Pathological gambling and other addictive behaviours in Parkinson's disease

Thesis submitted in fulfillment of the degree of

Doctor of Philosophy

Reta Lila Weston Institute of Neurological Studies

UCL Institute of Neurology

University College London

2013

Atbin Djamshidian-Tehrani

I, Atbin Djamshidian-Tehrani confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed:

Date:

Abstract

The phenomenology of impulsive compulsive behaviours in patients with Parkinson's disease (PD) treated with dopaminergic therapy has been reviewed. Neuropsychological studies have been conducted to explore the behavioural mechanisms responsible for these socially devastating disorders, which affect a substantial proportion of treated patients.

Results demonstrated that poor information sampling and impaired working memory capacity, especially when mental manipulation of information was required, distinguish PD patients with impulsive compulsive behaviours from those without. A direct comparison to non PD-patients with addictions revealed that impulsive PD patients closely resembled illicit drug abusers, whereas non-impulsive PD patients treated with a dopamine agonist performed similarly to pathological gamblers. PD patients who were not taking dopamine agonists performed as well as healthy volunteers, even when treated with deep brain stimulation. Therefore, dopamine agonists are the single most important risk factor for impulsive choice in PD.

Conversely, response inhibition and feedback learning were intact in medicated PD patients with impulsive compulsive behaviours. Furthermore, all PD patients became more risk prone after dopaminergic medication, but greater salivary cortisol release only correlated with risk taking behaviour in the PD group with behavioural addictions. Cortisol plays also a prominent role in stress regulation. Therefore, the literature was reviewed to explore links between emotional stress and PD.

Papers associated with this thesis

1) Djamshidian A, Cardoso F, Grossett D, Bowden-Jones H, Lees A. "Pathological Gambling in Parkinson's disease. A review of the literature". Mov Disord. 2011 Sep;26(11):1976-84.
2) Djamshidian A, Averbeck BB, Lees A, O'Sullivan SS. "Clinical aspects of impulsive compulsive behaviours in Parkinson's disease". J Neurol Sci. 2011 Nov 15;310(1-2):183-88.
3) Djamshidian A, Jha A, O'Sullivan SS, Silveira-Moriyama L, Jacobson C, Brown P, Lees A, Averbeck BB. "Risk and learning in impulsive and non- impulsive patients with Parkinson's disease". Mov Disord. 2010 Oct 15;25(13):2203-10.
4) Djamshidian A, O'Sullivan SS, Doherty KM, Lees A, Averbeck BB. "Altruistic punishment in patients with Parkinson's disease with and without impulsive behaviour". Neuropsychologia 2011 Jan;49(1):103-37.
5) Djamshidian A, O'Sullivan SS, Lees A, Averbeck BB. "Stroop test performance in impulsive and non-impulsive patients with Parkinson's disease". Parkinsonism Relat Disord. 2011 Mar;17(3):212-14.
6) Djamshidian A, O'Sullivan SS, Wittmann B. Lees A, Averbeck BB. "Novelty seeking behaviour in Parkinson's disease". Neuropsychologia. 2011 Jul;49(9):2483-88.
7) Djamshidian A, O'Sullivan SS, Sanotsky Y, Sharman S, Matviyenko Y, Foltynie T, Michalczuk R ,Aviles-Olmos I, Fedoryshyn L, Doherty KM, Filts Y, Selikhova M, Bowden-Jones H, Joyce E, Lees A, Averbeck BB. " Decision making impulsivity and addictions: Do Parkinson's disease patients jump to conclusions?" Mov Disord. 2012 Aug;27(9):1137-45.

8) Djamshidian A, O'Sullivan SS, Foltynie T, Aviles-Olmos I, Limousin P, Zrinzo L, Lees A, Averbeck BB. “Dopamine agonists cause reflection impulsivity in Parkinson’s disease, not Deep Brain Stimulation”. Journal of Parkinson’s disease 2013 3(2):139-44.

9) Djamshidian A, Sanotsky Y, Matviyenko Y, O;Sullivan SS, Sharman S, Selikova M, Fedoryshyn L, Filts Y, Bearn J, Lees A, Averbeck BB. “Increased reflection impulsivity in patients with ephedrone induced Parkinsonism”. Addiction 2012. Dec.11.

10) Djamshidian A, O'Sullivan SS, Papadopoulos A, Bassett P, Shaw K, Averbeck BB, Lees A. “Salivary cortisol levels in Parkinson's disease and its correlation to risk behaviour”. J Neurol Neurosurg Psychiatry. 2011 Oct;82(10):1107-11.

Related publications during the degree period

1) Djamshidian A, O'Sullivan SS, Lees A, Averbeck BB. “Effects of dopamine on sensitivity to social bias in Parkinson's disease”. PLoS One. 2012;7(3).e32889.

2) Averbeck BB, Djamshidian A, O'Sullivan SS, Housden CR, Roiser JP, Lees AJ. “Uncertainty about mapping future actions into rewards may underlie performance on multiple measures of impulsivity in behavioral addiction: evidence from Parkinson's disease”.Behav Neurosci. 2013 Apr;127(2):245-55.

3) 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 Apr;134(Pt 4):969-78.

4) O'Sullivan SS, Djamshidian A, Ahmed Z, Evans AH, Lawrence AD, Holton JL, Revesz T, Lees AJ. ” Impulsive-compulsive spectrum behaviors in pathologically confirmed progressive supranuclear palsy”. Mov Disord. 2010 Apr 15;25(5):638-42.

5) O'Sullivan SS, Djamshidian A, Evans AH, Loane CM, Lees AJ, Lawrence AD. "Excessive hoarding in Parkinson's disease". Mov Disord. 2010 Jun 15;25(8):1026-33.

List of abbreviations

ACC	Anterior cingulate cortex
AM	Amygdala
ANOVA	Analysis Of Variance
BOLD	Blood-Oxygen-Level Dependent
C	Congruent
CG	Cingulate gyrus
CO	Control
CO-O	Elderly Controls
CO-Y	Young Controls
COMT	Catechol-O-Methyl Transferase
DA	Dopamine Agonists
DAT	Dopamine Transporter Scan
DBS	Deep Brain Stimulation
DDS	Dopamine Dysregulation Syndrome
DRT	Dopamine Replacement Therapy
DSM-IV	Diagnostic and Statistical Manual, 4th Edition
FAB	Frontal Assessment Battery
fMRI	functional Magnetic Resonance Imaging
HC	Hippocampus
HIP	Hippocampus
HPA	Hypothalamo-Pituitary-adrenal Axis
I	Incongruent
IBS	Irritable Bowel Syndrome
ICBs	Impulsive Compulsive Behaviours
IGT	Iowa Gambling Task
I.V.	Intravenous
KHZ	Kilohertz
KMNO4	Potassium Permanganate

L-DOPA	Levodopa
LEU	L-dopa Equivalent Unit
LRRK2	Leucine- Rich Repeat-Kinase type 2
MAO-B	Monoamine Oxidase B
MMSE	Mini Mental State Examination
MPTP	1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSA	Multiple System Atrophy
NAc	Nucleus accumbens
NEG	Negative
NMDA	N-Methyl D-Aspartate
NS	Not Significant
6-OHDA	6-Hydroxydopamine
OCD	Obsessive Compulsive Disorder
OFC	Orbitofrontal cortex
PFC	Prefrontal cortex
PPA	Phenylpropranolamine
PANAS	Positive and Negative Affect Schedule
PD	Parkinson's disease
PD+ICB	PD patients with Impulsive Compulsive Behaviours
PD-ICB	PD patients without Impulsive Compulsive Behaviours
PD+PG	PD patients with Pathological Gambling
PET	Positron Emission Tomography
PG	Pathological Gambling
POS	Positive
PSP	Progressive Supranuclear Palsy
QUIP	Questionnaire for Impulsive Compulsive Disorders in Parkinson's disease
RAC	Raclopride
RLS	Restless Legs Syndrome

RT	Reaction Time
SD	Standard Deviation
SE	Standard Error
SEM	Standard Error of the Mean
SPECT	Single-Photon Emission Computed Tomography
SSRI	Selective Serotonin Reuptake Inhibitor
STN	Subthalamic Nucleus
UCLH	University College London Hospitals
UK	United Kingdom
UPDRS	Unified Parkinson's disease Rating Scale
VTA	Ventral tegmental area
WM	Working memory
YRS	Years

Table of contents

Abstract 3

Papers associated with this thesis 4

Related publications during the degree period 5

List of abbreviations 7

Table of contents 10

List of tables 14

List of figures 15

Chapter 1 - Introduction to Parkinson's disease 17

Overview and research aims 17

Clinical features of Parkinson's disease 18

Diagnosis of Parkinson's disease 19

Environmental factors 22

Pharmacological treatment of Parkinson's disease and motor complications 24

Chapter 2 - Addictive behaviours in Parkinson's disease 26

2.1 Pathological gambling in Parkinson's disease 26

Phenomenology of pathological gambling in Parkinson's disease 31

Prevalence of pathological gambling 32

Risk factors for pathological gambling 33

Mechanisms underlying pathological gambling in Parkinson's disease 36

Model of brain circuits involved in addictive behaviours in the general population 39

Imaging studies in patients with Parkinson's disease with pathological gambling 41

Treatment of patients with Parkinson's disease with pathological gambling 43

2.2. Other treatment related behavioural disturbances in Parkinson's disease 48

Phenomenology and prevalence of ICBs in Parkinson's disease 49

'Green flags' for the development of ICBs in Parkinson's disease 55

Personality traits, decision-making and reward processing in Parkinson's disease 57

Brain circuitry implicated in patients with Parkinson's disease with ICBs 60

Behavioural changes after dopamine agonist therapy *66*

Mechanisms underlying ICBs in Parkinson's disease *68*

Treatment of patients with Parkinson's disease with ICBs *69*

Conclusion *73*

Chapter 3 - Behavioural tests in patients with Parkinson's disease 75

Introduction *75*

***3.1. Risk and learning in Parkinson's disease* 81**

Introduction *81*

Patients and methods *81*

Statistical analysis *87*

Results *89*

Discussion *97*

Conclusion *101*

***3.2. Altruistic punishment in patients with Parkinson's disease with and without impulsive behaviour* 103**

Introduction *103*

Patients and methods *105*

Statistical analysis *109*

Results *110*

Discussion *114*

Conclusion *117*

***3.3. Stroop test performance in impulsive and non-impulsive patients with Parkinson's disease* 118**

Introduction *118*

Patients and methods *119*

Statistical analysis *122*

Results *123*

Discussion *126*

Conclusion *128*

***3.4 Novelty seeking behaviour in Parkinson's disease* 129**

Introduction *129*

Patients and methods *131*

Statistical analysis *135*

Results *138*

Discussion *142*

Conclusion *145*

3.5. Decision-making, impulsivity and addictions: Do Parkinson's disease patients jump to conclusions? **147**

Introduction *147*

Patients and methods *149*

Statistical analysis *154*

Results *158*

Sensitivity of the beads task versus the QUIP in detecting impulsive behaviours in PD *171*

Discussion *172*

Conclusion *177*

3.6. Dopamine agonists cause reflection impulsivity in Parkinson's disease, not Deep Brain Stimulation **179**

Introduction *179*

Patients and methods *180*

Statistical analysis *183*

Results *183*

Discussion *190*

Conclusion *193*

3.7. Jumping to conclusions behaviour in patients with ephedrone induced Parkinsonism **195**

Introduction *195*

Patients and methods *198*

Statistical analysis *202*

Results *203*

Discussion *210*

Conclusion *214*

Chapter 4 - The role of Stress in Parkinson's disease **215**

Introduction *215*

Psychogenic Parkinsonism *217*

Stress induced reversible Parkinsonism *218*

Stress induced neuronal damage *221*

Variants of stress *223*

Kinesia paradoxica in Parkinson's disease *224*

Stress induced functional somatic syndromes *226*

Clinical overlap between functional somatic syndromes and Parkinson's disease *229*

Striato-thalamo-cortical alterations in functional somatic syndromes *232*

The prodrome of Parkinson's disease *234*

Conclusion *237*

4.1. The role of cortisol in Parkinson's disease **239**

Introduction *239*

Patients and methods *240*

Discussion *250*

Conclusion *252*

Summary and general discussion **254**

Future work *258*

Acknowledgments **260**

Appendix **261**

Bibliography **263**

List of tables

Table 1. *Diagnostic criteria of pathological gambling DSM-IV.* 28

Table 2. *Proposed criteria for compulsive sexual behaviour.* 50

Table 3. *Diagnostic criteria for DDS.* 52

Table 4. *Diagnostic criteria for compulsive shopping.* 53

Table 5. *Diagnostic criteria for binge eating (DSM-IV).* 54

Table 6. *Behavioural studies performed in PD+ICBs patients until March 2011.* 59

Table 7. *Risk and learning task: Demographic characteristics.* 90

Table 8. *Altruistic punishment: Demographic characteristics.* 106

Table 9. *Stroop test: Demographic characteristics.* 121

Table 10. *Novelty task: Demographic characteristics.* 139

Table 11. *Beads task: Demographic characteristics.* 159

Table 12. *Beads task: Pairwise comparisons.* 164

Table 13. *WM task: Pairwise comparisons for WM performance.* 168

Table 14. *WM task: Pairwise comparisons for recalling the distractors.* 170

Table 15. *STN-DBS: Demographic characteristics.* 184

Table 16. *STN-DBS: Pairwise comparisons.* 188

Table 17. *Ephedrone: Demographic characteristics.* 200

Table 18. *Cortisol: Demographic characteristics.* 243

List of figures

Figure 1. *Queen Square Brain Bank criteria of PD.* 20

Figure 2. *Illustration of the relevant structures involved in addictive behaviours.* 39

Figure 3. *Increased "bottom up" mesolimbic dopamine release.* 60

Figure 4. *^{11}C-raclopride binding potential between PD patients with and without ICBs.* 62

Figure 5. *Learning and risk task.* 86

Figure 6. *WM performance.* 92

Figure 7. *Learning from positive and negative feedback.* 94

Figure 8. *Risk preference.* 96

Figure 9. *Average punishment score of participants in fair and unfair rounds.* 113

Figure 10. *Stroop test: Behavioural results.* 125

Figure 11. *Sequence of events in 3-armed bandit task.* 133

Figure 12. *Novelty seeking task: Behavioural results.* 141

Figure 13. *Beads task.* 153

Figure 14. *WM task.* 156

Figure 15. *WM task: Positive and neutral distractors.* 157

Figure 16. *Beads task: Average number of draws per condition by group.* 162

Figure 17. *Beads task: Number of times participants chose the opposite colour.* 165

Figure 18. *WM performance.* 167

Figure 19. *WM task: Remembering distractors (positive, neutral, negative).* 169

Figure 20. *STN-DBS: Average drawing behaviour per condition of different groups.* 187

Figure 21. *STN-DBS: Number of times participants chose the opposite colour.* 189

Figure 22. *Ephedrone: WM performance.* 204

Figure 23. *Ephedrone: Effects of memoranda on WM performance.* 206

Figure 24. *Ephedrone: Average drawing behaviour per condition of different groups.* 207

Figure 25. *Ephedrone: Number of times participants chose the opposite colour.* 208

Figure 26. *Ephedrone: Risk and learning behaviour.* 209

Figure 27. *Stress induced micrographia.* 219

Figure 28. *Schematic outline of the time course of saliva samples.* 242

Figure 29. *Cortisol levels of participants.* 246

Figure 30. *Log scores of diurnal salivary cortisol levels.* 248

Chapter 1 - Introduction to Parkinson's disease

Overview and research aims

In this thesis behavioural addictions such as pathological gambling, compulsive sexual behaviour, compulsive shopping, punding and binge eating, collectively termed as impulsive compulsive behaviours (ICBs) in treated Parkinson's disease (PD) have been assessed on a variety of different neuropsychological tasks. PD patients were tested once prior to and once after their usual dopaminergic medication. Healthy volunteers were tested in the same way but without taking any medication. In a follow up study PD patients were directly compared to patients with pathological gambling and to substance abusers on opioid replacement therapy who both did not have PD.

To assess the role of dopamine agonists in decision making, non-impulsive PD patients with dopamine agonist medication in combination with Levodopa (L-dopa) treatment were compared to PD patients who were taking L-dopa but not dopamine agonists. Further, these two patient groups were compared to PD patients who were treated with deep brain stimulation of the subthalamic nucleus and were taking either L-dopa or L-dopa in combination with a dopamine agonist.

Patients with ephedrone induced extrapyramidal disorders due to chronic manganism have been also compared to substance abusers on opioid replacement therapy to assess the role of the accumbens-pallidum connection in decision making.

In the final chapter the role of stress as a potential trigger factor of PD has been reviewed. Further, salivary cortisol samples of PD patients with and without ICBs were obtained and correlated to risk taking behaviour.

Clinical features of Parkinson's disease

Idiopathic PD, originally described by James Parkinson in 1817 (Parkinson 1817), is a chronic progressive neurodegenerative disorder characterized by dopaminergic cell loss in the substantia nigra (Kish, Shannak et al. 1988, Fearnley and Lees 1991). It is the second most common neurodegenerative disease after Alzheimer's disease (de Lau and Breteler 2006). The median age of disease onset is 60 years and the incidence increases with age and affects about 1% of people over 60 and 2-3% over 65. It is unclear whether the disease plateaus or even declines after the age of 80 (Hirtz, Thurman et al. 2007) or whether this decline is artificial since PD is less likely to be diagnosed in geriatric patients (Lees, Hardy et al. 2009). The mean survival after the diagnosis is 15 years, with the most common cause of death being aspiration pneumonia (Lees, Hardy et al. 2009).

The cardinal features of PD, bradykinesia, tremor, rigidity and postural instability, only emerge when more than 30% of the dopaminergic neurons in the ventrolateral tier of the pars compacta have been destroyed (Cheng, Ulane et al. 2010). Over the last decade depression, apathy, fatigue, pain and cognitive problems have been increasingly studied (Chaudhuri, Healy et al. 2006). In some patients these can be more disabling than the motor handicap.

Diagnosis of Parkinson's disease

PD is a clinical diagnosis relying on bradykinesia, defined as a progressive reduction in the speed and amplitude of sequential movements (sequence effect), a rhythmical pill rolling rest tremor (4-6 Hz), rigidity and postural instability (Lees, Hardy et al. 2009). A unilateral onset and persistent asymmetry is present in about two thirds of cases (Gelb, Oliver et al. 1999). However, the diagnosis of PD can be difficult and error rates even amongst movement disorder specialists as high as 24 per cent, may occur in the earliest stages of the disease (Tolosa, Wenning et al. 2006). The commonest sources of error in neurological practice are in distinguishing the disorder from multiple system atrophy (MSA) - parkinsonism and progressive supranuclear palsy (PSP) - parkinsonism. Rare secondary causes such as atypical and dystonic tremor, drug induced or toxic parkinsonism, normal pressure hydrocephalus, dopa-responsive dystonia and psychogenic parkinsonism may masquerade as PD but can be distinguished by dopamine transporter (DAT) scan. Most patients experience a greater than 30% improvement in motor handicap with L-dopa therapy which is sustained over many years. Scales most commonly used to assess the response to L-dopa and disease severity are the Unified Parkinson's Disease Rating Scale (UPDRS part 3) and the Hoehn and Yahr rating scale (Hoehn and Yahr 1967). The Queen Square Brain Bank criteria of PD (Gibb and Lees 1988) have improved diagnostic accuracy and only slight changes to these accepted criteria of PD have been made over the last years, replacing in step two CT scan with an MRI scan and not ruling out PD if other family members are affected (Figure 1).

Queen Square brain bank clinical diagnostic criteria (Gibb and Lees 1988)

Step 1

Diagnosis of parkinsonian syndrome

Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude or repetitive actions)

And at least one of the following:

a) Muscular rigidity
b) 4–6 Hz rest tremor
c) Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

Step 2

Exclusion criteria for Parkinson's disease

History of repeated strokes with stepwise progression of parkinsonian features
History of repeated head injury
History of definite encephalitis
Oculogyric crises
Neuroleptic treatment at onset of symptoms
More than one affected relative
Sustained remission
Strictly unilateral features after 3 years
Supranuclear gaze palsy
Cerebellar signs
Early severe autonomic involvement
Early severe dementia with disturbances of memory, language, and praxis
Babinski signs
Presence of a cerebral tumour or communicating hydrocephalus on CT scan
Negative response to large doses of L-dopa (if malabsorption excluded)
MPTP exposure

Step 3

Supportive prospective positive criteria of Parkinson's disease

Three or more required for diagnosis of definite Parkinson's disease
Unilateral onset
Rest tremor present
Progressive disorder
Persistent asymmetry affecting the side onset most
Excellent response (70–100%) to L-dopa
Severe L-dopa-induced chorea
L-dopa response for 5 years or more
Clinical course of 10 years or more
Hyposmia

Visual hallucination

Figure 1. *Queen Square Brain Bank criteria of PD.*

Pathology of Parkinson's disease

The basal ganglia are made up of the caudate, the putamen (together referred to as the corpus striatum), the nucleus accumbens (referred to as the ventral striatum), the globus pallidus, the subthalamic nucleus and the substantia nigra.

For the neuropathological diagnosis of PD Lewy body pathology and dopaminergic cell loss, particularly in the ventrolateral tier of the substantia nigra, a region that projects mainly to the putamen is necessary (Fearnley and Lees 1991, Daniel and Lees 1993). Lewy bodies are neuronal intracytoplasmatic inclusions, which are particularly rich in aggregated α-synuclein, but also contain other proteins, including components of the ubiqiuitin-proteasome system (Brundin, Li et al. 2008). In PD Lewy bodies occur in the brain stem but can also be found in the cerebral cortex. However, the diagnostic value of Lewy bodies is unclear. Lewy bodies are present in 10%-40% in patients with Alzheimer's disease and in various other neurodegenerative diseases such as ataxia teleangiectasia or pantothenate kinase 2. Further, Lewy bodies occur in about 12% of octogenarians dying without recorded PD or dementia (Gibb and Lees 1988), which has led to a debate of whether Lewy bodies are damaging or are actually a compensatory survival mechanism of the neuron and thus are beneficial (Dickson, Braak et al. 2009). In some autosomal recessive forms of PD (such as parkin mutations), Lewy bodies are usually absent and the pathological lesion may be more restricted (Dickson, Braak et al. 2009).

It has been estimated that nigral cell loss begins about seven years before the first motor symptoms appear but some suggested that the disease may begin much earlier than this

in the enteric nervous system, sympathetic ganglia, olfactory bulb and medulla oblongata (Braak, Del Tredici et al. 2003).

Environmental factors

In 1973 a 23 year old addict injected 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and developed severe parkinsonism which was partially responsive to L-dopa. In the early 1980s another cluster of identical young cases were reported in San Francisco, who injected the same substance, which was sold to them as “synthetic heroin”. Those patients developed severe parkinsonism, which responded well to L-dopa but resulted in severe early motor fluctuations and hallucinations. Around 100 other addicts exposed to the same dosage remained unaffected, indicating individual susceptibility as a factor. MPTP is an inhibitor of a mitochondrial enzyme complex 1, causes selective damage to the substantia nigra (Langston, Ballard et al. 1983) and has proved to be a useful non-human primate model of PD for preclinical drug testing.

Another mitochondrial respiratory chain inhibitor is 6-Hydroxydopamine (6-OHDA), which is often used to create rodent models of PD. 6-OHDA has to be stereotactically targeted into the substantia nigra as it fails to cross the blood brain barrier. 6-OHDA, similarly to MPTP rapidly destroys the catecholaminergic systems, causing degeneration of the nigrostrital system (Schober 2004).

Manganese neurotoxicity was first described in 1837 by James Couper in five Scottish workers employed grinding manganese dioxide ore. Since then a large number of cases have been reported with a constellation of extrapyramidal symptoms labelled “chronic

manganism". Patients develop dystonia, a typical cock gait, a vacant facial expression, sometimes termed as "masque manganique", bradykinesia, and dysarthria. They may also develop neuropsychiatric symptoms known as "locura manganica" or "manganese madness" (Lucchini, Martin et al. 2009). In contrast to idiopathic PD a typical resting tremor is less prominent and patients develop early postural instability with a tendency to fall backwards (Lucchini, Martin et al. 2009). Further, imaging studies show severe damage of the globus pallidus and the substantia nigra pars reticularis. DAT scans, however, have been reported as normal (Olanow 2004). As a consequence these patients do not benefit from L-dopa (Olanow 2004) but may improve with chelation therapy. Manganism can be found in welders, in those with chronic liver failure, in patients receiving long term parental nutrition and in methcathinone abusers, who use potassium permanganese as an oxidant (Lucchini, Martin et al. 2009).

Other toxins such as agricultural chemicals, rotenone, maneb and paraquat, when administered systemically, can also resemble PD. Weak associations between PD and other environmental factors such as well water ingestion, middle age obesity, lack of exercise and rural living have been reported. Smoking and coffee consumptions have been inversely associated with PD (Lees, Hardy et al. 2009).

Although several genes responsible for PD have been discovered, these account currently for a small proportion of cases and 95% of the cases are considered to be sporadic. In these cases non-genetic factors probably in combination with genetic susceptibility are thought to trigger the disease (de Lau and Breteler 2006).

Pharmacological treatment of Parkinson's disease and motor complications

L-dopa although reported in the early 1960s by Hornykiewicz and collaborators and later introduced by Cotzias (Cotzias, Papavasiliou et al. 1969), still remains the most efficacious treatment for PD (Lees, Hardy et al. 2009). Non ergoline dopamine agonists such as pramipexole, ropinirole and rotigotine are other albeit less effective drugs targeting mainly the dopamine D2 and D3 receptors. The only dopamine agonist, which has been found to be as effective as L-dopa is apomorphine, which both have the highest affinity to the dopamine D1 receptor. Dopamine agonists have been claimed to be particularly useful in younger onset PD patients because when used as monotherapy they rarely induce drug induced dyskinesias. However, increasing reports of devastating behavioural side effects directly triggered by dopamine agonists have limited its use. Further, motor deterioration requires the introduction of L-dopa therapy usually within 3 years after diagnosis (Lees, Hardy et al. 2009). Other therapies include selective type B monoamine oxidase inhibitors (MAO) selegeline and rasagiline, catechol-O-methyl transferase inhibitors (entacapone and tolcapone) or amantadine.

After about 3-5 years of treatment with L-dopa patients start to notice some wearing off of individual doses and attempts to overcome this by increasing dosage or frequency of L-dopa may lead to the emergence of inter-dose chorea or less commonly onset and end of dose dyskinesias. Nocturnal difficulties also increase with difficulties turning in bed and getting out of bed. As treatment continues capricious motor fluctuations likened to the switching on and off of a light switch may develop despite treatment modification.

Gait freezing, start hesitation, poor balance and falls are other causes of morbidity in the later stages. Dementia is one of the most debilitating consequences of PD with frequencies ranging between 30-80% of patients (Obeso, Rodriguez-Oroz et al. 2010).

Indeed four milestones of advanced PD have been described as markers for severe motor impairment: Frequent falls, visual hallucinations, dementia and need for residential care (Kempster, O'Sullivan et al. 2010). For those patients who have severe refractory motor fluctuations deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an option. However, STN-DBS has its limitations as it fails to improve some parkinsonian features such as freezing of gait, postural instability and can worsen dysphagia, cognitive function and speech (Weaver, Follett et al. 2009). Suicide and severe abulia are recognised rare risks of operated patients (Piasecki and Jefferson 2004). Although STN-DBS alleviates motor handicaps in both older and younger PD patients, postoperative quality of life only improves in patients who are younger than 65 years (Derost, Ouchchane et al. 2007). Pallidal DBS for dyskinesias and stimulation of the ventral intermediate nucleus of the thalamus for tremor are other commonly used targets in PD (Walter and Vitek 2004).

Alternative therapies, such as continuous subcutaneous apomorphine administration via a pump system and the enteral administration of an L-dopa formulation (duo-dopa), may have to be considered in suitable patients (Lees, Hardy et al. 2009).

Chapter 2 - Addictive behaviours in Parkinson's disease

2.1 Pathological gambling in Parkinson's disease

Gambling was first described more than 6000 years ago in ancient Egypt and was also popular in the ancient civilisations of China, Babylon and India. In Greek mythology the gods Zeus, Poseidon and Hades divided the universe by casting dice and descriptions of gaming can also be found in the Old Testament and the Koran (Arnold 1977). The first private lottery was founded in Florence in 1530, and gambling subsequently became a lucrative business in Europe. In England the first law prohibiting gambling was enacted in 1661 to prevent members of the lower classes from ruining their lives (Arnold 1977). It is also claimed that the devastating fire of Chicago in 1871 was caused by a preoccupied gambler accidentally knocking over a lantern while shooting dice in a barn (Flemming 1978).

The word *'risk'* derives from the Latin word *'risicare'* and means *'to dare'*. It necessitates an element of danger and uncertainty about outcome but can bring opportunity, and without an element of risk taking there can be no innovation or social progress, quoting a common saying: *"The biggest risk of life is not taking one"*. A degree of novelty seeking with its implicit risk taking is part of normal adolescence and contributes to independence from ones parents control (Kelley, Schochet et al. 2004).

Gambling involves risk taking on the outcome of an event determined by chance (Korn and Shaffer 1999) and in the market place has been considered an evolutionary response to risk management. Successful entrepreneurs balance risks and returns to ensure that profits compensate for their level of risk taking and often adopt one of the most common sayings on Wall Street *"cut your losses short and let your winners run"* in their everyday dealings. Risk managers also frequently take chances in order to make higher profits, but these decisions are logical and based on experience and knowledge rather than emotion. However, the path between Scylla and Charybdis is narrow, and overconfidence and misjudgement can easily occur, as seen in the *'Great crash'* of 1929 and the credit crunch of 2008.

In professional gambling for large sums of money, discipline is crucial, risks are measured and calculated, and emotions and passion are concealed. Casinos employ risk management strategies to keep their financial risks as low as possible and may ban consistently successful gamblers from their tables. Recreational gamblers minimise their loss by playing with friends for relatively short periods of time and for manageable losses, but occasionally in susceptible individuals this innocent pastime can lead on to problem gambling. Problem gamblers start to overestimate their chances of winning and start developing an *"illusion of control"* in games in which the probabilities of winning is at chance level (Langer 1975).

In recent years the popularity of all forms of gambling has increased in many countries, partly as a result of internet betting. According to the British Gambling Prevalence

Study 2007, approximately 32 million adults had participated in some form of gambling during the previous year (Wardle, Sproston et al. 2007).

Pathological gambling (PG) is defined as inappropriate, persistent, and maladaptive gaming behaviour, which has been included by psychiatrists within the broader category of impulse control disorders (American Psychiatric Association 2000). (See Table 1).

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

- is preoccupied with gambling (e.g. 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 jeopardized 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.

Table 1. *Diagnostic criteria of pathological gambling DSM-IV.*

(American Psychiatric Association 2000).

Vivid descriptions of the personality of the gambler appear in the world's great literature including Dostoevsky's autobiographical account of his own addiction in *'The Gambler'.* Pushkin's novel *'The Queen of Spades'* written in 1833, deals with human avarice, a superstitious belief of an invincible sequence of winning cards, and eventual madness of the protagonist, Hermann.

Pathological gamblers ruminate and become preoccupied with gambling to the detriment of everyday responsibilities; they lose self-control of their finances and become manipulative and deceitful, particularly where money is concerned. They gamble to relieve stress and escape into a make-believe world, which at first is exciting and rewarding. They withdraw socially and avoid former friends and contacts, lie and steal from family, friends and acquaintances. Personal relationships deteriorate, and they may lose their job due to increasing unreliability and absenteeism. They feel guilt and remorse but become irritable and hostile when deprived of the opportunity to gamble. Eventually they experience little or no pleasure on winning even large sums of money. Patients continue gambling to recover their losses, often known as *"loss chasing behaviour"* (Lesieur 1984). Loss chasing contributes significantly to pathological gambling as patients lose control over the amount of money spent (Lesieur 1979). This behaviour is driven mainly by anxiety over the already acquired debt and losses but on the other hand loss chasing is also driven by hope to win the jackpot (Campbell-Meiklejohn, Woolrich et al. 2008). "*It's one crisis after another and you gamble to get even…one big hit, make that one big hit, and pay off the bets and never gamble again"* (Lesieur 1984).

Patients also start feeling guilty, pessimistic and depressed. *"Then came the feeling of uneasiness within myself; a feeling of, probably you might call it of impending doom or disaster, that I had never had before. There was no way I wasn't going to blow everything"* (Lesieur 1984).

The clinical diagnosis of PG requires the presence of least five out of ten *'green flags'* on a structured interview whereas "problem gambling" is often used in the presence of only two or three of these warning signs (Shaffer, Hall et al. 1999, American Psychiatric Association 2000).

The British Gambling Prevalence Study 2007 have estimated a prevalence of problem gambling in the UK population of 0.6% (Wardle, Sproston et al. 2007). Higher figures have been reported in the United States of America where the lifetime prevalence of PG is considered to be 1.6% (Shaffer, Hall et al. 1999). A subgroup of patients with PD develops a constellation of socially disruptive behavioural addictions during long-term dopamine replacement. These include pathological gambling, hyperlibidinous behaviour and paraphilias, compulsive shopping, binge eating, hoarding and reckless generosity. One fourth of these patients exhibit more than one addictive behaviour at the same time (Weintraub, Koester et al. 2010).

PG in Parkinson's disease was first described 13 years ago in a South African patient prescribed pergolide (Seedat, Kesler et al. 2000) and is now generally accepted as a complication of dopaminergic therapy.

Illustrative case

A 52-year-old male with PD was initially treated with L-dopa. He took medication only on weekdays because he had a natural dislike of tablets. Four years after diagnosis L-dopa was stopped altogether on the patient's request, but deteriorating mobility led to the need for replacement with the dopamine agonist drug pramipexole, the dose of which was increased steadily to 3mg salt daily. Within a few months his wife reported that he had started to gamble uncontrollably and was spending £170-£200 per week on scratch cards and at bookmakers. He obsessively studied the form of jockeys and used lucky stones in the belief they would improve his chances of winning. He became devious and manipulative and hid scratch cards from his wife. In just over a year he lost £10,000 on gambling. At the same time he developed a craving for sweets and started binge eating. Once this behaviour came to medical attention, pramipexole was reduced and then stopped altogether, and L-dopa was reintroduced. Within a few weeks his behaviour returned to normal, and he lost all further interest in gambling.

Phenomenology of pathological gambling in Parkinson's disease

In the UK, the British Gambling Prevalence Study 2007 showed that online roulette and spread betting were the commonest gambling activities leading to PG (Wardle, Sproston et al. 2007). In the United States, pull tabs, a paper version of an electronic slot machine game where the player has to open tabs for winning symbol combinations, was most frequently reported, followed in descending order by casino games, bingo, lottery cards and betting on sporting events (Welte, Barnes et al. 2004). Several studies have reported

that PD patients with PG have a particular predilection for slot machines (Gallagher, O'Sullivan et al. 2007, Cilia, Siri et al. 2008). Slot machines offer rapid pay out intervals equally brief loss periods, giving patients little time to reflect and providing the opportunity for winnings to be re-gambled almost instantly (Griffiths 1999). Arousing lights and enticing coin chimes are powerful associated reinforcing sensory reward cues. Playing slot machines is mechanical, ritualistic and involves repetitive stereotyped movements similar to those seen in some types of punding (Voon, Hassan et al. 2006). Near misses and immediate rewards render these games highly addictive, especially for individuals who seek instant self-gratification (Voon, Reynolds et al. 2010). Scratch cards and lottery are other popular pursuits for PD gamblers whereas, poker, spread betting, and speculating on the stock exchange occur but seem to be less popular (Gallagher, O'Sullivan et al. 2007).

Prevalence of pathological gambling

Cross sectional studies have shown a lifetime prevalence of PG in treated PD between 3.4% and 6% (Avanzi, Baratti et al. 2006, Grosset, Macphee et al. 2006, Voon, Hassan et al. 2006, Weintraub, Koester et al. 2010). Higher prevalence rates have been reported in patients treated with a dopamine agonist (6-8%) (Grosset, Macphee et al. 2006, Singh, Kandimala et al. 2007). In a questionnaire survey of 3000 North American PD patients, PG was found to be more prevalent in the United States (5.5%) than in Canada (3.6%), possibly because of easier casino access and more explicit and overt advertising in the United States (Weintraub, Koester et al. 2010). Even these high figures of PG in

PD may be a significant underestimate, as many patients have a reduced insight into the social consequences of their behaviour or conceal it from their families because of shame or denial (Singh, Kandimala et al. 2007). An online survey has claimed a figure of 13%, but possible selection bias (online survey that requires registration focussing on gambling) and the lack of confirmation of the diagnosis of PD by neurological examination are important limitations of this study (Wicks and MacPhee 2009). Much lower prevalence rates between 0.32% and 1.3% for PG in PD have been reported in China and Korea where the opportunity to gamble is restricted (Fan, Ding et al. 2009, Lee, Kim et al. 2009).

Risk factors for pathological gambling

Comparison studies between patients with amyotrophic lateral sclerosis and treated PD patients showed that PG was significantly more common in PD, supporting the notion that aberrant pathways involving risk taking rather than a chronic neurological handicap are responsible for gambling (Wicks and MacPhee 2009). Pathological gambling was not reported in association with Parkinson's disease until the modern era of pharmacotherapy (Molina, Sainz-Artiga et al. 2000, Avanzi, Baratti et al. 2006). However, in 1822 Théodore Géricault painted the *Madwoman Obsessed With Gambling,* illustrating a woman with hypomimia, stooped shoulders, and a walking aid, who might be the first documented PD patient with PG (Healy 2007).

The large majority of PD patients with PG never gambled regularly before the onset of dopamine agonist therapy, and it is this single factor that contributes by far the greatest

risk. PG and other behavioural addictions have been described in atypical parkinsonism (O'Sullivan, Djamshidian et al. 2010) and also in patients with no evidence of striatal damage such as patients with restless legs syndrome (Ondo and Lai 2008), pituitary adenomas (Falhammar and Yarker 2009) and fibromyalgia when they have been treated with dopamine agonists (Holman 2009).

While the vast majority of PD patients develop PG on dopamine agonist medication (Gallagher, O'Sullivan et al. 2007), less than ten patients have been treated with L-dopa monotherapy (Ardouin, Voon et al. 2006, Avanzi, Baratti et al. 2006, Solla, Cannas et al. 2011) and one patient was taking a combination of selegiline and L-dopa (Drapier, Drapier et al. 2006). It is therefore likely that PG on L-dopa monotherapy corresponds roughly with the prevalence of PG in the general population. There is no convincing proof that non ergolene dopamine agonists (e.g. pramipexole and ropinirole) are more likely to induce PG than ergolene agonists such as bromocriptine and cabergoline (Gallagher, O'Sullivan et al. 2007). Less information is available yet for the more recently introduced transdermal rotigotine, a non ergolene dopamine receptor agonist, (Wingo, Evatt et al. 2009) which in common with pramipexole and ropinirole has a high affinity to dopamine D3 receptors (Gerlach, Double et al. 2003, Jenner 2005).

Animal studies have shown a potential benefit of dopamine D3 antagonists on craving behaviour in rats (Higley, Spiller et al. 2011),however, studies in humans have yet to be performed.

PG usually develops after a few months of drug therapy, suggesting either duration of treatment or cumulative dosage is an independent risk factor (Evans, Strafella et al.

2009). Although PG may occur at low doses of dopamine agonist medication, higher doses further increase the risk in susceptible individuals (Hassan, Bower et al. 2011) and the combination of lower doses of an agonist with L-dopa also seems to increase risk (Gallagher, O'Sullivan et al. 2007, Evans, Strafella et al. 2009, Bharmal, Lu et al. 2010, Weintraub, Koester et al. 2010, Hassan, Bower et al. 2011).

In common with pathological gambling in the general population (Petry, Stinson et al. 2005, Slutske, Caspi et al. 2005, Blanco, Hasin et al. 2006) male gender, a previous history of alcohol or substance abuse, a history of depression, and high novelty seeking personality traits have all been identified as risk factors in PD (Gallagher, O'Sullivan et al. 2007, Singh, Kandimala et al. 2007, Voon, Thomsen et al. 2007, Siri, Cilia et al. 2010). Young onset PD patients who are unmarried and smoke are also more vulnerable, particularly if there is a positive family history for addictive behaviours or pathological gambling (Weintraub, Koester et al. 2010). This is in sharp contrast to non-impulsive PD patients who have lower nicotine, alcohol and caffeine intake than the general population (Evans, Lawrence et al. 2006).

Apathy is linked with anxiety, depression and impulsivity and is more frequent in PD patients with PG compared to PD controls (Gallagher, O'Sullivan et al. 2007, Shapiro, Chang et al. 2007, Leroi, Andrews et al. 2009). It is often a prominent feature of the “off” state in patients who gamble when “on”. In these cases apathy may become a significant problem after dopamine agonist withdrawal (Czernecki, Schupbach et al. 2008, Thobois, Ardouin et al. 2010). Craving for sweets in PD patients is associated with dopamine agonist use, suggesting dopamine mediated alterations in reward

processing (Nirenberg and Waters 2006, Shahed, Davidson et al. 2006) and has been linked to novelty seeking and addictive behaviour in non PD patients (Lange, Kampov-Polevoy et al. 2010). Although approximately 20% of individuals with PG in the general population have a first degree relative who also has a gambling addiction (Ibanez, Blanco et al. 2003), no reliable genetic marker has yet been identified. Candidate gene studies on the TaqIA polymorphism, dopamine 1 and 4 receptor and the dopamine catechol-O-methyl transferase (COMT) gene have given conflicting results, and further work will be required to confirm these suggested associations (Comings, Gade et al. 1996, Vandenbergh, Rodriguez et al. 1997, Comings, Gonzalez et al. 1999, Eisen, Slutske et al. 2001, Foltynie, Lewis et al. 2005, da Silva Lobo, Vallada et al. 2007, Lobo, Souza et al. 2010).

Mechanisms underlying pathological gambling in Parkinson's disease

There are several similarities between PG and substance abuse, including an overriding desire to satisfy a craving, intrusive recurrent thoughts relating to the deleterious behaviour, and a loss of self-control (World Health Organization Geneva, 1992). It has been claimed that PG patients have more problems resisting the urge to gamble than drug abusers have in resisting their craving for 'a fix' (Castellani and Rugle 1995). PG is more prevalent amongst cocaine addicts (Hall, Carriero et al. 2000), and amphetamine can induce the desire to game in problem gamblers (Zack and Poulos 2004), suggesting that drugs that increase presynaptic dopaminergic terminal release increase the risk of

PG. Previous studies have proposed that slot machines and other electronic gaming machines are the “crack cocaine” of gambling with the highest addictive potential (Dowling, Smith et al. 2005). Pathological gamblers need to progressively increase the amount of money they risk over time in order to achieve equivalent levels of excitement, a behavioural response that resembles the dependence and tolerance observed in drug addicts. Withdrawal symptoms from PG similarly include depression, irritability and restlessness (Wray and Dickerson 1981). PD patients who gamble often report drug induced hypomania or euphoria on dopamine agonists (Voon, Thomsen et al. 2007). There is also a significant overlap between other addictions such as alcohol dependency, personality disorder and PG (Eisen, Slutske et al. 2001, Petry, Stinson et al. 2005).

In PD there is an uneven distribution of dopaminergic cell loss, with the dorsal striatum being much more severely damaged than the ventral striatum (Kish, Shannak et al. 1988). This has led to the hypothesis that exogenous dopaminergic medication, necessary to correct the depleted dopamine levels in the putamen, might over-stimulate the ventral circuitry (“cognitive overdose hypothesis”) leading to adverse behavioural and cognitive consequences (Gotham, Brown et al. 1988, Swainson, Rogers et al. 2000). Those PD patients with the most intact ventral striatum may therefore be at highest risk of developing PG. An opposing hypothesis is that the severity of the lesion in the A10 ventral tegmental area dictates the likelihood of treatment related behavioural disturbances, in the same way as the severity of the pars compacta nigral lesion predisposes to dyskinesias under pulsatile exogenous D2 stimulation (Jenner 2008).

Dopamine agonists increase activity in the ventral striatum during the anticipation of reward, but at the same time reduce interaction with the prefrontal cortex (Ye, Hammer et al. 2011). They also reduce reward processing in the lateral orbito frontal cortex and impair the negative reinforcing effect of losing (van Eimeren, Ballanger et al. 2009). Dopaminergic medication might also prevent dopamine dips that normally happen during negative feedback learning (Frank and O'Reilly R 2006). “Cool” or rational decision making is mediated via the dorsolateral prefrontal cortex and is necessary for risk/benefit evaluations and working memory, whilst “hot” decision making involves affective responses (Seguin, Arseneault et al. 2007). Modulation of this “hot” limbic versus “cool” executive balance caused by dopamine agonists is likely to lead to risky behaviour with impairment of long term negative feedback learning.

Model of brain circuits involved in addictive behaviours in the general population

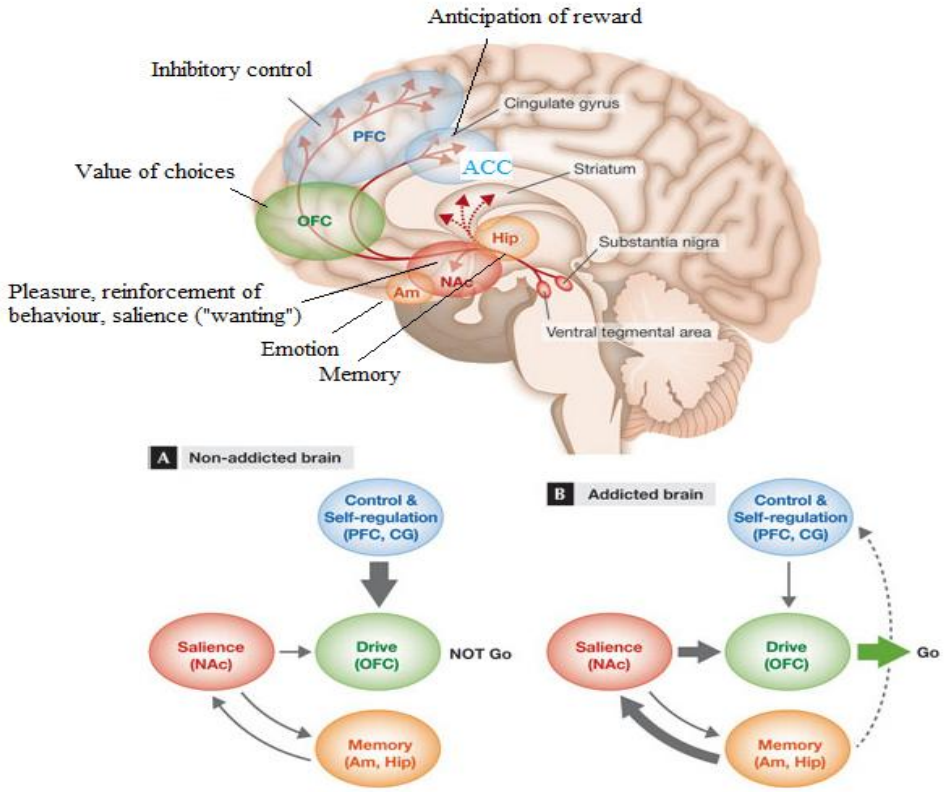

Figure 2. *Illustration of the relevant structures involved in addictive behaviours.*

A: In healthy controls inhibitory control from the PFC is sufficient to refrain stop an addictive behaviour. This regulatory mechanism is impaired in patients with addictions (B). Increased mesolimbic dopamine levels are responsible for an overvalue of an immediate action, causing pathological motivation. PFC=prefrontal cortex, CG=cingulate gyrus, ACC=anterior cingulate cortex, OFC=orbitofrontal cortex, Am=Amygdala, Hip=Hippocampus, NAc=nucleus accumbens. Permission to reproduce this figure was granted by the Nature publishing group. Figure adapted from Lee et al. (Lee, Carter et al. 2012).

The prefrontal cortex is necessary for inhibitory control (Aron, Robbins et al. 2004) and the orbitofrontal cortex is crucial for determining the value of a potential reward (Rolls 2000) (Figure 2). In healthy volunteers these brain areas prevent a behaviour to become addictive. In patients with addictions poor self-control impaired inhibitory control of the prefrontal cortex together with an overvalue of an outcome because of impaired orbitofrontal cortex function and an up regulation of mesolimbic dopamine release cause aberrant motivation (Figure 2) (Lee, Carter et al. 2012). Mesolimbic dopamine, originating from the ventral tegmental area and projecting to the prefrontal cortex via the ventral striatum and the amygdala, is known to reduce the reward threshold (Koob and Volkow 2010), causing the feeling of pleasure, which is necessary to reinforce an addictive behaviour. As the addiction continues, withdrawal symptoms and anxiety mediated via the amygdala occur (Koob and Volkow 2010). Projections from the amygdala to the ventral striatum reinforce pathological motivation to reverse the negative affect causing incentive salience ("wanting"). This model has been established for drug addiction and behavioural addiction in the general population (Koob and Volkow 2010, Lee, Carter et al. 2012), but can also explain addictive behaviours seen in PD. In fact, there are several studies strengthening the link between addictive behaviours seen in PD and drug addiction seen in the general population (Dagher and Robbins 2009, Koob and Volkow 2010).

Imaging studies in patients with Parkinson's disease with pathological gambling

Resting cerebral perfusion measured via single-photon emission computed tomography (SPECT) showed enhanced activation in the orbitofrontal cortex, the hippocampus, the amygdala, the insula, and the ventral pallidum in PD patients with PG. These alterations in the reward centres of the brain suggest possible drug induced overstimulation of an intact mesolimbic dopamine system (Cilia, Siri et al. 2008). A [^{11}C] raclopride positron emission tomography (PET) study measured striatal dopamine D2/D3 receptor binding and release of dopamine in seven PD patients with PG patients and seven patients without PG during the performance of a gambling task. PD patients with PG had a significant reduction of [^{11}C] raclopride bilaterally in the ventral striatum (Steeves, Miyasaki et al. 2009). Another recent PET study showed extra-striatal dopaminergic dysfunction in PD patients with PG, compared to non-impulsive PD patients. Increased midbrain dopamine release and a reduction of dopamine in the anterior cingulate were seen after 1 mg of pramipexole during gambling in PD patients with PG but not in PD controls. These dopaminergic changes correlated with impulsivity measured with the Barrat impulsivity scale (Ray, Miyasaki et al. 2012).

Some (Steeves, Miyasaki et al. 2009) but not all PET studies (Evans, Pavese et al. 2006, O'Sullivan, Wu et al. 2011) have also found lower D2/D3 receptor levels in PD patients with behavioural addictions posing an independent risk factor for developing an addictive behaviour (Nader, Morgan et al. 2006). A PET study measured regional cerebral blood flow during a computerized card game of seven PD patients with PG

patients versus control PD patients. Testing was done once prior to dopaminergic medication and once following the subcutaneous injection of 3 mg of apomorphine. Apomorphine caused reduced blood flow only in PD patients with PG, with reduction in the lateral orbitofrontal cortex, rostral cingulate zone, amygdala, and the globus pallidus externus. In contrast PD patients without PG had an increased blood flow in these regions, suggesting that dopamine agonists can affect areas that are critical for inhibition, negative feedback learning and executive control in vulnerable patients (van Eimeren, Pellecchia et al. 2010).

Functional MRI (fMRI) studies in a group of PD patients with PG and compulsive buying showed an increase in ventral striatum blood-oxygen-level dependent (BOLD) activity to reward after dopamine agonist medication. Correlation between imaging and behaviour suggests that impulsive PD patients have a higher positive prediction error and an increase in ventral striatum activity (Voon, Pessiglione et al. 2010). Another fMRI study in PD patients with PG patients also showed increased activation of the ventral striatum, mesial prefrontal and the anterior cingulate cortex following visual cues (Frosini, Pesaresi et al. 2010).

Taken together these findings indicate enhanced mesolimbic but also extra-striatal midbrain dopamine activation (“bottom up”) and reduced cortical dopamine (“top down”) levels during gambling in PD patients with PG.

Treatment of patients with Parkinson's disease with pathological gambling

Patients starting dopamine agonist therapy should be informed of the possible risk of PG and other treatment related behavioural disorders. In the UK all dopamine agonists now contain a warning about the risk of developing PG and other treatment related psychiatric disturbances in the product description. The information should be provided wherever possible in the presence of the family, who should also be advised to promptly report any changes that occur in the patient behaviour during agonist treatment (Grosset, Macphee et al. 2006, Singh, Kandimala et al. 2007). It is equally important to discuss the marked benefits that can occur with dopamine agonist treatment in a positive and encouraging fashion to avoid nocebo effects. A record of these discussions needs to be kept in the patient's case notes, and in the UK it is recommended to add a comment in the letter to the family physician that it has been carried out. Patients with a history of substance abuse, current smokers, those with younger onset of disease and who are single, are at increased risk of developing PG and require particularly close on-going supervision (Singh, Kandimala et al. 2007, Voon, Thomsen et al. 2007, Weintraub, Koester et al. 2010). In high risk patients L-dopa monotherapy may be a better initial treatment choice, regardless of the patient age. Although the highest risk of developing PG after dopamine agonist treatment is within the first few months (Evans, Strafella et al. 2009), clinicians must screen proactively for PG or other treatment induced psychiatric side effects at each clinic visit. If PG has developed, dopamine agonist therapy should be immediately reduced and in the absence of rapid improvement over

the next few weeks, discontinued altogether. L-dopa should be concurrently introduced or if the patient was already on combination therapy the dose slowly increased to control motor handicap.

Previous studies finding an increased risk of treatment related behavioural side effects in patients treated with L-dopa monotherapy or in combination with monoamine oxidase B inhibitors did not screen for dopamine dysregulation syndrome, which is more common with L-dopa (Weintraub, Koester et al. 2010). This is relevant, since a 4 year follow up study after dopamine agonists were withdrawn found a complete cessation of gambling behaviour in 15 out of 17 PD patients with PG patients, despite an increase of L-dopa from 615 to 881 mg (Macphee, Copeland et al. 2009).Therefore, monoamine oxidase B inhibitors and L-dopa remain the first and second line option in patients with PG (Grosset, Cardoso et al. 2011). Despite this, dopamine agonist withdrawal symptoms, which include anxiety, panic attacks, dysphoria, apathy and the subjective feeling of being “stiff “ may occur in one in five PD patients (Rabinak and Nirenberg 2010). These withdrawal symptoms sometimes remain refractory to antidepressants or cognitive behavioural therapy as well as further increases in L-dopa (Rabinak and Nirenberg 2010).

Family members should be instructed to limit access to money, credit cards, and the internet. Cognitive behavioural therapy focussing the patient more towards non gambling activities can be helpful in expert hands (Hodgins and Petry 2004). If agonist withdrawal fails to alleviate the problem, then patients and their families may need to seek advice from Gamblers Anonymous or help lines such as GamCare or be referred

(where available) to specialist gambling clinics. Depression (Gallagher, O'Sullivan et al. 2007), drug induced mood changes (Voon, Thomsen et al. 2007), and sleep disturbance (O'Sullivan, Loane et al. 2011) commonly occur in PD patients with PG and should be treated symptomatically with a tricyclic antidepressant (Menza, Dobkin et al. 2009) or an antidepressants with effects on noradrenergic uptake, for example, venlafaxine (Richard et al 2010, 2nd World Parkinson Congress, Glasgow Abstract P19.18), mirtazapine or reboxetine. Selective serotonin reuptake inhibitors (SSRIs) may not be the preferred initial treatment of choice for depression in PD (Skapinakis, Bakola et al. 2010). Antidepressants are also not beneficial in reducing gambling urges *per se* (Blanco, Petkova et al. 2002, Black, Arndt et al. 2007), and the evidence for using antipsychotic drugs in PD patients with PG is conflicting (Sevincok, Akoglu et al. 2007, McElroy, Nelson et al. 2008).

Recent preliminary studies with zonisamide and topiramate have shown promising initial results in reducing gambling urges in PD (Bermejo 2008, Bermejo, Ruiz-Huete et al. 2010). One double blind, placebo controlled, cross over study with open label extension using the N-methyl d-aspartate (NMDA) receptor antagonist amantadine was beneficial in 17 PD patients with PG patients, reducing or abolishing gambling urges and hours spent gambling. However, hallucinations were more common in treated patients and a relatively high number of patients with a disease duration over five years did not complete the study (Thomas, Bonanni et al. 2010). Furthermore, two other studies have shown that amantadine can increase the risk of PG and other treatment related behavioural disorders (Weintraub, Sohr et al. 2010, Lee, Kim et al. 2011).

Placebo responses in up to 59% in patients with PG have been reported, so that all these small open label studies need to be interpreted with great caution (Blanco, Petkova et al. 2002).

Conclusion

Pathological gambling is a serious complication of dopamine agonist therapy in Parkinson's disease. In contrast, L-dopa given in standard doses as monotherapy carries a very low risk of this particular dopaminergic treatment related behavioural disorder. Functional imaging suggests that there is a medication induced down-regulation of fronto-striatal connections, and up-regulation of striato-insular connections, which combine to induce impulsive behaviour. Further research is needed to explore whether there are differences between the gambling behaviour in non PD patients and pathological gambling in PD, and whether there are differences in the mechanisms underlying pathological gambling as opposed to other behavioural disorders in PD such as compulsive sexual behaviour.

Key Findings

- PG in PD can lead to financial ruin and social isolation.
- Early recognition is necessary, since patient's insight may be low.
- The main risk factor for PG in PD is dopamine agonist therapy.

- In patients with a previous or current history of addictive behaviours, L-dopa monotherapy rather than dopamine agonist therapy should be considered.
- In contrast to dopamine agonists, L-dopa does not increase the risk of PG in PD.
- If PG has been diagnosed in PD, dopamine agonists should be reduced and if necessary stopped.
- Reduction of dopamine agonist therapy can induce withdrawal symptoms and the subjective feeling of being more “off”. L-dopa should be cautiously increased in those cases to alleviate motor impairments.
- There is insufficient evidence that antipsychotic drugs are efficacious in reducing PG in PD.

2.2. Other treatment related behavioural disturbances in Parkinson's disease

Disruption of dopaminergic pathways from the substantia nigra to the striatum are accepted to have major responsibility for the cardinal motor features of PD (Lees, Hardy et al. 2009), and are also amongst the mesocortical and mesolimbic projections implicated in reward processing and addiction (Koob and Volkow 2010). Treatment consists of dopamine replacement therapy (DRT) but can lead to a heterogeneous group of treatment related pathological behaviours. These behaviours have been reported more frequently over the past few years and fall into the category of behavioural addictions (Holden 2001). ICBs are defined by the impairment of social and occupational functioning either to the individual or their carers and include pathological gambling, hypersexuality, compulsive shopping, binge eating, the compulsive overuse of dopaminergic medication (dopamine dysregulation syndrome), and punding (O'Sullivan, Evans et al. 2009, Weintraub, Koester et al. 2010).

More than a quarter of PD patients with ICBs have two or more other behavioural addictions (Ondo and Lai 2008, Weintraub, Koester et al. 2010). It is still unclear why a subgroup of PD patients develop these behaviours. Studying the cognitive differences and pathophysiological mechanisms implicated in ICBs may allow greater insight not only into the management of patients with PD, but also be relevant to the treatment of addiction in general.

Phenomenology and prevalence of ICBs in Parkinson's disease

The prevalence rate of ICBs in treated PD in UK and US clinics is considered to be 6% in PD patients without and up to 17% with dopamine agonist treatment (Voon, Hassan et al. 2006, Weintraub, Siderowf et al. 2006, Weintraub, Koester et al. 2010). Lower prevalence amongst Chinese (3.53%) PD patients may reflect cultural differences (Fan, Ding et al. 2009), or may be an underestimation since many patients disguise their behaviours due to shame, denial or they do not associate the behaviour with their DRT (Evans, Strafella et al. 2009). Further, these patients might lack insight regarding their addictive behaviour (Grosset, Macphee et al. 2006, Singh, Kandimala et al. 2007) and therefore might not be recognized in daily routine (Weintraub, Siderowf et al. 2006). However, it is also important to consider that an ICB can be tolerated or recognised as a disorder depending on social surroundings, financial situation and the tolerance of the family(Cormier, Muellner et al. 2013).

Compulsive sexual behaviour

Compulsive sexual behaviour ranges from increased sex drive to paraphilia (Voon, Hassan et al. 2006). Amongst treated PD patients hypersexuality is considered between 2% in smaller (Weintraub, Siderowf et al. 2006, Fan, Ding et al. 2009) and up to 3.5% in larger studies cross sectional multi centre studies (Weintraub, Koester et al. 2010). (See Table 2). It is, however, likely that compulsive sexual behaviour is still underdiagnosed and the actual prevalence rates might be higher.

Proposed criteria for pathological hypersexuality in PD	
A)	The sexual thoughts or behaviours are excessive or an atypical change from baseline marked by ≥ 1 of the following:
○	Maladaptive preoccupation with sexual thoughts
○	Inappropriately or excessively requesting sex from partner
○	Habitual promiscuity
○	Compulsive masturbation
○	Using telephone sex lines or viewing pornography
○	Paraphilias
B)	The behaviour must be persistent for ≥ 1 month
C)	The behaviour causes ≥ 1 of the following:
○	Marked distress
○	Attempts to control thought or behaviour are unsuccessful or result in marked anxiety or distress
○	Are time consuming
○	Interfere significantly with social or occupational functioning
D)	Not occurring exclusively during (hypo)manic periods
E)	If all criteria except C is fulfilled the disorder is subsyndromal

Table 2. *Proposed criteria for compulsive sexual behaviour.*

(Adapted from Voon et al.) (Voon, Hassan et al. 2006).

Punding

Punding is defined as stereotyped and repetitive behaviours, including an intense fascination with manipulations of technical equipment, the continual sorting of common objects, excessive hobbyism such as computer and internet use, pointless driving or walkabouts. Patients often describe their behaviour as soothing and calming (Evans, Katzenschlager et al. 2004). The prevalence of punding in PD varies between 1.4 % (Miyasaki, Al Hassan et al. 2007) to 4.2% (Lee, Kim et al. 2009), and up to 14% in patients taking higher doses (>800mg/day) of L-dopa (Evans, Katzenschlager et al. 2004). In contrast to the previously described ICBs, patients demonstrate more obsessive-compulsive symptoms and their stereotypies are idiosyncratic, depending on individual life histories (Evans, Katzenschlager et al. 2004).

Dopamine dysregulation syndrome

Dopamine dysregulation syndrome (DDS) is defined as the compulsive overuse of DRT, and has been described in 3.4% (Pezzella, Colosimo et al. 2005) to 4.1% of treated PD patients (Giovannoni, O'Sullivan et al. 2000). Patients typically identify avoidance of the distressing negative affective state during parkinsonian “off” periods as the most important reason for self-escalation of their DRT without their physicians approval (Bearn, Evans et al. 2004). A minority of patients also acknowledge a subjective “high” or mood benefit after taking short acting drugs (Giovannoni, O'Sullivan et al. 2000). As treatment continues, drug-induced dyskinesias emerge together with socially harmful behaviours (O'Sullivan, Evans et al. 2009), (Table 3).

Diagnostic criteria for DDS
○ Parkinson's disease with documented L-dopa responsiveness ○ Need for increasing doses of DRT in excess of those normally required to relieve parkinsonian symptoms and signs ○ Pattern of pathological use: expressed need for increased DRT in the presence of excessive and significant dyskinesias despite being "on", drug hoarding, drug seeking behaviour, unwillingness to reduce DRT, absence of painful dystonias ○ Impairment in social or occupational functioning: fights, violent behaviour, loss of friends, absence of work, loss of job, legal difficulties, arguments or difficulties with family ○ Development of hypomanic, manic or cyclothymic affective syndrome in relation to DRT ○ Development of a withdrawal state characterized by dysphoria, depression, irritability, and anxiety on reducing the level of DRT ○ Duration of disturbance for at least 6 months

Table 3. *Diagnostic criteria for DDS.*

(Giovannoni, O'Sullivan et al. 2000).

Compulsive shopping

In two large PD studies compulsive buying (McElroy, Keck et al. 1994) has been reported between 3.4% (Lee, Kim et al. 2009) and 5.7% (Weintraub, Koester et al. 2010), (Table 4).

Diagnostic criteria for compulsive shopping
Maladaptive preoccupation with buying or shopping that is manifested as impulses or behaviours that: ○ Are experienced as irresistible, intrusive and/or senseless ○ Result in frequent buying of more than can be afforded, items that are not needed, or ○ longer period of time than intended ○ Cause marked distress, are time consuming, significantly interfere with social and occupational functioning, or result in financial problems ○ Not occurring exclusive during (hypo)manic episodes

Table 4. *Diagnostic criteria for compulsive shopping.*

(McElroy, Keck et al. 1994).

Binge eating

Binge eating (American Psychiatric Association 2000) was reported in 4.3% of US-PD patients (Weintraub, Koester et al. 2010). In another study dopamine agonist use has been associated with food craving resulting in significant weight gain (Nirenberg and Waters 2006), (Table 5).

Diagnostic criteria for binge eating and compulsive eating	
	Recurrent binge eating characterized by eating large amounts in a discrete period, along with a loss of control
	≥ 3 of the following:
1.	Rapid eating
2.	Feeling uncomfortably full
3.	Eating large amounts when not hungry
4.	Eating alone because of embarrassment over amounts
5.	Feeling disgusted or guilty after overeating
○	Marked distress
○	Occurs 2 days/week over 6 months
○	Does not occur with compensatory behaviours or during anorexia or bulimia nervosa

Table 5. *Diagnostic criteria for binge eating (DSM-IV). (American Psychiatric Association 2000) and compulsive eating (Nirenberg and Waters 2006).*

Miscellaneous impulsive behaviours

Reckless generosity (O'Sullivan, Evans et al. 2010), excessive hoarding (O'Sullivan, Djamshidian et al. 2010), impulsive smoking (Bienfait, Menza et al. 2010), reckless driving (Avanzi, Baratti et al. 2008), aggression and walkabouts (Giovannoni, O'Sullivan et al. 2000) can add to the social and occupational impairments.

'Green flags' for the development of ICBs in Parkinson's disease

Whilst the greatest risk for the development of ICBs in PD is the use of dopaminergic medication, it is controversial whether higher dosage of DRT is an important risk factor (Gallagher, O'Sullivan et al. 2007, Weintraub, Koester et al. 2010). Although DDS and punding are more frequently seen in patients taking higher amounts of L-dopa (Evans, Katzenschlager et al. 2004), dopamine agonists are more implicated than L-dopa in other ICBs (Weintraub, Koester et al. 2010).

No difference in the frequency of ICBs has been reported between pramipexole and ropinirole (Weintraub, Siderowf et al. 2006, Ondo and Lai 2008, Weintraub, Koester et al. 2010). The development of ICBs have been described in relation to newer non-ergot derived dopamine agonists such as rotigotine, (Wingo, Evatt et al. 2009) as well as older ergot-derived agonists.

Alcohol addiction or illicit drug abuse, depression and high novelty seeking personality traits have also been identified as risk factors, especially in patients with DDS (Evans, Lawrence et al. 2005, Voon, Thomsen et al. 2007, O'Sullivan, Evans et al. 2009, Siri,

Cilia et al. 2010). Patients with early onset of PD, who are single and smoke, are also at higher risk, particularly if there is a positive family history for addictive behaviours (Evans, Lawrence et al. 2005, Weintraub, Koester et al. 2010).

Novelty seeking declines with age in healthy populations (Steinberg, Albert et al. 2008) and in excess is associated with increased impulsivity, addiction, inability to delay gratification, recklessness and aggressive behaviour (Barratt 1994, Belin, Mar et al. 2008).

Compulsive sexual behaviour has been more frequently reported in males, whereas compulsive shopping and binge eating is more common in female PD patients (Voon, Hassan et al. 2006, Weintraub, Koester et al. 2010). Most ICBs are reversible after reduction of dopaminergic medication which suggests that these behaviours are triggered by changes in baseline dopamine levels in susceptible patients.

Punding severity seems to be positively correlated to younger disease onset and male gender (Evans, Katzenschlager et al. 2004). Motor fluctuations are more common in ICB patients (Solla, Cannas et al. 2011) and early and severe dyskinesias (within the first 12-24 months) might be a warning sign for developing DDS.

Personality traits, decision-making and reward processing in Parkinson's disease

Although measures of cognition and reward processing in ICBs are not consistent, a number of findings have been reproduced, particularly regarding impulsive sensation seeking personality traits. PD patients with ICBs are more novelty seeking (Voon, Thomsen et al. 2007). This is in contrast to PD patients without ICBs who are usually risk averse, anhedonic and low in novelty seeking (Prick 1966, Todes and Lees 1985, Menza 2000, Evans, Lawrence et al. 2006, Ishihara and Bayne 2006).

PD patients with ICBs are more aggressive, disinhibited and more antisocial than PD patients without behavioural addictions (O'Sullivan, Evans et al. 2009, Rossi, Gerschcovich et al. 2010, Siri, Cilia et al. 2010). Further, impulsive PD patients have higher schizotypy scores, which measures the risk of psychosis, compared to controls (Housden, O'Sullivan et al. 2010). Increased mania symptoms scores were also seen across a spectrum of PD patients with ICBs regardless of the type of their addiction (O'Sullivan, Loane et al. 2011). Related to impulsivity, PD patients with ICBs show increased temporal discounting, (the inability to delay a reward) following DRT (Housden, O'Sullivan et al. 2010, Voon, Reynolds et al. 2010) and have faster reaction times compared to non-impulsive PD patients (Voon, Reynolds et al. 2010).

Interestingly reward learning in PD patients with ICBs has been reported to be normal in several studies (Housden, O'Sullivan et al. 2010, Voon, Pessiglione et al. 2010). This implies that ICBs in PD might be caused by risky behaviour combined with an inability to delay rewards in their "on" state and not necessarily related to an increased sensitivity

to rewards (Housden, O'Sullivan et al. 2010). Further, repeated exposure to DRT can, in susceptible patients, induce sensitization of the ventral striatum. DDS patients for example reported compulsively “wanting” their DRT without “liking” it (Evans, Pavese et al. 2006). This has led to the incentive sensitization theory, where drug effects are enhanced and cause pathological motivation in PD patients with ICBs (Evans, Pavese et al. 2006).

Some studies have suggested cognitive impairment with lower scores on Frontal Assessment Battery (FAB) tests in PD patients with PG versus control PD patients (Santangelo, Vitale et al. 2009). However, these results are in contrast with several other studies which did not find any differences in FAB scores between PD patients with or without ICBs (Voon, Thomsen et al. 2007) or even showed enhanced executive function in the PD patients with PG (Siri, Cilia et al. 2010). Furthermore, Stroop test performance was similar between PD patients with and without ICBs (Rossi, Gerschcovich et al. 2010).

PD patients with PG only showed selective impairment on the Iowa Gambling Task compared to PD patients without ICBs, whilst other decision making tasks were unimpaired (Rossi, Gerschcovich et al. 2010). Table 6 summarizes behavioural test done in PD patients with ICBs until March 2011.

Frontal lobe function	**Findings**	**References**
Frontal assessment battery (FAB)	PD+ICB worse than PD-ICB.	Santangelo et al.
Stroop test	No difference between PD+ICB and PD-ICB.	Rossi et al.
Frontal assessment battery (FAB)	No difference between PD+ICB and PD-ICB.	Voon et al. Siri et al.
Rey Auditory Verbal learning (RAVLT) Attentive matrices	PD+ICB performed better than PD-ICB patients.	Siri et al.
Risk taking		
Iowa Gambling Task (IGT)	PD+ICB had selective impairment on IGT.	Rossi et al.
Decision making		
Salience Attribution Test	Normal reward learning compared to controls.	Housden et al.
Probabilistic Learning Task	Normal reward learning in PD+ICB "on".	Voon et al.
Game of Dice Task, Investment Task	No difference between PD+PG and PD-ICB.	Rossi et al.
Temporal Discounting		
Experiential Discounting Task, Kirby delayed discounting questionnaire	Increased temporal discounting in PD+ICBs.	Voon et al. Housden et al.

Table 6. *Behavioural studies performed in PD+ICBs patients until March 2011.*

Brain circuitry implicated in patients with Parkinson's disease with ICBs

In healthy controls pramipexole increases activity of the mesolimbic dopamine system during anticipation of monetary rewards, but at the same time reduces interaction to the prefrontal cortex (Ye, Hammer et al. 2011). This modulation of the brain circuitry due to dopamine agonist treatment with increased "bottom up mesolimbic dopamine release" might play a key role for developing ICBs (Figure 3).

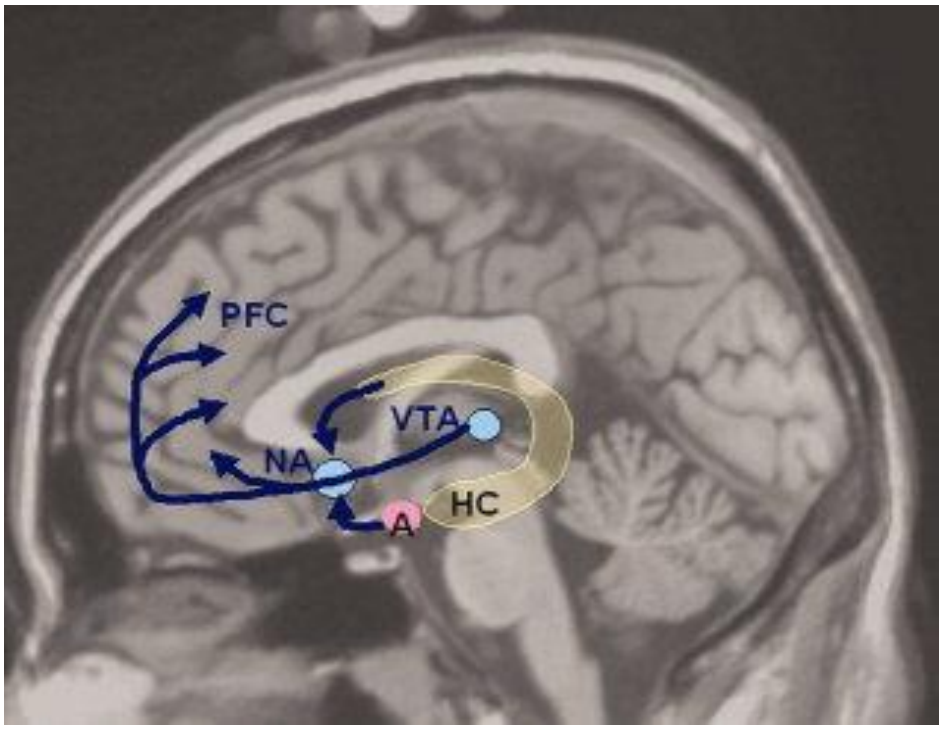

Figure 3. *Increased "bottom up" mesolimbic dopamine release.*

Dopamine originating from the ventral tegmental area (VTA) and projecting to the nucleus accumbens (NA) and prefrontal cortex (PFC). The amygdala (A) and the hippocampus (HC) send projections to the NA. Permission to reproduce this figure was granted by Dr. Evans. Figure taken from (Evans, Strafella et al. 2009).

Mesolimbic dopamine release from the ventral tegmental area via the nucleus accumbens might therefore result in prefrontal cortex dysfunction.

Functional imaging studies have strengthened the links between the ICBs seen in PD and addiction in general, demonstrating abnormalities of neural circuits involving the ventral striatum, the cingulate gyrus and the orbitofrontal cortex (Dagher and Robbins 2009, Koob and Volkow 2010). Evans and colleagues found that PD patients with DDS exhibited enhanced L-dopa-induced ventral striatal dopamine release during PET scanning compared with L-dopa treated patients with PD not compulsively taking dopaminergic drugs (Evans and Lees 2004). A PET study in eleven PD patients with a variety of treatment related behavioural disorders and eight control PD patients showed greater reduction of ventral striatum [^{11}C] raclopride binding in the PD group with ICBs following reward-related cue exposure. Reduction in raclopride binding is linked with higher dopamine release within the ventral striatum and occurred after patients were offered a variety of visual reward-related cues (O'Sullivan, Wu et al. 2011), whereas no differences were found when patients were exposed to neutral images (Figure 4) These results are consistent with a global sensitization to appetitive behaviours with dopaminergic therapy in vulnerable individuals (O'Sullivan, Wu et al. 2011).

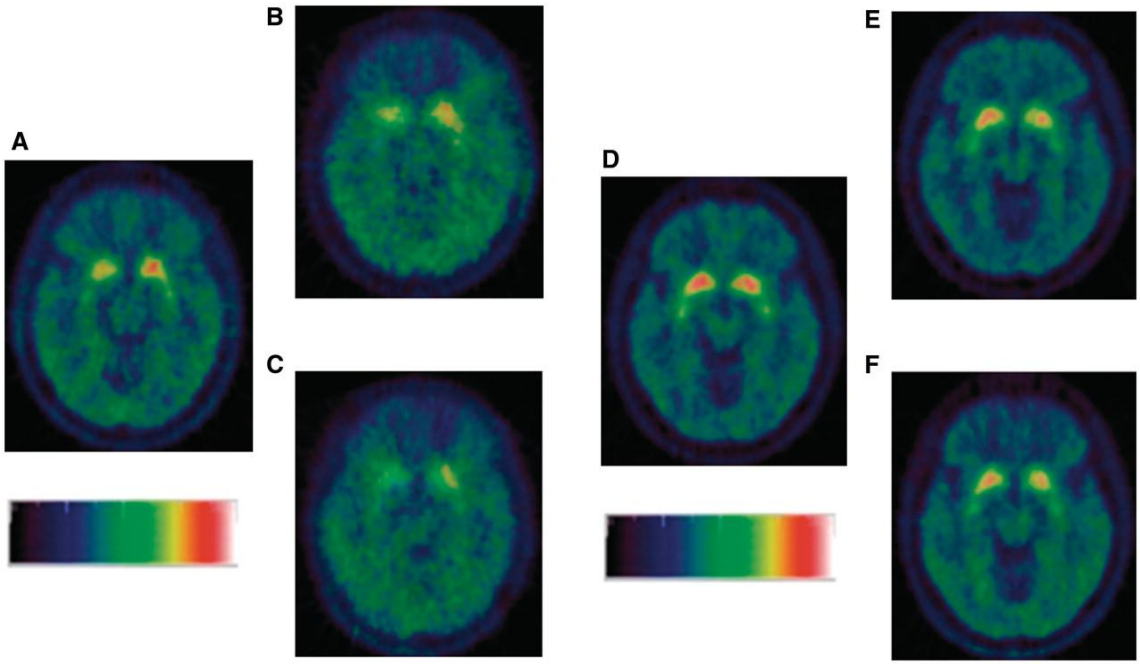

Figure 4. *^{11}C-raclopride binding potential between PD patients with and without ICBs.*

PD patients with ICBs (left) versus PD patients without ICBs (right). No group differences were seen when PD patients were exposed to neural images (A and B versus D and E). (A) PD patient with ICBs, off medication, exposed to neutral images. (B) PD patient with ICBs, on medication, neutral images. (D) PD patient without ICBs off medication, neutral images. (E) PD patient without ICBs off medication, on medications, neutral images. A significant reduction of ^{11}C-raclopride was found when patients were exposed to rewarded images. (C) PD patient with ICB, on medication, reward images. (F) PD patient without ICBs off medication, on medications, reward images. Permission to reproduce this figure has been granted by Dr. O'Sullivan. Figure taken from O'Sullivan et al (O'Sullivan, Wu et al. 2011).

Single-photon emission computed tomography (SPECT) in PD patients with PG showed increased brain perfusion in multiple regions, such as the orbitofrontal cortex, the hippocampus, the amygdala, the insula, and the ventral pallidum. This might reflect an overstimulation of an intact mesolimbic dopamine system due to DRT (Cilia, Siri et al. 2008). This sensitization of the ventral striatum during rewarded stimuli seems to be in contrast with some behavioural studies which did not show an increased sensitivity to rewards. However, in their “on” state PD patients with ICBs have intact feedback learning from positive and also negative stimuli (Voon, Pessiglione et al. 2010, Djamshidian, O'Sullivan et al. 2012). It is therefore possible that the increased sensitization within the ventral striatum manifests in risky rather than hedonic behaviour. More specifically, the subjects may learn the objective value of rewards appropriately, but they may subjectively over-value large rewards, even when they are improbable, leading to risky decisions.

Functional magnetic resonance imaging (fMRI) studies in PD patients with ICBs showed an increase in ventral striatum blood-oxygen-level dependent (BOLD) activity to reward after dopamine agonist medication (Frosini, Pesaresi et al. 2010, Voon, Pessiglione et al. 2010). One recent study recorded local field potentials of 3 groups of PD patients who underwent deep brain stimulation (DBS) of the subthalamic nucleus (Rodriguez-Oroz, Lopez-Azcarate et al. 2010). One group had a variety of different ICBs, another group consisted of PD patients with dyskinesias and the third group included PD controls. Results showed no difference in the “off” state between these groups. However, in the “on” state PD patients with ICBs and PD patients with dyskinesias showed significant changes in the theta alpha band. While for the ICB group

this frequency was generated in the ventral subthalamic area and was coherent with the frontal premotor frontal activity, the frequency derived from the dorsal subthalamic area was coherent with cortical motor activity in PD patients with dyskinesias (Rodriguez-Oroz, Lopez-Azcarate et al. 2010). Results suggest that the subthalamic nucleus might play an important role in generating impulsive and compulsive behaviours via its projections to associative limbic areas regardless of the type of addiction. This study also strengthens further the link between dyskinesias and ICBs.

A recent fMRI study in PD patients with hypersexuality demonstrated an increased sexual desire after exposure to sexual cues in impulsive patients compared to non-impulsive PD patients. Further, in ICB patients this desire was increased in the "on" versus "off" state, which correlated with enhanced activation in the ventral striatum, the anterior cingulate and the orbitofrontal cortex. However, no correlation was found with "liking" scores suggesting that in ICB patients dopaminergic medication causes compulsive seeking ("wanting") for a reward, without necessarily liking it (Politis, Loane et al. 2013).

Previous studies have explored the role of dopamine within the general population and found an inverse correlation between dopamine receptor binding and addiction. Lower dopamine D2 and D3 receptors within the striatum have been associated with a greater risk while high D2 and D3 act as a protection for developing an addiction (Volkow, Wang et al. 2006). Further, dopamine transporter (DAT) binding within the ventral striatum was reduced in PD patients with PG compared to control PD patients, which might reflect a genetically induced functional down regulation of membrane DAT

expression on intact dopamine neurons (Cilia, Ko et al. 2010). However, no differences in baseline ventral striatum D2 receptor binding were seen in patients with DDS (Evans, Pavese et al. 2006) and a variety of ICBs (O'Sullivan, Wu et al. 2011). Therefore abnormal baseline dopamine levels within the ventral striatum may not be a requirement for the development of ICBs. Despite various candidate gene studies including dopamine 1 and 4 receptor and the dopamine catechol-O-methyl transferase (COMT) no genetic marker to detect vulnerable patients has been found so far (Comings, Ferry et al. 1996, Foltynie, Lewis et al. 2005, Lobo, Souza et al. 2010). Large genome wide studies are needed to identify genetic risk factors for ICBs in PD.

Impulsive compulsive behaviour in atypical Parkinson's disease

ICBs in relation to dopamine agonist use have been also described in patients with pathologically proven progressive supranuclear palsy (PSP) (O'Sullivan, Djamshidian et al. 2010) and multisystem atrophy (MSA) (Klos, Bower et al. 2005).

Illustrative case of a patient with pathologically proven PSP

A 66 year old lady presented in 2005 with a 6 month history of unsteadiness, difficulties walking with occasional falls, particularly backwards, and rigidity. She had a previous history of depression for over 30 years. On examination she had blepharospasm, a flexed posture, reduced arm swing and micrographia. An MRI brain scan was normal and a diagnosis of possible PSP was made.

The introduction of L-dopa/carbidopa, with subsequent increase to 500 mg L-dopa/day in 2006, led to improvement of her writing and postural stability. By then a supranuclear vertical gaze palsy was noticed but she was still independent. In 2007 she developed some wearing off phenomena and treatment with rotigotine was started. She was falling more frequently and had become wheel-chair bound following a fractured femur, requiring a 24h carer. Cognitive impairment was not noted, and she denied having hallucinations. Her rotigotine dose was increased to 6mg/day, in addition she was taking 800mg L-dopa per day. Soon after this, she developed reckless generosity including giving thousands of pounds to Christian television organisations. She died in 2009 from a bronchopneumonia at the age of 71 (O'Sullivan, Djamshidian et al. 2010).

Behavioural changes after dopamine agonist therapy

Although recent studies (Arabia, Grossardt et al. 2010) have questioned the concept of the typical parkinsonian personality being anhedonic (Todes and Lees 1985), metric tasks have shown that untreated patients have deficits in reward learning. In one study never medicated PD patients were given pramipexole or ropinirole and were followed up for 12 weeks (Bodi, Keri et al. 2009). At baseline untreated patients had intact learning from negative feedback but impairment in reward learning. An opposite learning profile was found after dopamine agonist therapy, with significant impairment in avoidance of negative outcomes compared to controls but normal reward seeking behaviour. A similar opposite feedback learning “on” versus “off” medication was shown in PD patients after L-dopa administration (Frank, Seeberger et al. 2004).

However, in this study PD patients treated with L-dopa showed no impairment in negative feedback learning compared to controls (Frank, Seeberger et al. 2004).

PD patients with ICBs showed faster learning from rewards and had a greater reward prediction error, defined as the difference between expected and received reward (Sutton and Barto 1998), after receiving a dopamine agonist (Voon, Pessiglione et al. 2010).

An fMRI study demonstrated increased risky choice in PD patients without ICBs after pramipexole but not after L-dopa therapy. In this study, only pramipexole caused changes in orbitofrontal function with a relative increased activity during negative errors of reward prediction. It is possible that dopamine agonists prevent phasic decreases in dopamine transmission during negative feedback, which can result in risky decisions (van Eimeren, Ballanger et al. 2009). Consistent with these results PD patients with pathological gambling and compulsive shopping showed in another fMRI study increased risk taking behaviour after dopamine agonist therapy, which correlated with decreased orbitofrontal cortex and anterior cingulate function (Voon, Gao et al. 2011).

Increased temporal discounting, the preference of a smaller immediate over a delayed but higher reward, compared to controls was observed in PD patients without ICBs who were treated with a dopamine agonist. In addition, discounting in these patients was not effected by medication state which may imply that dopamine agonist therapy causes persistent behavioural changes (Milenkova, Mohammadi et al. 2011).

Dysfunction of reward prediction errors during a gambling task but intact orbitofrontal function were also found in an fMRI study in patients with restless legs syndrome (RLS) when treated with dopamine agonists, suggesting these patients were at risk to develop

pathological gambling, but intact orbitofrontal cortex activity suppresses an active ICB (Abler, Hahlbrock et al. 2009).

Mechanisms underlying ICBs in Parkinson's disease

The reduction in "top down control" of fronto-striatal connections but increased "bottom up activity" of striato-insular connections might play a key role for developing ICBs. There are also differences in receptor binding that might explain why ICBs are more commonly seen under dopamine agonist treatment compared to L-dopa monotherapy. Ropinirole and pramipexole have a 100 fold stronger dopamine D3 receptor affinity than D2 receptors and both have no affinity to the D1 dopamine receptor (Gerlach, Double et al. 2003). Similar receptor affinity has been reported with rotigotine (Jenner 2005). The ergoline derived dopamine agonist cabergoline has a 10 fold stronger dopamine D3 than D2 receptor affinity and a more than 400 fold D3 than D1 receptor affinity (Gerlach, Double et al. 2003). In contrast L-dopa stimulates mainly dopamine D1, D2 and to a lesser degree D3 receptors (Ahlskog 2011). Critically dopamine D3 receptors are mainly expressed in the limbic system which might explain why dopamine agonists are more likely to cause ICBs (Ahlskog 2011).

Finally dopamine agonists stimulate dopamine receptors more tonically than exogenous L-dopa which has consequences on learning behaviour. Reward prediction errors are mediated via phasic dopamine bursts during rewards (Hollerman, Tremblay et al. 1998) whilst pauses in dopamine firing occur during punishment (Schultz 2002). Dopamine

agonists might prevent dopamine dips, which are necessary for learning from negative consequences.

Treatment of patients with Parkinson's disease with ICBs

Non-pharmacological and general management

Doctors should inform patients and their family members of the potential risk of developing ICBs before prescribing dopamine agonist treatment (Grosset, Macphee et al. 2006, Singh, Kandimala et al. 2007). Family members should look out for behavioural changes and report them to the doctor. Patients who have had a history of illicit drug abuse in the past and have a younger onset of PD require especially careful monitoring (Singh, Kandimala et al. 2007, Voon, Thomsen et al. 2007, Weintraub, Koester et al. 2010). In these patients rescue doses and fast acting L-dopa doses or apomorphine pens should be avoided.

Extra attention should be paid in patients who develop dyskinesias, since these might be a preceding signs of DDS or other ICBs (Solla, Cannas et al. 2011). It is important to consider that an ICB usually does not start abruptly and subtle behavioural changes such as craving for sweets or increased spending might be harbingers. Cognitive behavioural therapy has been beneficial in non PD patients with pathological gambling (Hodgins and Petry 2004) and has been recently shown to improve ICB symptoms in PD (Okai, Askey-Jones et al. 2013). Depression (Gallagher, O'Sullivan et al. 2007), drug induced mood changes (Voon, Thomsen et al. 2007) and sleep pattern abnormalities (O'Sullivan,

Loane et al. 2011) are frequently reported in PD patients with ICBs and should be treated symptomatically.

Dopamine agonists should be slowly reduced and subsequently stopped (Evans, Strafella et al. 2009). Withdrawal symptoms are frequently seen in PD patients with ICBs and include panic attacks, dysphoria and the subjective feeling of being “off” (Nirenberg 2010). Frequently these symptoms do not improve after increasing L-dopa and escalating L-dopa in order to alleviate these non-motor symptoms might increase the risk of developing DDS (Nirenberg 2010).

Usually it takes several weeks and up to several months after dopamine agonists have been withdrawn until the ICBs have completely vanished. However, PET studies and behavioural tasks have demonstrated increased impulsivity in these patients, even after dopamine agonist medication has been stopped (O'Sullivan, Wu et al. 2011), suggesting irreversible changes in wide areas of brain networks induced by dopamine agonist therapy in susceptible patients.

The evidence for using neuroleptic treatment in PD patients with ICBs is conflicting (Sevincok, Akoglu et al. 2007, McElroy, Nelson et al. 2008). In addition antipsychotics lead to worsening of motor function and should therefore not be used as a long term treatment. Treatments found to be efficacious in ICBs in the general population may help PD-related ICBs, with several randomised clinical trials showing a benefit of opioid antagonists, particularly for pathological gambling (Leung and Cottler 2009). Large randomised controlled trials in the treatment of PD related ICBs are needed.

Management of different subtypes of ICBs

If compulsive shopping, pathological gambling or hypersexuality has been detected family members should cancel credit cards or limit access to money and internet. Conflicting reports have been published on amantadine with beneficial reports showing reduced gambling urges (Thomas, Bonanni et al. 2010) and punding behaviour (Kashihara and Imamura 2008). However, recently it has been suggested that amantadine can induce ICBs in PD (Weintraub, Sohr et al. 2010) and therefore it is not recommended as a treatment for ICBs in PD.

In patients with punding bed time L-dopa should be stopped, since this behaviour often occurs during night (Fasano and Petrovic 2010). Further, selegeline should be withdrawn because of amphetamine like metabolites (Shin 1997). Entacapone might be beneficial in preventing or reducing punding and to treat motor handicaps (Evans, Katzenschlager et al. 2004). Compulsive sexual behaviour is more often problematic in men than women and in those who continue to have hypersexuality despite stopping dopamine agonists, the anti-androgen cyproterone is sometimes required and involves endocrinological monitoring (Evans, Katzenschlager et al. 2004).

L-dopa should be reduced in patients with DDS, the family doctor and the pharmacist informed to avoid multiple prescriptions and drug hoarding. Access to medication should be restricted and patient's partner, spouses or carer should administer L-dopa to prevent misuse. During L-dopa reduction these patients are at high risk to become more aggressive and paranoid or experience or off period depression (Evans and Lees 2004) and may require hospital admission.

Functional surgery in patients with Parkinson's disease with ICBs

Bilateral DBS of the subthalamic nucleus (STN) in PD induced PG in one small study (Lu, Bharmal et al. 2006). However, larger studies did not report any occurrence of behavioural side effects of DBS. In fact, seven patients who had PG and six who had DDS improved after bilateral subthalamic nucleus stimulation and reduction of the overall dopaminergic medication (Ardouin, Voon et al. 2006). More recently, other studies also found beneficial outcome in ICBs after STN-DBS (Lim, O'Sullivan et al. 2009, Lhommee, Klinger et al. 2012). The variable outcomes regarding the effect of DBS on ICBs may reflect the retrospective nature of studies, where ICBs were not well recognised pre-operatively (Lim, O'Sullivan et al. 2009). Additionally, the potential influence of DBS electrode placement requires further investigation. The subthalamic nucleus has three subdivisions and ideally only the dorsolateral motor part of the subthalamic nucleus should be stimulated. In contrast, the medial region of the subthalamic nucleus is strongly associated with the limbic system (Groenewegen and Berendse 1990), whereas stimulation of the more ventral part may induce apathy (Drapier, Drapier et al. 2006).

PET studies have shown that subthalamic nucleus DBS is associated with increased regional cerebral blood flow in the anterior cingulate cortex (Limousin, Greene et al. 1997). The subthalamic nucleus has a volume of approximately 240mm^3 (Hardman, Henderson et al. 2002), with previous studies suggesting that there is an expected current spread of approximately 3mm radius (113mm^3 volume) (Saint-Cyr, Hoque et al. 2002). It is therefore possible that the differing responses to DBS in ICBs may be due to

the presence or absence of spread of stimulation effects into the “limbic” portion of the subthalamic nucleus (Broen, Duits et al. 2011). Factors predictive of good behavioural outcome post-DBS may include physician vigilance, motor outcome and patient compliance regarding rapid decreases of DRT (Lim, O'Sullivan et al. 2009).

Conclusion

ICBs in PD remain a challenge in clinical practise, and vigilance in the prescribing physician is of paramount importance. Awareness of risk factors may help detect those patients at risk, in particular young age at PD onset, the use of dopamine agonists, previous evidence of impulsivity, familial or personal history of alcoholism, and early onset dyskinesias.

Imaging studies have provided additional support to strengthen the link between dopamine replacement therapy induced up-regulation of mesolimbic dopaminergic pathways, impairment of “top down” control and ICBs in PD. Behavioural studies suggest increased novelty seeking, risky behaviour with an inability to delay gratification as important hallmarks of ICBs.

Key Findings

- ICBs in PD occur in about 15% of patients, but these numbers might be underestimated as some patients might hide their addictive behaviour due to shame or denial.
- Punding and DDS are more associated with L-dopa therapy, in contrast compulsive shopping, hypersexuality, binge eating and PG are more likely triggered by dopamine agonists.
- Risk factors for developing an ICB in PD are a previous or current history of addictive behaviours and younger onset of PD.
- STN-DBS may be a therapeutic option for ICBs in PD, although further studies are needed, as the data is still conflicting.
- Reduction of dopamine agonist therapy often results in a complete cessation of ICBs.
- In patients with DDS L-dopa needs to be reduced, which is, however, often challenging.

Chapter 3 - Behavioural tests in patients with Parkinson's disease

Introduction

Impulsivity may be looked upon as "a behaviour that is performed with little or inadequate forethought" (Evenden 1999) or the failure to resist an impulse. Self-rating scales have significant shortcomings in this area. For example impulsivity might directly interfere with the completion of the questionnaire, since impulsive people might give less consideration to responses. Further, insight into aberrant personal behaviours might be lower in impulsive patients and direct neuropsychological tests have been used more recently to assess impulsivity (Verdejo-Garcia, Lawrence et al. 2008).

Laboratory tests have been developed to assess mainly three categories of impulsivity. These include response inhibition, which measures the ability to stop an automatic response, temporal discounting, defined as the preference of a smaller immediate reward over a delayed higher reward and finally the broad concept of cognitive impulsivity. Cognitive impulsivity includes reflection impulsivity, which originally referred to the ability to gather and evaluate evidence before making a choice and decision making under risk (Verdejo-Garcia, Lawrence et al. 2008).

The relationship between dopamine levels and cognitive function in PD has been the subject of much interest (Frank, Seeberger et al. 2004, Cools 2006, Shiner, Seymour et al. 2012). In PD patients without ICBs L-dopa has a dual effect on cognition. While

dopaminergic medication (L-dopa plus dopamine agonists) improved task switching behaviour relative to the “off” state, anti-Parkinson medication also impaired reversal learning (Cools, Barker et al. 2001). This discrepancy may be explained by the fact that task switching relies on networks connecting the dorsolateral prefrontal cortex to the dorsal striatum, which is severely depleted in PD. In contrast reversal learning depends on orbitofrontal cortex and the ventral striatum, which is relatively intact in PD patients without ICBs (Cools, Barker et al. 2001). These results are also in keeping with the ‘overdose hypothesis’. In early PD there is a greater depletion in the dorsal striatum than in the ventral striatum (Kish, Shannak et al. 1988). Effective dopamine replacement in the dorsal striatum designed to reverse bradykinesia might, therefore overstimulate the relatively intact ventral striatum and lead to undesirable cognitive changes, referred to as the ‘cognitive overdose hypothesis’ (Gotham, Brown et al. 1988).

Dopaminergic state has also an effect on feedback learning. Non-impulsive PD patients “off” medication were more sensitive to negative feedback and had impaired positive feedback learning. An opposite learning profile was found after dopaminergic medication (Frank, Seeberger et al. 2004). These results were recently expanded by another study which showed that during an acquisition phase non-impulsive PD patients learned equally well in their “on” and “off” state to discern which of the two stimuli was more likely to be rewarded. However, during a performance phase when novel stimuli pairs were introduced and no feedback was given PD patients on medication were significantly better in selecting the correct image compared to those who were off medication. This suggests that PD patients off medication have intact learning, but have

difficulties transferring this knowledge and making correct choices when new stimuli were introduced (Shiner, Seymour et al. 2012).

Dopamine plays also a major role in addictive behaviours and most, if not all addictive drugs cause dopamine release (Robbins and Everitt 1999). Further, lesions within the dopamine system have been shown to reduce the rewarding effects of drugs in rodents (Robbins and Everitt 1999). Addiction can be regarded as an impairment of decision making, learning from previous outcomes and motivation (Berke and Hyman 2000). Hallmarks of an addiction are tolerance, dependence and sensitization. Psychostimulants initially increase well-being and alertness. After repeated use these acute effects diminish and patients develop tolerance. Other effects of the drugs might be enhanced (sensitization). Over time the repetitive use of addictive drugs can become habitual and compulsive (Berke and Hyman 2000, Dagher and Robbins 2009). The outcome of an action then becomes less important and the patient's behaviour shifts from "goal directed" to "stimulus-response" behaviours in which the stimulus (and not an outcome) drives an action. In contrast to goal directed behaviour, where actions have to be reassessed and learning is obligatory, habit-responses are automatic and are believed to be processed via the dorsolateral striatum (Muresanu, Stan et al. 2012).

Links between behavioural addictions in PD and drug addiction have been illustrated previously (Dagher and Robbins 2009). Given the central role of dopaminergic medication in triggering ICBs in PD, for this thesis the majority of PD patients were assessed prior to and after their usual anti-Parkinson medication.

Neuropsychological tests used for this thesis

One of the most well-known tasks to measure decision making under risky situations is the Iowa Gambling Task (IGT). In this task participants are required to choose from four decks of card, two are high risk decks offering high rewards but also high losses and are disadvantageous in the long run, whereas the two remaining decks offer smaller rewards but also smaller losses leading to overall gains. Through trial and error healthy volunteers learn to select the "good decks" that offer the smaller rewards from the "bad decks" that are leading to losses (Bechara, Damasio et al. 1994).

The IGT was used in PD patients with pathological gambling and results showed that these patients performed poorer than PD patients without addictive behaviours. In this study the authors also assessed risk taking but found no group differences (Rossi, Gerschcovich et al. 2010).

There are, however, some disadvantages of the IGT as this task includes both elements of risk taking and feedback learning. In other words, poorer performance on the IGT could be either because of impaired learning to identify the advantageous decks or because of increased risk taking behaviour. Therefore, for this thesis PD patients with and without ICBs performed a separate feedback learning and risk taking task to disentangle these two factors.

Another hypothesis was that PD patients with ICBs have a poorer working memory function, causing reduced capacity to store information and thus leading to immediate actions. Working memory was assessed using a digit forward span, measuring

immediate recall and a digit backward span, where mental manipulation of numbers is required.

PD patients with ICBs were also tested once prior to and once after their medication on an altruistic punishment task to examine whether they recognize norm violations and want to correct unfair behaviours towards themselves. Further, it was speculated that PD patients with ICBs punish more in their “on” compared to their “off” state.

The stroop test was performed to assess response inhibition as it was speculated that PD patients with addictive behaviours would perform worse than those without.

Increased novelty seeking in PD has been reported as a risk factor for developing pathological gambling (Voon, Thomsen et al. 2007) and DDS (Evans, Lawrence et al. 2005), but has not been assessed with a metric task in PD patients with a variety of different ICBs. Further, it was unclear whether increased novelty seeking is a personality trait or is caused by increased dopamine levels. To differentiate between “medication state versus personality trait” PD patients were tested once prior to and once after their usual dopaminergic medication. The prediction was that all PD patients with ICBs would be more novelty seeking than PD controls, regardless of their medication status.

The last task used was an information sampling task to assess “jumping to conclusion behaviour”, to assess cognitive impulsivity. PD patients with and without ICBs were directly compared to two patient groups who both did not have PD but had either pathological gambling or had a history of intravenous drug abuse. This study was performed to test the hypothesis that ICBs in PD resemble drug addiction. Results of

this study lead on to a follow up experiment to assess whether dopamine agonists or deep brain stimulation is causing impulsive choice on this task.

These tasks were selected to assess mainly two aspects of impulsivity, response inhibition (which was assessed with the stroop test) and cognitive impulsivity, which involves decision making under risk , feedback learning and information sampling (Verdejo-Garcia, Lawrence et al. 2008).

PD patients were screened for ICBs using suggested guidelines in a semi structured interview. In addition, a self-rated questionnaire for impulsive compulsive disorders in Parkinson's disease (QUIP) (Weintraub, Hoops et al. 2009) was used, after this questionnaire was validated. However, the disadvantage of the QUIP is that it does not measure the severity of the addiction. Therefore, semi structural interviews were necessary for all studies.

3.1. Risk and learning in Parkinson's disease

Introduction

This study sought to assess the learning profile, working memory (WM) performance and risk taking behaviour in PD patients with and without ICBs and compare results to healthy matched volunteers.

The prediction was that PD patients with ICBs (PD+ICB) would have significantly worse WM than both PD patients without ICBs (PD-ICB) and controls. Further, given the role of dopamine in learning, it was speculated that PD+ICB patients would be significantly more risk prone than PD-ICB patients and controls. Another hypothesis was that PD patients with associated ICBs may have elevated levels of dopaminergic activity in the ventral striatum, due to their symptom profile (Evans, Pavese et al. 2006, Steeves, Miyasaki et al. 2009). This would mean that their behavioural profile "off medication" would come to resemble that of PD patients "on medication", with relatively enhanced learning from positive feedback (reward) compared to negative feedback (punishment).

Patients and methods

Patients were recruited from a database of attendees at the National Hospital for Neurology and Neurosurgery, Queen Square, London,UK. Controls were usually recruited from amongst the patients' partners. Written informed consent was obtained from all participants. All patients were screened for sub-classes of ICBs.

Patients were asked to take no anti-parkinsonian medication overnight (12-18h) and were tested first between 8.00 a.m. and 9.00 a.m. prior to their morning medication. Patients then took their first L-dopa dose and the tests were repeated 50 minutes later. The therapeutic motor response to L-dopa was assessed by UPDRS scores (part 3) during “off” and “on” state. All patients had an excellent L-dopa response and had switched “on” at the second test. LEU (Levodopa equivalent units) were calculated as described previously (Evans, Katzenschlager et al. 2004) as followed:

L-dopa dose + L-dopa dose × 1/3 if on entacapone + bromocriptine (mg) × 10 + cabergoline or pramipexole (mg) × 67 + ropinirole (mg) × 20 + apomorphine (mg) × 8.

Testing was performed in the patient’s homes using a laptop computer. Distractions were minimized so that full attention could be devoted to the task. Controls were tested following a similar sequence: They were tested once, and then re-tested after 50 minutes, but received no medication. Patients who scored under 27/30 points on the Mini Mental State Examination (MMSE) were excluded from this study. Four controls performed just the working memory test. Two controls did not perform the computer tests. Two PD+ICB patients denied having active impulsive or compulsive behaviour at the time of testing but both had significant behavioural abnormalities within the last 12 months.

Patients also filled out a self-rating questionnaire and rated themselves on a 1-5 point rating scale for alertness, attentiveness and interest, where 1 is associated with “not at all” and 5 with “extremely”. On average patients scored 3.2 points on alertness, 3.5 on attentiveness and 4 on interest prior to treatment and 3.8 points for alertness, 3.9 points

for attentiveness and 4.3 points for interest one hour after L-dopa treatment and thus showing no signs of lack of motivation or concentration during this study.

Working memory task

The first task was a forward and backward digit span test (Wechsler 1997) to assess working memory. Instant recall was measured by the digit forward span, whilst attention and manipulation of the numbers was necessary for the digit backward span (Lezak 2004).

Forward span:		**Backward span:**	
5-8-2	6-9-4	2-4	5-8
6-4-3-9	7-2-8-6	6-2-9	4-1-5
4-2-7-3-1	7-5-8-3-6	3-2-7-9	4-9-6-8
6-1-9-4-7-3	3-9-2-4-8-7	1-5-2-8-6	6-1-8-4-3
5-9-1-7-4-2-8	4-1-7-9-3-8-6	5-3-9-4-1-8	7-2-4-8-5-6
5-8-1-9-2-6-4-7	3-8-2-9-5-1-7-4	8-1-2-9-3-6-5	4-7-3-9-1-2-8
2-7-5-8-6-2-5-8-4	7-1-3-9-4-2-5-6-8	9-4-3-7-6-2-5-8	7-2-8-1-9-6-5-3

Example of the digit forward and backward span (Wechsler 1997) used for this study.

Learning Task

The second task was an associative learning task in which participants were required, in each of four blocks of trials, to learn which of two stimuli was most often rewarded (Pessiglione, Seymour et al. 2006, Averbeck and Duchaine 2009). In each trial they selected one stimulus and were then told whether or not they had won on that trial. Winning probabilities for the two stimuli (75%/25% and 65%/35% were used in different blocks) were constant throughout each block and balanced across stimuli across blocks. Subjects were required to select one stimulus on each trial. After selecting the stimulus they were told whether they had lost money (5 pence) or earned a reward (10 pence). Participants were told to pick the most often rewarded stimulus as many times as possible to maximize their total wins. They were also told that their performance would influence their reward at the end. The task was administered in four blocks of 34 trials each. Between blocks subjects were told that the probabilities were being re-selected and that they should again determine which image was most often rewarded. In two of the blocks one of the stimuli was rewarded 65% of the time and the other 35% of the time and in the other two blocks one of the stimuli was rewarded 75% of the time and the other 25% of the time. The stimulus which was most often rewarded was balanced across blocks and the order of the high/low probability blocks was randomized across subjects and sessions. The block types were 75/25, 65/35, 25/75 and 35/65, where the first fraction refers to the reward for stimulus 1 and the second fraction refers to the reward for stimulus 2. The order of these block types was balanced, as much as possible, across subjects. (Figure 5A,B).

Risk task

The final task was a gambling task which was designed to probe the risk aversion of the subjects and programmed to match the description given of the task in Huettel et al. (Huettel, Stowe et al. 2006).

In each trial subjects were given a choice between two gambling options which were presented on the left and right of the screen. Each option had either a single sure outcome, or two possible outcomes. The probabilities associated with each outcome were represented by a pie.

For example, if the subjects had a 25% chance of winning £20 and a 75% chance of winning £5, the pie would be split 75/25, with the winning amount represented in each pie section. The sure options were simply solid circles, representing the 100% outcome. After selecting their preferred gambling choice subjects were told which of the two possibilities for the chosen gamble they had "won". (Figure 5C,D).

Despite telling participants that their reward depended on their performance they all received a modest financial reward (£20) after completing the study.

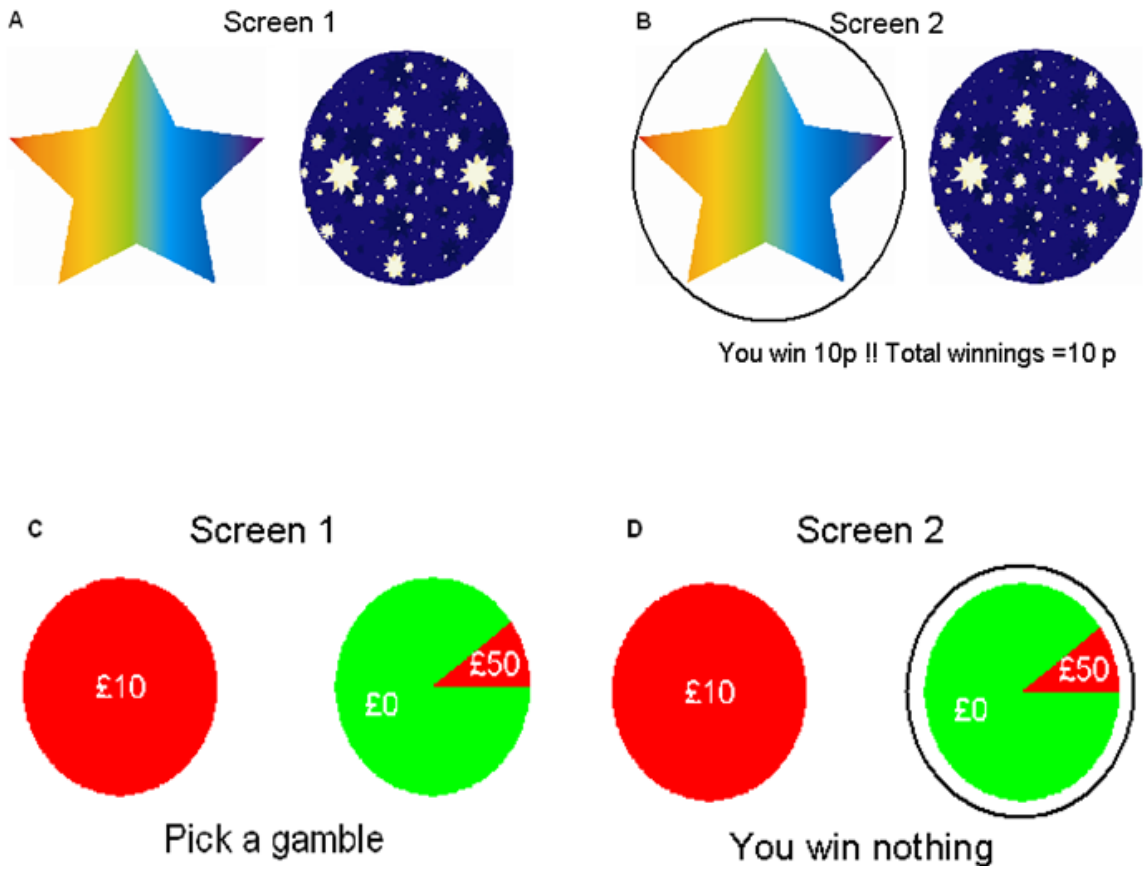

Figure 5. *Learning and risk task.*

Learning task: A: Screen 1: Participants had to select between these two objects and pick the rewarded stimulus as often as possible. B: Screen 2: Feedback was given immediately after making the choice. Individuals could either win 10p or lose 5p.

Risk task: C: Screen 1: Two gambles were presented. £10 for sure (left) or £0/£50(right), where participants had a 1/10 of a chance winning £50. D: Screen 2: After the choice, feedback was given immediately.

Statistical analysis

Working memory task

The raw scores of the digit span were converted to z-scores according to the age of the participant by using normative tables (Wechsler 1997). A mixed model ANOVA was then performed with the z-scores as the dependent variable. Task (backwards and forwards digit span) and condition (off versus on medication or 1st and 2nd trial in healthy controls) were modeled as within subject factors and group (PD, PD+ ICB and control) was modeled as a between subject factor. The model also included subject as a random factor, and the interactions between the three fixed factors (task, condition and group). All post-hoc comparisons were corrected by the Bonferroni method, and assumptions for the ANOVA were checked by examination of the residuals, which were found to be normally distributed.

Risk and learning tasks

Data analysis for the risk and learning tasks was carried out by fitting parametric decision making models to the behaviour of each individual subject, and comparing the distributions of parameter fits from the model between groups in a within subject design. Thus, the parameters of the model summarized the behaviour of each individual subject in each task, and by comparing the distributions of parameters differences in behaviour among groups were examined. Mixed effects ANOVA models were fit to behavioural variables. Subject was treated as a random effect nested under group. Group and session

were treated as fixed effects and session was treated as a within subject effect. All post-hoc comparisons were corrected using Tukey's HSD test. ANOVAs were carried out on parameters from computational models fit to the behavioural data of individual subjects. Learning was assessed using a Bayesian decision making model (Averbeck and Duchaine 2009). Because the outcome was either win or lose after one stimuli was chosen, the model was based upon a binominal distribution. For the learning task two parameters were fitted, which were treated as within subject factors. The first parameter characterized the amount that positive feedback, after selecting one of the stimuli, affected future decisions and the second parameter characterized the same for negative feedback. For the risk task two parameters were fitted. The first characterized how much the subjects valued large versus small rewards. Larger positive values of this parameter imply that subjects prefer small, sure rewards to large rewards with a lower probability. Thus, this parameter characterizes the amount of risk to which subjects are prone. The second parameter characterized whether subjects became more risky following a win. For the risk analysis, the ANOVAs were carried out separately for each parameter.

Results

Demographic characteristics

All patients fulfilled the Queen Square Brain Bank criteria for PD (Gibb and Lees 1988) and were taking L-dopa. Twelve patients with idiopathic PD without ICBs (3/12 female) and 18 PD patients with ICBs (5/18 female) were compared against 22 healthy controls (10/22 female). All PD+ICB patients had at least two ICBs. PD+ICB patients had an earlier disease onset ($t_{28} = 2.1$, $p = 0.04$). The average time lag between the diagnosis of an ICB and the testing was 5.6 months. Nine PD patients with impulsive compulsive behaviour were tested during reduction of their dopamine agonist medication. Seven PD patients had already reduced their dopamine agonist medication which had improved their addictive behaviour. At the time of testing they still fulfilled the criteria of ICBs with the exception of two patients, who had fulfilled these criteria within the previous twelve months. All patients with ICBs developed their behavioural abnormalities as a direct result of medication. An ANOVA to test difference between ages in the 3 groups just failed to reach significance ($F_{2,49} = 3.2$, $p = 0.051$). Post hoc comparisons were not significant between the PD-ICB group versus the control ($p = 0.07$) or PD+ICB group ($p = 0.098$). There was no difference in the morning($t_{28} = 1$, $p = 0.3$) and daily L-dopa dose between the patient groups ($t_{28} = 0.9$, $p = 0.36$). The timing of the last dopaminergic medication was not significantly different between the patient groups ($t_{25} = 0.3$, $p = 0.2$). Years of education was assessed in 17/22 controls, 9/12 PD-ICB patients and 14/18 PD+ICB patients and was not significantly different ($F_{2,37} = 1.98$, $p = 0.15$).

	Controls	PD-ICB	PD+ICB	p value
Participants in total (no.)	22	12	18	
Age (yrs)				
Currently	55 ± 3.0	63.6 ± 2.2	55 ± 2.1	0.051
At disease onset	-	50.9 ± 2.2	43.9 ± 2.1	0.04
Disease duration (yrs)	-	12.7 ± 2.1	10.9 ± 1.2	0.8
Education (yrs)	13.8 ± 0.7	14.2 ± 1.3	12.2 ± 0.9	>0.15
DDS	-	-	6	
Pathological Gambling	-	-	10	
Hypersexuality	-	-	9	
Compulsive Shopping	-	-	5	
Binge Eating	-	-	7	
Kleptomania	-	-	1	
Punding	-	-	2	
Morning L-dopa dose (mg)	-	170 ± 21	185 ± 32	0.3
Total L-dopa dose (mg)	-	604 ± 73	752 ± 109	0.36
LEU dose (mg)	-	732 ± 203	971 ± 183	0.1
DA (patients)	-	7	9	0.89
MAO inhibitor(patients)	-	5	6	0.6
Entacapone (patients)	-	5	6	0.6
UPDRS OFF medication	-	24 ± 1.6	38 ± 3.4	0.002
UPDRS ON medication	-	13 ± 1.4	18 ± 2.2	0.12
Average improvement in UPDRS (%)		46	53	

Table 7. *Risk and learning task: Demographic characteristics.*

DDS = Dopamine Dysregulation Syndrome; UPDRS = Unified Parkinson's Disease Rating Scale; LEU = L-dopa equivalent units; DA = dopamine agonist. All values are mean ± sem. Pathological gambling assessed with DSM IV criteria, compulsive shopping assessed with McElroy's criteria (McElroy, Keck et al. 1994), hypersexuality assessed with questionnaire suggested by Voon et al. (Voon, Hassan et al. 2006) and punding.

Working memory task

The WM task showed a main effect of group ($F_{2,47} = 6.9$, $p = 0.002$) and task ($F_{1,131}=16.0$, $p < 0.001$), and a significant interaction between these factors ($F_{2,131} = 3.3$, $p = 0.040$), but no effect of "off" versus "on" ($F_{1,131} = 0.007$, $p = 0.9$). To examine these effects in more detail, two additional ANOVAs with post-hoc comparisons were carried out, which revealed that the overall WM (digit forward + backward span) was significantly impaired in the PD+ICB group compared with both the control ($p = 0.006$) and the PD-ICB groups ($p = 0.014$), but there was no difference between the PD-ICB group and controls ($p = 1.00$; Figure 6A). More specifically PD+ICB patients performed significantly worse on the forward task than the PD-ICB and control groups (both $p < 0.001$) and also performed significantly worse on the backward task than the PD-ICB ($p = 0.01$) and control groups ($p < 0.001$).

There were no significant differences between PD-ICB patients and controls in the forwards task ($p = 0.09$) but the control group was significantly better than the PD-ICB group in the backwards task ($p = 0.01$) (Figure 6B).

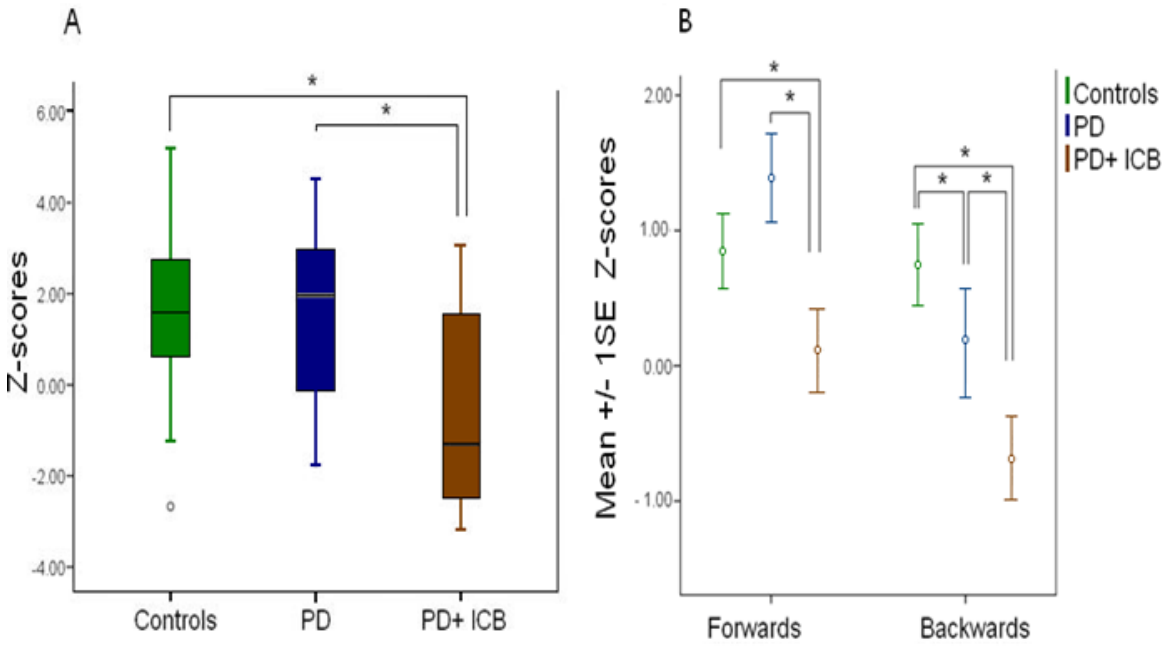

Figure 6. *WM performance.*

A. Box plot showing the median (horizontal line) within a box containing the central 50% of the observations (i.e., the upper and lower limits of the box are the 75th and the 25th percentiles) and extremes of the whiskers containing the central 95% of the ordered observations. Controls, Parkinson's disease without (PD) and with impulsive compulsive behaviours (PD+ICB). Outliner is shown as circle.

B. Working memory between the three groups, split by tasks (forwards backwards). Values are mean (± 1 sem). Significant differences were labelled with "" in both figures.*

Learning task

Learning was assessed in the instrumental task using a recently developed Bayesian decision making model (Averbeck and Duchaine 2009). The models were first fit separately to the 65/35 blocks and the 75/25 blocks in the learning task, but there were no significant differences between parameters ($p > 0.05$) so one model was then fit to all 4 of the blocks. Overall, the number of times that subjects picked the most rewarded image was similar between on and off conditions (Figure 7A-C).

The choices of the subjects were compared to an ideal observer that always made the optimal decision given the feedback up to the current trial in each block. All subject groups made the same choice as the ideal observer at above chance levels (PD+ICB off, $t_{19} = 4.7$, $p < 0.001$; PD+ICB on, $t_{19} = 4.1$, $p = 0.001$; PD-ICB off, $t_{11} = 3.2$, $p = 0.009$; PD-ICB on, $t_{11} = 3.1$, $p = 0.010$; Control 1, $t_{16} = 3.8$, $p = 0.002$; Control 2, $t_{16} = 3.8$, $p = 0.002$). A comparison of group and session in a mixed model ANOVA showed no significant effect of group ($F_{2,46} = 1.17$, $p = 0.319$), session ($F_{1, 46} = 0.14$, $p = 0.71$) or interaction ($F_{2,46} = 0.15$, $p = 0.857$).

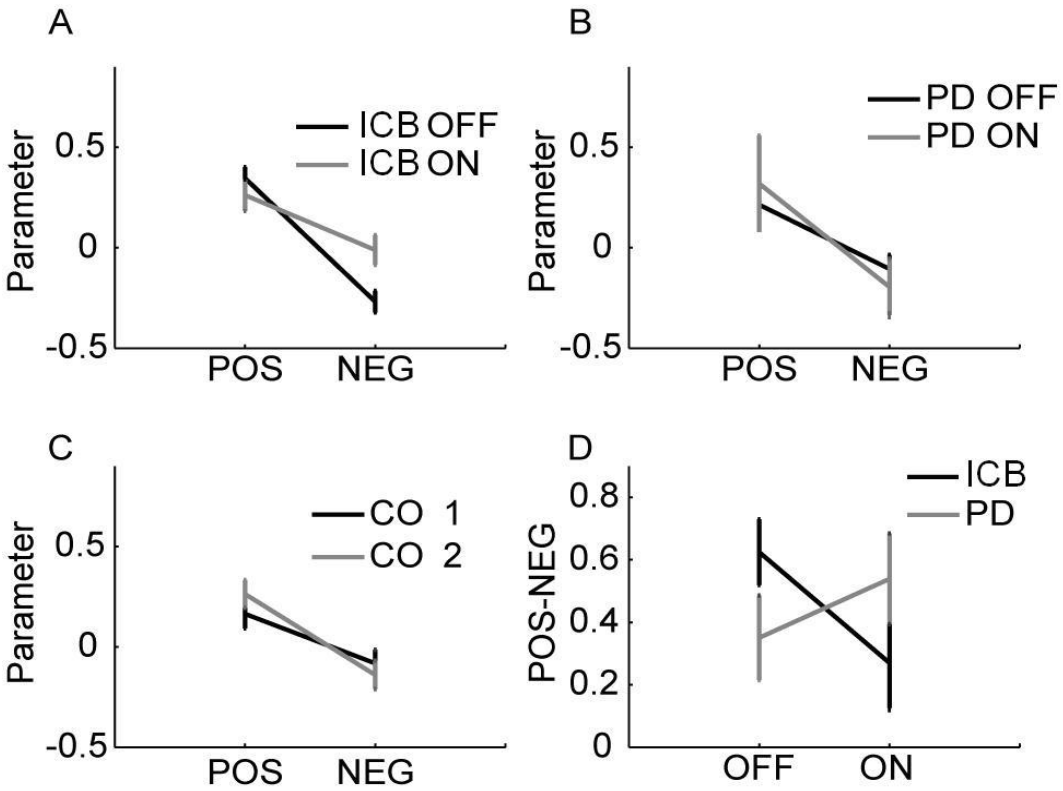

Figure 7. *Learning from positive and negative feedback.*

PD patients with and without ICBs and controls. All values are mean (± 1 sem).

A. Learning from positive and negative feedback on and off medication for PD+ICB.

B. Same as A for the PD group without ICBs. C. Learning from positive and negative feedback in first and second test session in control subjects. D. Within subject difference in learning from positive versus negative feedback for PD patients with ICBs versus non-impulsive patients off and on medication.

Next, learning from positive and negative feedback was compared across groups. When all three groups were compared, there was a significant effect of valence ($F_{1,46}$ = 65.9, $p < 0.001$) but there were no other significant effects. Subsequently, an ANOVA was carried out directly comparing the PD and ICB groups, excluding the control group. In these groups, there was a main effect of valence ($F_{1, 30}$ = 83.07, $p < 0.001$) but no other main effects or 2-way interactions. There was, however, a 3-way interaction between valence, group and session ($F_{1,30}$ = 6.55, p = 0.016; Figure 7D). Separate ANOVAs in the two individual groups showed a significant interaction between session and type of feedback for the PD+ICB group (Figure 7A; $F_{1,19}$ = 4.8, p = 0.041), as well as a significant main effect of feedback valence ($F_{1,19}$ = 12.43, p = 0.002). The PD-ICB group showed a main effect of feedback valence (Figure 7B; $F_{1,11}$ = 14.6, p = 0.003), but no interaction between session and valence ($F_{1,11}$ = 2.83, p = 0.121).

Risk task

Two effects in the risk task were modeled. The first was an overall risk aversion term and the second was whether subjects became more or less risk averse if they won in the previous trial. First, controls showed an increase in risk aversion in the second test session, whereas both patient groups showed an increase in risk preference in the second session relative to the first session (Figure 8). An ANOVA that included all three groups had no significant main effects of group or session but did show a significant interaction between group and session ($F_{2,48}$ = 4.2, p = 0.021). Post-hoc comparisons of the difference of the sessions showed that the controls were significantly different than the

PD-ICB subjects (p = 0.036) but did not differ significantly from the PD+ICB group (p = 0.052). Next, an ANOVA was carried out on only the PD-ICB and PD+ICB groups which showed no significant differences. However, when the PD-ICB group was compared to the subset of PD+ICB patients that had PG (n = 10 gamblers, Figure 8) there was a main effect of group ($F_{1,21} = 7.9$, $p = 0.011$) and session ($F_{1,21} = 4.77$, $p = 0.040$). It was also analysed whether subjects became more risk prone following a win. An ANOVA across all three groups showed a main effect of session ($F_{1,48} = 5.3$, $p = 0.030$) but no other main effects or interactions. When the analysis was restricted to PD-ICB and PD+ICB groups or the PD-ICB and PD+PG, there were no significant main effects or interactions.

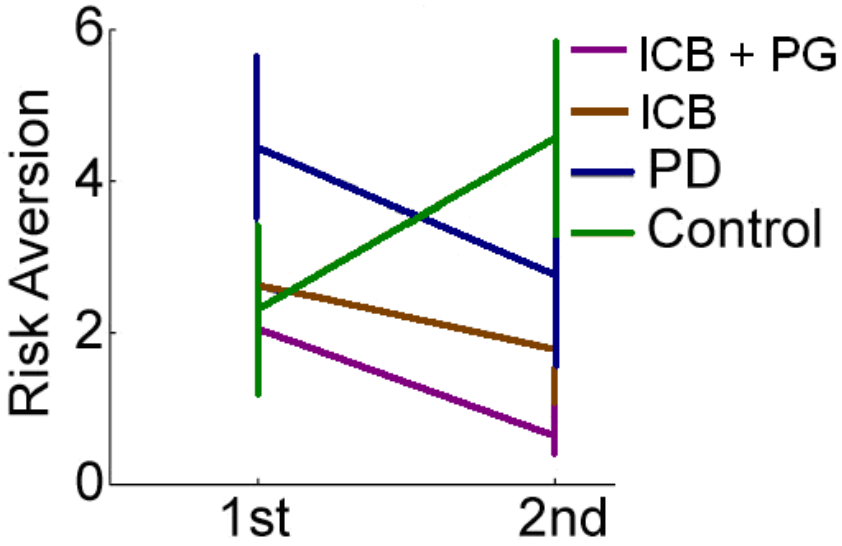

Figure 8. *Risk preference.*

All values are mean (± 1 sem). Risk preference by group on (2nd trial for patients) and off (1st trial for patients) dopamine medication.

Discussion

Increasing dopamine levels improves cognitive performance in some tasks while it impairs others (Swainson, Rogers et al. 2000, Cools, Barker et al. 2001). The deleterious effects of dopaminergic medication on reversal learning mediated via the ventral striatum have also been shown with functional fMRI in PD patients (Cools, Lewis et al. 2007). Functional imaging has also localized dopamine effects on reward based learning to the ventral striatum (Pessiglione, Seymour et al. 2006). Other studies have shown beneficial effects of medication on tasks which may depend more on the dorsal striatum, including task switching and working memory (Lange, Robbins et al. 1992, Cools, Barker et al. 2001). Similarly, PD patients in their "off" state have deficits in cognitive sequence learning (Shohamy, Myers et al. 2005) and in the "Tower of London" task (Lange, Robbins et al. 1992). Dopaminergic replacement improves learning from positive feedback but impairs learning from negative feedback while withdrawal from dopaminergic medication in PD patients leads to the reverse profile with increased learning from negative feedback but impairment in positive feedback learning (Frank, Seeberger et al. 2004, Cools, Altamirano et al. 2006). Consistent with this, similar results have been seen in drug naïve PD patients who were then treated with dopamine agonists (Bodi, Keri et al. 2009) and in healthy subjects given either dopamine agonists or antagonists (Frank and O'Reilly R 2006).

The results showed that PD+ICB patients had an opposite profile of effects on learning from positive versus negative feedback, depending on whether they were on or off medication compared with PD-ICB patients. The PD+ICB patients showed better

learning from positive versus negative feedback off medication compared to on medication, whereas the PD-ICB group showed a trend towards the previously described learning effects (Frank, Seeberger et al. 2004). A similar trend with relative improved negative feedback learning of PD+ICB patients in their “on” versus their “off” state was found in another study (Voon, Pessiglione et al. 2010). However, gain learning differed between this study and the study by Voon et al. They found improved reward learning in PD+ICB patients in their “on” state (Voon, Pessiglione et al. 2010) which was not found in this study. There are fundamental differences between their approach and the approach in this study that may account for these discrepancies. They used interleaved win (i.e. win $10/lose $0) and loss (i.e. lose $10/win $0) conditions and fit one learning rate parameter to the win condition and one to the loss condition. In this study, separate parameters to positive and negative outcomes were fit within a single condition. Further, Voon and colleagues tested for effects of dopamine agonists whereas in this study the acute effect of L-dopa on decision making was examined. The results presented in this thesis are also consistent with a more recent study which demonstrated that increased dopamine levels in the PD+ICB group increased sensitivity to negative feedback (Djamshidian, O'Sullivan et al. 2012).

WM in the forward and backward digit span was significantly reduced in PD+ICB patients compared to the PD-ICB and the control groups. PD-ICB patients showed impairment in the digit backward span test compared to controls, consistent with a previous study (Mamikonyan, Moberg et al. 2009). There was, however, no effect of medication despite the fact that dopamine levels are known to play an important role in working memory (Cools, Gibbs et al. 2008, Landau, Lal et al. 2009). Previous studies

have shown that working memory is reduced in impulsive patients with attention deficit/hyperactivity disorder and healthy controls who scored highly on an impulsivity questionnaire. These subjects had lower total striatal dopamine levels which seem to be associated with lower WM capacity (Cools, Sheridan et al. 2007, Frank, Santamaria et al. 2007). Other studies have shown impaired spatial memory in patients with impulse control disorders (Voon, Reynolds et al. 2010).

The prefrontal cortex is also involved in WM capacity (McNab and Klingberg 2008, Landau, Lal et al. 2009). In addition to the mid ventrolateral prefrontal cortex, which is activated during the digit forward span, the mid dorsolateral prefrontal cortex is activated for the backward digit span (Owen 2000) and patients with large lesions in the prefrontal cortex have defective decision making (Manes, Sahakian et al. 2002).

PET studies of dopamine release have shown that dopamine medication leads to elevated ventral striatal dopamine release in PD+ICB patients relative to PD patients without ICBs (Evans, Pavese et al. 2006, Steeves, Miyasaki et al. 2009). These observations and results of this study are consistent with the hypothesis that PD+ICB patients have elevated baseline dopamine levels in the ventral striatum, and that dopaminergic medication increases the levels further, reducing learning from positive feedback. This might be explained by the “inverted U” shape hypothesis (Williams and Goldman-Rakic 1995, Cools, Barker et al. 2003) where the ability to pick the rewarded stimulus might be impaired when PD+ICB subjects are pushed off the upper end of the curve by their medication.

The risk task was designed to test the hypothesis that patients with ICBs are more risk-prone than non-ICB patients (Voon, Thomsen et al. 2007). Previous authors have described the premorbid *parkinsonian personality* as one characterised by caution, risk aversion and anhedonia (Todes and Lees 1985). In contrast PD+ICB patients have a behavioural profile characterized by increased impulsiveness or novelty seeking (Voon, Thomsen et al. 2007) similar to subjects prone to substance abuse and behavioural addictions (Sher, Bartholow et al. 2000). Overall PD+ICB patients showed a trend to be more risk prone relative to non-impulsive PD patients, which did not reach significance. However, PD+PG patients were significantly more risk prone than the non-impulsive PD group. A tendency towards risky behaviour has also been found in pathological gamblers (Brand, Kalbe et al. 2005). Furthermore, dopaminergic medication led to increased risk preference in the PD-ICB group relative to healthy controls, and just missed significance in ICB patients versus controls. This is particularly interesting since risk taking decreases with age (Deakin, Aitken et al. 2004) and there was a trend for the non-impulsive PD group to be older than both groups. These findings are consistent with two recently published studies which showed that dopamine agonists lead to increased novelty seeking and a reduction in negative feedback learning (Abler, Hahlbrock et al. 2009, Bodi, Keri et al. 2009).

It is important to consider the limitations of this study. First, unbalanced gains (10 pence) and losses (5 pence) were used in the learning paradigm, so it might be the differential magnitude that the PD+ICB patients are sensitive to. However, it is unlikely that differential sensitivity to reward magnitude could underlie the group differences with respect to the effects of medication, as results showed that dopaminergic

medication status affected risk preference (which measures sensitivity to reward magnitude) in the same way in PD and PD+ICB patients, and yet medication had contrasting effects in the learning task. The valence effect that was seen across groups, however, could be due to the unbalanced gains and losses, as all groups appeared to learn more from gains than losses. Second, in order to minimise the effects of this study on patients, data collection was performed in one morning in fixed order; "off" medication then "on" medication. Thus practice effects cannot be separated from the "on" medication effects. Accordingly, healthy volunteers were also tested twice to attempt to control for practice effects through the morning. However, the latter does not negate the possibility of an interaction between practice and disease, so that practice effects may have been different in patients. In the light of the effects demonstrated in the current study a follow-up study is planned in which the order of drug states is counterbalanced across patients.

Conclusion

This study demonstrates differences in learning between PD patients with and without ICBs. These differences could be explained by higher ventral striatal dopamine levels in PD+ICB patients. In addition, PD patients with PG were more risk prone compared to non-impulsive PD patients and healthy controls. These findings may have therapeutic and clinical implications. The reduction in the overall dopaminergic medication with positive reinforcement of non-impulsive behaviour is likely to be more beneficial than aversion therapy in PD+ICB patients.

Key Findings

- PD+ICB patients performed worse than controls and PD-ICB patients on a digit forward and backward span.
- PD+ICB and PD-ICB patients showed an opposite learning profile depending on their dopamine status.
- All PD patients were more risk prone after dopaminergic medication, with PD+PG patients being significantly more risk prone than the PD-ICB group.

Limitations

- No counterbalanced testing.
- Unbalanced gains and losses in the learning task.

3.2. Altruistic punishment in patients with Parkinson's disease with and without impulsive behaviour

Introduction

Altruism derives from the Latin word "alter"-the other. Altruism can be regarded as the opposite of egoism since it does not result in a personal benefit and might even bear at a personal cost (de Quervain, Fischbacher et al. 2004). Violation of social norms or unfair behaviour by members of a group induces a desire for society to punish the miscreants (Fehr and Gachter 2002). Punishing violators of social norms is gratifying, as people are prepared to accept personal loss in order to serve up justice. Punishment when there is personal cost is known as altruistic punishment, and has been shown to reduce the amount of unfair behaviour within groups (Fehr and Gachter 2002).

A functional imaging study in healthy volunteers has shown that the dorsal striatum, in particular the caudate nucleus is critically involved in mediating punishment and greater activation in the ventral caudate is associated with higher altruistic punishment. This study also indicated that people derive satisfaction from punishing norm violations (de Quervain, Fischbacher et al. 2004). Other fMRI studies have demonstrated that the dorsolateral prefrontal cortex, the insula (Sanfey, Rilling et al. 2003) and the caudate nucleus (King-Casas, Tomlin et al. 2005) play important roles in processing fair and unfair behaviour. The dorsal-lateral prefrontal cortex and the caudate are directly

connected in a frontal-striatal loop (Haber, Kim et al. 2006), and therefore both regions are likely to be relevant in mediating responses to fair and unfair behaviour.

The dopamine innervation of the dorsal striatum is severely depleted in PD, leading to bradykinesia and rigidity. Dopaminergic replacement is used to correct the depleted dopamine levels and improve motor deficits. Patients with PD are commonly anhedonic (Todes and Lees 1985), but there is a subgroup of patients who during chronic dopaminergic treatment exhibit ICBs including pathological gambling, hypersexuality, compulsive shopping, binge eating, reckless generosity, punding and the compulsive use of dopaminergic medication (DDS) (American Psychiatric Association 2000, Lawrence, Evans et al. 2003, Weintraub and Potenza 2006, Brewer and Potenza 2008, O'Sullivan, Evans et al. 2009). Clinical data suggest that dopamine replacement medication, especially dopamine agonists, directly provoke these compulsive behaviours (Weintraub, Koester et al. 2010) and a recent study has demonstrated a positive association between impulsivity and altruistic punishment (Crockett, Clark et al. 2010).

PD+ICB and PD-ICB patients were tested “on” and “off” medication and results were compared with healthy controls matched for age and education. As PD+ICB patients violate social norms themselves, and given their deficits in learning from negative feedback, the hypothesis was that “off medication” they are less likely to punish others that violate social norms. It was further speculated that on dopaminergic medication both groups of patients would punish to a greater amount and more frequently than when off medication given the role of the striatum in mediating punishment, and the important role of dopamine in modulating behaviours mediated by the striatum.

Patients and methods

Patients were recruited from a database of attendees at the National Hospital for Neurology and Neurosurgery Queen Square, London, UK. All patients fulfilled the Queen Square Brain Bank criteria for the diagnosis of PD (Gibb and Lees 1988) and were taking L-dopa medication. Controls were usually recruited from amongst the patient's spouses or partners. Participants, who provided written informed consent to protocols approved by the UCLH Trust local ethics committee, were included. Patients who scored under 27/30 points on the MMSE were excluded from this study.

The study was performed between-groups, such that no patients were tested both off and on: this eliminates the possibility of order effects, which may be more likely with the task used in this study than other studies. Thirteen PD+ICB patients were tested off medication and 14 on medication. Similarly 12 PD-ICB patients were tested off medication and 14 on medication. Results were compared with 26 healthy controls. Table 8 includes detailed demographic information on all subjects.

All patients were screened for sub-classes of ICBs. Pathological gambling was defined using the DSM IV criteria, compulsive shopping was defined using McElroy's criteria (McElroy, Keck et al. 1994), hypersexuality was defined as suggested (Voon, Hassan et al. 2006). All PD patients were additionally screened for punding (Evans, Katzenschlager et al. 2004). Patients who were tested "off" performed the test between 8.00 a.m. and 9.00 a.m. prior to their morning medication and had not taken their medication for at least 12 hours.

	Control	PD+ICB on med.	PD+ ICB off med.	PD- ICB on med.	PD - ICB off med.	F value except *	p-value
Participants	26	14	13	14	12		
Age (yrs)	58±11	55.0 ± 11.9	56.6±6.4	66.3±8.0	64.2± 8.3	3.5	0.01
Gender(male)	15	11	9	12	10	χ^2=5.1 *	0.28
At disease onset (yrs)	-	44±10.5	49±7.6	54.1±9.5	53.1±8.8	3.5	0.023
Disease duration	-	11.3±5.2	7.7±4.7	12.2±7	11.1±6.9	1.45	0.24
Education	13.5±3	12.3± 2.3	14.7±3.5	14.0± 4.3	15.2±4.0	1.54	0.2
LEU (mg)	-	858±348	801±479	812±346	825±378	0.05	0.98
L-dopa (mg)	-	692.9±281	521±227	604±315	466±247	1.6	0.19
DA	-	8	9	10	9	χ^2=1.8 *	0.6
Active ICB	-	8	8	-	-		NS
Gambling	-	4	3	-	-		NS
Sex	-	6	8	-	-		NS
Shopping	-	6	8	-	-		NS
Punding	-	2	2	-	-		NS
Kleptomania	-	1	-	-	-		NS
UPDRS on	-	19.4±8.0	14.1±5.2	17.7±10.9	12.5±4.0	1.8	0.16
UPDRS off	-	36.8±15.4	29.2±11.1	27.7± 9.5	24.0± 7.0	2.3	0.09
Change in UPDRS (%)		46	52	36	48		

Table 8. *Altruistic punishment: Demographic characteristics.*

Controls, PD patients with and without ICBs. NS = not significant.

Patients who were tested on medication were assessed at a similar time of the morning when they felt that their motor symptoms had been well controlled, about 1 hour after their usual morning anti-Parkinson medication. The therapeutic motor response to L-dopa was assessed by UPDRS scores (part 3) during “off” and “on” state. All patients had an excellent L-dopa response. Levodopa equivalent units (LEU) were calculated as described previously (Evans, Katzenschlager et al. 2004). Testing was usually performed in patient’s homes or a hotel room using a laptop computer. Distractions were minimized as much as possible.

Altruistic punishment task

The task was a computerized trust game (de Quervain, Fischbacher et al. 2004) designed to assess altruistic punishment in fair and unfair rounds. Participants were told that they were playing live against eight human players, but in fact all were playing against the computer. To ensure that the participants believed they were playing against human participants several precautions were taken. The tests were administered on a laptop, often in the participant’s homes. Therefore an external modem which initiated a connection to the internet was used. During this connection process the screen displayed “connecting to the first player” and later on during play “your decision has been sent to your first partner”. Random time delays were also used while subjects waited to see if their “partner” would reciprocate.

Participants received an allowance at the start of play and were told that they could start the game by entrusting £10 or nothing to each of the eight trustees, as done previously

(de Quervain, Fischbacher et al. 2004). Participants played with one trustee per round. Thus, a single decision at the start of play dictated the amount entrusted by the player in all subsequent rounds. None of the subjects chose not to entrust the £10 at the start of play. Participants were told that each trustee had been given £10 already and that in each round the invested £10 was quadrupled. Thus, each of the eight players (trustees) received £50 in total. The trustee could either respond in a trustworthy manner and share (send back £25) or could keep all the money (£50). Following this the participants were given an additional £10, and had the option to punish the trustee which would result in a decrease in the amount of money the trustee was left with. However, participants were informed that they would lose £1 for every £2 they chose to punish the trustee. Their punishment options were £0, £5, £10, £15 and £20, at costs to the participant of £0, £2.50, £5.00, £7.50 and £10. In three of the eight rounds participants were treated in a fair manner (receiving £25 back), in the rest of the rounds they were treated in an unfair manner (receiving £0 back). All participants understood the rules. Participants either pressed the necessary computer key by themselves or if more convenient gave verbal commands and I pressed the keys on their behalf. Participants were given the average outcome across all rounds of play. Controls received on average £14, PD+ICB patients off medication on average £13, PD-ICB patients off medication £10 and PD patients on medication from both groups £9 for completing this study.

Statistical analysis

Analyses were carried out on the amount that the patients chose to punish in each round. The raw scores were 1 if participants did not punish or respectively 2 = £5, 3 = £10, 4 = £15 and 5 = £20. Analyses using standard linear models were carried out and presented in the results section. For the linear model, a mixed model ANOVA was performed with the scores as the dependent variable. Trials (round 1 to 8) and valence (fair and unfair) was modeled as within subject factors, with trial nested under valence. Group (PD-ICB off medication, PD-ICB on medication, PD+ICB off medication, PD+ICB on medication and controls) was also modeled and subject was included as a random factor nested under group. Interactions between the fixed effects were also assessed. All post hoc comparisons were Bonferroni corrected.

A second ANOVA on just the PD-ICB and PD+ICB groups was used to examine explicit medication and group (PD-ICB versus PD+ICB) effects. This model was identical in all other factors to the above model, except the group variable, which had 5 levels in the first analysis, was split into 2 factors each with 2 levels (as controls were excluded): patient diagnosis (+ICB/-ICB) and medication (on/off dopaminergic therapy).

As the dependent variable values took on a discrete set of values, a generalized linear model (SPSS) with a multinomial cumulative logit link function was also used to assess significance. The cumulative logit maintains the ordinal relation of the responses

without making the Gaussian assumption on the residuals. Wald chi-square was used to assess statistical significance. The results were closely replicated and listed below.

Results

Demographic characteristics

Groups were generally well matched demographically. However, there was a significant effect of age between the 5 groups ($F_{4,74} = 3.5$, $p = 0.01$; controls, PD-ICB on, PD-ICB off, PD+ICB on and PD+ICB off). Post hoc analysis revealed that the PD-ICB on group was older than the PD+ICB on ($p = 0.03$) but not to the PD+ICB off group ($p = 0.12$). There was no difference between the control and the PD-ICB on group ($p = 0.13$), no difference between the PD-ICB off and the PD+ICB on group ($p = 0.2$) and all other patients groups ($p > 0.57$). There was also a significant effect of age of onset ($F_{3,49} = 3.4$, $p = 0.03$). Post hoc analysis showed that the PD+ICB on group had an earlier disease onset ($p = 0.03$) than the PD-ICB on group, consistent with previous studies (Weintraub and Potenza 2006, Voon, Thomsen et al. 2007). There was no difference in age of disease onset between the PD+ICB on group and the PD-ICB off group ($p = 0.08$) nor between the other groups ($p > 0.92$). There was also no difference in the LEU dose ($F_{3,48} = 0.05$, $p = 0.98$) or the daily L-dopa dose ($F_{3,48} = 1.6$, $p = 0.19$).

Analysis of punishment behaviour

Mixed model ANOVA

An ANOVA with dependent variable the amount of punishment was carried out, with group entered as five levels (PD-ICB on, PD-ICB off, PD+ICB on, PD+ICB off, controls). There was a significant main effects of group ($F_{4,73} = 11.17$, $p < 0.001$) and valence ($F_{1,73} = 265.83$, $p < 0.01$), where valence was fair versus unfair outcome. There was also a significant interaction between group and valence ($F_{4,73} = 4.54$, $p = 0.002$). Given the interaction with valence, separate ANOVAs on the fair and unfair rounds were carried out. In the fair rounds there was no effect of group ($F_{4,73} = 1.95$, $p = 0.111$). In the unfair rounds there was a main effect of group ($F_{4,73} = 9.24$, $p < 0.001$).

Next the PD-ICB and PD+ICB groups were compared to directly examine a diagnosis of ICB as well as the effects of medication. Thus, group was split by ICB diagnosis (+ICB/-ICB) and medication (on/off dopamine replacement therapy). The main effect of group just missed significance ($F_{1,48} = 3.71$, $p = 0.060$). There was, however, a significant main effect of medication ($F_{1, 48} = 5.76$, $p = 0.020$) and a significant interaction between group and medication ($F_{1, 48} = 7.68$, $p = 0.008$). There was also a valence by group interaction ($F_{1,336} = 4.97$, $p = 0.026$) and a significant valence by group by medication interaction ($F_{1, 336} = 9.71$, $p = 0.002$).

As there was a difference in age between groups, age was added as a covariate but did not affect significance of any parameters. Given the interactions with valence, this ANOVA was split by valence and separate ANOVAs were performed. In the fair rounds

there was no effect of group ($F_{1, 48} = 0.04$, $p = 0.852$) or medication ($F_{1, 48} = 1.2$, $p = 0.279$) (Figure 9A). In the unfair rounds, however, there was a main effect of group ($F_{1, 48} = 4.05$, $p = 0.050$), an interaction between group and medication such that PD-ICB on and off punished strongly, whereas PD+ICB on also punished strongly, but PD+ICB off punished less ($F_{1, 48} = 8.24$, $p = 0.006$) (Figure 9B). The main effect of medication just missed significance ($F_{1, 48} = 3.96$, $p = 0.052$).

Next, pairwise post-hoc comparisons between all five groups in just the unfair rounds (Bonferroni corrected) were carried out. This analysis showed that PD-ICB on, PD-ICB off and PD+ICB on punished significantly more than controls ($p < 0.01$) whereas the PD+ICB off group punished similarly to controls ($p = 1.000$).

Furthermore, PD-ICB on and PD+ICB on punished significantly more than the PD+ICB off group ($p < 0.05$), but PD-ICB off only reached trend level versus the PD+ICB off group ($p = 0.067$).

As dopamine loss in PD progresses over the course of the disease a correlation between disease duration and the amount of punishment was made. However, correlations between disease duration and the amount of punishment in the unfair condition showed no significant effects ($p > 0.345$). There was also no correlation between UPDRS scores and punishment ($p > 0.405$).

Generalized linear model

A generalized linear model was used, with group entered as five levels (PD-ICB on, PD-ICB off, PD+ICB on, PD+ICB off, controls). There was a significant main effects of group (Wald $\chi^2 = 15.76$, $p = 0.003$) and valence (Wald $\chi^2 = 224.43$, $p < 0.001$) and a significant interaction between group and valence (Wald $\chi^2 = 10.20$, $p = 0.037$). Comparison to the PD-ICB and PD+ICB groups on and off medication showed no main effect of group (Wald $\chi^2 = 1.70$, $p = 0.192$). There was, however, a significant main effect of medication (Wald $\chi^2 = 8.38$, $p = 0.004$) and a significant interaction between group and medication (Wald $\chi^2 = 4.54$, $p = 0.033$). There was also a valence by group interaction (Wald $\chi^2 = 4.39$, $p = 0.036$) and a significant valence by group by medication interaction (Wald $\chi^2 = 6.23$, $p = 0.044$).

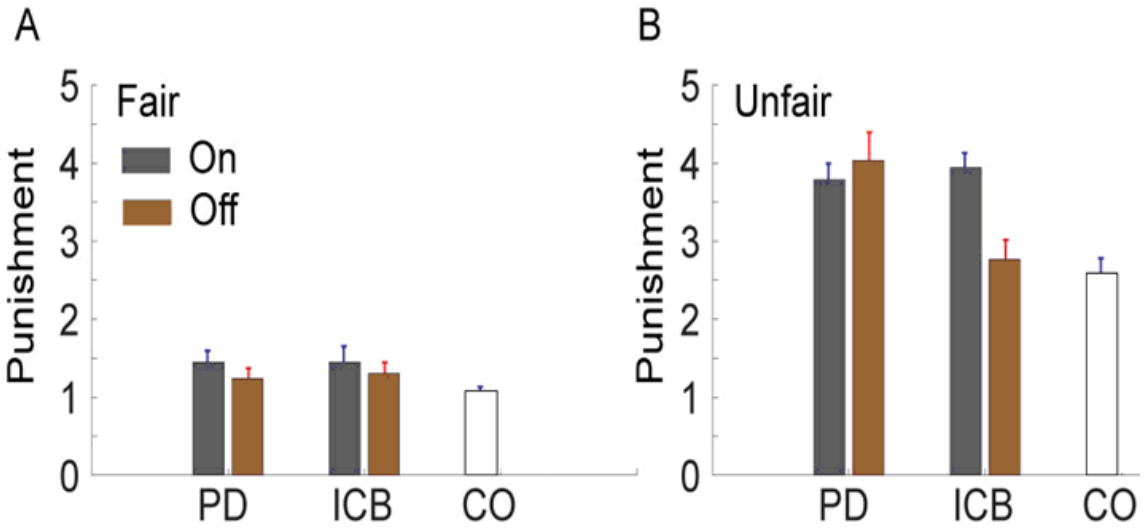

Figure 9. *Average punishment score of participants in fair and unfair rounds.*

Error bars are ± 1 sem.

Discussion

This study demonstrated increased altruistic punishment behaviour in PD+ICB patients on dopaminergic medication compared to controls. These patients behaved similarly to controls off medication, whereas PD-ICB patients punished more than controls whether they were medicated or not.

The decision to punish is likely influenced by the participant's response to the amount returned by the trustee. When the trustee reciprocates, the investor makes money on the transaction, and when the trustee withholds the investor loses money. Winning and losing money engage learning processes in non-social contexts, and extensive studies have shown that dopamine levels in PD are related to learning from positive and negative feedback (Cools, Barker et al. 2001, Frank, Seeberger et al. 2004, Bodi, Keri et al. 2009). Additionally, many subjects may be unwilling to punish trustees, even if they have a strong negative affective response to the lack of reciprocation, whereas others may punish even though they feel little resentment.

Results showed that PD+ICB patients off medication punished to the same degree as controls, whereas the PD+ICB group on medication punished more. Thus, even though dopamine medication can lead to the development of ICBs, and ICBs are inconsistent with social norms, PD+ICB patients enforce social norms more strongly on than off medication.

It is possible, therefore, that the PD+ICB off group may punish less than all the other patient groups because they are less sensitive to the lack of reciprocation by the trustee.

Additionally, dopaminergic medication has been shown to increase impulsive choice in PD+ICB patients (Voon, Reynolds et al. 2010) and impulsivity correlates positively with altruistic punishment in the "*Ultimatum Game"* (Crockett, Clark et al. 2010). Increased punishment in the PD+ICB group on medication could, therefore, be due to sensitivity to negative feedback and increased impulsivity.

The PD-ICB group punished more than controls both on and off medication. When the PD-ICB group was compared to the PD+ICB group, there was an interaction between medication status and group, and the difference between PD-ICB off and PD+ICB off just failed to reach significance. Interactions between medication and group have already been observed across a range of behaviours including impulsive choice (Voon, Reynolds et al. 2010), learning (Voon, Pessiglione et al. 2010), affective states and reward responsivity (Evans, Lawrence et al. 2010). In this study, only the PD+ICB patients were sensitive to behavioural changes induced by their dopaminergic medications. This is consistent with the observation that clinically impulsive behaviour arises due to medication in the PD+ICB group, but not in the normal PD group (Voon, Reynolds et al. 2010).

There are also differences in the pre-morbid personalities of PD-ICB and PD+ICB patients. PD-ICB patients have a lower premorbid risk of smoking, and tend to be anhedonic, moralistic, punctual, risk averse and altruistic with a strong adherence to social norms (Prick 1966, Todes and Lees 1985, Menza 2000, Evans, Lawrence et al. 2006, Ishihara and Bayne 2006). Recent studies have suggested that some of these behaviours may be related to the prefrontal cortex (Abe, Fujii et al. 2009).

In contrast, PD patients who develop ICBs are higher novelty seekers with an increased premorbid incidence of illicit drug or alcohol addiction (Potenza, Voon et al. 2007, Lim, Evans et al. 2008). The PD-ICB group therefore may punish more than the PD+ICB group off medication, due to their inherent personality traits. However, the exact neurobiological mechanisms that underlie these personality and task behavioural differences are not yet clear.

Brain imaging studies using a similar task have shown that the medial caudate nucleus is activated during punishment, and a ventral caudate focus correlates with the amount of punishment (de Quervain, Fischbacher et al. 2004). The desire to punish altruistically appears to be driven by negative emotions brought about by the fact that trustees fall short of social norms when they do not reciprocate (Fehr and Gachter 2002). However, it is unclear whether punishment in the patient groups is only driven by altruism or whether other factors such as aggression have to be taken into account.

Clinically PD+ICB patients can become quite aggressive and do not have insight that their behaviours are unacceptable to others. This would mean that punishing or criticizing PD+ICB patients for bad behaviour off medication would not be effective since they do not recognize norm violations which might contribute to the patient's low insight.

Further behavioural studies which include self-rating questionnaires to tap the motivation of altruistic punishment are required to clarify findings of this study.

Conclusion

Results of this study showed that PD patients with ICBs respond differently than non-impulsive PD patients in a trust game in which patients can deliver punishment altruistically. Both groups of medicated patients punished more than controls, but off medication the PD-ICB group still punished more than controls, whereas there was no difference between the PD+ICB patients and healthy controls. Unravelling the factors that lead to these differences will provide important insight into impulsive compulsive behaviours, as well as the neural, pharmacological and anatomical mechanisms that underlie these tasks.

Key Findings

- PD-ICB patients punished more often than controls regardless of dopaminergic state.
- PD+ICBs punished more than controls on medication, but similar to controls off medication.
- Only PD+ICB patients changed their behaviour after dopaminergic medication.
- PD+ICB patients on medication might therefore want to enforce social norms, but have difficulties following them.

3.3. Stroop test performance in impulsive and non-impulsive patients with Parkinson's disease

Introduction

The Stroop Colour Word test is a simple but reliable and well researched test for examining cognitive flexibility. The task requires participants to respond to the ink colour and suppress the more familiar word identity. Several versions of the Stroop test exist. In the standard form participants have to read out 100 congruent and incongruent words and the total time for each card is recorded. In the computerized form congruent, incongruent and neutral non coloured words are presented one at the time and reaction time can be recorded (Lansbergen, Kenemans et al. 2007). Whilst responses in congruent settings are relatively automatic, incongruency between the letters and ink colour requires keen attention and leads to slower responses. Stroop interference is defined as the difference between naming the colour of a word in incongruent versus congruent or neutral trials (Lansbergen, Kenemans et al. 2007).

Impairment in the Stroop test has been described in patients with frontal lobe damage, drug abusers (Simon, Domier et al. 2002), patients with schizophrenia (Barch, Carter et al. 2004) and PD patients (Hsieh, Chen et al. 2008). However, an item by item Stroop test has never been used in PD patients with ICBs such as pathological gambling, compulsive shopping, hypersexuality, and binge eating. These patients have poorer working memory assessed by the digit span as described earlier, but it is unclear whether fast cognitive updating as required in the Stroop test will be also impaired.

Further, PD+ICB patients develop these behavioural abnormalities as a direct result of dopaminergic medication. Therefore, all patients were tested once prior and once after dopaminergic medication to assess the effect of medication on cognitive flexibility. The hypothesis was that PD+ICB patients would perform worse than PD-ICB patients and normal controls on a task that requires inhibition of competing responses. It was predicted that all patients would show improvement in cognitive flexibility, reflecting an improved ability to respond to changing task demands, after dopaminergic medication.

Patients and methods

Twenty-four PD-ICB, 28 PD+ICB patients and 24 healthy controls were tested on an item by item Stroop test. Most PD+ICB patients had more than one addictive behaviour, which is in line with the hypothesis that all ICBs share common risk factors regardless of their type of impulsive compulsive behaviour (Torta and Castelli 2008). The ICBs included compulsive sexual behaviour (13 patients), pathological gambling (11 patients), compulsive buying (8 patients), punding (4 patients) and kleptomania (1 patient). None of the patients was clinically depressed at the time of testing and only 4 out of 28 PD+ICB patients and 2 out of 24 PD-ICB patients were taking antidepressant medications (see Table 9). All patients were recruited from the National Hospital for Neurology and Neurosurgery, Queen Square, London. Healthy controls were mainly recruited from amongst the patient's partners. Participants who provided written informed consent to protocols approved by the UCLH Trust local ethics committee were included. Patients who scored under 27/30 points on the Mini Mental State Examination

were excluded. Testing was done in a quiet environment either in the patient's home or in a hotel room using a laptop computer and a microphone. The patient groups were matched for disease duration, motor disability and medication.

PD patients were tested in either an on or off medication state in a counterbalanced order. Results were compared with 24 healthy volunteers who were matched to the PD+ICB group.

Patients who were tested "off" first performed the task between 8.00 a.m. and 9.00 a.m. and had not taken their medication for at least 12 hours. They were then retested in their on medication state 1 hour after taking their first dopaminergic medication of the day. Those patients who were tested on medication first performed this task usually in mid-morning at a similar time of the day when their symptoms were well controlled. They were revisited on the following day prior to their medication for the second test, again between 8.00 a.m. and 9.00 a.m. Controls were tested in the same way, but did not take any anti-Parkinson medication. All patients had an excellent L-dopa response which was assessed by the UPDRS (part 3) motor score during the off and on state. Levodopa equivalent units (LEU) were calculated as described previously (Evans, Katzenschlager et al. 2004).

	Controls	PD+ICB	PD-ICB	t value except * and **	p-value
Participants (no.)	24	28	24		
Age (yrs)	57.8 ± 10.7	54.6 ± 9.2	64,2 ±10.1	F = 7.0 **	0.002
Gender (male)	14	21	21	$\chi^2 = 5.3$ *	0.071
At disease onset (yrs)	-	44.5 ± 8.7	52.5 ± 9.6	t = 3.1	0.03
Disease duration (yrs)	-	10.1 ± 5.5	11.7 ± 7.2	t = 0.88	0.39
Education (yrs)	13.2 ± 2.9	13.4 ± 3.0	14.7 ± 3.6	F = 1.7 **	0.18
LEU dose(mg/day)	-	832 ± 425	821 ± 400	t = 0.1	0.9
DA (patients)	-	14	16	$\chi^2 = 1.4$	0.27
UPDRS on	-	15.5 ± 8.3	14.4 ± 5.8	t = 0.5	0.6
UPDRS off	-	27.3 ± 9.1	26.8 ± 6.7	t = 0.2	0.8
Improvement in UPDRS (%)	-	43.2	46.2		
Gambling	-	11	-		
Hypersexuality	-	13	-		
Shopping	-	8	-		
Punding	-	4	-		
Kleptomania	-	1	-		

Table 9. *Stroop test: Demographic characteristics.*

Stroop test

To account for age related differences in performance an item by item Stroop test consisting of four colours (green, red, blue or yellow) was used and measured reaction time for each trial separately. Each word appeared centrally on a black background. Participants were asked to name the colour of the word as quickly as possible and had a maximum of 4 sec to respond. Sixteen trials were recorded, 8 were congruent and 8 incongruent in a pseudo randomized order, giving four possible patterns of testing namely incongruent followed by incongruent trial, congruent by incongruent, incongruent by congruent and congruent by congruent trials (Figure 10C). A standard microphone (Logitech) was used for recording responses. Reaction time (RT) was computed by finding significant ($p < 0.01$) deviations of the recorded variance in the speech signal, relative to a 200 ms initial baseline.

Statistical analysis

A mixed model ANOVA was performed. The dependent variable was either the error rate or the reaction time, averaged by condition. Condition (off versus on and 1st and 2nd session in normal controls) were modeled as within subject factors and group (PD-ICB, PD+ICB and normal controls) was modeled as a between subject factor. Subject was included as a random factor. Since there was a significant age-difference between the groups age was added as a cofactor in all analyses.

Results

Demographic characteristics

There was a significant effect of age between the 3 groups ($F_{(2,74)} = 7.0$, $p = 0.002$). Post hoc analysis revealed that the PD-ICB group was older than the PD+ICB ($p = 0.001$) and a trend to be older than the control group ($p = 0.058$). Results showed a significant effect of age of onset between the patient groups ($t_{49} = 3.1$, $p = 0.03$). There was no difference in the LEU dose, disease duration and UPDRS (part 3) motor score, across the groups (see Table 9).

Analysis of Stroop test

PD-ICB and PD+ICB groups were compared "off" and "on" medication to healthy controls and pairwise (Bonferroni corrected for 4 comparisons) comparison was made.

For errors (Figure 10A) there was a main effect of group. PD-ICB patients off medication ($F_{(1, 34)} = 7.18$, $p = 0.037$) and PD+ICB patients off medication ($F_{(1, 36)} = 8.25$, $p = 0.022$) made more errors than controls. Thus, off medication all patients made more errors than healthy volunteers, but on medication there was no difference between patients and healthy volunteers ($p > 0.05$). In all cases there were significant effects of congruency, i.e. whether the trial was congruent or incongruent ($p < 0.01$). There were no other significant effects or interactions. For RT there were no significant differences between groups (Figure 10B).

Comparing PD-ICB and PD+ICBs on and off medication showed a main effect of congruency ($F_{(1, 164)} = 51.82$, $p < 0.001$) and an effect of medication ($F_{(1, 164)} = 3.89$, $p = 0.050$), but no main effect of group ($F_{(1, 39)} = 0.21$, $p = 0.649$) on the error rates. There were no significant interactions ($p > 0.535$). For RT there were no significant main effects or interactions ($p > 0.153$).

The data for the PD-ICB and PD+ICB subjects was then split depending on whether the trial followed a trial of the same type, or switched (i.e. congruent followed by congruent, or congruent followed by incongruent, etc.) to examine cognitive flexibility (Figure 10C).

Thus, in addition to a main effect of congruency an effect of switch versus no switch was included, which reflected the previous trial type. For errors there was no main effect of group ($F_{(1, 32)} = 0.04$, $p = 0.847$) and the main effect of medication just missed significance ($F_{(1, 1402)} =3.66$, $p = 0.056$). There was a main effect of congruency ($F_{(1, 1402)} = 15.69$, $p < 0.001$) and a switch by congruent interaction ($F_{(1, 1402)} = 13.85$, $p < 0.001$). For RT there was no significant effect of group ($F_{(1, 35)} = 2.35$, $p = 0.135$), but there was a main effect of medication ($F_{(1,1406)} = 7.41$, $p = 0.007$) and a switch by congruent interaction ($F_{(1, 1406)} = 5.69$, $p = 0.017$).

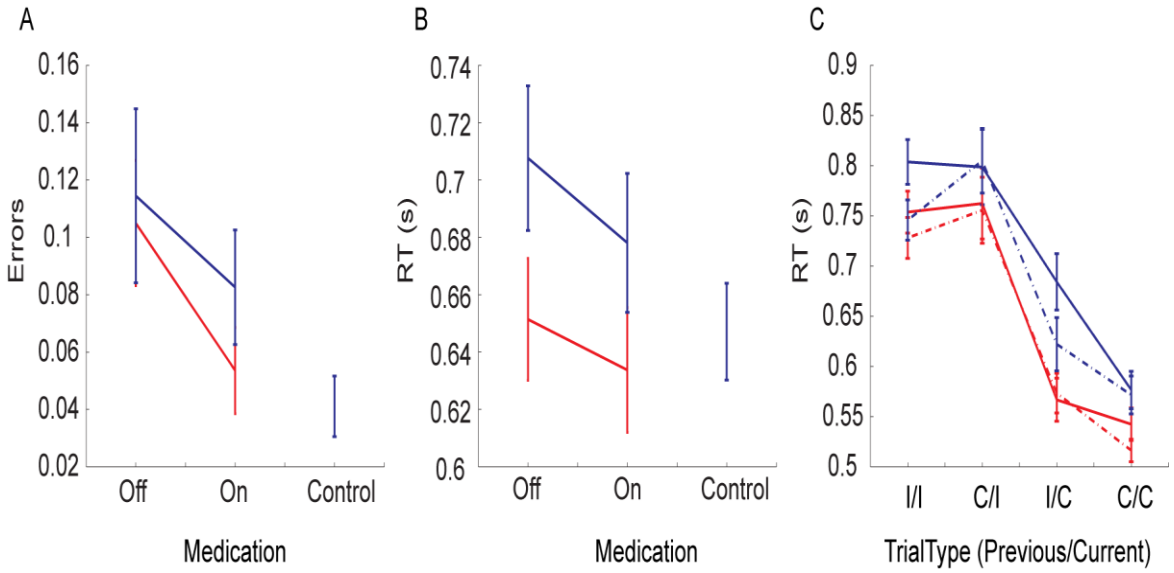

Figure 10. *Stroop test: Behavioural results.*

A. Error rates for each subject group. Blue = PD patients with ICB, red = PD patients without ICB.

B. Reaction times. C. Reaction times for switch and non-switch trials in the patient group. Solid lines = off medication, dotted lines = on medication, I = incongruent, C = congruent.

Discussion

There was a significant Stroop interference effect in all participants. Furthermore, results demonstrated that all PD patients made more errors than healthy volunteers when off medication. Results showed that in their "on" state patients had a shorter RT on switching behaviour between congruent and incongruent trials, in keeping with previous studies (Jahanshahi, Ardouin et al. 2000, Cools, Barker et al. 2003). Findings of this study are also consistent with previous studies showing improvement of Stroop performance in PD patients with and without deep brain stimulation (Jahanshahi, Ardouin et al. 2000, Fera, Nicoletti et al. 2007). There was no difference in RT between PD patients and controls in keeping with previous studies (Fera, Nicoletti et al. 2007). Further, patients on medication showed a trend to be slower in RT in congruent trials followed by incongruent trials compared to incongruent trials followed by incongruent trials (Figure 10C). This might be explained by an increased awareness caused by the previous conflicting trial. There was no difference in error rates between the patient groups which implies that the inability to suppress automatic responses and the inability to suppress, for example, the urge to gamble depend on different processes and neural systems. Findings of this study are also in line with two other studies which have shown no impairment on the FAB scores in PD patients with pathological gambling compared to those without ICBs (Voon, Thomsen et al. 2007, Siri, Cilia et al. 2010). Thus, PD+ICB patients seem to be unimpaired in tasks that are mediated by frontal cortex, as for example occurs also with response suppression tasks (Botvinick, Nystrom et al. 1999). Results of this study are also consistent with another study done in PD patients

with pathological gambling, which showed impairment in a risk assessment task but not in other cognitive domains including a Stroop test (Rossi, Gerschcovich et al. 2010). The results of this study extend the current literature and demonstrate that there is no difference in cognitive flexibility between PD controls and patients with impulse control disorders irrespective of the type.

Brain imaging studies in non PD pathological gamblers versus controls, which used a Stroop test paradigm, showed differences only in the left ventromedial prefrontal cortex (Potenza, Leung et al. 2003). These minor changes might explain why impairment in the Stroop test in impulsive patients could be found in some (Kertzman, Lowengrub et al. 2006) but not all reported studies (Potenza, Leung et al. 2003). Furthermore, performance of the Stroop test might not trigger mesolimbic dopamine release and could fail to activate limbic and "reward centres" of the brain which are known to be abnormal in PD+ICB patients. In line with this notion is the finding that there was no correlation between amygdala activation and Stroop performance (Glahn, Lovallo et al. 2007).

Since cognitive performance may vary during the day (West, Murphy et al. 2002), patients were tested in their "off" condition on average at about 8.30 a.m. and patients of the "on" group at a similar time point, on average at 10.30 a.m.

There are, however, some limitations in this study. Patients who were tested first "on" then "off" were tested on separate days, whereas patients tested first "off" and then "on" were tested on the same day. Thus, the test-retest interval differed between the two groups and conceivably might have influenced the results. However, results of this study

are within-subject effects comparing “off” versus “on”, and they did not depend on the order of testing.

Conclusion

There was no difference in the Stroop test performance between PD patients with and without ICBs suggesting that response inhibition is not a hallmark of ICBs in PD. Future work using an emotionally charged Stroop test, which is more likely to activate the limbic system, could potentially demonstrate differences between the two PD groups.

Key Findings

- All PD patients made more errors prior to their usual medication than controls which resolved after medication.
- All patients on medication made fewer errors and had a shorter RT.
- Response inhibition required in the Stroop test does not differentiate impulsive from non-impulsive PD patients.

Limitation

- The test-retest interval between PD “off” and “on” groups was significantly different.

3.4 Novelty seeking behaviour in Parkinson's disease

Introduction

Humans and animals are inherently attracted to new stimuli as these can be potentially rewarding (Daffner, Mesulam et al. 1998, Hughes 2007). High novelty seeking is part of adolescence and may help in normal development and the acquisition of independence (Kelley, Schochet et al. 2004): adults with novelty seeking personality traits on the other hand often have increased impulsivity, addiction, inability to delay gratification, recklessness and aggressive behaviour(Barratt 1985, Belin, Mar et al. 2008). While self-report questionnaires have suggested that the subgroup of PD+ICB patients with DDS (Evans, Lawrence et al. 2005) and those with pathological gambling (Voon, Thomsen et al. 2007) have high levels of novelty seeking, this has not been formally studied using metric tests.

The trade-off between choosing options of known value and exploring novel options is known as exploration vs. exploitation (Daw, O'Doherty et al. 2006). Exploring novel choices and learning the value of stimuli based on reward feedback have been linked to the ventral striatum, the substantia nigra and the ventral tegmental area of the midbrain (Wittmann, Daw et al. 2008, Guitart-Masip, Bunzeck et al. 2010) as well as the hippocampus (Guitart-Masip, Bunzeck et al. 2010, Voon, Pessiglione et al. 2010). These areas either contain dopamine neurons or receive strong dopaminergic innervation. Additional studies have examined the dopamine link to learning and

exploration. For example, behavioural studies in PD have shown that dopamine levels play an important role in reward learning (Cools, Clark et al. 2002, Frank, Seeberger et al. 2004, Voon, Pessiglione et al. 2010). Complimenting this work, functional magnetic resonance imaging (fMRI) studies in healthy controls and positron emission tomography (PET) studies in PD+ICB patients have localized reward responsivity to the ventral striatum (O'Doherty, Critchley et al. 2003, Steeves, Miyasaki et al. 2009, Evans, Fleming et al. 2010).

One of the circuits that has been proposed to mediate novelty effects includes the hippocampal projection to the ventral striatum. Specifically, the hippocampus forms a functional loop with the ventral striatum and the mid-brain dopamine neurons. The hippocampus is activated by novel information (all information that is not stored in long term memory) and regulates, via the ventral striatum, dopamine neuron firing rates (Lisman and Grace 2005). Neuropathological studies have shown that the parahippocampal gyrus is affected in later stages of PD (Braak, Ghebremedhin et al. 2004). Thus, abnormal and increased activity in the ventral striatum might be triggered by earlier neuropathological changes in the hippocampus in PD+ICB patients.

The aim of the present study was to compare novelty seeking between impulsive and non-impulsive PD patients, and also to examine the role of dopaminergic medication on novelty seeking. It was hypothesized that PD+ICB as a group would be more novelty seeking than PD-ICB patients on a task which allows for exploration of novel options. PD+ICB and PD patients without ICB (PD-ICB) were tested on and off their dopaminergic medication on a modified “three armed bandit” choice task (Wittmann,

Daw et al. 2008), where all participants played for real money. Results of PD-ICB and PD+ICB patients on and off their medication were compared with a group of healthy controls who were matched for age and education to the patients group.

Patients and methods

PD patients were recruited from a database of attendees at the National Hospital for Neurology and Neurosurgery Queen Square, London. All patients fulfilled the Queen Square Brain Bank criteria for the diagnosis of PD (Gibb and Lees 1988) and were taking L-dopa medication. Patients with structural lesions on their brain scans were excluded from this study. Some of the patients had also had raclopride PET scanning and results of this study are presented elsewhere. (O'Sullivan et al, Brain 2011). All patients showed a significant improvement (>35% improvement) after L-dopa intake which was assessed by the UPDRS (part 3) motor score. There was no significant difference in UPDRS motor scores between the 2 patient groups. L-dopa equivalent units (LEU) of patients' regular daily dopamine replacement therapies were calculated as described elsewhere (Evans, Katzenschlager et al. 2004). Controls were usually recruited from amongst the patient's spouses or partners. Participants who provided written informed consent to protocols approved by the UCLH Trust local ethics committee were included. Patients who scored under 27/30 points on the Mini Mental State Examination (MMSE) (Folstein, Folstein et al. 1975) were excluded from this study.

Twenty seven PD+ICB and 25 PD-ICB patients were recruited and results were compared with 24 healthy controls. PD+ICB patients were diagnosed using proposed criteria (Lawrence, Evans et al. 2003, Evans, Katzenschlager et al. 2004, Voon, Potenza et al. 2007). Most PD+ICB patients had more than 1 ICB. The ICBs included compulsive sexual behaviour (12 patients), pathological gambling (11 patients), compulsive buying (8 patients), punding (4 patients) and kleptomania (1 patient).

Novelty task

A three-armed bandit task, modified from the "four armed bandit choice task" used previously was performed (Wittmann, Daw et al. 2008). The task was administered on a laptop computer. Participants performed 60 trials of the task. In each trial three black and white picture post-cards were presented on the screen (Figure 11). After presentation of the pictures, the participant was required to select one of the three pictures, and after the option was selected, they were told whether they had "won" or "lost". Auditory feedback (5 Khz for winning and 2.5 Khz for losing) to reinforce feedback learning was provided. Following an inter-trial interval, during which the screen was blank, the participants were again presented with the 3 choice options and they could make another decision. The location of each picture was randomized from trial to trial to prevent habituation. The participants were told to pick the most often rewarded picture as many times as possible to maximize their winnings.

During the task, as the participants were making their choices and learning the reward value of the pictures, novel stimuli were introduced. This was done by replacing one of the images from which participants had been choosing with a new image, which was

then a novel choice option. A novel choice option was introduced on 20% of trials, or on average every 5 trials. These novel choices were of two types - unfamiliar and familiar.

Figure 11. *Sequence of events in 3-armed bandit task.*

After familiarization, participants were asked to choose one of the three pictures. Images were presented at randomized positions that changed on each trial. Unfamiliar and familiar pictures appeared during the test. Participants were told that each picture had some probability of winning 20p and participants should pick the rewarded picture as many times as possible. Visual and acoustic feedback was given immediately after each trial.

Unfamiliar stimuli were images that the patients had never seen before, whereas familiar stimuli were images that the patients had seen in pre-task training. It is important to note that both unfamiliar and familiar images refer to pictures that were introduced into the on-going 3-armed bandit task, replacing one of the pictures that the participants had been selecting from. Familiarization was done by sending 18 black and white pictures to participant's homes prior to the experiment, and asking them to guess which country each picture was taken from. I called all participants prior to testing to ensure that participants were familiar with the set of images. On the day of testing and prior to each session I familiarized participants again. Different sets of pictures were used for each session. Therefore, participants were re-familiarized with nine of the 18 pictures prior to the first session, and the other nine pictures prior to the second session. Pictures were counterbalanced from the set with which the subjects were familiarized across medication conditions, so approximately half the subjects were familiarized with one half the pictures for their medicated session, and the other half of the subjects were familiarized with the other half of the pictures for their medicated session. None of the subjects knew the purpose of familiarization. There were no differences in reward values between familiar and unfamiliar pictures in the choice task. At the beginning of each of the two choice experiments, in the first trial, all participants were asked: "which picture is unfamiliar?" They all recognized the unfamiliar image among the three in the first trial.

PD patients were tested prior and after their usual anti-Parkinson medication in a counterbalanced sequence to account for order effects. All patients who were tested in their "off medication state" did not take their usual anti-Parkinson medication, including

both L-dopa and any dopamine agonists, for at least 12 hours. Results were compared with 24 controls who were matched for age to the PD+ICB group. Patients who were tested first prior to their usual anti-Parkinson medication ("off medication") performed the task between 8.00am and 9.00am. They were then retested in their "on medication" state one hour after taking their first dopaminergic medication of the day. Those patients who were tested "on medication" first performed this task usually in mid-morning when their motor symptoms were well controlled. They were re-visited on the following day prior to their medication for the second test. Controls were tested in the same way but did not take any anti-Parkinson medication. At the end of the study all participants got a modest amount of money depending on their final score (usually £5-£10).

Statistical analysis

Statistical analyses were performed using SPSS, version 18. For the demographic variables, age, gender, years of education, age of disease onset UPDRS scores, LEU dose were used as dependent variables and group (PD-ICB, PD+ICB and control) was modelled as a between subject factor. ANOVA, t-test or χ^2 test was used where appropriate. For the behavioural variables models were fit to the choice data of individual participants to parameterize the value they assigned to novel stimuli, which in effect characterized the probability that they would select a novel stimulus. A higher value indicates a higher probability of selecting a novel stimulus. An ANOVA was then fit to the parameters derived from the model comparing the effect of novel stimuli in PD and ICB groups off and on medication.

Reinforcement learning model

A reinforcement learning model was also fit to the choice behaviour of the subjects to assess whether or not they were disposed to selecting novel stimuli. This model computes the value of a novel stimulus, to the participant, before it has had any reward feedback. In general, the model updates the value, *v*, of the chosen option, *i*, based on reward feedback, *r* in trial *t* as:

$$v_i(t) = v_i(t-1) + \alpha(r(t) - v_i(t-1)).$$

Thus, the new value of an option is given by its old value, $v_i(t-1)$ plus a change based on the reward prediction error ($r(t)-v_i(t-1)$), multiplied by the learning rate parameter, α. When a novel stimulus is introduced in trial *t*, there is no reward history. The value of that image to the participant can be interfered, by examining how often the participant picks that image, relative to how often they pick the other options with known reward histories. Thus, it is possible to fit, $v_i(t)$, where *t* = the first trial for a novel option, *i*, as a free parameter. Different parameters, $v_i(t)$, for example $v_{familiar}(t)$ and $v_{unfamiliar}(t)$ were fit, to allow us to examine the effects of familiarization on the initial values. Effectively the participants will have some on-going value estimates of the options, *i*, and the relative propensity of the participants to pick the novel option allows us to estimate the value of that option relative to the other options. If participants tend to pick the novel option, it implies that new options are relatively more valuable than the other options, with which the participant has some experience. The model is fit by maximizing the likelihood of the choice behaviour of the participants, given the model parameters. Specifically, the choice probability $d_i(t)$ was calculated using:

$$d_i(t) = \frac{\exp(v_i(t))}{\sum_{k=1}^{3} \exp(v_k(t))}$$

And then calculate the log-likelihood as

$$ll = \sum_{t=1}^{T} log \sum_{k=1}^{a} c_k(t) d_k(t),$$

Where $c_k(t)$=1 when the subject chooses option k in trial t and $c_k(t)$=0 for all unchosen options. Thus, $c_k(t)$ is an indicator variable which selects the choice probability d_k that corresponds to the choice the subject made in trial t, such that the log-likelihood is summed over the chosen options across trials. In other words, the model maximizes the choice probability ($d_k(t)$) of the actual choices the participants made. T is the total number of trials in the session for each participant. Parameters were maximized using standard techniques (Averbeck and Duchaine 2009).

Results

Demographic characteristics

There was a significant effect of age between the 3 groups ($F_{(2,73)}$=7.58, p=0.001). Post hoc analysis revealed that the PD-ICB group was older than the PD+ICB (p=0.001) and a trend to be older than the control group (p=0.055). There was no difference between controls and PD+ICB patients (p=0.54). Further, PD+ICB patients had a significantly younger age of disease onset (t_{49}=3.39, p=0.001). There was no difference in the LEU dose, disease duration, UPDRS motor score (part 3) and years of education across the groups (Table 10). Of note, 15 out of 27 PD+ICB patients and 5 out of 25 PD-ICB patients tested report a sweet tooth, and these proportions were significantly different (χ^2 = 6.9, p = 0.009). All patients had an excellent response to L-dopa and improved by more than 35% on the UPDRS (part 3) motor score in their 'on state' compared to their 'off state. There was no significant difference in UPDRS motor scores between the two patient groups . There was also no difference in MMSE scores between the patient groups, $t_{(50)}$=0.56, p=0.57 (mean MMSE scores in the PD+ICB group=28.7 vs PD-ICB=28.9). Further all patients were tested on a stroop task which showed no difference between impulsive and non-impulsive PD patients. Thus, the PD+ICB and PD-ICB groups were matched for disease duration and other variables, but differed in age.

	Controls	PD+ICB	PD-ICB	t value, χ^2 and F-value	p-value
Participants (no)	24	27	25		
Age (yrs)	57.8 ± 10.7	54.2 ± 9.2	64.2 ± 8.0	F = 7.6	0.001*
Gender (male)	14	22	21	χ^2 = 5.2	0.073
At disease onset	-	44.1 ± 8.7	52.8 ± 9.5	t = 3.2	0.001*
Disease duration (yrs)	-	10.2 ± 5.5	11.4 ± 7.2	t = 0.68	0.5
Education (yrs)	13.2 ± 2.9	13.4 ± 3.0	14.7 ± 3.5	F = 1.5	0.23
LEU dose(mg/day)	-	832 ± 425	805 ± 400	t = 0.2	0.8
DA (patients)	-	14	16	χ^2 = 3.7	0.4
UPDRS on	-	16.6 ± 9.4	14.4 ± 5.8	t = 0.8	0.4
UPDRS off	-	27.3 ± 9.0	26.9 ± 6.7	t = 0.19	0.85
Improvement in UPRDS (%)	-	39.2	46.4		

Table 10. *Novelty task: Demographic characteristics.*

All values are mean ± SD. Significant differences are labelled with "".*

Analysis of Novelty task

An ANOVA on the PD and PD+ICB groups was carried out, with main effects of group, medication, and image familiarization, to assess whether or not there were differences in choice patterns for novel stimuli (Figure 12). An age covariate was included in all ANOVAs. There was a main effect of group ($F_{(1, 45)} = 7.03$, $p = 0.011$), such that ICBs selected novel stimuli whether they were unfamiliar or familiar more often than PDs (Figure 12A). The main effect of medication showed a non-significant trend ($F_{(1, 45)} = 3.2$, $p = 0.076$) with patients on medication being less likely to select novel images. There was however no effect of unfamiliar relative to familiar new images ($F_{(1, 45)} = 1.63$, $p = 0.205$), and there were no significant interactions. The effects of medication in PD patients with and without ICBs was examined by running separate ANOVAs within each group, with main effects of medication and image familiarity. There was no significant effect of medication in the PD group ($F_{(1, 24)} = 0.84$, $p = 0.364$) or in the ICB group ($F_{(1, 21)} = 2.59$, $p = 0.112$). Next, the 4 clinical groups (PD and ICB off and on medication) were comapred pair-wise with the control group (Bonferroni corrected). The ICB group off ($F_{(1, 38)} = 10.75$, $p = 0.002$) and on ($F_{(1, 38)} = 4.86$, $p = 0.034$) medication selected novel stimuli more often than controls. The PD group did not differ significantly from controls off or on medication.

In the final analysis the learning rate parameter, which measures the extent to which subjects integrate feedback to update their decisions was assessed (Figure 12B). There were, however, no significant differences after controlling for the effects of age ($F_{(1, 45)} = 1.91$, $p = 0.174$).

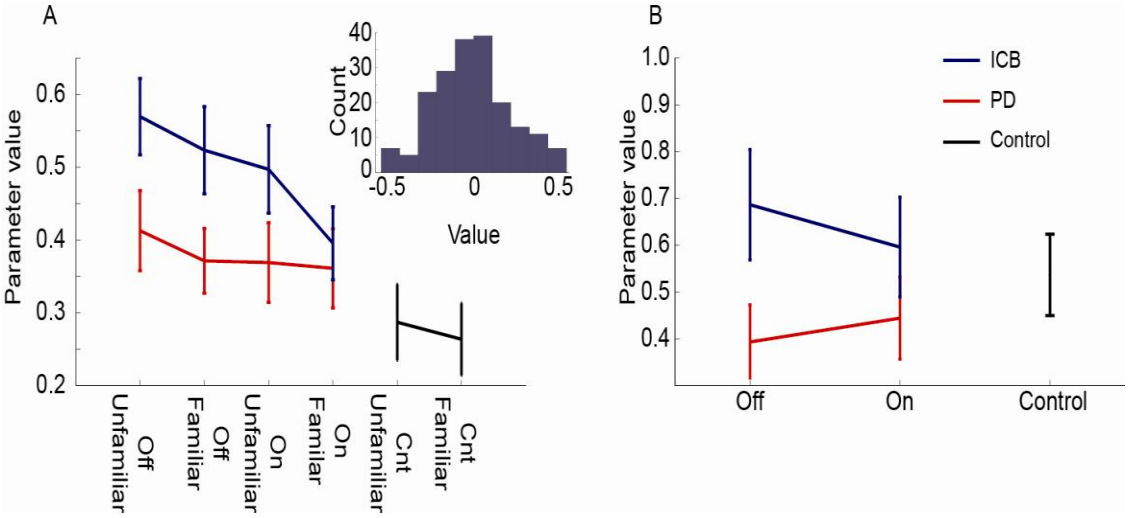

Figure 12. *Novelty seeking task: Behavioural results.*

A. Weight given to unfamiliar and familiar novel stimuli by each group of subjects. Off indicates off medication, on indicates on medication. Unfamiliar refers to stimuli with which the subjects had not seen prior to the choice task and familiar refers to stimuli with which subjects had seen. Inset shows residual of ANOVA model. B. Values for learning rate parameter for each group.

Discussion

Results demonstrated that PD+ICB patients were more attracted to newly introduced pictures, than either the PD-ICB patients or normal controls, regardless of their medication status and across a group of ICBs with various diagnoses. This was true regardless of whether the novel picture came from the set with which the patient had been familiarized (familiar) or from the set with which the patient had never seen before (unfamiliar). This result is consistent with previous studies which have shown high novelty seeking personality traits in PD patients with DDS (Evans, Lawrence et al. 2005) and patients with pathological gambling (Voon, Thomsen et al. 2007) using self-rating questionnaires. Although self-rating questionnaires are helpful in diagnosis they must be interpreted with care, especially in patient groups where insight may be low, such as PD patients with ICBs (Ferrara and Stacy 2008, Lim, Evans et al. 2008), and patients with substance abuse (Goldstein, Craig et al. 2009). PD+ICB patients are also known to have significantly higher schizotypy scores than PD patients without ICBs (Housden, O'Sullivan et al.) another factor known to reduce the validity of questionnaires (Lenzenweger 2010). Thus, results of this study bring novelty seeking into an explicit metric framework using a task with a known neural substrate (Wittmann, Daw et al. 2008).

fMRI studies using a four option choice task have shown that activation of the ventral striatum significantly correlated with reward predication errors and exploring novel, unfamiliar stimuli (Wittmann, Daw et al. 2008). An increase in ventral striatal dopamine levels, measured with PET, has been demonstrated in the PD+ICB group in

response to medication, gambling and reward-related cues (Steeves, Miyasaki et al. 2009, O'Sullivan, Wu et al. 2011). Related work has shown reduced levels of the dopamine transporter (DAT) in the ventral striatum of PD patients who had pathological gambling relative to a control group of PD patients without pathological gambling (Cilia, Ko et al. 2010). Reduced membrane DAT levels could lead to the increased synaptic dopamine levels. Thus, converging evidence suggests increased ventral-striatal dopamine levels in the PD+ICB group. In some cases, this increased dopamine signalling appears to contribute to increased sensitivity to behaviours mediated by the ventral striatum, including temporal discounting (Voon, Reynolds et al. 2009) and feedback learning (Voon, Pessiglione et al. 2010). Also consistent with this, many of the PD+ICB patients tested report a sweet tooth with a penchant for chocolate, and a recent study has shown an association between sweet liking, novelty seeking and addictive behaviour (Lange, Kampov-Polevoy et al. 2010).

In spite of the data which suggests that increased dopamine levels contribute to impulsivity in PD, there was no effect of acute changes in dopamine levels on novelty seeking in the current study. This suggests that the mechanism that mediates novelty, as has been operationalized, may be unrelated to acute changes in dopamine levels brought about by withholding medication for at least 12 hours. Thus, long-term changes brought about by chronic increases in dopamine levels, rather than an acute change of dopamine level, might trigger novelty seeking behaviour in PD. This is one factor which may account for differences between our study and a previous study which found increased novelty seeking in PD-ICB patients after dopamine agonist therapy (Bodi, Keri et al. 2009). Thus, the effects seen in the Bodi et al. study may be mediated by chronic

changes in levels of dopamine stimulation, as opposed to the acute changes that was used here. Specifically, the Bodi et al. study compared a group of never medicated patients, to a group of patients medicated for periods of several months with dopamine agonists. There are other important differences between the Bodi et al., study and this study. First, patients in this study were treated with a combination of dopamine agonists and L-Dopa, as opposed to just dopamine agonists. When patients were tested off medication, both the dopamine agonists and the L-dopa were withheld, but only acutely. Second, the study of Bodi et al., found increased novelty seeking using self-report questionnaires, as opposed to a metric behavioural task. It is not clear that self-report questionnaires and metric behavioural tasks measure the same construct. Thus, the inconsistencies between the study of Bodi et al. and this study are likely due to methodological differences.

Although participants were pre-trained on a set of pictures, so that novel stimuli could be either unfamiliar or familiar, these manipulations reached only trend levels and were not significant, unlike previous studies (Wittmann, Daw et al. 2008). It is possible that the pre-training was not sufficient in this group of elderly participants, as there was also no an effect in matched controls, although, participants were all able to identify the novel picture in the first trial of the task. All participants scored higher than 27 on the MMSE examination and were non-demented. Therefore, it unlikely that they were not able to remember 9 pictures prior to each session. Additional exposure to the pictures may have been useful, however, in finding an effect of unfamiliar versus familiar images. It is also possible that familiarity biases are smaller in elderly adults, and that more extensive training might not overcome this.

Results have shown that impulsive PD patients are more novelty prone. However, animal studies have used outbred rats to separate novelty seeking, operationalized as an increased locomotor response in a novel environment, and impulsivity, operationalized as premature responses in a serial reaction time task (Belin, Mar et al. 2008). This study found that rats prone to novelty seeking tended to acquire cocaine self-administration more readily than their impulsive counter-parts, whereas impulsive rats tended to convert to compulsive drug use more readily than their novelty seeking counterparts. This suggests that the combination of these traits would lead individuals to be particularly prone to developing addictive behaviour. Novelty seeking could lead, for instance, to playing slot machines, which is not only the most commonly played gamble in PD but is considered to be the "crack cocaine" of gambling with the highest addictive potential (Dowling, Smith et al. 2005). Novelty seeking could lead to initiation of a potentially addictive behaviour, which then turns into addiction as a consequence of an impulsive personality trait.

Conclusion

In summary increased novelty seeking in all PD+ICB patients was found using a 3 option choice task. Overall, these results are consistent with the hypothesis, that the ventral striatum underlies novelty seeking, perhaps due to input from the hippocampus. Additional work within this setting may further clarify the role of the ventral striatum in various choice behaviours and in social processing.

Key Findings

- All PD patients with ICBs were more novelty seeking than PD patients without ICBs and healthy controls.
- Dopaminergic medication had no effects on novelty seeking in PD patients, suggesting that increased novelty seeking in the ICB patients might be a personality trait.
- There was no difference in feedback learning across the groups.

3.5. Decision-making, impulsivity and addictions: Do Parkinson's disease patients jump to conclusions?

Introduction

Although not necessarily maladaptive, impulsive decision making is often linked with addiction and has been reported in patients with substance abuse and pathological gambling (Simon, Mendez et al. 2007, Michalczuk, Bowden-Jones et al. 2011). It is also seen in PD patients who develop ICBs on dopaminergic medication (Voon, Reynolds et al. 2010). It remains unclear why some PD patients are predisposed to ICBs, but identified risk factors include younger age of disease onset, male gender and a premorbid or family history of substance abuse. ICBs have also been associated with 'behavioural addictions' (Stacy 2009) sharing clinical withdrawal symptoms of dysphoria, depression and anxiety with substance abuse (Koob and Volkow 2010, van Eimeren, Pellecchia et al. 2010). Functional imaging studies have demonstrated aberrant striatal dopaminergic "reward pathways" and altered function in frontal cortical regions in PD+ICB and non-PD patients with addictive behaviours (Potenza 2008, Dagher and Robbins 2009, Koob and Volkow 2010).

The 'beads task' (Huq, Garety et al. 1988) was used to compare decision making in PD patients with and without ICBs, pathological gamblers and substance abusers. In addition to the MMSE, a WM task was included to assess whether impairments in decision making reflected a more generalized cognitive deficit. The beads task assesses

how much information participants gather before making a decision that has been referred to as "*reflection impulsivity"* (Evenden 1999, Clark, Robbins et al. 2006). This differs from 'motor' impulsivity, the inability to stop an on-going process and from 'waiting' impulsivity, the inability to delay an action (Dalley, Everitt et al. 2011). Early decision on the beads task or 'jumping to conclusions' has been also seen in patients with schizophrenia (Fine, Gardner et al. 2007). Delusional patients gather minimal further information in situations where more information is available and yet are highly confident with their decisions (Warman, Lysaker et al. 2007). The advantage of using the beads task in assessing decision making processes is that this task is emotionally neutral which ensures that general reasoning is being studied and not decision making under salient conditions (Warman, Lysaker et al. 2007). In a modified version of this task a positive association between impulsivity and problem gambling or recreational gambling has been reported (Mishra, Lalumiere et al. 2010).

The prediction was that all impulsive patient groups would jump to conclusions and that PD+ICB patients would perform similarly to illicit substance abusers and make choices which were more impulsive than PD-ICB. Another hypothesis was that both PD groups would perform worse than matched controls and that gamblers would gather less information than the PD-ICB group.

Patients and methods

All participants provided written informed consent according to the declaration of Helsinki and the study was approved by the UCLH Trust and the University of Lvov ethics committee.

PD and elderly control groups

Twenty seven PD-ICB and 26 PD+ICB patients were recruited from the National Hospital for Neurology and Neurosurgery, Queen Square, London. All patients fulfilled the Queen Square Brain Bank criteria for the diagnosis of PD (Gibb and Lees 1988) and were taking L-dopa. Twenty-one of 27 PD-ICB patients were taking a dopamine agonist, whereas only 13 of 26 PD+ICB patients were still on a dopamine agonist. Eighteen healthy elderly volunteers, mainly the PD patient's spouses or partners, matched for age, gender and education were recruited. Patients who scored under 26 of 30 points on the MMSE were excluded. All participants were screened for sub-classes of ICBs in a semi-structured interview, using accepted diagnostic criteria for pathological gambling (American Psychiatric Association 2000), compulsive shopping (McElroy, Keck et al. 1994), compulsive sexual behaviour (Voon, Hassan et al. 2006) and punding (Evans, Katzenschlager et al. 2004). A self-rated validated questionnaire for impulsive compulsive disorders in Parkinson's disease (QUIP) was also used (Weintraub, Hoops et al. 2009) (see appendix).

PD patients performed the beads test only on medication to minimize off dysphoria and anxiety (Lim, Evans et al. 2008).

For the working memory task, patients were tested both off and on medication, in a counterbalanced order. Patients, who were tested off medication did not take their anti-Parkinson medication for at least 12 hours and performed the task between 8.00 a.m. and 9.00 a.m. They were then retested in their on medication state the following day, usually mid-morning. Those patients who were tested on medication first performed this task usually in mid-morning when their motor symptoms were well controlled. They were revisited on the following day prior to their medication for the second test. Elderly controls were tested in the same way but did not take any anti-Parkinson medication. The therapeutic motor response to L-dopa was assessed by UPDRS (part 3) scores during "off" and "on" state. All PD patients had an excellent L-dopa response.

L-dopa equivalent units (LEU – Table 11) were calculated as described previously (Evans, Katzenschlager et al. 2004).

Pathological gamblers, substance abusers and matched controls

All these patient groups were tested only once usually mid-morning. Twenty-three patients with pathological gambling, according to DSM-IV criteria (American Psychiatric Association 2000) were recruited from the National Problem Gambling Clinic, UK. None had a current history of substance abuse, one patient had taken illicit drugs in the past but not in the 3 months prior to testing. All gamblers had stopped gambling only recently. Thirteen patients with a recent history of illicit drug abuse,

meeting DSM-IV criteria for substance dependence (American Psychiatric Association 2000) were also tested. Patients were recruited from the Replacement Therapy Unit of Lviv, regional Clinical Narcological Dispensary and were receiving buprenorphine. None fulfilled DSM-IV criteria for dementia. Twelve out of 13 patients had a long standing history of intravenous opioid abuse, for a detailed list of drugs of abuse see Table 10.

All the gamblers, who agreed to participate in this study and 12/13 of the illicit substance abusers, were males. Their results were compared with 18 age matched male controls.

Beads task

The beads task was performed on a laptop computer, usually in the participant's home or in a quiet room to minimize distractions. Participants were required to guess from which of two cups coloured beads were being drawn. The cups differed in the proportion of blue and green beads they contained. For example, one of the cups may have contained 80% blue beads and 20% green beads, whereas the other cup may have contained 80% green beads and 20% blue beads.

Participants were first shown a bead draw, which was either blue or green. They were then asked whether they wanted to draw another bead, or guess that the bead was being drawn from the predominantly green or blue cup (Figure 13). This was repeated until they chose to guess one of the cups. The behavioural measures of interest were the number of beads drawn before the participant guessed a cup and whether the cup choice

represented a rational (e.g. if more blue beads were drawn the participant guessed blue) or irrational (i.e. the cup colour guessed was not most probably correct, given the beads drawn) choice. This is referred to as opposite colour choice.

Participants completed 4 blocks of 3 trials each. Two blocks contained an 80/20 ratio of beads and 2 blocks a 60/40 ratio of beads in each cup. They won 10 units for correct choices. For incorrect choices they lost nothing in two blocks, or 10 units in two blocks. Thus there were four blocks: 80/20 loss of 10, 80/20 loss of 0, 60/40 loss of 10 and 60/40 loss of 0. Participants were informed of the loss condition and beads ratio before each trial.

They knew that they could draw up to 10 beads before making a decision. They were, however, "charged" 0.2 units for each additional draw, so additional draws reduced the amount they would win. After finishing the test participants received a monetary reward, depending on the units they accumulated during the experiment (usually between £8-£15). The four conditions were presented in a randomized order.

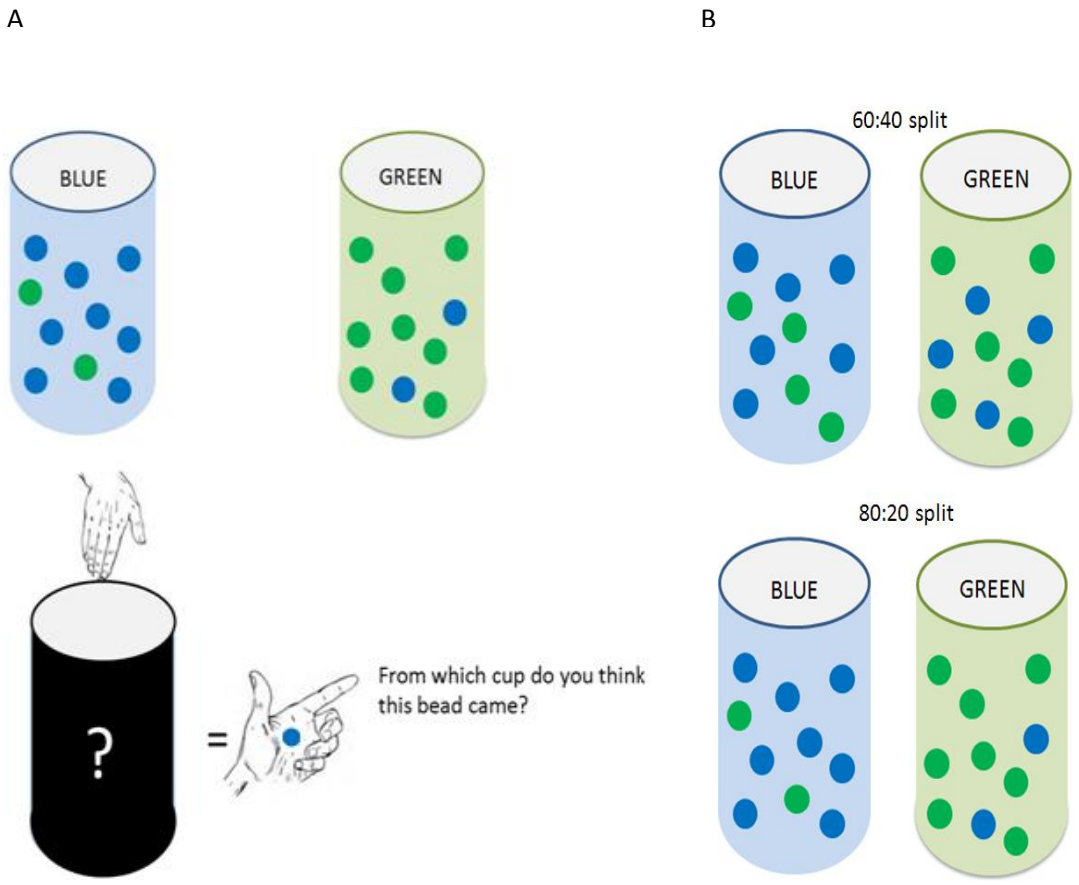

Figure 13. *Beads task.*

A: The blue cup contained more blue beads than green beads, the green cup more green than blue beads. The computer drew from one of these cups and showed a coloured bead. Participants could then ask for up to 10 additional draws before deciding from which cup they thought the bead was drawn.

B: Two different ratios were used. One 60/40 split where the ratio is closer to chance (above) and one 80/20 split (below).

To practice and explain the task, I brought two cups, with the blue cup containing more blue than green beads and vice versa for the green cup. The distribution in these cups resembled an 80/20 condition. Three practise trials were performed to make sure that all participants understood the rules.

Statistical analysis

For the behavioural variables analyses using a generalized linear model (SPSS) were performed because the dependent variables were counts and not continuous values. Beads ratio (80/20 or 60/40) and loss condition (loss, no loss), were modelled as fixed factors. Group (PD-ICB, PD+ICB, Control-Old, Control-Young, non PD gamblers and illicit substance abusers) was modelled as a between factor and participant was a random factor nested under group. Age was also included as a cofactor in the analysis of the beads data. However, it did not change any results and thus, all results were reported without it included.

A further analysis was carried out in which the number of draws in the 80/20 condition was used to predict group membership, between PD+ICB and PD-ICB. The number of draws was submitted to linear discriminant analysis in SPSS, using leave-one-out cross validation and covariance matrices pooled across groups.

For cross validation, one participant was pulled from the data, discriminant functions were calculated using the remaining participants, and then those discriminant functions were used to classify the participant which had been held out. This was repeated for all

participants. Thus, this analysis attempts to estimate how well a novel participant would be classified.

Working memory task

PD patients were tested prior and after their usual anti-Parkinson medication in a counterbalanced sequence to account for order effects. Twenty four trials of a WM task were completed on a laptop computer (Figure 14). Participants were asked to memorize either 2 or 3 geometric figures which were shown for 3 seconds on a black background, followed by a delay of 2 seconds.

During the delay, distractor images were shown. Then another geometric figure was presented and participants were asked whether this figure was within the set that they had to remember before. In half of the trials (12 of 24) 2 geometric figures and in the other half 3 had to be remembered.

Participants had to press either “Y” for yes or “N” for no. Distractors could be positive, neutral or negative images taken from the validated International Affective Picture System (Lang, Bradley et al. 2008).

Figure 14. *WM task.*

A: Participants were asked to remember either 2 or 3 geometric figures.

B: Distractors, in this case neutral ones, were shown for 2 seconds. C. Another geometric figure was shown and participants were asked whether this figure was in the set that they had to remember before.

At the end participants were shown 24 distractor images on a black screen and were asked whether they thought they had seen the images before. In half of the 24 trials distractors that had been used during the WM task were shown. Participants had to press "Y" for yes or "N" for no.

Positive pictures had a valence above 6.4. Negative pictures had a valence below 3.1 and neutral pictures had valence from 4.5 to 5.5 (Figure 15). Salient and neutral pictures contained mainly human characters. Both geometrical figures and distracters were presented in colour. Positive distractors contained food or sexual motives, negative pictures included scenes of violence.

Figure 15. *WM task: Positive and neutral distractors.*

Four Samples of neutral distractors (A) and 4 samples of positive distractors (B) shown during WM task. Negative distractors not shown.

Analysis was done using a generalized linear model (SPSS) with a binary logistic function encoding whether the participant was correct or not on each trial. Distractor type (positive, neutral or negative), number of memoranda (either 2 or 3 geometric figures), choice and actual shown picture were modelled as fixed factors. Group (PD-ICB, PD+ICB, Control-Old, Control-Young, pathological gamblers and illicit substance abusers) was modelled as a between factor and subject was a random factor nested under group. When analysing the recall of distractors, correct versus incorrect was again modelled as a binary dependent variable. Distractor type, choice, and whether the distractor was actually shown, were modelled as fixed factors, with group and subject modelled as described above.

Results

Demographic characteristics

Demographic variables (Table 11) were analysed using ANOVA, t-test or χ^2 tests where appropriate. There were no differences between the control groups and the matched patient groups on any demographic variables. Significantly more PD-ICB (21 of 27) than PD+ICB (13 of 26) patients were taking a dopamine agonist ($p = 0.024$), which is in line with accepted clinical guidelines of managing an ICB in PD.

Consistent with the literature PD+ICB patients had a significantly younger disease onset relative to PD-ICB patients ($t_{52}=3.28$, $p = 0.002$). There was no difference in LEU dose, UPDRS (part 3) motor scores or disease duration between the PD groups. LEU doses were calculated as previously described (Evans, Katzenschlager et al. 2004) as followed:

L-dopa dose + L-dopa dose × 1/3 if on entacapone + bromocriptine (mg) × 10 + cabergoline or pramipexole (mg) × 67 + ropinirole (mg) × 20 + apomorphine (mg) × 8.

	CO-O	CO-Y	PD+ICB	PD-ICB	Addicts	Gambler	t value, χ^2 and F-value	p-value
Participants(no.)	18	18	26	27	13	23		
Age (yrs)	58.9±12.7	33.2±5.5	58.7±10.0	65.3±5.3	32.0±7.1	38.0±9.3	F=58.8	**<0.001***
Gender (male)	15	18	22	24	12	23	χ^2=6.8	0.25
At PD onset (yrs)			47.7±9.5	55.3±7.4			t=3.28	**0.002***
PD Disease duration (yrs)			11.0±4.1	10.0±6.5			t=0.52	0.48
Education (yrs)	13.6±3.2	13.9±2.2	13.1±2.8	14.8±2.5	12.0±1.9	14.5±2.0	F=3.1	**0.011***
ICB current ICB (>3-12months) Gambling (yrs) Gambling stopped (months) Drug abuse (yrs) Opioid therapy (yrs)			20 6		 12.0±5.1 1.4±1.3	 12.1±7.4 1.8±2.7		
LEU dose(mg/day)			934.2±407	740.1±369			t=1.8	0.072
PD patients on DA (N)			13/26	21/27			χ^2=5.1	**0.024***
UPDRS on UPDRS off Improvement in %			16.2±10.6 31.0±11.3 47.7	21.1±9.0 32.1±10.6 34.2			t=1.7 t=0.5	0.09 0.6
Hypersexuality PG Casino games Sport betting Stock markets Slot machines Bingo Scratch cards Punding Shopping Substance abuse i.v. opiods i.v.heroin cannabis cocaine morphine			12 13 - 2 - 8 4 2 7 5 3(past)		 3 13 12 4 3 1 1	 23 15 12 2 3 - - 1 (past)		

Table 11. *Beads task: Demographic characteristics.*

LEU = L-dopa equivalent units; DA = dopamine agonists. All values are mean ± SD. Significant differences are labelled with "". Controls (CO-O, elderly controls; CO-Y, young controls), PD patients with (PD+ICB) and without (PD-ICB) impulsive compulsive behaviours, illicit substance abusers and pathological gamblers.*

As expected there was a significant age difference between the younger participants (young controls, illicit substance abusers, pathological gamblers) and the older participants (PD groups and elderly controls; $F_{(5,118)}=58.8$, $p < 0.001$). Post hoc analysis showed that the PD-ICB group was borderline-significantly older than the PD+ICB group ($p = 0.10$). There was no difference between the PD groups and the elderly control group ($p > 0.22$). There was a significant difference in years of education between the groups ($F_{(5,108)}=3.1$, $p = 0.011$). Post hoc analysis showed that the PD-ICB and the pathological gambling groups had significantly higher education than illicit substance abusers (PD-ICB versus illicit substance abusers: $p = 0.01$, pathological gamblers versus illicit substance abusers: $p = 0.047$). There was no difference between the other groups ($p > 0.29$).

QUIP questionnaires

Consistent with previous studies (Weintraub, Hoops et al. 2009, Papay, Mamikonyan et al. 2011) results showed a high sensitivity to detect an ICB (96.1%) for both the patient and caregiver rated QUIP. A total of 40.7% of PD-ICB patients, who did not meet the diagnostic criteria for having an ICB, had at least one ICB symptom either self-rated or by their caregiver, consistent with a previous study (Papay, Mamikonyan et al. 2011).

Correlation of the QUIP and drawing behaviour

There was no correlation between drawing behaviour on the beads task and scores on the QUIP for the PD-ICB group ($r= -0.273$, $p = 0.2$) or for the PD+ICB group ($r= 0.69$, $p = 0.7$).

Beads task

First, the number of draws each participant made in the different conditions was examined (Figure 16).

Results showed a significant effects of group (Wald $\chi^2 = 191.0$, $p < 0.001$), beads ratio (Wald $\chi^2 = 167.9$, $p < 0.001$). There was also a significant beads ratio by loss condition interaction (Wald $\chi^2 = 9.4$, $p = 0.002$). There was no significant difference between the two control groups (Wald $\chi^2 = 1.0$, $p > 0.3$). Further, the correlations between age and number of draws in the control groups was examined but showed no significant effect ($r=-0.15$, $p > 0.37$). Thus, the two control groups were combined to simplify analyses.

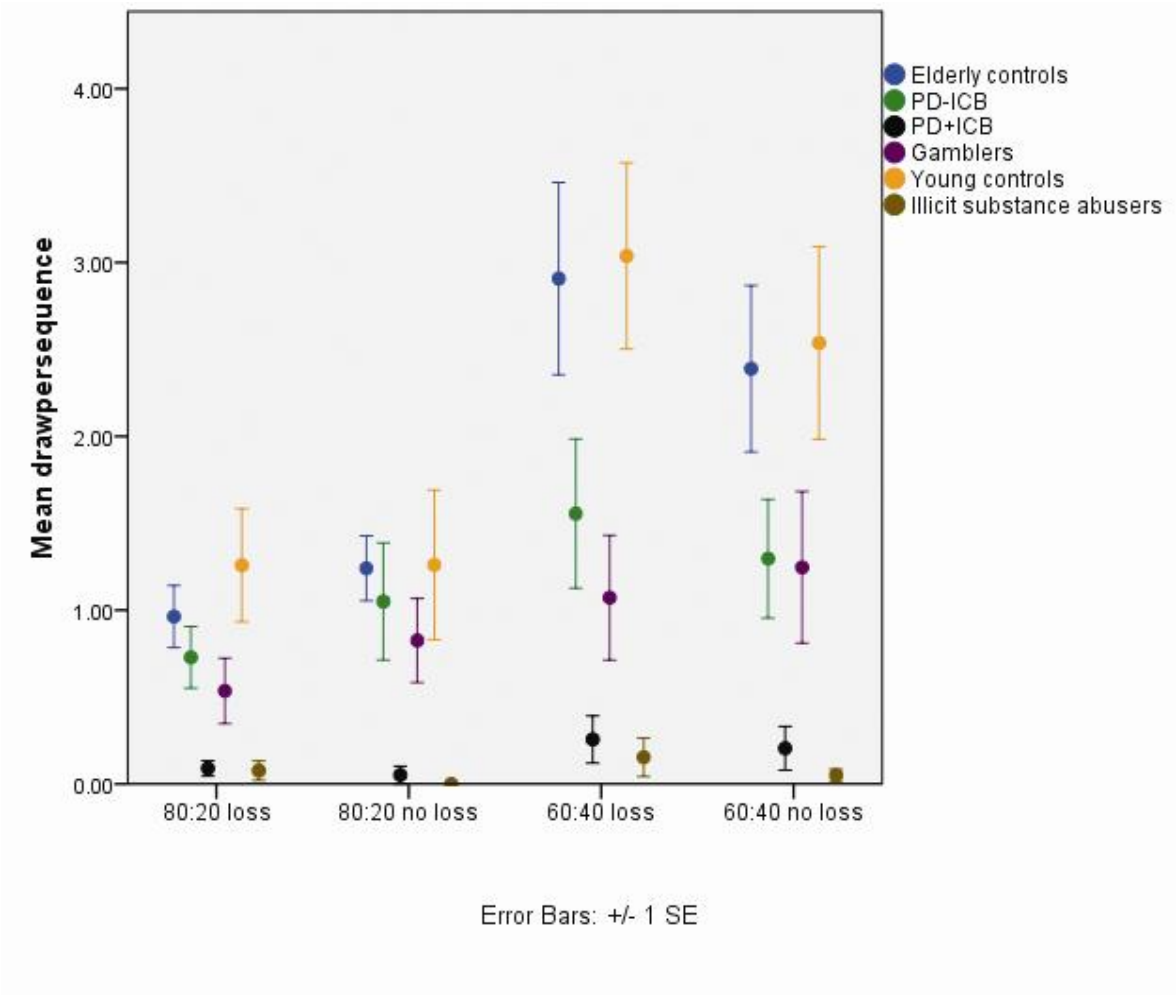

Figure 16. *Beads task: Average number of draws per condition by group.*

One bead is always shown before the participant must make a decision, so total beads seen are mean draws plus one.

Pairwise comparisons between the control group, the PD+ICB group and the other groups were made to examine whether or not the PD+ICB group would perform similar to the other groups.

Results showed significant group effects (always PD+ICBs drawing fewer than the other group) for PD+ICBs versus PD-ICBs (Wald $\chi^2 = 27.1$, $p < 0.001$), pathological gamblers (Wald $\chi^2 = 13.9$, $p < 0.001$) and controls (Wald $\chi^2 = 75.1$, $p < 0.001$). For completeness all other group comparisons were reported (See Table 12).

Opposite colour choice

Next, the number of times participants made an irrational choice, summed across all conditions was examined (Figure 17). There was a main effect of group (Wald $\chi^2 = 72.1$, $p < 0.001$) and therefore pairwise comparisons between groups were made. Again there was no differences between the two control groups (Wald $\chi^2 = 0.07$, $p = 0.8$), so they were combined.

Pairwise comparisons showed that illicit substance abusers chose the opposite colour significantly more often than PD+ICBs (Wald $\chi^2 = 12.2$, $p < 0.001$) and PD+ICBs chose the opposite colour significantly more often than controls (Wald $\chi^2 = 30.3$, $p < 0.001$).

Group (χ^2, p-value)	**PD-ICB**	**Illicit substance abusers**	**Gamblers**	**Controls**
PD+ICB				
Draws	**27.1, p < 0.001**	0.38, p = 0.53	**13.9, p < 0.001**	**75.1, p < 0.001**
Opposite	4.0, p = 0.044	**12.2, p < 0.001**	3.6, p = 0.055	**30.3, p < 0.001**
PD-ICB				
Draws		13.4, p < 0.001	0.45, p = 0.8	65.1, p < 0.001
Opposite		29.4, p < 0.001	0.001, p > 0.97	15.0, p < 0.001
Addicts				
Draws			8.3, p = 0.004	34.8, p < 0.001
Opposite			24.0, p < 0.001	60.8, p < 0.001
Gamblers				
Draws				34.0, p < 0.001
Opposite				13.9, p < 0.001

Table 12. *Beads task: Pairwise comparisons.*

Pairwise comparisons between groups for number of draws (above) and for opposite colour choices (below). All p-values shown are uncorrected. Values less than 0.0125 (highlighted in bold) for the PD+ICB group are significant. All p-values in this and subsequent tables are for main effect of group.

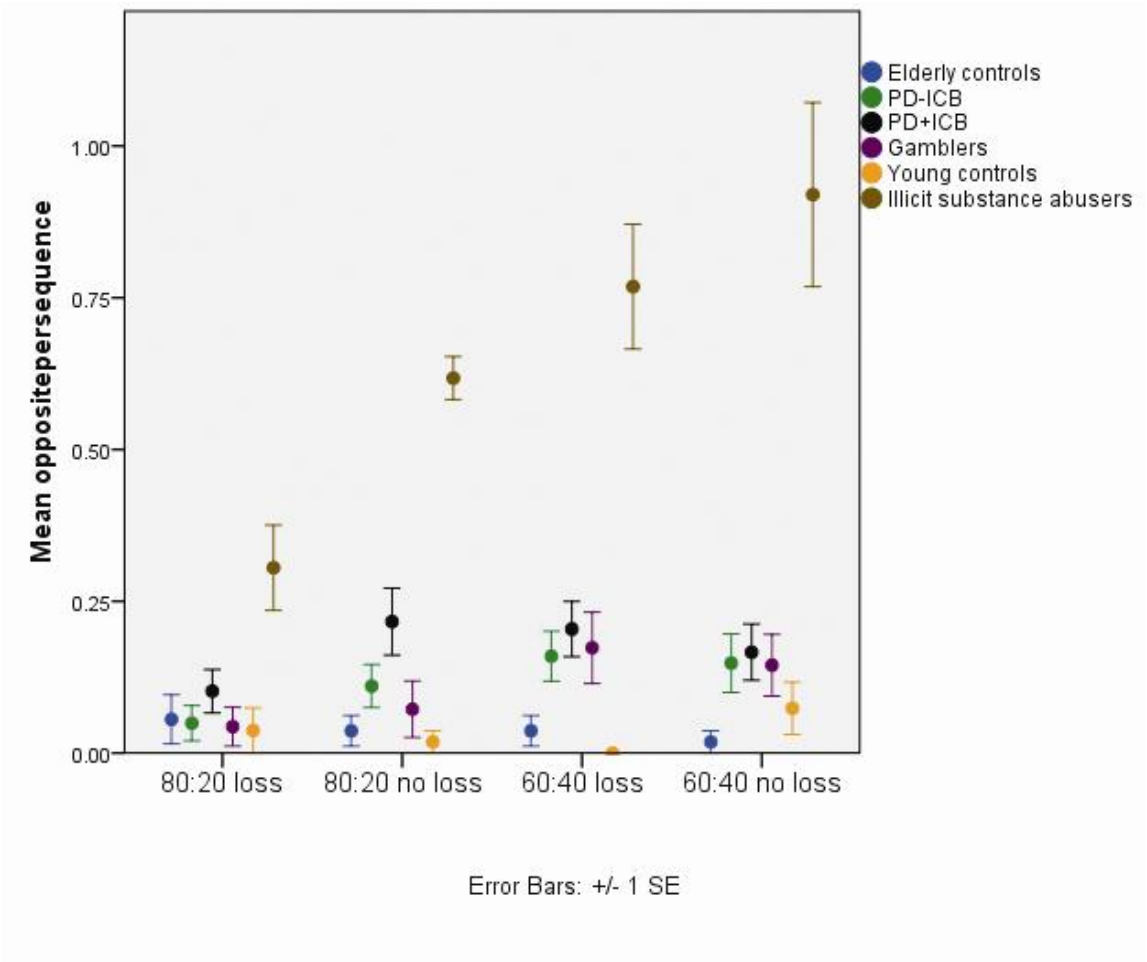

Figure 17. *Beads task: Number of times participants chose the opposite colour.*

Classification of PD+ICBs on the basis of drawing behaviour

Additional analyses were carried out in which the drawing behaviour of individual participants in the 80/20 loss condition was used to try to predict group membership between the PD+ICB and PD-ICB groups. Twenty-five out of 26 (> 96%) PD+ICB patients were correctly classified. Further, 44% of PD-ICB patients were also correctly classified as not having an ICB, giving a positive predictive value of 62.5% and a negative predictive value of 92.3%.

Working memory task

First working memory performance was analysed (Figure 18). As there was no effect of medication within the PD-ICB (Wald $\chi^2 = 0.16$, $p = 0.68$) or the PD+ICB group (Wald $\chi^2 = 0.24$, $p = 0.62$) the PD-ICB and the PD+ICB groups were collapsed across medication. There was a significant effect of group (Wald $\chi^2 = 24.0$, $p < 0.001$), a significant effect of distractor type (Wald $\chi^2 = 29.6$, $p < 0.001$), and a borderline effect of working memory load (2 or 3 items) (Wald $\chi^2 = 6.9$, $p = 0.08$).

Pairwise comparison showed that all groups performed better than substance abusers (Table 13). Results confirmed that there was no correlation between WM and beads performance across the groups (Pearson correlation=0.79, $p > 0.4$) or during pairwise comparisons.

Next it was examined how well the groups recalled the distractors that had been used during the working memory task (Figure 19). There was a main effect of group for remembering distractors in the WM task (Wald $\chi^2 = 59.7$, $p < 0.001$) and pairwise comparisons showed that PD+ICB patients (Wald $\chi^2 = 7.2$, $p = 0.007$) and pathological gamblers (Wald $\chi^2 = 15.4$, $p < 0.001$) remembered distractors significantly better than PD-ICB patients. Again, there was no effect of medication within the PD-ICB (Wald $\chi^2 =0.18$, $p > 0.9$) or the PD+ICB groups (Wald $\chi^2 =1.2$, $p = 0.26$) so the PD-ICB and the PD+ICB groups were collapsed across medication (see Table 14).

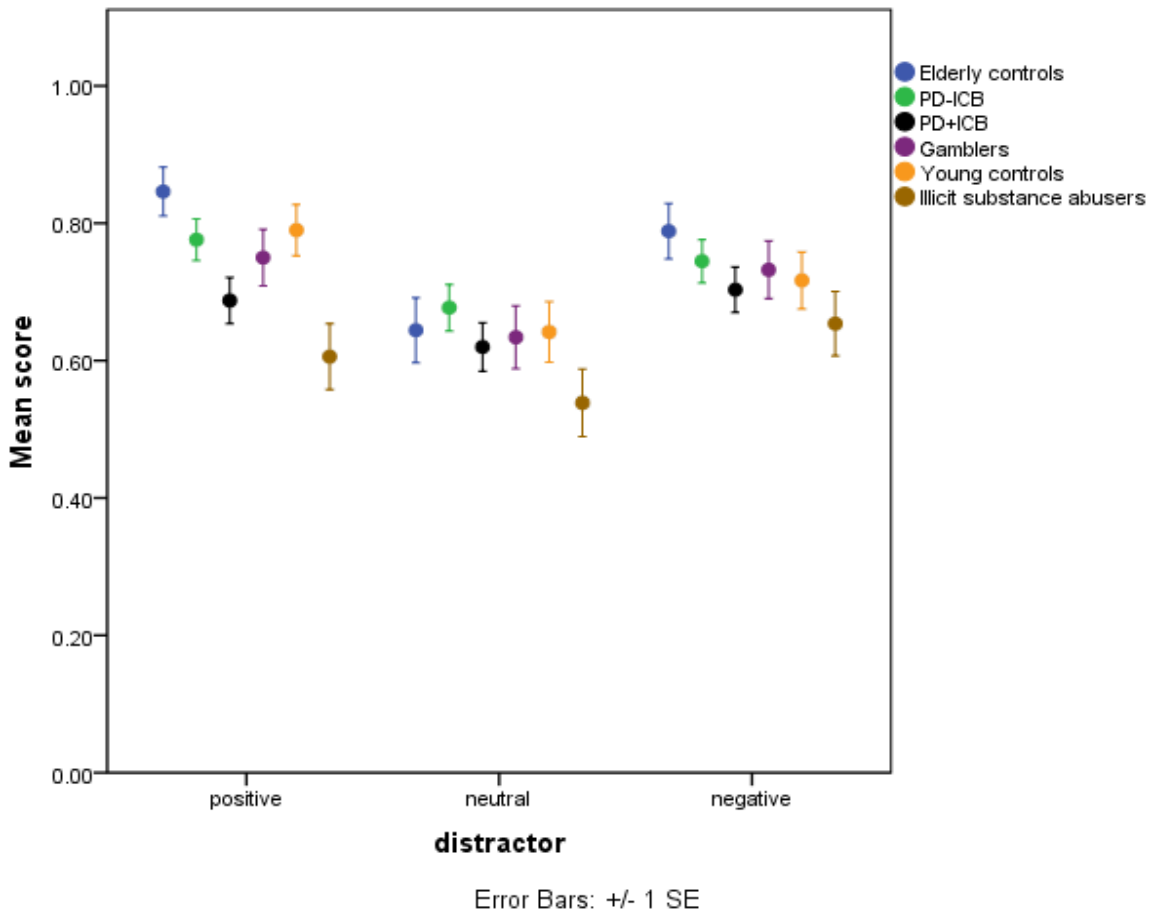

Figure 18. *WM performance.*

Plot shows fraction of correctly remembered images for each group, as a function of distractor type.

Group (χ^2, p-value)	**PD-ICB**	**Addicts**	**Gamblers**	**Controls Old**	**Controls Young**
PD+ICB	2.05,p = 0.15	**7.2,p = 0.007**	0.3, p > 0.58	4.3, p = 0.038	0.74, p = 0.38
PD-ICB		17.0,p < 0.001	0.44, p > 0.5	0.86, p > 0.35	0.1, p > 0.74
Addicts			9.3, p = 0.002	18.8,p < 0.001	10.1, p = 0.001
Gamblers				1.9, p = 0.16	0.78, p > 0.7
Controls Old					1.1, p > 0.28

Table 13. *WM task: Pairwise comparisons for WM performance.*

All p-values shown are uncorrected. Values less than 0.0125 (highlighted in bold) for the PD+ICB group are significant. All p-values in this and subsequent tables are for main effect of group.

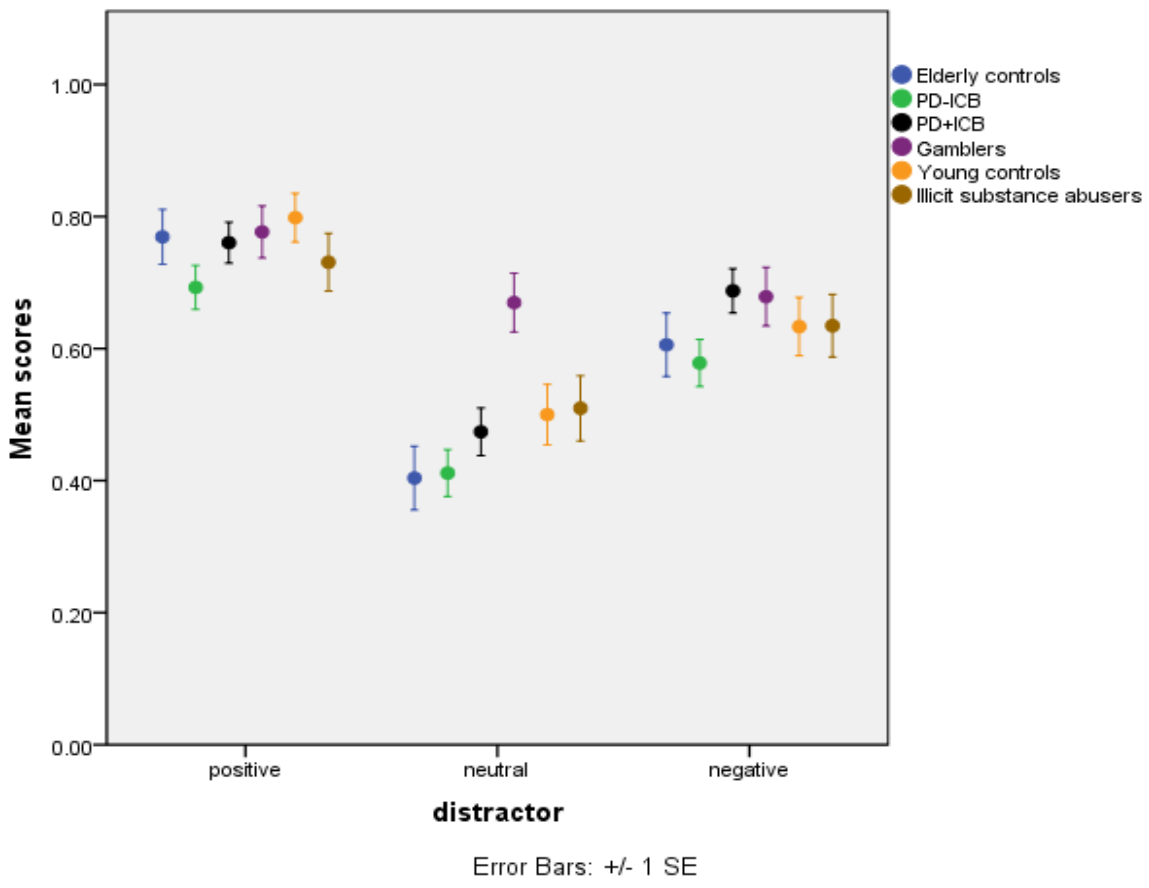

Figure 19. *WM task: Remembering distractors (positive, neutral, negative).*

Plot shows fraction of distractors that were recognized when tested following the working memory task.

Group (χ^2, p-value)	**PD-ICB**	**Addicts**	**Gamblers**	**Controls Old**	**Controls Young**
PD+ICB	**22.8,p < 0.001**	0.6, p > 0.4	**12.2, p < 0.001**	5.1, p = 0.023	0.002, p > 0.9
PD-ICB		10.1, p = 0.001	59.8, p = 0.001	2.4, p = 0.1	15.8,p < 0.001
Addicts			13.8, p < 0.001	1.6, p = 0.2	0.46, p = 0.5
Gamblers				24.3, p = 0.001	8.2, p = 0.004
Controls Old					3.7, p = 0.055

Table 14. *WM task: Pairwise comparisons for recalling the distractors.*

All p-values shown are uncorrected. Values less than 0.0125 are significant and highlighted in bold for PD patients with ICBs.

Sensitivity of the beads task versus the QUIP in detecting impulsive behaviours in PD

Both, the QUIP and the beads task show a high sensitivity to detect a current or past history of ICB in PD (>96%). Using the QUIP questionnaire around 41% PD patients without an ICB, had at least one ICB symptom which is in line with studies using a larger sample size (Papay, Mamikonyan et al. 2011).

In contrast using the beads task 56% of PD-ICB patients were classified as being impulsive and the minority was classified as being non-impulsive. Consistent with this classification are the results of this study, which demonstrate that non-impulsive PD patients resembled pathological gamblers who were waiting to be treated.

Of particular interest is, however, that all PD-ICB patients were also treated with a dopamine agonist and it is possible that a proportion of these patients will develop an addictive in the future. My results suggest that the beads task may be an even more sensitive tool than the QUIP to detect subclinical impulsivity in PD. A disadvantage of the QUIP rating scale is that it does not assess the severity of the addictive behaviour. However, at this point the sample size of PD patients with and without ICBs tested on the beads task is too small to confirm this hypothesis. Therefore, a prospective study in drug naïve PD patients is currently underway and a multicentre study in a larger cohort of PD patients with and without ICBs is planned to address this question.

Discussion

In this study, ‘reflection impulsivity’ was examined using the beads task, an information gathering paradigm in which participants controlled the amount of information they gathered before making a decision (Furl and Averbeck 2011). PD patients with and without ICBs, pathological gamblers and substance abusers were compared and results showed evidence for impairment even in treated PD patients without clinically apparent ICBs. Across groups results showed an effect of the beads ratios, such that participants drew more when the beads ratios were closer to chance (60/40) than when the ratio was greater between the cups (80/20). In addition, the loss condition interacted with the beads ratio condition, such that subjects drew relatively more in the higher loss conditions.

Despite all groups showing behaviour adaptive to the specific condition, the PD+ICB group drew significantly fewer beads than controls, PD-ICBs and pathological gamblers before making a decision. Significantly less PD+ICB than PD-ICB patients were taking a dopamine agonist and yet they still gathered less information. The fact that the PD+ICB group drew fewer beads than pathological gamblers is interesting, given that half of the PD+ICB patients had clinically defined pathological gambling. Slot machines, scratch cards and bingo were the most commonly played gambles in PD. Pathological gamblers preferred skilled games, such as spread betting and electronic casino games (Gallagher, O'Sullivan et al. 2007, Wardle, Sproston et al. 2007). This difference in the type of preferred gambling may be of relevance in the interpretation of the results.

Direct comparison between groups on the beads task suggests greater similarities between PD+ICB patients and illicit drug abusers, compared to the pathological gamblers or PD-ICB patients. PET studies have shown sensitization of the ventral striatum in PD+ICB patients (Evans, Pavese et al. 2006, Steeves, Miyasaki et al. 2009) and also in patients with substance abuse (Dagher and Robbins 2009, Kaplan, Leite-Morris et al. 2011). Furthermore, *'reflection impulsivity'* does not recover, even after prolonged abstinence in substance abusers (Clark, Robbins et al. 2006). This is consistent with the fact that dopamine agonists have often been withdrawn for a long period in the PD+ICB group, leading to alleviation of impulsive symptoms, and yet they still make impulsive choices in the beads task. PD+ICB patients also become irritable when their addictive behaviour is restricted (Evans, Katzenschlager et al. 2004, Evans, Strafella et al. 2009), reminiscent of withdrawal symptoms in drug abusers.

Analysis of the QUIP revealed that 41% of PD-ICB patients had at least 1 symptom of an ICB, either self-rated or rated by their caregiver consistent with previous studies (Papay, Mamikonyan et al. 2011). Using the beads tasks 56% of PD-ICB patients were classified as having tendencies towards impulsivity, suggesting that this task may be a more sensitive screening tool to detect hidden impulsive traits. Consistent with this, there was no difference in the behavioural pattern between PD-ICB patients and pathological gamblers. This finding is particularly interesting, because none of the gamblers had received any treatment for their impulsivity and none of the PD-ICB patients had clinically defined ICBs. Further, PD-ICB patients also drew significantly less than matched controls.

Several studies have demonstrated increased impulsivity and changes on behavioural tasks in PD-ICB patients after starting dopaminergic medication (Cools, Barker et al. 2003, Frank, Seeberger et al. 2004, Bodi, Keri et al. 2009) in contrast to treatment naïve PD patients who perform similarly to controls (Poletti, Frosini et al. 2010). Whether impulsivity arises as a result of increased impulsive drive, decreased inhibitory control or a combination of both is still unclear. However, the results in the PD-ICB group could reflect an underlying increased impulsivity driven by excessive dopamine levels in the ventral striatum. In PD, there is much less dopamine loss in the ventral than the dorsal striatum (Gotham, Brown et al. 1988). Therefore, treatment with dopaminergic medication to increase dopamine levels in the dorsal striatum may lead to excessive levels in the ventral striatum. This may result in a tendency, in all treated patients, to increased impulsivity, which, however, does not manifest as clinically significant impulsiveness due to intact inhibitory cortico-striatal pathways. Hypoactivation of the orbitofrontal cortex is seen in pathological gamblers, illicit substance abusers (Potenza and Winters 2003, Volkow, Fowler et al. 2004) and in treated PD+ICB patients, but not in PD-ICB patients (van Eimeren, Pellecchia et al. 2010). The ventromedial plus the orbitofrontal part of the prefrontal cortex is important for impulse control (Bechara, Tranel et al. 2000, O'Doherty, Kringelbach et al. 2001, van Eimeren, Pellecchia et al. 2010) and is associated with ‘jumping to conclusions’ on the beads task (Lunt, Bramham et al. 2012). Thus, intact inhibitory control driven by these cortical areas might prevent PD-ICB patients from clinical impulsivity (van Eimeren, Pellecchia et al. 2010).

Jumping to conclusions can also occur in psychosis (Garety and Freeman 1999). In line with this, previous work has shown that PD+ICB participants score highly on measures of schizotypy, a personality trait related to psychosis (Housden, O'Sullivan et al. 2010). Delusional thinking, defined as a belief based on incorrect inference (American Psychiatric Association 2000), has been reported in PD+ICB patients (Gallagher, O'Sullivan et al. 2007, Wolters, van der Werf et al. 2008) and has been positively correlated with fewer draws on the beads task in delusional patients with and without schizophrenia (Fine, Gardner et al. 2007). Both PD groups also guessed the opposite colour more often than controls and anecdotally some stated that they *"anticipated"* that the opposite colour was more likely and therefore chose the less likely cup. Others said *"that the computer tried to trick me, so I chose the opposite cup to outsmart the computer"*. In fact there was no group difference between the PD group and patients with pathological gambling. However, patients with substance abuse chose the opposite colour significantly more often than all other groups. Excessive dopamine levels in the associative striatum have been consistently reported in PET studies in patients with schizophrenia (Abi-Dargham, Gil et al. 1998, Kegeles, Abi-Dargham et al. 2010). Substance abuse is relatively common in schizophrenia (Gut-Fayand, Dervaux et al. 2001) and patients with schizophrenia are also more impulsive than matched controls groups (Enticott, Ogloff et al. 2008).

Early decisions in this task are also not likely related to temporal discounting. The standard temporal discounting task (Voon, Reynolds et al. 2010) is more closely related to self-report questionnaires than metric tasks, and measures sensitivity to rewards delayed by weeks or months. In contrast to this, drawing more in the current task only delayed possible rewards by seconds. Further, in the beads task, not drawing often leads to not winning, or losing in the loss blocks. This is different than waiting for a larger reward, which is the case in temporal discounting.

Since memory plays an important role in reward learning (Hyman, Malenka et al. 2006), it was tested whether the results on the beads task could have been confounded by poor WM. In this WM task the role of distractibility during the delay interval was examined. There was no correlation between the beads task and WM capacity, which suggests that early decisions relating to the beads task were not driven by poor cognitive capacity. Substance abusers had also a significantly worse WM capacity than the other groups. This is consistent with previous studies demonstrating poorer attention in substance abusers when required to ignore salient stimuli during WM tasks (Hester and Garavan 2009). However, this finding has to be interpreted with caution since the substance abusers were under treatment with opioid replacement therapy, which is known to interfere with WM function (Rapeli, Fabritius et al. 2009).

PD patients without ICBs remembered distractors significantly less than all other patients during working memory tests, which suggests that intact cortical processing in combination with less distractibility may protect them from developing ICBs.

Many patients with ICBs conceal their behaviour due to denial (Singh, Kandimala et al. 2007). By analysing data from the 80/20 loss condition it was possible to correctly identify ICB patients with a sensitivity of 96%. The beads task might therefore provide a simple screening tool to detect patients at greater risk of ICBs or confirm a clinically suspected but concealed ICB. These results also suggest that a significant proportion of PD-ICB patients is at risk of developing impulsive behaviour and thus over time may develop ICBs (Joutsa, Martikainen et al. 2012). Poor performance on this task suggests that these patients should be monitored frequently by their treating physician and the results taken into consideration when deciding on the use of dopamine agonist treatment. This study is free from the limitations of an indirect study design (Gartlehner and Moore 2008) and contains a large number of different groups.

Conclusion

These results might have clinical implications, since they imply that PD+ICB patients should be treated like substance abusers rather than patients with behavioural addictions. Additional studies comparing PD-ICB patients “on” and “off” dopamine agonists will be necessary to explore the role of dopaminergic medication in cognitive impulsivity.

Key Findings

- All patients gathered significantly less information and made more irrational choices than controls.
- PD patients, who had an ICB, showed similar behaviour to illicit substance abusers on opioid replacement therapy, whereas PD patients without ICBs resembled more closely pathological gamblers.
- There was no difference in working memory performance between the two PD groups. However, PD patients without ICBs remembered distractors significantly less than all other patients.
- Analysing 3 trials of the 80/20 loss condition correctly classified 96% of the PD patients with respect to whether or not they had an ICB with a negative prediction value of 92.3%.
- The beads task may prove to be a powerful screening tool to detect an ICB in PD.
- Less distractibility in PD patients without ICBs may explain why these patients do not develop addictive behaviours.

3.6. Dopamine agonists cause reflection impulsivity in Parkinson's disease, not Deep Brain Stimulation

Introduction

Results of the beads task with increased reflection impulsivity, even in PD patients without ICBs, have led to a follow up study to assess effects of dopaminergic medication on decision making. Although L-dopa remains the most efficacious drug to ameliorate motor handicaps in PD, patients are often first treated with dopamine agonists (DA) to minimize the long term risk of L-dopa induced dyskinesias, or reduce current severity of dyskinesias (Tsouli and Konitsiotis 2010). More recently, "L-dopa phobia" regarding its early use may be decreasing (Vlaar, Hovestadt et al. 2011), largely because of increased awareness of an association between DA and potentially devastating behavioural side effects. Although DA have been suggested to be the major risk factor for developing ICBs in PD (Weintraub, Koester et al. 2010), no direct comparison between PD patients with and without DA on metric tests has been performed so far.

In a subgroup of advanced PD patients sufficient motor control cannot be achieved with conventional anti-Parkinson medication and deep brain stimulation (DBS) of the subthalamic nucleus (STN) may be necessary (Foltynie, Zrinzo et al. 2010). The motor benefit obtained from STN-DBS has been consistently demonstrated, and is an increasingly important therapeutic option for managing PD (Foltynie, Zrinzo et al. 2010). However, clinical confidence in STN-DBS is tempered by conflicting results on

its clinical effect on PD-associated ICBs, with some reports showing benefit of ICBs after DBS (Ardouin, Voon et al. 2006, Lhommee, Klinger et al. 2012) and others worsening (Halbig, Tse et al. 2009, Lim, O'Sullivan et al. 2009, Zahodne, Susatia et al. 2011). Similarly, neuropsychological tests done in PD patients with DBS showed impairment in decision making with increased impulsive choice (Frank, Samanta et al. 2007) and loss chasing behaviour (Rogers, Wielenberg et al. 2011) in some studies, whilst others found an improvement in learning behaviour (van Wouwe, Ridderinkhof et al. 2011).

In this study, the role of dopamine agonists and the role of DBS in "reflection impulsivity" was assessed by using the beads task (Furl and Averbeck 2011).

The prediction was that PD patients on DA (PD+DA) would gather significantly less information and make more irrational choices than PD patients without DA treatment (PD-DA). Another hypothesis was that the PD-DA group would perform similarly to controls and that DBS alone would not affect performance on the beads task, but those patients with DBS and a DA would perform worse than all other groups.

Patients and methods

All participants provided written informed consent according to the declaration of Helsinki and the study was approved by the UCLH Trust.

Standard protocol approvals and patient consents

All patients had attended the Specialist Movement Disorders Clinic at the National Hospital for Neurology and Neurosurgery, London, UK. Informed consent was obtained from all participants, and the study had local ethics committee approval.

Patients

All patients were recruited from the National Hospital for Neurology and Neurosurgery London, fulfilled the Queen Square Brain Bank criteria for the diagnosis of PD (Gibb and Lees 1988) and were taking L-dopa. Thirty-four PD patients, who were taking oral medication, were recruited. Twenty were taking L-dopa in combination with a DA (PD+DA) and 14 were on L-dopa therapy but were never treated with a DA or did not tolerate treatment with a DA due to side effects (other than ICBs) and had been off the DA for at least 14 months (PD-DA). Further, 27 PD patients who had undergone bilateral STN-DBS were included. Sixteen were treated with L-dopa in combination with DA (DBS+DA). Eleven patients were on L-dopa but were not taking DA (DBS-DA).

L-dopa equivalent units (LEU - doses) were calculated as described previously (Evans, Katzenschlager et al. 2004). Results were compared with 18 healthy matched elderly volunteers. Participants who scored under 26/30 points on the MMSE were excluded. Patients with a current or past history of an ICB assessed in a semi-structured interview using accepted diagnostic criteria for pathological gambling (American Psychiatric

Association 2000), compulsive shopping (McElroy, Keck et al. 1994), compulsive sexual behaviour (Voon, Hassan et al. 2006) and punding (Evans, Katzenschlager et al. 2004) were excluded.

All patients were tested in their "on" state usually mid-mornings when their motor symptoms were best controlled and had an excellent L-dopa response. The therapeutic motor response to L-dopa was assessed by UPDRS (part 3) scores during "off" and "on" state.

Beads task

The same task as described previously was used for this study. Again the task was performed in the participant's home or in a quiet room to minimize distractions. A practice trial was performed in all participants to ensure that they understood the rules. Participants either pressed the keys on the laptop computer themselves, or gave verbal commands and keys were pressed on their behalf.

Statistical analysis

For the behavioural variables a generalized linear model (SPSS) was used. Beads ratio (80/20 or 60/40) and loss condition (loss, no loss), DA (yes/no), DBS (yes/no) were modeled as fixed factors and age was included as a covariate. Subject was a random factor nested under DBS and DA. Demographic variables (Table 15) were analysed using ANOVA, t-test or χ 2 tests where appropriate and as indicated.

Results

Demographic characteristics

There were significant differences in age, age at onset and disease duration across the 4 groups as shown in Table 15. Adjustment for these confounders was therefore made in subsequent models. There was no difference in years of education between controls and patients and no difference between UPDRS (part 3) motor scores or LEU doses between the patient groups. DA-LEU doses did not differ between the PD+DA (216mg) and the DBS+DA (205mg) group.

	Controls	PD-DA	PD+DA	DBS-DA	DBS+DA	t value, χ^2 and F-value	p-value
Participants	18	14	20	11	16		
Gender (male)	15	11	19	10	11	χ^2=5.1	0.27
Age (yrs)	58.9±13	67.2±7.5	64.3±5.2	57.0±7.0	59.1±11.6	F=3.0	=0.023
Age of diagnosis		61.1±2.2	53.2±1.8	42.5±2.3	43.7±2.2	F=15.9	<0.001*
Disease duration (yrs)		6.2±3.8	11.1±7.0	14.4±5.0	15.6±6.0	F=7.3	<0.001*
DBS (yrs)				3.4±3.3	3.6±2.2	t=0.2	0.8
Education (yrs)	13.6±3.2	14.8±3.1	14.5±2.5	13.9±2.8	13.7±2.8	F=0.4	0.75
LEU dose DA dose (LEU)		511±321	854.2±356 216.0±109	739.2±409	771.4±337 204.9±97.1	F=2.6 t=0.3	0.058 0.7
UPDRS on		16.0±2.3	19.4±11.6	16.5±4.4	17.6±4.4	F=0.5	0.6

Table 15. *STN-DBS: Demographic characteristics.*

Significant differences are labelled with "".*

Beads task

The patient data, excluding controls, were analysed using a generalized linear model that included DBS (yes/no), DA (yes/no), beads ratio and loss as factors. Age was included as a covariate, although it was not significant (Wald $\chi^2 = 0.28$, $p > 0.59$). There was a significant effect of DA (Wald $\chi^2 = 11.4$, $p = 0.001$) and beads ratio (Wald $\chi^2 = 34.8$, $p < 0.001$). There were no effects of loss condition (Wald $\chi^2 = 0.06$, $p = 0.7$), DBS (Wald $\chi^2 = 0.6$, $p = 0.4$) and no interaction of DBS and DA (Wald $\chi^2 = 0.03$, $p = 0.8$) or beads ratio and loss condition (Wald $\chi^2 = 1.2$, $p = 0.2$).

Pairwise comparison between all groups including controls was also performed. There was a significant effect of group (Wald $\chi^2 = 138.4$, $p < 0.001$). PD+DA and DBS+DA both drew significantly less than controls before making a decision ($p < 0.001$), PD-DA and DBS-DA patients ($p < 0.001$), (see Table 16, Figure 20).

Opposite colour choice

Next the number of times participants made an irrational choice and picked the less likely cup given the information they had at the time of drawing was examined.

First effects of DA and DBS on irrational choices were compared and results showed a significant effect of DA (Wald $\chi^2 = 13.8$, $p < 0.001$) and beads ratio (Wald $\chi^2 = 4.3$, $p = 0.039$).

PD+DA made more irrational decisions than PD-DA, DBS-DA and healthy controls

($p \leq 0.002$). Similarly the DBS+DA group made significantly more irrational choices than DBS-DA ($p = 0.01$) and PD-DA and controls ($p \leq 0.003$). Further details are illustrated in Figure 21.

There was no effect of loss condition (Wald $\chi^2 = 3.3$, $p = 0.07$), DBS (Wald $\chi^2 = 0.03$, $p = 0.8$) and also no interaction of DBS and DA (Wald $\chi^2 = 0.3$, $p = 0.6$).

Age was modeled as a covariate but was not significant (Wald $\chi^2 = 0.01$, $p = 0.9$). Next, pairwise comparisons including the control group and all patient groups were made.

There was a significant effect of group (Wald $\chi^2 = 32.7$, $p < 0.001$). Age was again modeled as a covariate (Wald $\chi^2 = 0.9$, $p = 0.3$). Results of pairwise comparison between all groups are shown in Table 16.

Dopamine agonist dose and task performance

There was no significant correlation between mean draws per trial and LEU-DA dose (Pearson correlation = -0.18, $p = 0.9$). There was also no correlation between irrational choices and LEU-DA dose (Pearson correlation = 0.42, $p = 0.8$).

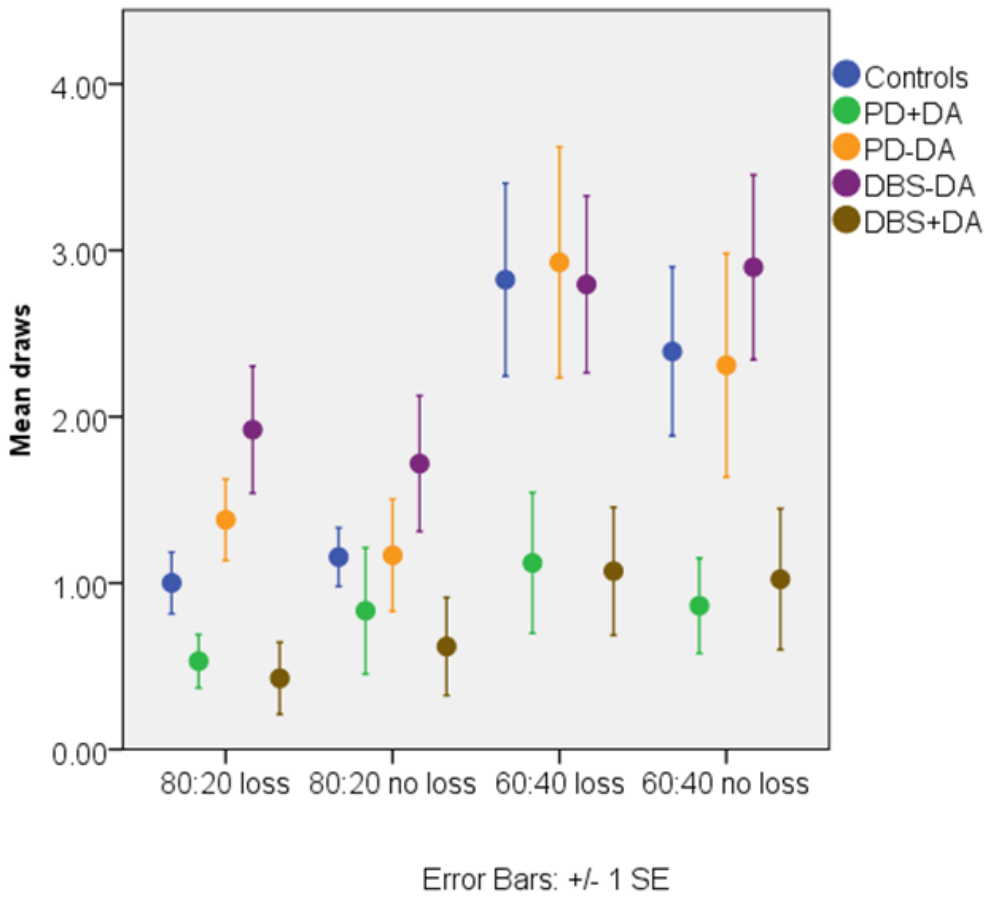

Figure 20. *STN-DBS: Average drawing behaviour per condition of different groups. One bead is always shown before the participant must make a decision, so total beads seen are mean draws plus one.*

Group (χ^2, p-value)	**PD-DA**	**DBS+DA**	**DBS-DA**	**Controls**
PD+DA Draws Opposite	 **101.6,p < 0.001** **11.1, p = 0.001**	 0.06, p = 0.7 0.7, p = 0.3	 **84.6 p < 0.001** **9.1, p = 0.002**	 **87.3, p < 0.001** **13.2, p < 0.001**
PD-DA Draws Opposite		 **71.5, p < 0.001** **12.5, p < 0.001**	 1.4, p = 0.2 0.2, p = 0.7	 0.3, p = 0.56 0.6, p =0. 42
DBS+DA Draws Opposite			 **75.3, p < 0.001** **6.1, p = 0.01**	 **63.6, p < 0.001** **9.1, p = 0.003**
DBS-DA Draws Opposite				 5.1, p = 0.023 0.002, p = 0.96

Table 16. *STN-DBS: Pairwise comparisons.*

Pairwise comparisons between groups for number of draws. All p-values shown are uncorrected. Values less than 0.0125 (highlighted in bold) are significant. All p-values in this table are for main effect of group. Age was included as a covariate.

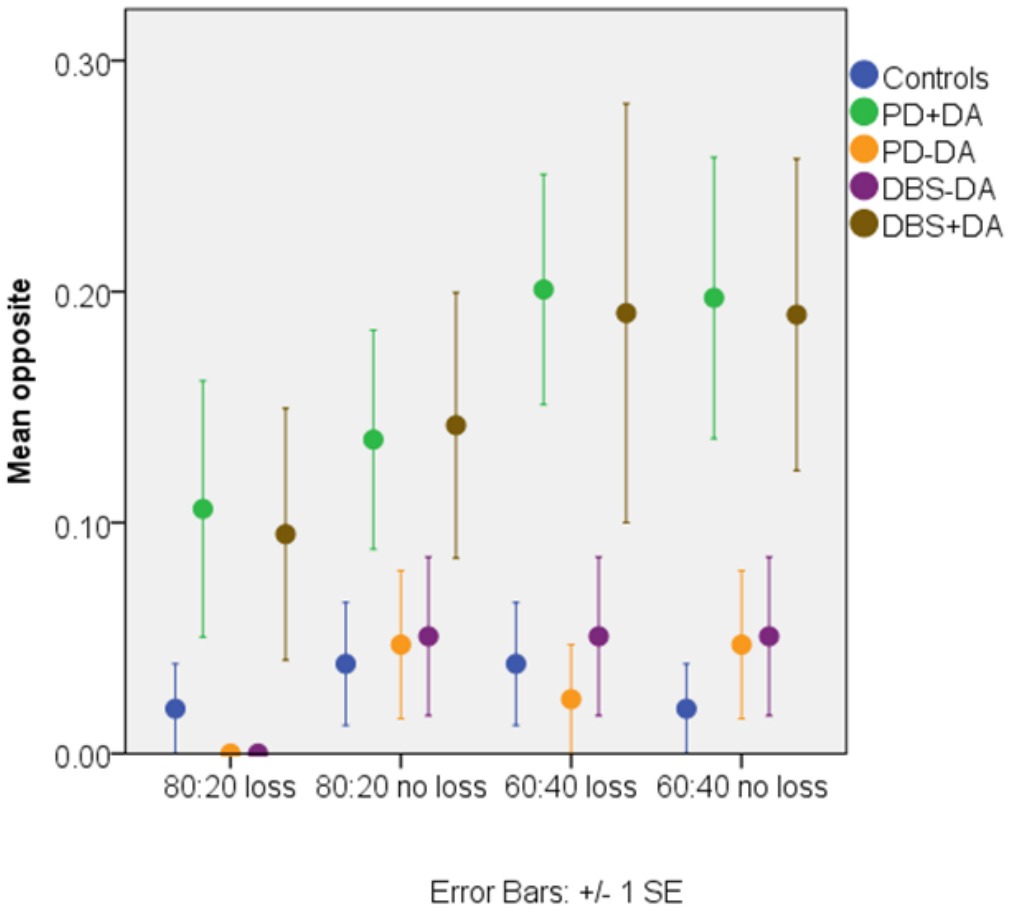

Figure 21. *STN-DBS: Number of times participants chose the opposite colour.*

Discussion

Both DA medication (Weintraub, Siderowf et al. 2006) and DBS have been implicated in increased impulsivity (Frank, Samanta et al. 2007, Cavanagh, Wiecki et al. 2011). However, an examination of the effects of DA and DBS within a single study, while controlling for the effects of DA in DBS has not been previously reported. This study directly compared PD patients with and without DA treatment and with and without STN-DBS. Patients treated with a DA gathered significantly less evidence and made more irrational choices than patients not treated with a DA, whether or not they received DBS. DBS had no effect and there was no interaction between DBS and DA, which is in line with previous results (Halbig, Tse et al. 2009). In addition, patients not taking a DA did not differ from controls, whereas those that were taking a DA did. Thus, the hypothesis that DBS in combination with a DA would further increase reflection impulsivity was incorrect. Recent work has shown that the most important factor for risky decisions is the total amount of dopaminergic medication including a combination of DA and L-dopa. The authors also tested PD patients on and off STN-DBS, but found no group effect (Lule, Heimrath et al. 2012). Good outcome and reduction in ICBs after DBS has been observed in those patients who had significant reduction in dopaminergic medication (Demetriades, Rickards et al. 2011). One prospective study showed significant improvement of ICBs and dopamine dysregulation syndrome in all patients after STN-DBS, except for one individual in whom reduction of DA was not possible, suggesting that other individual factors, such as electrode misplacement outside the STN and consequently failure of reduction of DA, might be responsible for worsening or new

onset of ICBs after DBS (Lhommee, Klinger et al. 2012). In this study, total LEU doses were not significantly different between PD+DA and PD patients treated with DBS and yet only those treated with a DA made impulsive choices. Thus, DA alone appears to trigger impulsive choices in PD patients who do not have an ICB in the past or present. Increased temporal discounting, the preference of a smaller immediate over a delayed but higher reward was observed in PD patients without ICBs who were treated with a dopamine agonist. Discounting in these patients was not affected by medication state, which may imply that dopamine agonist therapy causes persistent long term behavioural changes (Milenkova, Mohammadi et al. 2011) possibly via sensitization. These results are also consistent with the previous study which demonstrated that PD patients without ICBs but on a DA were performing similarly to non PD patients with pathological gambling.

My results also expand on previous studies showing no impairment in decision making and risk taking in drug naïve PD patients (Poletti, Frosini et al. 2010) and suggest that L-dopa alone or in combination with DBS does not cause increased reflection impulsivity. These findings also suggest that L-dopa without a DA does not increase the risk of pathological gambling in PD. DA are also known to change reward learning. In one study drug-naïve PD patients had intact learning from negative feedback but impaired reward learning. An opposite learning profile was found after 12 weeks of dopamine agonist therapy, with significant impairment in avoidance of negative outcomes compared to controls but restored reward seeking behaviour (Bodi, Keri et al. 2009).

It has been suggested that the STN acts as a “brake” on the cortico-striatal loop in high conflict situations to “buy more time” before making a decision (Frank, Samanta et al. 2007). In PD patients treated with DBS, impulsive choice is increased by reducing a decision threshold (Cavanagh, Wiecki et al. 2011). In this study, patients with STN-DBS showed no increased impulsivity. However, in the previous studies most PD patients were taking a DA in addition to DBS. Further, these studies examined the acute effects of DBS stimulation, which is known to cause impulsive behaviour (Lhommee, Klinger et al. 2012) whereas here STN-DBS patients under stable conditions were tested. Finally, the main outcome measure in previous studies was reaction time (Frank, Samanta et al. 2007, Cavanagh, Wiecki et al. 2011), whereas in this study the main interest was number of draws. Decision thresholds are, however, more clearly defined in this task, as an explicit choice to stop sampling must be made (Furl and Averbeck 2011). Therefore ‘reflection impulsivity’ is distinct from ‘motor’ impulsivity, the inability to stop an on-going process and from ‘waiting’ impulsivity, the inability to delay an action was examined (Dalley, Everitt et al. 2011). The STN may be more involved in decisions made under time pressure, than decisions that can be made without time pressure, as is the case in this task. Consistent with this, imaging work in healthy controls demonstrated activation of the anterior cingulate, the ventral striatum and insula during the beads task, but not STN (Furl and Averbeck 2011). It is possible that DA medication causes a reduction in “top down” cortical control of the basal ganglia. An fMRI study showed a reduced orbitofrontal cortex and anterior cingulate activity PD patients with pathological gambling and compulsive shopping after DA therapy, which correlated with increased risky choice (Voon, Gao et al. 2011). Both brain areas are essential for

feedback learning and switching behaviours when necessary (Rolls 2004, Kennerley, Walton et al. 2006).

Differences in the mechanisms of action of L-dopa and DA likely explain why ICBs and impulsive choice are more commonly seen under DA treatment than L-dopa monotherapy. Dopamine agonists stimulate dopamine receptors more tonically than L-dopa, which has consequences on learning behaviour. Further, the nowadays commonly used DA have a much stronger dopamine D3 receptor affinity than D2 or D1 receptors (Gerlach, Double et al. 2003, Jenner 2005) and D3 receptors are primarily expressed in the limbic system (Ahlskog 2011). This might explain why DA are more likely to trigger ICBs (Ahlskog 2011) than L-Dopa.

However, having excluded patients with known ICBs, a co-existing interaction between L-dopa therapy and STN-DBS that may be relevant in individuals or subgroups of patients cannot be excluded.

Conclusion

In summary, increased impulsive choices and irrational decisions in patients treated with a DA, regardless of whether they had DBS or not, was demonstrated. In contrast, there was no difference between controls and patients who were not treated with a DA. Results of this study also suggest that neither STN-DBS nor L-dopa monotherapy increases impulsive choices in the context of information sampling in a cohort of PD patients who never had an ICB.

Further, this study showed that PD patients treated with a DA generally have increased, albeit controlled, impulsivity. The clinical implication of these results is that DBS may be considered as a potential treatment for ICBs where motor deficits prevent decreases in dopamine replacement therapies. Careful preoperative planning, exact placement of the electrodes within the STN are in combination with post-operative reduction of DA likely to be key factors predictive of a good behavioural outcome.

Key Findings

- All PD patients treated with a dopamine agonist gathered significantly less information and made more irrational decisions than controls and PD patients without a dopamine agonist.
- There was no difference in performance on the beads task between controls and PD patients without a dopamine agonist, regardless of whether they had been treated with STN-DBS or not.
- Dopamine agonists are the main risk factor for reflection impulsivity and irrational choices in PD.

3.7. Jumping to conclusions behaviour in patients with ephedrone induced Parkinsonism

Introduction

Methcathinone also known as ephedrone and mephedrone, is one of several homemade synthetic cathinones with amphetamine-like stimulant activity. Ephedrone users inject themselves several times per day in binges over several days. In eastern Europe, it is generally manufactured on a small scale using commercially available nasal decongestants including phenylpropranolamine (PPA) and pseudoephedrine, potassium permanganate (KMnO4), used as an oxidant and disinfectant (Chintalova-Dallas, Case et al. 2009) and vinegar. During this reaction, as a side product, manganese ions are formed, which then accumulate in the brain and cause dystonia, postural instability, a quiet slurred pallidal speech, dopaminergic unresponsive bradykinesia and later a typical "cock gait" (Sanotsky, Lesyk et al. 2007). Concerns about the misuse of KMnO4 have led to restrictions in its sale in recent years.

Ephedrone is often used in small groups, sharing paraphernalia and engaging in the practice of "front loading", whereby drugs are transferred from one syringe to another. There have been no post-mortem examinsations so far, but MRI scans of the brain revealed that the disorder affects mainly the globus pallidus, the substantia nigra and to a lesser degree the subthalamic nucleus, the putamen and the caudate nucleus (Sikk, Haldre et al. 2011). However, DAT scans show an intact nigrostriatal pathway (Sanotsky, Lesyk et al. 2007). Although the white matter appears to be normal on T1-

weighted MRI, diffusion tensor imaging studies showed extensive white matter changes particularly in the frontal and premotor areas and widespread damage to cortico-pallidal connections (Stepens, Stagg et al. 2010). Despite these extensive abnormalities on brain imaging only mild deficits in executive function have been reported (Selikhova, Fedoryshyn et al. 2008, Stepens, Logina et al. 2008, Stepens, Stagg et al. 2010). Individual case reports have pointed towards a tendency towards impulsivity (Yildirim, Essizoglu et al. 2009) but this has never been studied systematically. However, drug addiction is associated with executive, memory and decision making dysfunction (Koob and Volkow 2010). Opiate and amphetamine dependent patients have difficulties in planning, learning and memory (Ersche, Clark et al. 2006) which persist during opiate replacement therapy (Prosser, Cohen et al. 2006). Patients on opioid replacement therapy also make more risky decisions which may reflect abnormal patterns of orbitofrontal cortex activation (Ersche, Fletcher et al. 2006).

In this study, a comparison was made between patients with ephedrone induced extrapyramidal symptoms to substance abusers without neurological deficits who were taking opioid replacement therapy and healthy volunteers on a WM, feedback learning, risk taking test and the beads task. The beads task examines how much information participants gather before making a decision sometimes referred as "*reflection impulsivity"* (Evenden 1999, Clark, Robbins et al. 2006). Again the WM and the beads tasks were combined because it has been suggested that jumping to conclusions might be a specific strategy to reduce WM load (Dudley, John et al. 1997). Emotionally salient and neutral distractors were also used, given the negative effects of task irrelevant information on WM performance (Dolcos and McCarthy 2006).

Apart from reflection impulsivity cognitive impulsivity also includes decision making under risk (Verdejo-Garcia et al 2008). For this study it was of special interest to assess whether reflection impulsivity is simply driven by risky choices or is triggered due to impaired feedback learning.

A key role was also to assess differences between former addicts with ephedrone toxicity and current drug dependent patients, in the context of the distinctive structural MRI changes in ephedrone patients compared to normal MRI scans in opioid dependence. Clinical impression has suggested that most patients with ephedrone induced basal ganglia damage lose their craving for illicit substances and cease abusing drugs. It is unclear whether their physical disability or damage from the accumbens-pallidum circuitry is responsible for this change in behaviour. Studies in rodents have shown that the globus pallidus plays a key role in the reinforcing effects of illicit drugs (Koob and Volkow 2010), and its damage might therefore abolish craving.

It is possible that both patient groups are likely to have orbitofrontal cortex dysfunction, considering its important role in drug preoccupation and impulsivity (Volkow and Fowler 2000). Therefore, the prediction was that ephedrone patients would perform similarly to opiate dependent patients in tasks measuring reflection impulsivity, since jumping to conclusions is known not to recover even after prolonged abstinence in substance abusers (Clark, Robbins et al. 2006). On other tasks, such as risk taking and feedback learning, it was speculated that ephedrone patients would perform better than substance abusers on opioid replacement therapy given differences in drug craving and shorter duration of illicit drug abuse. It was expected that both patient groups would be

worse on the WM task, especially when salient distractors were presented but would on the other hand remember distractors significantly better than healthy controls.

Patients and methods

All participants provided written informed consent. The protocol was approved by the UCLH Trust or Ukrainian local ethics committee. All participants scored more than 26/30 on the MMSE and were tested once usually mid-mornings. Participants received a modest reward (between £10-15) depending on their performance.

Ephedrone patients

Fifteen patients with ephedrone induced extrapyramidal symptoms were recruited from the department of Neurology of Lviv Regional Clinical Hospital, Ukraine. All patients had moderate to severe extrapyramidal symptoms, dystonia and had decrement in finger tapping with some axial rigidity, induced by ephedrone. Fourteen patients developed extrapyramidal symptoms after intravenous methcathinone abuse, 1 patient after recurrent oral intake. A detailed neurologic examination was performed by a movement disorder specialist on the day of testing. No patient had a resting tremor or was treated with dopamine replacement therapy. All patients had gait problems with moderate to severe impairment of postural stability. One patient was wheelchair bound at the time of assessment. Seven of 15 patients developed a characteristic “cock-gait” and had a characteristic pallidal speech, similar to patients with progressive supranuclear palsy. No patient had taken any illicit drugs within the last 2 years. Manganese levels have been

measured in pubic hair samples in nine of 15 patients confirming the diagnosis of manganese toxicity. For further details see (Selikhova et al 2008).

Substance abusers on opioid replacement therapy

Thirteen male patients with a recent history of illicit drug abuse, meeting DSM-IV criteria for substance dependence (American Psychiatric Association 2000) were included in this study. Eleven were recruited from the Replacement Therapy Unit of Lviv, regional Clinical Narcological Dispensary. Two patients were inpatients at the department of Lviv Regional Clinical Narcological Dispensary, Ukraine. All patients had clinically normal cognitive function, and were on opioid replacement therapy with buprenorphine. Neurological examination was normal in all patients. Twelve of 13 patients had a long standing history of intravenous opioid abuse. (For a detailed list of drugs of abuse see Table 17). All tests were performed prior to their dose of buprenorphine. Only those patients who were able to tolerate a delay of their buprenorphine dose were included. Patients who suffered from clinically evident withdrawal symptoms were excluded. None of these patients reported taking any additional illicit substances at the time of testing.

Controls

Results were compared with 18 age matched healthy male volunteers. For additional demographic characteristics see Table 17.

	Controls	Ephedrone	Substance abusers	t value, χ^2 and F-value	p-value
Participants (no)	18	15	13		
Age (yrs)	32.3±5.5	34.0±7.2	32.0±7.1	0.34	0.71
Gender (male)	18	13	12	2.4	0.3
Education	13.8±2.8	12.2±1.4	12.0±1.9	5.1	0.01*
Drug abuse (yrs)			12.0±5.1		
Replacement therapy (yrs)			1.4±1.3		
Ephedrone abuse (yrs)		1.5±1.2			
Ephedrone stopped (yrs)		6.2±2.6			
Parkinsonism (yrs)		7.0±2.4			
Substance abuse (no)		15	13		
i.v. opioid		4	12		
i.v.heroin		2	4		
Cannabis		3	3		
Cocaine		1	1		
Morphine		0	1		
Ephedrone (i.v/oral)		14/1	0		

Table 17. *Ephedrone: Demographic characteristics.*

Details about past history of substance abuse presented. All values are mean ± SD. Significant difference is labelled with "".*

Working memory task and beads task

The same WM and beads task has been used as described earlier. In the WM task participants were asked to memorize either 2 or 3 geometric figures. Further, positive, neutral or negative distractors were shown. At the very end of the task participants had to say whether they thought they have been exposed previously to the distractor.

In the beads task all participants performed a practice trial to ensure that they understood the rules.

Risk task

The same version of the gambling task was used as described earlier. Previous studies have shown that addicts are more risk prone on the Iowa Gambling task (Bechara 2003). However, the Iowa Gambling task includes both elements of risk and feedback learning. Therefore, these elements have been split into separate tasks for this study to get a more straightforward assessment.

Feedback learning task

The ability of participants to integrate positive and negative feedback within a learning context was assessed using an instrumental learning task. The task had four blocks of 24 trials (Pessiglione, Seymour et al. 2006). In each trial participants were shown two stimuli and they had to select one of them. After choosing a stimulus they were informed of the outcome. Each block contained a fixed probability of winning or losing

associated with each stimulus, and one stimulus was more often rewarded, or less often punished than the other. Participants were asked to select the stimulus that they thought was more likely to win in 2 “winning blocks” or less likely to lose in 2 “losing blocks”. In “winning blocks” participants could either win 0.5 units or win nothing, in the other 2 “losing blocks” subjects should avoid a loss or could lose 0.5 units. Feedback was given immediately. Winning probabilities for the two stimuli were 70%/30%. Different abstract stimuli were used in each block.

Statistical analysis

Statistical analysis was performed using SPSS, version 18. For the demographic variables, age, gender, years of education were used as dependent variables and groups (ephedrone, substance abusers and controls) were modeled as a between subject factor. ANOVA, t-test or χ^2 tests were used where appropriate. Years of education was modeled as a cofactor for all analyses but did not change any results.

Working memory task

A generalized linear model (SPSS) with a binary logistic distribution was used. As a dependent variable score (correct response = 1 or incorrect response = 0) was used. Distractor (positive, neutral or negative), number of memoranda (2 or 3 geometric figures), choice (yes, no) and actual shown figure (yes, no) were modeled as fixed factors. Groups (ephedrone, substance abusers and controls) were modeled as a between subject factor and subject was a random factor nested under group.

Beads task

Analyses using a generalized linear model (SPSS) were performed. As a dependent variable either the number of draws before making a decision or opposite colour choice was used. As these are both count variables a Poisson model, which had a loglinear link function, was used. For the first analysis beads ratio (80:20 or 60:40) and loss condition (loss, no loss) were modeled as fixed factors. Groups (ephedrone, controls, substance abusers) were modeled as a between factor and subject was a random factor nested under group.

Risk task and feedback learning task

Data analysis for the risk and learning tasks was carried out by fitting parametric decision making models to the behaviour of each individual subject, and comparing the distributions of parameter fits from the model between groups in a within subject design. Further details have been described earlier (see chapter 3.1).

Results

Demographic characteristics

There was no age difference between the 3 groups ($F_{(2,44)}$=0.34, p = 0.7), but there was a significant difference in years of education controls ($F_{(2,42)}$=5.1, p = 0.01). Post hoc analysis showed that controls had significantly more years of education than ephedrone patients (p = 0.033) and substance abusers (p = 0.022).

Working memory task

There was a significant effect of group (Wald $\chi^2 = 16.0$, $p < 0.001$), a significant effect of distractor type (Wald $\chi^2 = 17.8$, $p < 0.001$) (Figure 22) and a significant distractor by number of memoranda interaction (Wald $\chi^2 = 10.0$, $p = 0.007$).

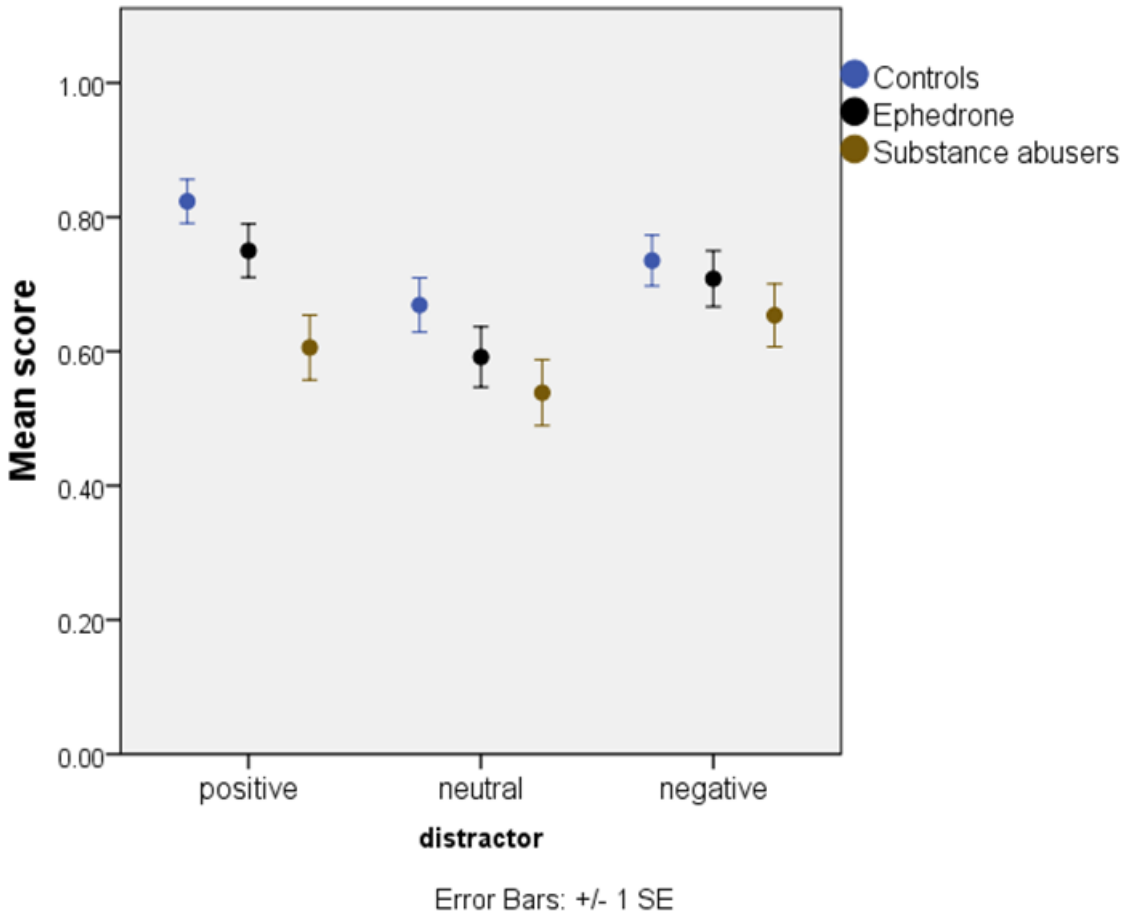

Figure 22. *Ephedrone: WM performance.*

Positive (left), neutral (middle) and negative (right) distractors.

Results showed no effect of memoranda (Wald χ^2 =1.4, p = 0.2) (Figure 23). Pairwise analysis between the groups showed that substance abusers on opioid replacement therapy performed significantly worse than ephedrone patients (Wald χ^2 =6.2, p = 0.013) and controls (Wald χ^2 =15.4, p < 0.001). There was, however, no difference between controls and ephedrone patients (Wald χ^2 =2.3, p = 0.12). Analysis was done to see how often the distractors could be remembered at the end of the experiment, but no group differences were found (Wald χ^2 =4.3, p = 0.5).

Beads task

First the number of draws each participant made in the different conditions was examined (Figure 24). Results showed a significant main effects of group (Wald χ^2 = 73.0, p < 0.001), beads ratio (Wald χ^2 = 4.5, p = 0.033), a significant group by loss condition interaction (Wald χ^2 = 6.5, p = 0.037) and a significant group by ratio interaction (Wald χ^2 = 9.5, p = 0.009). Subsequently a series of pairwise comparisons between the 3 groups were performed which showed a significant group by loss interaction between the ephedrone group and addicts (Wald χ^2 = 5.5, p = 0.019) and a significant group by ratio interaction between the ephedrone and the control group (Wald χ^2 = 9.3, p = 0.02).

Ephedrone patients drew significantly less often than controls (Wald χ^2 = 45.3, p < 0.001) and showed a trend to draw more than substance abusers on opioid replacement therapy (Wald χ^2 = 3.2, p = 0.076). Substance abusers also gathered less information

than controls (Wald $\chi^2 = 30.0$, $p < 0.001$). Education was added as a cofactor but there was no significant correlation (Wald $\chi^2 = 0.87$, $p = 0.7$).

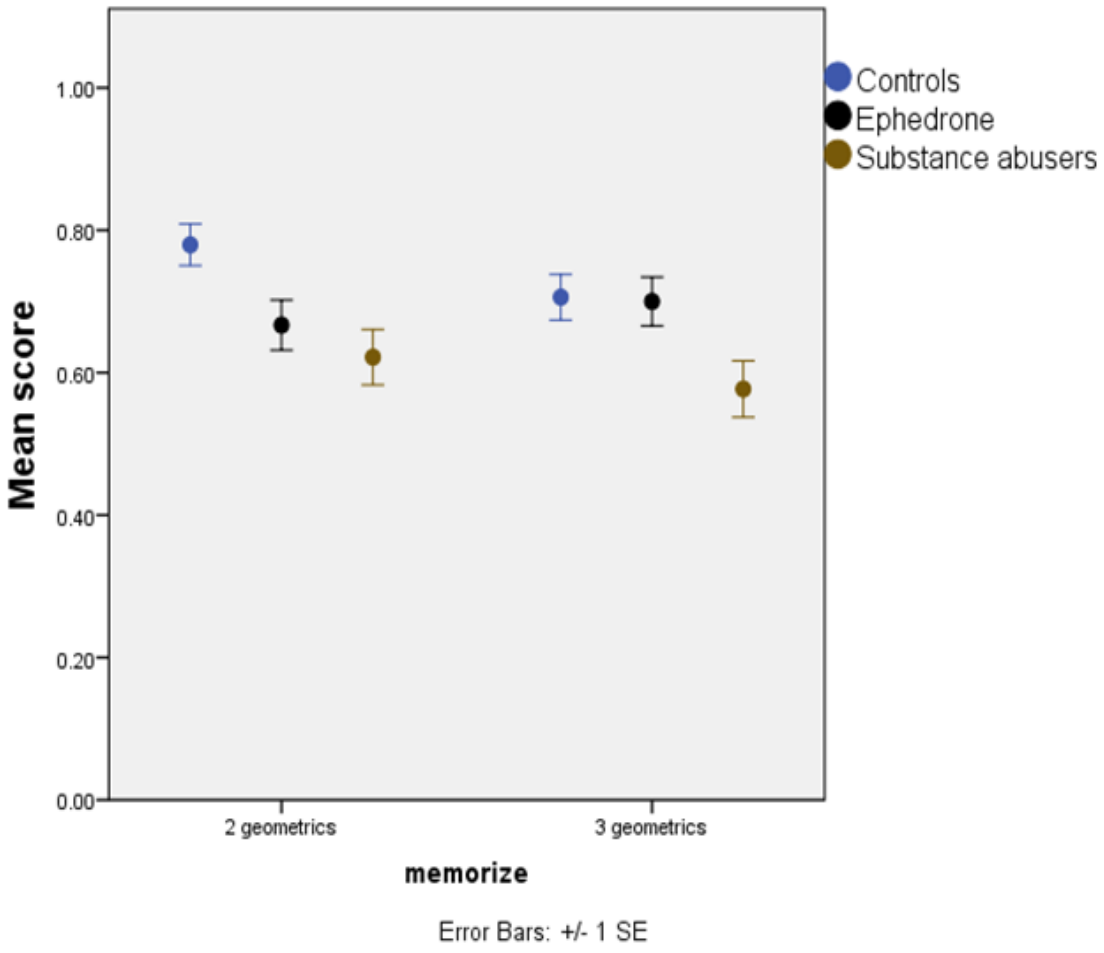

Figure 23. *Ephedrone: Effects of memoranda on WM performance.*

Two geometric figures (left) versus 3 (right).

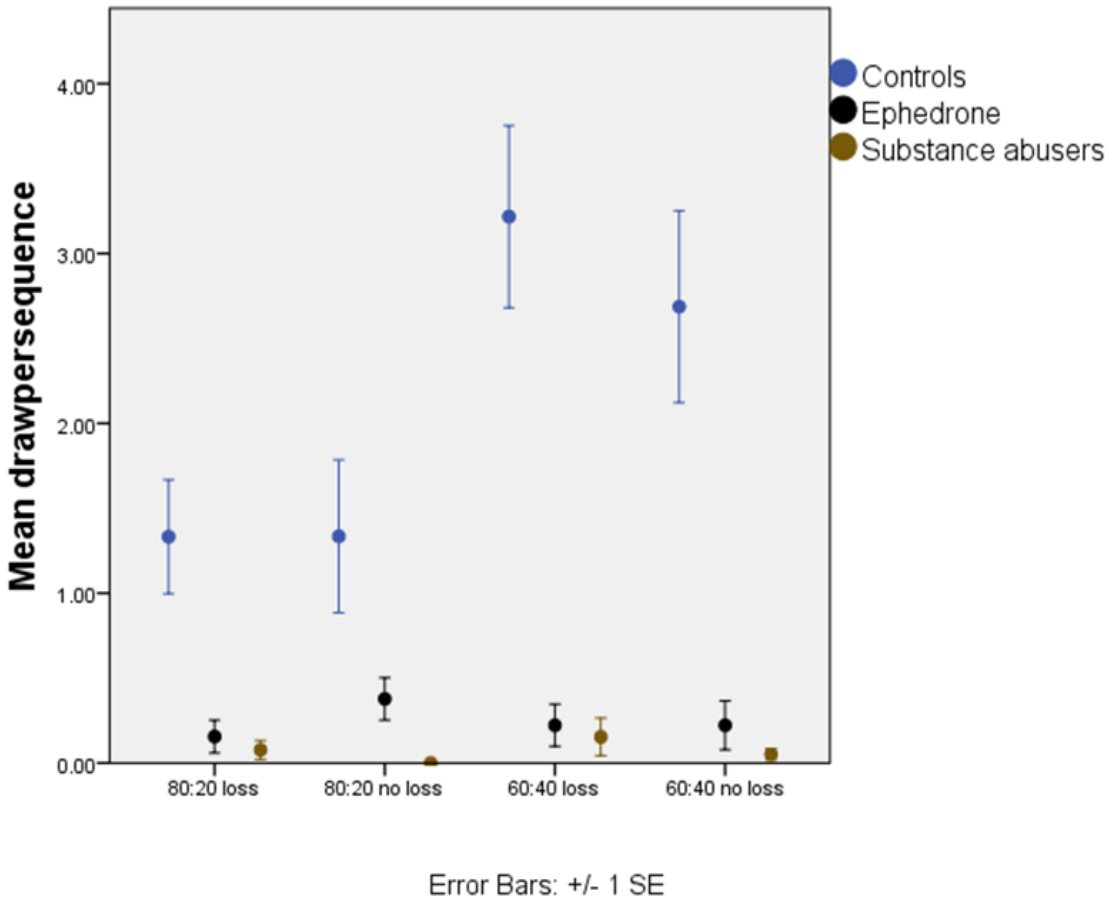

Figure 24. *Ephedrone: Average drawing behaviour per condition of different groups.*

One bead is always shown before the participant must make a decision, so total beads seen are mean draws plus one.

Opposite colour choice

Subsequently the number of times participants chose the opposite colour, or the less probable cup, given the beads that had been drawn was examined (Figure 25). Results

showed a significant main effect of group (Wald $\chi^2 = 34.6$, $p < 0.001$). Ephedrone patients (Wald $\chi^2 = 30.1$, $p < 0.001$) and substance abusers (Wald $\chi^2 = 34.1$, $p < 0.001$) chose the less likely cup significantly more often than controls. There was no difference between the ephedrone group and substance abusers (Wald $\chi^2 = 0.54$, $p = 0.46$).

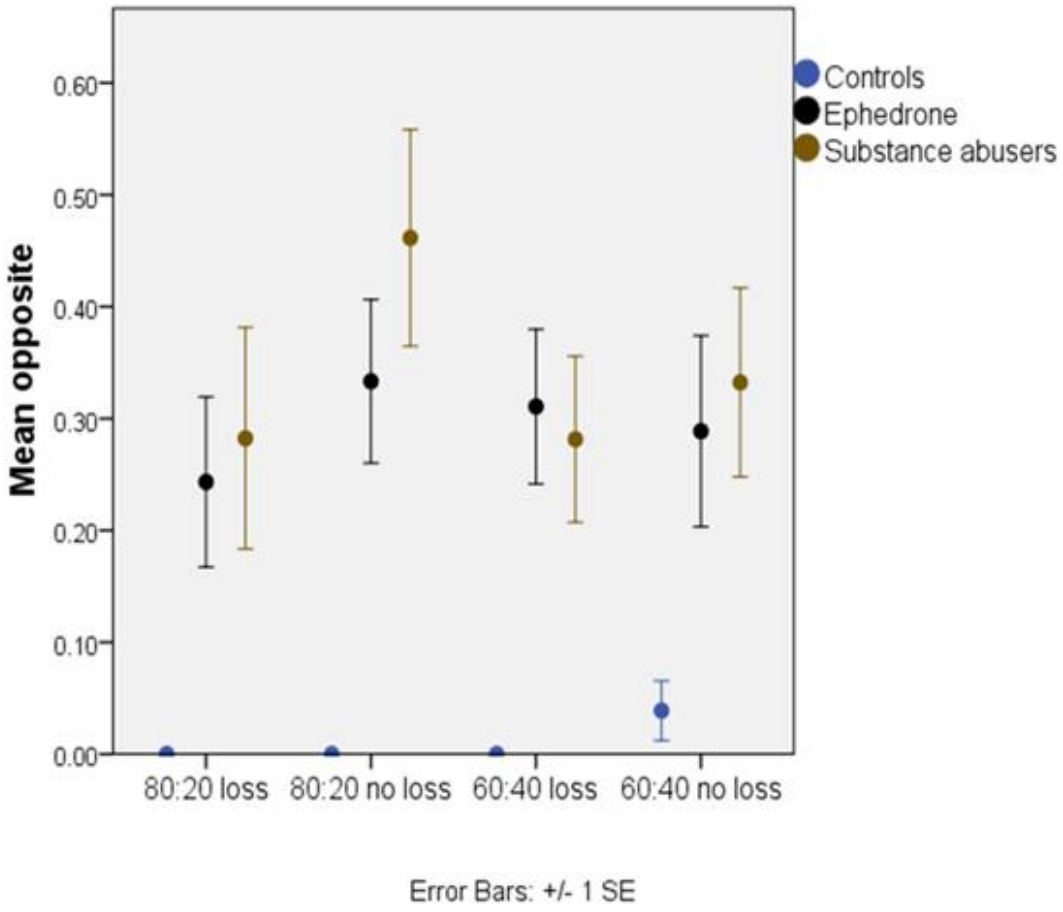

Figure 25. *Ephedrone: Number of times participants chose the opposite colour.*

Risk task

There were group differences in preference for risky gambles ($F_{2, 45} = 7.06$, $p = 0.002$). Post-hoc comparisons (Bonferroni corrected) showed that the opiate addicts were more risk prone than controls ($F_{1, 30}=14.75$, $p=0.002$). Ephedrone abusers were not more risk prone than controls ($F_{1,31} = 4.67$, $p = 0.11$) and did not differ from addicts ($F_{1,29} = 2.03$, $p = 0.49$) (Figure 26A).

Learning task

Performance on the learning task was analysed by fitting separate learning rate parameters to the positive and negative feedback conditions (Voon, Pessiglione et al. 2010). All groups learned equally well ($F_{2, 43} =1.78$, $p = 0.173$). There was no difference in how groups responded to either learning to win or learning to avoid losing, measured as a group by feedback type interaction ($F_{2, 43}= 1.07$, $p = 0.345$) (Figure 26B).

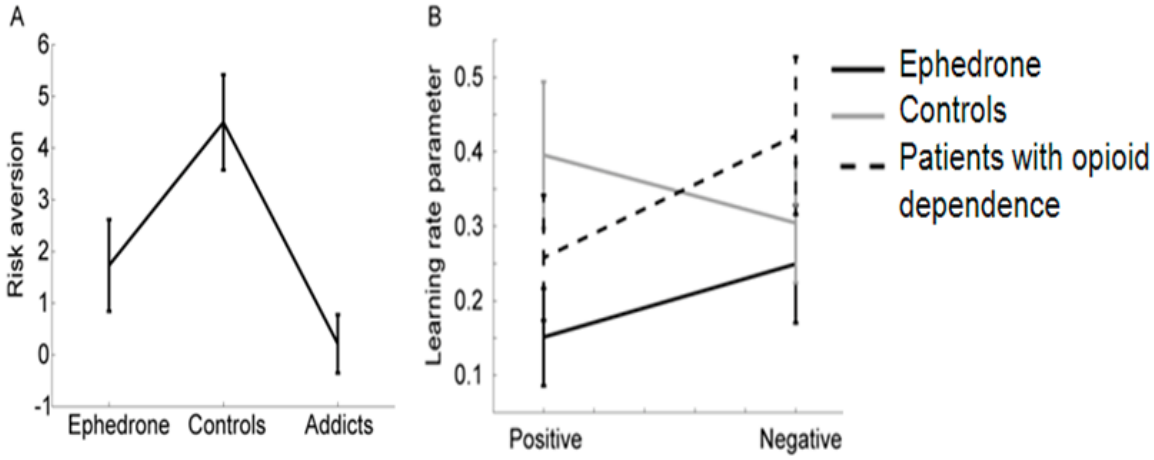

Figure 26. *Ephedrone: Risk and learning behaviour.*

Discussion

This is the first study to systematically analyse WM, feedback learning, risk taking and information gathering in patients with ephedrone induced parkinsonism. Results were compared directly with substance abusers on opioid replacement therapy and healthy volunteers. There was no difference in WM performance between controls and ephedrone patients even when salient distractors were shown. Both these groups performed significantly better than opiate dependent patients.

Previous studies have demonstrated poor attention in substance abusers when required to ignore salient stimuli during WM tasks (Hester and Garavan 2009). Results presented in this thesis are also consistent with previous studies showing impaired WM performance in opiate dependent patients (Rapeli, Kivisaari et al. 2006). All patients on opioid replacement therapy were tested prior to their daily buprenorphine dose and therefore conceivably might have had subtle withdrawal symptoms and low brain dopamine levels (Koob and Volkow 2010). Thus impaired WM performance in this group might be explained by the inverted "U-shape" hypothesis, suggesting that too low or excessive dopamine levels impair cognitive function (Cools, Barker et al. 2003).

It is, however, also possible that subclinical anxiety due to withdrawal might have contributed to poor WM performance in this patient group. The normal WM performance in the ephedrone group is in keeping with other studies showing normal scores on MMSE and FAB scores (Sikk, Taba et al. 2007, Stepens, Logina et al. 2008). Interestingly, controls and ephedrone patients performed better when salient distractors

were presented. Emotional stimuli can enhance cognitive functions (e.g. precise recall of a moment during an emotional event) but can also worsen WM capacity, particularly when they need to be ignored (Dolcos and McCarthy 2006). Thus, the hypothesis that WM performance would decline with salient distractors proved incorrect. One possible explanation is that during high cognitive load the impact of salient distractors is reduced, while activity in the dorsolateral prefrontal cortex increases (Van Dillen, Heslenfeld et al. 2009). An easier version of the task might have led to stronger effects of distractors on WM performance.

Results also showed a relative improvement of WM performance with positive distractors. Implicit exposure to positive images might induce striatal dopamine release and might boost WM performance indirectly, given the role of striatal dopamine in WM (Landau, Lal et al. 2009). However, there was no similar effect in opiate dependent patients. It is possible that in this group, due to changes of the amygdala during addiction (Koob and Volkow 2010), salient photos might be stimulating to a lesser extent and therefore fail to lead to a memory-enhancing effect. Chronic buprenorphine abuse has been also shown to reduce the salience of the drug-associated cues (Sorge and Stewart 2006), and might have reduced attention to salient cues in this task.

Decision making on the beads task is processed via a circuit involving the anterior cingulate, the parietal cortex, the insula and the ventral striatum (Furl and Averbeck 2011). Healthy volunteers who gathered more information had more parietal cortex activation (Furl and Averbeck 2011). The anterior cingulate is necessary for optimal decision making and to integrate risks (Kennerley, Walton et al. 2006). Thus, damaged

connections from the anterior cingulate to the striatum and globus pallidus-cortical circuits in substance abusers and ephedrone patients (Rogers, Everitt et al. 1999, Selikhova, Fedoryshyn et al. 2008, Stepens, Stagg et al. 2010), albeit due to different mechanisms, could explain the impaired performance on the beads task.

In this study, controls drew significantly more beads before making a decision than patients. Both patient groups also made significantly more irrational decisions and chose the less likely cup more often than controls. Although group difference between ephedrone patients and substance abusers only reached trend levels, a significant group by loss interaction was found. Thus, ephedrone patients gathered more evidence in the no loss conditions than patients on opioid replacement therapy.

Various deficits in decision making have been reported in substance abusers (Paulus 2007). Irrational decision making has also been found in patients with ventromedial prefrontal cortex lesions (Koenigs and Tranel 2007). “Delusional thinking”, defined as a belief based on incorrect inference (American Psychiatric Association 2000), has been reported in treated PD patients with impulsive compulsive behaviours (Gallagher, O'Sullivan et al. 2007, Wolters, van der Werf et al. 2008), who also chose the opposite cup significantly more often than controls as described earlier. Delusional thinking has been also positively correlated with fewer draws on the beads task in patients with schizophrenia (Fine, Gardner et al. 2007). My results are also in line with other studies showing a positive correlation of jumping to conclusion behaviour and prefrontal cortex dysfunction during task performance (Lunt, Bramham et al. 2012).

Thus, lesions within the anterior cingulate circuit in the ephedrone patients (Stepens, Stagg et al. 2010) might explain poor performance on the beads task, while the dorsolateral prefrontal loop, necessary for WM, may be relatively intact. This discrepancy between impairment in “reflection impulsivity” but intact WM function is consistent with other studies suggesting a dissociation of WM and decision making processing within the prefrontal cortex (Bechara, Damasio et al. 1998). Increased reward seeking behaviour with a reduced sensitivity to negative feedback or more likely insensitivity to unpredictable future consequences are possible explanations for impulsivity in patients with lesions in the prefrontal cortex (Bechara, Damasio et al. 1998). However, the feedback learning task where reward and punishment learning was separately assessed, did not reveal any group differences.

Risk taking behaviour was also examined across groups and results demonstrated that only opiate dependent patients made more risky decisions than controls, while group differences between ephedrone and controls only reached trend levels.

A limitation of this study is that participants were not tested on a full battery of standard neuropsychological tasks and only two tasks assessing cognitive impulsivity were performed. However, adding further neuropsychological tests would increase testing session time significantly and would possibly lead to fatigue in the subjects. The tasks presented here were interrelated, but each was meant to assess a distinct cognitive process.

Conclusion

In summary results confirmed *'reflection impulsivity'* in patients with brain damage due to ephedrone toxicity but intact WM and feedback learning. Additional studies are needed to further delineate the behavioural and neuropsychological sequelae of this tragic and devastating consequence of illicit drug abuse in Eastern Europe. Comparison with patients with chronic manganese toxicity from other causes (Schuler, Oyanguren et al. 1957, Josephs, Ahlskog et al. 2005) who have been reported to suffer from compulsive behaviour and emotional lability (Cotzias 1958) would be of considerable interest.

Key Findings

- Ephedrone patients resembled opiate dependent patients on the beads task.
- Both patient groups gathered less information and made more irrational choices than controls.
- There was no difference in WM and risk taking behaviour between ephedrone patients and controls.
- Opioid dependent patients made significantly more risky decisions and had poorer WM compared to controls.

Chapter 4 - The role of Stress in Parkinson's disease

Introduction

It is uncertain whether chronic stress can actually cause PD despite the fact that many patients are convinced that their illness followed shortly after a period of chronic emotional strain or a particular stressful event. Further, it is unclear whether being diagnosed with PD and experiencing progressive worsening of motor symptoms might actually contribute to the development of impulsivity (Potenza, Voon et al. 2007, Lim, Evans et al. 2008). Sometimes PD patients with ICBs justify their behaviour by saying that they want to enjoy their life as long as they are physically not too disabled.

Anxiety and depression for example is more frequently seen in PD patients with ICBs than in non-impulsive PD patients (Leroi, Andrews et al. 2011). Off period dysphoria, panic attacks, withdrawal symptoms and depression are particularly common amongst PD patients with DDS and may induce compulsive overuse of medication (Lim, Evans et al. 2008).

In this chapter I speculate that chronic stress can not only temporarily worsen the symptoms of PD but can also cause nigrostriatal damage. The role of salivary cortisol levels as a surrogate marker of stress in PD patients with and without ICBs is then examined.

The idea that chronic stress can worsen PD is not new. More than 120 years ago Charcot speculated that *"acute moral emotions",* such as *"fright, terror, the sudden communication of bad news"* could influence the onset and severity of PD. Gowers later wrote that prolonged anxiety and emotional shock are "*the most common antecedents of Parkinson's disease*" and advised that sufferers refrain from *"all causes of mental strain and of physical exhaustion….Life should be quiet and regular, freed, as far as may be, from care and work."* Later in 1922 146 patients with PD were studied and the authors described 3 types of patient groups being more susceptible of developing PD: Six patients (4%) were found to have a *"history of acute mental symptoms following a shock at or before onset of the first symptom of the disease".* These stressors "occurred within a year before the onset" and symptoms included *"marked grief following death of wife, frightened by burglar, great emotional shock and strain".* The second category contained seven patients (4.8%) who had depression preceding onset of PD up to 10 years. The largest group in their cohort contained 20 patients (13.7%) who were *"very nervous, high-strung, worrisome of nervous temperament, easily upset and excited at least provocation"* (Patrick and Levy 1922). Jeliffe speculated that some symptoms of PD might be a result of some chronic conflict in the patient's life (Jelliffe 1940) and Prichard hypothesized that prolonged stress might cause irreversible chemical changes within the brain and unmasks Parkinson's disease (Prichard, Schwab et al. 1951).

A clinical study in the 1960s showed that tremor was exacerbated in PD patients under stress such as anxiety or anger (Schwab and Zieper 1965). Others reported that fatigue and emotional stress greatly reduced the effect of L-dopa therapy (Lees, Shaw et al. 1977) and that motor fluctuations can be aggravated by emotional or physical stress

(Shaw, Lees et al. 1980). Tremor in PD patients has been reported to be initially only visible in stressful situations and later on in the disease worsens in amplitude during stress (Fahn 2003).

More recently others have speculated about the link between PD and stress (Smith, Castro et al. 2002, Miller and O'Callaghan 2008) and dopaminergic dysfunction induced by stress (Pani, Porcella et al. 2000). A Swedish study showed that the incidence of developing PD was significantly increased after being admitted for a psychiatric disorder such as a mood or neurotic personality disorder, especially before the age of 50 (Li, Sundquist et al. 2008). Proneness to psychological stress has been associated not only with PD but also with other neurodegenerative diseases such as Alzheimer's disease (Kelly and Filley 2004).

Psychogenic Parkinsonism

Psychogenic parkinsonism is rare and accounts for less than 10% of all psychogenic movement disorders (Hallett 2011). Physical or mental trauma has been recognized as the major trigger factor for developing psychogenic movement disorders, even if the stressors are not acknowledged by the patient due to denial or poor insight (Hallett 2011). A significant proportion of patients considered to have psychogenic parkinsonism have underlying Parkinson's disease (Hallett 2011). For example one study examined nine patients with suspected psychogenic parkinsonism using neurophysiological assessment and ^{123}I-FP-CIT SPECT. Seven of those presented with tremor and tremor recording was compatible with the diagnosis of organic PD in

combination with psychogenic tremor in two (Benaderette, Zanotti Fregonara et al. 2006). [^{123}I]-FP-CIT SPECT scans were abnormal in five of nine patients and a final diagnosis of PD in combination with psychogenic parkinsonism was made in six of nine patients (Benaderette, Zanotti Fregonara et al. 2006). Similarly in another SPECT study two of five patients who were diagnosed having psychogenic parkinsonism had abnormal putaminal dopamine transporter tracer uptake (Felicio, Godeiro-Junior et al. 2010).

Stress induced reversible Parkinsonism

Reversible parkinsonism has been observed in seven patients who suffered from acute alcohol withdrawal. Three were followed up but none developed PD even after 9-11 years (Shandling, Carlen et al. 1990). It is possible that sympathetic overactivity may have been responsible for these cases as alcohol has been reported to aggravate parkinsonian signs in some patients with PD (Shandling, Carlen et al. 1990).

Acute alcohol intoxication has been also reported to induce cogwheeling, dystonia and akathisia in patients who are taking neuroleptic medication (Lutz 1976).

Two patients who were firmly diagnosed with PD for several years both fully recovered following the resolution of longstanding chronic stress. One of these was found to have a mildly abnormal fluorodopa PET scan and responded to L-dopa (Figure 27).

Iatrogenic, toxic and infectious causes were not identified in either case and there was no history of the use of complementary therapies.

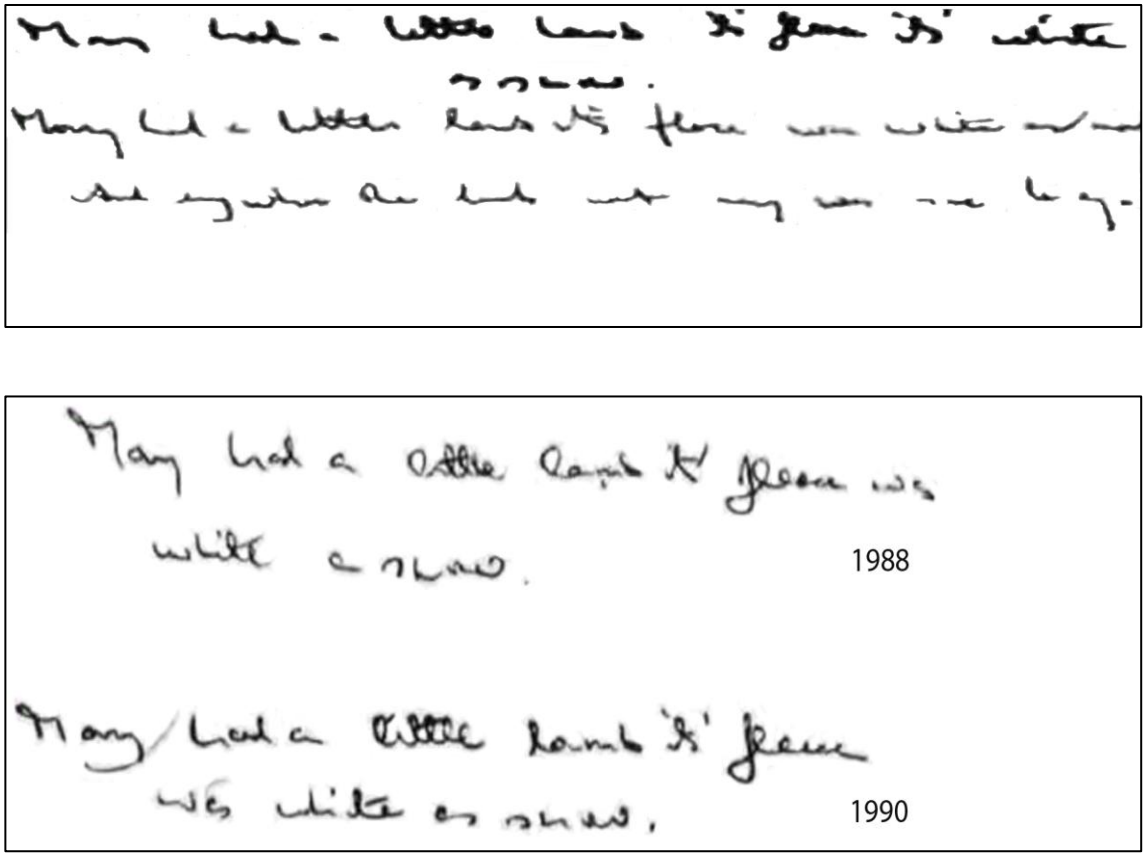

Figure 27. *Stress induced micrographia.*

Above: Small handwriting of a patient who was diagnosed with Parkinson's disease.

Below: Same patient after removal of chronic stress.

Rare examples of stress induced reversible parkinsonism were also reported amongst the casualties of *'shell shock', 'neurasthenia' and 'war neurosis'.* Chronic fatigue, joint pain, poor sleep, tremors, anxiety and *'gastric troubles'* were all commonly reported in English, German and French soldiers (Mott 1919).

Although the surviving cine films of these cases showed clear signs pointing towards a non-organic movement disorder, a few cases closely resembled PD. In his book *'War Neuroses And Shell Shock'* Mott described one World War One soldier: *"The eyes were wide open and had a pained vacant stare […], when given a paper and a pencil to write, so great was his difficulty in holding the pencil, and so pronounced was the tremor, that the pencil only marked a tangled skein on the paper [..]. He cannot move his legs, which are rigid […]. As in many of these patients the sole of the foot is shuffled along the ground. Another form of tremor which is coarser and less rapid than the preceding, viz. 5-6 per sec, is that which resembles paralysis agitans."* Others observed similar findings reporting *"On standing the head is flexed forward on the neck and protrudes in front of the body. Balance is maintained with difficulty since the trunk is flexed anteriorly and the legs are partially bent at the knees. The arms hang low and stiffly at the sides, giving a simian appearance to the whole posture. Coarse tremors develop in the hands and legs (….), the facies are mask-like without expression. The chew and swallow slowly as if wishing to keep food in their mouth"* (Ginker and Spiegel 1943). At the same time similar symptoms were observed amongst German soldiers and were referred to as 'Kriegszitterer' ("War-tremblers"). In 1940 during the battle of Dunkirk, some soldiers developed a *"coarse pill rolling tremor"* and *"nodding movement of the head"* which resembled parkinsonism. Ex-prisoners of war had a significantly higher incidence of developing PD several decades after their release in some studies (Gibberd and Simmonds 1980).

These observations emphasise that prolonged chronic stress can induce a clinical picture closely resembling PD, albeit being fully or at least partly reversible. Gowers reflected

on the body language of fear in Clifford Albutt's System of Medicine in 1904. "*If the movement of escape is impossible, tremor results, and thus we have the word tremble as a synonym for fear. He who trembles is said to be paralysed by fear, and he is, in fact, for the moment suffering from paralysis agitans.*"

Stress induced neuronal damage

Stress-induced elevated glucocorticoid levels in rodent models worsened motor performance and higher corticosterone levels led to a greater permanent loss of nigral neurons (Smith, Jadavji et al. 2008). 6-hydroxydopamine (6-OHDA) lesioned rats moved much more slowly, froze more often and became rigid when challenged with stressors but reverted to normal when left alone in their home cage (Snyder, Stricker et al. 1985). Foot-shock, tail-pinch or other stressors have all been shown to increase striatal dopamine release and turnover in rodents (Pei, Zetterstrom et al. 1990) and it has been suggested that this could excite striatal dopamine nerve terminals to death through increased oxidative stress (Hastings, Lewis et al. 1996).

Chronic stress can lead to reduced dopaminergic activity within the ventral tegmental area in rodents (Moore, Rose et al. 2001) and cause increased cortisol levels.

In rats chronic stress significantly decreased dopamine levels in the frontal cortex, striatum and the hippocampus (Rasheed, Ahmad et al. 2009). Catecholamines such as dopamine are inert when stored in vesicles but it is possible that in susceptible patients chronic stress shifts catecholamines into the cytosol where they become toxic via auto-oxidation. Oxidation of cathecholamines leads to quinones which can cause lipid

peroxidation and membrane disruption (Goldstein 2011) and might ultimately cause neurodegeneration. Support for this hypothesis comes from additional preclinical studies, which have shown that chronic stress induces oxidative stress and increased protein and lipid peroxidation (Lucca, Comim et al. 2009).

Central noradrenergic degeneration in the locus ceruleus and subsequent degeneration of nerve terminals in the hippocampus might explain cognitive impairment (Zweig, Cardillo et al. 1993) and also possibly REM sleep behaviour abnormalities (Gesi, Soldani et al. 2000). Profound cardiac noradrenergic denervation has been described in PD (Amino, Orimo et al. 2005) which might be partly responsible for fatigue (Nakamura, Hirayama et al. 2011).

Stress reduces regulatory T-lymphocytes by 50% in patients who suffered from post-traumatic stress disorder (Sommershof, Aichinger et al. 2009) and a similar profound reduction has been found in PD (Baba, Kuroiwa et al. 2005). Dysfunction of regulatory T-lymphocytes might contribute to dopaminergic cell loss and vaccination in animal models of PD with these regulatory lymphocytes can attenuate nigrostriatal degeneration (Reynolds, Stone et al. 2010).

A convincing link between chronic stress and neurodegeneration has now been established in patients with Alzheimer's disease. Emotionally stressed patients have a 2.7% higher risk of developing the disease and stressed dementia patients have a more rapid disease progression. This is likely to be due to a dysregulation of the hypothalamo-pituitary-adrenal (HPA)-axis causing dendritic remodelling, dysfunction of

neurogenesis, apoptosis in hippocampal neurons and result in increased oxidative stress (Rothman and Mattson 2010).

Variants of stress

Stress is part of modern society and without it life would be colourless and unstimulating. “Good stress” is often referred to as short self-limiting and has been demonstrated to improve the immune system (Segerstrom and Miller 2004). Short outbursts of stress, such as ‘examination nerves’, evoke “fight and flight” reactions, via the sympathetic nervous system, which releases catecholamines.

In contrast chronic stress or “bad stress” is emotional draining, physically exhausting and induce wear and tear on brain and body. The inability of shutting down stress induced activation of the HPA is the hallmark of chronic stress (McEwen 2007) and can adversely affect the immune system (Segerstrom and Miller 2004). The *“weathering hypothesis”* suggests that socioeconomic stressors might lead to accelerate aging (Geronimus 1992). Indeed life-style diseases such as diabetes, gastric ulcers or hypertension have been linked to chronic stress (Liu and Mori 1999).

Stress in the prenatal period or during aging was also associated with a reduction in hippocampal volume later in life and with depression (Lupien, McEwen et al. 2009). The *“Glucocorticoid Cascade Hypothesis“* states that chronic stress induced prolonged exposure to high levels of glucocorticoids results in hippocampal atrophy which then in return causes higher glucocorticoid levels and more hippocampal damage (Sapolsky, Krey et al. 1986). Furthermore, glucocorticoid levels in the aged population have been

linked with memory impairment and to a 14% reduction in the volume of the hippocampus (Lupien, Fiocco et al. 2005). Stress can cause dendritic retractions and neuronal atrophy within the hippocampus (Conrad 2008), the striatum (Smith, Jadavji et al. 2008) and triggers neuroplasticity resulting in sensitization or habituation within the stress processing network, containing the limbic system, the hypothalamus and the brainstem (Ulrich-Lai and Herman 2009).

Kinesia paradoxica in Parkinson's disease

In rare instances, such as acute life threatening stress, PD patients can dramatically override motor handicap which has been called paradoxical kinesia (Souques 1921). Such rare examples have been observed during an earthquake, after a car crash or during war (Bonanni, Thomas et al. 2010). There are, however, other occasions when PD patients can overcome bradykinesia without any strong emotions. In 1967 Purdon-Martin demonstrated that white lines on the floor could reduce festination and freezing in patients with post encephalitic parkinsonism (Purdon-Martin 1967). Immobile patients have been shown to catch a ball when thrown at them (Schlesinger, Erikh et al. 2007) and videos of PD patients who show improvement of freezing and festination during ball games can be found online (http://www.pmarc.ed.ac.uk/video/intrinsic-basis-of-action/paradoxicalmovement.html).

Similarly rhythmic auditory cues have been reported to improve velocity and stride length in PD (Rubinstein, Giladi et al. 2002) and loud unexpected auditory stimuli

improved reaction time and grip force in PD patients, which was independent of the medication state (Anzak, Tan et al. 2011).

Following mechanisms have been postulated to explain paradoxical kinesia in PD:

Acute severe stress can lead to noradrenalin activation, which then increases alertness and attention and might result in improved motor function (Schlesinger, Erikh et al. 2007). Consistent with this, rats treated with haloperidol and showing motor impairments could overcome their motor deficits by stress induced noradrenalin activation (Keefe, Salamone et al. 1989).

Activation of the basal ganglia reserves due to fear of reward might also induce paradoxical kinesia. PET studies have shown ventral striatal dopamine release in PD patients after administration of placebo, which was of similar magnitude to that found in controls after given amphetamine (de la Fuente-Fernandez, Phillips et al. 2002). Therefore anticipation of an event, such as reward or fear might also result in motor benefit.

Whilst under these exceptional mechanisms motor performance improves, chronic anxiety and stress might result in reduction of striatal dopaminergic cells and lead to dopamine dysfunction (Moore, Rose et al. 2001), which might explain worsening of motor handicaps in PD.

Stress induced functional somatic syndromes

Fibromyalgia

Fibromyalgia is a chronic disorder characterized by widespread pain of unknown aetiology. In 1904 William Gowers introduced the term *'fibrositis'* which he observed to occur frequently in elderly ladies (Gowers 1904). The term '*fibrositis'* was modified in the mid-70s (Inanici and Yunus 2004) in order to emphasise that it is characterised by *myalgia* (muscle pain) and that there is no evidence of inflammation (Smythe and Moldofsky 1977). According to the American College of Rheumatology the diagnostic criteria for fibromyalgia include diffuse pain for at least 3 months and pain on palpation in at least 11 of 18 tender points (Wolfe, Smythe et al. 1990). A tender point is considered to be positive when 4kg of pressure has been applied (Schmidt-Wilcke and Clauw 2010). Although both genders can be affected fibromyalgia is diagnosed ten times more often in females (Wolfe, Smythe et al. 1990). The arbitrary cut off of 11/18 positive tender points might artificially skew the gender distribution and make fibromyalgia look like an almost exclusively female disorder (Clauw and Crofford 2003). However, all functional somatic syndromes are more commonly seen in females and some have speculated that biological and psychological changes are responsible for gender differences (Yunus 2001).

Hyperalgesia (increased discomfort to painful stimuli) or allodynia (pain to non-painful stimuli) are other key components of fibromyalgia. Prevalence rates range from 0.5% to

5.8% and comprise 15% of referrals to rheumatology clinics (Neumann and Buskila 2003, Hauser, Thieme et al. 2010).

The mean age of onset is typically in the fifth decade of life (Wolfe, Smythe et al. 1990), although younger onset cases do occur (Eraso, Bradford et al. 2007). Apart from pain patients often complain of a variety of co-morbidities including mild orthostatic hypotension (Bou-Holaigah, Calkins et al. 1997), insomnia (Moldofsky 2002), urinary frequency and urgency (Wolfe, Smythe et al. 1990, Littlejohn 1996), depression, anxiety and chronic fatigue (Chakrabarty and Zoorob 2007). Forgetfulness and poor concentration often referred to as *'fibrofog'* occur in up to 90% of affected individuals (Bennett, Jones et al. 2007, Schmidt-Wilcke and Clauw 2010).

Clinical guidelines have suggested the '*FIBRO'* mnemonic in patients with fibromyalgia, where 'F' stands for fatigue, 'I' for insomnia, 'B' for blues (depression and anxiety), 'R' for rigidity and 'O' for ow! (pain and disability) (Boomershine and Crofford 2009).

Chronic fatigue syndrome

Chronic fatigue syndrome, also sometimes called *'myalgic encephalomyelitis'* in the UK, is characterized by a period of persistent fatigue lasting at least six months and accompanied by four of eight 'minor' symptoms: impaired memory; sore throat; tender cervical or axillary lymph nodes; muscle pain, multi-joint pain without joint swelling or redness; stiffness; new headaches; unrefreshing sleep and post-exertional malaise (Fukuda, Straus et al. 1994).

It has been defined as severe mental and physical exhaustion, which is not attributable to exertion or diagnosable disease (Fukuda, Straus et al. 1994). Urinary frequency and urgency, painful bladder syndrome and psychiatric comorbidities such as major depression and anxiety are also frequently reported (Lane, Manu et al. 1991, Nickel, Tripp et al. 2010). Females are predominantly affected, with a peak age of presentation in the fourth and fifth decades of life. Estimates of prevalence vary between 0.007% and 2.8%. However, chronic fatigue, defined as fatigue failing the diagnostic criteria of chronic fatigue syndrome, is common in the UK with a prevalence rate up to 11% (Wessely, Chalder et al. 1997).

In many parts of the world chronic fatigue syndrome is not recognised but a similar and possibly identical malady termed neurasthenia is. Neurasthenia is a more generic term embracing all cases of chronic fatigue syndrome and usually overlaps with depression (Harvey, Wessely et al. 2009).

Irritable bowel syndrome

Irritable bowel syndrome (IBS) is defined as chronic abdominal pain and bowel dysfunction without evidence of abnormalities on physical examination. Women are three to four times more likely to develop IBS with a peak incidence between ages 30 to 50. Estimated prevalence rates range between 4.4% up to 21% (Drossman, Camilleri et al. 2002). IBS is associated with a variety of different medically unexplained co-morbidities such as poor sleep, chronic back pain, palpitation and headaches (Riedl, Schmidtmann et al. 2008). Fibromyalgia is also common in IBS patients with a

prevalence rate between 26-65% (Sperber, Atzmon et al. 1999, Riedl, Schmidtmann et al. 2008).

Chronic fatigue syndrome in IBS has been less well studied but has been considered to be common by some authorities (Wessely, Nimnuan et al. 1999). Excessive sleepiness during the day is also commonly seen in IBS (Sperber and Tarasiuk 2007). Conversely, IBS occurs in up to 51% of patients with chronic fatigue syndrome (Whitehead, Palsson et al. 2002). Urinary urgency, frequency, nocturia and incomplete bladder emptying occur in about half of all patients with IBS and quoted figures for sexual dysfunction range from 24% to 83% (Riedl, Schmidtmann et al. 2008). Psychiatric comorbidities, such as panic and anxiety disorder and major depression are also frequent with a prevalence range just under 50% (Lydiard 2001).

Clinical overlap between functional somatic syndromes and Parkinson's disease

Musculoskeletal pain, unusual pelvic and rectal discomfort, poor sleep, fatigue and depression, features characteristic for functional somatic syndromes, are common in PD (Gallagher, Lees et al. 2010). Mental fatigue, sometimes referred to as *'central fatigue'*, a typical feature of patients with chronic fatigue syndrome, can be found in up to 70% of PD patients at some stage of the illness (Friedman, Abrantes et al. 2011). Chronic fatigue, depression and anxiety can sometimes lead to the misdiagnosis of a functional disorder, especially in younger patients and delay appropriate treatment for several decades (Ling, Braschinsky et al. 2011).

Fatigue was a common feature of the pandemic of encephalitis lethargica of 1916-1929. A relatively frequent sequelae of the neurasthenic phase of the illness was parkinsonism while other patients appeared to recover only to develop parkinsonism months or years later. Similarly during an outbreak of chronic fatigue syndrome in the 1940s (Akureyi myalgic encephalomyelitis) three children are said to have died of juvenile PD (Gibson, Taylor et al. 2011).

Features of IBS including abdominal bloating, and alternating diarrhoea and constipation occur commonly in PD (Edwards, Pfeiffer et al. 1991). Constipation, a variant of IBS associated with more abdominal colic and bloating than the IBS-diarrhoea variant (Talley, Dennis et al. 2003), is one of the most common non-motor complains of patients with PD (Savica, Rocca et al. 2010) and may precede bradykinesia, rigidity and tremor (Ashraf, Pfeiffer et al. 1997). The long term follow up studies of the Honolulu-Asia Aging Study showed that constipation was associated with a higher risk of developing PD (Abbott, Petrovitch et al. 2001) and those who had constipation without PD had significantly lower substantia nigra neuronal densities and more incidental Lewy body pathology in the substantia nigra (Petrovitch, Abbott et al. 2009).

Lewy neurites have been also found on routine colonoscopies in 72% of PD patients a finding which correlated significantly with disease severity (Lebouvier, Neunlist et al. 2010).

Conversely, symptoms that are typical for PD have been found in patients with functional somatic syndromes. For example over 75% of patients with chronic fatigue

complain of ‘slow thinking’ (Lane, Manu et al. 1991), which can be an early feature of PD often referred to as bradyphrenia. Slowness of initiation of movement is seen in retarded depression and in common with PD it can be partially overcome by external cues (Rogers, Bradshaw et al. 2000). Reduction in stride length, slowness, impairment of flexing and bending knees and hips and trouble keeping up on treadmills all occur in patients with chronic fatigue syndrome (Boda, Natelson et al. 1995). Further, a reduction in velocity during simple and complex hand movements and a similar 3-5 bursts electromyography pattern during task performance has been observed in both depression and PD patients (Sachdev and Aniss 1994).

Restless legs syndrome (RLS) and muscle and joint stiffness are frequently reported by patients with fibromyalgia (Stehlik, Arvidsson et al. 2009) as are tremor, stiffness and poor coordination (Wolfe, Smythe et al. 1990). Olfactory dysfunction with increased sensitivity to unpleasant smells and reduced appreciation of pleasant odours has been also described in fibromyalgia (Schweinhardt, Sauro et al. 2008) and PD.

Pharmacological studies further strengthen a potential link between fibromyalgia, chronic fatigue and PD. Pramipexole significantly improved pain and fatigue in fibromyalgia after 14 weeks of treatment (Holman and Myers 2005). However, this result could not be replicated with two other dopamine agonists, ropinirole and rotigotine (GlaxoSmithKline. 2008, UCB-News. 2009). A significant proportion of treated patients developed pathological gambling or compulsive shopping after dopamine agonist treatment (Holman 2009).

In PD, L-dopa has been found helpful for physical fatigue (Lou, Kearns et al. 2003) but treatment of non-motor fatigue in PD has proved more challenging (Friedman, Abrantes et al. 2011). Although amantadine is often empirically used to treat fatigue in PD, no controlled studies have been published (Friedman, Abrantes et al. 2011) and amantadine is said to be ineffective in chronic fatigue syndrome (Plioplys and Plioplys 1997).

On the other hand trials with the selective Type B monoamine oxidase inhibitor selegiline and the dopamine and noradrenaline reuptake inhibitor bupropion have shown efficacy in reducing central fatigue (Pae, Marks et al. 2009).

Striato-thalamo-cortical alterations in functional somatic syndromes

Dopamine plays an essential role in pain modulation. Electrical stimulation of the basal ganglia or administration of dopaminergic agents can reduce defensive reaction to pain in animals (Magnusson and Fisher 2000). In contrast blocking endogenous dopamine release or lesioning dopaminergic pathways increases nociception (Magnusson and Martin 2002). In PD for example L-dopa administration can significantly reduce pain (Nebe and Ebersbach 2009).

Increased prolactin response to buspirone, a partial dopamine antagonist that acts on the pituitary gland, provided indirect evidence for altered dopamine D2 receptor dysfunction in patients with fibromyalgia (Malt, Olafsson et al. 2003), chronic fatigue

syndrome (Sharpe, Clements et al. 1996) and also in patients with non-ulcer dyspepsia, which is part of irritable bowel syndrome (Dinan, Mahmud et al. 2001).

In fibromyalgia low concentrations of dopamine metabolites in the cerebrospinal fluid (Russell, Vaeroy et al. 1992), decreased 6-[(18)F]fluoro-DOPA tracer uptake within the ventral tegmental area and the substantia nigra (Wood, Patterson et al. 2007) and blunted dopamine release in response to painful stimuli have been reported (Wood, Schweinhardt et al. 2007).

Reduction in cerebral blood flow in the caudate nucleus and the thalamus were found in both fibromyalgia (Mountz, Bradley et al. 1995, Kwiatek, Barnden et al. 2000) and chronic fatigue syndrome (Costa, Tannock et al. 1995). In addition, reduced cerebral blood flow in the anterior cingulate has been found in patients with chronic fatigue (Schmaling, Lewis et al. 2003). Dysfunction in the anterior cingulate is particularly interesting since it is known to have the greatest dopamine innervation in the cortex (Lewis, Foote et al. 1988) and has been associated with depression and apathy in PD (Remy, Doder et al. 2005).

Functional magnetic imaging (fMRI) studies in IBS patients showed significant deactivation of the amygdala, the right cortex and the basal ganglia after inducing rectal pain (Bonaz, Baciu et al. 2002). Further, in these patients a significantly reduced striatal dopamine D2 receptor binding in the caudate nucleus was found (Braak, Booij et al. 2012).

This data raises the possibility that changes in the striato-thalamo-cortical loops due to reduction in dopamine activity may be responsible for fatigue (Chaudhuri and Behan

2000), pain, IBS and other neuropsychiatric symptoms commonly found in functional somatic syndromes. In support of this notion, axonal damage in the striato-thalamo-cortical loops has been associated with fatigue in patients with multiple sclerosis (MS) (Calabrese, Rinaldi et al. 2010) and with post stroke fatigue due to lacunar infarcts (Tang, Chen et al. 2010).

The prodrome of Parkinson's disease

Onset of PD is gradual and it is often difficult to determine when exactly bradykinesia and rigidity appear. Several studies have found that PD patients have a lower premorbid risk of smoking, and tend to be anhedonic, moralistic, punctual, risk averse and altruistic with a strong adherence to social norms (Todes and Lees 1985). This has led to the concept of the "*Parkinsonian personality"* suggesting that these patients are more likely to be emotionally inflexible, and of a neurotic type (Todes and Lees 1985), which has been, however, challenged more recently (Arabia, Grossardt et al. 2010).

Ray Kennedy, the Arsenal and Liverpool international football player described non-motor symptoms at least 14 years before the diagnosis of PD was made. *"I realised that nobody had my after match routine. Usually the adrenaline is still pumping and most of the lads would be talking about what happened on the pitch, grabbing a coke or chicken leg. They were always doing something-all except me. I used to slump hunched in my seat too tired to talk or move"* (Lees 1992).

Recent papers have attempted to retrospectively examine the nature and frequency of these non-specific features before the diagnosis of PD. Gonera and colleagues

performed a retrospective case control study where the authors studied the primary health care medical records of 60 PD patients and 58 controls over the 10 years prior to the diagnosis of PD. During this period the PD patients had visited their GPs more frequently than age matched controls and had complained of more symptoms (Gonera, van't Hof et al. 1997). Neuropsychological complaints which were reported in almost half of the PD cases included depression, anxiety and nervousness. Musculoskeletal symptoms were equally common and included low back pain, shoulder pain, arthralgia and ischialgia. Further, 68% of these patients had fibromyalgia before the motor onset of PD (Gonera, van't Hof et al. 1997). In another study frozen shoulder was the initial complain of 8% of patients who developed PD up to 2 years later (Riley, Lang et al. 1989).

Symptoms suggestive of autonomic dysfunction such as fainting, cardiovascular disturbances including hypertension, arrhythmia and angina and other symptoms such as pain, paraesthesia, headache and memory problems were also recorded more common in PD patients than controls (Gonera, van't Hof et al. 1997). Another interesting finding was that 18% of these patients had complained of diarrhoea for which no specific cause was found (Gonera, van't Hof et al. 1997) raising the possibility that this was irritable bowel syndrome.

A significantly higher frequency of medically unexplained symptoms has been associated with PD (7%) and dementia with Lewy bodies (12%) compared with other neurodegenerative diseases such as MSA, PSP and Alzheimer’s disease (0-3%). The most common symptoms found were multilocalized pain with gastrointestinal

symptoms, hypochondriasis and paresis. These somatoform disorders preceded the diagnosis of PD by from 6 months up to 10 years (Onofrj, Bonanni et al. 2010). These findings raise the possibility that functional somatic syndromes can be a premotor feature of PD.

In another study structured telephone interviews using non-motor and motor questionnaires, were applied retrospectively to assess in 93 PD patients their perception of the prodromal phase of PD. Hyposmia, disturbed sleep, depression, apathy, moodiness, increased sweating and constipation were the most frequently reported symptoms in the decade prior to the diagnosis of PD (Gaenslen, Swid et al. 2011).

The cardinal motor features of PD only emerge when about 30% of dopaminergic neurons are damaged (Cheng, Ulane et al. 2010) and nigral cell loss may begin about 7 years before the first motor symptoms appear. Alpha synuclein on colonic biopsy was found 2-5 years prior to the onset of motor symptoms (Shannon, Keshavarzian et al. 2012) but Braak and colleagues based on neuroanatomical studies in which they used Lewy bodies as a surrogate marker for nerve cell dysfunction have claimed that the disease may begin much earlier than this in the enteric nervous system, sympathetic ganglia, olfactory bulb and medulla oblongata (Braak, Del Tredici et al. 2003). Non-motor complaints were the initial presentation of 21% of pathologically proven PD cases. Pain (53%), urinary dysfunction (16.5%), anxiety and depression (12.1%) were the most commonly reported complaints (O'Sullivan, Williams et al. 2008). There is no data on the prevalence of chronic fatigue in the prodromal stage of PD but it is

recognised by experienced neurologists that fatigue frequently accompanies the earliest motor symptoms.

Conclusion

Hypersensitivity to stress is thought to be genetically determined (Gilad and Gilad 1995) and variations in the serotonin 5HTR2C receptor have been associated with greater cortisol release and emotional responses to mental stress (Brummett, Kuhn et al. 2012).

Insufficient stress coping strategies may therefore lead to dopaminergic cell loss and may ultimately trigger PD in susceptible individuals. Chronic emotional stress can result in alterations of DNA methylation which is known to regulate α-synuclein expression (Babenko, Kovalchuk et al. 2012). A stochastic event triggered by chronic emotional stress might therefore explain why a pair of identical twins who were both Leucine-rich repeat-kinase type 2 (LRRK2) carriers showed a discordant phenotype after more than ten years of follow up (Xiromerisiou, Houlden et al. 2012). Screening PD patients and patients with functional somatic syndromes for polymorphisms that are known to be important for stress regulation may represent one important future line of epigenetic research.

Physical exercise was associated with a reduced risk of PD later on in life (Thacker, Chen et al. 2008), and is also a recognized approach to stress management. Randomized controlled studies assessing whether a significant reduction of chronic stress, achieved for example with cognitive behavioural therapy (Fjorback, Arendt et al. 2011), may also lead to a reduced incidence of PD would be of significant interest.

Prospective long term follow up studies in the middle aged population measuring stress hormones such as cortisol levels from hair, which has shown to be a valid biomarker for measuring the long-term cortisol secretion (Meyer and Novak 2012), and inflammatory markers such T-lymphocytes may further clarify the role of stress in PD.

Key Findings

- It is possible that chronic emotional stress causes striatal damage in susceptible individuals and triggers PD.
- Emotional stress can lead to reversible symptoms that resemble PD, including tremor, gait disturbance and postural instability.
- Acute short lasting life-threatening stress can temporarily improve bradykinesia in PD. Conversely, chronic stress can worsen motor symptoms in patients with PD.

4.1. The role of cortisol in Parkinson's disease

Introduction

It has been difficult to confirm the adverse effects of chronic stress in PD with biological measures. However, in animal models of PD elevated cortisol levels have been associated with dopaminergic cell loss and motor handicap (Smith, Jadavji et al. 2008). Higher cortisol levels have been described in depression (Bhagwagar, Hafizi et al. 2005), anxiety (Vreeburg, Zitman et al. 2010) and also in Alzheimer's disease and PD (Hartmann, Veldhuis et al. 1997). An acute increase of cortisol levels has been reported during intake of illicit drugs (Goeders 2002). Although a large proportion of addiction-related research has highlighted the importance of dopaminergic pathways (Koob and Volkow 2010), there is also a line of evidence supporting the role of cortisol in the development of addictive or impulsive behaviours (Lovallo 2006, Koob and Kreek 2007). Given the link between cortisol and addiction in the non-PD population (King, Jones et al. 1990), and between addiction and the development of ICBs in PD, the hypothesis was that cortisol levels might be lower in impulsive PD patients relative to PD patients without ICBs.

In this study, salivary cortisol levels from PD patients with (PD+ICB) and without ICBs (PD-ICB) and healthy controls were measured and correlated with the performance on a risk task (Huettel, Stowe et al. 2006). Increased salivary cortisol levels have also been positively correlated with risk taking in non-PD pathological gamblers (Meyer, Hauffa

et al. 2000). Therefore, a correlation between cortisol and risk taking behaviour was made.

Patients and methods

Cortisol samples from 13 PD-ICB, 15 PD+ICB patients and 14 healthy controls were collected. All patients were recruited from the National Hospital for Neurology and Neurosurgery Queen Square, London, fulfilling the Queen Square Brain Bank criteria for PD (Gibb and Lees 1988) and were taking L-dopa. PD+ICB patients were diagnosed using proposed criteria (Evans, Katzenschlager et al. 2004, Voon, Thomsen et al. 2007). Most PD+ICB patients had more than one ICB. Healthy controls were usually recruited from amongst the patient's partners and were not taking any medication that could influence cortisol measurement. None of the participants was taking steroids. Written informed consent was obtained from all subjects according to approved ethical protocols from the regional and local research ethics committee. Participants who scored under 27/30 points on the MMSE and who had a current or past medical history of an anxiety disorder and patients with current depression were excluded. Patients without a known previous diagnosis of anxiety or depression were screened for these conditions in a semi-structured clinical assessment. Further, all participants were asked to fill out the positive and negative affect schedule (PANAS), which has been recommended to use as a supplement to measure anxiety and depression (Crawford and Henry 2004). Samples were obtained in a quiet environment usually at patient's homes to control for and reduce the amount of stress. To control for the potential effects of food (Van Cauter,

Kerkhofs et al. 1992) and L-dopa (Muller and Muhlack 2007) on cortisol levels, PD patients were asked not to take their usual anti-Parkinson medication for at least 12 hours and not to have breakfast on the day of testing. All participants woke up between 6.00 a.m. and 7.00 a.m. The morning samples were obtained together with me and the other samples were collected by the participants themselves.

Cortisol

Participants were instructed to collect saliva samples by turning the cotton roll for 2-3 min in their mouth. In total five saliva samples were collected from controls and 10 samples from patients. Samples from all participants were obtained between 8.15 a.m. and 8.45 a.m. -baseline level. All patients were tested in their "off condition" in the morning, which was assessed by the UPDRS (part 3) motor score. Further, five more saliva samples were collected from the patient group. One was obtained immediately prior to the risk task, one just after the risk test and prior to medication, the next 5 min after medication, then 15 min after medication, 30 min after medication and 45 min after medication. Sixty minutes after medication between 9.15 a.m. and 9.45 a.m. and after the second test ("on condition" in patients) another sample was taken, this time from both groups controls and patients (Figure 28). All participants then collected samples between 1-2 p.m., between 7-8 p.m. and 10-11 p.m. on their own. These times were deliberately flexible for patients to ensure that the cortisol sampling was undertaken approximately one hour after taking their usual dopamine replacement therapy. Controls were tested in the same way without taking any medication in between.

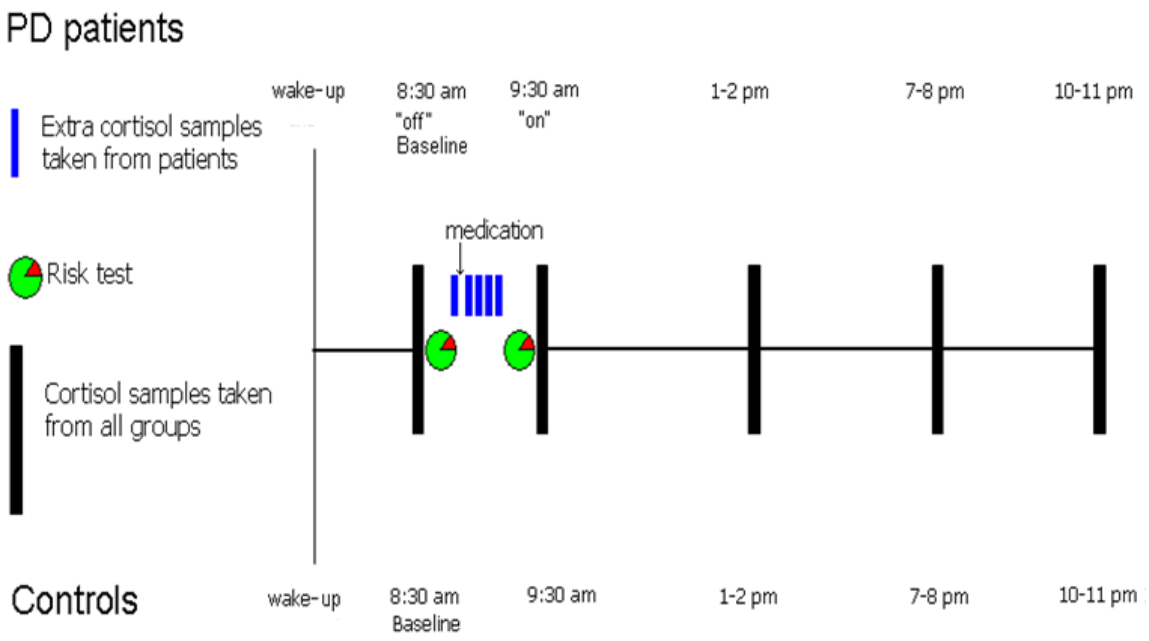

Figure 28. *Schematic outline of the time course of saliva samples.*

Ten salivary samples were obtained from patients and five samples from controls. Subjects were asked to avoid excessive physical activity, stress and heavy meals on the study day, and were provided with a collection diary where they entered the time of saliva collection and their activity during the hour prior to each cortisol sample. In addition participants were instructed not to eat anything at least 30 min prior to collecting a sample. The therapeutic motor response to L-dopa was assessed by UPDRS scores (part 3) during “off” and “on” state. All patients had an excellent L-dopa response and had a similar improvement in the UPDRS scores (see Table 18). All patients were “on” at the time of the second risk task. LEU (Levodopa equivalent units) was calculated as described previously (Evans, Katzenschlager et al. 2004).

	Controls	PD-ICB	PD+ICB	t-value F-value χ^2	p value
Participants in total (no.)	14	13	15		
Gender (male)	6	11	10	χ^2=5.2, df=2	p=0.075
Age (yrs)					
At time of testing (yrs)	58 ± 3	64 ± 2	56 ± 3	F=2.5, df=2	p=0.09
At disease onset (yrs)	-	52 ± 2	43 ± 3	t=2.6, df=24	p=0.014*
	-				
Disease duration (yrs)	-	11 ± 2	12 ± 2	t=0.4, df=24	p=0.7
Pathological Gambling	-	-	9		
Hypersexuality	-	-	6		
Compulsive Shopping	-	-	5		
Binge Eating	-	-	4		
Punding	-	-	2		
Morning L-dopa dose (mg)	-	170 ± 22	185 ± 25	t=0.4, df=24	p=0.6
Total L-dopa dose (mg)	-	580 ± 74	625 ± 100	t=0.3, df=24	p=0.7
LEU dose (mg)	-	722 ± 85	797 ± 100	t=0.5, df=24	p=0.6
DA (patients)	-	8	5	χ^2=1.6, df=1	p=0.2
UPDRS OFF medication	-	25 ± 1	32 ± 4	t=1.9, df=24	p>0.07
UPDRS ON	-	14 ± 2	19 ± 3	t=1.8, df=24	p=0.08
Average improvement in UPDRS (%)	-	44	41		

Table 18. *Cortisol: Demographic characteristics.*

UPDRS = Unified Parkinson's Disease Rating Scale; LEU = L-dopa equivalent units; DA = dopamine agonists. All values are mean ± sem. Significant difference is labelled with "". Controls, Parkinson's disease without (PD-ICB) and with impulsive compulsive behaviour (PD+ICB).*

Risk task

All patients were tested on a validated computerized gambling task to assess risk behaviour (Huettel, Stowe et al. 2006) as described in chapter 3. PD patients performed the task once in their "off medication" state after their first salivary cortisol sampling, and once in their "on medication" state approximately 50 minutes after receiving their usual morning anti-Parkinson medications. Controls were tested in the same way but did not take dopaminergic medication between the tests. Participants had to choose between two gambles with varying levels of risks – either a low risk or a high risk gamble, where participants could win real money. Feedback was given immediately. For further details see chapter 3.1.

Biochemical measurements

Saliva samples for the determination of cortisol concentration were collected in "Salivettes" (Sarstedt, Leicester, UK) and stored at -20 Celsius until analysed. Saliva cortisol concentrations were determined using the chemiluminescence assay of "Immulite"- DPC's automated Immunoassay analyser (Babson 2001) and the aid of a Robotic Sample processor (Tecan Genesis 100). Details about the analysis were published elsewhere (Mondelli, Dazzan et al. 2010).

Statistical analysis

Demographic and clinical features

Data analyses were performed using SPSS, version 18. Age, gender, age of onset UPDRS scores, L-dopa and LEU dose were used as dependent variables and group (PD-ICB, PD+ICB and control) was modeled as a between subject factor. An ANOVA, t-test or χ^2 test was used where appropriate.

Cortisol Salivary samples

The data was positively skewed as cortisol levels show a diurnal variation with a peak during the morning (Figure 29A and B). As a result the data was log transformed and residuals were checked and found to be normally distributed.

A linear mixed model ANOVA was performed with the log transformed scores as the dependent variable, group (PD-ICB, PD+ICB and control) was modeled as a between subject factor. The model also included subject as a random factor, and the interactions between the two fixed factors (time and group).

All post-hoc comparisons were corrected by the Bonferroni method, the level of significance was $p < 0.05$. For the diurnal cortisol measurement those extra samples that were obtained from the patients between the tests were excluded.

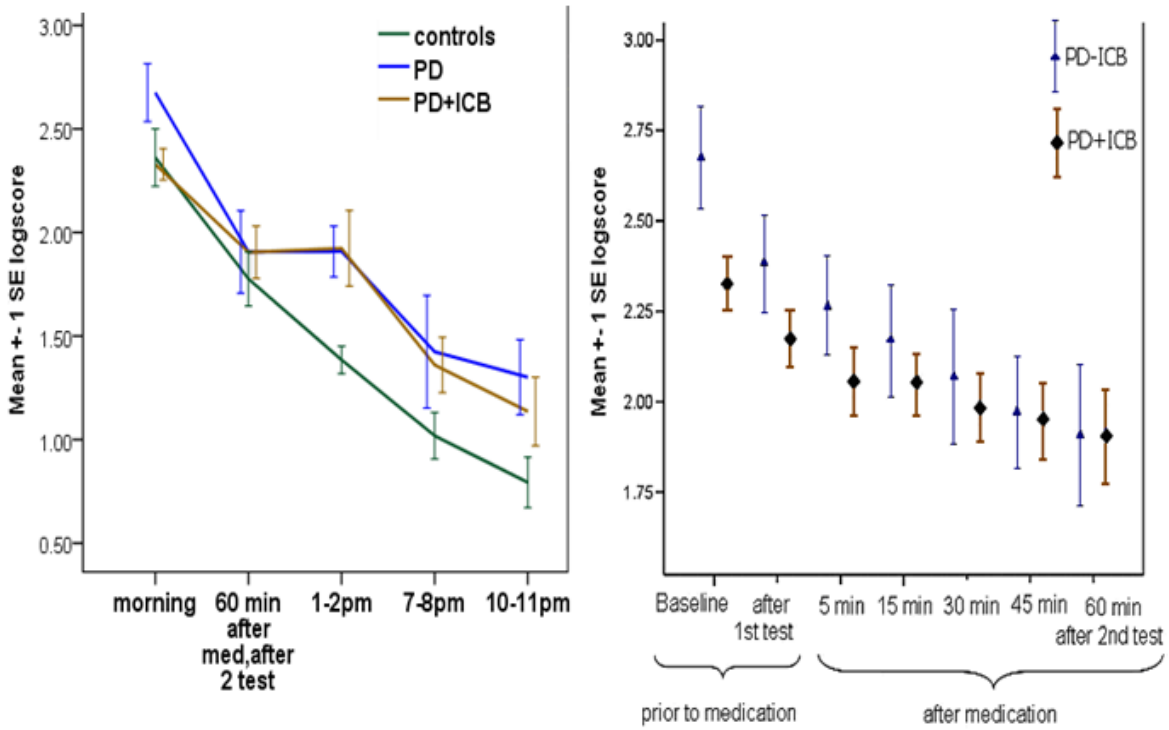

Figure 29. *Cortisol levels of participants.*

A: Diurnal cortisol levels of all three groups. B: Cortisol levels between Parkinson's disease patients without (PD−ICB) and with (PD+ICB) impulsive compulsive behaviour. All values are mean (±1 SE). Although not significantly different, baseline morning cortisol levels were lower in the PD+ICB group.

Risk task

Changes in risk aversion and change in cortisol levels was correlated. This is a within-subjects analysis. Specifically, the correlation coefficient was calculated between: ΔR and ΔC, where $\Delta R = R_1 - R_2$ is the difference in risk aversion in the first and second test session, ΔC was defined accordingly for cortisol levels. One value for ΔR and one for

ΔC was derived for each subject, and these values were then correlated using Pearson's correlation test.

Results

Demographic characteristics

Groups were generally well matched. There was no significant age difference between the groups $F_{(2,38)} = 2.5$, $p = 0.091$. However, PD+ICB patients had an earlier disease onset ($t_{24} = 2.6$, $p = 0.014$). There was no difference in the daily L-dopa doses or the dose given in the morning, LEU dose, UPDRS (part 3) scores or disease duration (see Table 18).

Cortisol levels

There was a main effect of group ($F_{(2,37)} = 4.6$, $p = 0.016$) and a main effect of time ($F_{(4,144)} = 51.0$, $p < 0.001$), with the highest cortisol level being in the morning.

There was no interaction between time and group, ($F_{(8,144)} = 0.9$, $p = 0.48$). Post hoc analysis revealed that the PD-ICB group had significantly higher cortisol levels than the control group ($p = 0.019$) (Figure 30). There was no difference between the control and the PD+ICB group ($p = 0.1$) and no difference between the patient groups ($p = 1.0$). There was no significant difference in the morning cortisol levels between the patient groups after excluding the control group ($t_{24} = 2.4$, $p = 0.2$). There was also no correlation between UPDRS off score and baseline cortisol levels, (all p-values > 0.4).

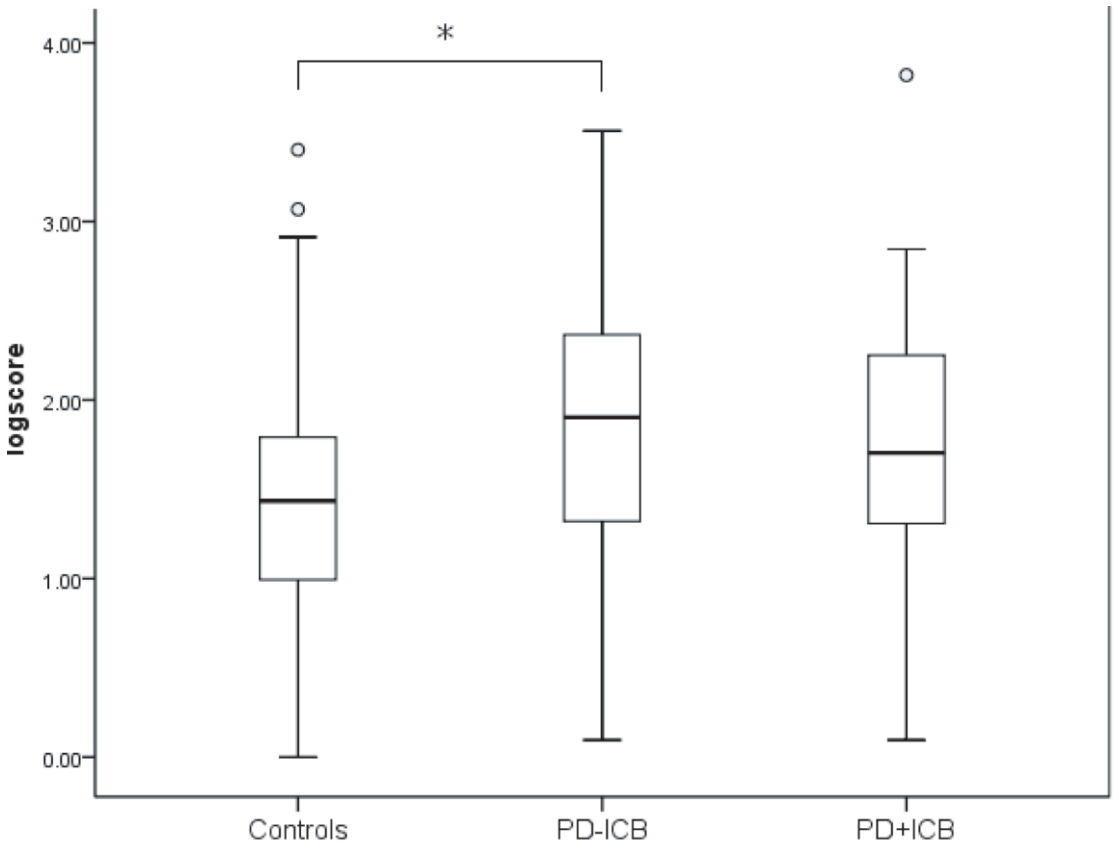

Figure 30. *Log scores of diurnal salivary cortisol levels.*

*Controls, PD−ICB and PD+ICBs. Box plot showing the median (horizontal line) within a box containing the central 50% of the observations (the upper and lower limits of the box are the 75th and 25th percentiles). Outliners are shown as a circle symbol. *Significant difference.*

Risk task

Participants were tested twice on a behavioural task that assessed risk taking behaviour (Huettel, Stowe et al. 2006), once off medication and once on medication. Cortisol samples were taken just before each administration of the task. The task assessed the extent to which participants preferred large, low probability rewards to smaller more probable rewards.

This study focusses on the relationship between cortisol and risk taking behaviour. In the PD+ICB group, there was a significant correlation between change in risk from the first to the second test session (from the off medication state to the on medication state) and change in cortisol levels measured just before each test session ($r = -0.617$, $p = 0.0144$, $n = 15$). Specifically, increased risk preference was associated with increased cortisol levels. In the PD-ICB group the correlation was not significant ($r = 0.166$, $p = 0.669$, $n = 11$).

Furthermore, the correlation coefficients were significantly different between the PD-ICB and the PD+ICB groups ($Z = 1.99$, $p = 0.047$), such that there was a significantly stronger correlation in the PD+ICB group than in the PD-ICB group.

Discussion

As expected, cortisol levels were found to be highest in the morning in all participants and decreased over the day (Figure 25A). Furthermore, results showed a significantly higher daily salivary cortisol levels in PD-ICB patients compared to healthy controls but no difference between PD+ICB patients and controls. Increased irritability and lability, higher scores of disinhibition and novelty seeking and a previous history of addictive behaviours have been reported in PD+ICB patients (Voon, Thomsen et al. 2007, Siri, Cilia et al. 2010).

In this study, it is not possible to determine whether changes in cortisol are a cause or effect of the impulsive-compulsive behaviours. However, impulsiveness, carelessness, and aggressive behaviour have been associated with attenuated cortisol levels in adolescences and adults (Bergman and Brismar 1994, Ramirez 2003, Susmann 2006). Impulsive adults with illicit drugs abuse (King, Jones et al. 1990), patients with antisocial behaviour (Susmann 2006) and controls with reduced negative feedback learning (van Honk, Schutter et al. 2003) had also lower cortisol levels. Increased temporal discounting, the tendency to choose earlier, smaller over delayed, larger rewards has been found only in PD+ICB patients (Housden, O'Sullivan et al. 2010) and has been associated with attenuated cortisol levels in healthy controls (Takahashi 2004).

However, there was no difference between the two patient groups and between the control and PD+ICB group. Previous studies found sustained elevated cortisol levels in Aborigines after receiving their wages which they planned to gamble with (Schmitt, Harrison et al. 1998). Therefore, the expectance of being tested, the subsequent modest

monetary reward for completing the study could have led to an increase of baseline cortisol levels in PD+ICB patients. Another possible explanation is that Parkinson's disease itself is associated with increased cortisol levels (Hartmann, Veldhuis et al. 1997), while personality traits typical for PD+ICB patients are linked with lower cortisol levels. This might explain why there was no difference between PD+ICB patients and the two other groups. Critically there was, however, a change of direction of cortisol levels only in the PD+ICB group during gambling. This change of direction in cortisol levels following a stressor has been linked with antisocial behaviour (Susmann 2006).

As reported previously all PD patients were more risk prone on medication compared to controls with a subgroup of PD+ICB with pathological gambling taking the most risky decisions. When correlating changes in cortisol levels with risk taking behaviour, results showed a significant interaction in the PD+ICB group but not in the PD-ICB group, despite both groups showing similar performance on the risk task. These findings are consistent with previous studies in male non-PD gamblers showing a rise in salivary cortisol levels (Meyer, Hauffa et al. 2000, Franco, Paris et al. 2009) and blood cortisol levels (Meyer, Schwertfeger et al. 2004) during gambling. Acutely raised cortisol has been linked with anticipation of increased chances of making money and can be euphorogenic (Erickson, Drevets et al. 2003, Coates and Herbert 2008). Alcohol and nicotine induce an increase in cortisol levels (Kirschbaum, Wust et al. 1992, Lovallo 2006) and addicts have an increased activation of the hypothalamic-pituitary-axis during drug intake (Lovallo 2006). Several preclinical studies have also shown that cortisol acts as a positive reinforcer and causes addiction (Deroche, Piazza et al. 1993). Self-administration of cocaine leads to elevated cortisol levels in rodents (Koob and Kreek

2007), non-human primates (Sarnyai, Mello et al. 1996) and humans (Heesch, Negus et al. 1995).

The relative increase in cortisol in PD+ICB patients during risk taking further strengthens the link between biological and drug addictions. These results are especially interesting since L-dopa has a dual effect on cortisol and behaviour. It increases risky behaviour in all PD patients and high doses of L-dopa can reduce cortisol levels (Muller and Muhlack 2007). The latter finding contrasts with results presented here, but in the study by Muller and colleagues a control group was not included, morning samples were obtained at a time of the day when cortisol levels decrease fastest and no information on circadian cortisol levels was provided.

Conclusion

This is the first study that has tested salivary samples in PD+ICB patients. Results suggest that in general, cortisol levels are elevated in PD-ICB patients compared to controls but not in the PD+ICB group. This is in keeping with the literature which links lower cortisol levels with antisocial behaviour, and further links ICBs with substance addiction. Additionally, there was a significant correlation between risk-taking behaviour and cortisol levels in the PD+ICB group with higher cortisol levels being associated with risk prone behaviour but no significant interaction in the PD-ICB group.

Key Findings

- PD-ICB patients had significantly higher diurnal salivary cortisol levels than healthy controls.
- There was no difference in cortisol levels between the PD+ICB group and controls.
- Increased cortisol levels correlated with increased risk taking behaviour in PD+ICB patients, but not in the PD-ICB group.

Summary and general discussion

The data presented in this thesis suggests that jumping to conclusions, irrational beliefs and risky choices rather than hedonic behaviours or lack of response inhibition are responsible for ICBs in PD.

Dopaminergic medication restored negative feedback learning, but did not enhance positive feedback learning in PD patients with ICBs when studied in their “on” state. This contrasts to the findings in PD patients without ICBs who have intact learning from reward but impaired learning from punishment in their “on” state and vice versa in their “off” state (Frank, Seeberger et al. 2004).

Dopaminergic medication affects cognitive performance in PD patients with and without ICBs in a complex fashion with improvement in some tasks and deterioration in others. Anti-Parkinson medication improved response inhibition in both PD groups. Reaction times and error rates were restored on the Stroop test in the “on” state without any group differences. These results suggest that response inhibition is unlikely to play a prominent role in addictive behaviours in PD.

On other tests such as the WM task, dopaminergic medication had no effect on performance. PD patients with ICBs performed significantly worse on the digit forward and backward span. Furthermore, there was no group difference between PD patients with and without ICBs on a working memory test, which utilized abstract geometrical images instead of digits. PD patients with ICBs, however, remembered distractors significantly better than the non-impulsive PD group. The ability to suppress task

irrelevant stimuli may prevent PD patients without ICBs from developing behavioural addictions.

In an altruistic punishment task medication did not change performance in the non-impulsive PD group, whereas PD patients with ICBs punished significantly more in their "on" compared to their "off" state. These findings imply that PD patients with ICBs recognize social norms in their "on" state but have difficulties following them.

Cognitive impulsivity was assessed with a gambling task and the beads task. All PD patients became more risk prone on medication and those with pathological gambling made the most risky choices of all raising the possibility of *"loss chasing"* behaviour (Campbell-Meiklejohn, Woolrich et al. 2008).

To assess *"reflection impulsivity"* PD patients with and without ICBs, non PD-gamblers and substance abusers were tested on the beads task. Results showed that all PD patients gathered significantly less evidence and made more irrational decisions than controls. In addition, PD patients with ICBs performed similarly to substance abusers on opioid replacement therapy and gathered significantly less information than PD patients without ICBs, who more closely resembled pathological gamblers. The majority of PD patients without ICBs were taking L-dopa in combination with a dopamine agonist. Thus, the combination of L-dopa and dopamine agonists likely triggers reflection impulsivity in all PD patients, but intact cortical inhibition prevents the majority from developing an ICB. It remains, however, possible that more of these patients will develop an ICB in the future as treatment continues. Half of the PD patients with ICBs had been weaned off dopamine agonist therapy at the time of testing but were still as

impulsive as those ICB patients still receiving a dopamine agonist. These findings imply that dopamine agonists may cause lasting changes within cortico-striatal-pallidal-thalamo-cortical networks and strengthen the link between ICBs and drug dependency. Analysis of three trials in the 80/20 loss condition correctly identified ICB patients with a sensitivity of 96%.

To explore the role of dopamine agonists and the role of STN-DBS on reflection impulsivity, PD patients on L-dopa therapy treated with and without a dopamine agonist were compared to patients who were treated with STN-DBS who were either taking L-dopa or L-dopa in combination with a dopamine agonist. Previous studies in PD patients with STN-DBS were inconclusive with some studies showing improvement and some worsening of ICBs. However, in most other studies PD patients with STN-DBS were treated with a dopamine agonist.

In the present research PD patients on L-dopa therapy performed as well as controls, whereas patients who were taking L-dopa in combination with a dopamine agonist gathered significantly less evidence and made more irrational choices. There was no difference between STN-DBS patients treated with a dopamine agonist and the PD group treated with dopamine agonists. Similarly, there was no difference between the two PD groups who were not taking dopamine agonists, demonstrating that STN-DBS per se did not influence performance on the beads task.

Taken together these results imply that the single most important risk factor for reflection impulsivity in PD is dopamine agonist therapy. It is, however, important to note that all patients who had a history of ICBs were excluded from this study. This was

necessary as it was anticipated that a past history of ICBs would cause permanent reflection impulsivity and therefore would confound results on the beads task. Thus, a damaging interaction between L-dopa and deep brain stimulation in individuals with pre-operative ICBs cannot be excluded.

The beads task may be useful as a screening test for the risk of developing ICB in clinical practice. Drug naïve PD patients, who do not gather evidence and make irrational choices, should not be treated initially with a dopamine agonist. A prospective study testing never medicated PD patients on the beads task and retesting them after 12 weeks with either L-dopa monotherapy or dopamine agonist monotherapy is currently underway to test this suggestion.

Patients with ephedrone induced parkinsonism, who are known to have severe damage in the corpus striatum and globus pallidus, were tested to assess whether changes in these structures and their circuitry cause impairments in decision making. Ephedrone patients were compared to substance abusers on opioid replacement therapy, as both share a similar premorbid personality, whereas only the ephedrone group has severe damage within the basal ganglia. Clinically, ephedrone patients suffer from chronic progressive severe extrapyramidal deficits without evidence of dopaminergic dysfunction on dopamine transporter SPECT scans.

Ephedrone patients performed similarly to opioid dependent patients on the beads task, with both patient groups gathering significantly less evidence and making more irrational choices than controls. However, only opioid dependent patients were more risk prone and had poorer WM than healthy volunteers, which might explain why

relapse rates are higher in these patients compared to patients with ephedrone induced parkinsonism. It is therefore possible that neuronal changes in the connections between the anterior cingulate, the nucleus accumbens and the pallidum are responsible for reflection impulsivity.

In the final chapter, the literature was reviewed to determine whether chronic stress can induce striatal damage. Several preclinical studies in rodents have demonstrated nigrostriatal degeneration after exposure to chronic stress. Chronic stress could theoretically trigger dopaminergic damage in susceptible patients. To explore the link between stress and impulsivity in PD, salivary cortisol levels of PD patients with and without ICBs were obtained. Results showed significantly raised cortisol levels in the non-impulsive PD group. However, an acute rise in cortisol levels during gambling was only seen in PD patients with ICBs, which may suggest that cortisol plays a role in risk taking in PD patients with ICBs.

Future work

The recognition of ICBs in PD patients on dopaminergic therapy has led to renewed interest in ventral striatal dysfunction in PD. Behavioural studies combining fMRI or PET imaging to measure potential differences in cortico-striatal networks and neuropsychological profiles in patients with different predominant impulsive compulsive behaviours (for example pathological gambling compared with compulsive sexual behaviour) is likely to be instructive. Whilst patients with compulsive sexual

disorder are clinically more aggressive and egoistic, patients with compulsive shopping seem to be less self-centred.

The role of stress in PD has been poorly studied. Assessing cortisol in scalp hair rather than salivary, blood or urine cortisol levels has been shown to be a more valid method for measuring the HPA-axis and long-term cortisol secretion (Meyer and Novak 2012). Hair cortisol measurements also permit retrospective correlation with physical stressors such as motor fluctuations and emotional stressors such as anxiety, which are known to be more prevalent amongst PD patients with ICBs.

It is also unclear whether reward induced endogenous ventral striatal dopamine release can temporarily improve motor handicaps in PD. I am planning to conduct a study comparing PD patients with and without pathological gambling on various decision making tasks and perform simultaneous tremor recordings and use an accelerometer to assess bradykinesia. PD patients with pathological gambling, who are known to exhibit a higher reward induced ventral striatal dopamine release during gambling, might be expected to have subtle improvement in their PD motor symptoms. This would also be in line with the clinical impression that PD patients report a temporary subjective improvement of their motor deficits after performing rewarding actions such as dancing to preferred music or eating chocolate.

In the long term clinico-genetic studies combining neuropsychological tests with genome wide association studies on a large number of PD patients with ICBs may help to define a genetic predisposition, which ultimately might help treating physicians to identify patients at particular risk of developing behavioural addictions.

Acknowledgments

I owe a huge debt of gratitude to my supervisor and inspirational teacher Professor Andrew Lees.

I am also deeply grateful to Bruno Averbeck. Bruno provided me with all the tasks, helped me with the analysis and interpretation of the data.

Professor Lees and Bruno were the masterminds behind this thesis but I would also like to thank Professor Peter Brown, for all his advice and who helped me to feel at home here at Queen Square.

I am grateful to the “Lees fellows” (Helen Ling, Laura Silveira Moriyama, Karen Doherty, Nadia Magdalinou and Alastair Noyce), to Iliyana Komsiyska and to Susan Stoneham for their support. I am especially grateful to Sean O’Sullivan for all his help throughout the years.

This thesis would not have been possible without the help of my collaborators, who are too many to mention, but I gratefully acknowledge Dr. Patricia Limousin, Dr. Tom Foltynie from the DBS group, my colleagues and friends in Lviv, Professor Eileen Joyce, Professor Cardoso, Dr. Grosset and the team of the Soho gambling clinic. I would also like to thank all patients and family members who participated in my studies.

Finally I would like to thank my family for their support.

Appendix

Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP-Anytime During PD-Full)

Reported by: _____ Patient _____ Informant* _____ Patient and Informant

Patient name: _____

Date: _____

*If information reported by an informant, answer questions based on your understanding of the patient.

Answer ALL QUESTIONS based on BEHAVIORS ANYTIME DURING PD LASTING AT LEAST 4 WEEKS

A. IMPULSE CONTROL DISORDERS

1. Do [Did] you or others think that you have [had] an issue with too much gambling, sex, buying, or eating behaviors? Answer for all four behaviors listed below.

Gambling (such as casinos, internet gambling, lotteries, scratch tickets, betting, or slot or poker machines) __**Yes** __**No**

Sex (such as making sexual demands on others, promiscuity, prostitution, change in sexual orientation, masturbation, internet or telephone sexual activities, or pornography) __**Yes** __**No**

Buying (such as too much of the same thing or things that you don't need or use) __**Yes** __**No**

Eating (such as eating larger amounts or different types of food than in the past, more rapidly than normal, until feeling uncomfortably full, or when not hungry) __**Yes** __**No**

2. Do [Did] you think too much about the behaviors below (such as having trouble keeping thoughts out of your mind or feeling guilty)?

Gambling	____**Yes**	____ **No**
Sex	____**Yes**	____ **No**
Buying	____**Yes**	____ **No**
Eating	____**Yes**	____ **No**

3. Do [Did] you have urges or desires for the behaviors below that you feel are [felt were] excessive or cause [caused] you distress (including becoming restless or irritable when unable to participate in the behavior)?

Gambling	____**Yes**	____ **No**
Sex	____**Yes**	____ **No**
Buying	____**Yes**	____ **No**
Eating	____**Yes**	____ **No**

4. Do [Did] you have difficulty controlling the behaviors below (such as increasing them over time, or having trouble cutting down or stopping them)?

Gambling	____**Yes**	____ **No**
Sex	____**Yes**	____ **No**
Buying	____**Yes**	____ **No**
Eating	____**Yes**	____ **No**

QUIP-ANYTIME DURING PD-FULL
Version 1.0 (7/01/08)
Copyright © University of Pennsylvania 2008

Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease
(QUIP-Anytime During PD-Full)

5. Do [Did] you engage in activities specifically to continue the behaviors below (such as hiding what you are [were] doing, lying, hoarding things, borrowing from others, accumulating debt, stealing, or being involved in illegal acts)?

Gambling	____**Yes**	____ **No**
Sex	____**Yes**	____ **No**
Buying	____**Yes**	____ **No**
Eating	____**Yes**	____ **No**

B. OTHER BEHAVIORS

1. Do [Did] you or others think that you spend [spent] too much time….

A. On specific tasks, hobbies or other organized activities (such as writing, painting, gardening, repairing or dismantling things, collecting, computer use, working on projects, etc.)? __**Yes** __**No**

B. Repeating certain simple motor activities (such as cleaning, tidying, handling, examining, sorting, ordering, or arranging objects, etc.)? __**Yes** __**No**

C. Walking or driving with no intended goal or specific purpose? __**Yes** __**No**

2. Do [Did] you or others think you have [had] difficulty controlling the amount of time spent on these activities? __**Yes** __**No**

3. Do [Did] these activities interfere with daily functioning, or cause relationship or work difficulties? __**Yes** __**No**

C. MEDICATION USE

1. Do [Did] you or others (including your physicians) think that you consistently take [took] too much of your Parkinson's medications? __**Yes** __**No**

2. Have [Had] you over time increased on your own, without medical advice, your overall intake of Parkinson's medications for psychological reasons, such as improved mood or motivation? __**Yes** __**No**

3. Have [Had] you over time increased on your own, without medical advice, your overall intake of Parkinson's medications because you only feel fully "on" when you are dyskinetic? __**Yes** __**No**

4. Do [Did] you have difficulty controlling your use of Parkinson's medications (such as experiencing a strong desire for more medication, or having worse mood or feeling unmotivated at a lower dosage)? __**Yes** __**No**

5. Do [Did] you hoard or hide your Parkinson's medications to increase the overall dosage? __**Yes** __**No**

Bibliography

Abbott, R. D., H. Petrovitch, et al. (2001). "Frequency of bowel movements and the future risk of Parkinson's disease." Neurology **57**(3): 456-462.

Abe, N., T. Fujii, et al. (2009). "Do parkinsonian patients have trouble telling lies? The neurobiological basis of deceptive behaviour." Brain **132**(5): 1386-1395.

Abi-Dargham, A., R. Gil, et al. (1998). "Increased striatal dopamine transmission in schizophrenia: confirmation in a second cohort." Am J Psychiatry **155**(6): 761-767.

Abler, B., R. Hahlbrock, et al. (2009). "At-risk for pathological gambling: imaging neural reward processing under chronic dopamine agonists." Brain **132**(9): 2396-2402.

Ahlskog, J. E. (2011). "Pathological behaviors provoked by dopamine agonist therapy of Parkinson's disease." Physiol Behav **104**(1): 168-172.

American Psychiatric Association (2000). Diagnostic and statistical manual of mental disorders (4th ed., text rev.). Washington, DC.

Amino, T., S. Orimo, et al. (2005). "Profound cardiac sympathetic denervation occurs in Parkinson disease." Brain Pathol **15**(1): 29-34.

Anzak, A., H. Tan, et al. (2011). "Improvements in rate of development and magnitude of force with intense auditory stimuli in patients with Parkinson's disease." Eur J Neurosci **34**(1): 124-132.

Arabia, G., B. R. Grossardt, et al. (2010). "Novelty seeking and introversion do not predict the long-term risk of Parkinson disease." Neurology **75**(4): 349-357.

Ardouin, C., V. Voon, et al. (2006). "Pathological gambling in Parkinson's disease improves on chronic subthalamic nucleus stimulation." Mov Disord **21**(11): 1941-1946.

Arnold, P. (1977). "The Encyclopedia of Gambling." Chartwell books.

Aron, A. R., T. W. Robbins, et al. (2004). "Inhibition and the right inferior frontal cortex." Trends Cogn Sci **8**(4): 170-177.

Ashraf, W., R. F. Pfeiffer, et al. (1997). "Constipation in Parkinson's disease: objective assessment and response to psyllium." Mov Disord **12**(6): 946-951.

Avanzi, M., M. Baratti, et al. (2006). "Prevalence of pathological gambling in patients with Parkinson's disease." Mov Disord **21**(12): 2068-2072.

Avanzi, M., M. Baratti, et al. (2008). "The thrill of reckless driving in patients with Parkinson's disease: an additional behavioural phenomenon in dopamine dysregulation syndrome?" Parkinsonism Relat Disord **14**(3): 257-258.

Averbeck, B. B. and B. Duchaine (2009). "Integration of social and utilitarian factors in decision making." Emotion **9**(5): 599-608.

Baba, Y., A. Kuroiwa, et al. (2005). "Alterations of T-lymphocyte populations in Parkinson disease." Parkinsonism Relat Disord **11**(8): 493-498.

Babenko, O., I. Kovalchuk, et al. (2012). "Epigenetic programming of neurodegenerative diseases by an adverse environment." Brain Res **1444**: 96-111.

Babson, A. L. (2001). "Unitised Reagent Random Access Analysers - Immulite " In The Immunoassay Handbook, D Wild, Editor, 2nd Edition.

Barch, D. M., C. S. Carter, et al. (2004). "Factors influencing Stroop performance in schizophrenia." Neuropsychology **18**(3): 477-484.

Barratt, E. S. (1985). "Impulsiveness defined within a systems model of personality." In E. P. Speilburger, & J. N. Butcher (Eds.), Advances in personality assessment (pp. 113-132). Hillsdale, NJ: Lawrence Erlbaum Associates.

Barratt, E. S. (1994). " Impulsiveness and aggression. ." J. Monahan, & H. Steadman (Eds.), Violence and mental disorder: Developments in risk assessment. Chicago: University of Chicago Press.: 61-79.

Bearn, J., A. Evans, et al. (2004). "Recognition of a dopamine replacement therapy dependence syndrome in Parkinson's disease: a pilot study." Drug Alcohol Depend **76**(3): 305-310.

Bechara, A. (2003). "Risky business: emotion, decision-making, and addiction." J Gambl Stud **19**(1): 23-51.

Bechara, A., A. R. Damasio, et al. (1994). "Insensitivity to future consequences following damage to human prefrontal cortex." Cognition **50**(1-3): 7-15.

Bechara, A., H. Damasio, et al. (1998). "Dissociation Of working memory from decision making within the human prefrontal cortex." J Neurosci **18**(1): 428-437.

Bechara, A., D. Tranel, et al. (2000). "Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions." Brain **123** (11): 2189-2202.

Belin, D., A. C. Mar, et al. (2008). "High impulsivity predicts the switch to compulsive cocaine-taking." Science **320**(5881): 1352-1355.

Benaderette, S., P. Zanotti Fregonara, et al. (2006). "Psychogenic parkinsonism: a combination of clinical, electrophysiological, and [(123)I]-FP-CIT SPECT scan explorations improves diagnostic accuracy." Mov Disord **21**(3): 310-317.

Bennett, R. M., J. Jones, et al. (2007). "An internet survey of 2,596 people with fibromyalgia." BMC Musculoskelet Disord **8**: 27.

Bergman, B. and B. Brismar (1994). "Hormone levels and personality traits in abusive and suicidal male alcoholics." Alcohol Clin Exp Res **18**(2): 311-316.

Berke, J. D. and S. E. Hyman (2000). "Addiction, dopamine, and the molecular mechanisms of memory." Neuron **25**(3): 515-532.

Bermejo, P. E. (2008). "Topiramate in managing impulse control disorders in Parkinson's disease." Parkinsonism Relat Disord **14**(5): 448-449.

Bermejo, P. E., C. Ruiz-Huete, et al. (2010). "Zonisamide in managing impulse control disorders in Parkinson's disease." J Neurol **257**(10): 1682-1685.

Bhagwagar, Z., S. Hafizi, et al. (2005). "Increased salivary cortisol after waking in depression." Psychopharmacology (Berl) **182**(1): 54-57.

Bharmal, A., C. Lu, et al. (2010). "Outcomes of patients with Parkinson disease and pathological gambling." Can J Neurol Sci **37**(4): 473-477.

Bienfait, K. L., M. Menza, et al. (2010). "Impulsive smoking in a patient with Parkinson's disease treated with dopamine agonists." J Clin Neurosci **17**(4): 539-540.

Black, D. W., S. Arndt, et al. (2007). "Bupropion in the treatment of pathological gambling: a randomized, double-blind, placebo-controlled, flexible-dose study." J Clin Psychopharmacol **27**(2): 143-150.

Blanco, C., D. S. Hasin, et al. (2006). "Sex differences in subclinical and DSM-IV pathological gambling: results from the National Epidemiologic Survey on Alcohol and Related Conditions." Psychol Med **36**(7): 943-953.

Blanco, C., E. Petkova, et al. (2002). "A pilot placebo-controlled study of fluvoxamine for pathological gambling." Ann Clin Psychiatry **14**(1): 9-15.

Boda, W. L., B. H. Natelson, et al. (1995). "Gait abnormalities in chronic fatigue syndrome." J Neurol Sci **131**(2): 156-161.

Bodi, N., S. Keri, et al. (2009). "Reward-learning and the novelty-seeking personality: a between- and within-subjects study of the effects of dopamine agonists on young Parkinson's patients." Brain **132**(9): 2385-2395.

Bonanni, L., A. Thomas, et al. (2010). "Protracted benefit from paradoxical kinesia in typical and atypical parkinsonisms." Neurol Sci **31**(6): 751-756.

Bonaz, B., M. Baciu, et al. (2002). "Central processing of rectal pain in patients with irritable bowel syndrome: an fMRI study." Am J Gastroenterol **97**(3): 654-661.

Boomershine, C. S. and L. J. Crofford (2009). "A symptom-based approach to pharmacologic management of fibromyalgia." Nat Rev Rheumatol **5**(4): 191-199.

Botvinick, M., L. E. Nystrom, et al. (1999). "Conflict monitoring versus selection-for-action in anterior cingulate cortex." Nature **402**(6758): 179-181.

Bou-Holaigah, I., H. Calkins, et al. (1997). "Provocation of hypotension and pain during upright tilt table testing in adults with fibromyalgia." Clin Exp Rheumatol **15**(3): 239-246.

Braak, B., J. Booij, et al. (2012). "The dopaminergic system in patients with functional dyspepsia analysed by single photon emission computed tomography (SPECT) and an alpha-methyl-para-tyrosine (AMPT) challenge test." Eur J Nucl Med Mol Imaging **39**(4): 642-650.

Braak, H., K. Del Tredici, et al. (2003). "Staging of brain pathology related to sporadic Parkinson's disease." Neurobiol Aging **24**(2): 197-211.

Braak, H., E. Ghebremedhin, et al. (2004). "Stages in the development of Parkinson's disease-related pathology." Cell Tissue Res **318**(1): 121-134.

Brand, M., E. Kalbe, et al. (2005). "Decision-making impairments in patients with pathological gambling." Psychiatry Res **133**(1): 91-99.

Brewer, J. A. and M. N. Potenza (2008). "The neurobiology and genetics of impulse control disorders: relationships to drug addictions." Biochem Pharmacol **75**(1): 63-75.

Broen, M., A. Duits, et al. (2011). "Impulse control and related disorders in Parkinson's disease patients treated with bilateral subthalamic nucleus stimulation: a review." Parkinsonism Relat Disord **17**(6): 413-417.

Brummett, B. H., C. M. Kuhn, et al. (2012). "Cortisol responses to emotional stress in men: association with a functional polymorphism in the 5HTR2C gene." Biol Psychol **89**(1): 94-98.

Brundin, P., J. Y. Li, et al. (2008). "Research in motion: the enigma of Parkinson's disease pathology spread." Nat Rev Neurosci **9**(10): 741-745.

Calabrese, M., F. Rinaldi, et al. (2010). "Basal ganglia and frontal/parietal cortical atrophy is associated with fatigue in relapsing-remitting multiple sclerosis." Mult Scler **16**(10): 1220-1228.

Campbell-Meiklejohn, D. K., M. W. Woolrich, et al. (2008). "Knowing when to stop: the brain mechanisms of chasing losses." Biol Psychiatry **63**(3): 293-300.

Castellani, B. and L. Rugle (1995). "A comparison of pathological gamblers to alcoholics and cocaine misusers on impulsivity, sensation seeking, and craving." Int J Addict **30**(3): 275-289.

Cavanagh, J. F., T. V. Wiecki, et al. (2011). "Subthalamic nucleus stimulation reverses mediofrontal influence over decision threshold." Nat Neurosci **14**(11): 1462-1467.

Chakrabarty, S. and R. Zoorob (2007). "Fibromyalgia." Am Fam Physician **76**(2): 247-254.

Chaudhuri, A. and P. O. Behan (2000). "Fatigue and basal ganglia." J Neurol Sci **179**(S 1-2): 34-42.

Chaudhuri, K. R., D. G. Healy, et al. (2006). "Non-motor symptoms of Parkinson's disease: diagnosis and management." Lancet Neurol **5**(3): 235-245.

Cheng, H. C., C. M. Ulane, et al. (2010). "Clinical progression in Parkinson disease and the neurobiology of axons." Ann Neurol **67**(6): 715-725.

Chintalova-Dallas, R., P. Case, et al. (2009). "Boltushka: a homemade amphetamine-type stimulant and HIV risk in Odessa, Ukraine." Int J Drug Policy **20**(4): 347-351.

Cilia, R., J. H. Ko, et al. (2010). "Reduced dopamine transporter density in the ventral striatum of patients with Parkinson's disease and pathological gambling." Neurobiol Dis **39**(1): 98-104.

Cilia, R., C. Siri, et al. (2008). "Functional abnormalities underlying pathological gambling in Parkinson disease." Arch Neurol **65**(12): 1604-1611.

Clark, L., T. W. Robbins, et al. (2006). "Reflection impulsivity in current and former substance users." Biol Psychiatry **60**(5): 515-522.

Clauw, D. J. and L. J. Crofford (2003). "Chronic widespread pain and fibromyalgia: what we know, and what we need to know." Best Pract Res Clin Rheumatol **17**(4): 685-701.

Coates, J. M. and J. Herbert (2008). "Endogenous steroids and financial risk taking on a London trading floor." Proc Natl Acad Sci U S A **105**(16): 6167-6172.

Comings, D. E., L. Ferry, et al. (1996). "The dopamine D2 receptor (DRD2) gene: a genetic risk factor in smoking." Pharmacogenetics **6**(1): 73-79.

Comings, D. E., R. Gade, et al. (1996). "Exon and intron variants in the human tryptophan 2,3-dioxygenase gene: potential association with Tourette syndrome, substance abuse and other disorders." Pharmacogenetics **6**(4): 307-318.

Comings, D. E., N. Gonzalez, et al. (1999). "Studies of the 48 bp repeat polymorphism of the DRD4 gene in impulsive, compulsive, addictive behaviors: Tourette syndrome, ADHD, pathological gambling, and substance abuse." Am J Med Genet **88**(4): 358-368.

Conrad, C. D. (2008). "Chronic stress-induced hippocampal vulnerability: the glucocorticoid vulnerability hypothesis." Rev Neurosci **19**(6): 395-411.

Cools, R. (2006). "Dopaminergic modulation of cognitive function-implications for L-DOPA treatment in Parkinson's disease." Neurosci Biobehav Rev **30**(1): 1-23.

Cools, R., L. Altamirano, et al. (2006). "Reversal learning in Parkinson's disease depends on medication status and outcome valence." Neuropsychologia **44**(10): 1663-1673.

Cools, R., R. A. Barker, et al. (2001). "Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands." Cereb Cortex **11**(12): 1136-1143.

Cools, R., R. A. Barker, et al. (2003). "L-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease." Neuropsychologia **41**(11): 1431-1441.

Cools, R., L. Clark, et al. (2002). "Defining the neural mechanisms of probabilistic reversal learning using event-related functional magnetic resonance imaging." J Neurosci **22**(11): 4563-4567.

Cools, R., S. E. Gibbs, et al. (2008). "Working memory capacity predicts dopamine synthesis capacity in the human striatum." J Neurosci **28**(5): 1208-1212.

Cools, R., S. J. Lewis, et al. (2007). "L-DOPA disrupts activity in the nucleus accumbens during reversal learning in Parkinson's disease." Neuropsychopharmacology **32**(1): 180-189.

Cools, R., M. Sheridan, et al. (2007). "Impulsive personality predicts dopamine-dependent changes in frontostriatal activity during component processes of working memory." J Neurosci **27**(20): 5506-5514.

Cormier, F., J. Muellner, et al. (2013). "Genetics of impulse control disorders in Parkinson's disease." J Neural Transm **120**(4): 665-671.

Costa, D. C., C. Tannock, et al. (1995). "Brainstem perfusion is impaired in chronic fatigue syndrome." QJM **88**(11): 767-773.

Cotzias, G. C. (1958). "Manganese in health and disease." Physiol Rev **38**(3): 503-532.

Cotzias, G. C., P. S. Papavasiliou, et al. (1969). "L-dopa in parkinson's syndrome." N Engl J Med **281**(5): 272.

Crawford, J. R. and J. D. Henry (2004). "The positive and negative affect schedule (PANAS): construct validity, measurement properties and normative data in a large non-clinical sample." Br J Clin Psychol **43**(Pt 3): 245-265.

Crockett, M. J., L. Clark, et al. (2010). "Impulsive choice and altruistic punishment are correlated and increase in tandem with serotonin depletion." Emotion **10**(6): 855-862.

Czernecki, V., M. Schupbach, et al. (2008). "Apathy following subthalamic stimulation in Parkinson disease: a dopamine responsive symptom." Mov Disord **23**(7): 964-969.

da Silva Lobo, D. S., H. P. Vallada, et al. (2007). "Dopamine genes and pathological gambling in discordant sib-pairs." J Gambl Stud **23**(4): 421-433.

Daffner, K. R., M. M. Mesulam, et al. (1998). "Regulation of attention to novel stimuli by frontal lobes: an event-related potential study." Neuroreport **9**(5): 787-791.

Dagher, A. and T. W. Robbins (2009). "Personality, addiction, dopamine: insights from Parkinson's disease." Neuron **61**(4): 502-510.

Dalley, J. W., B. J. Everitt, et al. (2011). "Impulsivity, compulsivity, and top-down cognitive control." Neuron **69**(4): 680-694.

Daniel, S. E. and A. J. Lees (1993). "Parkinson's Disease Society Brain Bank, London: overview and research." J Neural Transm Suppl **39**: 165-172.

Daw, N. D., J. P. O'Doherty, et al. (2006). "Cortical substrates for exploratory decisions in humans." Nature **441**(7095): 876-879.

de la Fuente-Fernandez, R., A. G. Phillips, et al. (2002). "Dopamine release in human ventral striatum and expectation of reward." Behav Brain Res **136**(2): 359-363.

de Lau, L. M. and M. M. Breteler (2006). "Epidemiology of Parkinson's disease." Lancet Neurol **5**(6): 525-535.

de Quervain, D. J., U. Fischbacher, et al. (2004). "The neural basis of altruistic punishment." Science **305**(5688): 1254-1258.

Deakin, J., M. Aitken, et al. (2004). "Risk taking during decision-making in normal volunteers changes with age." J Int Neuropsychol Soc **10**(4): 590-598.

Demetriades, P., H. Rickards, et al. (2011). "Impulse control disorders following deep brain stimulation of the subthalamic nucleus in Parkinson's disease: clinical aspects." Parkinsons Dis **2011**: 658415.

Deroche, V., P. V. Piazza, et al. (1993). "Rats orally self-administer corticosterone." Brain Res **622**(1-2): 315-320.

Derost, P. P., L. Ouchchane, et al. (2007). "Is DBS-STN appropriate to treat severe Parkinson disease in an elderly population?" Neurology **68**(17): 1345-1355.

Dickson, D. W., H. Braak, et al. (2009). "Neuropathological assessment of Parkinson's disease: refining the diagnostic criteria." Lancet Neurol **8**(12): 1150-1157.

Dinan, T. G., N. Mahmud, et al. (2001). "A double-blind placebo-controlled study of buspirone-stimulated prolactin release in non-ulcer dyspepsia--are central serotoninergic responses enhanced?" Aliment Pharmacol Ther **15**(10): 1613-1618.

Djamshidian, A., S. S. O'Sullivan, et al. (2012). "Effects of dopamine on sensitivity to social bias in Parkinson's disease." PLoS One **7**(3): e32889.

Dolcos, F. and G. McCarthy (2006). "Brain systems mediating cognitive interference by emotional distraction." J Neurosci **26**(7): 2072-2079.

Dowling, N., D. Smith, et al. (2005). "Electronic gaming machines: are they the 'crack-cocaine' of gambling?" Addiction **100**(1): 33-45.

Drapier, D., S. Drapier, et al. (2006). "Pathological gambling secondary to dopaminergic therapy in Parkinson's disease." Psychiatry Res **144**(2-3): 241-244.

Drapier, D., S. Drapier, et al. (2006). "Does subthalamic nucleus stimulation induce apathy in Parkinson's disease?" J Neurol **253**(8): 1083-1091.

Drossman, D. A., M. Camilleri, et al. (2002). "AGA technical review on irritable bowel syndrome." Gastroenterology **123**(6): 2108-2131.

Dudley, R. E., C. H. John, et al. (1997). "The effect of self-referent material on the reasoning of people with delusions." Br J Clin Psychol **36** (4): 575-584.

Edwards, L. L., R. F. Pfeiffer, et al. (1991). "Gastrointestinal symptoms in Parkinson's disease." Mov Disord **6**(2): 151-156.

Eisen, S. A., W. S. Slutske, et al. (2001). "The genetics of pathological gambling." Semin Clin Neuropsychiatry **6**(3): 195-204.

Enticott, P. G., J. R. Ogloff, et al. (2008). "Response inhibition and impulsivity in schizophrenia." Psychiatry Res **157**(1-3): 251-254.

Eraso, R. M., N. J. Bradford, et al. (2007). "Fibromyalgia syndrome in young children: onset at age 10 years and younger." Clin Exp Rheumatol **25**(4): 639-644.

Erickson, K., W. Drevets, et al. (2003). "Glucocorticoid regulation of diverse cognitive functions in normal and pathological emotional states." Neurosci Biobehav Rev **27**(3): 233-246.

Ersche, K. D., L. Clark, et al. (2006). "Profile of executive and memory function associated with amphetamine and opiate dependence." Neuropsychopharmacology **31**(5): 1036-1047.

Ersche, K. D., P. C. Fletcher, et al. (2006). "Differences in orbitofrontal activation during decision-making between methadone-maintained opiate users, heroin users and healthy volunteers." Psychopharmacology (Berl) **188**(3): 364-373.

Evans, A. H., R. Katzenschlager, et al. (2004). "Punding in Parkinson's disease: its relation to the dopamine dysregulation syndrome." Mov Disord **19**(4): 397-405.

Evans, A. H., A. D. Lawrence, et al. (2010). "Compulsive use of dopaminergic drug therapy in Parkinson's disease: reward and anti-reward." Mov Disord **25**(7): 867-876.

Evans, A. H., A. D. Lawrence, et al. (2005). "Factors influencing susceptibility to compulsive dopaminergic drug use in Parkinson disease." Neurology **65**(10): 1570-1574.

Evans, A. H., A. D. Lawrence, et al. (2006). "Relationship between impulsive sensation seeking traits, smoking, alcohol and caffeine intake, and Parkinson's disease." J Neurol Neurosurg Psychiatry **77**(3): 317-321.

Evans, A. H. and A. J. Lees (2004). "Dopamine dysregulation syndrome in Parkinson's disease." Curr Opin Neurol **17**(4): 393-398.

Evans, A. H., N. Pavese, et al. (2006). "Compulsive drug use linked to sensitized ventral striatal dopamine transmission." Ann Neurol **59**(5): 852-858.

Evans, A. H., A. P. Strafella, et al. (2009). "Impulsive and compulsive behaviors in Parkinson's disease." Mov Disord **24**(11): 1561-1570.

Evans, S., S. M. Fleming, et al. (2010). "Effects of Emotional Preferences on Value-based Decision-making Are Mediated by Mentalizing Not Reward Networks." J Cogn Neurosci.

Evenden, J. L. (1999). "Varieties of impulsivity." Psychopharmacology (Berl) **146**(4): 348-361.

Fahn, S. (2003). "Description of Parkinson's disease as a clinical syndrome." Ann N Y Acad Sci **991**: 1-14.

Falhammar, H. and J. Y. Yarker (2009). "Pathological gambling and hypersexuality in cabergoline-treated prolactinoma." Med J Aust **190**(2): 97.

Fan, W., H. Ding, et al. (2009). "Impulse control disorders in Parkinson's disease in a Chinese population." Neurosci Lett **465**(1): 6-9.

Fasano, A. and I. Petrovic (2010). "Insights into pathophysiology of punding reveal possible treatment strategies." Mol Psychiatry **15**(6): 560-573.

Fearnley, J. M. and A. J. Lees (1991). "Ageing and Parkinson's disease: substantia nigra regional selectivity." Brain **114** (5): 2283-2301.

Fehr, E. and S. Gachter (2002). "Altruistic punishment in humans." Nature **415**(6868): 137-140.

Felicio, A. C., C. Godeiro-Junior, et al. (2010). "Degenerative parkinsonism in patients with psychogenic parkinsonism: A dopamine transporter imaging study." Clin Neurol Neurosurg **112**(4): 282-285.

Fera, F., G. Nicoletti, et al. (2007). "Dopaminergic modulation of cognitive interference after pharmacological washout in Parkinson's disease." Brain Res Bull **74**(1-3): 75-83.

Ferrara, J. M. and M. Stacy (2008). "Impulse-control disorders in Parkinson's disease." CNS Spectr **13**(8): 690-698.

Fine, C., M. Gardner, et al. (2007). "Hopping, skipping or jumping to conclusions? Clarifying the role of the JTC bias in delusions." Cogn Neuropsychiatry **12**(1): 46-77.

Fjorback, L. O., M. Arendt, et al. (2011). "Mindfulness-based stress reduction and mindfulness-based cognitive therapy: a systematic review of randomized controlled trials." Acta Psychiatr Scand **124**(2): 102-119.

Flemming, A. (1978). "Something for nothing: A history of gambling." New York: Delacorte Press.

Folstein, M. F., S. E. Folstein, et al. (1975). ""Mini-mental state". A practical method for grading the cognitive state of patients for the clinician." J Psychiatr Res **12**(3): 189-198.

Foltynie, T., S. G. Lewis, et al. (2005). "The BDNF Val66Met polymorphism has a gender specific influence on planning ability in Parkinson's disease." J Neurol **252**(7): 833-838.

Foltynie, T., L. Zrinzo, et al. (2010). "MRI-guided STN DBS in Parkinson's disease without microelectrode recording: efficacy and safety." J Neurol Neurosurg Psychiatry **82**(4): 358-363.

Franco, C., J. J. Paris, et al. (2009). "Male gamblers have significantly greater salivary cortisol before and after betting on a horse race, than do female gamblers." Physiol Behav **99**(2): 225-229.

Frank, M. J. and C. O'Reilly R (2006). "A mechanistic account of striatal dopamine function in human cognition: psychopharmacological studies with cabergoline and haloperidol." Behav Neurosci **120**(3): 497-517.

Frank, M. J., J. Samanta, et al. (2007). "Hold your horses: impulsivity, deep brain stimulation, and medication in parkinsonism." Science **318**(5854): 1309-1312.

Frank, M. J., A. Santamaria, et al. (2007). "Testing computational models of dopamine and noradrenaline dysfunction in attention deficit/hyperactivity disorder." Neuropsychopharmacology **32**(7): 1583-1599.

Frank, M. J., L. C. Seeberger, et al. (2004). "By carrot or by stick: cognitive reinforcement learning in parkinsonism." Science **306**(5703): 1940-1943.

Friedman, J. H., A. Abrantes, et al. (2011). "Fatigue in Parkinson's disease." Expert Opin Pharmacother **12**(13): 1999-2007.

Frosini, D., I. Pesaresi, et al. (2010). "Parkinson's disease and pathological gambling: results from a functional MRI study." Mov Disord **25**(14): 2449-2453.

Fukuda, K., S. E. Straus, et al. (1994). "The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group." Ann Intern Med **121**(12): 953-959.

Furl, N. and B. B. Averbeck (2011). "Parietal cortex and insula relate to evidence seeking relevant to reward-related decisions." J Neurosci **31**(48): 17572-17582.

Gaenslen, A., I. Swid, et al. (2011). "The patients' perception of prodromal symptoms before the initial diagnosis of Parkinson's disease." Mov Disord **26**(4): 653-658.

Gallagher, D. A., A. J. Lees, et al. (2010). "What are the most important nonmotor symptoms in patients with Parkinson's disease and are we missing them?" Mov Disord **25**(15): 2493-2500.

Gallagher, D. A., S. S. O'Sullivan, et al. (2007). "Pathological gambling in Parkinson's disease: risk factors and differences from dopamine dysregulation. An analysis of published case series." Mov Disord **22**(12): 1757-1763.

Garety, P. A. and D. Freeman (1999). "Cognitive approaches to delusions: a critical review of theories and evidence." Br J Clin Psychol **38** (2): 113-154.

Gartlehner, G. and C. G. Moore (2008). "Direct versus indirect comparisons: a summary of the evidence." Int J Technol Assess Health Care **24**(2): 170-177.

Gelb, D. J., E. Oliver, et al. (1999). "Diagnostic criteria for Parkinson disease." Arch Neurol **56**(1): 33-39.

Gerlach, M., K. Double, et al. (2003). "Dopamine receptor agonists in current clinical use: comparative dopamine receptor binding profiles defined in the human striatum." J Neural Transm **110**(10): 1119-1127.

Geronimus, A. T. (1992). "The weathering hypothesis and the health of African-American women and infants: evidence and speculations." Ethn Dis **2**(3): 207-221.

Gesi, M., P. Soldani, et al. (2000). "The role of the locus coeruleus in the development of Parkinson's disease." Neurosci Biobehav Rev **24**(6): 655-668.

Gibb, W. R. and A. J. Lees (1988). "The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease." J Neurol Neurosurg Psychiatry **51**(6): 745-752.

Gibberd, F. B. and J. P. Simmonds (1980). "Neurological disease in ex-Far-East prisoners of war." Lancet **2**(8186): 135-137.

Gibson, I., R. Taylor, et al. (2011). "The Nightingale Myalgic Encephalomyelitis (M.E.) Definition, Presented at the IACFS/ME Research & Clinical Conference in Ottawa Canada, September 22-25 ".

Gilad, G. M. and V. H. Gilad (1995). "Strain, stress, neurodegeneration and longevity." Mech Ageing Dev **78**(2): 75-83.

Ginker, R. R. and J. P. Spiegel (1943). "War neurosis in North Africa, The Tunisian Campaign, January to May 1943Josiah Macy Foundation, New York."

Giovannoni, G., J. D. O'Sullivan, et al. (2000). "Hedonistic homeostatic dysregulation in patients with Parkinson's disease on dopamine replacement therapies." J Neurol Neurosurg Psychiatry **68**(4): 423-428.

Glahn, D. C., W. R. Lovallo, et al. (2007). "Reduced amygdala activation in young adults at high risk of alcoholism: studies from the Oklahoma family health patterns project." Biol Psychiatry **61**(11): 1306-1309.

GlaxoSmithKline. (2008). "A randomized, double-blind, placebo-controlled, parallel-group study to investigate the safety and efficacy of controlled-release ropinirole 1–24 mg q.d. administered for 12 weeks in subjects with fibromyalgia. ." Protocol summary of ROF102100. [Internet. Accessed October 12, 2008.] Available from: http://ctr.gsk.co.uk/Summary/Ropinirole/II_ROF102100.pdf.

Goeders, N. E. (2002). "Stress and cocaine addiction." J Pharmacol Exp Ther **301**(3): 785-789.

Goldstein, D. S. (2011). "Stress, allostatic load, catecholamines, and other neurotransmitters in neurodegenerative diseases." Endocr Regul **45**(2): 91-98.

Goldstein, R. Z., A. D. Craig, et al. (2009). "The neurocircuitry of impaired insight in drug addiction." Trends Cogn Sci **13**(9): 372-380.

Gonera, E. G., M. van't Hof, et al. (1997). "Symptoms and duration of the prodromal phase in Parkinson's disease." Mov Disord **12**(6): 871-876.

Gotham, A. M., R. G. Brown, et al. (1988). "'Frontal' cognitive function in patients with Parkinson's disease 'on' and 'off' levodopa." Brain **111** (2): 299-321.

Gowers, W. R. (1904). "A Lecture on Lumbago: Its Lessons and Analogues: Delivered at the National Hospital for the Paralysed and Epileptic." Br Med J **1**(2246): 117-121.

Griffiths, M. (1999). "Gambling Technologies: Prospects for Problem Gambling." J Gambl Stud **15**(3): 265-283.

Groenewegen, H. J. and H. W. Berendse (1990). "Connections of the subthalamic nucleus with ventral striatopallidal parts of the basal ganglia in the rat." J Comp Neurol **294**(4): 607-622.

Grosset, D. G., F. Cardoso, et al. (2011). "Dopamine agonists vs levodopa in impulse control disorders." Arch Neurol **68**(4): 544-545; author reply 545-546.

Grosset, K. A., G. Macphee, et al. (2006). "Problematic gambling on dopamine agonists: Not such a rarity." Mov Disord **21**(12): 2206-2208.

Guitart-Masip, M., N. Bunzeck, et al. (2010). "Contextual novelty changes reward representations in the striatum." J Neurosci **30**(5): 1721-1726.

Gut-Fayand, A., A. Dervaux, et al. (2001). "Substance abuse and suicidality in schizophrenia: a common risk factor linked to impulsivity." Psychiatry Res **102**(1): 65-72.

Haber, S. N., K. S. Kim, et al. (2006). "Reward-related cortical inputs define a large striatal region in primates that interface with associative cortical connections, providing a substrate for incentive-based learning." J Neurosci **26**(32): 8368-8376.

Halbig, T. D., W. Tse, et al. (2009). "Subthalamic deep brain stimulation and impulse control in Parkinson's disease." Eur J Neurol **16**(4): 493-497.

Hall, G. W., N. J. Carriero, et al. (2000). "Pathological gambling among cocaine-dependent outpatients." Am J Psychiatry **157**(7): 1127-1133.

Hallett, M. (2011). "Psychogenic parkinsonism." J Neurol Sci **310**(1-2): 163-165.

Hardman, C. D., J. M. Henderson, et al. (2002). "Comparison of the basal ganglia in rats, marmosets, macaques, baboons, and humans: volume and neuronal number for the output, internal relay, and striatal modulating nuclei." J Comp Neurol **445**(3): 238-255.

Hartmann, A., J. D. Veldhuis, et al. (1997). "Twenty-four hour cortisol release profiles in patients with Alzheimer's and Parkinson's disease compared to normal controls: ultradian secretory pulsatility and diurnal variation." Neurobiol Aging **18**(3): 285-289.

Harvey, S. B., S. Wessely, et al. (2009). "The relationship between fatigue and psychiatric disorders: evidence for the concept of neurasthenia." J Psychosom Res **66**(5): 445-454.

Hassan, A., J. H. Bower, et al. (2011). "Dopamine agonist-triggered pathological behaviors: surveillance in the PD clinic reveals high frequencies." Parkinsonism Relat Disord **17**(4): 260-264.

Hastings, T. G., D. A. Lewis, et al. (1996). "Role of oxidation in the neurotoxic effects of intrastriatal dopamine injections." Proc Natl Acad Sci U S A **93**(5): 1956-1961.

Hauser, W., K. Thieme, et al. (2010). "Guidelines on the management of fibromyalgia syndrome - a systematic review." Eur J Pain **14**(1): 5-10.

Healy, D. G. (2007). "Did Gericault's "Madwoman Obsessed With Gambling" have Parkinson's disease?" Mov Disord **22**(8): 1069-1070.

Heesch, C. M., B. H. Negus, et al. (1995). "Effects of cocaine on cortisol secretion in humans." Am J Med Sci **310**(2): 61-64.

Hester, R. and H. Garavan (2009). "Neural mechanisms underlying drug-related cue distraction in active cocaine users." Pharmacol Biochem Behav **93**(3): 270-277.

Higley, A. E., K. Spiller, et al. (2011). "PG01037, a novel dopamine D3 receptor antagonist, inhibits the effects of methamphetamine in rats." J Psychopharmacol **25**(2): 263-273.

Hirtz, D., D. J. Thurman, et al. (2007). "How common are the "common" neurologic disorders?" Neurology **68**(5): 326-337.

Hodgins, D. C. and N. M. Petry (2004). "Cognitive and behavioral treatments." In Grant JE, Potenza MN, editors. Pathological gambling: a clinical guide to treatment. Washington DC, American Psychiatric press: 169-188.

Hoehn, M. M. and M. D. Yahr (1967). "Parkinsonism: onset, progression and mortality." Neurology **17**(5): 427-442.

Holden, C. (2001). "'Behavioral' addictions: do they exist?" Science **294**(5544): 980-982.

Hollerman, J. R., L. Tremblay, et al. (1998). "Influence of reward expectation on behavior-related neuronal activity in primate striatum." J Neurophysiol **80**(2): 947-963.

Holman, A. J. (2009). "Impulse control disorder behaviors associated with pramipexole used to treat fibromyalgia." J Gambl Stud **25**(3): 425-431.

Holman, A. J. and R. R. Myers (2005). "A randomized, double-blind, placebo-controlled trial of pramipexole, a dopamine agonist, in patients with fibromyalgia receiving concomitant medications." Arthritis Rheum **52**(8): 2495-2505.

Housden, C. R., S. S. O'Sullivan, et al. "Intact reward learning but elevated delay discounting in Parkinson's disease patients with impulsive-compulsive spectrum behaviors." Neuropsychopharmacology **35**(11): 2155-2164.

Housden, C. R., S. S. O'Sullivan, et al. (2010). "Intact reward learning but elevated delay discounting in Parkinson's disease patients with impulsive-compulsive spectrum behaviors." Neuropsychopharmacology **35**(11): 2155-2164.

Hsieh, Y. H., K. J. Chen, et al. (2008). "Cognitive and motor components of response speed in the stroop test in Parkinson's disease patients." Kaohsiung J Med Sci **24**(4): 197-203.

Huettel, S. A., C. J. Stowe, et al. (2006). "Neural signatures of economic preferences for risk and ambiguity." Neuron **49**(5): 765-775.

Hughes, R. N. (2007). "Neotic preferences in laboratory rodents: issues, assessment and substrates." Neurosci Biobehav Rev **31**(3): 441-464.

Huq, S. F., P. A. Garety, et al. (1988). "Probabilistic judgements in deluded and non-deluded subjects." Q J Exp Psychol A **40**(4): 801-812.

Hyman, S. E., R. C. Malenka, et al. (2006). "Neural mechanisms of addiction: the role of reward-related learning and memory." Annu Rev Neurosci **29**: 565-598.

Ibanez, A., C. Blanco, et al. (2003). "Genetics of pathological gambling." J Gambl Stud **19**(1): 11-22.

Inanici, F. and M. B. Yunus (2004). "History of fibromyalgia: past to present." Curr Pain Headache Rep **8**(5): 369-378.

Ishihara, L. and C. Bayne (2006). "What is the evidence for a premorbid parkinsonian personality: A systematic review." Mov Disord **21**(8): 1066-1072.

Jahanshahi, M., C. M. Ardouin, et al. (2000). "The impact of deep brain stimulation on executive function in Parkinson's disease." Brain **123** (6): 1142-1154.

Jelliffe, S. E. (1940). "The Parkinsonian Body Posture: Some Considerations on Unconscious Hostility." Psychoanal. Rev., 27:467-479.

Jenner, P. (2005). "A novel dopamine agonist for the transdermal treatment of Parkinson's disease." Neurology **65**(2 Suppl 1): S3-5.

Jenner, P. (2008). "Molecular mechanisms of L-DOPA-induced dyskinesia." Nat Rev Neurosci **9**(9): 665-677.

Josephs, K. A., J. E. Ahlskog, et al. (2005). "Neurologic manifestations in welders with pallidal MRI T1 hyperintensity." Neurology **64**(12): 2033-2039.

Joutsa, J., K. Martikainen, et al. (2012). "Impulse control disorders and depression in Finnish patients with Parkinson's disease." Parkinsonism Relat Disord **18**(2): 155-160.

Kaplan, G. B., K. A. Leite-Morris, et al. (2011). "Opiate Sensitization Induces FosB/DeltaFosB Expression in Prefrontal Cortical, Striatal and Amygdala Brain Regions." PLoS One **6**(8): e23574.

Kashihara, K. and T. Imamura (2008). "Amantadine may reverse punding in Parkinson's disease--observation in a patient." Mov Disord **23**(1): 129-130.

Keefe, K. A., J. D. Salamone, et al. (1989). "Paradoxical kinesia in parkinsonism is not caused by dopamine release. Studies in an animal model." Arch Neurol **46**(10): 1070-1075.

Kegeles, L. S., A. Abi-Dargham, et al. (2010). "Increased synaptic dopamine function in associative regions of the striatum in schizophrenia." Arch Gen Psychiatry **67**(3): 231-239.

Kelley, A. E., T. Schochet, et al. (2004). "Risk taking and novelty seeking in adolescence: introduction to part I." Ann N Y Acad Sci **1021**: 27-32.

Kelly, J. P. and C. M. Filley (2004). "Proneness to psychological distress is associated with risk of Alzheimer's disease." Neurology **63**(5): 941; author reply 941.

Kempster, P. A., S. S. O'Sullivan, et al. (2010). "Relationships between age and late progression of Parkinson's disease: a clinico-pathological study." Brain **133**(Pt 6): 1755-1762.

Kennerley, S. W., M. E. Walton, et al. (2006). "Optimal decision making and the anterior cingulate cortex." Nat Neurosci **9**(7): 940-947.

Kertzman, S., K. Lowengrub, et al. (2006). "Stroop performance in pathological gamblers." Psychiatry Res **142**(1): 1-10.

King-Casas, B., D. Tomlin, et al. (2005). "Getting to know you: reputation and trust in a two-person economic exchange." Science **308**(5718): 78-83.

King, R. J., J. Jones, et al. (1990). "Plasma cortisol correlates of impulsivity and substance abuse." Pers Indiv Diff **11**: 287–291.

Kirschbaum, C., S. Wust, et al. (1992). "'Normal' cigarette smoking increases free cortisol in habitual smokers." Life Sci **50**(6): 435-442.

Kish, S. J., K. Shannak, et al. (1988). "Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. Pathophysiologic and clinical implications." N Engl J Med **318**(14): 876-880.

Klos, K. J., J. H. Bower, et al. (2005). "Pathological hypersexuality predominantly linked to adjuvant dopamine agonist therapy in Parkinson's disease and multiple system atrophy." Parkinsonism Relat Disord **11**(6): 381-386.

Koenigs, M. and D. Tranel (2007). "Irrational economic decision-making after ventromedial prefrontal damage: evidence from the Ultimatum Game." J Neurosci **27**(4): 951-956.

Koob, G. and M. J. Kreek (2007). "Stress, dysregulation of drug reward pathways, and the transition to drug dependence." Am J Psychiatry **164**(8): 1149-1159.

Koob, G. F. and N. D. Volkow (2010). "Neurocircuitry of addiction." Neuropsychopharmacology **35**(1): 217-238.

Korn, D. A. and H. J. Shaffer (1999). "Gambling and the Health of the Public: Adopting a Public Health Perspective." J Gambl Stud **15**(4): 289-365.

Kwiatek, R., L. Barnden, et al. (2000). "Regional cerebral blood flow in fibromyalgia: single-photon-emission computed tomography evidence of reduction in the pontine tegmentum and thalami." Arthritis Rheum **43**(12): 2823-2833.

Landau, S. M., R. Lal, et al. (2009). "Striatal dopamine and working memory." Cereb Cortex **19**(2): 445-454.

Lane, T. J., P. Manu, et al. (1991). "Depression and somatization in the chronic fatigue syndrome." Am J Med **91**(4): 335-344.

Lang, P. J., M. M. Bradley, et al. (2008). "International affective picture system (IAPS): Affective ratings of pictures and instruction manual. ." Technical Report A-8. Gainesville, FL, USA: University of Florida.

Lange, K. W., T. W. Robbins, et al. (1992). "L-dopa withdrawal in Parkinson's disease selectively impairs cognitive performance in tests sensitive to frontal lobe dysfunction." Psychopharmacology (Berl) **107**(2-3): 394-404.

Lange, L. A., A. B. Kampov-Polevoy, et al. (2010). "Sweet liking and high novelty seeking: Independent phenotypes associated with alcohol-related problems." Alcohol Alcohol **45**(5): 431-436.

Langer, E. J. (1975). "The illusion of control." J. Pers. Soc. Psychol. **32** 311–328.

Langston, J. W., P. Ballard, et al. (1983). "Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis." Science **219**(4587): 979-980.

Lansbergen, M. M., J. L. Kenemans, et al. (2007). "Stroop interference and attention-deficit/hyperactivity disorder: a review and meta-analysis." Neuropsychology **21**(2): 251-262.

Lawrence, A. D., A. H. Evans, et al. (2003). "Compulsive use of dopamine replacement therapy in Parkinson's disease: reward systems gone awry?" Lancet Neurol **2**(10): 595-604.

Lebouvier, T., M. Neunlist, et al. (2010). "Colonic biopsies to assess the neuropathology of Parkinson's disease and its relationship with symptoms." PLoS One **5**(9): e12728.

Lee, J. Y., H. J. Kim, et al. (2011). "Is pathological gambling in Parkinson's disease reduced by amantadine?" Ann Neurol **69**(1): 213-214; author reply 214-215.

Lee, J. Y., J. M. Kim, et al. (2009). "Association between the dose of dopaminergic medication and the behavioral disturbances in Parkinson disease." Parkinsonism Relat Disord **16**(3): 202-207.

Lee, N. M., A. Carter, et al. (2012). "The neurobiology of overeating. Treating overweight individuals should make use of neuroscience research, but not at the expense of population approaches to diet and lifestyle." EMBO Rep **13**(9): 785-790.

Lees, A. J. (1992). "When did Ray Kennedy's Parkinson's disease begin?" Mov Disord **7**(2): 110-116.

Lees, A. J., J. Hardy, et al. (2009). "Parkinson's disease." Lancet **373**(9680): 2055-2066.

Lees, A. J., K. M. Shaw, et al. (1977). "Deprenyl in Parkinson's disease." Lancet **2**(8042): 791-795.

Lenzenweger, M. F. (2010). "Schizotypy and schizophrenia: The view from experimental psychopathology." Guilford Press.

Leroi, I., M. Andrews, et al. (2009). "A comparison of apathy in impulsivity in Parkinson's disease(abstract)." Movement Disorders Society Annual Meeting, Paris.

Leroi, I., M. Andrews, et al. (2011). "Apathy and impulse control disorders in Parkinson's disease: a direct comparison." Parkinsonism Relat Disord **18**(2): 198-203.

Lesieur, H. R. (1979). "The compulsive gambler's spiral of options and involvement." Psychiatry **42**(1): 79-87.

Lesieur, H. R. (1984). "The chase: Career of the Compulsive Gambler." Schenkman, Cambridge, Massachusetts

Leung, K. S. and L. B. Cottler (2009). "Treatment of pathological gambling." Curr Opin Psychiatry **22**(1): 69-74.

Lewis, D. A., S. L. Foote, et al. (1988). "The dopaminergic innervation of monkey prefrontal cortex: a tyrosine hydroxylase immunohistochemical study." Brain Res **449**(1-2): 225-243.

Lezak (2004). Neuropsychological Assessment. 4. New York: Oxford University Press.

Lhommee, E., H. Klinger, et al. (2012). "Subthalamic stimulation in Parkinson's disease: restoring the balance of motivated behaviours." Brain **135**(Pt 5): 1463-1477.

Li, X., J. Sundquist, et al. (2008). "Impact of psychiatric disorders on Parkinson's disease : a nationwide follow-up study from Sweden." J Neurol **255**(1): 31-36.

Lim, S. Y., A. H. Evans, et al. (2008). "Impulse control and related disorders in Parkinson's disease: review." Ann N Y Acad Sci **1142**: 85-107.

Lim, S. Y., S. S. O'Sullivan, et al. (2009). "Dopamine dysregulation syndrome, impulse control disorders and punding after deep brain stimulation surgery for Parkinson's disease." J Clin Neurosci **16**(9): 1148-1152.

Limousin, P., J. Greene, et al. (1997). "Changes in cerebral activity pattern due to subthalamic nucleus or internal pallidum stimulation in Parkinson's disease." Ann Neurol **42**(3): 283-291.

Ling, H., M. Braschinsky, et al. (2011). "Decades of delayed diagnosis in 4 levodopa-responsive young-onset monogenetic parkinsonism patients." Mov Disord **26**(7): 1337-1340.

Lisman, J. E. and A. A. Grace (2005). "The hippocampal-VTA loop: controlling the entry of information into long-term memory." Neuron **46**(5): 703-713.

Littlejohn, G. O. (1996). "Rheumatology. 2. Fibromyalgia syndrome." Med J Aust **165**(7): 387-391.

Liu, J. and A. Mori (1999). "Stress, aging, and brain oxidative damage." Neurochem Res **24**(11): 1479-1497.

Lobo, D. S., R. P. Souza, et al. (2010). "Association of functional variants in the dopamine D2-like receptors with risk for gambling behaviour in healthy Caucasian subjects." Biol Psychol **85**(1): 33-37.

Lou, J. S., G. Kearns, et al. (2003). "Levodopa improves physical fatigue in Parkinson's disease: a double-blind, placebo-controlled, crossover study." Mov Disord **18**(10): 1108-1114.

Lovallo, W. R. (2006). "Cortisol secretion patterns in addiction and addiction risk." Int J Psychophysiol **59**(3): 195-202.

Lu, C., A. Bharmal, et al. (2006). "Gambling and Parkinson disease." Arch Neurol **63**(2): 298.

Lucca, G., C. M. Comim, et al. (2009). "Effects of chronic mild stress on the oxidative parameters in the rat brain." Neurochem Int **54**(5-6): 358-362.

Lucchini, R. G., C. J. Martin, et al. (2009). "From manganism to manganese-induced parkinsonism: a conceptual model based on the evolution of exposure." Neuromolecular Med **11**(4): 311-321.

Lule, D., J. Heimrath, et al. (2012). "Deep brain stimulation and behavioural changes: is comedication the most important factor?" Neurodegener Dis **9**(1): 18-24.

Lunt, L., J. Bramham, et al. (2012). "Prefrontal cortex dysfunction and 'Jumping to Conclusions': bias or deficit?" J Neuropsychol **6**(1): 65-78.

Lupien, S. J., A. Fiocco, et al. (2005). "Stress hormones and human memory function across the lifespan." Psychoneuroendocrinology **30**(3): 225-242.

Lupien, S. J., B. S. McEwen, et al. (2009). "Effects of stress throughout the lifespan on the brain, behaviour and cognition." Nat Rev Neurosci **10**(6): 434-445.

Lutz, E. G. (1976). "Neuroleptic-induced akathisia and dystonia triggered by alcohol." JAMA **236**(21): 2422-2423.

Lydiard, R. B. (2001). "Irritable bowel syndrome, anxiety, and depression: what are the links?" J Clin Psychiatry **62** (8): 38-47.

Macphee, G. J., C. Copeland, et al. (2009). "Clinical follow up of pathological gambling in Parkinson's disease in the West Scotland study." Mov Disord **24**(16): 2430-2431.

Magnusson, J. E. and K. Fisher (2000). "The involvement of dopamine in nociception: the role of D(1) and D(2) receptors in the dorsolateral striatum." Brain Res **855**(2): 260-266.

Magnusson, J. E. and R. V. Martin (2002). "Additional evidence for the involvement of the basal ganglia in formalin-induced nociception: the role of the nucleus accumbens." Brain Res **942**(1-2): 128-132.

Malt, E. A., S. Olafsson, et al. (2003). "Altered dopamine D2 receptor function in fibromyalgia patients: a neuroendocrine study with buspirone in women with fibromyalgia compared to female population based controls." J Affect Disord **75**(1): 77-82.

Mamikonyan, E., P. J. Moberg, et al. (2009). "Mild cognitive impairment is common in Parkinson's disease patients with normal Mini-Mental State Examination (MMSE) scores." Parkinsonism Relat Disord **15**(3): 226-231.

Manes, F., B. Sahakian, et al. (2002). "Decision-making processes following damage to the prefrontal cortex." Brain **125**(3): 624-639.

McElroy, S. L., P. E. Keck, Jr., et al. (1994). "Compulsive buying: a report of 20 cases." J Clin Psychiatry **55**(6): 242-248.

McElroy, S. L., E. B. Nelson, et al. (2008). "Olanzapine in the treatment of pathological gambling: a negative randomized placebo-controlled trial." J Clin Psychiatry **69**(3): 433-440.

McEwen, B. S. (2007). "Physiology and neurobiology of stress and adaptation: central role of the brain." Physiol Rev **87**(3): 873-904.

McNab, F. and T. Klingberg (2008). "Prefrontal cortex and basal ganglia control access to working memory." Nat Neurosci **11**(1): 103-107.

Menza, M. (2000). "The personality associated with Parkinson's disease." Curr Psychiatry Rep **2**(5): 421-426.

Menza, M., R. D. Dobkin, et al. (2009). "A controlled trial of antidepressants in patients with Parkinson disease and depression." Neurology **72**(10): 886-892.

Meyer, G., B. P. Hauffa, et al. (2000). "Casino gambling increases heart rate and salivary cortisol in regular gamblers." Biol Psychiatry **48**(9): 948-953.

Meyer, G., J. Schwertfeger, et al. (2004). "Neuroendocrine response to casino gambling in problem gamblers." Psychoneuroendocrinology **29**(10): 1272-1280.

Meyer, J. S. and M. A. Novak (2012). "Minireview: Hair cortisol: a novel biomarker of hypothalamic-pituitary-adrenocortical activity." Endocrinology **153**(9): 4120-4127.

Michalczuk, R., H. Bowden-Jones, et al. (2011). "Impulsivity and cognitive distortions in pathological gamblers attending the UK National Problem Gambling Clinic: a preliminary report." Psychol Med: 1-11.

Milenkova, M., B. Mohammadi, et al. (2011). "Intertemporal choice in Parkinson's disease." Mov Disord **26**(11): 2004-2010.

Miller, D. B. and J. P. O'Callaghan (2008). "Do early-life insults contribute to the late-life development of Parkinson and Alzheimer diseases?" Metabolism **57** (2): S44-49.

Mishra, S., M. Lalumiere, et al. (2010). "Gambling as a form of risk-taking: Individual differences in personality, risk-accepting attitudes, and behavioral preferences for risk." Personality and Individual Differences **49**(6): 616-621

Miyasaki, J. M., K. Al Hassan, et al. (2007). "Punding prevalence in Parkinson's disease." Mov Disord **22**(8): 1179-1181.

Moldofsky, H. (2002). "Management of sleep disorders in fibromyalgia." Rheum Dis Clin North Am **28**(2): 353-365.

Molina, J. A., M. J. Sainz-Artiga, et al. (2000). "Pathologic gambling in Parkinson's disease: a behavioral manifestation of pharmacologic treatment?" Mov Disord **15**(5): 869-872.

Mondelli, V., P. Dazzan, et al. (2010). "Abnormal cortisol levels during the day and cortisol awakening response in first-episode psychosis: the role of stress and of antipsychotic treatment." Schizophr Res **116**(2-3): 234-242.

Moore, H., H. J. Rose, et al. (2001). "Chronic cold stress reduces the spontaneous activity of ventral tegmental dopamine neurons." Neuropsychopharmacology **24**(4): 410-419.

Mott, W. (1919). "War Neuroses and Shell Shock " Oxford Medical Publications.

Mountz, J. M., L. A. Bradley, et al. (1995). "Fibromyalgia in women. Abnormalities of regional cerebral blood flow in the thalamus and the caudate nucleus are associated with low pain threshold levels." Arthritis Rheum **38**(7): 926-938.

Muller, T. and S. Muhlack (2007). "Acute levodopa intake and associated cortisol decrease in patients with Parkinson disease." Clin Neuropharmacol **30**(2): 101-106.

Muresanu, D. F., A. Stan, et al. (2012). "Neuroplasticity and impulse control disorders." J Neurol Sci **316**(1-2): 15-20.

Nader, M. A., D. Morgan, et al. (2006). "PET imaging of dopamine D2 receptors during chronic cocaine self-administration in monkeys." Nat Neurosci **9**(8): 1050-1056.

Nakamura, T., M. Hirayama, et al. (2011). "Does cardiovascular autonomic dysfunction contribute to fatigue in Parkinson's disease?" Mov Disord **26**(10): 1869-1874.

Nebe, A. and G. Ebersbach (2009). "Pain intensity on and off levodopa in patients with Parkinson's disease." Mov Disord **24**(8): 1233-1237.

Neumann, L. and D. Buskila (2003). "Epidemiology of fibromyalgia." Curr Pain Headache Rep **7**(5): 362-368.

Nickel, J. C., D. A. Tripp, et al. (2010). "Interstitial cystitis/painful bladder syndrome and associated medical conditions with an emphasis on irritable bowel syndrome, fibromyalgia and chronic fatigue syndrome." J Urol **184**(4): 1358-1363.

Nirenberg, M. J. (2010). "Dopamine agonist withdrawal syndrome and non-motor symptoms after Parkinson's disease surgery." Brain **133**(11): 155-156.

Nirenberg, M. J. and C. Waters (2006). "Compulsive eating and weight gain related to dopamine agonist use." Mov Disord **21**(4): 524-529.

O'Doherty, J., H. Critchley, et al. (2003). "Dissociating valence of outcome from behavioral control in human orbital and ventral prefrontal cortices." J Neurosci **23**(21): 7931-7939.

O'Doherty, J., M. L. Kringelbach, et al. (2001). "Abstract reward and punishment representations in the human orbitofrontal cortex." Nat Neurosci **4**(1): 95-102.

O'Sullivan, S. S., A. Djamshidian, et al. (2010). "Impulsive-compulsive spectrum behaviors in pathologically confirmed progressive supranuclear palsy." Mov Disord **25**(5): 638-642.

O'Sullivan, S. S., A. Djamshidian, et al. (2010). "Excessive hoarding in Parkinson's disease." Mov Disord **25**(8): 1026-1033.

O'Sullivan, S. S., A. H. Evans, et al. (2009). "Dopamine dysregulation syndrome: an overview of its epidemiology, mechanisms and management." CNS Drugs **23**(2): 157-170.

O'Sullivan, S. S., A. H. Evans, et al. (2010). "Reckless generosity in Parkinson's disease." Mov Disord **25**(2): 221-223.

O'Sullivan, S. S., C. M. Loane, et al. (2011). "Sleep disturbance and impulsive-compulsive behaviours in Parkinson's disease." J Neurol Neurosurg Psychiatry **82**(6): 620-622.

O'Sullivan, S. S., D. R. Williams, et al. (2008). "Nonmotor symptoms as presenting complaints in Parkinson's disease: a clinicopathological study." Mov Disord **23**(1): 101-106.

O'Sullivan, S. S., K. Wu, et al. (2011). "Cue-induced striatal dopamine release in Parkinson's disease-associated impulsive-compulsive behaviours." Brain **134**(Pt 4): 969-978.

Obeso, J. A., M. C. Rodriguez-Oroz, et al. (2010). "Missing pieces in the Parkinson's disease puzzle." Nat Med **16**(6): 653-661.

Olanow, C. W. (2004). "Manganese-induced parkinsonism and Parkinson's disease." Ann N Y Acad Sci **1012**: 209-223.

Ondo, W. G. and D. Lai (2008). "Predictors of impulsivity and reward seeking behavior with dopamine agonists." Parkinsonism Relat Disord **14**(1): 28-32.

Onofrj, M., L. Bonanni, et al. (2010). "Cohort study on somatoform disorders in Parkinson disease and dementia with Lewy bodies." Neurology **74**(20): 1598-1606.

Owen, A. M. (2000). "The role of the lateral frontal cortex in mnemonic processing: the contribution of functional neuroimaging." Exp Brain Res **133**(1): 33-43.

Pae, C. U., D. M. Marks, et al. (2009). "Pharmacological treatment of chronic fatigue syndrome: focusing on the role of antidepressants." Expert Opin Pharmacother **10**(10): 1561-1570.

Pani, L., A. Porcella, et al. (2000). "The role of stress in the pathophysiology of the dopaminergic system." Mol Psychiatry **5**(1): 14-21.

Papay, K., E. Mamikonyan, et al. (2011). "Patient versus informant reporting of ICD symptoms in Parkinson's disease using the QUIP: validity and variability." Parkinsonism Relat Disord **17**(3): 153-155.

Parkinson, J. (1817). "An essay on the shaking palsy." London: Sherwood, Neely, Jones.

Patrick, H. and D. Levy (1922). "Parkinson's disease. A clinical study of one hundred and forty-six cases." Arch NeurPsych. **7**(6): 711-720.

Paulus, M. P. (2007). "Decision-making dysfunctions in psychiatry--altered homeostatic processing?" Science **318**(5850): 602-606.

Pei, Q., T. Zetterstrom, et al. (1990). "Tail pinch-induced changes in the turnover and release of dopamine and 5-hydroxytryptamine in different brain regions of the rat." Neuroscience **35**(1): 133-138.

Pessiglione, M., B. Seymour, et al. (2006). "Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans." Nature **442**(7106): 1042-1045.

Petrovitch, H., R. D. Abbott, et al. (2009). "Bowel movement frequency in late-life and substantia nigra neuron density at death." Mov Disord **24**(3): 371-376.

Petry, N. M., F. S. Stinson, et al. (2005). "Comorbidity of DSM-IV pathological gambling and other psychiatric disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions." J Clin Psychiatry **66**(5): 564-574.

Pezzella, F. R., C. Colosimo, et al. (2005). "Prevalence and clinical features of hedonistic homeostatic dysregulation in Parkinson's disease." Mov Disord **20**(1): 77-81.

Piasecki, S. D. and J. W. Jefferson (2004). "Psychiatric complications of deep brain stimulation for Parkinson's disease." J Clin Psychiatry **65**(6): 845-849.

Plioplys, A. V. and S. Plioplys (1997). "Amantadine and L-carnitine treatment of Chronic Fatigue Syndrome." Neuropsychobiology **35**(1): 16-23.

Poletti, M., D. Frosini, et al. (2010). "Decision making in de novo Parkinson's disease." Mov Disord **25**(10): 1432-1436.

Potenza, M. N. (2008). "Review. The neurobiology of pathological gambling and drug addiction: an overview and new findings." Philos Trans R Soc Lond B Biol Sci **363**(1507): 3181-3189.

Potenza, M. N., H. C. Leung, et al. (2003). "An FMRI Stroop task study of ventromedial prefrontal cortical function in pathological gamblers." Am J Psychiatry **160**(11): 1990-1994.

Potenza, M. N., V. Voon, et al. (2007). "Drug Insight: impulse control disorders and dopamine therapies in Parkinson's disease." Nat Clin Pract Neurol **3**(12): 664-672.

Potenza, M. N. and K. C. Winters (2003). "The neurobiology of pathological gambling: translating research findings into clinical advances." J Gambl Stud **19**(1): 7-10.

Prichard, J. S., R. S. Schwab, et al. (1951). "The effects of stress and the results of medication in different personalities with Parkinson's disease." Psychosom Med **13**(2): 106-111.

Prick, J. (1966). "Genuine parkinsonism. A psychosomatic, anthropological-psychiatric approach." Abs World Congress of Psychiatry. Madrid **4**.

Prosser, J., L. J. Cohen, et al. (2006). "Neuropsychological functioning in opiate-dependent subjects receiving and following methadone maintenance treatment." Drug Alcohol Depend **84**(3): 240-247.

Purdon-Martin, J. (1967). "The basal ganglia and posture." Pitman, London.

Rabinak, C. A. and M. J. Nirenberg (2010). "Dopamine agonist withdrawal syndrome in Parkinson disease." Arch Neurol **67**(1): 58-63.

Ramirez, J. (2003). "Hormones and aggression in childhood and adolescence " Aggression and Violent Behavior **8**(6): 621-644.

Rapeli, P., C. Fabritius, et al. (2009). "Memory function in opioid-dependent patients treated with methadone or buprenorphine along with benzodiazepine: longitudinal change in comparison to healthy individuals." Subst Abuse Treat Prev Policy **4**: 6.

Rapeli, P., R. Kivisaari, et al. (2006). "Cognitive function during early abstinence from opioid dependence: a comparison to age, gender, and verbal intelligence matched controls." BMC Psychiatry **6**: 9.

Rasheed, N., A. Ahmad, et al. (2009). "Differential response of central dopaminergic system in acute and chronic unpredictable stress models in rats." Neurochem Res **35**(1): 22-32.

Ray, N. J., J. M. Miyasaki, et al. (2012). "Extrastriatal dopaminergic abnormalities of DA homeostasis in Parkinson's patients with medication-induced pathological gambling: a [11C] FLB-457 and PET study." Neurobiol Dis **48**(3): 519-525.

Remy, P., M. Doder, et al. (2005). "Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system." Brain **128**(Pt 6): 1314-1322.

Reynolds, A. D., D. K. Stone, et al. (2010). "Regulatory T cells attenuate Th17 cell-mediated nigrostriatal dopaminergic neurodegeneration in a model of Parkinson's disease." J Immunol **184**(5): 2261-2271.

Riedl, A., M. Schmidtmann, et al. (2008). "Somatic comorbidities of irritable bowel syndrome: a systematic analysis." J Psychosom Res **64**(6): 573-582.

Riley, D., A. E. Lang, et al. (1989). "Frozen shoulder and other shoulder disturbances in Parkinson's disease." J Neurol Neurosurg Psychiatry **52**(1): 63-66.

Robbins, T. W. and B. J. Everitt (1999). "Drug addiction: bad habits add up." Nature **398**(6728): 567-570.

Rodriguez-Oroz, M. C., J. Lopez-Azcarate, et al. (2010). "Involvement of the subthalamic nucleus in impulse control disorders associated with Parkinson's disease." Brain **134**(Pt 1): 36-49.

Rogers, M. A., J. L. Bradshaw, et al. (2000). "Parkinsonian motor characteristics in unipolar major depression." J Clin Exp Neuropsychol **22**(2): 232-244.

Rogers, R. D., B. J. Everitt, et al. (1999). "Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteers: evidence for monoaminergic mechanisms." Neuropsychopharmacology **20**(4): 322-339.

Rogers, R. D., B. Wielenberg, et al. (2011). "Deep brain stimulation of the subthalamic nucleus transiently enhances loss-chasing behaviour in patients with Parkinson's disease." Exp Neurol **231**(1): 181-189.

Rolls, E. T. (2000). "The orbitofrontal cortex and reward." Cereb Cortex **10**(3): 284-294.

Rolls, E. T. (2004). "The functions of the orbitofrontal cortex." Brain Cogn **55**(1): 11-29.

Rossi, M., E. R. Gerschcovich, et al. (2010). "Decision-making in Parkinson's disease patients with and without pathological gambling." Eur J Neurol **17**(1): 97-102.

Rothman, S. M. and M. P. Mattson (2010). "Adverse stress, hippocampal networks, and Alzheimer's disease." Neuromolecular Med **12**(1): 56-70.

Rubinstein, T. C., N. Giladi, et al. (2002). "The power of cueing to circumvent dopamine deficits: a review of physical therapy treatment of gait disturbances in Parkinson's disease." Mov Disord **17**(6): 1148-1160.

Russell, I. J., H. Vaeroy, et al. (1992). "Cerebrospinal fluid biogenic amine metabolites in fibromyalgia/fibrositis syndrome and rheumatoid arthritis." Arthritis Rheum **35**(5): 550-556.

Sachdev, P. and A. M. Aniss (1994). "Slowness of movement in melancholic depression." Biol Psychiatry **35**(4): 253-262.

Saint-Cyr, J. A., T. Hoque, et al. (2002). "Localization of clinically effective stimulating electrodes in the human subthalamic nucleus on magnetic resonance imaging." J Neurosurg **97**(5): 1152-1166.

Sanfey, A. G., J. K. Rilling, et al. (2003). "The neural basis of economic decision-making in the Ultimatum Game." Science **300**(5626): 1755-1758.

Sanotsky, Y., R. Lesyk, et al. (2007). "Manganic encephalopathy due to "ephedrone" abuse." Mov Disord **22**(9): 1337-1343.

Santangelo, G., C. Vitale, et al. (2009). "Cognitive dysfunctions and pathological gambling in patients with Parkinson's disease." Mov Disord **24**(6): 899-905.

Sapolsky, R. M., L. C. Krey, et al. (1986). "The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis." Endocr Rev **7**(3): 284-301.

Sarnyai, Z., N. K. Mello, et al. (1996). "Effects of cocaine on pulsatile activity of hypothalamic-pituitary-adrenal axis in male rhesus monkeys: neuroendocrine and behavioral correlates." J Pharmacol Exp Ther **277**(1): 225-234.

Savica, R., W. A. Rocca, et al. (2010). "When does Parkinson disease start?" Arch Neurol **67**(7): 798-801.

Schlesinger, I., I. Erikh, et al. (2007). "Paradoxical kinesia at war." Mov Disord **22**(16): 2394-2397.

Schmaling, K. B., D. H. Lewis, et al. (2003). "Single-photon emission computerized tomography and neurocognitive function in patients with chronic fatigue syndrome." Psychosom Med **65**(1): 129-136.

Schmidt-Wilcke, T. and D. J. Clauw (2010). "Pharmacotherapy in fibromyalgia (FM)--implications for the underlying pathophysiology." Pharmacol Ther **127**(3): 283-294.

Schmitt, L. H., G. A. Harrison, et al. (1998). "Variation in epinephrine and cortisol excretion rates associated with behavior in an Australian Aboriginal community." Am J Phys Anthropol **106**(2): 249-253.

Schober, A. (2004). "Classic toxin-induced animal models of Parkinson's disease: 6-OHDA and MPTP." Cell Tissue Res **318**(1): 215-224.

Schuler, P., H. Oyanguren, et al. (1957). "Manganese poisoning; environmental and medical study at a Chilean mine." Ind Med Surg **26**(4): 167-173.

Schultz, W. (2002). "Getting formal with dopamine and reward." Neuron **36**(2): 241-263.

Schwab, R. S. and I. Zieper (1965). "Effects of mood, motivation, stress and alertness on the performance in Parkinson's disease." Psychiatr Neurol (Basel) **150**(6): 345-357.

Schweinhardt, P., K. M. Sauro, et al. (2008). "Fibromyalgia: a disorder of the brain?" Neuroscientist **14**(5): 415-421.

Seedat, S., S. Kesler, et al. (2000). "Pathological gambling behaviour: emergence secondary to treatment of Parkinson's disease with dopaminergic agents." Depress Anxiety **11**(4): 185-186.

Segerstrom, S. C. and G. E. Miller (2004). "Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry." Psychol Bull **130**(4): 601-630.

Seguin, J. R., L. Arseneault, et al. (2007). "The contribuition of "cool" and "hot" components of decision-making in adolescence: implications for psychopathology." Cognitive Development **22**: 530-543.

Selikhova, M., L. Fedoryshyn, et al. (2008). "Parkinsonism and dystonia caused by the illicit use of ephedrone--a longitudinal study." Mov Disord **23**(15): 2224-2231.

Sevincok, L., A. Akoglu, et al. (2007). "Quetiapine in a case with Parkinson disease and pathological gambling." J Clin Psychopharmacol **27**(1): 107-108.

Shaffer, H. J., M. N. Hall, et al. (1999). "Estimating the prevalence of disordered gambling behavior in the United States and Canada: a research synthesis." Am J Public Health **89**(9): 1369-1376.

Shahed, J., T. Davidson, et al. (2006). "Craving sweets in Parkinson's disease." Mov Disord **21**(S 599).

Shandling, M., P. L. Carlen, et al. (1990). "Parkinsonism in alcohol withdrawal: a follow-up study." Mov Disord **5**(1): 36-39.

Shannon, K. M., A. Keshavarzian, et al. (2012). "Is alpha-synuclein in the colon a biomarker for premotor Parkinson's Disease? Evidence from 3 cases." Mov Disord **27**(6): 716-719.

Shapiro, M. A., Y. L. Chang, et al. (2007). "The four As associated with pathological Parkinson disease gamblers: anxiety, anger, age, and agonists." Neuropsychiatr Dis Treat **3**(1): 161-167.

Sharpe, M., A. Clements, et al. (1996). "Increased prolactin response to buspirone in chronic fatigue syndrome." J Affect Disord **41**(1): 71-76.

Shaw, K. M., A. J. Lees, et al. (1980). "The impact of treatment with levodopa on Parkinson's disease." Q J Med **49**(195): 283-293.

Sher, K. J., B. D. Bartholow, et al. (2000). "Personality and substance use disorders: a prospective study." J Consult Clin Psychol **68**(5): 818-829.

Shin, H. S. (1997). "Metabolism of selegiline in humans. Identification, excretion, and stereochemistry of urine metabolites." Drug Metab Dispos **25**(6): 657-662.

Shiner, T., B. Seymour, et al. (2012). "Dopamine and performance in a reinforcement learning task: evidence from Parkinson's disease." Brain **135**(Pt 6): 1871-1883.

Shohamy, D., C. E. Myers, et al. (2005). "The role of dopamine in cognitive sequence learning: evidence from Parkinson's disease." Behav Brain Res **156**(2): 191-199.

Sikk, K., S. Haldre, et al. (2011). "Manganese-Induced Parkinsonism due to Ephedrone Abuse." Parkinsons Dis **2011**: 865319.

Sikk, K., P. Taba, et al. (2007). "Irreversible motor impairment in young addicts--ephedrone, manganism or both?" Acta Neurol Scand **115**(6): 385-389.

Simon, N. W., I. A. Mendez, et al. (2007). "Cocaine exposure causes long-term increases in impulsive choice." Behav Neurosci **121**(3): 543-549.

Simon, S. L., C. P. Domier, et al. (2002). "Cognitive performance of current methamphetamine and cocaine abusers." J Addict Dis **21**(1): 61-74.

Singh, A., G. Kandimala, et al. (2007). "Risk factors for pathologic gambling and other compulsions among Parkinson's disease patients taking dopamine agonists." J Clin Neurosci **14**(12): 1178-1181.

Siri, C., R. Cilia, et al. (2010). "Cognitive status of patients with Parkinson's disease and pathological gambling." J Neurol **257**(2): 247-252.

Skapinakis, P., E. Bakola, et al. (2010). "Efficacy and acceptability of selective serotonin reuptake inhibitors for the treatment of depression in Parkinson's disease: a systematic review and meta-analysis of randomized controlled trials." BMC Neurol **10**: 49.

Slutske, W. S., A. Caspi, et al. (2005). "Personality and problem gambling: a prospective study of a birth cohort of young adults." Arch Gen Psychiatry **62**(7): 769-775.

Smith, A. D., S. L. Castro, et al. (2002). "Stress-induced Parkinson's disease: a working hypothesis." Physiol Behav **77**(4-5): 527-531.

Smith, L. K., N. M. Jadavji, et al. (2008). "Stress accelerates neural degeneration and exaggerates motor symptoms in a rat model of Parkinson's disease." Eur J Neurosci **27**(8): 2133-2146.

Smythe, H. A. and H. Moldofsky (1977). "Two contributions to understanding of the "fibrositis" syndrome." Bull Rheum Dis **28**(1): 928-931.

Snyder, A. M., E. M. Stricker, et al. (1985). "Stress-induced neurological impairments in an animal model of parkinsonism." Ann Neurol **18**(5): 544-551.

Solla, P., A. Cannas, et al. (2011). "Behavioral, neuropsychiatric and cognitive disorders in Parkinson's disease patients with and without motor complications." Prog Neuropsychopharmacol Biol Psychiatry **35**(4): 1009-1013.

Sommershof, A., H. Aichinger, et al. (2009). "Substantial reduction of naive and regulatory T cells following traumatic stress." Brain Behav Immun **23**(8): 1117-1124.

Sorge, R. E. and J. Stewart (2006). "The effects of chronic buprenorphine on intake of heroin and cocaine in rats and its effects on nucleus accumbens dopamine levels during self-administration." Psychopharmacology (Berl) **188**(1): 28-41.

Souques, A. (1921). "Rapports sur les syndromes parkinsoniens." Rev. Neurol. (Paris)(37): 534–715.

Sperber, A. D., Y. Atzmon, et al. (1999). "Fibromyalgia in the irritable bowel syndrome: studies of prevalence and clinical implications." Am J Gastroenterol **94**(12): 3541-3546.

Sperber, A. D. and A. Tarasiuk (2007). "Disrupted sleep in patients with IBS--a wake-up call for further research?" Nat Clin Pract Gastroenterol Hepatol **4**(8): 412-413.

Stacy, M. (2009). "Impulse control disorders in Parkinson's disease." F1000 Med Rep **1**.

Steeves, T. D., J. Miyasaki, et al. (2009). "Increased striatal dopamine release in Parkinsonian patients with pathological gambling: a [11C] raclopride PET study." Brain **132**(Pt 5): 1376-1385.

Stehlik, R., L. Arvidsson, et al. (2009). "Restless legs syndrome is common among female patients with fibromyalgia." Eur Neurol **61**(2): 107-111.

Steinberg, L., D. Albert, et al. (2008). "Age differences in sensation seeking and impulsivity as indexed by behavior and self-report: evidence for a dual systems model." Dev Psychol **44**(6): 1764-1778.

Stepens, A., I. Logina, et al. (2008). "A Parkinsonian syndrome in methcathinone users and the role of manganese." N Engl J Med **358**(10): 1009-1017.

Stepens, A., C. J. Stagg, et al. (2010). "White matter abnormalities in methcathinone abusers with an extrapyramidal syndrome." Brain **133**(12): 3676-3684.

Susmann, E. (2006). "Psychobiology of persistent antisocial behavior: Stress,early vulnerabilities and the attenuation hypothesis." Neuroscience and Biobehavioral Reviews **30**: 376-389.

Sutton, R. and A. Barto (1998). "Reinforcement Learning: An Introduction." MIT Press: Cambridge, MA.

Swainson, R., R. D. Rogers, et al. (2000). "Probabilistic learning and reversal deficits in patients with Parkinson's disease or frontal or temporal lobe lesions: possible adverse effects of dopaminergic medication." Neuropsychologia **38**(5): 596-612.

Takahashi, T. (2004). "Cortisol levels and time-discounting of monetary gain in humans." Neuroreport **15**(13): 2145-2147.

Talley, N. J., E. H. Dennis, et al. (2003). "Overlapping upper and lower gastrointestinal symptoms in irritable bowel syndrome patients with constipation or diarrhea." Am J Gastroenterol **98**(11): 2454-2459.

Tang, W. K., Y. K. Chen, et al. (2010). "Acute basal ganglia infarcts in poststroke fatigue: an MRI study." J Neurol **257**(2): 178-182.

Thacker, E. L., H. Chen, et al. (2008). "Recreational physical activity and risk of Parkinson's disease." Mov Disord **23**(1): 69-74.

Thobois, S., C. Ardouin, et al. (2010). "Non-motor dopamine withdrawal syndrome after surgery for Parkinson's disease: predictors and underlying mesolimbic denervation." Brain **133**(Pt 4): 1111-1127.

Thomas, A., L. Bonanni, et al. (2010). "Pathological gambling in Parkinson disease is reduced by amantadine." Ann Neurol **68**(3): 400-404.

Todes, C. J. and A. J. Lees (1985). "The pre-morbid personality of patients with Parkinson's disease." J Neurol Neurosurg Psychiatry **48**(2): 97-100.

Tolosa, E., G. Wenning, et al. (2006). "The diagnosis of Parkinson's disease." Lancet Neurol **5**(1): 75-86.

Torta, D. M. and L. Castelli (2008). "Reward pathways in Parkinson's disease: clinical and theoretical implications." Psychiatry Clin Neurosci **62**(2): 203-213.

Tsouli, S. and S. Konitsiotis (2010). "How should we treat a patient with early Parkinson's disease?" Int J Clin Pract **64**(9): 1210-1219.

UCB-News. (2009). "UCB announces top-line outcomes for proof-of-concept studies [media release]." Available from URL:http://www.search.ucb-group.com/media-room/newsdetail/?det=1292262&select-year=&select-archieve=) [accessed 2010 March 14] **Feb 20 (online)**.

Ulrich-Lai, Y. M. and J. P. Herman (2009). "Neural regulation of endocrine and autonomic stress responses." Nat Rev Neurosci **10**(6): 397-409.

Van Cauter, E., M. Kerkhofs, et al. (1992). "A quantitative estimation of growth hormone secretion in normal man: reproducibility and relation to sleep and time of day." J Clin Endocrinol Metab **74**(6): 1441-1450.

Van Dillen, L. F., D. J. Heslenfeld, et al. (2009). "Tuning down the emotional brain: an fMRI study of the effects of cognitive load on the processing of affective images." Neuroimage **45**(4): 1212-1219.

van Eimeren, T., B. Ballanger, et al. (2009). "Dopamine agonists diminish value sensitivity of the orbitofrontal cortex: a trigger for pathological gambling in Parkinson's disease?" Neuropsychopharmacology **34**(13): 2758-2766.

van Eimeren, T., G. Pellecchia, et al. (2010). "Drug-induced deactivation of inhibitory networks predicts pathological gambling in PD." Neurology **75**(19): 1711-1716.

van Honk, J., D. J. Schutter, et al. (2003). "Low cortisol levels and the balance between punishment sensitivity and reward dependency." Neuroreport **14**(15): 1993-1996.

van Wouwe, N. C., K. R. Ridderinkhof, et al. (2011). "Deep brain stimulation of the subthalamic nucleus improves reward-based decision-learning in Parkinson's disease." Front Hum Neurosci **5**: 30.

Vandenbergh, D. J., L. A. Rodriguez, et al. (1997). "High-activity catechol-O-methyltransferase allele is more prevalent in polysubstance abusers." Am J Med Genet **74**(4): 439-442.

Verdejo-Garcia, A., A. J. Lawrence, et al. (2008). "Impulsivity as a vulnerability marker for substance-use disorders: review of findings from high-risk research, problem gamblers and genetic association studies." Neurosci Biobehav Rev **32**(4): 777-810.

Vlaar, A., A. Hovestadt, et al. (2011). "The treatment of early Parkinson's disease: levodopa rehabilitated." Pract Neurol **11**(3): 145-152.

Volkow, N. D. and J. S. Fowler (2000). "Addiction, a disease of compulsion and drive: involvement of the orbitofrontal cortex." Cereb Cortex **10**(3): 318-325.

Volkow, N. D., J. S. Fowler, et al. (2004). "The addicted human brain viewed in the light of imaging studies: brain circuits and treatment strategies." Neuropharmacology **47** (S1): 3-13.

Volkow, N. D., G. J. Wang, et al. (2006). "High levels of dopamine D2 receptors in unaffected members of alcoholic families: possible protective factors." Arch Gen Psychiatry **63**(9): 999-1008.

Voon, V., J. Gao, et al. (2011). "Dopamine agonists and risk: impulse control disorders in Parkinson's disease." Brain **134**(Pt 5): 1438-1446.

Voon, V., K. Hassan, et al. (2006). "Prevalence of repetitive and reward-seeking behaviors in Parkinson disease." Neurology **67**(7): 1254-1257.

Voon, V., K. Hassan, et al. (2006). "Prospective prevalence of pathologic gambling and medication association in Parkinson disease." Neurology **66**(11): 1750-1752.

Voon, V., M. Pessiglione, et al. (2010). "Mechanisms underlying dopamine-mediated reward bias in compulsive behaviors." Neuron **65**(1): 135-142.

Voon, V., M. N. Potenza, et al. (2007). "Medication-related impulse control and repetitive behaviors in Parkinson's disease." Curr Opin Neurol **20**(4): 484-492.

Voon, V., B. Reynolds, et al. (2009). "Impulsive choice and response in dopamine agonist-related impulse control behaviors." Psychopharmacology (Berl).

Voon, V., B. Reynolds, et al. (2010). "Impulsive choice and response in dopamine agonist-related impulse control behaviors." Psychopharmacology (Berl) **207**(4): 645-659.

Voon, V., T. Thomsen, et al. (2007). "Factors associated with dopaminergic drug-related pathological gambling in Parkinson disease." Arch Neurol **64**(2): 212-216.

Vreeburg, S. A., F. G. Zitman, et al. (2010). "Salivary cortisol levels in persons with and without different anxiety disorders." Psychosom Med **72**(4): 340-347.

Walter, B. L. and J. L. Vitek (2004). "Surgical treatment for Parkinson's disease." Lancet Neurol **3**(12): 719-728.

Wardle, H., K. Sproston, et al. (2007). "British Gambling Prevalence Survey." London. Stationary office.

Warman, D. M., P. H. Lysaker, et al. (2007). "Jumping to conclusions and the continuum of delusional beliefs." Behav Res Ther **45**(6): 1255-1269.

Weaver, F. M., K. Follett, et al. (2009). "Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial." JAMA **301**(1): 63-73.

Wechsler, D. (1997). Wechsler Adult Intelligence Scale-3rd Edition. San Antonio: The Psychological Corporation.

Weintraub, D., S. Hoops, et al. (2009). "Validation of the questionnaire for impulsive-compulsive disorders in Parkinson's disease." Mov Disord **24**(10): 1461-1467.

Weintraub, D., J. Koester, et al. (2010). "Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients." Arch Neurol **67**(5): 589-595.

Weintraub, D. and M. N. Potenza (2006). "Impulse control disorders in Parkinson's disease." Curr Neurol Neurosci Rep **6**(4): 302-306.

Weintraub, D., A. D. Siderowf, et al. (2006). "Association of dopamine agonist use with impulse control disorders in Parkinson disease." Arch Neurol **63**(7): 969-973.

Weintraub, D., M. Sohr, et al. (2010). "Amantadine use associated with impulse control disorders in Parkinson disease in cross-sectional study." Ann Neurol **68**(6): 963-968.

Welte, J. W., G. M. Barnes, et al. (2004). "Risk factors for pathological gambling." Addict Behav **29**(2): 323-335.

Wessely, S., T. Chalder, et al. (1997). "The prevalence and morbidity of chronic fatigue and chronic fatigue syndrome: a prospective primary care study." Am J Public Health **87**(9): 1449-1455.

Wessely, S., C. Nimnuan, et al. (1999). "Functional somatic syndromes: one or many?" Lancet **354**(9182): 936-939.

West, R., K. J. Murphy, et al. (2002). "Effects of time of day on age differences in working memory." J Gerontol B Psychol Sci Soc Sci **57**(1): P3-10.

Whitehead, W. E., O. Palsson, et al. (2002). "Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications?" Gastroenterology **122**(4): 1140-1156.

Wicks, P. and G. J. MacPhee (2009). "Pathological gambling amongst Parkinson's disease and ALS patients in an online community (PatientsLikeMe.com)." Mov Disord **24**(7): 1085-1088.

Williams, G. V. and P. S. Goldman-Rakic (1995). "Modulation of memory fields by dopamine D1 receptors in prefrontal cortex." Nature **376**(6541): 572-575.

Wingo, T. S., M. Evatt, et al. (2009). "Impulse control disorders arising in 3 patients treated with rotigotine." Clin Neuropharmacol **32**(2): 59-62.

Wittmann, B. C., N. D. Daw, et al. (2008). "Striatal activity underlies novelty-based choice in humans." Neuron **58**(6): 967-973.

Wolfe, F., H. A. Smythe, et al. (1990). "The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee." Arthritis Rheum **33**(2): 160-172.

Wolters, E., Y. D. van der Werf, et al. (2008). "Parkinson's disease-related disorders in the impulsive-compulsive spectrum." J Neurol **255**(S5): 48-56.

Wood, P. B., J. C. Patterson, 2nd, et al. (2007). "Reduced presynaptic dopamine activity in fibromyalgia syndrome demonstrated with positron emission tomography: a pilot study." J Pain **8**(1): 51-58.

Wood, P. B., P. Schweinhardt, et al. (2007). "Fibromyalgia patients show an abnormal dopamine response to pain." Eur J Neurosci **25**(12): 3576-3582.

World Health Organization (Geneva, 1992). "International Statistical Classification of Diseases and Related Health Problems."

Wray, I. and M. G. Dickerson (1981). "Cessation of high frequency gambling and "withdrawal' symptoms." Br J Addict **76**(4): 401-405.

Xiromerisiou, G., H. Houlden, et al. (2012). "Identical twins with Leucine rich repeat kinase type 2 mutations discordant for Parkinson's disease." Mov Disord **27**(10): 1323.

Ye, Z., A. Hammer, et al. (2011). "Pramipexole modulates the neural network of reward anticipation." Hum Brain Mapp **32**(5): 800-811.

Yildirim, E. A., A. Essizoglu, et al. (2009). "[Chronic manganese intoxication due to methcathinone (ephedron) abuse: a case report]." Turk Psikiyatri Derg **20**(3): 294-298.

Yunus, M. B. (2001). "The role of gender in fibromyalgia syndrome." Curr Rheumatol Rep **3**(2): 128-134.

Zack, M. and C. X. Poulos (2004). "Amphetamine primes motivation to gamble and gambling-related semantic networks in problem gamblers." Neuropsychopharmacology **29**(1): 195-207.

Zahodne, L. B., F. Susatia, et al. (2011). "Binge eating in Parkinson's disease: prevalence, correlates and the contribution of deep brain stimulation." J Neuropsychiatry Clin Neurosci **23**(1): 56-62.

Zweig, R. M., J. E. Cardillo, et al. (1993). "The locus ceruleus and dementia in Parkinson's disease." Neurology **43**(5): 986-991.