related stimuli (such as sexual visual cues), triggering pursuit

('wanting') of sex and, in the case of CSB, sex cues may be attributed with pathological incentive salience (Berridge et al., 2009). Incentive sensitisation theory further holds that the 'wanting' of rewards, mediated by VS dopamine-related neurocircuitry, may grow over time independently of reward 'liking' as an individual develops compulsive reward seeking (Berridge et al., 2009), and it is notable here that dopamine increased cue-evoked sexual desire ('wanting') but not rated 'liking' of the sexual images in PD CSB patients.

Since the majority (8/12) of PD CSB patients had at least one additional ICD (e.g. pathological gambling, binge eating, etc), I wanted to test whether the changes in behavioral assessments and brain activation following reward cue exposure were specific to sex or extended to other rewards. Self-reported desire and liking for gambling, drugs and food were not different within or between the groups of PD CSB and PD controls before and after the ON and OFF scans. Similarly, there were no differences between PD CSB and PD controls in neural response to other rewarding visual cues in the fMRI analysis indicating that our imaging results were also specific to CSB. However, I also wanted to explore the specific brain activity related to sexual visual cues compared to other rewards. The findings revealed strong activation in both ON and OFF state scans in OFC, ACC, PCC, VS, aPFC, dorsolateral PFC, PHG and hypothalamus, confirming the specific importance of these regions in sexual motivation and desire, at least in the context of CSB.

This selective enhancement for sexual cues is notable. Work in animal models by Berridge and colleagues has shown that stimulating opioid circuitry in the amygdala and striatum can focus cue-triggered 'wanting' very narrowly in a winner-take-all fashion. Under such conditions, a single favourite reward cue becomes a highly potent

'motivational magnet' that pulls all attraction to itself at the expense of other reward cues, even in animals that were also attracted to those other rewards (DiFeliceantonio & Berridge, 2012; Mahler & Berridge, 2009, 2012). Similarly, the sexual reward cues were associated with enhanced amygdala activity relative to other reward cues in CSB individuals and may have been selectively targeted with enhanced incentive salience in a 'winner-take-all manner', even in those individuals with comorbid ICDs.

The increased activation in VS could be related to increased dopamine release in VS (Schott et al., 2008), consistent with PET data (O'Sullivan et al., 2011) and previous studies showing increased DA release related to sexual cues in the VS of sensitized animals (Fiorino & Phillips, 1999b). Lesions in hypothalamus and amygdala are known to impair sexual motivation in male and female rodents and hypothalamic and amygdala activation tracks sexual arousal in fMRI studies (Hamann, Herman, Nolan, & Wallen, 2004). The hypothalamus has been shown to play a central role in sexual behavior and is believed to be involved in the autonomic component of sexual arousal (Allen, Drabman, & Schleser, 1989; Kupfermann, 1991).

The ACC is another paralimbic area connected to forebrain regions and controlling a number of autonomic and neuroendocrine functions (Stoleru et al., 1999). Previous studies have connected the activation of ACC with the degree of penile tumescence (Redoute et al., 2000) and with the motivational component of sexual arousal and desire (Arnow et al., 2002; Karama et al., 2002; Redoute et al., 2000; Walter et al., 2008). Parietal areas and the PCC have also been linked to cue specificity in reward desire (Garavan et al., 2000). The OFC has been linked to explicit ratings of anticipated pleasure and desire and it is believed to have a role in mediating subjective

reward experience (Kringelbach, 2005). Furthermore, activation of OFC and PFC has been suggested to be associated with a pleasant bodily sensation being internally represented during sexual arousal (Stoleru et al., 2003). In this study, the rated sexual desire was correlated with activity in cortical regions (including ACC and OFC) in addition to VS, which may be consistent with the notion that incentive salience 'wanting' is not directly experienced in conscious awareness, and that explicit, conscious 'wanting' requires additional cortical processing of VS outputs (Berridge & Robinson, 1998).

Results of my study showed enhanced brain activity after exposure to sexual cues was not influenced by the administration of L-DOPA as suggested by the similar BOLD signal increases in ON and OFF medication scans. However, the absence of acute L-DOPA effect does not eliminate the effect of synergistic interaction of mesolimbic dopamine state and the presence of sexual cues in stimulating enhanced 'wanting' for sexual reward in the PD CSB group (Berridge, 2012; Oei et al., 2012). The PD CSB patients, even in the OFF state, are not entirely drug free and are presumably sensitized, and in animal studies, although acute amphetamine and sensitization effects can be additive (Tindell, Berridge, Zhang, Pecina, & Aldridge, 2005), sensitization caused by previous amphetamine administration causes reward cues to trigger excessive pursuit of their associated reward, even when sensitized rats are tested in a drug-free state (Wyvell & Berridge, 2001).

Interestingly, in the PD CSB group of patients, after acute L-DOPA challenge, the decreases observed when OFF their drugs and in the OFF and ON state in PD controls (reduced BOLD signal during exposure to sexual vs. neutral visual cues in ICG, PHG,

cuneus, insula and claustrum) were eliminated (for a similar effect of dopaminergic drug challenge in cocaine addiction, see (Volkow et al., 2010). These results suggest that dopamine drugs could eliminate the deactivation of brain regions, which may be related to plastic changes in an effort to inhibit CSB stimulation. Although it is difficult to translate excitation or inhibition of neuronal firing into BOLD signal increases or decreases in activated voxels, dopamine drugs could release this inhibition through the activity of inhibitory interneurons acting within local neuronal circuits in the cerebral cortex. The release of neuronal inhibition in ICG, PHG, cuneus, insula and claustrum when patients are ON their dopaminergic drugs could be associated with concurrent behavioral changes, as in this study, was an associated increase in sexual desire scores. This theory is supported by the complete cessation of CSB after withdrawal from dopamine receptor agonist medications (Mamikonyan et al., 2008; Munhoz, Fabiani, Becker, & Teive, 2009).

Inhibition of deactivation of insula through DA drugs could lead to the expression of pathological sexual behavior as this paralimbic area forms connections to regions involved in autonomic regulation (Oppenheimer, 1992), relates highly processed sensory information with motivational states (Stoleru et al., 1999) and in combination with the secondary somatosensory cortex has been reported to be involved in the perceived urge to express overt sexual behavior (Mouras et al., 2003). The claustrum has also been shown to be involved in emotional and motivational responses in animals (Hamamura & Ichimaru, 1997) and humans (Reiman, Fusselman, Fox, & Raichle, 1989) and is thought to be associated with sexual motivation (Rees & Noyes, 2007). Deactivation in parahippocampal regions has been reported following presentation of sexually explicit video clips, however the potential role of these

deactivations are not well understood (Redoute et al., 2000).

The findings of this study are novel in that it is the first to examine the mechanisms underlying CSB in Parkinson's disease. The ability to trigger increased neural response as a result of passive viewing of visual cues has potential implications for similar exposure via mass media to influence pathological sexual behaviour in Parkinson's disease patients.

7.4 Pathological Internet use in Parkinson's disease patients

Using the Y-BOCS-Internet scale, I found that PD patients (without ICDs) had similar scores to HV, but those with PD and ICD scored significantly higher compared to the other two groups. The differences in scores are most notable on items regarding time occupied by thoughts about Internet use (Q1), time actually spent on the Internet, the patients' drive to use the Internet and the amount of effort exerted in resisting thoughts on Internet. By comparing the ICD subtypes within the PD–ICD group, I found that those who utilise the Internet to facilitate activities related to their ICD are mainly patients with CSB and PG, and approximately half of the patients for CB.

Studies in the general population on subjects with PIU/Internet addiction (variously defined) found that they are most likely to engage in a range of activities, such as File Transfer Protocol, Internet gambling, online gaming, web surfing, use of remote support communication software, online shopping and online community activities. Results of this study on PD patients with ICDs, particularly CSB and PG, are similar to the above subjects in the general population with PIU / Internet addiction, where

individuals use the Internet for browsing sites of a sexual nature, engage in cybersex as part of online communities, and access Internet gambling sites; those with CB uses online shopping websites.

In non-PD populations, PIU frequently co-occurs with other psychiatric conditions, PIU may preferentially occur with conditions related to the content browsed on the Internet (e.g. gambling, pornography). For example, in a Canadian population-based study of non-PD pathological gamblers comparing 8,456 offline gamblers and 111 online gamblers, a disproportionate number of men, young people and students participate in online gambling, and gambling behaviours were more excessive on the Internet. Comparing with offline gamblers, online gamblers report more co-occurring alcohol and cannabis use (Kairouz, Paradis, & Nadeau, 2012). Research conducted on non-PD men with sexual compulsivity found that the Internet use of these subjects played a role in facilitating their compulsions for problematic sexual thoughts and behaviours (Grov et al., 2008). These evidence dovetail with the results of this study. A number of other studies have also found that subjects with CSB use the Internet to seek sexual partners and for cybersex, particularly if they are geographically isolated (Schnarrs et al., 2010) –these results also draw parallels with PD patients whom are socially isolated due to limited mobility.

Although not included as a psychiatric diagnosis in the DSM, PIU/Internet addiction has often been modelled after impulse control disorders. Interestingly, Shapira et al found that 55 per cent of subjects in the general population with PIU had a lifetime diagnosis of an ICD (Shapira et al., 2000). In another study, participants with PIU were noted to have neuropsychological and personality traits similar to sufferers with

other types of ICDs, such as increased levels of trait impulsivity comparable to subjects with PG (H. W. Lee et al., 2012). Further, a study of a random sample of 940 university students found that those with a diagnosis of CB, or intermittent explosive disorder or pyromania are more likely to have PIU compared to students without the diagnosis. Cao and colleagues showed a specific relationship between impulse control and Internet addiction in a sample of Chinese adolescents (Cao, Sun, Wan, Hao, & Tao, 2011). Results of these and other studies suggest that Impulse-compulsive disorders are closely linked to PIU behaviour and that PIU share the multi-faceted characteristics of ICDs. This also appears to be the case in the context of ICDs in PD.

The association of PIU with well-established ICDs such as gambling disorder together with the finding that PIU may preferentially occur with those ICDs related to the content browsed on the Internet (such as gambling-related) raises the question as to whether PIU exists as a distinct entity, as opposed to the Internet serving as an outlet for other ICDs. However, studies examining Internet-use behaviour in people with pathological gambling or compulsive sexual behaviour support the notion that PIU is a distinct entity. Studies that examine gambling or compulsive sexual behaviour found only a proportion of subjects manifest them via the Internet (Grov et al., 2008; Kairouz et al., 2012), and in others Internet use only partially plays a role in facilitating their maladaptive behaviours (Schnarrs et al., 2010), i.e. people with compulsive sexual behaviour seek sexual partners online but meet to perform their act in person. Further, there is general consensus that PIU is associated with material and psychological consequences (Mitchell, 2000) and that further research need to investigate the dimensional spectrum of PIU in different groups (Pomerantz, 1990; Redoute et al., 2000). On this front, my study has reported an increased use of the

Internet in individuals with ICDs in PD, and assessed the obsessive-compulsive nature of Internet use in and its relation to the clinical features in PD.

Although a number of screening scales for maladaptive Internet and computer use have already been published, these were primarily developed in young (student) populations and are therefore not ideal for use in an older age group consistent with the PD population (Meerkerk, Van Den Eijnden, Vermulst, & Garretsen, 2009; Nichols & Nicki, 2004; K. S. Young, 1998). I believe that the Y-BOCS-Internet scale may serve as a more suitable assessment tool for an older adult population, having been validated in the context of ICDs in several different patient groups with a wide age range. Also each question provides a measure of severity, which gives greater depth for assessment, and in the future may be useful for diagnosis as well as monitoring of progress during treatment. Furthermore, our results have shown that it discriminates PD ICD individuals from the PD and HV control groups, has good internal consistency and a strong correlation between the obsessive and compulsive elements. More generally, despite an increasing literature, there are currently no standard diagnostic criteria and scales for PIU / Internet addiction (with the exception of Internet gaming disorder) and a key goal for future research should be to define the maladaptive features of Internet use and obtain data on the reliability and validity of specific diagnostic criteria in order to examine its associated biological features.

7. 5 Clinical implications of the results from this thesis

This thesis presents several novel findings in helping to understand the pathophysiology behind ICDs in Parkinson's patients. Firstly, that PD patients with

ICD preferentially release dopamine in response to a varied range of passive exposure of reward-related cues compared to PD controls. The observations that similar amount of dopamine is release in response to these cues despite subjects having different 'disease load' suggest similar degree of ventral sensitisation by the dopaminergic medication. Secondly, using fMRI and a block design paradigm of passive exposure to sexual versus non-sexual cues, I found that PD individuals with CSB are able to display a motivational impetus for seeking sexual reward through increased and decreased activations of cerebral cortex. The results from both PET and fMRI study suggest an incentive sensitisation process of the dopaminergic reward system and raise the possibility that individuals with behavioural addictions are likely to undergo almost constant activations of their aberrant reward circuitry from the sort of reward-related cues that are typically employed in advertising (such as pop-up Internet advertisements), thus potentially maintaining the behaviour and making it more difficult for abstinence to occur. These findings potentially have important implications for decision-making policies relating to advertising, which has a powerful impact and relies strongly on reward-related imagery. Thirdly, I observed that, similar to sufferers of obsessive-compulsive disorder, patients with PD who exhibits stereotypical behaviours such as punding often lack insight and have associated social withdrawal. They were also found to have D2/D3 downregulation in the dorsal, but not ventral, striatum compared to controls. This neuroimaging finding is comparable to non-PD individuals with OCD (Denys et al., 2004) and lends support to the role of dopamine in the dorsal striatum, rather than ventral striatum, in mediating stereotypies through chronic dopaminergic medication use (Berridge & Aldridge, 2000b), as well as a role for habit formation through cue-conditioned learning (Everitt & Robbins, 2005).

Lastly, I found that PD ICD patients have increased tendencies towards excessive, maladaptive Internet use, particularly those displaying pathological gambling or compulsive sexual behaviours. This shows similarities with evidence from studies in the general population showing non-PD individuals with ICDs are more likely to have problematic Internet use, suggesting that PIU should be viewed as a distinct impulse control disorder by both physicians and patients.

Overall, this thesis has constructed a model for experimenting with the dopaminergic basis implicated in ICDs and related addictive behaviours in Parkinson's disease patients. The results would be clinically useful to inform management of PD patients with impulse control and addictive behaviours and to benefit and facilitate further scientific research.

7.6 Strengths and limitations

Several strengths in this thesis project are notable. The patients in these studies had a range of ICDs, unlike many other studies that focused only on a single ICD subtype. As such my studies are a better representative of the 'real' population of ICD patients. It also allowed for examination of the complex issue of comorbidity. The use of passive reward-related visual cues in the PET and fMRI studies, as opposed to a hypothetical paradigm that models a specific ICD behaviour, to investigate dopamine neurotransmission in PD ICD patients is a 'better fit' of the stimuli from the 'real world', where visual stimuli were representative of that seen in the mass media. As such the results are directly relevant and can be translated into the clinical setting to inform management. This thesis not only explored the neurobiology of ICDs but also

examined related behaviour such as punding and pathological Internet use, providing new knowledge into related fields of behavioural stereotypies and addiction in the context of Parkinson's disease.

However, the data need to be interpreted in light of several limitations. Although sufficient to test statistical differences, the studies in this thesis project are limited by a relatively small sample size. This was due to difficulties in recruiting PD patients who have ICDs, and whom were also willing to undergo quite a lengthy research protocol that involves exposure to relative increased amount of radiation and antiparkinsonian drug withdrawal on several occassions. Patients in these studies were recruited from large academic tertiary movement disorder centres, with a higher proportion of male subjects, and may not be representative of the general PD population. In addition, as I was involved in every aspect of the study (study conception and protocol design, recruitment, conducting the study, analysis and writing up), it was not possible to be blinded to the study groups. Although this may have introduced bias into the interpretation of the answers during the face-to-face interviews, the presence or absence of any punding or impulse control disorders was usually very clear and without ambiguity. All the studies in this thesis project are cross sectional in nature and cannot determine the longitudinal effect of medication as a risk factor.

7.7 Future directions

Impulse control disorders are a group of heterogenous entities separated by their distinct behaviours, but studies have suggested that they may be sub-grouped by similar features. For example, food and sex are natural rewards, whereas gambling

and shopping are secondary or learned rewards. Further studies are therefore warranted to explore whether there could be any overlap between these in terms of behavioural characteristics or underlying reward mechanisms. The precise motivational mechanisms underpinning the various behavioural symptoms manifested in ICDs are also important topics for future investigations. A larger number of subjects needs to be examined for their Internet behaviour to determine the precise role of Internet in the context of ICDs, and whether this behaviour should be classed as a distinct entity in its own right.

In a wider context, impulse control can be due to dopaminergic pathways in the striatum as well as underactivity of the prefrontal cortex in inhibiting impulsivity behaviours. Studies in drug addiction have suggested that impulsivity may in part be due to hypoactivation of frontal brain regions subserving response inhibition in the healthy brain – this would also be an area of interest for further research of ICDs in PD subjects.

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APPENDICES

Appendix 1. UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria for probable Parkinson's disease

Reproduced from (Hughes et al., 1992)

Step 1. Diagnosis of parkinsonian syndrome

Bradykinesia and at least one of the following:

- muscular rigidity
- rest tremor (4–6 Hz)
- postural instability unrelated to primary visual, cerebellar, vestibular or proprioceptive dysfunction

Step 2. Exclusion criteria for Parkinson's disease (PD)

History of :

- repeated strokes with stepwise progression
- repeated head injury
- antipsychotic or dopamine-depleting drugs
- definite encephalitis and/or oculogyric crises on no drug treatment
- more than one affected relative
- sustained remission
- negative response to large doses of levodopa (if malabsorption is excluded)
- strictly unilateral features after 3 years
- other neurological features: supranuclear gaze palsy, cerebellar signs, early severe autonomic involvement, Babinski sign, early severe dementia with

disturbances of language, memory or praxis

- exposure to known neurotoxin
- presence of cerebral tumour or communicating hydrocephalus on neuroimaging

Step 3. Supportive criteria for PD

Three or more of the following are required for diagnosis of definite PD:

- unilateral onset
- excellent response to levodopa
- rest tremor present
- severe levodopa-induced chorea
- progressive disorder
- levodopa response for over 5 years
- persistent asymmetry affecting the side of onset most clinical course of over 10 years

Appendix 2. DSM-IV diagnostic criteria for pathological gambling

Reproduced from DSM-IV manual (American_Psychiatric_Association, 2000)

A. Persistent and recurrent maladaptive gambling behaviour is indicated by five (or more) of the following:

- is preoccupied with gambling (e.g. is preoccupied with reliving past gambling experiences, handicapping or planning the next venture, or thinking of ways to get money with which to gamble)
- needs to gamble with increasing amounts of money in order to achieve the desired excitement
- has repeated unsuccessful efforts to control, cut back, or stop gambling
- is restless or irritable when attempting to cut down or stop gambling
- gambles as a way of escaping from problems or of relieving a dysphoric mood (e.g. feelings of helplessness, guilt, anxiety, depression)
- after losing money gambling, often returns another day to get even ('chasing' one's losses)
- lies to family members, therapist, or others to conceal the extent of involvement with gambling
- has committed illegal acts such as forgery, fraud, theft, or embezzlement to finance gambling
- has jeopardised or lost a significant relationship, job, or educational or career opportunity because of gambling
- relies on others to provide money to relieve a desperate financial situation caused by gambling

B. The gambling behaviour is not better accounted for by a manic episode.

Appendix 3. Diagnostic criteria for compulsive sexual behaviour

Assessment of compulsive sexual behaviour was based on proposed operational diagnostic criteria as previously published (Voon et al., 2006):

A. The sexual thoughts or behaviours are excessive or atypical from baseline marked by one or more of the following:

1. Maladaptive preoccupation with sexual thoughts
2. Inappropriately or excessively requesting sex from spouse or partner
3. Habitual promiscuity
4. Compulsive masturbation
5. Telephone sex lines or pornography
6. Paraphilias

B. The behaviour must have persisted for at least 1 month.

C. The behaviour causes at least one or more of the following:

1. Marked distress
2. Unsuccessful attempts to control thoughts or behaviour, and results in marked anxiety or distress
3. Time-consumption
4. Significant interference with social or occupational functioning

D. These behaviours do not occur exclusively during periods of hypomania or mania.

Appendix 4. Diagnostic criteria for compulsive buying

Assessment of compulsive buying behaviour was based on McElroy's criteria (McElroy, Keck, Pope, Smith, & Strakowski, 1994).

A. Maladaptive preoccupation with buying or shopping, whether impulses or behaviour, that:

1. are experienced as irresistable, intrusive and/or senseless
2. results in frequent buying of more than can be afforded and items that are not needed or buying/shopping for longer periods of time than intended

B. Causes marked distress, is time-consuming, significantly intereferes with social or occupational functioning, and/or results in financial problems

C. The behaviours do not occur exclusively during periods of hypomania or mania.

Appendix 5. Diagnostic criteria for binge eating

Assessment of binge eating behaviour was based on the DSM IV-TR research diagnostic criteria for binge eating (American_Psychiatric_Association, 2000).

A. Recurrent binge eating characterised by eating large amounts in a discrete period along with loss of control.

B. Three or more of the following:

1. Rapid eating
2. Feeling uncomfortably full
3. Eating large amounts when not hungry
4. Feeling disgusted or guilty after overeating
5. Eating alone because of embarrassment of amount

C. Marked distress

D. Occurs at least 2 days per week for at least 6 months

E. Does not occur with compensatory behaviours or during anorexia or bulimia nervosa

Appendix 6. Diagnostic criteria for dopamine dysregulation syndrome (DDS)

Diagnosis of DDS (also known as hedonistic homeostatic dysregulation syndrome) was based on the criteria set out by Giovannoni and colleagues

(Giovannoni et al., 2000).

A. Parkinson's disease with documented levodopa responsiveness

B. Need for increasing doses of DRT in excess of those normally required to relieve Parkinsonian symptoms and signs

C. Pattern of pathological use: expressed need for increased DRT in the presence of excessive and significant dyskinesias despite being 'on', drug hoarding or drug seeking behaviour, unwillingness to reduce DRT, absence of painful dystonias

D. Impairment in social or occupational functioning: fights, violent behaviour, loss of friends, absence from work, loss of job, legal difficulties, arguments or difficulties with family

E. Development of hypomanic, manic, or cyclothymic affective syndrome in relation to DRT

F. Development of a withdrawal state characterised by dysphoria, depression, irritability, and anxiety on reducing the level of dopaminergic medication.

G. Duration of disturbance of at least 6 months

Appendix 7. Diagnostic guidelines of punding in Parkinson's disease

Reproduced from (Evans et al., 2004; A. J. Lawrence et al., 2007).

A. Each participant is asked whether they spend any prolonged period of time on any particular tasks or their hobby-related activities, such as:

Cleaning and tidying

Gardening

DIY

Collecting and collections

Repairing and/or dismantling things

Sorting

Computer use

B. If a particular activity is identified, then this is followed up with further questions related to their activity, such as:

When did you become interested in it (years)?

How do you feel when you engage with your hobby, or, why do you do it?

Do you find your hobby soothing? Calm? Fascinating?

Are you driven to it in response to obsession? Fear? Anxiety?

Do you sometimes spend excessive amounts of time on your hobby?

Do you ever do it if you can't sleep at night?

Have you ever missed a whole night's sleep because of it?

Are you easily distracted when you are engaged with your hobby?

How do you feel when you are interrupted when you are engaged with your hobby (i.e. do you ever get angry or upset? Do you 'go off'?)?

Are you interested in your hobby only when 'on' or when you are 'on' and 'off'?

Do you make much of a mess when you are pursuing your pastimes or hobbies?

Do you have difficulties in finishing projects?

Appendix 8. Yale-Brown Obsessive Compulsive Scale, adapted for Internet use

INSTRUCTIONS:
The following questionnaire asks about your use of the Internet in the last 12 months. 'Internet use' in this questionnaire relates to non-essential Internet usage (non-business or non-academic use) and includes access to the Internet via any electronic medium, such as laptop and desktop computers, tablet computers, smart phones and any other media through which Internet can be accessed.

Please circle the number corresponding to the statement that best describes how you feel.

1. **How much of your time is occupied by thoughts about using the Internet, whether it be for a specific task or generally browsing on the Internet?**
    0- None
    1- Mild (less than 1 hour per day or occasional intrusion)
    2- Moderate (1 to 3 hours per day, or frequent intrusion)
    3- Severe (3 to 8 hours per day, or very frequent intrusion)
    4- Extreme (more than 8 hours per day, or near constant intrusion)

2. **How much do your thoughts about Internet use interfere with your social, work or role functioning?**
    0- None
    1- Mild, slight interference with social or occupational activities but overall performance is not impaired
    2- Moderate, definite interference with social or occupational performance, but still manageable
    3- Severe, causes substantial impairment in social or occupational performance
    4- Extreme, incapacitating

3. **How much distress do your thoughts about Internet use cause you?**
    0- None
    1- Mild, not too disturbing
    2- Moderate, disturbing but still manageable
    3- Severe, very disturbing
    4- Extreme, near constant and disabling distress

4. **How much effort do you make to resist thoughts about Internet use? How often do you try to disregard these thoughts as they enter your mind?**
    0- Always make an effort to resist, or symptoms so minimal that active resistance is not needed
    1- Try to resist most of the time
    2- Make some effort to resist
    3- Yield to all thoughts without attempting to control them, but do so with some resistance
    4- Completely and willingly yield to all thoughts about the use of Internet

5. **How much control do you have over your thoughts about Internet use? How successful are you in stopping or diverting these thoughts? Can you dismiss them?**
    0- Complete control
    1- Much control, usually able to divert thoughts with some effort and concentration

2- Moderate control, sometimes able to stop or divert thinking
3- Little control, rarely successful in stopping or dismissing thinking, can only divert attention with difficulty
4- No control, experience is completely involuntary, rarely able even momentarily to alter thoughts about Internet use

6. How much time do you spend on the Internet?

0- None
1- Mild (less than an hour per day)
2- Moderate (1 to 3 hours per day)
3- Severe (3 to 8 hours per day)
4- Extreme (more than 8 hours per day)

7. How much does your Internet use interfere with your social, work or role functioning? Is there anything you don't do because of this?

0- None
1- Mild, slight interference with social or occupational activities but overall performance is not impaired
2- Moderate, definite interference with social or occupational performance but still manageable
3- Severe, causes substantial impairment in social or occupational performance
4- Extreme, incapacitating

8. How would you feel if you were prevented from using the Internet? How anxious would you be?

0- None
1- Mild, only slightly anxious if prevented from activity
2- Moderate, anxiety would mount but would remain manageable
3- Severe, prominent, and very disturbing increase in anxiety
4- Extreme, incapacitating anxiety

9. How much of an effort do you make to resist using the Internet?

0- Always make an effort to resist, or symptoms so minimal that active resistance is not needed
1- Try to resist most of the time
2- Make some effort to resist
3- Yield to all thoughts without attempting to control them, but do so with some resistance
4- Completely and utterly yield to all thoughts about using the Internet

10. How strong is your drive to use the Internet? How much control do you have over it?

0- Complete control
1- Much control, usually able to control
2- Moderate control, strong pressure to use the Internet but can control it with difficulty
3- Little control, strong pressure to use the Internet
4- No control, experience is completely involuntary

Appendix 9. Unified Parkinson's disease rating scale (UPDRS) – Part III

Speech

0 – normal
1 – slight loss of expression, diction, volume
2 – monotone, slurred but understandable, moderate impaired
3 – marked impairment, difficult to understand
4 – unintelligible

Facial Expression

0 – Normal
1 – slight hypomymia, could be poker face
2 – slight but definite abnormal diminution in expression
3 – mod. hypomimia, lips parted some of time
4 – masked or fixed face, lips parted 1/4 of inch or more with complete loss of expression

Tremor at Rest

Face
0 – absent
1 – slight and infrequent
2 – mild and present most of time
3 – moderate and present most of time
4 – marked and present most of time

Right Upper Extremity (RUE)
0 – absent
1 – slight and infrequent
2 – mild and present most of time
3 – moderate and present most of time
4 – marked and present most of time

Left Upper Extremity (LUE)
0 – absent
1 – slight and infrequent
2 – mild and present most of time
3 – moderate and present most of time
4 – marked and present most of time

Right Lower Extremity (RLE)
0 – absent
1 – slight and infrequent
2 – mild and present most of time
3 – moderate and present most of time
4 – marked and present most of time

Left Lower Extremity (LLE)
0 – absent
1 – slight and infrequent
2 – mild and present most of time
3 – moderate and present most of time
4 – marked and present most of time

Action or Postural Tremor

RUE
0 – absent
1 – slight, present with action
2 – moderate, present with action
3 – moderate present with action and posture holding
4 – marked, interferes with feeding

LUE
0 – absent
1 – slight, present with action
2 – moderate, present with action
3 – moderate present with action and posture holding
4 – marked, interferes with feeding

Rigidity

Neck
0 – absent
1 – slight or only with activation
2 – mild/moderate
3 – marked, full range of motion
4 – severe

RUE
0 – absent
1 – slight or only with activation
2 – mild/moderate
3 – marked, full range of motion
4 – severe

LUE
0 – absent
1 – slight or only with activation
2 – mild/moderate
3 – marked, full range of motion
4 – severe

RLE
0 – absent
1 – slight or only with activation
2 – mild/moderate
3 – marked, full range of motion

4 – severe

LLE
0 – absent
1 – slight or only with activation
2 – mild/moderate
3 – marked, full range of motion
4 – severe

Finger taps

Right
0 – normal
1 – mild slowing, and/or reduction in amplitude
2 – moderately impaired; definite and early fatiguing, may have occasional arrests
3 – severely impaired; frequent hesitations and arrests
4 – can barely perform

Left
0 – normal
1 – mild slowing, and/or reduction in amplitude
2 – moderately impaired; definite and early fatiguing, may have occasional arrests
3 – severely impaired; frequent hesitations and arrests
4 – can barely perform

Hand Movements (open and close hands in rapid succession)

Right
0 – normal
1 – mild slowing, and/or reduction in amplitude
2 – moderately impaired; definite and early fatiguing, may have occasional arrests
3 – severely impaired, frequent hesitations and arrests
4 – can barely perform

Left
0 – normal
1 – mild slowing, and/or reduction in amplitude
2 – moderately impaired; definite and early fatiguing, may have occasional arrests
3 – severely impaired; frequent hesitations and arrests
4 – can barely perform

Rapid Alternating Movements (pronate and supinate hands)

Right
0 – normal
1 – mild slowing, and or reduction in amplitude

2 – moderately impaired; definite and early fatiguing, may have occasional arrests
3 – severely impaired; frequent hesitations and arrests
4 – can barely perform

Left
0 – normal
1 – mild slowing, and/or reduction in amplitude
2 – moderately impaired; definite and early fatiguing, may have occasional arrests
3 – severely impaired; frequent hesitations and arrests
4 – can barely perform

Leg Agility (tap heel on ground, amplitude should be 3 inches)

Right
0 – normal
1 – mild slowing, and/or reduction in amplitude
2 – moderately impaired; definite and early fatiguing, may have occasional arrests
3 – severely impaired; frequent hesitations and arrests
4 – can barely perform

Left
0 – normal
1 – mild slowing, and/or reduction in amplitude
2 – moderately impaired; definite and early fatiguing, may have occasional arrests
3 – severely impaired; frequent hesitations and arrests
4 – can barely perform

Arising From Chair (patient arises with arms folded across chest)

0 – normal
1 – slow, may need more than one attempt
2 – pushes self up from arms or seat
3 – tends to fall back, may need multiple tries but can arise without assistance
4 – unable to arise without help

Posture

0 – normal erect
1 – slightly stooped, could be normal for older person
2 – definitely abnormal, moderately stooped, may lean to one side
3 – severely stooped with kyphosis
4 – marked flexion with extreme abnormality of posture

Gait

0 – normal
1 – walks slowly, may shuffle with short steps, no festination or propulsion
2 – walks with difficulty, little or no assistance, some festination, short steps or propulsion
3 – severe disturbance, frequent assistance
4 – cannot walk

Postural Stability (retropulsion test)

0 – normal
1 – recovers unaided
2 – would fall if not caught
3 – falls spontaneously
4 – unable to stand

Body Bradykinesia/ Hypokinesia

0 – none
1 – minimal slowness, could be normal, deliberate character
2 – mild slowness and poverty of movement, definitely abnormal, or decreased amplitude of movement
3 – moderate slowness, poverty, or small amplitude
4 – marked slowness, poverty, or amplitude