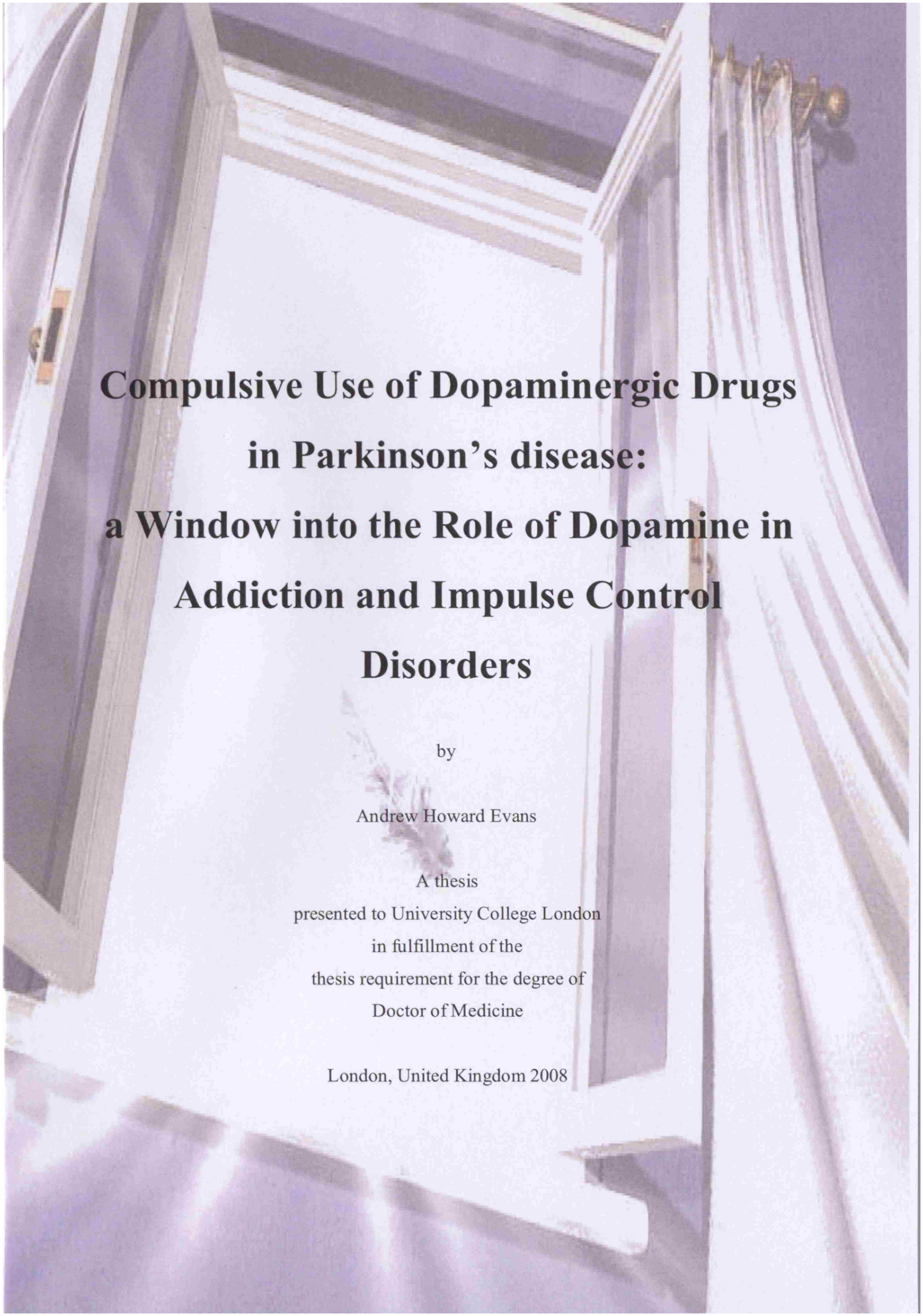

Compulsive Use of Dopaminergic Drugs in Parkinson's disease: a Window into the Role of Dopamine in Addiction and Impulse Control Disorders

by

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List of Abbreviations

AIMS	Abnormal Involuntary Movements Scale
ANOVA	Analysis of variance
BAS	Behavioural Approach Scale
BP	Binding potential
CARROT	Card Arranging Reward Responsivity Objective Test
DA	Dopamine agonist
DBS	Deep brain stimulation
DCI	Dopa-decarboxylase inhibitor
DDS	Dopamine Dysregulation Syndrome
DEQ	Drug effects questionnaire
DIY	Do-it-yourself
DRT	Dopamine replacement therapy
DSM-IV	Diagnostic and statistical manual, 4th edition
ECG	Electrocardiogram
fMRI	functional Magnetic resonance imaging
GABA	Gamma-aminobutyric acid
GDS	Geriatric Depression Scale
GPi	Globus pallidus pars interna
GPe	Globus pallidus pars externa
H&Y	Hoehn and Yahr score
HHD	Hedonic homoeostatic dysregulation
HPA	Hypothalamic-pituitary-adrenal
ICD-10	International classification of disease and related health problems, 10th revision
^{123}I FP-CIT	[^{123}I]-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl)-nortropane
ISS	Impulsive sensation seeking
IST	Incentive sensitisation theory
IT	Information technology
L-dopa	L-3,4-dihydroxyphenylalanine
LEU	L-dopa equivalent unit

LRRK2	Leucine rich repeat kinase 2
MAO-B	Monoamine oxidase B
MMP	Minimental Parkinson
MMSE	Minimental state examination
MPH	Methylphenidate
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRI	Magnetic resonance imaging
NA	Negative affect
NET	Norepinephrine transporter
NS	Novelty seeking
OCD	Obsessive compulsive disorder
OCI	Obsessive Compulsive Inventory
6-OHDA	6-Hydroxydopamine
PA	Positive affect
PANAS	Positive and negative affect schedule
PD	Parkinson's disease
PET	Positron emission tomography
RAC	^{11}C-labelled raclopride
ROI	Region of interest
SD	Standard deviation
SEM	Standard error of the mean
SNc	Substantia nigra pars compacta
SNr	Substantia nigra pars reticulatum
SPM	Statistical parametric mapping
SSS	Sensation Seeking Scale
STN	Subthalamic nucleus
TAC	Time activity curve
TCI	Temperament and Character Inventory
UCHL1	Ubiquitin carboxyterminal hydrolase 1
UCLH	University College London Hospitals
UK	United Kingdom

UPDRS	Unified Parkinson's Disease Rating Scale
VAS	Visual analogue scales
VL	Ventrolateral thalamic nuclei
VP	Ventral pallidum
VTA	Ventral tegmental area
VS	Ventral striatum

Abstract

A small group of patients with Parkinson's disease (PD) compulsively use dopaminergic medications despite the frequent emergence of harmful physical, psychiatric and social effects. This behavioural syndrome has been termed the dopamine dysregulation syndrome (DDS) and although closely related, should be distinguished from impulse control disorders. The phenomenology, risk factors and neurobiology of DDS have been explored in a series of observational, neuropsychological and pharmacological clinical studies.

Dopaminergic drug-responsive complex repetitive stereotypical behaviours (punding) were identified and characterised in PD outpatients selected on the basis of their dopaminergic drug intake. In animal models of Parkinson's disease, stereotypies are known to index the neuroadaptive changes of sensitisation. Punding was found to be associated with DDS, dyskinesia severity and harmful neuropsychiatric disturbances raising the possibility that the biological mechanisms underlying drug-reward and these behaviours may overlap.

Psychostimulant drugs have powerful effects on dopamine release and re-uptake in the presynaptic dopamine system and are capable of inducing neuroplastic changes in the basal ganglia particularly after their intermittent administration. Psychostimulant drugs have dopaminergic effects but have only been demonstrated to have weak anti-Parkinsonian effects. The acute effects of L-dopa and methylphenidate were examined (which has effects similar to psychostimulant drugs) in 15 untreated PD patients, before and again after a mean 18 months of sustained dopaminergic drug therapy. After sustained dopaminergic therapy, the motor effects of L-dopa and the euphoriant effects of methylphenidate were augmented. This provided clinical support in humans for the first time that sustained dopaminergic drug therapy may result in psychomotor sensitisation.

In an effort to facilitate early identification of DDS and for planning prompt therapeutic interventions personality traits were examined in PD patients with DDS and compared to those without DDS and healthy controls. DDS patients were found to differ from control PD patients and age-matched healthy controls in personality dimensions linked with substance dependence i.e. high impulsive sensation seeking traits, low harm avoidance, reward dependence, self-directedness and cooperativeness. Impulsive sensation seeking traits in particular, in addition to premorbid addictive

behaviour were also found to predict the emergence of DDS suggesting a common neurobiological vulnerability.

DDS patients complain of an aversive drug withdrawal state akin to the withdrawal state seen in other forms of addiction. Many patients attribute avoidance of aversive "offs" as the reason behind their compulsive drive to self-medicate. This aversive "off"-state was examined in 20 DDS patients and PD controls and found to be associated with behaviours that may lead to sensitisation of brain reward systems.

Most authorities believe that compulsive drug-taking and associated behavioural disorders are mediated through the mesolimbic dopaminergic projections and the nucleus accumbens. DDS was investigated using a two-scan ^{11}C-Raclopride protocol. Drug-induced sensitisation of ventral striatal-circuitry appeared to mediate compulsive drug "wanting" – providing the first evidence of such in humans.

Greater understanding of compulsive dopaminergic drug use in PD should not only inform the management of PD but may provide insight into the mechanisms underlying impulse control disorders.

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Chapter 1
INTRODUCTION

Summary

Parkinson's disease is a common neurodegenerative disease characterised by bradykinesia, rigidity and rest tremor. Symptomatic treatment with drugs acting on brain dopaminergic systems has proved very effective in reducing motor disability. However, abnormal involuntary movements may mar the long term therapeutic response to chronic treatment in some patients.

A few individuals appear to compulsively use dopaminergic medications well in excess of a dose that might be expected to achieve good motor control and despite the emergence of harmful drug-responsive behaviours. This study aimed to define the range of behaviours that result from dopaminergic drugs and explore individual variables that may predispose to their genesis. The findings may provide ways of detecting vulnerable patients at an early stage and thereby prevent the inevitable catastrophic behavioural and social sequelae of dopamine dysregulation and have broader implications for the better understanding of the mechanisms underlying addictive behaviour.

1.1 Clinical aspects of Parkinson's disease

PD was first fully described in 1817 by the Shoreditch apothecary James Parkinson (Parkinson, 1817; Arnett *et al.* 1997). Two centuries later the cause of the "Shaking Palsy" remains largely elusive, its diagnosis dependent on clinical acumen, and its management problematic. It is a slowly progressive, degenerative, neurological disorder that destroys selected brain regions and depletes nigrostriatal dopamine. In the UK around one in 500 people, or 120,000 individuals, have PD. Increasing age is the greatest risk factor for PD. However, up to 5% of patients who receive the diagnosis are under the age of 40 years. Men are slightly more prone to developing PD than women (Lang and Lozano, 1998a). Diagnosis of a Parkinsonian syndrome depends on the presence of bradykinesia with at least one of the following; muscular rigidity, 4-6 Hz rest tremor and postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction (Hughes *et al.* 1992).

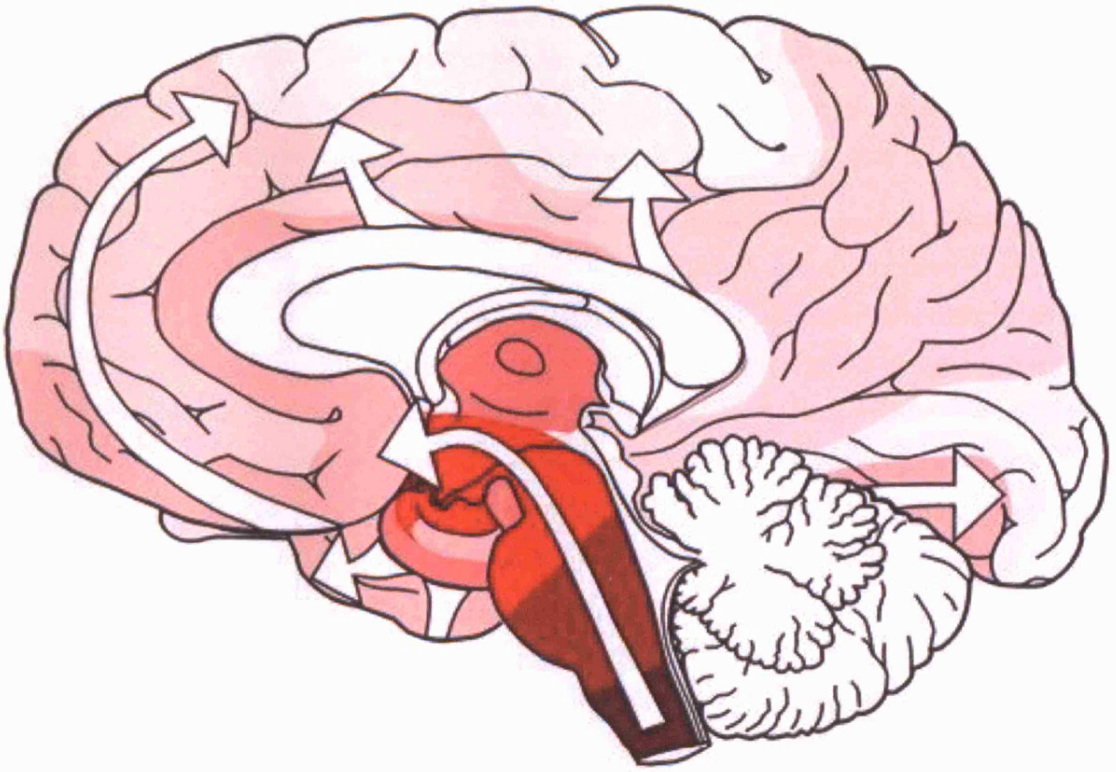
Patients with PD may also have distressing autonomic and neuropsychiatric symptoms which sometimes precede the primary disturbances of movement.

Depression (Schuurman *et al.* 2002), constipation (Abbott *et al.* 2001) and anosmia (Henderson *et al.* 2003) have all been reported to antedate the motor symptoms of PD by many years in some cases.

1.2 Neuropathology of Parkinson's disease

PD is a multisystem disorder that involves nerve cells in specific regions of the human nervous system. The formation of intraneuronal inclusions—pale bodies and Lewy bodies in cell somata, as well as Lewy neurites in the cellular processes of a few vulnerable nerve cell types are considered by most neurologists to be an essential prerequisite for the pathological confirmation of the clinical diagnosis. Misfolded and aggregated alpha-synuclein is present in Lewy bodies (Golbe, 1999). Braak and colleagues have recently proposed a challenging and controversial hypothesis that the pathological process of PD starts in the enteric nervous system, the anterior olfactory structures and the dorsal motor nucleus of the vagus and then progresses rostrally to finally involve the neocortex (Figure 1-1) (Braak *et al.* 2004).

Figure 1-1: Diagram showing the ascending pathological process of Parkinson's disease (white arrows) – adapted from Braak *et al.* 2004.



Worsening motor symptoms during the course of PD are thought to reflect degeneration particularly within the dopaminergic pathways. There are three main dopaminergic cell groups in the midbrain, the A8 group in the lateral reticular formation, the A9 group in the substantia nigra and the A10 group in the medial and dorsal tegmentum. The nigrostriatal system, which originates in the zona compacta of the substantia nigra, is identified most strongly with motor function. Fibres from this subdivision project primarily to the caudate–putamen (dorsal striatum). More medial are the mesolimbic and mesocortical dopamine systems, which are more important for motivational function and arise from the dopamine cells that are associated with the ventral tegmentum. Cell loss from the substantia nigra occurs in a region-specific manner. The most severe loss of dopaminergic neurons occurs in the

ventrolateral part of the substantia nigra pars compacta (Fearnley and Lees, 1991) and follows a stereotyped temporospatial progression with a global caudal-to-rostral, lateral-to-medial and ventral-to-dorsal direction of progression (Damier *et al.* 1999). The loss of midbrain dopamine neurons is most severe and occurs earliest in ventral cell groups that project to the putamen (motor striatum) compared to dorsal cell groups that innervate the caudate nucleus (Gibb and Lees, 1991). The resulting selective loss of putaminal dopamine is thought to be responsible for the appearance of motor symptoms once the striatal dopamine loss exceeds the threshold value of 60% (Hornykiewicz and Kish, 1986).

There are smaller numbers of dopaminergic neurons in the A8 and A10 regions compared to the A9. Post-mortem studies of neuronal loss within the extranigral cell groups are difficult to interpret because of difference in anatomical methods and subject selection. The A8 cell group has been reported by some to be preserved in PD (McRitchie *et al.* 1997; Mouatt-Prigent *et al.* 1994) whereas others have found significant reductions in dopaminergic cells in this region (Damier *et al.* 1999; German *et al.* 1989; Hirsch *et al.* 1988). Studies of the A10 area in PD have more consistently shown reductions in both dopaminergic (between 8-85%) and nondopaminergic neuron numbers (around 21%) but this cell loss is highly variable and appears unrelated to subject age or disease duration (Damier *et al.* 1999; German *et al.* 1989; Hirsch *et al.* 1988; McRitchie *et al.* 1997; Uhl *et al.* 1985). For instance, the dopamine cell depletion appears to particularly affect the parabrachial pigmented and parapeduncular nuclei. Moreover there is a reduction in tyrosine hydroxylase-immunoreactive positive cells in some A10 cell clusters (caudal linear nucleus and paranigral nucleus) without evidence of neurodegeneration (McRitchie *et al.* 1997). Therefore, other factors such as ageing or medication effects may be important in the aetiology of dopamine neuron loss within the extranigral regions. As a consequence of ventral tegmentum dopamine cell loss in PD, the concentrations of dopamine and its major metabolite, homovanillic acid, in the nucleus accumbens are reduced by 50-60% (Hornykiewicz, 1998) at death. Cortical dopamine is also reduced (Hornykiewicz and Kish, 1986; Scatton *et al.* 1983). However, in life, PD patients with advanced disease have been reported to show a normal capacity to release endogenous dopamine from prefrontal regions after a pharmacological challenge (Piccini *et al.* 2003).

1.2.1 The pathological substrate for dementia in Parkinson's disease

In the late stages, the degenerative process involves higher order centers of the limbic loop in particular. The amygdala is pivotal within the limbic system and undergoes severe pathological changes in the course of PD. The amygdala receives a broad range of afferents, allowing integration of exteroceptive information with interoceptive data. It generates major projections to the isocortex (the prefrontal cortex in particular), limbic system (hippocampus and entorhinal region) and centers which regulate endocrine and autonomic functions. Lewy degeneration occurs in a specific manner throughout the amygdalar nuclear complex and the lesional pattern displays only minor interindividual variation. The most prominent changes occur in the accessory cortical and central nuclei. In primates, the central nuclei give projections to the nucleus basal nucleus of Meynert, ventral tegmental area, raphe and locus coerulus and subsequently mediate ascending influences on arousal. The cortical, accessory basal and granular nuclei show less severe alterations, while the basal and lateral nuclei, as well as the intercalated cell masses, generally remain uninvolved (Braak *et al.* 1994). Additionally, all of the limbic and autonomic centers bidirectionally connected with the amygdala display intense PD related changes. These structures include the periacqueductal grey, the parabrachial region, the gigantocellular nucleus of the reticular formation, the intermediate reticular zone, and the dorsal vagal area, together with the centres for regulation of the digestive tract, respiratory organs, and the cardiovascular system (Braak and Braak, 2000). Lewy bodies and Lewy neurites are also frequently seen in the hippocampal formation and are greatest in the CA2-3 fields (Churchyard and Lees, 1997). In the human thalamus, a specific and highly stereotypical distribution pattern of Lewy bodies and neurites evolves. The components of human thalamus which form part of the limbic loop bear the brunt of the PD-related pathology compared to the striatal, cerebellar and primary sensory nuclei of the thalamus which show at best a mildly developed pathology (Rub *et al.* 2002). Cortical Lewy bodies are frequently found in other limbic sites such as the entorhinal cortex, agranular insular cortex (layer VI), cingulate gyrus and frontotemporal neocortex (Braak and Braak, 2000) but spare pre- and post- central gyri, the parietal and occipital cortices.

Lewy degeneration within limbic regions appears to correlate moderately well with dementia. The presence of dementia in PD predicts more severe neuronal loss within A10 nuclei compared to nondemented PD subjects, higher Lewy body density in the limbic cortex (Zweig *et al.* 1993), hippocampal CA2 region (Churchyard and Lees, 1997) and neocortex (Apaydin *et al.* 2002). Lewy degeneration of limbic and related structures may inhibit the flow of data between the neocortex and

the higher order centers of the limbic system, as well as hampering their influence on the prefrontal cortex and contribute to the cognitive decline, bradyphrenia, mood disturbance, autonomic and reward dysfunction of PD. In some individuals, however, cognitive decline can develop in the presence of mild PD-related cortical pathology and, conversely, widespread cortical lesions do not necessarily lead to cognitive decline (Colosimo *et al.* 2003). On the other hand, Alzheimer type pathology is frequently (10-60%) found in PD patients (Mahler and Cummings, 1990) and also significantly correlates with the presence of dementia (Braak *et al.* 1996; Jellinger *et al.* 2002; Mattila *et al.* 2000). Alzheimer change is more frequently found as the density of Lewy body change increases (Apaydin *et al.* 2002). Co-existent Alzheimer change may further contribute to development of dementia or represent a marker of pathological severity. Moreover, the APOE epsilon4 allele may also influence the prevalence of dementia in PD (Huang *et al.* 2006).

The role of other neurotransmitter systems in the neuropsychiatric and motoric manifestations of PD is poorly understood. Neuronal loss also occurs within the cholinergic nucleus basalis of Meynert, the noradrenergic locus coeruleus, and the serotonergic raphe nuclei. There is evidence that cholinergic deficits due to degeneration of the ascending cholinergic pathways contribute to cognitive impairment and dementia in patients with PD. A decrease in cholinergic innervation of the cerebral cortex and severe cellular loss in the basal nucleus of Meynert is found in patients with PD (Dubois *et al.* 1983); this deficit and cellular loss correlates with the level of cognitive impairment and presence of dementia (Perry *et al.* 1985; Hilker *et al.* 2005). Cognitive impairment appears to be most closely associated with cholinergic, but not monoaminergic, deficits in temporal and archicortical areas (Perry *et al.* 1991). Conversely, anticholinergics cause memory impairment in non-demented patients with PD but not in healthy control individuals (Dubois *et al.* 1987) and have been linked to acceleration of amyloidosis and senile plaque formation in the aging brain in subjects with PD (Perry *et al.* 2003). A recent study of a cholinesterase inhibitor for PD dementia found statistically significant improvements in measures of cognitive performance and several behavioural measures relative to placebo (Emre *et al.* 2004). Over a 6 month period, clinically meaningful (moderate or marked) improvement occurred in 5.3% more patients on rivastigmine, and meaningful worsening occurred in 10.1% more patients on placebo (Maidment *et al.* 2006). Noradrenaline depletion has been linked to depression (Remy *et al.* 2005) and serotonergic dysfunction to tremor (Doder *et al.* 2003).

1.3 Aetiology of Parkinson's disease

In recent years, the discovery of a number of genes and several more loci has provided important insight into the molecular aetiology. Some genes may cause PD through promoting protein aggregation. However, the presence of Lewy bodies in carriers of mutations in some genes and their absence in carriers of others, still point towards a complex pathogenic network, with PD as a common clinical end point. Despite knowledge of genetics in familial PD, knowledge of the common, late-onset form of PD remains limited. In non-familial PD, genes and environment probably interact to give rise to the disease.

1.3.1 Genetic factors

There is increasing evidence that genetic factors have an important role in PD. Epidemiological studies with varying designs have consistently suggested a higher prevalence of PD among first-degree relatives of index patients compared to the general population (e.g. (Sveinbjornsdottir *et al.* 2000)). Since 1997, six "PARK" genes have been identified using genetic linkage methods in families segregating autosomal dominant (Alpha-synuclein, UCHL1, LRRK2) and autosomal recessive (Parkin, PINK1 and DJ1) forms of PD (Table 1-1). Then, the discovery of PD-causing, dominantly-acting-synuclein mutations (PARK 1 (Polymeropoulos *et al.* 1997)) and its association between a polymorphic marker in the promoter region of alpha-synuclein gave insight into PD in its common, "sporadic" form (Farrer *et al.* 2001). Upon the identification of the mutations in its encoding gene, it was identified to be a principal component of Lewy bodies (Spillantini *et al.* 1997). The physiological role of alpha-synuclein is still somewhat obscure, but its abundant localisation at presynaptic terminals and some functional studies indicate a possible role in synaptic plasticity and vesicular transport. The mutant protein results in increased apoptotic responses, enhanced susceptibility to oxidative stress, and facilitates fibril formation giving rise to Lewy bodies (Alves da Costa, 2003). Most recently, leucine-rich repeat kinase 2 (LRRK2) was identified as an important causative gene in families linked to the autosomal dominantly inherited PARK8 locus on chromosome 12p11.2–q13.1. The predicted product of the LRRK2 gene is a large protein with 2527 amino acids; sequence comparison suggests that it may function as a protein kinase (Paisan-Ruiz *et al.* 2004). It is implicated in up to 10% of autosomal dominant PD cases (Di Fonzo *et al.* 2006) and is associated with a variety of histopathological findings (Galpern and Lang, 2006). A mutation in the gene encoding ubiquitin carboxyterminal hydrolase 1 (UCHL1) has been described in a single small German kindred with

autosomal dominantly inherited PD (PARK5 (Leroy *et al.* 1998)) and the S18Y polymorphism in the UCHL1 gene may be associated with decreased risk for PD (Maraganore *et al.* 2004a).

Table 1-1: Loci and genes linked and associated with PD (adapted from Mata *et al.* 2004)

PD locus	Chromosome	Gene	Mode of inheritance*	Clinical features	Reference
PARK1	4q21.3	α-synuclein	AD	Early onset	(Polymeropoulos *et al.* 1997)
PARK2	6q25.2-27	Parkin	AR	Early onset	(Kitada *et al.* 1998)
PARK3	2p13	-	AD	Late onset	(Gasser *et al.* 1998)
PARK5	4p14	UCHL-1	AD	Late onset	(Leroy *et al.* 1998)
PARK6	1p35-36	PINK1	AR	Early onset	(Valente *et al.* 2004)
PARK7	1p36	DJ1	AR	Early onset	(Bonifati *et al.* 2003)
PARK8	12q12-q13.1	LRRK2	AD	Late onset	(Paisan-Ruiz *et al.* 2004; Zimprich *et al.* 2004)
PARK9	1p36	ATP13A2	AR	Early onset	(Ramirez *et al.* 2006)
PARK10	1p32	-	Complex	Late onset	(Hicks *et al.* 2002)
PARK11	2q36-37	-	Complex		(Pankratz *et al.* 2002)
-	2q24.1	Nurr1	Complex	Late onset	(Le *et al.* 2003)

*AR=autosomal recessive, AD=autosomal dominant inheritance

Parkin mutations are the most common cause of autosomal recessive PD. It is typically young-onset without Lewy degeneration. Parkin localises to the Lewy bodies of PD in those patients who do not carry Parkin mutations (Hague *et al.* 2005). In addition, polymorphisms in the Parkin gene may be associated with idiopathic PD (West *et al.* 2002). Both parkin and UCHL1 are involved in the ubiquitin dependent degradation of intracellular misfolded, unassembled, or damaged proteins by the proteasome, a multicatalytic complex. Autosomal recessive mutations in the DJ-1 gene (PARK7) are thought to be a rare cause of PD with prominent behavioural disturbances early in the course of the disease. DJ-1 mutations are associated with impaired oxidative stress defense, lead to reduced DJ-1 protein stability, and the mutant protein is rapidly degraded through the ubiquitin–proteasome system

(Miller *et al.* 2003). DJ-1 polymorphisms may also confer increased susceptibility to sporadic PD (Maraganore *et al.* 2004b). Autosomal recessively inherited mutations in the PTEN induced kinase 1 on chromosome 1p36 (PARK6) are also implicated in PD. Cell culture studies suggest that PINK1 is mitochondrially located and may exert a protective effect on the cell that is abrogated by the mutations, resulting in increased susceptibility to cellular stress (Valente *et al.* 2004). Although abnormal protein inclusions characterise many genetic forms of PD, there is incomplete understanding of the nature of these protein interactions, the triggers for inclusion formation, and their role in disease pathogenesis.

1.3.2 Environmental factors

One factor consistently associated with a reduced risk of PD is smoking. Three recent meta-analyses of case-control and cohort studies have examined the association between smoking and PD (Allam *et al.* 2004; Hernan *et al.* 2002; Sugita *et al.* 2001). Compared to never-smokers, the pooled relative risk of PD for ever-smokers was 0.51–0.59, for past smokers 0.66–0.80, and for current smokers 0.35–0.39. PD risk also decreases with cumulative exposure to smoking: the relative risk per 10 additional pack-years was between 0.78–0.84. This relationship has been claimed to exist even after adjusting for possible genetic influences on addictive behaviours (Hernan *et al.* 2002). Caffeine intake also appears to be protective against PD independently of smoking (Hernan *et al.* 2002). A meta-analysis showed a pooled relative risk of PD of 0.69 (95% CI 0.59–0.80) for coffee drinkers compared to non-coffee drinkers (Hernan *et al.* 2002). An independent predictive relationship between alcohol intake and PD is less clear (Hernan *et al.* 2003) and transient Parkinsonism has even been described after alcohol withdrawal and excess (Fernandez and Lees, 1992). A possible explanation is that the central actions of caffeine and nicotine may improve the health of brain dopamine systems (Allam *et al.* 2004) and protect against PD (Quik, 2004).

However, it is possible that these findings are epiphenomena rather than being causally linked. Certain personality characteristics of individuals destined to develop PD may make them less prone to start smoking (and/or more likely to stop) (Menza *et al.* 1994; Evans *et al.* 2006a). A distinctive ananacastic behavioural profile has been anecdotally associated with PD. As a group they tend to be industrious, anhedonic, obsessive, cautious, inflexible and disinclined to take risks (Hubble and Koller, 1995; Menza *et al.* 1993; Paulson and Dadmehr, 1991; Todes and Lees, 1985). These personality variants may antedate the motor changes in PD by decades (Poewe *et al.* 1990). Novelty

seeking and related personality variants have been characterised by reduced novelty seeking scores and are proposed to be related to variations in dopaminergic function in the mesolimbic system. They strongly predict the uptake and maintenance of drug-taking behaviours (Cloninger, 1987a; Zuckerman, 1994). Certain genes such as polymorphisms in genes involved in dopamine catabolism (Checkoway *et al.* 1998) might also modify behaviours such as smoking, caffeine and alcohol intake.

A number of causative factors have been found to induce Parkinsonism similar to that of idiopathic PD, including vascular insults to the brain, repeated head trauma, neuroleptic drugs, and manganese toxicity (Adler, 1999). The toxicant 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine caused acute Parkinsonism similar to the idiopathic disease in a small group of drug addicts (Langston *et al.* 1983) and spawned an interest in the possible role of exogenous toxicants in the development of PD.

A rural environment has generally, although not always, been found to be associated with an elevated risk of PD. There is varying support for a relation with such factors as the use of herbicides or pesticides and consumption of well water (Priyadarshi *et al.* 2001), farming, and rural living. However, epidemiology and toxicology studies are limited by methodologic weaknesses and fail to account for gene-environment interactions. Even if one accepts the role of pesticide use, the proportion of patients with such exposure, and therefore the importance of this risk to the public health, is limited to approximately 10 percent of the population with PD (Semchuk *et al.* 1992). Also most of these chemicals have only been used for the last 40 years (Rajput *et al.* 1987).

1.4 Motor features of Parkinson's disease

The most frequent presentation for PD is an asymmetrical resting tremor in a limb, most commonly one hand that disappears with voluntary movement. It frequently emerges in a hand while the person is walking. Rest tremor is virtually pathognomonic of PD and may involve the tongue, head, trunk and chin (Nutt and Wooten, 2005). The bradykinesia of PD begins asymmetrically in about 75 percent of patients (Gelb *et al.* 1999). It is often described by the patient as a weakness of a hand or leg, but strength testing reveals no abnormalities. However, assessment of dexterity by finger tapping and toe tapping shows slowing, reduced amplitude of movement, and irregular cadence that become more apparent as the patient continues the movement. Fine movements are affected more than large movements, so that the patient first notices difficulty using small tools and fastening buttons.

Repetitive movements also suffer; for example, brushing the teeth may be difficult. Bradykinesia also manifests as micrographia, hypomimia, reduced blink rate, and hypophonia.

The rigidity of PD may be experienced as stiffness associated with vague aching and discomfort of a limb suggesting musculoskeletal syndromes, particularly bursitis and tendinitis. In the arm, this rigidity may progress to a frozen shoulder. Early PD may cause slowing of gait, dragging of the foot, and decreased arm swing on the affected side. Patients may notice difficulty getting out of cars, rising from deep chairs, and rolling over in bed. Shuffling gait, freezing, and falls develop in the course of the disease. Disease progression leads to the bilateral spread of symptoms, but asymmetry is maintained in the degree of symptoms experienced with the onset side generally remaining the most affected throughout the disease.

1.5 Symptomatic therapy of Parkinson's disease

1.5.1 Early medical treatment

None of the currently available treatments for PD are capable of replacing or restoring the degenerating neurons. The perceived selective nature of the presynaptic nigrostriatal degeneration constituted the biochemical rationale for the first use of dopaminergic drug therapies in targeting disease symptoms (Hornykiewicz and Kish, 1986). Drugs are warranted when the patient is sufficiently bothered by symptoms to desire treatment or when the disease is producing disability; patients' preferences are critical to making this decision. If the patient needs treatment for motor symptoms, efficacious agents for initial therapy include L-dopa, dopamine agonists, anticholinergics agents, amantadine, and selective monoamine oxidase B (MAO-B) inhibitors. Dopaminergic agents are more potent than the anticholinergic agents, amantadine, and selective MAO-B inhibitors in attenuating the motor symptoms. L-Dopa, a dopamine precursor, is considered the most effective anti-Parkinsonian agent. In randomised trials comparing L-dopa and a dopamine agonist, activities of daily living and motor features of PD improved with L-dopa by about 40 to 50 percent (as compared with approximately 30 percent with dopamine agonists) (Nutt and Wooten, 2005). Although dopamine agonists are slightly less effective than L-dopa, they are alternative first-line agents for PD. The various dopamine agonists have similar efficacy. One potential advantage of these agents is that, as compared with L-dopa, their use is associated with a lower risk by a factor of two or three of dyskinesia and motor fluctuations in the first four to five years of treatment, particularly among

patients receiving dopamine-agonist monotherapy (Nutt and Wooten, 2005). However, it is common for L-dopa to be needed in addition to dopamine-agonist therapy within a few years after diagnosis to control advancing symptoms. In general, a slightly lower incidence of motor complications is achieved by initiating a dopamine agonist at the expense of significantly worse disability scores throughout the first years of therapy (Lees *et al.* 2001). Dopamine agonists are avoided in the treatment of patients with dementia because of the drugs' propensity to produce hallucinations.

1.5.2 Late medical treatment

The main symptoms of PD respond inconsistently. Tremor may be more resistant to medical therapy than other symptoms. With disease progression patients develop persistent and progressive disability even in "on" periods (those characterised by greater mobility due to the beneficial actions of L-dopa) of motor fluctuations. Motor fluctuations occur in ~50% of patients after 5 years of L-dopa therapy (at this time they usually affect patients for <25% of their waking hours). The proportion of patients affected increases to ~70% among those treated for more than 15 years (Miyawaki *et al.* 1997). Motor fluctuations include predictable "off" periods (predictable periods of immobility or greater severity of other Parkinsonian symptoms when medications wear "off" - i.e., "wearing off"), and unpredictable "off" periods (or "on"-"off" fluctuations). With ongoing treatment, patients with motor fluctuations may notice an increase in the interval between a dose of medication and the patient's experience of an "on" response ("delayed on") and the absence of a response to an individual dose ("dose failure" or "no on"). Motor fluctuations are typically more troublesome in patients with young-onset PD (Jankovic, 2005).

L-Dopa-induced dyskinesias are clinically and pharmacologically heterogeneous. Dystonic posturing of a limb may coincide with low levels of dopaminergic stimulation, such as occurs in the "off" periods. Early on many patients are unaware of the presence of their choreoathetotic movements, which usually occur when the effect of the medication is at its peak. With time, these dyskinesias may become a source of considerable disability and may persist throughout the response to an individual dose. Some patients have enhanced dyskinesia, especially involving the lower body, at the onset or end of the response to medication (so-called diphasic dyskinesias) (Lang and Lozano, 1998b).

A large body of preclinical evidence and clinical data indicate that L-dopa-induced motor complications arise from pulsatile stimulation of striatal dopamine receptors (Kuoppamaki *et al.*

2002). Pulsatile stimulation of dopamine receptors leads to gene and protein changes in striatal neurons with alterations in neuronal firing patterns and the consequent development of motor complications (Obeso *et al.* 2000). These changes in the postsynaptic medium spiny neurons of the striatum, particularly involve glutamatergic receptors, and in striatopallidal circuits. Disease severity and half life of the dopaminergic agent employed are important factors in the pathophysiology of motor fluctuations (Widnell, 2005). L-Dopa-induced dyskinesia emerge within days in 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) monkeys where there is a 95% loss of nigral neurons, whereas they develop over months or years in PD patients where there is typically a 30-60% loss of dopamine neurons at the time symptoms first appear. Studies in MPTP lesioned monkeys also illustrate the importance of plasma half life in the induction of dyskinesia (Obeso *et al.* 2000; Pearce *et al.* 1998). Short-acting dopaminergic agents such as L-dopa provide benefit that is associated with dyskinesia. In contrast, long-acting dopamine agonists provide lesser benefit, but with a marked reduction in both the severity and frequency of dyskinesia. Indeed, dyskinesias are seen with pulsatile administration of a short-acting dopamine agonist, but not when the same agent is administered by continuous infusion (Bibbiani *et al.* 2005). This hypothesis is supported by the progressive improvement in fluctuations and dyskinesias, in the response to treatment in patients treated with continuous methods of dopaminergic stimulation, such as with subcutaneous apomorphine pumps (Katzenschlager *et al.* 2005).

1.5.3 Nonpharmacological therapies

L-Dopa–related motor complications are a reason why patients with PD may be referred for surgery. Neurosurgical approaches in advanced PD have concentrated on placing a discrete lesion or electrode into the subthalamic (STN) or globus pallidus pars interna (GPi) with the aim of disrupting basal-ganglia pathways back towards normal. These techniques were initially developed in the 1950s. With improvement in surgical techniques, deep brain stimulation (DBS) of the subthalamic nucleus (STN) is now generally regarded as the most effective form of surgical therapy for PD (Volkmann *et al.* 2004). Persistent improvement (with no evidence of tolerance to the stimulation) in L-dopa–responsive motor features has been demonstrated for a number of years after STN DBS in the "off-medication" state (i.e. reduction in "off" scores; tremor, rigidity, akinesia and disabling "off"-period dystonia). Doses of dopaminergic drugs can be substantially reduced and in part because of this and in part because of an antidyskinetic effect of chronic stimulation, L-dopa–induced dyskinesias are

improved. The symptoms experienced by patients in their best "on" response to L-dopa are not affected (Krack *et al.* 2003). Whereas motor improvement has been consistently documented, cognitive dysfunction, mood changes, behavioural disturbances, and apathy are potential complications of STN DBS (Burkhard *et al.* 2004; Funkiewiez *et al.* 2004). Preoperative psychiatric vulnerability, the effects of surgery, stimulation, medication changes, and psychosocial adjustment have been proposed as causative factors. Cautious preoperative screening and careful postoperative follow-up is likely to be required to optimise treatment response.

1.6 Non-motor features of Parkinson's disease

Patients report a broad spectrum of non-motor symptoms and in some these symptoms may come to overshadow the motor disability. They include neurobehavioural disturbances, psychosis, cognitive impairment, autonomic disturbances involving cardiovascular regulation, swallowing, bladder and bowel function, sensory symptoms such as pain and REM sleep behaviour disorder and deficits of olfaction.

The incidence of dementia has been estimated to be four times greater than in controls. Several features are consistently reported to be associated with prevalent dementia. Risk factors for dementia include age at onset, age at the time of study, duration of the disease, predominant akinetic-rigid features, depression, and atypical neurological features (such as early occurrence of autonomic failure, symmetrical disease presentation, and moderate response to dopaminergic treatment). Dementia is a major risk factor for nursing home placement and the risk of death in patients with PD is substantially higher for those with dementia (Emre, 2003).

Some patients develop a paranoid psychosis with a prominent pathological jealousy which improves following reduction of anti-Parkinsonian therapy. Vesperal visual hallucinations, usually of people, and animals, are common as are extracampine and passage hallucinations and may be associated with delirium and daytime somnolence. Misidentification syndromes are also frequently reported by family members (Adler, 2005). Antipsychotic medications are often used to treat neuropsychiatric complications (such as hallucinations) of PD (Emre *et al.* 2004) but these are not always effective and recently cholinomimetics have been proposed as an alternative for the hallucinations (Ondo *et al.* 2002; Emre *et al.* 2004; Ondo *et al.* 2005). Clozapine to date remains the only atypical antipsychotic drug with proven efficacy in 2 small short-term placebo-controlled

randomised controlled trials in PD patients with drug-induced psychosis (The Parkinson Study Group, 1999; Pollak *et al.* 2004). Adverse effects include sedation, subjective worsening of Parkinsonism, postural hypotension, neutropenia and sialorrhea. All of the atypical antipsychotics are associated with an adverse metabolic syndrome (Newcomer, 2005) and carry an increased risk of death (Schneider *et al.* 2005).

There seems to be a reciprocal relationship between PD and depression; depression is frequently associated with PD (figures ranging between 2.7% and 70% (Burn, 2002a)) and developing depression in mid-adult life is an independent risk factor for the subsequent development of PD (Schuurman *et al.* 2002). Significant anxiety is also frequently associated with depression in PD. Depressive symptoms may increase the risk of subsequent dementia and are closely related to quality of life, sleep disturbance and sexual dysfunction in the PD patient. They are also an important and consistent contributor to caregiver distress (Burn, 2002a).

1.6.1 Non-motor fluctuations

The majority of L-dopa treated patients with PD experience non-motor fluctuations in the course of their illness (Gunal *et al.* 2002; Witjas *et al.* 2002). They typically occur after the appearance of motor fluctuations and are often equally or even more disabling (Witjas *et al.* 2002). Non-motor symptoms have also been linked to increased disability due to motor complications but this correlation is not invariable (Witjas *et al.* 2002). About two-thirds of patients describe mood fluctuations (Nissenbaum *et al.* 1987; Witjas *et al.* 2002) characterised by withdrawal, anxiety, fatigue, irritability, lassitude, sadness, transient suicidal feelings and panic (Gunal *et al.* 2002; Hillen and Sage, 1996; Witjas *et al.* 2002): described under the rubric "dysphoria" (Maricle *et al.* 1998). More distressing "off" symptoms include hallucinosis, guilt, aggression, moaning and screaming (Riley and Lang, 1993; Gunal *et al.* 2002; Hillen and Sage, 1996; Steiger *et al.* 1991; Witjas *et al.* 2002). In contrast, euphoria, hypomania, aggression and hyperactivity are occasionally associated with the "on"-state (Lawrence *et al.* 2003; Gunal *et al.* 2002; Witjas *et al.* 2002). Recognition that these capricious mood changes are coupled with striking motor fluctuations has led to a view that these mood fluctuations might represent a psychological reaction to worsening motor disability (Menza *et al.* 1990) or be the independent result of changing brain dopamine levels (Nissenbaum *et al.* 1987; Hardie *et al.* 1984; Friedenberg and Cummings, 1989; Cantello *et al.* 1986). Mood changes may not, however, be inextricably linked with motor "offs". Several reports have highlighted cases where

severe diurnal mood fluctuations dominate the clinical picture (Riley and Lang, 1993). In one study using L-dopa infusions, the resultant mood changes preceded motor benefit by several minutes (Maricle *et al.* 1998). Another study using patient diaries failed to find consistent temporal relationships between mood and motor state (Richard *et al.* 2001). A comparison of the mood response to L-dopa challenge versus stimulation of the subthalamic nucleus has shown that L-dopa clearly has a more potent psychotropic effect despite equivalent motor benefits (Funkiewiez *et al.* 2003).

Cognitive performance may become part of the fluctuating cycles but it does not appear to be strongly influenced by affect-arousal states (Gotham *et al.* 1988). Dopaminergic medication improves or impairs cognitive performance depending on the nature of the task (Cools *et al.* 2003).

The precise origin of pain and other sensory symptoms in PD is unknown although the thalamus and corpus striatum have been implicated. Pain and sensory symptoms usually but not invariably develop ipsilateral to the body area with worse motor function and may precede the diagnosis of PD (Koller, 1984). As the illness progresses, many patients report fluctuating pain that occurs with akinesia that may overshadow all motor symptoms (Goetz *et al.* 1986b) but others may relate the pain to "on"-periods or dyskinesias (Quinn *et al.* 1986). The pain is often diffuse but can be difficult to discriminate from radicular or neuropathic causes (Quinn *et al.* 1986). Cryptogenic painful oral and genital syndromes poorly responsive to therapy have also been described (Ford *et al.* 1996). Patients with pain that is unresponsive to dopatherapy have been found to have lower pain tolerance levels and lower cerebrospinal fluid levels of monoamine metabolites (5-hydroxy-indole acetic acid) suggesting that other neurotransmitter systems may also be involved (Urakami *et al.* 1990). Akathisia (Lang and Johnson, 1987), paraesthesia, dysaesthesia, tight feelings, numbness (Gunal *et al.* 2002; Witjas *et al.* 2002) and a clinically unapparent internal tremor (Shulman *et al.* 1996) are other common sensory phenomena. Sensory symptoms frequently fluctuate with medication dosing and often cause considerable nocturnal distress.

Fluctuating patients may demonstrate autonomic signs that include sweating, pallor, hyperpyrexia, and tachycardia at the inception of their "off" states (Barbeau, 1972). Patients on chronic therapy have been shown to have higher resting pulse rate, greater orthostatic fall in blood pressure, and increased sweating responses to a heat stimulus in the "off" state (Goetz *et al.* 1986a). Subjective breathlessness typically occurs in the "off"-state (Witjas *et al.* 2002; Raudino, 2001) but occasionally accompanies

dyskinesia (Jankovic and Nour, 1986). Urinary symptoms cause significant nocturnal morbidity. They are primarily irritative (frequency, urgency, urge incontinence) and correlate with the urodynamic finding of involuntary detrusor contractions at early stages of bladder filling (detrusor hyperreflexia) (Singer, 1998). In fact, L-dopa has been shown to aggravate detrusor hyperreflexia despite improving voiding symptoms (Uchiyama *et al.* 2003). The presence of early urinary symptoms has been linked to greater reductions in striatal [^{123}I]-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl)-nortropane ([123I]-FP-CIT) uptake (Sakakibara *et al.* 2001). Off period urinary hesitancy or even retention may occur. Abdominal discomfort, aerophagy, and flatulence, bloating and feelings of constipation can cause significant "off" period distress. Unpredictable visual blurring, drooling, oral dryness, distal cold sensations and facial flushing are common. Chest pain, paroxysmal hunger, fever, "off" nausea, belching and coughing are less common symptoms (Witjas *et al.* 2002).

Some non-motor symptoms have been previously linked to disease-related parameters such as motor scores (Gunal *et al.* 2002; Nissenbaum *et al.* 1987), disease duration, dementia, psychosis or fixed depression (Racette *et al.* 2002). In contrast, other symptoms appear to be associated with the duration or dose of dopatherapy (Witjas *et al.* 2002). Questionnaire and interviewed based studies of non-motor symptoms in PD highlight the burden and range of symptomatology reported in the "off" state (Gunal *et al.* 2002; Nissenbaum *et al.* 1987; Racette *et al.* 2002; Witjas *et al.* 2002; Hillen and Sage, 1996).

1.7 Compulsive use of dopaminergic drugs in Parkinson's disease – "Dopamine Dysregulation Syndrome"

1.7.1 Essential features of patients who compulsively use dopaminergic drugs

A small subgroup of PD patients starts to take increasing quantities of medication well beyond the dose required to treat their motor disabilities in the early years of their disease. These patients request higher and higher medication doses, complain of medication ineffectiveness and tend to increase their drugs contrary to medical advice. Later on in the course of the illness, they take large quantities of drugs (over 1.5grams of L-dopa a day) and in spite of this continue to request more dopaminergic drug therapy in the face of disabling dyskinesias and distressing behavioural disturbances (Giovannoni *et al.* 2000; Merims *et al.* 2000; Spigset and von Scheele, 1997). Many self medicate using somatic cues to take their next dose of medication and any attempt by the physician to reduce

the medications is met with strong resistance. Hoarding of medication and secret pill-popping are characteristic. These patients typically identify avoidance of the distressing negative off period affective state as the reason why they need frequent dosing schedules (Beam *et al.* 2004) and some acknowledge a subjective "kick", "rush", "high" or mood benefit after taking short acting dopaminergic drugs (Giovannoni *et al.* 2000). They become preoccupied with the timing and dosing of their medication.

1.7.2 Medication tolerance

Tolerance to dopamine replacement therapy and withdrawal has proved difficult to demonstrate clinically because of the efficacy of dopaminergic medication in relieving symptoms although dose requirements generally increase somewhat over time. The development of tolerance to L-dopa is also complicated by pharmacokinetic changes related to progressive dopaminergic denervation and loss of presynaptic dopamine storage mechanisms. The duration of benefit from a single dose of L-dopa tends to reduce slightly over time but motor fluctuations are more related to an increase in baseline disability with an increased amplitude of motor response (Colosimo *et al.* 1996). Clinical pharmacological studies with intravenous dopa have demonstrated tolerance within days of initiating therapy and resensitisation to its effect occurs within a similar time period (Gancher *et al.* 1996; Nutt *et al.* 1994). These findings were part of the basis for the former recommendation of "drug-holidays" by some physicians.

1.7.3 Medication withdrawal

PD patients often describe feeling "off" despite the absence of significant worsening in the motor signs of Parkinsonism (non-motor off) and may only perceive themselves as being "on" when they have developed severe peak-dose dyskinesias. Typical "withdrawal" reactions from dopaminergic drug therapy may be masked by the severe motor impairment but motor and behaviour changes frequently occur during "on" or "off" states. These very distressing psychic fluctuations seem to parallel the motor state in many patients but in others "off" period anxiety and dysphoria can precede the motor "off" by some time. The mood during Parkinsonian "off" periods is identical to the negative affective state of withdrawal from psychostimulants in dependent individuals and is characterised by depression and anxiety which is quickly alleviated by a further drug dose (Menza *et al.* 1990).

1.7.4 Medication intoxication

Like many drugs which act on the dopaminergic system, intoxication with dopaminergic therapy leads to an organic psychosis (toxic confusional state) usually manifest as delirium and hallucinations and this can resolve on dose reduction. An acute paranoid psychosis associated with pathological jealousy similar to that seen with amphetamine and cocaine use may also occur. Thinking becomes disorganised and they display poor judgement. Rapid mood shifts are common and aggressive behaviour occurs in some patients (Giovannoni *et al.* 2000). Patients become very demanding, with irritability, and low frustration tolerance. Mania may promptly resolve after reductions in anti-Parkinson medications (Courty *et al.* 1997; Tack *et al.* 1988) but is often replaced by a negative affective state with varying degrees of dysphoria, depression, irritability and anxiety. A few patients overuse their medication deliberately to induce hypomania and euphoria (O'Brien *et al.* 1971; Przedborski *et al.* 1992).

1.7.5 Is this syndrome a substance dependence disorder or an addiction?

Tolerance, withdrawal, and hypomanic mood swings are insufficient to diagnose a Diagnostic and Statistical Manual, 4th edition (DSM-IV) "substance dependence disorder" (American Psychiatric Association, 1994) in a patient with a progressive incurable neurological disease. Under DSM-IV criteria (American Psychiatric Association, 1994), substance dependence involves a maladaptive pattern of substance use. The correct use of dopaminergic drugs in PD is to treat the motor symptoms of the disease. In a study of patients from a London clinic, structured psychiatric interviews were used in an attempt to distinguish between a "physiological" adaptive dependence with PD and a "pathological" or maladaptive dependence. In 10 patients thought to be misusing drug therapy and a group of age-matched patients with PD from the same clinic who were not thought to be misusing drug therapy, a significantly larger proportion of misusers reported anxiety and depression when unmedicated (Bearn *et al.* 2004). Avoiding being unmedicated was the reason given by most misusers for taking more medications. In addition, a significant number of misusers reported that their medications had a negative impact on their quality of life. A past history of alcohol use was greater in the misusing group, and previous illicit drug use was reported in a small number of patients. The use of dopaminergic therapy therefore appears maladaptive in some PD patients, and thus they appear to meet DSM-IV criteria for dependence.

The International Classification of Disease and related health problems, 10th revision (ICD-10) criteria for "addiction" (World Health Organization, 1990) differ from DSM-IV criteria for "dependence", but present similar difficulties when applied to PD. Nevertheless, it is clear that the individuals in the above study (Bearn *et al.* 2004) would meet ICD-10 criteria: they show difficulties in controlling their substance-taking behaviour, have a strong compulsion to take the substance, and continue to use the substance despite clear evidence of harmful consequences.

The terms dependence and addiction, however, may be unnecessarily stigmatising and inappropriate given an inexorably progressive neurodegenerative disorder. The label DDS reflects the disorder's salient features, and indicates compulsive and dysregulated drug use beyond that needed to achieve relief of motor symptoms, resulting in harmful consequences.

1.7.6 Clinical profiles of compulsive dopaminergic drug therapy use

DDS is a pattern of pathological dopamimetic medication use characterised as compulsive and beyond that needed to control the motor symptoms. This use then results in further physical, emotional, social and financial difficulty independent of the disability related to Parkinsonism. Proposed criteria for identifying the syndrome are given in (Table 1-2). Compulsive use can continue despite unsuccessful efforts by the physician, carer or patient to cut down the total daily medication dose.

Table 1-2: Current working diagnostic criteria for compulsive dopaminergic drug use (adapted from Giovannoni *et al.* 2000)

Parkinson's disease with documented L-dopa responsiveness
Need for increased doses of dopaminergic drugs in excess of those normally required to relieve Parkinsonian symptoms and signs
Pattern of pathological use: expressed need for increased dopaminergic drug therapy in the presence of excessive and significant dyskinesias despite being "on", drug hoarding or drug-seeking behaviour, unwillingness to reduce drugs
Impairment of social or occupational functioning due to the presence of disabling drug-induced psychomotor disorders
Development of hypomanic, manic, or cyclothymic affective syndrome in relation to dopaminergic drugs
Development of a withdrawal state characterised by dysphoria, depression, irritability, and anxiety with reduction of dopaminergic drugs
Duration of disturbance is of at least 6 months

A review of published case reports reveals that the majority of affected patients is male and have younger onset PD with an estimated mean age of disease onset around 48 years (Table 1-3). Past heavy alcohol intake or past experimental drug use may predispose to developing DDS (Bearn *et al.* 2004; Soyka and Huppert, 1992). Dopamine neural networks are specifically implicated in the syndrome. Dysregulation in these patients seems specific to dopaminergic drugs as these patients do not overuse anticholinergic medications which are abused by other patient groups (Dose and Tempel, 2000). Compulsive use is most frequently reported with L-dopa but may occur with both ergot and non-ergot derived dopamine agonists (Table 1-3). Many case reports highlight the use of acute "rescue" drugs, such as dispersible oral formulations of L-dopa and subcutaneous apomorphine. The addition of intermittent apomorphine injections to the therapeutic regimen can unmask or trigger medication overuse

(Giovannoni *et al.* 2000). Although there are no reports of its compulsive use, treatment with the dopaminergic, monoamine oxidase-B inhibitor selegiline can induce hypomania, compulsive spending, and transvestic fetishism (Kurlan and Dimitsopulos, 1992; Menza and Golbe, 1988; Riley, 2002). Interestingly, there are also rare reports of compulsive use of implanted subthalamic nucleus deep brain stimulators with constant demands for increases in stimulation parameters (Houeto *et al.* 2002).

The overall incidence of dopaminergic dysregulation in PD is unknown. At one centre, the incidence was estimated at 4% (Giovannoni *et al.* 2000). At another centre, the incidence was similar at 3.5% (Pezzella *et al.* 2005) but the incidence in patients with PD is likely to be considerably lower than this because of difficulties in case identification and referral bias. Management is difficult. A concerted attempt to slowly reduce the total daily dose of dopaminergic therapy under regular medical supervision is mandatory. If an impulse control disorder or disabling punding has been identified, patients who are able to discontinue or significantly decrease dopamine agonist treatment can be expected to achieve full remission or a clinically significant reduction in symptomatology without deterioration in motor control (Mamikonyan *et al.* 2008; Kimber *et al.* 2008). Attempts to achieve concordance with the patient and enforcement of dose reduction by the family are important if clandestine self-medication is to be avoided.

Table 1-3: Case reports of compulsive dopaminergic drug use in PD

Author	Pts	Age PD onset *	Age DDS onset *	Premorbid psychiatric history/ drug history	Daily LEU*	Withdrawal	Relapse after attempted reduction	Hoarding, seeking, craving meds	Punding	Dyskinesias	Behaviour	Euphoria/ hypomania	Aggression	Psychosis, delusions, paranoia	Social or relationship breakdown
(Solla *et al.* 2006)	1M	58	62	No	700++	---	Yes	---	---	Yes	S			No	Yes
(Witjas *et al.* 2005)	2M	39 (30-48)	45 (38-53)	1 alcohol	2.3g	No	Yes	---	No	Yes	2S	Yes (2)	Yes	Yes (1)	Yes
(Nirenberg and Waters, 2005)	2M	47 (45-50)	---	1 nicotine	600mg	No	Yes	---	---	---	2G, E 1S	No	---	Yes (1)	---
(Borek and Friedman, 2005)	2M	51 (36-66)	62 (49-75)	No	5g	Yes (1)	Yes	---	---	Yes (1)	2S	1	Yes (1)	Yes (1)	No
(Avanzi *et al.* 2004)	2M	50 (48-52)	57 (53-61)	No	800mg	No	No	---	---	---	2G	Yes (1)	No	No	Yes
(Muller *et al.* 2002)	1M	27	35	Nicotine	1.4	Yes	No	Yes	---	Yes	E, H	---	Yes	Yes	Yes
(Serrano-Duenas, 2002)	3M, 1F	56 (49-62)	66 (59-71)	---	2.6g (2.4-2.9g)	Yes (2)	---	---	Yes	Yes (3)	4G, 1E	---	---	---	Yes (4)
(Houeto *et al.* 2002)	2M	45	59 (58-61)	Alcohol, illegal drugs, bipolar	<1.4g	Yes (1)	Yes (1)	Yes (1)	---	Yes (2)	2S, 2G	Yes (1)	Yes (2)	No	Yes (2)
(Gschwandtner *et al.* 2001)	1M	---	62	No	1.0g	---	No	---	---	Yes	G	Yes	No	No	Yes
(Merims *et al.* 2000)	1M	60	78	---	2.2g	Yes	---	Yes	---	Yes	No	Yes	---	Yes	No
(Giovannoni *et al.* 2000)	4M, 1F	39 (36-42)	---	1 alcohol, 3 depression	3.2g (2.0-5.5g)	Yes (3)	Yes (1)	---	---	Yes (4)	3S	Yes (2)	---	Yes (3)	Yes
(Courty *et al.* 1997)	4M	50 (46-57)	59 (50-65)	1 alcoholism, 1 depression	1.3 g (0.9-1.7g)	Yes (2)	Yes (2)	---	---	---	4S	---	Yes (4)	Yes (2)	Yes (4)
(Spigset and von Scheele, 1997)	2M	54 (51-58)	59 (52-66)	---	1.7g (1.5-2.0g)	No	Yes (1)	---	---	Yes (2)	---	Yes (2)	No	Yes (1)	Yes
(Weinman and Ruskin, 1995)	1M	53	63	---	3.5g+	---	Yes	---	---	Yes	1S	Yes	Yes	---	Yes
(Soyka and Huppert, 1992)	1M	---	---	Alcoholism	---	Yes	---	---	---	Yes	---			---	
(Uitti *et al.* 1989)	1M	37	64	No	1g	---	No	---	---	---	1S	Yes	---	Yes	Yes
(Tack *et al.* 1988)	1F	18	25	Slow psychomotor development	Up to 2.5g	---	Yes	Yes	---	Yes	1 Theft		Yes	Yes	Yes
(Nausieda, 1985)	5M	50 (41-55)	54.4 (46-60)	---	1.9g (1.5-2.5g)	Yes (3)		Yes (4)	---	Yes (5)	1H, 2 S	Yes (4)	Yes (2)	Yes (2)	Yes (5)
(Priebe, 1984)	1F	60	49	---	5g (no DCI)	---		---	---	Yes	---	Yes	No	---	Yes
(Vogel and Schiffter, 1983)	1M	46	48	---	Up to 2.0g/day	---		---	---	Yes	1S	---	Yes	Yes	Yes
(Quinn *et al.* 1983)	1M	44	47	premorbid increased sexual interest	Up to 4g	No		Yes	Yes	Yes	1S	---	No	---	Yes

* Values given are mean (range), LEU – L-dopa equivalent unit as per Evans *et al.* 2004, DCI – dopa decarboxylase inhibitor, S – hypersexuality, G – gambling, E – eating, H – buying

Lack of adherence to recommended therapy is commonplace and is related to various factors such as the type of treatment, patient beliefs, physician or factors such as cost and availability of medications (Balkrishnan, 1998). Fear of perceived adverse events is an increasingly common explanation for non-adherence with proposed treatment schedules. Less commonly, however, excessive use of prescribed medications can occur with agents such as analgesics, anticholinergic agents, corticosteroids, tranquilisers and psychostimulants (American Psychiatric Association, 1994) and may relate to the medications' benefits on mood and psychological state. The primary therapeutic aims in PD are the relief of symptoms without the introduction of adverse events, and improved quality of life. There are many reasons why a regular dosing of dopaminergic replacement therapy may not always achieve the therapeutic aims. For instance, medications may not be effectively absorbed or be timed effectively for a patient's needs. This short duration response leads to cycles of gratifying mobility alternating with dips in motor performance associated with a return of motor impairment, dysphoria and depression which patients find extremely unpleasant. The majority of patients can effectively self-regulate medication dosing in partnership with the treating physician to achieve adequate symptom control without spiraling drug increases. However, a few take it upon themselves to take higher than recommended doses to avoid at all costs any "off" periods. There is an increasing compulsion to take dopaminergic therapy, and a loss of control in limiting its intake. These patients repeatedly ask their doctors for larger doses of dopaminergic therapy. Excessive chronic dopaminergic stimulation when combined with the pathological substrate of PD can involve alterations in neuroanatomic circuitry that regulate reward, incentive motivation behavioural constraint and addictive behaviour and result in DDS. This may be triggered by the emergence of a short duration response to medication with disagreeable motor and mental "off" periods.

As anti-Parkinsonian treatment is available on prescription for a well defined medical condition, there is no need for patients to devote time to illicitly procuring them. However, they often devote large amounts of time to complex dosing schedules and hoard extra medication, which they then surreptitiously use to supplement their prescribed medication. Prescriptions are sometimes acquired from different health providers. Drug hoarding may become apparent when attempts are made to restrict the supply of medication during hospitalisation. The family and carers may be forced to store medication in locations where the patient is not able access them and resort to strict dosing schedules to limit dose escalation. Patients with DDS request additional tablets despite being dyskinetic and

may retain them for future use. Similarly, they often insist on frequent rescue "boosters". Dishonesty, manipulation and addictive denial systems are usually coupled with complete lack of insight.

1.7.7 Common disabling phenomenology in dopamine dysregulation syndrome

DDS is characterised by impulsivity, compulsivity, and an overwhelming pre-occupation with a particular behaviour pattern or mood state. The significant additional impact on social and occupational functioning that often brings the dopaminergic drug misuse to the attention of others can lead to divorce, breakdowns in close interpersonal relationships, financial difficulties related to compulsive spending, and legal difficulties due to inappropriate sexual advances and aggressive behaviour (Giovannoni *et al.* 2000). The disability due to PD is usually sufficient in itself to affect social and occupational function but in those with DDS the behavioural changes have a significant distressing impact on their families and friends. Demands for medication, inappropriate sexual behaviour, financial difficulties related to compulsive spending, and aggressive behaviour frequently lead to divorce increasing isolation and even criminal proceedings.

1.7.7.1 Craving

Patients sometimes adopt devious manipulative strategies (e.g. simulation of akinetic (Vogel and Schiffter, 1983) tremor states, bizarre distressing dystonic postures or even bribery (Muller *et al.* 2002)) or aggressive outbursts to access additional medication. I am aware of an incident resulting in a life-threatening injury in which one patient assaulted another for the purpose of procuring extra L-dopa. Craving can often occur in the absence of withdrawal or "off" states (Courty *et al.* 1997). An impatient, intense desire for further dopatherapy may be induced by its actual administration; particularly if the first dose is perceived as suboptimal. Patients sometimes develop idiosyncratic perseverative patterns of self-administration as well as stereotyped patterns of behaviour around dosing times. Compulsive foraging for dopatherapy is also occasionally observed (Tack *et al.* 1988) – one patient has been known to scrounge through sharps disposal containers for apomorphine residues (unpublished observation).

1.7.7.2 Euphoria and hypomania

Feelings of euphoria, perceived omnipotence, invulnerability and inappropriate joy can occur during the peak medication effects with racing thoughts and grandiose ideation (Serrano-Duenas, 2002). Paradoxically, the patient may complain of depression and threaten suicide (Muller *et al.*

2002) despite their euphoric appearance (Courty *et al.* 1997). Pathological jealousy (Othello Syndrome), disorganisation or pressure of speech and thought processes, an increasing inability to distinguish reality from fantasy, insomnia and psychomotor agitation may bring the disorder to the physician's attention. The indiscriminate enthusiasm for interpersonal interaction seen classically in mania, however, is absent. Furthermore these feelings are usually cyclical or short-lived (hours or days), and punctuated by episodic blunting of emotional response, social withdrawal, and apathy.

1.7.7.3 Dysphoria and non-motor offs

Withdrawal of dopaminergic drugs is characterised by feelings of sadness, exaggerated psychomotor slowing, dysphoria, fatigue, anhedonia (Funkiewiez *et al.* 2003) and apathy (Czernecki *et al.* 2002). Somatic complaints also include cryptogenic abdominal discomfort, painful limb and trunk sensations and autonomic disturbances such as profuse sweating (Witjas *et al.* 2002). In DDS, marked anxiety, irritability, exaggerated rebound depressive, dysphoric, anergic and somatic symptoms are described which may occur in the absence of "off period motor disability" (Giovannoni *et al.* 2000; Serrano-Duenas, 2002). "off"-period panic attacks also occur.

1.7.7.4 Appetitive behaviours

Various disorders of impulse control characterise DDS. Hypersexuality is a common disabling feature with both an increase in libido and in males, recurrent penile erections. This can lead to great marital disharmony (Berger *et al.* 2003; Lawrence *et al.* 2003) as a result of compulsive, disinhibited masturbation, persistent and forceful and occasionally aggressive sexual demands on partners, use of sex phone lines, internet sites, pornographic literature and prostitutes (Giovannoni *et al.* 2000). Paraphilias including exhibitionism, pederasty (Berger *et al.* 2003), sadomasochism, zoophilia (Jimenez-Jimenez *et al.* 2002), and fetishism (Quinn *et al.* 1983) may occur in individuals with a history of similar, possibly "repressed" proclivities. A few cases of serious sexual assault on strangers have also occurred.

Pathological gambling occurs particularly in individuals with a premorbid history of an interest in betting. Alterations in function of dopaminergic reward systems as well as dysfunctional impulse control are implicated in pathological gambling (Potenza *et al.* 2003; Voon, 2004). Family fortunes can be squandered, and huge debts run up causing terrible family distress (Kurlan, 2004). The gambling behaviour has been noted to be medication responsive (Gschwandtner *et al.* 2001; Molina

et al. 2000). In particular, switching or reducing dopamine agonists may lead to resolution of the problem (Driver-Dunckley *et al.* 2003; Dodd *et al.* 2005).

Compulsive shopping, eating disorders (Giovannoni *et al.* 2000; Muller *et al.* 2002) and binge eating (Lawrence *et al.* 2003; Nirenberg and Waters, 2005) may also be features of hypomanic phases. Some patients develop severe and uncontrollable food cravings.

1.7.7.5 Aggression

The dopamine system is implicated in the processing of signals of aggression (Lawrence *et al.* 2002). Heightened aggression is common in DDS and includes irritability, low tolerance of frustration, angry outbursts, use of insulting language or gestures, jealousy, threats of homicide and occasional violence. Patients report brief exaggerated feelings of power and dominance.

1.7.7.6 Psychosis

Depression, mood swings, paranoia, panic attacks and psychosis are common complications of habitual cocaine use (Harris and Batki, 2000). Psychiosis in methamphetamine and cocaine addicts has been linked to dopaminergic neuroadaptations within mesocortical systems (Sekine *et al.* 2003). In DDS, unchecked dopaminergic drug use leads to intoxication and a dose-dependent reversible organic psychosis. Delirium, paranoid ideation, fears of persecution, panic, and auditory, visual or tactile hallucinations may all be present. Severe dyskinesias, sleep disturbance, and extreme motor agitation are common accompaniments.

1.7.7.7 Compulsive behaviours (stereotypies)

Punding is an intense fascination with repetitive tasks such as collecting, arranging, or dismantling objects and it may cause isolation from or conflict with other people. These complex repetitive behaviours develop from prepotent habits, which are idiosyncratic, and depend on an individual's occupation, interests and pastimes. Punding was first described in amphetamine addicts (Rylander, 1966; Schiorring, 1977) but has been more recently been recognised in PD (Friedman, 1994). Long term dopatherapy-use (Kurlan, 2004) or frequent dopatherapy-dosing are also risk factors and it may resolve or improve with reductions in dopaminergic drug therapy (Fernandez and Friedman, 1999). Men tend to repetitively tinker with technical equipment such as radio sets, clocks, watches and car engines; the parts of which may be analysed, arranged, sorted, and catalogued but rarely put back together. Women, by contrast, incessantly sort through their handbags, tidy continuously, brush their

hair, or polish their nails. Office workers and clerks may shuffle papers or fiddle purposelessly with computers. A seamstress may collect and arrange buttons. A dissociation between knowledge and behaviour develops as individuals become unable to control automatic stimulus-response selection mechanisms i.e. patients know they are disruptive and unproductive, but continue to perform them.

1.7.7.8 Dyskinesias

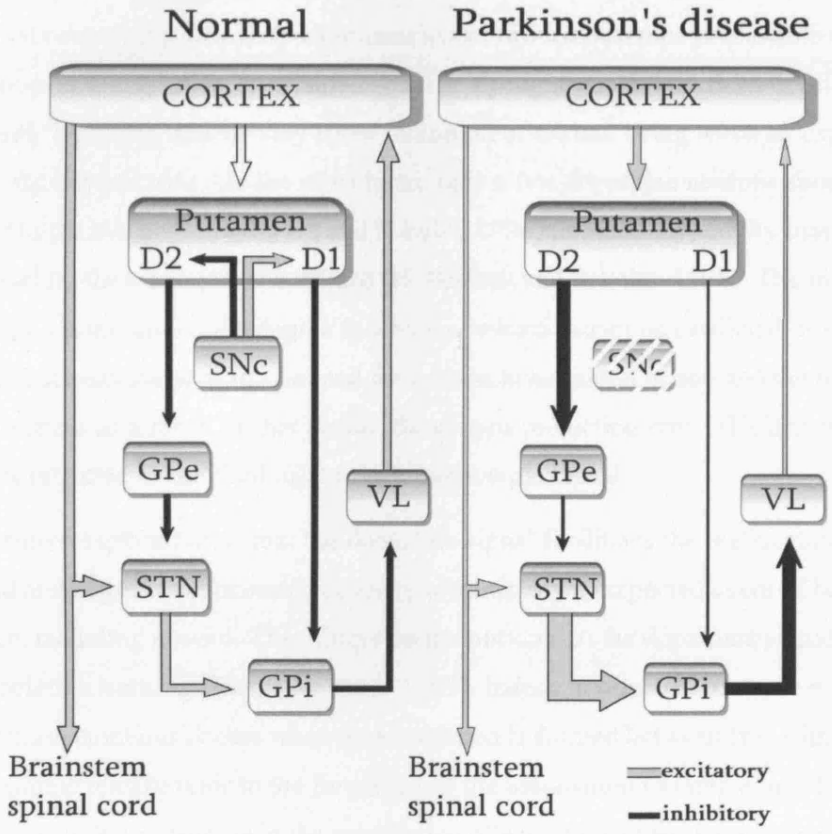
DDS patients commonly identify restriction of social activities due to embarrassment about dyskinesia as their most disabling problem. Physical and psychological problems reported by patients include repeated injury because of dyskinesias (Beam *et al.* 2004). Also during the "on" or high phase of medications, these patients will often become restless and develop akathisia with an urge to walk. They can walk great distances without purpose and lose track of time.

1.8 Basal ganglia circuits in health and disease

The organisation of corticostriatal systems has been considered in terms of segregated parallel circuits which connect limbic, prefrontal, oculomotor, and motor cortical areas through subregions of the basal ganglia and the ventral thalamic nuclei to analogous cortical areas. The basal ganglia are thought to modulate the release or inhibition of movements by way of direct and indirect pathways that act as a push-pull system of cortico-basal ganglia circuits. Functional integration within these pathways is retained by means of neuromodulation occurring through striatal dopaminergic receptors (Figure 1-2). In PD, this modulation is lost due to dorsal striatal dopamine depletion: resultant increased activity in the output nuclei then leads to increased inhibition of the glutamatergic excitation of the motor cortex and a subsequent reduction in voluntary movement. This simple brake-accelerator view of basal ganglia pathways has been refined by the realisation that it is not simply the total neural activity but the pattern of neural activity that determines the operation of these pathways. The leading surgical therapies for PD are now modelled on this direct-indirect pathway concept: i.e. to improve movement, a lesion of the motor part of the globus pallidus pars interna (GPi) is made in the ventrolateral pallidotomy procedure and in therapies based on deep-brain stimulation, inactivation of the subthalamic nucleus is brought about by a chronically implanted stimulator device.

Figure 1-2: Schematic representation of basal ganglia function in health and Parkinson's disease

1. the ventrolateral thalamic nuclei (VL) excite the motor cortex, causing motor activity; VL is normally inhibited by the globus pallidus pars interna (GPi)
2. dopaminergic neuronal loss in PD leads to greater activity of the GPi (and linked subthalamic nucleus), causing less net motor activity (akinetic, rigid syndrome)
3. subthalamic nucleus lesion (hemiballismus) or putaminal dopaminergic neuronal loss lessens GPi activity, causing excessive, spontaneous motor activity



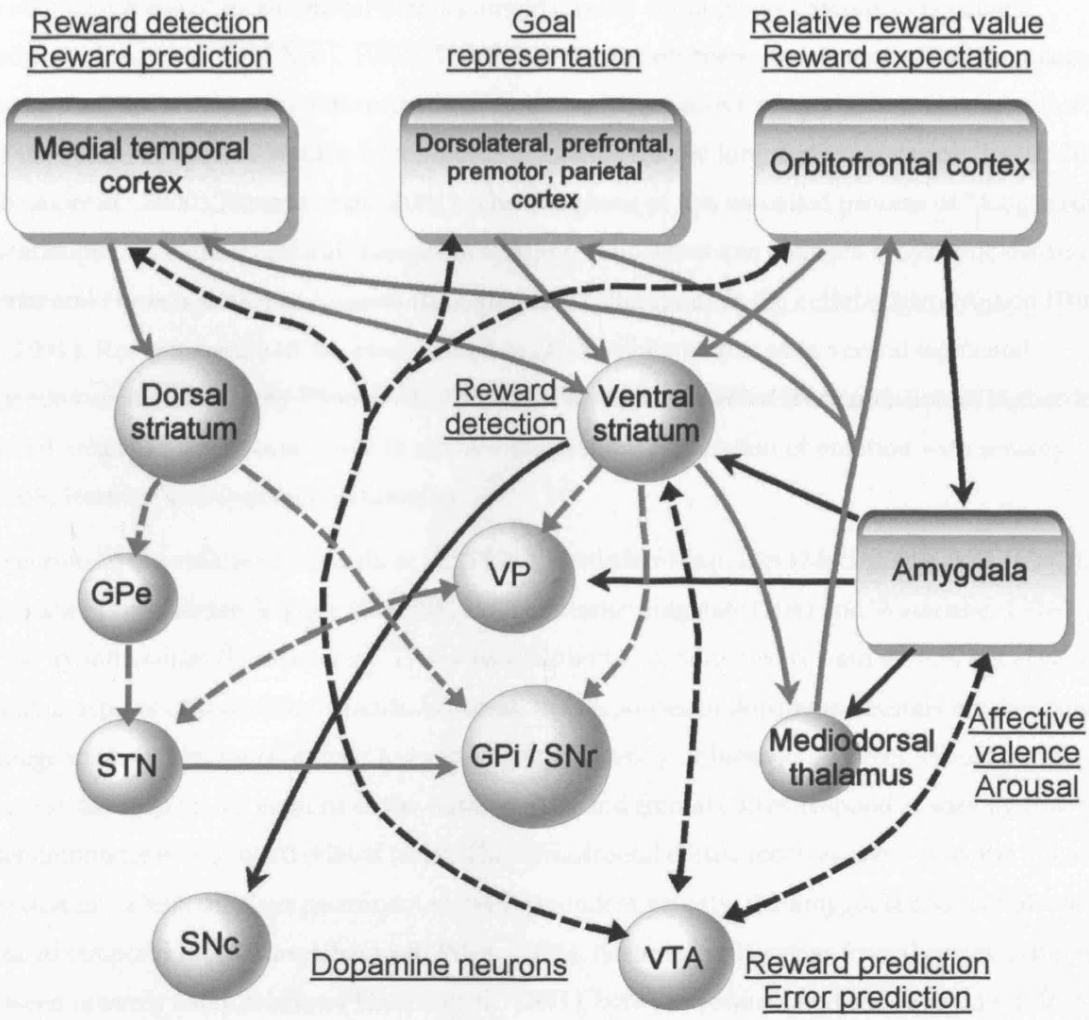
SNc: Substantia nigra pars compacta, **GPi**: Globus pallidus pars interna, **GPe**: Globus pallidus pars externa, **S'T'N**:

1.9 Dopamine functions in motivation and learning

Another theme of basal ganglia research mainly based on experimental laboratory work is that the basal ganglia have important functions in relation to learning and memory. Electrophysiological studies of the activity of single neurons in behaving animals highlight a role for dopamine beyond simple reward function. After presentation of reward, short, phasic activation of dopamine neurons are common (70-80% of neurons) in the medial tegmental regions that project to the nucleus accumbens and frontal cortex but are also found in intermediate and lateral sectors that project to the caudate and putamen (Schultz, 2000). While these neurons are phasically excited by the receipt of an unanticipated reward, this response habituates as the reward becomes predictable and the cells fire instead in response to reliable predictors – such as a programmed light flash or an apparatus noise – of the reward. The same neuron may show inhibition of normal firing when an expected reward fails to arrive at the normal time. On the other hand, only a few dopamine neurons show phasic activation in response to punishers (Mirenowicz and Schultz, 1996) or neuronal activity may be depressed rather than activated by the omission of a reward (Hollerman and Schultz, 1998). The midbrain dopaminergic signal reports the degree to which a reward cannot be predicted. It is indicated by the discrepancy between the reward obtained for a given behavioural action and the reward that was predicted to occur as a result of that action (the reward prediction error) (Hollerman and Schultz, 1998) and is reflected in the final midbrain dopaminergic signal.

An alternative explanation is that the dopamine signal facilitates the reallocation of limited behavioural and cognitive processing capacity towards any unexpected event of behavioural significance, including reward. This hinges on the notion that the dopamine signal has a more general role in associative learning (Redgrave *et al.* 1999). Indeed, a selective increase in dopamine release in the nucleus accumbens occurs when an association is formed between two stimuli neither of which induce dopamine release prior to the formation of the association (Young *et al.* 1998). This suggests a role for mesolimbic dopamine in the modulation of associative learning in general, not only that involving reinforcement.

Figure 1-3: Areas implicated in reward



VTA – ventral tegmental area, SNc – substantia nigra pars compacta, VP – ventral pallidum, STN – subthalamic nucleus, GPe – external globus pallidum, GPi – internal globus pallidum, SNr – substantia nigra pars reticulatum.

Dopaminergic mediated learning and memory invokes molecular and cellular adaptations and dopamine has been proposed to have a role in the modulation of long-term potentiation within the ventral tegmental area (VTA). In this model, once a contingency is learned, the same conditioned stimulus will activate output neurons, with no need for ongoing activity of dopaminergic neurons. As

a contingency is learned, there is habituation of mesolimbic dopamine transmission. At the same time, the responsiveness of mesocortical outputs amplify as the contingency extends to become a conditioned stimulus (Di Chiari, 1998). If the contingency reverses, the synapses from the neurons representing the previous conditioned stimulus are no longer active when the output neuron is active, and the synapses become weaker by a process of heterosynaptic long-term depression (Rolls, 2000; Thomas *et al.* 2000; Thomas *et al.* 2001). The late phase of this so-called process of "long-term potentiation" involves structural changes in synaptic connection and changes in synaptic density (Berke and Hyman, 2000) and occurs through related alterations in the cellular transcription (Bibb *et al.* 2001). Reorganisation of the cerebral cortex can be directly related to ventral tegmental dopamine-mediated activity (Bao *et al.* 2001) and dopamine-enabled reorganisation of higher-level cortical areas has an important role in sensory integration, association of emotion with sensory stimuli, learning and operant conditioning.

Neurons in the striatum (Apicella *et al.* 1991), subthalamic nucleus (Matsumura *et al.* 1992), pars reticulata of the substantia nigra (Schultz, 1986), anterior cingulate (Niki and Watanabe, 1976), and lateral hypothalamus (Burton *et al.* 1976) also respond to conditioned reward stimuli but encode different aspects of rewarding stimuli. Whereas, the responses of dopamine neurons display rather homogenous population responses to reward, predominantly influenced by event unpredictability, other reward responsive neurons in the basal ganglia and frontal cortex respond at varying times to other components of reward related tasks. The orbitofrontal cortex receives trans-synaptic inputs from the striatum, which displays prominent reward-dependent activity, the amygdala and rostral and medical temporal lobe (Carmichael and Price, 1996). Neurons in the orbitofrontal cortex distinguish between rewards and punishers (Thorpe *et al.* 1983), between rewards and conditioned reinforcers, and also discriminate between different liquid or food rewards. Many of these behaviours reflect the incentive motivational value relative to the available alternative reward, as inferred from the animals' preference in overt choice behaviour (Tremblay and Schultz, 1999). In contrast, many neurons of the ventrolateral prefrontal cortex appear to primarily process the visual features of environmental objects (Kubota and Niki, 1971) and derive inputs from posterior parietal and inferotemporal cortex (Pandya and Yeterian, 1996). Striatal neurons display a large spectrum of reward-dependent responses. The nature of striatal responses indicate that the expectation of reward strongly influences striatal activities and relate to the behaviour producing these rewards. So, the striatal neurons are seen to respond to reward-dependent movement preparatory instructions, to reward-dependent movement

preparatory instructions, to reward-dependent movement triggers, during reward expectation and to primary reward (Apicella *et al.* 1991; Apicella *et al.* 1992; Schultz *et al.* 1992). Other neurons display activations which are related to the magnitude of rewards (amygdala (Pratt and Mizumori, 1998)). Neurons of other brain structures, such as the striatum, orbitofrontal cortex, and amygdala, appear to code the quality, quantity, and preference of rewards and possibly even reflect representations of goals. Activations in these brain structures may serve to provide selective teaching signals for certain groups of neurons whereas the homogeneous reward response of dopamine neurons might be characterised as broadcasting a global reinforcing signal along divergent projections to large numbers of neurons in the striatum and frontal cortex (Schultz, 2001).

1.10 Do models of psychostimulant addiction help to understand compulsive dopaminergic drug use in PD?

Current theories of addiction incorporate the idea that drugs activate and, via neuroadaptive processes, change dopaminergic neurotransmission in the nucleus accumbens and related circuitry, altering important reward-related processes (although different theories posit different processes) (Robinson and Berridge, 2003).

1.10.1 Do the dopaminergic drugs used to treat PD activate brain "reward" pathways?

There are some data on the activation of accumbens-related reward pathways by dopaminergic drugs used to treat PD. Conditioned place-preference is used as one index of reward. In the learning phase of this procedure, animals receive a stimulus in one compartment of the place-conditioning chamber, and receive a control stimulus in another. In the test phase, animals do not receive a stimulus and are free to go to either compartment. Rewards such as food, sexual stimuli, and psychostimulant drugs cause conditioned place preferences to occur: animals spend more time in the compartment previously paired with reward (Bardo and Bevins, 2000).

In rats, L-dopa combined with the catechol-*O*-methyltransferase inhibitor entacapone induces a conditioned place preference similar to that induced by psychostimulants such as amphetamine (Katajamaki *et al.* 1998). This effect is also produced by the dopamine agonists apomorphine (Papp, 1988; van der Kooy *et al.* 1983) and bromocriptine (Hoffman *et al.* 1988), suggesting they are "rewarding". Such conditioned place preference is accompanied by increased dopamine turnover in the accumbens, and lesions to the accumbens disrupt apomorphine-induced place preference (van der Kooy

et al. 1983) and self-administration (Zito *et al.* 1985). Pramipexole increases activity in accumbens-related circuitry (Black *et al.* 2002). In normal humans, dopamine agonist therapy seems to have relatively minor effects on mood. However, occasionally when used in the treatment of prolactinoma, a reversible psychosis (Boyd, 1995), mania (Kemperman and Zwanikken, 1987), hypersexuality and pathological gambling (Press Association, 2001; Evans and Butzkueven, 2007) may occur. The abuse potential of these drugs has also been described in healthy humans (Manoharan *et al.* 2002; Steiner and Wirguin, 2003) and in patients with nonneurodegenerative illnesses (Ross and Ward, 1992; Steiner and Wirguin, 2003). Dopaminergic drug therapy used to treat PD seems to share at least some of the properties of potentially addictive drugs.

1.10.2 Theories of compulsive psychostimulant use

1.10.2.1 Pleasure models

The oldest explanation for addictions is that they are driven by feelings of pleasure (Aristotle, 1976). Contemporary variants of pleasure theories—such as Wise's hedonia theory (Wise, 1985)—assume that drugs act as rewards because they induce some kind of pleasure, and that this is what compulsive drug users seek. Ethological theories of reward are commonly applied to comparative studies of drug seeking: any stimulus that elicits locomotor approach behaviour will serve as a reward or "positive reinforcer" (Vaccarino *et al.* 1989). Wise (Wise, 1985) equated the approach responses induced by rewards—as seen in conditioned place preference—with the experience of pleasure: "It is the approach response and the motivational arousal caused by rewards which I believe to be most clearly associated with pleasure". In PD patients, an acute L-dopa dose can lead to small increases in "happiness" and "positive mood", which may increase with escalating doses and over time (Brown *et al.* 1984; Maricle *et al.* 1998). Although a few DDS patients report peak-dose feelings of euphoria and joy, there is little evidence that they experience greater L-dopa-induced euphoria than individuals who do not develop it. In fact, large doses of L-dopa often lead to unpleasant feelings (Table 1-3) and increases in "positive mood" are not reported early on in the course of treatment of PD (Maricle *et al.* 1998).

There are general problems for pleasure theories of addiction (Berridge and Robinson, 1998; Robinson and Berridge, 2000; Robinson and Berridge, 2003). People will work for small doses of drugs (e.g., cocaine) that lack discernible pleasurable effects (Comer and Collins, 2002; Lamb *et al.*

1991) (i.e., the motivation to take drugs can be dissociated from drug-induced pleasure) (Berridge and Robinson, 1998; Robinson and Berridge, 1993; Robinson and Berridge, 2003). Attempts to rescue the pleasure theory of addiction suggest that the pleasurable effects of drugs may only be open to verbal report if they exceed a given threshold (Panksepp *et al.* 2002; Shizgal, 1999). Most psychologists accept that a lack of verbally reported pleasure does not mean a lack of pleasure experience. Although pleasure is often defined as a conscious feeling, it can exist without conscious awareness—which is the product of a constructive process—rather than being a direct "readout" of the underlying affective state (Frijda, 2001).

There are further problems for the hedonia model. If all compulsively used drugs activate accumbens dopamine systems, and if the use of these drugs is motivated by pleasure, then destruction of dopamine neurons should abolish pleasure (Wise, 1985). Berridge and colleagues (Berridge and Robinson, 1998) have studied the role of dopamine in the mediation of pleasure—by use of the taste-reactivity paradigm—based on stereotyped reactions emitted by rats to tastes, which are thought to be homologous to human reactions to highly palatable food (Steiner *et al.* 2001). Contrary to the hedonia hypothesis, near total dopamine depletion induced by neurotoxins does not diminish facial expressions of pleasure to sweet tastes, even though it abolishes motivation to eat (Berridge and Robinson, 1998). So, even if the "pleasure" experienced by addicts is unconscious, it is not the same as the sensory pleasure experienced when eating, for example, sweet foods (Berridge and Robinson, 1998). In human beings, dopaminergic blockade diminishes self-reported drug "Wanting" but not drug "liking" (Berridge and Robinson, 1998).

It may still be possible to argue for a pleasure theory of addiction, if it is accepted that there may be different kinds of pleasure, and that not all pleasures are sensory pleasures (Nuttin, 1973; Frijda, 2001; Rozin, 1999). Frijda (Frijda, 2001) distinguishes sensory, aesthetic, achievement/mastery, activity, relief, and social pleasures; Rozin (Rozin, 1999) distinguishes sensory, aesthetic, and mastery pleasures. Although dopamine does not mediate sensory pleasure, it could mediate other forms of pleasure that could be causally related to drug euphoria and to compulsive drug use (Drevets *et al.* 2001; Volkow *et al.* 2002a). Panksepp and colleagues (Panksepp *et al.* 2002) have proposed a similar approach. They argue that ultrasonic vocalisations are expressions of particular emotional states in rats. Rats emit vocalisations of about 50 kHz in several reward-related situations (e.g., during playful interactions, before sexual intercourse, and while anticipating food) (Panksepp *et al.* 2002).

50 kHz ultrasonic vocalisations are also emitted in places associated with previous psychostimulant administration and can be elicited by injection of dopamine agonists into the accumbens (Panksepp *et al.* 2002). Panksepp suggests that these responses are homologous to states of euphoria, excitement, or joyful anticipation in human beings.

1.10.2.2 Hedonic homeostatic dysregulation

Several models of addiction suggest that addicts are motivated to take drugs not only for pleasure, but also – and perhaps eventually primarily – by the desire to avoid unpleasant withdrawal symptoms. Opponent process theory (Solomon and Corbit, 1974) proposes that pleasant doses of a drug activate a dose-dependent "a" process in brain reward circuits, which in turn triggers activation of an unpleasant opposite "b" process, and which serves to restore homoeostasis (Solomon and Corbit, 1974). The subjective state of the individual is created from summation of the "a" and "b" processes. The "a" process causes euphoria. The "b" process initially manifests as a decay of euphoria after initial peak (Solomon and Corbit, 1974). With repeated drug use, the "b" process becomes strengthened and manifests as tolerance to euphoria. Unpleasant withdrawal is caused when the drug effects wear "off", since the "b" process is assumed to last longer than the "a" state. It is only the "b" process that is assumed to grow in magnitude and duration with repeated drug use: even a small dose will reinstate it and trigger withdrawal (Solomon and Corbit, 1974). Abstinence from the drug decays the "b" process, and once it returns to normal, the individual is no longer addicted (Solomon and Corbit, 1974).

The hedonic homoeostatic dysregulation (HHD) model of Koob and Le Moal (Koob and Le Moal, 1997; Koob and Le Moal, 2001) is a variant of opponent process theory based on allostatic, rather than homoeostatic, adaptation. Allostasis is the maintenance of stability outside the normal homoeostatic range in response to chronic demands. In HHD, before addiction, the anticipation and experience of drug-induced pleasure motivates the individual. However, HHD defines addiction as the presence of an unpleasant emotional state of dysphoria, irritability, and anxiety during abstinence (Koob and Le Moal, 2001). With repeated drug intake, the "b" process does not return to normal homoeostatic baseline, resulting in an allostatic state. This unpleasant state (allodynia or anhedonia [loss of pleasure]) reflects a decrease in baseline pleasure levels – associated with reduced dopamine function (Barr *et al.* 2002) – and an increase in drug intake is needed to compensate for the shift in baseline reward. There is evidence that some patients with PD show reduced reward-related brain

activity (Kunig *et al.* 2000), which, according to HHD, would confer increased vulnerability to dopaminergic drug addiction (Koob and Le Moal, 1997; Koob and Le Moal, 2001). A history of depression with associated anhedonia may be a predisposing factor in some cases (Table 1-3).

Robinson and Berridge (Robinson and Berridge, 1993; Robinson and Berridge, 2003) criticise the use of the term "hedonic" in HHD. They argue that low dopamine concentrations are not associated with anhedonia. The notion of multiple types of pleasure (Frijda, 2001; Rozin, 1999), however, could be used to counter this criticism. Another problem with HHD is that the acute and chronic neural adaptations to drug use can take anywhere from minutes to weeks to return to their normal sensitivity but do not appear to be sufficiently long-lasting to be involved in the tendency of addicted individuals to relapse. Furthermore, dopamine innervation of the ventral striatum may not exclusively subserve reward. Stimuli with aversive qualities (e.g. footshock, restraint stress and anxiogenic drugs) can, like reinforcing stimuli, increase nucleus accumbens dopamine transmission (Imperato *et al.* 1992; Horger *et al.* 1995; Kalivas and Duffy, 1995; McCullough and Salamone, 1992). In addition, conditioned punishment, which is another learning paradigm, as well as conditioned reinforcement, is also potentiated by systemic administration of amphetamine (Killcross *et al.* 1997).

In their initial account of compulsive dopaminergic drug use in PD, Giovannoni and colleagues (Giovannoni *et al.* 2000) labelled it as a form of HHD. Prominent unpleasant symptoms can be a feature of the withdrawal state and these form part of current working diagnostic criteria (Giovannoni *et al.* 2000). Patients also report feeling "relief" when given dopaminergic drugs. Bearn and colleagues (Bearn *et al.* 2004) emphasise that the avoidance of being unmedicated was the primary reason given for increasing drug intake. However, although the withdrawal syndrome may explain many of the features of addiction, definitions of substance dependence emphasise a pattern of compulsive substance use which may lead to reductions in social, occupational, or recreational activities (American Psychiatric Association, 1994). The neural substrate underlying these features is likely to involve wider neural networks than solely the dopaminergic mesolimbic system. There are also cases of long-term compulsive dopaminergic use that show no subjectively unpleasant withdrawal signs (Table 1-3). A further problem for withdrawal based explanations of compulsive dopaminergic drug use is that drug craving is often elicited by drug administration itself—in association with euphoria— at the moment when withdrawal symptoms should be at their weakest (Giovannoni *et al.* 2000). Moreover, at least one report suggests that pharmacological relief of

unpleasant withdrawal symptoms does not reduce compulsive dopaminergic drug use (Courty *et al.* 1997).

Withdrawal may have a role in compulsive drug use for reasons other than simply the desire to avoid unpleasant feelings. An alternative to avoidance theory views withdrawal states as equivalent to natural motivational states such as hunger (Berridge and Robinson, 1998; Hutcheson *et al.* 2001). Incentive motivational accounts of addiction assume that the withdrawal-state induced by depriving an addict of drugs increases the incentive value of the drug to such an extent that drug seeking becomes the dominant behaviour (Hutcheson *et al.* 2001).

According to incentive motivational accounts, patients with PD undergoing withdrawal are experiencing drug "hunger", rather than just a desire to overcome an unpleasant feeling. Indeed, some of the reports of compulsive users describe severe feelings of urgency on withdrawal, "driving" them to take more (Nausieda, 1985).

1.10.2.3 Habit theory

Habit theory is a recent approach to addiction that downplays the part of emotions, and places greater emphasis on learning mechanisms (Everitt and Wolf, 2002). A habit is an automatic action in a given situation, without direct reference to the goal of that action. The premise of habit models is that, despite beginning as a goal-directed action, in which individuals seek drugs based on the knowledge and desire of the pleasure they produce, there is an eventual progression to a form of automatic behaviour in which voluntary control over drug use is lost (Hogarth *et al.* 2003). In addition, stimuli consistently present in the environment gain motivational power through their predictive association with drugs, and thereby elicit and support drug-seeking and cause relapse via associative-learning mechanisms (Everitt *et al.* 2001; Everitt and Wolf, 2002).

This approach has gained attention partly owing to the finding that dopamine neurons signal errors in reward prediction that are critical for associative learning (Waelti *et al.* 2001). Repeated exposure to psychostimulants facilitates such learning and triggers neuroadaptations in dopamine systems and intracellular signalling-pathways similar to those seen during learning (Berke and Hyman, 2000). Striatal dopamine is also clearly involved in the development and reinforcement of automatic stimulus-response habits (Everitt *et al.* 2001; Everitt and Wolf, 2002; Ito *et al.* 2004).

Habit theory provides a good explanation for the stereotypical behaviour seen in punding —a common feature of compulsive dopaminergic drug use in PD. These stereotyped behaviours include prepotent, habitual routines (e.g., grooming), which are homologous to the complex stereotyped responses seen in rats during hyperdopaminergic states (Berridge and Aldridge, 2000a; Young and Thiessen, 1991). Strong stimulus-response habits form the basis of such routine activities. Stereotypy represents the culmination of a continuous process of psychomotor stimulation and behavioural competition (Robbins *et al.* 1990; Toates, 1998). Smaller doses of psychostimulant drugs potentiate the approach responses to rewards, which are mediated by accumbens dopamine (Ikemoto and Panksepp, 1999; Robbins *et al.* 1990). With increased doses, prepotent stimulus-response habits—mediated by the dorsal striatal structures—are potentiated and gain control over behaviour (Robbins *et al.* 1990; Whishaw *et al.* 1992). Stereotypies develop from prepotent habits (Toates, 1998), which are idiosyncratic, depending on individual life histories (e.g., office workers stereotypically shuffle papers, a seamstress will stereotypically collect and arrange buttons). Individuals become unable to control automatic stimulus response selection mechanisms (i.e., stereotypies are purposeless, and there is a dissociation between knowledge and behaviour) (Robbins *et al.* 1990; Toates, 1998). Patients realise that these behaviours are irrational, but are unable to stop them.

Habit theory explains other features of compulsive dopaminergic drug use in PD less well. This theory may mistake automatic, habitual action for motivational compulsion: no matter how habitual drug-taking becomes, automatic stimulus-response processes cannot in themselves confer compulsive qualities to drug seeking and intake (Robinson and Berridge, 2003). In defense of habit theory, it has been argued (Wise, 2002) that the effects of vast doses of dopa drugs are far in excess of any normal physiological range, and thus habits may have supranormal qualities. Habit models cannot easily explain the apparently flexible goal directed actions that patients with PD use to obtain dopa drugs (e.g., feigned akinetic states).

The habit model does not explain why most patients with PD are not addicted to dopaminergic drugs. Drug use should become habitual in all patients, but the incidence of compulsive dopaminergic drug use in PD is very low. Habit theorists must posit extra pathology in susceptible individuals. For example, frontal cortical pathology could cause additional loss of regulation of habitual behaviours (Jentsch and Taylor, 1999). Rats with lesions to the frontal cortex show persistent responses to cocaine that are no longer under the control of contingent presentation of cocaine-associated cues

(Weissenborn *et al.* 1997). The ability to modulate habits and conditioned responses can be impaired in some patients with PD, and such deficits are exacerbated by L-dopa (Cools *et al.* 2001; Cools *et al.* 2003). Furthermore, the stereotyped collecting behaviour seen in compulsive dopaminergic drug users resembles that seen in patients with frontal-lobe damage who have "forced collectionism" (Volle *et al.* 2002). However, even with this additional pathology, the criticism that habitual response and motivational compulsion are not equivalent seems valid.

1.10.2.4 Incentive Sensitisation Theory

According to Robinson and Berridge's incentive sensitisation theory (IST) (Robinson and Berridge, 2000; Robinson and Berridge, 2003), compulsive drug use results from progressive and persistent neuroadaptations induced in dopamine projections to the accumbens-related circuitry (Robinson and Berridge, 2000; Robinson and Berridge, 2003). These neuroadaptations can include: long-lasting changes in dopaminergic and GABAergic neurotransmission, changes in intracellular signalling pathways activated by these neurotransmitters, and even persistent changes in the physical structure of neurons themselves (Berke and Hyman, 2000; Robinson and Berridge, 2000; Robinson and Berridge, 2003).

The critical neuroadaptations for compulsive drug use make these neural systems hypersensitive, or sensitised, where sensitisation is a progressive increase in drug effect with repeated administration, to the incentive motivational or rewarding effects of drugs (Robinson and Berridge, 2000; Robinson and Berridge, 2003). The systems sensitised, according to this theory, mediate a subcomponent of reward termed incentive salience (Berridge and Robinson, 1998; Robinson and Berridge, 2000; Robinson and Berridge, 2003). Incentive salience is neither a hunger, nor a withdrawal state. Rather, it is one component of normal appetite which, if attributed to stimuli, causes them to become attractive and "Wanted", which triggers approach and pursuit (Robinson and Berridge, 2000; Robinson and Berridge, 2003). This "Wanting" is quite separate from "liking"(sensory pleasure) (Berridge and Robinson, 1998).

The process of neural sensitisation in the accumbens circuitry eventually leads to excessive incentive salience attribution to the drugs and drug-related stimuli that activate this circuitry, making them highly attractive and pathologically "Wanted" or craved (Berridge and Robinson, 1998; Robinson and Berridge, 2000; Robinson and Berridge, 2003). According to incentive sensitisation theory, the system that causes incentive salience attribution can produce drug seeking not only in the absence of subjective pleasure (mediated by the "liking" system), but also in the absence of conscious

awareness of "Wanting" itself (i.e., it can act as an unconscious motivational process) (Robinson and Berridge, 2000; Robinson and Berridge, 2003). Incentive salience is not the same as incentive learning, although IST suggests a role for associative learning in the expression of sensitisation (Robinson and Berridge, 2000; Robinson and Berridge, 2003). For example, increased incentive salience following chronic amphetamine treatment in rats can increase the salience of appetitive stimuli in the environment which the animal has had no opportunity to consume and learn the reward value of these stimuli (Nocjar and Panksepp, 2002). Incentive sensitisation theory can be contrasted with theories that emphasise incentive learning mechanisms (Di Chiara, 1999; Hutcheson *et al.* 2001).

Psychomotor sensitisation is used as a marker of neural sensitisation, because it is assumed that the neural substrate that mediates the psychomotor-activating effects of drugs is either the same as, or at least overlaps with, the neural substrate for reward effects (Robinson and Berridge, 2000; Robinson and Berridge, 2003; Wise and Bozarth, 1987). L-Dopa-induced dyskinesia is generally thought to be a sensitisation phenomenon (Graybiel *et al.* 2000; Olanow *et al.* 2000). The development of dyskinesia in animal models of PD requires the same drug schedule as that necessary to induce psychomotor sensitisation by psychostimulants (Graybiel *et al.* 2000). Stimulant-induced locomotor sensitisation is only seen when drugs are given intermittently, and the most robust sensitisation occurs when injections are widely spaced over time (Robinson and Berridge, 2003). Sensitisation is strongest when high or rapidly escalating doses are given (Robinson and Berridge, 2003). Sensitised locomotor responses in rats are sensitive to stress (Robinson and Berridge, 2000; Robinson and Berridge, 2003), as are dyskinesias in PD (Durif *et al.* 1999). "On" dyskinesias – including dystonic, choreic, or stereotyped movements – are commonly seen in individuals who compulsively use dopaminergic drug therapy (Table 1-3). Additionally, sensitised synaptic dopamine responses in the dorsal striatum also correlate with dyskinesia severity (Pavese *et al.* 2006). The stereotypical actions seen in punding may also result from psychomotor sensitisation processes (Graybiel *et al.* 2000).

The neuroadaptations that cause dyskinesias and punding are similar to those seen after psychomotor sensitisation by, for example, amphetamine (Berke and Hyman, 2000; Graybiel *et al.* 2000; Robinson and Berridge, 2003). They occur, however, in the dorsolateral striatum, rather than the accumbens-related circuitry (Graybiel *et al.* 2000). Although there is evidence of a role for "motor" structures such as the dorsolateral striatum in reward processing (Ito *et al.* 2004; Salamone *et al.* 2003; Volkow *et al.* 2002b), and that both motor and incentive phenomena share key characteristics, there are clear dissociations

between them. Locomotor sensitisation that follows chronic amphetamine administration in rats does not necessarily predict incentive sensitisation (Nocjar and Panksepp, 2002). Furthermore, even though compulsive dopaminergic drug use in PD is associated with dyskinesias, few dyskinetic patients are compulsive drug users.

Changes at the neuronal level induced by chronic L-dopa may be region specific and involve primarily the dorsolateral striatum (Mura *et al.* 2002). However, data for unilaterally 6-hydroxydopamine-lesioned rats – the rodent analogue of PD (Cenci *et al.* 2002) – shows that repeated administration of L-dopa triggers dopamine D3 receptor overexpression in the accumbens (Gullin *et al.* 2001), which is a neuroadaptation involved in compulsive drug use (Berke and Hyman, 2000; Gullin *et al.* 2001).

Many of the symptoms seen in DDS patients are consistent with the drugs having increased incentive salience. Craving – in the absence of either heightened pleasure or unpleasant withdrawal symptoms – can be seen. Patients will go to extreme lengths to obtain medication, despite the risk of harmful consequences (Giovannoni *et al.* 2000), and will also report being "driven" to take more drugs (Nausieda, 1985). Hoarding – itself an accumbens dopamine dependent process (Kelley and Stinus, 1985) – of drugs has been described, consistent with the drug's increased "attractiveness" (Giovannoni *et al.* 2000).

According to IST, the ability of sensitisation to enhance responsiveness to rewards is not confined to drug rewards: it also applies to other appetitive behaviours (Robinson and Berridge, 2000; Robinson and Berridge, 2003). For example, an animal's willingness to work for various rewards can be increased by repeated exposure to psychostimulants (Robinson and Berridge, 2000; Robinson and Berridge, 2003). In one study (Nocjar and Panksepp, 2002), chronic amphetamine treatment in rats increased both amphetamine-induced place preference and appetitive behaviour for food and sexual rewards. Animals that developed the strongest amphetamine-induced place preference, however, were not necessarily the same animals that developed magnified food and sex-seeking behaviours. Such individual differences may be due to pre-existing temperament factors (Nocjar and Panksepp, 2002).

A global sensitisation of appetitive behaviours readily accounts for symptoms of hypersexuality and compulsive eating in PD. Furthermore, both money (Knutson *et al.* 2001; Koepp *et al.* 1998) and consumer goods (Erk *et al.* 2002) activate the accumbens circuitry, which means that symptoms of compulsive shopping and gambling could also be explained by IST. These findings are relevant to the debate as to whether or not behavioural and chemical addictions share the same substrates (Holden, 2001).

Similarly, certain forms of aggression can be considered as appetitive behaviours and are mediated by accumbens dopamine release (Lawrence *et al.* 2002).

Excessive "Wanting" of dopaminergic drugs can override more stable life goals and priorities, leading to impaired decision making. The ability of salient incentives to momentarily override the influence of current goals on behaviour can lead to the exploitation of novel opportunities and, therefore, can be beneficial. When this behaviour becomes excessive, potentially ruinous drug pursuit and the control of behaviour by salient stimuli rather than long-term goals can result (Driver-Dunckley *et al.* 2003; Wyvell and Berridge, 2001). There are also data to suggest that chronic long-term administration of large doses of psychostimulants can lead to impairment in regions of the prefrontal cortex that are important for regulation of behaviour by long-term goals. A synergistic increase of incentive sensitisation and impaired goal-directed behaviour could lead to the DDS in PD.

In contrast to pleasure theories, IST supposes that accumbens dopamine also has a role in threat-related motivation, and it has been suggested that heightened salience of threatening stimuli can explain symptoms of anxiety, panic, and psychosis seen after very high drug intake.

Individual variability is an important feature of sensitisation in both its development and its expression (Robinson and Berridge, 2000; Robinson and Berridge, 2003). Pharmacological, genetic, sex-related, age-related, temperamental, activity-level dependent, social, and experiential factors are all important (Abarca *et al.* 2002; Laviola *et al.* 2001; Marinelli and Piazza, 2002; Robinson and Berridge, 2000; Robinson and Berridge, 2003). Experiential factors include cross-sensitisation between stress and psychostimulants, and cross-sensitisation between different drugs (Robinson and Berridge, 2000; Robinson and Berridge, 2003). Individual differences like these may eventually help to explain the profile of patients with PD who are vulnerable to developing DDS: young-onset male cases, with a past history of heavy alcohol or illegal-drug use, and poor social circumstances (Giovannoni *et al.* 2000).

Another feature of sensitisation is that it is not an inevitable consequence of repeated drug exposure (Robinson and Berridge, 2000; Robinson and Berridge, 2003). Rather, the ability of drugs to induce sensitisation – and the expression of such sensitisation – is modulated by learning and contextual factors (Robinson and Berridge, 2000; Robinson and Berridge, 2003). The ability of drugs to induce sensitisation is greater in new than in familiar environments; whereas the expression of incentive sensitisation appears greatest in contexts distinctly related to drug-taking in the past, and is also influenced by the diurnal state of the animal (Abarca *et al.* 2002; Robinson and Berridge, 2000; Robinson and Berridge,

2003). Notably, the effects of L-dopa on locomotor processes in rats are modulated by learning and contextual factors (Carey, 1992).

1.10.2.5 Individual differences in vulnerability to addiction

Another group of addiction theories focus on why particular individuals are more susceptible to addiction than others. Genetic variation may partially underlie a substantial proportion of vulnerability to addictive diseases – as well as complex personality and physiological traits – such as impulsivity, risk taking and stress responsivity. For instance, in animal models, there are marked strain differences in acquisition of drug seeking that are potentially influenced by behavioural temperament (Dellu *et al.* 1996) and this susceptibility appears to be polygenic (Crabbe *et al.* 1999). The behavioural traits that increase an animal's susceptibility to drug reinforcement resemble some of the features of high-sensation seeking in humans. Conversely, norepinephrine transporter (NET), vesicular monoamine transporter gene (Wang *et al.* 1997), metabotrobic glutamate receptors (Chiamulera *et al.* 2001), 5HT1B gene (Castanon *et al.* 2000) and nicotinic acetylcholine receptor influence an animal's susceptibility to psychostimulants (Xu *et al.* 2000). NET is implicated in dopamine uptake in brain regions with low level of dopamine transporter (Moron *et al.* 2002) such as the frontal cortex and noradrenergic inputs to the bed nucleus of the stria terminalis from the caudal medulla are critically involved in the aversion of opiate withdrawal (Delfs *et al.* 2000).

In humans, novelty seeking (Cloninger, 1987b) and sensation seeking (Zuckerman, 1994) personality traits, are useful constructs to predict human risk-taking behaviours (such as risky and stressful activities and unsafe sexual practices that are avoided by others). These personality traits, called Impulsive Sensation Seeking (ISS), might have distinct neurochemical and genetic substrates mediated by genetic variability in the transmission of dopamine as well as other neurotransmitters (Kreek *et al.* 2005).

Furthermore, personality and physiological traits themselves differentially affect the various stages of addiction, defined chronologically as initiation of drug use (Cloninger *et al.* 1988), regular drug use, addiction/dependence (Hawkins *et al.* 1992; Cloninger *et al.* 1988; Nathan, 1988) and potentially relapse. The predictive relationship between ISS traits and addiction vulnerability purportedly reflects some rewarding aspect of experiencing novelty and suggests that novelty-elicited exploration and drug stimuli may interact in biologically and behaviourally meaningful ways.

Phenotypic differences in sensitivity to addictive drugs can also be responsive to environmental factors and stress. Stress, corticosterone, and mesencephalic dopaminergic neurons seem to be organised in a pathophysiological chain determining a vulnerability to addiction. The mesolimbic dopaminergic system has been shown to have a stimulatory action upon the hypothalamic-pituitary-adrenal (HPA) axis and *visa versa* (Piazza and Le Moal, 1998). Thus, corticosterone itself is readily self-administered by animals and stimulates dopamine release (Piazza *et al.* 1993). Moreover, these effects are mediated by individual differences in responses to novelty (Dellu *et al.* 1996).

Childhood and adolescence are periods of brain plasticity during which maturation continues through neuroanatomical, neurochemical, and neurophysiological changes which correspond to significant shifts in cognitive, psychological and social development. During maturation, ISS traits are important adaptive components to exploration behaviour, sociability and sexual and consummatory behaviour. Consistent with this, adult behavioural phenotypes are modified by early childhood and adolescent experiences. For example, early deleterious rearing influences the development of brain monoaminergic systems that result in undercontrolled and immature behaviours in adulthood which may be associated with excess alcohol use (Higley *et al.* 1996). Early drug exposure in childhood confers individual susceptibility to recurrent drug use via enhancing the affective response to a new drug or inducing long-lasting neurochemical changes within mesolimbic structures that may predispose to heightened reinforcing effects. In animals, even a single exposure to morphine can induce long-lasting behavioural and neurochemical changes in the brain e.g. (Vanderschuren *et al.* 2001). Along similar lines, one study in humans found that current alcohol use, prior recreational use of stimulants, and baseline level of self-reported arousal appeared to influence subjective response to the common drug caffeine (Chait, 1992).

1.10.2.6 Role for dopamine in the behavioural functions of the prefrontal corticostriatal system – dysfunctional inhibition?

Another phenomenon seen with addiction may contribute to a reduced capacity for cognitive control, leading to impairment in regulating behaviour. Regions of the frontal cortex involved in inhibitory response control may be directly affected by long-term exposure to drugs of abuse. The descending influences on striatal mechanisms from the prefrontal cortex may have a role in the progressive loss of control over drug-seeking in addiction as separate to its consolidation as habitual drug-seeking (Everitt *et al.* 2001). As discussed, forebrain dopaminergic transmission results in an

increased propensity to emit conditioned responses to stimuli with appetitive or aversive value. This net change in behaviour is likely subserved by a potentiation of stimulus-reward learning (by dopamine actions in the amygdala) and an augmentation in conditioned reinforcement (by dopamine actions in the striatum). Dopamine also has an important role in mediating many cognitive functions of the frontal cortex (Cohen *et al.* 2002). Chronic exposure to drugs of abuse has been shown to be neurotoxic to monoaminergic neurons, causes reductions in brain monoamine neurotransmitter concentrations (Ridley *et al.* 1982), and long-term impairments in frontal cortical function (Jentsch and Taylor, 1999). Subsequently, the cortical deficits in function associated to long-term exposure to drugs of addiction may lead to a decrement in the inhibitory modulation of conditioned responses (by dopamine actions in the frontal cortex) and underlie the persistent and strong propensity for relapse, especially in the presence of drug-associated stimuli in the addict's environment.

Lesions of the frontal cortex in humans produce deficits such as impulsivity, perseveration, deficits in working memory, impairments of inhibitory control, impairments of cognitive set shifting, impairments of reversal of stimulus-reward contingencies and deficits in behavioural modulations in the face of changing motivational valences of stimuli (Baylis and Gaffan, 1991; Collins *et al.* 1998; Dias *et al.* 1997; Robbins *et al.* 1990; Robbins, 1996; Tucker *et al.* 1995). The mesocorticolimbic dopamine system plays an important role in cognitive processes related to the prefrontal cortex including working memory (Brozoski *et al.* 1979; Castner *et al.* 2000) and reward based learning (Hollerman and Schultz, 1998). Stimulation or depletion of mesocorticolimbic dopamine has adverse effects on mesocorticolimbic function; e.g., excessive, as well as insufficient stimulation of dopamine D1 receptors in the prefrontal cortex impairs working memory (Zahrt *et al.* 1997).

Drug abusers also show behavioural traits reminiscent of impaired prefrontal cortex function such as a reduced concern for the consequences of their actions, difficulties with decision making, and a lack of judgement. On detailed cognitive testing, chronic drug users show evidence of cognitive impairments relating to cortico-striatal circuitry dysfunction such as impaired reversal learning and perseveration, similar to patients who have damage to the orbitofrontal prefrontal cortex. These cognitive deficits relate to alterations in the motivational attributes of a stimulus and the changes in the balance between expectation of immediate reward and prediction of long-term losses. Other disorders of compulsive behaviour, such as pathological gambling, also linked to dysfunction of the striato-thalamo-orbitofrontal circuit, are often seen in association with drug addiction. These

cognitive changes are not seen in patients with damage to other sectors of the prefrontal cortex such as the dorsolateral cortex (Bechara *et al.* 2001; Ornstein *et al.* 2000; Rogers *et al.* 1999).

In the earliest stages of PD, a similar pattern of neuropsychological impairment has also been found. The frontal deficit of untreated patients with PD has been shown to extend across a variety of neuropsychological functions including attentional set-shifting and task set shifting (Lees and Smith, 1983). Deficits of frontal lobe functions are differentially affected with disease stage (Owen *et al.* 1992) and, in medicated Parkinson's patients, are exaggerated by L-dopa withdrawal, suggesting an involvement of brain dopamine systems (Lange *et al.* 1992). However, dopamine modulation in PD can have dissociated effects on frontal cognitive processes as some aspects of memory and cognition in PD have demonstrated impairment secondary to dopaminergic "replacement" (Cools *et al.* 2001; Cools *et al.* 2003). Functional imaging techniques have shed insight into the processes which mediate the effect of dopaminergic medication on high level cognitive functioning in Parkinson's patients (Cheesman *et al.* 2005; Cools *et al.* 2002; Lewis *et al.* 2003). Analysis of reward processing in PD patients reveals dysfunction of dopaminergic mesolimbic pathways. The brain reward response, assessed with positron emission tomography (PET), shows selective failure of striatal activation (Kunig *et al.* 2000) and reduced activation of the limbic regions (Goerendt *et al.* 2004). However, both L-dopa medication and STN deep brain stimulation restore activation of ventromedial prefrontal cortical areas with the presentation of rewards compared to the "off" state. Connectivity analysis indicates that the two treatments achieve this via different modulatory effects. Medication appears to exert its neuromodulatory influence through activation of the mesolimbic dopaminergic pathways while deep brain stimulation exerts its neuromodulatory influence through activation of basal ganglia-frontal circuitry. Furthermore, reward responsivity is enhanced with either STN stimulation or dopaminergic therapy (Goerendt *et al.* 2006).

Functional imaging techniques in addicted humans also occupy a pivotal role in mapping the neuropsychological impairments and investigating the persistent behavioural states characteristic of addiction. Drug addicted individuals show cerebral hypoperfusion in the periventricular, frontal and other neocortical regions and these changes correlate with specific cognitive impairments. In protracted withdrawal, the orbitofrontal cortex of drug abusers is hypoactive in proportion to the levels of dopamine D2 receptors in the striatum (Volkow *et al.* 1993) and these changes correlate with behavioural measures of inhibition. Moreover, drug-induced craving specifically activates limbic

regions in functional imaging studies (Childress *et al.* 1999; London *et al.* 2000) and has been shown to induce increased levels of dopamine in the nucleus accumbens (Fontana *et al.* 1993; Grant *et al.* 1996; London *et al.* 2000; Self, 1998; Sell *et al.* 1999).

1.11 Functional neuroimaging

PET is a non-invasive imaging technique that uses molecules that are labeled with short-lived radioisotopes that are injected intravenously. These molecules can then be traced in the brain and their kinetic properties and anatomical distribution can be determined. Quantitive relationships between drug binding *in vivo* and drug effects in patients can be compared using this technique.

An important prerequisite for drug development is that the molecule maintains its properties after labelling. This is the reason for the common use of the positron-emitting radionuclide ^{11}C; the substitution of naturally occurring ^{12}C with ^{11}C does not change the biochemistry or the pharmacology of the molecules (Farde, 1996).

At a PET measurement, a radiolabelled molecule (ligand) is injected intravenously and is distributed via the bloodstream to all parts of the body. The radioligand passes the blood-brain-barrier and binds to target receptors as well as non-target proteins and extracellular matrix. When the radioactive atom in the molecule decays it emits a positron that collides with an electron one to a few millimeters away and annihilate. The annihilation produces two 511keV gamma rays (i.e. two photons). The photons travel at approximately 180° angle and are detected by a coincidence detector system outside the subject.

By using a complicated algorithm, an image of the regional radioactive decay can be calculated. In neuroreceptor imaging studies the regional radioactivity is corrected for decay and plotted versus time to yield time-activity curves (TACs). Different mathematical models are then applied on these TACs to calculated biological parameters describing ligand-receptor binding *in vivo*.

^{11}C-labeled raclopride (RAC) is used in PET to study the function of dopaminergic synapses. RAC binds to dopamine D2 receptors and is a highly selective, rapidly reversible inhibitor of dopaminergic D2 receptor function (Farde *et al.* 1985).

Chapter 2

IS DOPAMINERGIC DRUG THERAPY CAPABLE OF INDUCING PSYCHOMOTOR SENSITISATION IN HUMANS?

Summary

The stimulant effects of two dopaminergic drugs (L-dopa and methylphenidate) before and after initiating regular dopaminergic drug therapy in patients with PD were studied. The motor, psychomotor and reward-potentiating effects of oral L-dopa and methylphenidate (MPH) were assessed in 15 medication-naïve patients on separate occasions under double-blind (medication-naïve) conditions after a placebo and then repeated the testing sessions in the same (medication-experienced) patients following a mean period of 18 months continuous dopaminergic drug therapy. In the medication-naïve condition active drugs did not improve affect and only L-dopa improved motor function. In the medication-experienced condition, active drugs improved positive affect compared to the medication-naïve condition and there was a significantly enhanced effect of L-dopa on motor function. Reward-responsivity was enhanced by both L-dopa and methylphenidate. In conclusion, sustained dopaminergic drug therapy augments the motor effects of an acute challenge with L-dopa and induces euphoriant effects to L-dopa and methylphenidate challenges.

2.1 Introduction

The long term effects of repeated pulsatile dopaminergic drug therapy in PD may induce various neuroadaptations. Sensitisation of striatal dopaminergic neurons may cause dyskinesias whereas drug tolerance may manifest as a shortening of duration of drug effect with the emergence of end-of-dose deterioration. Dopaminergic drugs may also lead to complex repetitive stereotypies (Friedman, 1994), impulse control disorders (Voon *et al.* 2006b) and compulsive self-administration via sensitisation of ventral striatal dopamine systems (Lawrence *et al.* 2003).

The mood, psychomotor, and reward-potentiating effects of L-dopa (which was expected to primarily enhance motor function) and methylphenidate (MPH – expected to have a euphoriant effect) in previously untreated PD patients were assessed. It was predicted that the motor effects of L-dopa would be enhanced and that the euphoriant effects of methylphenidate might be sensitised by long-term dopaminergic drug therapy. L-dopa and MPH were administered on separate occasions

under double-blind conditions and then again after sustained dopaminergic therapy for a mean period of eighteen months.

2.2 Methods

2.2.1 Patient selection

15 patients (8 males and 7 females) who fulfilled Queen Square Brain Bank Criteria for the diagnosis of PD ranging in age from 38–79 years (mean 59 years) were recruited from a specialist clinic prior to initiating dopaminergic drug therapy. Disease duration ranged from 2–9 years (median 4.0 years). Three patients smoked, 4 were ex-smokers, 2 had previous binge or hazardous alcohol use and 2 reported prior non-medical use of cannabis. Patients gave written informed consent for protocols approved by the Joint Ethics Committee of the National Hospital for Neurology and Neurosurgery and Institute of Neurology. Patients scored a minimum of 25 of a possible 32 on the mini-mental Parkinson (Mahieux *et al.* 1995). Thirteen patients receiving MPH had a normal ECG within 2 weeks of baseline testing and 2 with a history of heart disease did not undergo any MPH challenges.

2.2.2 Study design

Medication-naïve PD patients attended the outpatient department on consecutive days for testing. Patients were informed that the purpose of the testing was to examine how different drugs influence mood and motor symptoms and whether any observed effects changed over time. Patients were informed that they would "receive placebo and an active drug (L-dopa and MPH) in a random order on one day, and placebo and the other active drug in a random order on the next". The same testing procedure would be repeated following a period of sustained anti-Parkinson drug treatment. Testing in the medication-experienced state was done after overnight withdrawal of the patients' normal anti-Parkinson medications (except in the case of cabergoline which was withheld for 3 days prior to testing). To reduce the possibility of nausea, domperidone 20mg three times per day was administered for 3 days prior to each of the study days. Unbeknown to the patient, each test involved administration of placebo (lactose) followed approximately 75 minutes later by the active drug. The purpose of the placebo was to minimise expectancy effects. Active drugs (L-dopa and MPH) were identical in appearance to the placebo and were prepared and dispensed in a predetermined random order controlled by a pharmacist. Patients were blinded to the order of medication administration and

the expected medication effects. After each pair of challenges in the medication-naïve and medication-experienced conditions, patients were asked to identify which drug in each testing session they thought was inactive. The rater (AE) was blinded to the identity of the active drug. Blinding was maintained until after the database was unlocked at the conclusion of the study.

The testing was repeated after a mean 18 months (range 2–24) of sustained dopaminergic drug therapy in 14 individuals using a separate predetermined randomisation code. Twelve patients had received a minimum of 15 months of therapy. One patient was lost to follow up and another retrospectively revealed to treating physicians that he had used therapy only intermittently until 2 months prior to retesting. Another requested earlier repeat testing at 6 months. The latter 2 patients were included in the analysis as affective responses to L-dopa have been previously reported to occur as early as with the second dose (Maricle *et al.* 1998). At the time of the repeat testing, patients were taking L-dopa (n=7; mean daily dose 300mg), cabergoline (2; mean 2mg), pergolide (2; mean 2mg), ropinirole (2; mean 14.5mg), and bromocriptine (1; mean 30mg). L-dopa patients were older than agonist patients (mean 66.0 years ±SD 9.6, versus 52.8 ±9.5, p=0.020).

2.2.3 Challenge protocol

At 9:30am patients completed baseline questionnaires. Pulse and blood pressure were monitored at 20 minute intervals. At 10:30am, the placebo was given followed by the active medication approximately 75 minutes later.

2.2.4 Affect and drug ratings

Visual analogue scales (VAS) were used to quantify aspects of positive affect (PA) and anxiety (Bond and Lader, 1974) at baseline and then at 20 minute intervals for 60 minutes after placebo and 100 minutes after active drug. Patients were asked to rate their feelings at each observation time. A summary score for PA was calculated from the mean score of ratings on a 100-mm line for each of the adjectives 'stimulated', 'active', 'competitive', 'excited', 'enthusiastic', 'happy', 'self-confident' with anchors of 'not at all' at 0mm and 'extremely' at 100mm. Patients were also asked to rate 'anxious'. Significant increases in VAS ratings of PA have consistently been reported following an oral dose of a psychostimulant drug compared to placebo in both drug-naïve and -experienced humans and are thought to be indicative of a drug's abuse liability (Foltin and Fischman, 1991).

2.2.5 Reward responsivity

The Card Arranging Reward Responsivity Objective Test (CARROT) (Powell *et al.* 1996) was done at baseline, 60 minutes after placebo and 80 minutes after active drug. The patient is asked to sort cards displaying series of digits into three piles on four occasions (Task1, Task2, Task3, and Task4). Task1 is the time to sort 60 cards as quickly as possible and is used for subsequent trials. The mean number of cards sorted in Task2 and Task4, in which the patient is asked to sort the cards as quickly as possible, represents the ''nonrewarded'' rate. In Task3 the patient is asked to sort the cards as quickly as possible and is told that for every five cards sorted, he would receive a 10 pence reward, and the number of cards sorted represents the ''rewarded'' rate. ''Reward responsivity'' is computed as (rewarded - nonrewarded) ÷ nonrewarded x 100.

2.2.6 Motor performance

The Unified Parkinson Disease Rating Scale (UPDRS) motor scale (Fahn *et al.* 1987) was done at baseline, 60 minutes after placebo and 80 minutes after active drug.

2.2.7 Analysis

The assumptions of normality and constant variance of the model residuals were reasonably met for each of the analyses. Although anxiety scores after baseline were generally toward the lower end of the scale (range of mean scores 19.8-31.4mm) and somewhat right-skewed.

The change in PA and anxiety after placebo were examined with two-way repeated measures ANOVAs to examine the nature of the time-course effect across the four trials (2 trials [T1 and T2] in the medication-naïve condition and 2 trials [T3 and T4] in the medication-experienced condition). TIME (0, 20, 40, and 60 minutes) and TRIAL (4 levels; T1, T2, T3 and T4) served as repeated measures. The effects of repeated placebo administration on UPDRS and reward responsivity was examined using two-way repeated measures ANOVAs across the 4 trials in which the placebo was administered. STATE (at baseline and after placebo) and TRIAL (4 levels) served as the within-subject repeated measures.

The effects of L-dopa and MPH on PA, anxiety from the medication-naïve to the medication-experienced condition were compared using three-way repeated measures ANOVAs to examine the nature of the time-course effect. TIME (0, 20, 40, 60, 80 and 100 minutes after drug), DRUG (L-dopa and MPH) and CONDITION (i.e. medication-naïve versus medication-experienced) served as

repeated measures. The effects of L-dopa and MPH administration on UPDRS and reward responsivity were examined using three-way repeated measures ANOVAs. STATE (after placebo and after active drug), DRUG (L-dopa and MPH) and CONDITION (i.e. medication-naïve versus medication-experienced) served as repeated measures. To examine whether there was a change in the magnitude of effect on the UPDRS with drug from the medication-naïve to the medication-experienced condition, the change in UPDRS (i.e. UPDRS after drug – UPDRS after placebo) was examined with a two way repeated measures ANOVA. DRUG (L-dopa and MPH) and CONDITION (i.e. medication-naïve versus medication-experienced) served as repeated measures.

2.3 Results

Patients correctly guessed which drug was the placebo in 19 of the 28 trials in the medication-naïve condition, and 21 of the 26 challenges in the medication-experienced condition. Only 4 patients correctly identified the placebo in every trial and, at the end of the study, when asked, none were aware of the intention to administer placebo first.

2.3.1 Change after placebo

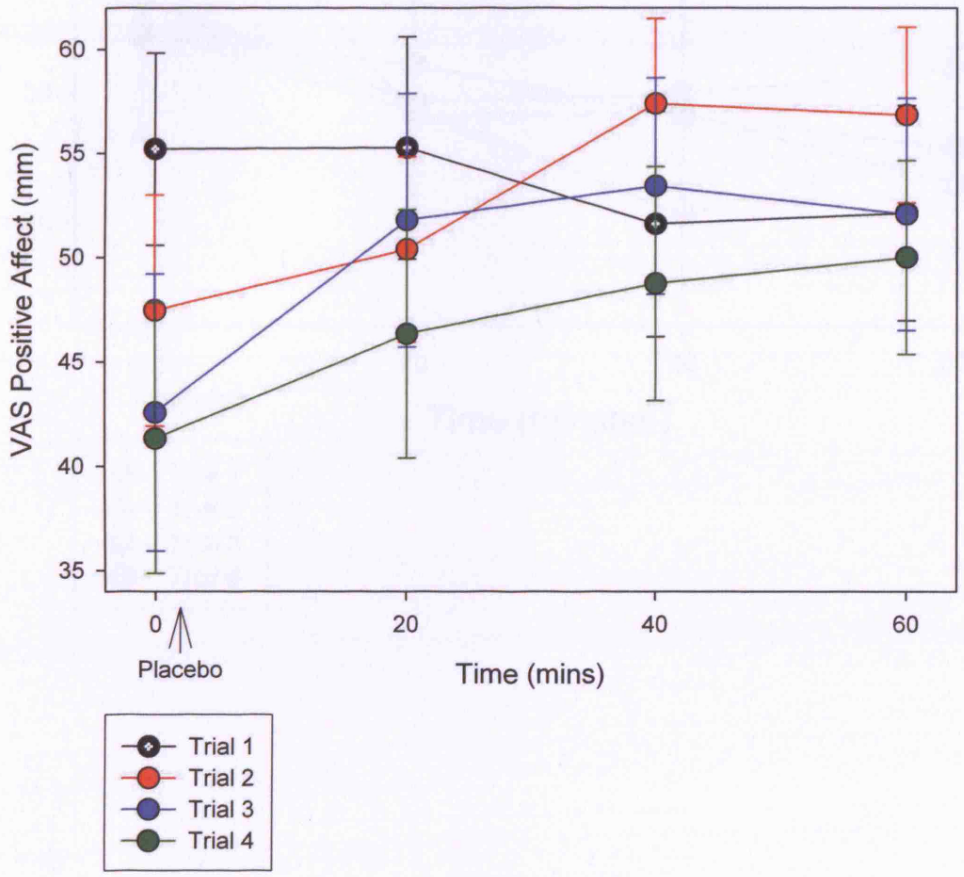
2.3.1.1 Subjective state

Figure 2-1A illustrates patient ratings of PA at baseline and after placebo for T1-T4. There was a significant TRIAL *x* TIME interaction ($F(9,99)=1.98$; $p=0.049$) for PA. Figure 2-1B illustrates patient ratings of anxiety at baseline and after placebo for T1-T4. There was a significant TRIAL x TIME interaction $F(9,99)=3.74$; $p=0.001$ for anxiety. These interactions suggest that the changes in PA and anxiety across time after administration of the placebo were not consistent across the four trials. Post-hoc pairwise comparisons of change in PA and anxiety comparing 0 minutes with 20, 40 and 60 minutes after placebo were of most interest and are given in Table 2-1. Moreover, preplacebo (0 minutes) PA ratings at Trial 1 were significantly higher than Trial 4 (mean difference 15.2, SE 6.6, $p=0.041$, CI 0.7 – 29.6) but there was no difference between Trial 2 and 3. In T1 there were no differences in mean PA between the time points. In T2-T4, PA ratings were lower at 0 minutes compared to later time point. Preplacebo (0 minutes) anxiety ratings at Trial 1 were significantly higher than Trial 2 (mean difference 17.2, SE 7.2, $p=0.033$, CI 1.6 – 32.8) and Trial 3 (mean difference 22.1, SE 8.0, $p=0.016$, CI 4.8 – 39.3). Ratings of anxiety were higher at 0 minutes

compared to later time points in T1 and T2 only but not at T3 or T4. No differences between 20, 40 and 60 minutes were observed for PA or anxiety (data not shown).

Figure 2-1: Mean visual analogue scale ratings of A. positive affect and B. anxiety at baseline, 20, 40 and 60 minutes after administration of placebo in Trial 1, 2, 3, and 4. Error bars represent SEM.

A.



B.

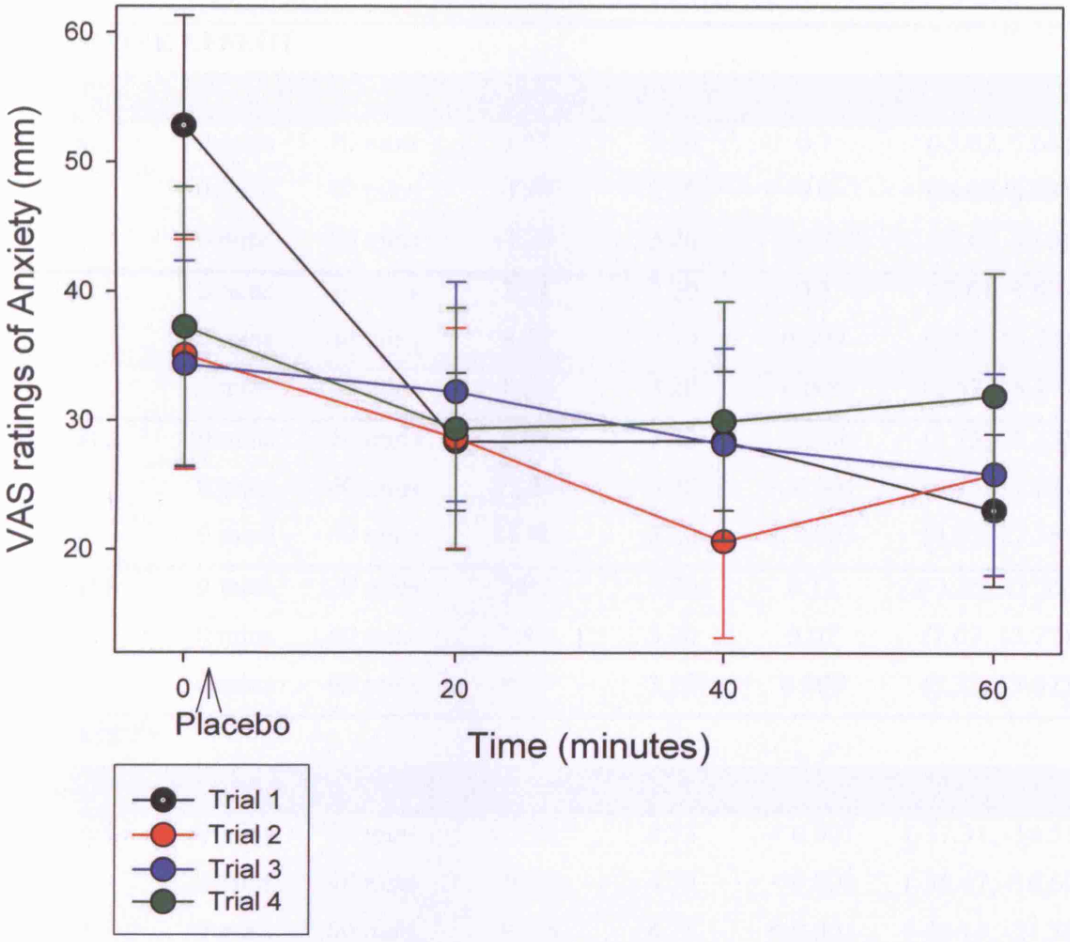

VAS ratings of Anxiety (mm)
60
50
40
30
20
0
Placebo
20
40
60
Time (minutes)
Trial 1
Trial 2
Trial 3
Trial 4

Table 2-1: Post-hoc pairwise comparisons of visual analogue ratings of positive affect and anxiety at time points within TRIALs 1, 2, 3, and 4.

POSITIVE AFFECT						
Trial	Time A	Time B	Difference	St Error	*P*-value	95% CI
Trial 1	0 mins	20 mins	1.33	3.20	0.7	(-5.02, 7.68)
	0 mins	40 mins	-1.67	3.20	0.6	(-8.02, 4.68)
	0 mins	60 mins	-1.25	3.20	0.7	(-7.60, 5.10)
Trial 2	0 mins	20 mins	3.34	3.20	0.3	(-3.01, 9.69)
	0 mins	40 mins	9.42	3.20	0.004	(3.07, 15.77)
	0 mins	60 mins	8.92	3.20	0.006	(2.57, 15.27)
Trial 3	0 mins	20 mins	9.08	3.20	0.006	(2.73, 15.43)
	0 mins	40 mins	11.50	3.20	< 0.001	(5.15, 17.85)
	0 mins	60 mins	11.00	3.20	< 0.001	(4.65, 17.35)
Trial 4	0 mins	20 mins	5.00	3.20	0.12	(-1.35, 11.35)
	0 mins	40 mins	7.42	3.20	0.02	(1.07, 13.77)
	0 mins	60 mins	8.67	3.20	0.008	(2.32, 15.02)
ANXIETY						
Trial	Time A	Time B	Difference	St Error	P-value	95% CI
Trial 1	0 mins	20 mins	-27.92	4.73	< 0.001	(-37.31, -18.53)
	0 mins	40 mins	-26.08	4.73	< 0.001	(-35.47, -16.69)
	0 mins	60 mins	-30.75	4.73	< 0.001	(-40.14, -21.36)
Trial 2	0 mins	20 mins	-7.08	4.73	0.14	(-16.47, 2.31)
	0 mins	40 mins	-15.66	4.73	0.001	(-25.05, -6.27)
	0 mins	60 mins	-9.91	4.73	0.04	(-19.30, -0.52)
Trial 3	0 mins	20 mins	-2.92	4.73	0.5	(-12.31, 6.47)
	0 mins	40 mins	-7.33	4.73	0.12	(-16.72, 2.06)
	0 mins	60 mins	-8.17	4.73	0.09	(-17.56, 1.22)
Trial 4	0 mins	20 mins	-7.92	4.73	0.10	(-17.31, 1.47)
	0 mins	40 mins	-7.33	4.73	0.12	(-16.72, 2.06)
	0 mins	60 mins	-5.33	4.73	0.3	(-14.72, 4.06)

2.3.1.2 UPDRS and reward responsivity

No significant change after placebo was found on the UPDRS scores (main effect of STATE $F(1,10)=1.48, p=0.125$) or reward responsivity (STATE $F(1,10)=2.56, p=0.141$).

2.3.2 L-dopa and methylphenidate effects in medication-naïve and medication-experienced conditions

To reduce confounding effects of pre-baseline affect on drug response, active drugs were equally represented in the first and second trials for each condition. A one factor within-subjects ANOVA of predrug VAS ratings showed that participants did not differ in PA ($F(3,33)=0.993; p=0.408$) or anxiety ($F(3,33)=0.475; p=0.702$) immediately prior to the administration of L-dopa or MPH on any trial (i.e. at TIME=0 or 60minutes after placebo).

2.3.2.1 Subjective effects after active drug administration

For PA, three-way interaction between CONDITION *x* DRUG *x* TIME was not significant ($F(5,55)=0.261, p=0.933$) and therefore removed from the model. There was a significant interaction between CONDITION *x* TIME ($F(5,55)=2.52, p=0.040$) (Figure 2-2) for PA. Post-hoc mean comparisons of time points within conditions showed this was due to an effect on PA by active drug in the experienced condition compared to the naïve condition (Table 2-1). In the naïve condition, there were no differences in mean PA between the 6 time points. In the experienced condition, mean PA was significantly lower at 0 mins and 20 mins compared to 60 mins, 80 mins and 100 mins and the mean PA at 40 mins, was significantly lower than at 100 mins. There were no significant differences between 60 mins, 80 mins and 100 mins (data not shown). The other two factor interaction CONDITON *x* DRUG was not statistically significant $F(1,11) = 0.05, p=0.83$.

Figure 2-2: Mean visual analogue ratings of Positive Affect (±SEM): CONDITION (medication-naïve and medication-experienced) by TIME interaction.

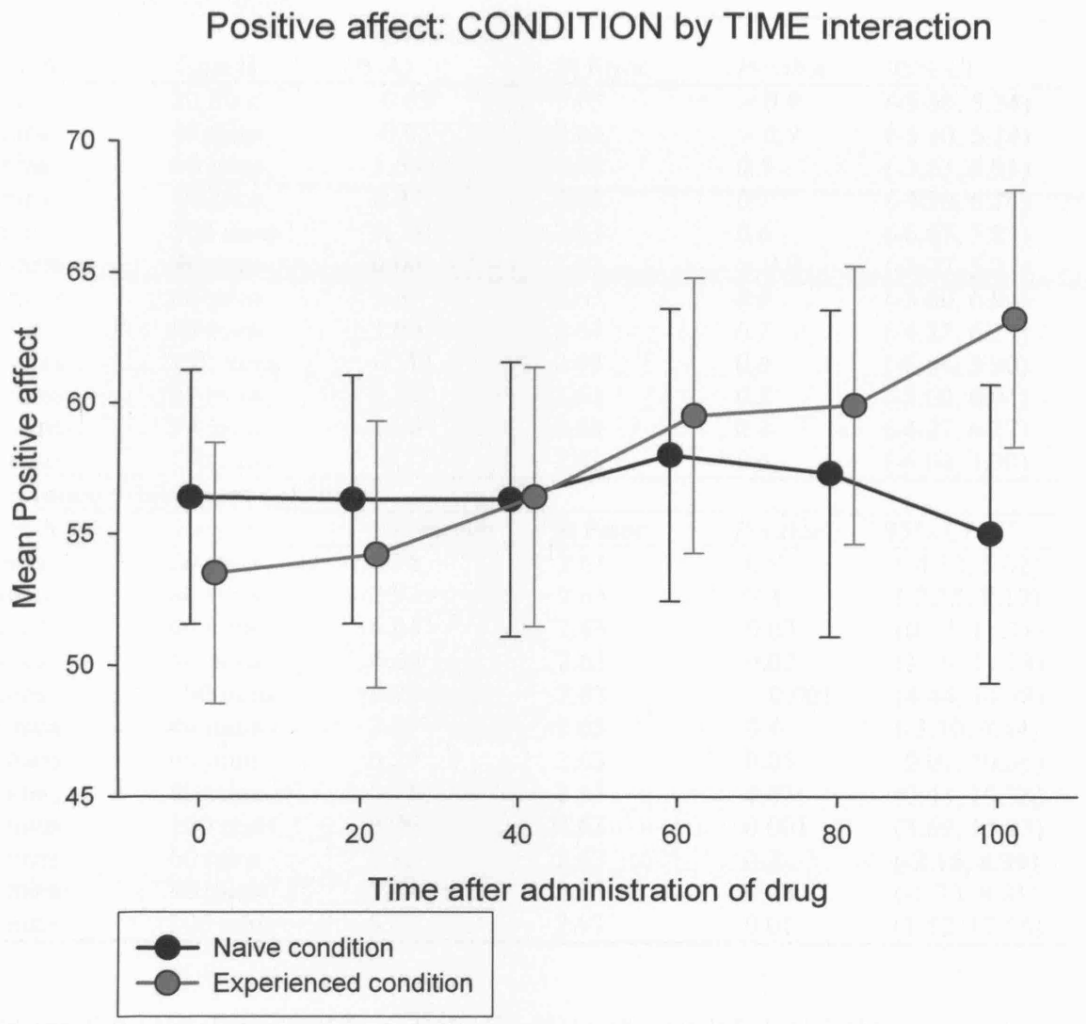


Table 2-2: Post-hoc pairwise comparisons for visual analogue ratings of Positive Affect scores between different times for both L-dopa and methylphenidate in the medication-naïve and medication-experienced conditions.

Medication-naïve condition					
Time A	Time B	Difference (B-A)	St Error	*P-value*	95% CI
0 mins	20 mins	-0.03	2.63	*> 0.9*	(-5.30, 5.24)
0 mins	40 mins	-0.03	2.63	*> 0.9*	(-5.30, 5.24)
0 mins	60 mins	1.64	2.63	*0.5*	(-3.63, 6.91)
0 mins	80 mins	0.97	2.63	*0.7*	(-4.30, 6.24)
0 mins	100 mins	-1.40	2.63	*0.6*	(-6.67, 3.87)
20 mins	40 mins	0.00	2.63	*> 0.9*	(-5.27, 5.27)
20 mins	60 mins	1.67	2.63	*0.5*	(-3.60, 6.94)
20 mins	80 mins	1.00	2.63	*0.7*	(-4.27, 6.27)
20 mins	100 mins	-1.37	2.63	*0.6*	(-6.64, 3.90)
40 mins	60 mins	1.67	2.63	*0.5*	(-3.60, 6.94)
40 mins	80 mins	1.00	2.63	*0.7*	(-4.27, 6.27)
40 mins	100 mins	-1.37	2.63	*0.6*	(-6.64, 3.90)
Medication-experienced condition					
Time A	Time B	Difference	St Error	*P*-value	95% CI
0 mins	20 mins	0.75	2.63	0.8	(-4.52, 6.02)
0 mins	40 mins	2.92	2.63	0.3	(-2.35, 8.19)
0 mins	60 mins	6.04	2.63	0.03	(0.77, 11.31)
0 mins	80 mins	6.46	2.63	0.02	(1.19, 11.73)
0 mins	100 mins	9.71	2.63	< 0.001	(4.44, 14.98)
20 mins	40 mins	2.17	2.63	0.4	(-3.10, 7.44)
20 mins	60 mins	5.29	2.63	0.05	(0.02, 10.56)
20 mins	80 mins	5.71	2.63	0.03	(0.44, 10.98)
20 mins	100 mins	8.96	2.63	0.001	(3.69, 14.23)
40 mins	60 mins	3.12	2.63	0.2	(-2.15, 8.39)
40 mins	80 mins	3.54	2.63	0.18	(-1.73, 8.81)
40 mins	100 mins	6.79	2.63	0.01	(1.52, 12.06)

There was also a significant DRUG *x* TIME ($F(5,55)=3.18, p=0.014$) for PA (Figure 2-3). Post-hoc pairwise comparisons of time points within drugs showed no significant differences in mean PA between the 6 time points for L-dopa. However, for MPH, mean PA was significantly lower at 0 mins and 20 mins compared to 60 mins, 80 mins and 100 mins (Table 2-3). In addition, comparison of conditions within time points showed the mean PA was significantly higher for MPH compared to L-dopa at 80 minutes (mean difference 9.33, SEM 3.99, $p=0.02$, 95% CI 1.41 – 17.25). Other time points failed to reach significance.

Figure 2-3: Mean visual analogue ratings of Positive Affect (±SEM): DRUG (L-dopa versus MPH) by TIME interaction.

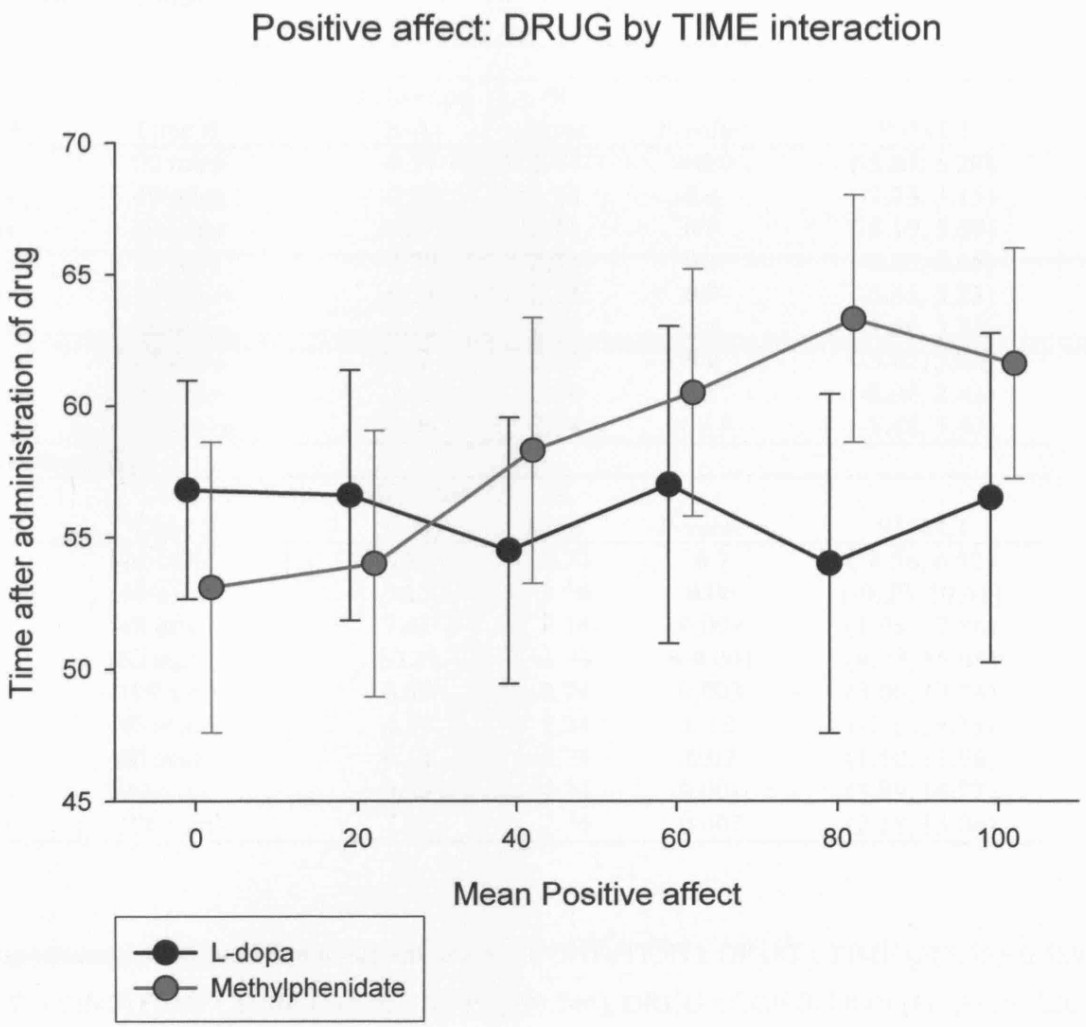


Table 2-3: Post-hoc pairwise comparisons for visual analogue ratings of Positive Affect scores between different times for L-dopa and methylphenidate across the medication-naïve and experienced conditions.

L-dopa					
Time A	Time B	Difference (B-A)	St Error	*P-value*	95% CI
0 mins	20 mins	-0.17	2.74	*> 0.9*	(-5.61, 5.27)
0 mins	40 mins	-2.29	2.74	*0.4*	(-7.73, 3.15)
0 mins	60 mins	0.25	2.74	*0.9*	(-5.19, 5.69)
0 mins	80 mins	-2.79	2.74	*0.3*	(-8.23, 2.65)
0 mins	100 mins	-0.21	2.74	*0.9*	(-5.65, 5.23)
20 mins	40 mins	-2.12	2.74	*0.4*	(-7.56, 3.32)
20 mins	60 mins	0.42	2.74	*0.9*	(-5.02, 5.86)
20 mins	80 mins	-2.62	2.74	*0.3*	(-8.06, 2.82)
20 mins	100 mins	-0.04	2.74	*> 0.9*	(-5.48, 5.40)
Methylphenidate					
Time A	Time B	Difference (B-A)	St Error	*P*-value	95% CI
0 mins	20 mins	0.88	2.74	0.7	(-4.56, 6.32)
0 mins	40 mins	5.17	2.74	0.06	(-0.27, 10.61)
0 mins	60 mins	7.42	2.74	0.009	(1.98, 12.86)
0 mins	80 mins	10.21	2.74	< 0.001	(4.77, 15.65)
0 mins	100 mins	8.50	2.74	0.003	(3.06, 13.94)
20 mins	40 mins	4.29	2.74	0.12	(-1.15, 9.73)
20 mins	60 mins	6.54	2.74	0.02	(1.10, 11.98)
20 mins	80 mins	9.33	2.74	0.001	(3.89, 14.77)
20 mins	100 mins	7.62	2.74	0.007	(2.18, 13.06)

No significant effects were found for anxiety; i.e. CONDITION *x* DRUG *x* TIME ($F(5,55)=0.589$, $p=0.708$), CONDITION *x* TIME ($F(5,55)=0.539$, $p=0.746$), DRUG *x* CONDITION ($F(1,11)=0.220$, $p=0.649$) and DRUG *x* TIME ($F(5,55)=0.582$, $p=0.714$). Anxiety scores after placebo were towards the lower end of the scale. Hence, the scale might have been relatively unresponsive to further decreases in anxiety score.

2.3.2.2 Incentive motivational effects

Three-way ANOVA revealed that the three factor interaction between CONDITION, DRUG and STATE was not statistically significant for reward responsivity ($F(1,11)=0.47, p=0.51$); nor were any of the two-factor interactions. The only statistically significant effect was the main effect of STATE ($F(1,11)=20.42, p=0.001$) indicating that L-dopa and MPH both acted to increase reward responsivity. Post-hoc pairwise comparison of showed significantly higher reward responsivity across the medication-naïve and experienced conditions (after placebo mean -0.5%, after drug mean 4.1%, SE 1.0%, $p=0.001$, 95%CI 2.4% – 6.9%) (see Table 2-4). The main effects of condition and drug were not statistically significant ($F(1,11)=0.81, p=0.39$ and $F(1,11)=0.002, p=0.97$ respectively).

Table 2-4: Mean reward responsivity by CONDITION, DRUG and STATE.

Condition	Drug	State	Mean	Standard Deviation
Naïve	L-DOPA	After placebo	-0.7%	5.5%
		After drug	3.9%	6.2%
	MPH	After placebo	-1.3%	7.2%
		After drug	2.6%	5.8%
Experienced	L-DOPA	After placebo	-0.3%	4.4%
		After drug	4.2%	5.4%
	MPH	After placebo	0.1%	4.3%
		After drug	5.8%	8.0%

Table 2-5: Posthoc pairwise comparison for UPDRS of state within condition and drug combination

Condition	Drug	STATE A	STATE B	Difference (B-A)	St Error	*P*-value	95% CI
Naïve	L-dopa	Prior to drug	After drug	-5.16	1.35	0.003	(-8.13, -2.19)
	MPH	Prior to drug	After drug	-2.09	1.35	0.15	(-5.06, 0.88)
Experienced	L-dopa	Prior to drug	After drug	-10.33	1.35	< 0.001	(-13.30, -7.36)
	MPH	Prior to drug	After drug	-0.92	1.35	0.5	(-3.89, 2.05)

Table 2-6: Posthoc pairwise comparison for change in UPDRS in naïve versus experienced condition for L-dopa versus methylphenidate

Drug	Mean change in UPDRS under Naïve condition	Mean change in UPDRS under Experienced condition	Mean difference (Experienced – Naïve)	Standard error of difference	*P*-value	95% CI for mean difference
L-DOPA	–4.80	–9.57	–4.77	1.69	0.03	(–9.28, –0.27)
MPH	–1.77	–0.92	0.85	1.83	0.97	(–4.00, 5.70)

Table 2-7: Post-hoc pairwise comparisons for visual analogue ratings of positive affect scores between different times for L-dopa and methylphenidate across the medication-naïve and experienced conditions.

L-dopa					
Time A	Time B	Difference	St Error	*P-value*	95% CI
0 mins	20 mins	-0.17	2.74	*> 0.9*	(-5.61, 5.27)
0 mins	40 mins	-2.29	2.74	*0.4*	(-7.73, 3.15)
0 mins	60 mins	0.25	2.74	*0.9*	(-5.19, 5.69)
0 mins	80 mins	-2.79	2.74	*0.3*	(-8.23, 2.65)
0 mins	100 mins	-0.21	2.74	*0.9*	(-5.65, 5.23)
20 mins	40 mins	-2.12	2.74	*0.4*	(-7.56, 3.32)
20 mins	60 mins	0.42	2.74	*0.9*	(-5.02, 5.86)
20 mins	80 mins	-2.62	2.74	*0.3*	(-8.06, 2.82)
20 mins	100 mins	-0.04	2.74	*> 0.9*	(-5.48, 5.40)
Methylphenidate					
Time A	Time B	Difference	St Error	*P*-value	95% CI
0 mins	20 mins	0.88	2.74	0.7	(-4.56, 6.32)
0 mins	40 mins	5.17	2.74	0.06	(-0.27, 10.61)
0 mins	60 mins	7.42	2.74	0.009	(1.98, 12.86)
0 mins	80 mins	10.21	2.74	< 0.001	(4.77, 15.65)
0 mins	100 mins	8.50	2.74	0.003	(3.06, 13.94)
20 mins	40 mins	4.29	2.74	0.12	(-1.15, 9.73)
20 mins	60 mins	6.54	2.74	0.02	(1.10, 11.98)
20 mins	80 mins	9.33	2.74	0.001	(3.89, 14.77)
20 mins	100 mins	7.62	2.74	0.007	(2.18, 13.06)

No significant effects were found for anxiety; i.e. CONDITION *x* DRUG *x* TIME ($F(5,55)=0.589$, $p=0.708$), CONDITION *x* TIME ($F(5,55)=0.539$, $p=0.746$), DRUG *x* CONDITION ($F(1,11)=0.220$, $p=0.649$) and DRUG *x* TIME ($F(5,55)=0.582$, $p=0.714$). Anxiety scores after placebo were towards

the lower end of the scale. Hence, the scale might have been relatively unresponsive to further decreases in anxiety score.

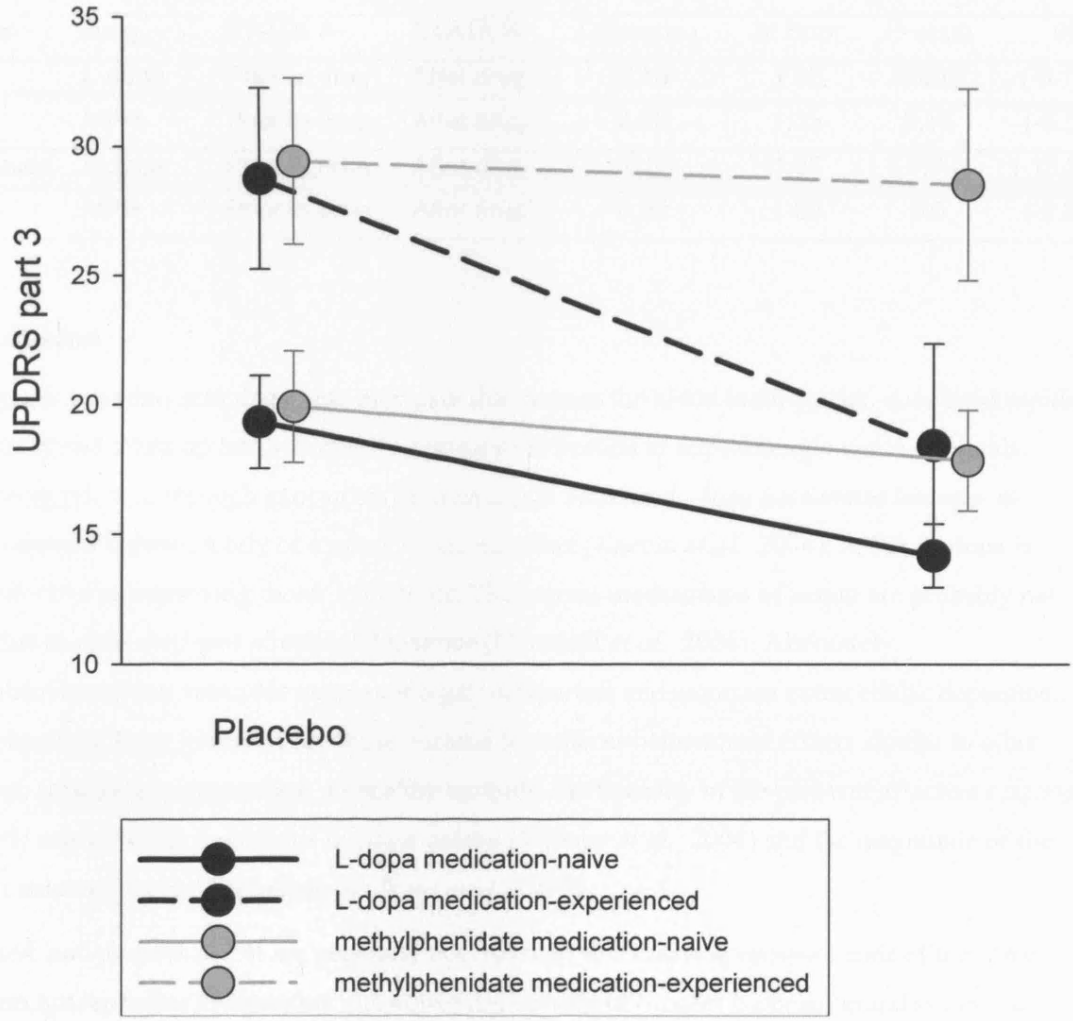
2.3.2.3 Incentive motivational effects

Three-way ANOVA found a significant main effect of STATE (i.e. state after placebo versus after drug) for reward responsivity ($F(1,11)=20.42, p=0.001$) indicating that L-dopa and MPH both acted to increase reward responsivity. Post-hoc pairwise comparison showed significantly higher reward responsivity across the medication-naïve and experienced conditions (after placebo mean -0.5%, after drug mean 4.1%, SE 1.0%, p=0.001, 95%CI 2.4% – 6.9%).

2.3.2.4 Motor effects

A significant interaction was found for STATE *x* DRUG *x* CONDITION ($F(1,11)=11.75, p=0.006$) (Figure 2-4). The change from after placebo to after drug was similar for MPH in the naïve and experienced conditions, however the change is larger for L-dopa in the experienced condition compared to the naïve condition (Table 2-8). Lower order interactions were as follows: CONDITION *x* DRUG interaction: $F(1,11)=3.79, p=0.08$, CONDITION *x* STATE interaction: $F(1,11)=2.31$, $p=0.16$, DRUG *x* STATE interaction: $F(1,11)=16.57, p=0.002$, CONDITION main effect: $F(1,11)=9.81, p=0.01$, DRUG main effect: $F(1,11)=28.02, p<0.001$, STATE main effect: $F(1,11)=36.29, p<0.001$.

Figure 2-4: UPDRS part 3 after placebo versus drug (L-dopa or methylphenidate) in the medication-naïve and medication-experienced condition.



Change in UPDRS induced by drug was calculated. The interaction between DRUG and CONDITION was statistically significant $F(1,50)=5.10, p=0.028$). This means the comparison between the conditions should be done separately for each drug. These are shown in Table 2-5. The

mean change in UPDRS differed statistically significantly between the naïve and experienced conditions for L-dopa (p-value 0.03) but not for MPH (p-value = 0.96).

Table 2-8: Posthoc pairwise comparison for UPDRS of state within condition and drug combination

Condition	Drug	STATE A	STATE B	Difference	St Error	*P*-value	95% CI
Naïve	L-dopa	Prior to drug	After drug	-5.16	1.35	0.003	(-8.13, -2.19)
	MPH	Prior to drug	After drug	-2.09	1.35	0.15	(-5.06, 0.88)
Experienced	L-dopa	Prior to drug	After drug	-10.33	1.35	< 0.001	(-13.30, -7.36)
	MPH	Prior to drug	After drug	-0.92	1.35	0.5	(-3.89, 2.05)

2.4 Discussion

L-Dopa is an amino acid dopamine precursor that crosses the blood brain barrier, converted rapidly to dopamine and taken up into vesicles by a transporter protein in dopaminergic nerve terminals, before being released through exocytosis of presynaptic vesicles. L-dopa accelerates learning in healthy controls independently of a minor effect on affect (Knecht *et al.* 2004). In PD, L-dopa is highly effective in improving motor symptoms. The precise mechanisms of action are probably not simply due to replenishment of striatal dopamine (Goerendt *et al.* 2006). Alternately, methylphenidate alters vesicular monoaminergic transporters and increases extracellular dopamine. Methylphenidate has a potential for abuse because it produces behavioural effects similar to other stimulants such as d-amphetamine. In healthy controls, the intensity of the pleasant affective response with MPH relates to the rapidity of its brain uptake (Volkow *et al.* 2004) and the magnitude of the resultant striatal dopamine response (Volkow *et al.* 1999).

Negative and positive affect are generally not regarded as occupying opposite ends of the same dimension but represent independent subjective dimensions of broader biobehavioural systems of approach and withdrawal corresponding to separate reaction systems in the brain (Watson *et al.* 1999). The purpose of placebo administration prior to active drug in this study was to reduce the effects of conscious expectancy on reported drug effects - thus parsing out the effects of expectancy from true drug effects. In PD the placebo response can result in enhanced brain dopamine release and

many studies have reported objective improvements in motor performance (de la Fuente-Fernandez *et al.* 2001). Dissociable changes in positive and negative affect were found after the administration of placebo that appeared to be influenced by expectancy as well as possibly the development of a medication-withdrawal state characterised by reduced levels of positive affect. With successive trials, baseline measures of anxiety and positive affect tended to decrease, the change in positive affect after placebo increased, and the change in anxiety decreased. There was also a dissociable response in aspects of positive and negative affect after methylphenidate administration in the medication-experienced condition.

Patients in this study received sustained therapy with L-dopa or dopamine agonists. L-Dopa and dopamine agonists have similar psychostimulant effects to those extensively studied in animal experiments of sensitisation (Henry *et al.* 1998; Hoffman *et al.* 1988), as both can induce dyskinesias and motor fluctuations. Both classes of drugs may also evoke compulsive self-administration in vulnerable individuals with PD (Lawrence *et al.* 2003) and in non-Parkinsonian patients (Steiner and Wirguin, 2003) and alleviate apathy following bilateral subthalamic nucleus deep brain stimulation to treat refractory motor deficits in PD (Funkiewiez *et al.* 2004).

A variety of drug effects were found to change following chronic dopaminergic therapy. Subjective euphoriant effects (i.e. enhanced PA) of active drug became evident only after a period of regular dopaminergic therapy. These findings are in line with studies that have demonstrated the development of a "mood" response to L-dopa after treatment initiation in early PD. It has been shown that dopaminergic drugs can have "rewarding" effects in laboratory animals (Hoffman *et al.* 1988; Katajamaki *et al.* 1998) and can produce cross-sensitisation to other drugs (McDaid *et al.* 2005) or naturally motivated behaviours (Fiorino and Phillips, 1999). In a study by Nutt and colleagues, MPH appeared to have no acute effect on mood in 8 PD patients with advanced disease but they did not discriminate between positive and negative affect. The 8 patients had also received L-dopa therapy for several years and may therefore have been better able to distinguish between L-dopa, MPH and placebo. Nutt and colleagues also reported that both mood and motor performance were significantly enhanced by a combination of oral MPH with a L-dopa infusion (Nutt *et al.* 2004). In our study, it is possible that the mood response to the second dose of MPH may be due to the effects of repeated dosing with MPH – i.e. sensitisation rather than cross-sensitisation. However, these findings are consistent with the notion that sustained dopaminergic therapy may cross-sensitise patients to the

euphoriant, as well as the motoric effects of MPH but the effects are modified according to disease stage.

Brain dopamine systems are not only relevant to movement, but also mediate some of the rewarding effects of food, sex, as well as culturally learned rewards (e.g. money) (Knutson *et al.* 2001). In this study, an acute challenge with both L-dopa and MPH enhanced responding for a small financial reward during the CARROT. This is consistent with clinical observations in which dopamine agonists have been linked to the development of a variety of impulse control disorders such as pathological gambling (Voon *et al.* 2006b), food bingeing, compulsive shopping and hypersexuality (Evans and Lees, 2004). Furthermore, a small sub-group of PD patients can also become sensitised to the rewarding effects of dopaminergic drugs and begin to compulsively and inappropriately self-medicate.

Dopamine has a broad role in the control of movement and it may be difficult to distinguish between the ability to move and the motivation to move (Wise, 2004). Patients in our study were told that one of two medications, given one hour and a quarter apart, might enhance movement or mood. Despite methylphenidate's effect on enhancing striatal dopamine, no demonstrable effect was found on the motor UPDRS score. In contrast, L-dopa gave a consistent and highly significant motor benefit. Moreover, the motor benefit with L-dopa became significantly greater after chronic dopaminergic therapy compared to the medication-naïve condition. In general, a greater amplitude of motor response with L-dopa in dopa-naïve patients predicts earlier onset of motor fluctuations (a form of drug tolerance), a greater augmentation in L-dopa's motor effects, and the development of dyskinesias (McColl *et al.* 2002; Nutt, 2007) (regarded as sensitisation effects that result from pulsatile dopaminergic drug dosing (Graybiel *et al.* 2000)).

The relatively small number of study participants and the multiple statistical comparisons require caution with interpretation of the data. However, many of the variables measured are conceptually related (such as explicit measures of positive and negative affect), the primary effects of interest were few - the potential euphoriant effects of MPH and motoric effects of L-dopa and incentive motivational effects were consistently found with both drugs and are relevant to clinical observations in patients treated with dopaminergic drugs. Further, evaluation is not blinded with respect to the patient so that one or more readings for any particular patient may be biased.

In conclusion, in this study, the psychomotor effects that are believed to be enhanced by acute challenge with drugs acting on mesolimbic and mesostriatal monoaminergic systems were found to be sensitised by sustained intermittent dopaminergic drug therapy in PD and it can be concluded that neuroadaptive changes may mediate a number of drug-induced behavioural disturbances seen in the course of dopaminergic therapy for PD.

Chapter 3

PUNDING IN PARKINSON'S DISEASE: ITS RELATION TO THE DOPAMINE DYSREGULATION SYNDROME

Summary

Punding is a term that was coined originally to describe complex prolonged, purposeless and stereotyped behaviour in chronic amphetamine users. A structured interview of 50 patients with higher dopamine replacement therapy requirements (>800LEU/day) from 123 unselected patients with PD in a Parkinson's clinic identified 17 (14%) patients with punding. Punding was acknowledged as disruptive and unproductive by the patients themselves, but forcible attempts by family to interrupt the behaviour led to irritability and dysphoria. Punding was associated with very high doses of dopamine replacement therapy often related to a pattern of chronic inappropriate overuse of dopaminergic medication. This is an under-reported, socially disabling phenomenon which is commonly associated with the syndrome of dopamine dysregulation and is phenomenologically distinct from both obsessive-compulsive disorder and mania.

3.2 Introduction

Punding was first described in amphetamine addicts by Rylander in California (Rylander, 1972) and Schiorring in Denmark (Schiorring, 1981). Punding is a complex stereotyped behaviour characterised by an intense fascination with repetitive manipulations of technical equipment, the continual handling, examining and sorting common objects, grooming, hoarding, pointless driving or walkabouts, and the engagement in extended monologues devoid of content. It has occasionally been reported in association with dopaminergic therapy in PD (Fernandez and Friedman, 1999; Friedman, 1994). Other likely examples of L-dopa-induced punding in PD can be found in the literature described as "obsessive-compulsive behaviour" or "hypomania" (Serrano-Duenas, 2002). Patients were systematically surveyed a specialist PD clinic for punding and related behavioural disorders.

3.3 Methods

Consecutive outpatients fulfilling Queen Square Brain Bank criteria for PD (Hughes *et al.* 1992) were interviewed and Mini Mental State Examination (MMSE) was administered. The Unified

Parkinson's Disease Rating Scale (UPDRS) part 2 was done in the "on" state. Patients were asked to provide a list of all current medications and their dosages. Patterns of compulsive use were looked for using recently proposed criteria (Giovannoni *et al.* 2000) and previous episodes of treated psychosis recorded. Treated psychosis was defined as the presence of hallucinations that required reduction in dopamine replacement therapy (DRT) or introduction of antipsychotic medications. Calculation of a daily L-dopa equivalent unit (LEU) dose for each patient was based on theoretical equivalence to L-dopa (similar to previous reports (Parkin *et al.* 2002)) as follows; L-dopa dose + L-dopa dose *x* 1/3 if on entacapone + bromocriptine (mg) *x* 10 + cabergoline or pramipexole (mg) *x* 67 + ropinirole (mg) *x* 20 + pergolide (mg) *x* 100 + apomorphine (mg) *x* 8. Patients taking a daily dose greater than or equal to 800 LEU were then contacted and asked to undertake a standardised interview about their hobbies or pastimes (see Appendix A). The interview approach was developed from preliminary discussions with PD patients who had been identified as punders, animal models of drug related stereotypies and from a previous published questionnaire designed to identify punding in psychostimulant users (Schiorring, 1977). Punding was defined as a repetitive stereotypical behaviour that was recognised by the patient as disruptive (i.e. preventing sleep, eating, timing of medication doses or everyday social interactions) but associated with feelings of calmness / relief. Each subject was rated as having no, mild, moderate or severe punding independently by two investigators (Andrew Evans and Regina Katzenschlager). Punding was rated as severe if the patient had engaged in a single activity all night leading to loss of sleep in the last month and causing social disruption; moderate if there was social disruption and lesser degrees of sleep disturbance and mild if there was no significant or very mild social disruption. The patients completed an obsessive-compulsive inventory (Foa *et al.* 1998); the categories of which correspond to the content domains of the six most common primary obsessions and the six most common primary compulsions. Patients were also asked about the presence of hypomanic symptoms. Data were analysed with SPSS Version 11.0, SPSS Inc., Chicago, Ill. Means were compared using Students *t* test, or Mann Whitney U test as appropriate. The chi-squared test was used for proportions in a two-by-two contingency table. Associations were tested with Spearman rank correlation.

3.4 Illustrative case

A 55-year-old woman developed PD at the age of 37. She responded well to L-dopa but increasing motor handicap soon forced her to stop working as a seamstress. Within seven years of disease,

refractory motor fluctuations led to the introduction of continuous subcutaneous apomorphine infusion. She required very high doses of apomorphine by infusion and additional frequent rescue injections to prevent distressing "off" periods each of which were heralded by a tight feeling in the jaw. She is maintained on apomorphine monotherapy (450mg apomorphine/24hours: 10-24 intermittent apomorphine rescue injections per day on a background of a continuous subcutaneous infusion). Over the last few years, she had experienced cycles of virtually continuous wakefulness lasting 24-48 hours during which she required frequent apomorphine rescue injections. These were followed by periods of severe exhaustion, tension and chaotic disorganisation before she finally fell into an exhausted slumber. As her DRT requirements increased, she developed an intense fascination with buttons. She sorted through a growing collection, numbering a few thousand; arranging them by size, color and type but never succeeded in finishing her cataloguing and categorising despite continuing the activity for many hours during the day and overnight. She described the sorting as "incredibly soothing" and became very irritated if she was interrupted. She also spent excessive time unproductively tidying rooms and turning out drawers, washing clothes and dishes. The tidying was purposeless, did not occur in response to a fear of germs or dirt and the house became more and more disorganised the longer she continued. She was often frustrated by her inability to stop the activity, describing it "like being on a merry-go-round". Introduction of paroxetine up to a daily dose of 40mg was of no benefit. Quetiapine, 25mg nocte, normalised her sleeping pattern and "calmed" the behaviour but was poorly tolerated because of sedation.

3.5 Results

Clinical data were obtained from 123 of 179 consecutive outpatients with PD. The remainder either did not return information regarding medication dosing or did not consent. Of the respondents, 58 patients took a daily dose of 800 or more LEU and fifty of these were able to complete the more detailed interview; 6 patients were lost to follow up and 2 died during the study.

None of the patients in the lower dose group were suspected by the treating clinicians (AJL, AE, DP, and RK) to be punders although the semi-structured interview was not systematically applied to this group. Complex repetitive stereotypies (punding) were identified in 17 of the 50 patients interviewed in the higher dose group. Punders were of comparable age, disease duration and disability to non-punders but took a significantly higher total daily dose of DRT and required more daily rescue doses of medication (Table 3-1). Punders took L-dopa (16), apomorphine via continuous infusion (9),

cabergoline (6), pergolide (2), amantadine (2), selegiline (1), entacapone (1) and bromocriptine (1). Nonpunders took L-dopa (33), entacapone (14), pergolide (10), amantadine (7), ropinirole (6), apomorphine (4), cabergoline (3), pramipexole (2), bromocriptine (2) and selegiline (1). Punders were significantly more likely to use apomorphine (χ^2=9.71; df=1; p=0.002), cabergoline (χ^2=5.21; df=1; p=0.022) and less likely to take entacapone (χ^2=7.13; df=1; p=0.008). Forty-five of the 50 patients who undertook the structured interview were also able to complete the obsessive-compulsive inventory (OCI). Five were unable to complete it because of concomitant medical illness (1), active psychosis (1), and poor understanding of the questions (3). There was a general trend to increased subscale and total scores for frequency and distress ratings in the punders versus non-punders (Table 3-2). However, only the doubting distress (z=1.953; p=0.051) and hoarding distress (z=2.317; p=0.02) subscales approached significance. All patients remained under regular outpatient review. No patients were observed in the course of clinical follow up to develop euphoric or more cheerful mood, and none displayed evidence of an elevated, expansive or irritable behaviour, flight of ideas, inflated self-esteem, grandiosity, or excessive self-confidence consistent with hypomanic mood disorder. One patient with moderately severe dementia (MMSE 21) had simple behavioural stereotypies in isolation (repetitive arranging of bed linen overnight) and was not included in the punding group. The severity of punding was rated on the basis of time consumed and the social repercussions, by the clinician interviewers as mild in 7, moderate in 8 and severe in 2.

Table 3-1: Characteristics of punders versus nonpunders

	Punders	Nonpunders	
Number (female)	17 (5)	33 (14)	$\chi 2$=0.806; p=0.369
Age (range)	59.4 (46-76)	63.4 (47-80)	t=1.618; p=0.103
Disease duration (range)	14.8 (8-25)	14 (4-27)	t= -0.701; p=0.487
MMSE (range)	28.4 (26-30)	28.1 (21-30)	Z=0.042; p=0.97
UPDRS Part 2 (range)	18.4 (12-26)	17.7 (5-29)	T= -0.192; p=0.83
Daily LEU dose (range) mg	1707 (800-3600)	1130 (800-1533)	Z=3.681; p<0.001
Daily rescue doses (range)	3 (0-20)	0.2 (0-2)	Z=5.042; p<0.001
Number using nocturnal rescue doses (%)	10/17 (58%)	2/33 (6%)	$\chi 2$=17.125; p<0.001
Hrs sleep/night (range)	3.6 (2-6)	5.7 (3-9)	Z=4.101; p<0.001
Hours/day at primary hobby/pastime (range)	6.6 (2-16)	3.9 (1-7)	Z=3.64; p<0.001

Table 3-2: Means (M) and standard deviations (SD) of the Obsessive Compulsive Inventory (OCI) frequency and distress ratings

		Punders (N=16)	Non punders (N=29)	
OCI Total Score	Frequency M (SD)	27.6 (17.4)	24.0 (19.6)	t= -1.281; p=0.207
	Distress M (SD)	14.8 (12.6)	10.0 (11.5)	t= -0.594; p=0.541

The stereotyped behaviours reported were often influenced by the subject's previous occupation (Table 3-3). Increasing clinical severity of the punding behaviour significantly correlated with higher total daily LEU dose (r_s=0.53, p<0.001), younger age (r_s= -0.31, p=0.03), reduced sleep time overnight (r_s= -0.64, p<0.001) and average number of daily rescue doses (r_s=0.72, p<0.001).

Table 3-3: Description of stereotypical behaviours

Age/sex	Occupation	Behaviour	Comments
70M	Retired engineer	Sorts rock collection, collects wood	Apomorphine injection prior to bed would often lead to early waking - after taking a late injection, he would prepare his rocks by the bedside for sorting
70M	Retired electrician	Obsessed with photography, dismantled 5 cameras, collects music	Required quetiapine for organic psychosis/morbid jealousy
65M	Retired businessman	Dismantles radios, pens, video and clock, repetitive paper shuffling, purposeless tidying/straightening up	Day centre for carer relief.
62M	Retired clergyman	Repetitively writing poetry, fills pockets with useless objects, tinkers with computer, dismantled voice amplifier	
61M	Retired biologist	Dismantles cars/lawnmowers, excessive DIY (Do-it-yourself), fascination with birds and fish, removes batteries from electric goods, surreptitious food theft	Medications dispensed daily to restrict supply
60M	Retired machinist	DIY, sorts stamps overnight, dismantled electric drills, paces in backyard overnight	Reduction in evening controlled release medications improved symptoms
59M	Accountant	Tinkers with model railway, dismantled fridge, video recorder and apomorphine pump, excessive DIY	Past alcohol excess, libidousness resolved with enforced DRT reduction (carer) and addition of cyproterone. Amitriptilline improved insomnia.
58M	Retired architect	Preoccupied with computers, "unfocussed" tinkering, dismantled home office	
57M	Retired accountant	Gardening fanatic, senseless paper shuffling, tinkering on computer, dismantled and collected bikes, but unable to reassemble, aimless bike rides, dismantled apomorphine pump	Libidousness resolved with dose reduction
53M	Clerk	Excessive paper shuffling	
50M	Ret. carpenter	Collects tools, excessive DIY, unnecessarily felled tree	DRT reduction and cyproterone for excessive libido
46M	Retired IT engineer	Meaningless and disruptive manipulation of graphics and animation software	Noted increased libido with DRT increases
76F	Housewife	Gardening (impossible to distract when "on"), turns out drawers unnecessarily	
58F	Retired seamstress	Constantly tidying (but makes more mess), repetitively sorts buttons	After punding all night, would occasionally use quetiapine to abort behaviours, regular clomipramine reduced nocturnal punding and improved sleep
57F	Ret. musician	Repetitive drawing, constantly tidying	Past alcohol excess, DRT dose restricted after psychosis
56F	Retired musician	Constantly "untidying", repetitive hair brushing, singing songs with invented lyrics	Quetiapine prescribed for psychotic episode led to some improvement in punding.
54F	Housewife	Collects and sorts nails/rubber bands, repetitive labelling and tidying	Clomipramine reduced nocturnal disturbance from punding. After punding all night, often took a high protein meal to deliberately abort the behaviours

Punders often admitted that time and money spent on their behaviours was excessive and inappropriate. They typically complained of difficulty in finishing their projects and usually admitted to creating chaos while punding. They were often irritable when distracted from their tasks (Table 3-4). Insomnia, previously treated psychosis, and hyperlibidinous behaviour were common co-morbidities.

Table 3-4: Other behavioural associations

	Punders (N=17)	**Nonpunders (N=33)**	
Collections	10	4	χ^2=12.139; p<0.001
Difficulties finishing projects/ineffective	17	3	χ^2=38.636; p<0.001
Creates mess pursuing hobby/pastime	17	5	χ^2=32.782; p<0.001
Hobby pursued overnight	15	3	χ^2=30.504; p<0.001
Difficult to distract from pastime/hobby	13	2	χ^2=26.488; p<0.001
Interested in hobby when "on" only	11	13	χ^2=2.88; p=0.09
Pattern of compulsive medication use	10	0	χ^2=24.265; p<0.001
Increased gambling	1	1	χ^2=0.238; p=0.626
Morbid jealousy	1	0	χ^2=19.81; p=0.159
Increased libido	4	1	χ^2=5.239; p=0.022
Treated for past psychosis	5	4	χ^2=2.273; p=0.132

3.6 Discussion

The stereotyped behaviours described here are very similar to those described with high dose chronic psychostimulant use (Anggard *et al.* 1970; Ellinwood, Jr. *et al.* 1973; Brady *et al.* 1991; Scher, 1966; Schiorring, 1977; Rylander, 1972) and consistent with previous reports of punding in PD (Fernandez and Friedman, 1999; Friedman, 1994; Meseguer Gancedo and Garcia Ruiz, 2002). These behaviours were complex and repetitive and often resulted in isolation from or conflict with other people. Just as in previous reports, the punding behaviours that were observed often arose from prepotent idiosyncratic habits and pastimes and only exceptionally changed over time. The punding was compulsive in the sense that the person could be distracted from the intrusive behaviour but

would become irritable if prevented from resuming. It often caused social avoidance and disintegration of family relationships. The majority of patients had not been treated in the past for psychosis (Table 3-4). In 10 of the cases, punding was associated with a pattern of compulsive medication overuse satisfying the proposed Giovannoni criteria (Giovannoni *et al.* 2000) for DDS (Table 3-4).

Punding is derived from Swedish slang and literally translates into "block-head". Under the influence of psychostimulants, users lose the ability to perform complex sequential acts and become disorganised and perseverative in thought and action. In Rylander's original description of 154 patients who abused Preludin (MPH), this aimless protracted continuation of an activity was found in 40 cases (26%) (Rylander, 1972). Punding has also been reported to occur with cocaine dependence (Brady *et al.* 1991). The repetitive nature of the behaviour has led some authors to describe punding as "being hung-up" (Scher, 1966), "pottering" (Anggard *et al.* 1970) or "knick-knacking " (Ellinwood, Jr. *et al.* 1973). The punder is aware of the inapposite obtuse nature of the behaviour but even self-injury resulting from the stereotypies does not abort it; e.g. one woman filed her nails until they bled (Ellinwood, Jr. *et al.* 1973), a guitarist played without stopping for three days until his fingers gave in (Schiorring, 1977) and another woman picked at her skin until it ulcerated (Scher, 1966). The behaviour is reported as soothing/calming and associated with an intense curiosity. Punders often relate in elaborate detail how they like to examine, sort and dismantle. There is a report of a gang of Scandinavian motorcyclists and amphetamine abusers who drove 200 times around the same block of houses (Schiorring, 1977). In another account, a swindler wrote out hundreds of counterfeit cheques when high (Rylander, 1966). A few devote themselves excessively to some sort of artistic occupation, like drawing, painting, writing or playing an instrument. In another report, individuals were described who liked to bathe in a tub all day long, hold a note or phrase of music, or engage in nonejaculatory intercourse for extended periods (Ellinwood, Jr. *et al.* 1973).

While involved in their chosen activity, punders withdraw into themselves, become tacit and unresponsive and give the impression of absent-mindedness (or "snowed under" (Schiorring, 1981)). Hunger, thirst and the desire to defeacate are often ignored (Rylander, 1972). Invitations to take more drugs or fear of sanctions such as imminent arrest are more likely to abort the abnormal behaviour. Over time, in addition to worsening social isolation, regular psychostimulant users frequently develop

delusions of persecution, morbid jealousy, ideas of reference, visual, auditory and olfactory hallucinations, disorientation, hyperactivity and aggressiveness (Ellinwood, 1969).

Punding has been reported with a L-dopa-induced state in PD (Fernandez and Friedman, 1999; Friedman, 1994; Meseguer Gancedo and Garcia Ruiz, 2002) (Table 3-5). Like the punding seen with the psychostimulant drugs, the phenomenology of punding with DRT in PD is also shaped by previous occupation and hobbies; an accountant engaged in the shuffling of papers (Friedman, 1994) and a retired carpenter in senseless home repairs (Table 3-3); a woman incessantly examined jewellery (Fernandez and Friedman, 1999), a seamstress became fascinated with buttons; a musician sang repetitively; and the IT consultant became increasingly fascinated by computer animation (Table 3-3).

None of the punders fulfilled the core criteria for hypomania (American Psychiatric Association, 1994) even if the link between this behavioural disorder and DRT is ignored. Hypomania and mania may superficially resemble punding and result in insomnia and increased goal-directed activity. In contrast to punding, the expansive quality of the mood in hypomania is characterised by indiscriminate enthusiasm for interpersonal interactions and the increase in goal-directed activity often involves excessive planning of, and excessive participation in, multiple activities (American Psychiatric Association, 1994). The manic patient's flight of ideas precludes sustained motor activity of one sort for any length of time.

The stereotyped behaviours seen in punding are likely homologous to the complex stereotyped behaviours seen in animals with amphetamine-stereotypies (Robbins *et al.* 1990); cage stereotypies (Garner and Mason, 2002); and isolation-induced (Lewis *et al.* 1990; Sahakian *et al.* 1975) stereotypies. Punding, like these other forms of stereotypy represents the culmination of a continuous process of psychomotor stimulation (mediated by ventral striatal structures) and behavioural competition (mediated by dorsal striatal structures) (Robbins *et al.* 1990; Toates, 1998; Whishaw *et al.* 1992). Lower doses of psychostimulant drugs and dopaminergic agents potentiate approach responses to reward, a process mediated by nucleus accumbens-related dopamine (Ikemoto and Panksepp, 1999). Indeed, several of the punding group showed evidence of enhanced appetitive behaviours: Four patients in the punding group became hyperlibidinous, two of whom required anti-testosterone therapy (cyproterone). One patient also reported excessive gambling after treatment for PD (Table 3-4) and another started surreptitiously stealing food after DRT dose escalation (Table

3-3). Lastly, the frequent concurrence of punding with compulsive DRT use suggests that punding might represent an important step in the eventual progression to a form of automatic behaviour in which voluntary control over drug use is lost (Lawrence *et al.* 2003).

With increasing doses, prepotent stimulus-response habits mediated by dopamine in dorsal striatal structures are potentiated and come to gain control over behaviour (Berridge and Aldridge, 2000a; Robbins *et al.* 1990; Whishaw *et al.* 1992). Stereotypies develop from prepotent habits, which are idiosyncratic, depending on individual life histories and, in humans include prepotent habits such as work-related behaviours, hobbies and past-times. Here, men tended to dismantle technical equipment such as radio sets, clocks, watches and car engines; the parts of which may be analysed, arranged, sorted, filled and catalogued but rarely put back together (Ellinwood, Jr. *et al.* 1973). Women, by contrast, repetitively sort through their handbags, tidy, continuously brush their hair (Randrup and Munkvad, 1972), or polish their nails (Rylander, 1972). Office workers and clerks stereotypically shuffle papers, a seamstress will stereotypically collect and arrange buttons, and so on (Table 3-3). Individuals become unable to control automatic response selection mechanisms; i.e. stereotypies are purposeless and there is a dissociation between knowledge and behaviour (Garner and Mason, 2002; Toates, 1998). Patients know they are disruptive and unproductive, but continue to perform them. This inability to modulate automatic routines is likely due to impaired cognitive control, resulting from impaired frontal lobe function (Jentsch and Taylor, 1999). Large frontal lesions are associated with highly stereotyped behaviours, including forced collectionism (hoarding) (Volle *et al.* 2002).

Punding has previously only been described in PD patients taking L-dopa. L-Dopa acts via D1 and D2 receptor subtypes which are both involved in the genesis of stereotypies in animals (Berridge and Aldridge, 2000b; Chartoff *et al.* 2001; Chen *et al.* 2001; Nakazato and Akiyama, 2002). In the present study, there was no identifiable pattern to the dopamine receptor stimulation profile of the medications used by the punders compared to the non-punders. Long-acting and short-acting dopaminergic drugs were used by both groups; the differences in types of medication used by the groups likely reflect clinician's strategies to reduce concomitant dyskinesias. However, the observed use of intermittent rescue medications by punders suggests that punding may represent a form of (psychomotor) sensitisation phenomenon similar to dyskinesias (Graybiel *et al.* 2000).

Patients rarely volunteer descriptions of their punding behaviour to the treating clinician although occasionally family members may highlight it as a problem. Dyskinesias (often disabling) were

present in all but one of the punders and most complain of distressing motor fluctuations although this was not specifically examined. Disability due to social isolation in these individuals was also not examined but sleep disturbance due to DRT induced behavioural activation was common (Table 3-3). Degrees of insomnia were reported in all of the punders and some subjects reported punding all night (Table 3-1). The ensuing insomnia often contributes to a spiraling perception of worsening Parkinsonism and subsequently higher DRT requirements.

It has been argued that the ritualistic behaviours seen in obsessive-compulsive disorder (OCD) may be homologous to stereotyped behaviours seen in animals in a hyperdopaminergic state (Graybiel and Rauch, 2000) and that these result from hyperdopaminergia in dorsal basal ganglia structures (Graybiel and Rauch, 2000). There are reports of OCD in basal ganglia disorders, including both Parkinson's (Muller *et al.* 1997) and Huntington's disease (De Marchi *et al.* 1998), encephalitis lethargica (Cheyette and Cummings, 1995) and pallidal lesions (Laplane *et al.* 1989), and there is evidence for altered dorsal basal ganglia activity in OCD (Graybiel and Rauch, 2000). Punding induced by large quantities of DRT in PD provides a clinical syndrome directly relevant for testing the link between OCD and dorsal striatal hyperdopaminergia in humans. The current study suggests that there are clear similarities, but also important differences between punding and OCD. Punding, like certain ritualistic behaviours seen in OCD is purposeless, representing a dissociation between knowledge and performance. Like punding, the phenomenology of OCD is influenced both by gender and life history factors (Lensi *et al.* 1996; Roy, 1979; Dowson, 1977) and this is a further reflection of the potentiation of personal habitual routines and species typical sequential behaviours, as in the case of amphetamine-induced and cage stereotypies in animals (Berridge and Aldridge, 2000a; Garner and Mason, 2002). Also, performance of complex stereotypies produces feelings of calm and relief, somewhat similar to OCD. By contrast with OCD, however, punding is not associated with obsessionality, including religious, aggressive, sexual, checking, symmetry, ordering, counting, contamination and cleaning/washing compulsions (Rauch *et al.* 1998). Therefore, while certain features of stereotyped routine behaviours might be common to both punding in PD and OCD, the compulsive phenomena of OCD seem quite distinct from hyperdopaminergic stereotypies, including punding. Notably, Rauch et al., (1998) in a PET imaging study found that only certain OCD symptoms were related to striatal regional cerebral blood flow, including checking behaviours, ordering/arranging symptoms, and repeating rituals. In the current study, the elements of the OCI that were (mildly) enhanced in punders relative to non-punders were feelings of doubt and hoarding

behaviours. Therefore, OCD symptoms related to basal ganglia dysfunction, and the OC-like symptoms in punders (especially hoarding) may represent stereotyped behaviours resulting from the potentiation of psychomotor processes and habitual, routine behaviours. Hoarding contains elements of appetitive and routine like behaviours and is known to be sensitive to dopamine lesions in other mammals (Kelley and Stinus, 1985). Feelings of doubt / checking might be related to impaired basal-ganglia mediated action-monitoring functions (Lawrence, 2000). However, there are many clear differences between punding and other OCD-related phenomena including a lack of response to selective serotonin reuptake inhibitors (Illustrative case).

In conclusion, punding in PD is much more common than has been previously described, that it can occur with dopamine agonist monotherapy as well as L-dopa and that the resultant social disability is often overlooked. Requirements for large doses of DRT, frequent rescue doses and use of rescue medications overnight might warrant specific enquiry into a patient's pastimes. Patients complaining of sleep disturbance should also be specifically asked how they cope with the periods of sleep deprivation. Punding may also be suspected if the addition of further DRT at night exacerbates a patient's insomnia rather than benefits it. Management of these stereotypies involves careful and repeated explanation of the relationship with high daily DRT dosage, limitation of rescue medications and enforced medication rationing (especially during the night) and management of the sleep disturbance.

Table 3-5: Other reported cases of punding in PD

Author	Age PD onset	Age punding onset	Daily medication dose: L/C mg	Punding behaviour	Comorbidities	H&Y	Comments	Social disintegration
(Miyasaki *et al.* 2007)		Mean disease duration 8.7 years	Mean 850mg L-dopa, pramipexole in 3 and ropinirole in 1	2 computer gaming, 1 tidying, 1 building and dismantling objects	Dementia 2		Estimated 1.4% of outpatients in questionnaire based survey	
(Kummer *et al.* 2006)	58M	61	L-dopa/carbidopa 250/25 up 30/day, pramipexole 4 mg, amantadine 300 mg	Repetitive journal writing	None	2		
(Shapiro *et al.* 2006)							Two cases of early onset PD who experienced paraphilia and hypersexuality when selegiline was initiated, and later developing obsessive–compulsive and punding behaviour with the addition of dopamine agonists.	
(Fasano *et al.* 2006)	44M	47	Pramipexole 3mg, L-dopa/DCI 400	Computer, excel spreadsheets	None	2		Y
(Nirenberg and Waters, 2005)	47F		pramipexole	Purposeless rearrangement of items	Binge eating			
(Kurlan, 2004)	49F	53	1000mg/day	Continual cleaning and reorganisation overnight when "on"	"off" dysphoria insomnia, motor fluctuations		No improvement with therapy reductions	Y
(Kurlan, 2004)	55F	70	1,800mg/day	Continual cleaning, rearranging mainly at night when "on"	Insomnia, mild cognitive impairment, hallucinations, motor fluctuations		Unresponsive to SSRIs, antipsychotics, and sleeping tables	Y
(Kurlan, 2004)	57F	73	800mg/day, tolcapone	Continual cleaning reordering when "on"	Dementia, hallucinations		No improvement with antipsychotic medication	Y
(Kurlan, 2004)	62M	72	1200mg	Rearranging letters, financial papers when "on"	Euphoric, insomnia		No response to dose reduction, SSRI, responded to clozapine	Y
(Kumar, 2005)	56F	69	1500mg, bromocriptine 5mg,	Rearranging dresses	Peak dose dyskinesias			

			selegiline 10mg					
(Miwa and Kondo, 2005)	26M	32	300mg, cabergoline 5mg, pergolide 1.5mg	Repetitive writing	Hallucinations			
(Miwa *et al.* 2004)	46M	54	500mg, cabergoline 5mg, droxidopa	Checking electrical cords	Psychosis		Aggressive if interrupted, Punding onset with initiation of quetiapine and ceased on reduction from 200 to100mg	Y
(Miwa *et al.* 2004)	65F	67	450mg	Repeated opening closing handbag	Psychosis		Symptoms appeared after initiating quetiapine and improved on dose reduction 100 to 50mg	
(Serrano-Duenas, 2002)	54F	64	2250 mg, bromocriptine 37.5mg	Repetitive hair brushing	Pathological gambling, compulsive medication use	2		Y
(Serrano-Duenas, 2002)	40M	50	2500mg, bromocriptine 42.5mg	Repetitive washing, eating 10 times/day and changing clothes	Pathological gambling, compulsive medication use	2		Y
(Meseguer Gancedo and Garcia Ruiz, 2002)	58M	72	N/A	Collecting and manipulating paper figurines and paper clip on clothes	Difficult to treat motor fluctuations			?
(Fernandez and Friedman, 1999)	60F	70	1350/150mg, pergolide 3mg, oxybutynin 1.5mg	Persistent reading, purposeless gardening, examining jewellery, collecting and stacking magazines	Normal mental status	2.5	Improved after reducing levodopa to 1000/100mg (no change after stopping oxybutynin or reducing pergolide)	Y
(Fernandez and Friedman, 1999)	53F	67	1700/250mg, selegiline 10mg, pergolide 0.45mg	Picking threads from rugs, persistent gardening.	Normal mental status, dyskinesias present	3.0	Resolved after cessation of selegiline and pergolide	Y
(Fernandez and Friedman, 1999)	53F	53	500/125mg, 1.5mg pramipexole	Presented age 72 with 19 year history of repeatedly picking up objects, hoarding and dismantling things	Associated psychosis for 9 months	3.0	Psychosis resolved & punding improved after reducing levodopa to 400/100mg	Y
(Friedman, 1994)	59M	65	900/225mg, selegiline 10mg, trazadone 50mg	Singing, senseless adding of number tables, meaningless joking, paper shuffling,	Normal mental status	2.5	Improved after reducing levodopa to 500/125	Y

Chapter 4

FACTORS INFLUENCING SUSCEPTIBILITY TO DOPAMINE DYSREGULATION SYNDROME

Summary

In the course of treatment, a small group of PD patients develop a harmful pattern of compulsive dopaminergic drug use – DDS. Individual factors may influence susceptibility. In this study predisposing factors to DDS were sought in a population of PD outpatients. Clinical features, impulsive sensation seeking (ISS) personality traits, past experimental drug use, alcohol consumption, smoking behaviours and depressive symptoms in 25 DDS patients were compared to an outpatient sample of 100 PD patients who were not compulsively overusing dopaminergic medication. DDS patients had a significantly younger age of disease onset, higher dopaminergic drug intake, greater past experimental drug use, more depressive symptoms, scored higher on ISS ratings and tended to have higher alcohol intake. Using logistic regression analysis, novelty seeking personality traits, depressive symptoms, alcohol intake and age of PD onset were significant predictors of DDS. These factors may help to identify early patients who are more vulnerable to developing a pattern of compulsive dopaminergic drug use and help minimise its consequences.

4.1 Introduction

PD is primarily regarded as a disorder of movement associated with progressive degeneration of the dopaminergic nigrostriatal pathway. The degree of putaminal dopamine loss loosely correlates with the severity of bradykinesia. Dopaminergic drug therapy relieves the motor symptoms of PD, improves quality of life and modestly improves survival. However, if used injudiciously and excessively, it may lead to damaging behavioural complications.

In susceptible individuals, sensitisation of brain dopamine systems mediating reward by dopaminergic drugs is proposed to underlie the development of DDS (Lawrence *et al.* 2003). These patients demand medication increases early in the course of treatment and complain of early tolerance to any observed beneficial effects. They feel dysphoric and undertreated much of the time despite the external appearance of adequate motor symptom control and the appearance of increasingly severe peak-dose dyskinesias. Compulsive dopaminergic drug use is associated with a number of drug-responsive behavioural effects (Evans *et al.* 2004) including punding, a form of complex behavioural

stereotypy (Evans *et al.* 2004). Pathological gambling, hypersexuality and mood changes also frequently accompany DDS (Giovannoni *et al.* 2000). Most fulfill core DSM-IV diagnostic criteria for substance dependence due to the negative effects that their compulsive pattern of dopaminergic drug use has on their social, psychological and physical well-being (Beam *et al.* 2004).

Many longitudinal and cross-sectional studies using diverse samples and measures demonstrate a clear relationship between ISS personality traits and addiction proneness (Cloninger *et al.* 1988; Johnson *et al.* 2003; Zuckerman, 1994). Humans scoring highly on ISS personality traits demonstrate a wide range of responses to novel stimuli and cues predictive of reward; including positive affect (elation and expectation), increased energy, and enhanced psychomotor activity. ISS traits are considered to be mediated by the dopaminergic projections from the midbrain to accumbens-related circuitry, a component of the brain reward system (Pickering and Gray, 2001). Stress (Herman *et al.* 1984) and previous exposure to other drugs, such as alcohol, may enhance the effects of dopaminergic drugs on brain reward systems (so called "cross-sensitisation") (Saal *et al.* 2003) and so, in addition to ISS-traits, depression and alcohol use were predicted to be associated with DDS.

Little attention has been given to DDS despite its devastating social consequences and, apart from younger age PD onset (Lawrence *et al.* 2003), and possibly dopaminergic agonist use as opposed to L-dopa (Pezzella *et al.* 2005), no predisposing factors have been suggested. Clinical features and ISS traits in a group of DDS patients were compared to a representative sample of PD patients who did not compulsively overuse dopaminergic medication. Smoking behaviours, alcohol consumption and illicit drug use were discretely enquired about in both groups.

4.2 Patients and methods

Consecutive outpatients attending a specialist PD clinic were carefully assessed for the presence of DDS and were included as part of a larger questionnaire-based study of personality in PD. Proposed criteria (Giovannoni *et al.* 2000) were used to identify these patients following structured interviews. All patients were screened using the minimental state examination (MMSE) and those scoring less than 26 were excluded because of the requirement to complete the personality and mood rating scales. In the recruitment period, 167 PD patients were identified; 29 were ineligible due to their MMSE, and 32 either didn't consent or didn't return the questionnaires. Eight patients were identified in this group as having DDS, and 6 of these completed the questionnaires. The Unified Parkinson's Disease

Rating Scale (UPDRS) part 2 was rated in the "on" state by the treating physician and demographic data including age, gender, and age of PD symptom onset was collected. Calculation of a daily L-dopa equivalent unit (LEU) dose for each patient was based on theoretical equivalence to L-dopa (Evans *et al.* 2004).

An additional 32 previously identified patients fulfilling clinical criteria for DDS (Giovannoni *et al.* 2000) were independently approached to participate in the study. Two were uncontactable, 3 declined and 8 more were too cognitively impaired (MMSE≤24). Of the 19 further DDS patients who agreed to participate, 8 had been referred by other physicians for management and 11 had been diagnosed in the PD clinics within University College London Hospitals Foundation Trust (UCLH), a number of whom were part of the original series (Giovannoni *et al.* 2000). Twenty-three of a total of 25 DDS patients had MMSE scores ≥ 26. The other 2 (MMSE 24 & 25) were considered by the treating physician able to complete the required questionnaires. Clinical details were obtained during routine interview and by review of medical records. Dyskinesia disability was rated using item 33 of the UPDRS in the "on" state and patients provided a list of all current medications and their dosages. Treated psychosis was defined as the presence of hallucinations, delusions, paranoid beliefs and agitation that required significant reduction (i.e.>20%) in dopaminergic drug therapy or the introduction of antipsychotic medications. Caregivers were independently interviewed about the presence of aggressive behaviour (assault or violent outbursts). Each DDS case was also individually matched by age (±5 years) and gender to a non-Parkinsonian control participant. Fifteen suitable partners or friends of participating patients attending the outpatient department and without PD or dementia agreed to participate and the remaining controls (N=10) were recruited at random from the Medical Research Council Cognition and Brain Sciences Unit healthy volunteer panel.

4.2.1 **Questionnaires**

Participants who provided written informed consent to protocols approved by the UCLH Trust local ethics committee were given a series of questionnaires to complete in their own time and return in a reply-paid envelope. These included measures of the ISS trait cluster; a short version of the sensation seeking scale (Zuckerman, 1994; Merrems and Brannigan, 1998) (SSS), novelty seeking (Cloninger *et al.* 1993) (NS) from the Temperament and Character Inventory (TCI), and the Behavioural Inhibition System/Behavioural Approach System (BIS/BAS) scales (Carver and White, 1994). Sensation seeking is linked to a variety of illegal and risky behaviours such as illicit drug use

(Palmgreen *et al.* 2001), sexual risk-taking, reckless driving, smoking, and alcohol use (Zuckerman, 1994). The TCI is a 125-item, self-administered, true-false instrument assessing 4 stable, moderately hereditable dimensions of temperament (Cloninger *et al.* 1993) and 3 of character. The NS dimension explores the tendency towards exhilaration or excitement in response to novelty and cues of potential reward, causing exploration and pursuit. Harm avoidance is the tendency toward an inhibitory response to signals of aversive stimuli and correlates with anxiety; reward dependence is seen as a bias in the maintenance or continuation of ongoing behaviour; and persistence reflects the perseverance of behaviour despite frustration and fatigue. Characters refer to self-concepts and individual differences in goals and values that are moderately influenced by socio-cultural learning and include self-directedness, cooperativeness and self-transcendence. The BAS has 13-items designed to reflect variations in a behavioural activation system that underlies appetitive motivation and includes 3 subscales; reward responsiveness, drive and fun seeking (Carver and White, 1994). These measures of ISS correlate with one another (Zuckerman and Cloniger, 1996; Carver and White, 1994). The Geriatric Depression Scale (Yesavage *et al.* 1982) (GDS) consists of 30 "yes" or "no" questions.

Data was collected on present and past cigarette smoking. Current alcohol intake was assessed with a food frequency questionnaire. The reproducibility and validity of assessing alcohol intake has been established with a similar questionnaire (Giovannucci *et al.* 1991). For each beverage, a commonly used portion size was specified and the participants were asked how often, on average, over the past month they had consumed that amount. The alcoholic beverages assessed included pints of low alcohol beer, normal strength beer, 150ml glass of wine and a standard measure of liquor. There were seven possible response categories ranging from "never or rarely" to "six or more times per day". The alcohol content (in grams) in each serving was estimated as follows: low alcohol beer 6, beer 18, wine 12, and liquor 14. The weekly intake in alcohol units (where a unit of alcohol was 8 grams) was obtained by multiplying the estimated weekly consumption frequency of each alcohol beverage by its estimated alcohol content. Patients were also given the option to indicate whether they had used experimental drugs in the past.

4.2.2 Data analysis

Data were analyzed with SPSS Version 11, SPSS Inc., Chicago, Ill. Medians/means were compared using Mann Whitney U test or Student's *t* test where appropriate. Variables found to be predictive of

the diagnosis of DDS were entered into a forward stepwise logistic regression model to identify those factors that were independently associated with DDS. Variables controlled for in the multivariable model were selected by considering their univariate associations with the diagnosis of DDS. The following possible explanatory variables were used: age, age of PD onset, disease duration, sex, alcohol intake, GDS, SSS, BAS subscale scores and NS. The multivariable models were examined for how well they fit the data using Hosmer-Lemeshow goodness-of-fit tests.

4.3 Results

During the clinical interview, all DDS patients reported severe withdrawal dysphoria relieved by dopaminergic drug therapy. Clinical features of the DDS patients are given in Table 4-1.

Table 4-1: Clinical features of DDS patients

	DDS group (N = 25)
Severe "off"-period dysphoria	**25**
Disabling dyskinesias (UPDRS item 33 ≥ 2)	**23**
Punding	**22**
Aggression	**14**
Psychosis	**15**
Social breakdown	**16**
Behavioural compulsions (sex, shopping, compulsive eating, gambling, stealing)	**16**

UPDRS – Unified Parkinson's Disease Rating Scale

Table 4-2: Characteristics of patients fulfilling criteria for DDS versus PD patients recruited from a tertiary referral outpatient clinic. Median values are given followed by range in parentheses. Chi-squared test was performed if the predictive variable was categorical.

	DDS (N=25)	Healthy controls (N=25)	PD outpatient clinic controls (N=100[a])
Age PD onset (years)	43 (17–57)††		**56 (21–76)**
Disease duration	13 (4–25)†		**9.5 (2–40)**
Sex	19 male	19 male	**59 male**
UPDRS part 2	17 (6–28)		**14 (3–37)**
MMSE	29 (23–30)		**29 (26–30)**
LEU dose	2000 (700–3200)††		**700 (0–1600)**
Dopamine agonist therapy	20/25		**61/99**
Never smokers	12	6	**52**
Past experimental drug use	8/22*††	2/22	**5/97**
GDS	19 (4–30)**††	5 (0–28)	**10 (0–23)[b]**
Novelty Seeking	13 (5–19)*††	9 (2–15)	**8 (1–16)**
Harm avoidance	11 (2–19)	8 (1–20)	**12 (2–20)**
Reward dependence	7 (1–13)†	9 (2–14)	**9 (3–14)**
Persistence	3 (0–5)	3 (0–5)	**3 (0–5)**
Self-directedness	13 (3–22)*††	18 (3–25)	**17 (1–25)**
Cooperativeness	17 (6–23)††	19 (9–24)	**21 (2–25)**
Self-transcendence	4 (0–12)	4 (0–11)	**5 (0–14)**
BAS drive	11 (5–16)†	11 (5–16)	**10 (4–16)**
BAS fun seeking	12 (8–16)†	12 (7–15)	**10 (4–16)**
BAS reward responsiveness	17 (13–20)†	17 (7–20)	**15 (9–20)**
SSS	4 (1–12)	4 (0–10)	**3 (0–8)**
Alcohol intake	**9.5 (0–79.8)**	**16.8 (0–94.5)**	**3.0 (0–80.5)**

*$p<0.05$, **$p<0.01$ compared to healthy controls, † $p<0.05$, †† $p<0.01$ compared to PD controls
UPDRS–Unified Parkinson's Disease Rating Scale, MMSE–Minimental state examination, LEU–L-dopa equivalent unit, GDS–Geriatric Depression Scale, BAS–Behavioural activation scale, SSS–Sensation seeking scale. [a]missing data <3%, [b]N=94

Table 4-2 shows the characteristics of patients fulfilling criteria for DDS compared to non-demented PD patients recruited from a tertiary referral clinic without this complication. Compared to the control PD patients, DDS patients had a significantly younger age of disease onset, higher LEU use, greater past experimental drug use, more depressive symptoms, scored higher on ISS ratings, lower on reward dependence traits and tended to have higher alcohol intake (Table 4-2). DDS patients also had higher novelty seeking scores and depressive symptoms than a group of matched healthy control patients. In the patients with PD, logistic regression using these variables and clinical variables identified factors which were independent predictors of DDS (Table 4-3) including; age of PD symptom onset, NS, GDS and current alcohol intake. The final model including all of these variables accounted for a moderately large degree of the variance (model R^2=.653). Inclusion of past experimental drug use or dopamine agonist therapy did not alter the structure of the model. To examine whether these variables may be influenced by the disease process or may relate to dyskinesias (a psychomotor drug sensitisation phenomenon) they were correlated with disease duration and dyskinesia severity. GDS correlated significantly with disease duration (r_s=0.249, p=0.006, df=117), and dyskinesia severity (r_s=0.421, p<0.001, df=101). Disease duration and dyskinesia severity did not correlate with alcohol intake or novelty seeking.

Table 4-3: Logistic regression analysis examining the influence of personality variables, GDS, age of PD symptom onset, sex, disease duration and alcohol intake on the binary variable PD patients with DDS versus PD outpatient controls using a forward selection procedure.

Variable	Model R^2	p Value on entry to model
Novelty seeking	0.324	<0.001
GDS	0.518	<0.001
Alcohol intake	0.597	0.006
Age PD onset	0.653	0.016

GDS–Geriatric Depression Scale

Hosmer-Lemeshow goodness-of-fit statistic=10.5; 8 df; p=0.231

4.4 Discussion

DDS frequently leads to a constellation of behavioural and psychiatric problems which stem directly from excessive and inappropriate dopaminergic drug use and is frequently associated with severe "off"-period dysphoria, disabling dyskinesias, and punding. There is also a high incidence of hypersexuality, compulsive eating and other appetitive behavioural compulsions. As a consequence of motivational "spill-over" from the effects of dopaminergic drugs on brain reward systems ("cross-sensitisation"), enhanced "Wanting" of natural rewards, such as sex (Fiorino and Phillips, 1999) and appetising foods (Harmer and Phillips, 1998) occurs in some individuals. DDS patients are also at risk of organic psychosis; characterised by paranoid delusions, auditory hallucinations, and hypomania. Reductions in anti-Parkinson medications usually ameliorate disabling behavioural compulsions (Lawrence *et al.* 2003) but relapses are frequent and may recur with even lower drug doses.

In an effort to facilitate early identification of DDS and for planning prompt therapeutic interventions personality traits in DDS patients were compared with controls. PD patients with DDS were found to differ from control PD patients and age-matched healthy controls in personality dimensions linked traits with substance dependence (i.e. high ISS traits, and low harm avoidance, reward dependence, selfdirectedness and cooperativeness (Cloninger, 1987b; Hosak *et al.* 2004; Sher *et al.* 2000)). Novelty seeking was most strongly associated with DDS compared to both healthy controls and control PD patients. ISS traits have a basis in animal models of compulsive drug seeking and, in humans, mediate biological responses to novelty (Bardo *et al.* 1996) and individual variability of drug-induced dopamine neurotransmission in the ventral striatum (Leyton *et al.* 2002). In individuals with substance dependence, ISS traits also influence craving (Zilberman *et al.* 2003), vulnerability to relapse (Meszaros *et al.* 1999) and social influences on drug taking (Audrain-McGovern *et al.* 2003).

In adolescence, higher ISS traits influence willingness to use alcohol and experiment with various drugs of abuse (Zuckerman, 1994) and portend the later development of alcohol abuse (Cloninger *et al.* 1988) and substance dependence (Sher *et al.* 2000). Significantly more DDS patients had a past history of experimental-drug use. In adults, higher ISS traits predict preference for alcoholic beverages (Logue and Smith, 1986) and current alcohol beverage drinking frequency (Earlywine *et al.* 1992). In general, despite the tendency of PD patients to have lower alcohol intake than healthy

controls, alcohol intake independently predicted DDS compared to PD controls. In animal studies, high ethanol drinkers show heightened striatal dopaminergic responsiveness (Nestby *et al.* 1999). The current data suggest that compulsive dopaminergic drug use and alcohol intake may be related phenomena independent of ISS score.

Age critically mediates vulnerability to addiction. Earlier age of exposure to addictive drugs influences subsequent development and severity of substance dependence (Chambers *et al.* 2003). Addiction proneness as well as ISS traits subsequently decline after adolescence. Although PD generally appears in middle age and patients typically display personality characteristics at the lower pole of the ISS dimension (i.e. stoicism, industriousness, and inflexibility), younger age of exposure to anti-Parkinson drugs independently predicted DDS.

Depression commonly complicates PD, and has a major impact on a patient's quality of life (Burn, 2002a). The comorbidity of depression with drug abuse is well established and has important therapeutic and prognostic implications (Volkow, 2004). In the current study depressive symptoms strongly independently predicted DDS. Additionally, all DDS patients reported severe "off"-period dysphoria characterised by apathy, depression and anxiety which may resemble the negative affective state of withdrawal from psychostimulants in dependent individuals. Depression in patients with DDS may be reactive, however it is possible that compulsive drug use arises from self-medication for an existing depressive state or self-medication of a drug-generated aversive state (Koob *et al.* 2004). Further, repeated experience with end-of-dose wearing "off" and co-existence of a chronic depressive state may enhance the incentive value of the drug to such an extent that dopaminergic drug seeking becomes the over-riding behaviour. The link that was found between depression scores and disease duration and dyskinesias might indicate that, in the course of the disease, neurobiological changes occur that may increase the risk of depression. These neural mechanisms may overlap with those that lead to DDS as well as the development of dyskinesias with long-term exposure to L-dopa (Guigoni *et al.* 2005).

Nearly all patients who receive a diagnosis of PD are treated with dopaminergic drugs, yet only a small group develop DDS. Other potential risk factors such as impaired cognitive control, cognitive impulsivity, and environmental, social, genetic and pharmacological factors were not specifically examined. In addition, the study was cross-sectional in design. However, the regression model using the factors novelty seeking, alcohol use, depression and age of PD onset accounted for a moderately

large degree of variance. Prospectively identifying individuals who may be vulnerable to DDS will hopefully reduce the devastating physical, psychiatric and social consequences which ensue. *De novo* patients could be screened for novelty seeking traits, use of alcohol, and illicit drugs in order to pick up potentially vulnerable individuals for watchful management in the course of the disease. Vulnerable individuals may be counselled early in the course of management about the potential small risk of compulsive use of dopaminergic drug therapy and particular efforts made to limit drug increases. Disabling dyskinesias and distressing "off" period dysphoria in these individuals may respond to continuous dopaminergic stimulation via subcutaneous apomorphine infusion (Katzenschlager *et al.* 2005). The careful administration of low dose clozapine or quetiapine for short periods may also help individual cases. In others, functional neurosurgery may allow reductions of dopaminergic therapy (Witjas *et al.* 2005).

Chapter 5

COMPULSIVE USE OF DOPAMINERGIC DRUG THERAPY IN PARKINSON'S DISEASE: REWARD AND ANTI-REWARD

Summary

Background: A few Parkinson patients develop a disabling pattern of compulsive dopaminergic drug use ("dopamine dysregulation syndrome" - DDS). DDS patients commonly identify aversive dysphoric "OFF" mood-states as a primary motivation to compulsively use their drugs. We compared motoric, affective, non-motor symptoms and incentive arousal after overnight medication withdrawal and after L-dopa in DDS and control PD patients.

Methods: Twenty DDS patients were matched to 20 control PD patients for age, gender and disease duration and underwent a standard L-dopa challenge. Somatic symptomatology, positive and negative affective states, drug effects, reward responsivity, motor disability and dyskinesias were tested in the "OFF"-state after overnight withdrawal of medications, and then after a challenge with a standard dose of L-dopa, after a full "ON"-state was achieved.

Results: In the "OFF"-state, DDS patients reported lower positive affect, higher negative affect and more motor and non-motor disability. In the "ON"-state, DDS patients had higher expressions of drug "wanting", reward responsivity, and dyskinesias. Positive and negative affect, non-motor symptomatology and motor disability were comparable.

Conclusion: These findings suggest that the neurobiological mechanisms associated with affective, motivational and motoric disturbances in PD are involved in the transition to compulsive drug use in individuals who inappropriately overuse their dopaminergic medication.

5.2 Introduction

DDS individuals have higher rates of other Axis I psychopathology including depressive symptoms, psychosis, and a premorbid history of alcohol dependence (Evans *et al.* 2005). The association of this syndrome with a range of impulse control disorders (ICDs), e.g. pathological gambling, suggests a global sensitisation to dopaminergically-mediated behaviours and there are also overlaps with punding (Evans *et al.* 2004; Evans *et al.* 2006b). Personality and

physiological traits that differentially affect various stages of substance dependence in general are also relevant to mediating the development of DDS, especially novelty-seeking (Evans *et al.* 2005).

Drug addiction is a chronically relapsing disorder that can be characterised by (a) compulsion to seek and take the drug, (b) loss of control in limiting intake, and (c) emergence of a negative emotional state during withdrawal (Koob and Le, 2008). DDS patients commonly report self-medicating to avoid the negative affect of a withdrawal state as well as to improve motor function. Their "OFF"-state dysphoria or withdrawal symptoms appear to be characterised by a range of aversive affective symptoms; depression, anxiety, pessimism, tiredness, restlessness, irritability, fear, and withdrawal. Somatic withdrawal symptoms including shaking, palpitations, tachypnoea, feelings of impending death, nausea, flushing and severe precordial oppression are also reported (Lawrence *et al.* 2003). Distressing chronic pain alone has been reported to powerfully motivate the compulsive self-administration of dopaminergic drugs (Stein and Read, 1997). Seemingly, only a small number of patients justify their overuse of dopaminergic medication on a desire to experience positive euphoriant effects, "highs" or "buzzes" (Bearn *et al.* 2004). Based on clinical observations, several authors have proposed a common mechanism for the behavioural features of compulsive dopamine replacement therapy use and the distress related to non-motor symptoms (Soyka and Huppert, 1992).

The withdrawal syndrome forms part of working criteria for DDS (Giovannoni *et al.* 2000) and it was initially linked to negative reinforcement views of addiction ("Hedonistic Homeostatic Dysregulation"). This view suggests that addicts are motivated to take drugs not for the initial pleasure that results, but by the desire to avoid unpleasant affective symptoms (Koob and Le Moal, 1997). Conversely, the role of the central nervous system in mediating incentive motivation for dopaminergic drugs has more recently been highlighted.

The aim here was to characterise the severity and nature of non-motor symptoms that define the withdrawal syndrome in DDS compared to a group of PD patients with medication-response fluctuations without compulsive use. One prediction was that DDS patients would have greater affective, incentive motivational (reward responsivity) and motor responses to L-dopa and that depressive symptoms and personality measures might mediate these responses. Further, it was predicted that DDS patients would show heightened expressions of drug "wanting" after an acute challenge with L-dopa.

5.3 Methods

The study was carried out in accordance with the declaration of Helsinki and involved patients fulfilling Queen Square Brain Bank criteria for PD (Hughes *et al.* 1992) receiving regular dopaminergic drug therapy, with no significant intellectual impairment as defined by a Mini-Mental State Examination (MMSE) score ≤24, and adequate language comprehension who consented to protocols approved by the Joint Ethics Committee of the National Hospital for Neurology and Neurosurgery and Institute of Neurology. Forty non-demented patients with PD experiencing motor fluctuations on treatment (32 male, 8 female) were studied. Half had harmful compulsive dopaminergic drug use and fulfilled working criteria for DDS (Lawrence *et al.* 2003) and half did not use drugs compulsively. The DDS group was matched for sex, disease duration, stage and loosely for age with control PD patients. The presence and severity of complex repetitive motor stereotypies (punding) was assessed according to previous guidelines (Evans *et al.* 2004) and a daily L-dopa equivalent unit (LEU) dose was calculated (Evans *et al.* 2004). Disease stage was rated with the Hoehn and Yahr score (H&Y) and depressive symptoms were rated with the Geriatric Depression Scale (GDS) (Yesavage *et al.* 1982) in an "ON"-state. Novelty seeking personality traits were assessed using the Temperament and Character Inventory (TCI) (Cloninger *et al.* 1993). Characteristics of the patients are given in Table 5-1.

Table 5-1: Patient characteristics

	Control PD Mean (SD)	DDS Mean (SD)	*t-test*
Age	59.5 (7.9)	55.4 (7.6)	t=5.90, p<0.001
Disease duration	13.6 (8.0)	14.0 (5.7)	t=-0.25, p=0.806
GDS	9.0 (4.9)	17.6 (6.4)	t=-4.52, p<0.001
NS	8.4 (3.9)	12.9 (3.5)	t=-5.16, p<0.001
	Median (Range)	**Median (Range)**	***Mann-Whitney U test***
Daily LEU dose	859 (150-2800)	1935 (933-4000)	Z=-4.45, p<0.001
Corrected L-dopa dose	584 (0-2800)	1425 (0-3000)	Z=-2.25, p=0.025
DA LEU dose	190 (0-600)	800 (0-3600)	Z=-2.47, p=0.014
H & Y	2.5 (2.0 – 3.0)	2.5 (2.0 – 4.0)	Z=-1.56, p=0.118
Punding severity	0 (0 – 1)	2 (1 – 3)	Z=-3.89, p<0.001
MMSE	29.1 (27 – 30)	29 (24 – 30)	Z=-0.466, p=0.641

H&Y – Hoehn & Yahr scale, MMSE – Mini-Mental State Examination, LEU – L-dopa equivalent unit, DA – dopamine agonist, GDS – Geriatric Depression Scale, NS – Novelty Seeking score

5.3.1 L-dopa challenge

Patients were examined in the morning after overnight withdrawal of anti-Parkinson medications and once patients were fully "switched on" after taking a suprathreshold dose of oral L-dopa (mean 274mg, range 200-500) plus peripheral decarboxylase inhibitor (Albanese *et al.* 2001). Patients were evaluated by movement disorder specialists using the UPDRS motor scale and patients completed questionnaires evaluating the non-motor symptoms (see next section) in the "OFF"-medication and "ON"-medication states. Patients' ratings of subjective L-dopa effects were evaluated using a Drug Effects Questionnaire (DEQ) (de Wit *et al.* 1987). In the "ON"-state, patients rated drug effects (Leyton *et al.* 2002; de Wit *et al.* 1987) on four VASs, with the

questions: "Do you *feel* any drug effects?", "Do you *like* the effects you are feeling right now?"; "Are you *high*?", and "Do you *want* more of what you consumed, right now?". The patient's reward responsivity, as measured by speeding of responses in the presence of a small monetary reward, was assessed using the Card Arranging Reward Responsivity Objective Test (CARROT) (Powell *et al.* 1996). Dyskinesias were assess using the Goetz rating scale (Goetz *et al.* 1994) modified by removing scoring for dystonic movements and by using a mental subtraction method.

5.3.2 Non-motor symptom item generation

Rating scale items were generated from a review of publications identifying items reported to fluctuate in response to L-dopa therapy (Gunal *et al.* 2002; Racette *et al.* 2002; Riley and Lang, 1993; Witjas *et al.* 2002). 31 items were selected, given a common five-point response option, and formatted into a questionnaire. Patients were asked to rate each item on a Likert scale according to the extent to which they experienced that emotion or sensation at that moment in time from 0 being "very little or not at all" to 4 "extremely". As a quantitative measure for the severity of non-motor symptoms for each individual, if an item in the "OFF"- or "ON"-states was endorsed by the individual (i.e. rated >0), then it was scored as present or 1. The number of endorsed items by each individual was added to form a total score for the "OFF"- and "ON"-states. 17 items were categorised as "Somatic" and 14 "Affective". A version of the positive and negative affect schedule (PANAS) (Laurent *et al.* 1999) was also used which presented 15 positive affect (PA) (e.g. "excited") and 15 negative affect (e.g. "scared") adjectives, which were endorsed by the patient on a 5 point Likert scale ranging from 1 = not at all to 5 = extremely. The PANAS was presented in its state version; i.e. patients were asked to rate how they felt "right now".

5.3.3 Data analysis

Statistical analyses of clinical data were performed with SPSS version 11.0 (SPSS Inc., Chicago, IL, USA). The assumptions of normality and constant variance of the model residuals were reasonably met for each of the analyses. Each measure (affect, reward responsivity, motor and non-motor symptoms) was analyzed in separate mixed design ANOVAs with GROUP (DDS patients or PD control) as the between-subject variable and effect of L-DOPA (two levels: OFF medication and ON medication) as the within subjects variable. Where appropriate, post-hoc two-tailed tests were performed to explore differences between groups and between conditions. In each group, correlations between changes in PA and NA and individual depression and novelty seeking scores using Pearson's correlation coefficient were tested. In DDS patients, punding severity was also correlated with reward responsivity. To determine whether "OFF" symptoms or

expressions of drug salience in "ON" were independently associated with DDS, motor UPDRS, PA, and NA in "OFF" and VAS scores of drug "wanting" in "ON" were entered into a forward stepwise logistic regression model.

5.4 Results

5.4.1 Motor scores

The significant interaction between L-DOPA effect and GROUP [$F(1,38)=18.24$; $p<0.001$] (Table 5-2) indicate that the change in UPDRS from OFF to ON was greater in the DDS group compared to the control group. In "ON" DDS patients had comparable UPDRS scores (t=-1.15, p=0.255) but more disabling dyskinesias (Table 5-4).

Table 5-2: Results of mixed design 2 way ANOVAs with GROUP (DDS patients or PD control) and AGE as between-subject variables and effect of L-DOPA (two levels: OFF medication and ON medication) as the within subjects variable for UPDRS pt3, somatic and affective symptoms, reward responsivity (%), and positive and negative affect. Scores indicate mean (standard error of the mean).

Group	L-DOPA state	UPDRS pt3	Somatic symptoms	Affective symptoms	Reward responsivity	Positive affect	Negative affect
Control PD	"OFF"	33.1 (2.5)	5.9 (1.0)	5.8 (0.9)	3.1 (2.0)	32.7 (2.1)	22.6 (2.6)
	"ON"	19.2 (2.5)	3.2 (1.0)	3.7 (0.9)	-1.3 (2.0)	38.4 (2.1)	20.7 (2.6)
DDS	"OFF"	53.4 (2.5)	7.6 (1.0)	10.9 (0.9)	4.0 (2.3)*	20.9 (2.1)	32.6 (2.6)
	"ON"	22.7 (2.5)	4.2 (1.0)	5.6 (0.9)	10.9 (2.0)	35.0 (2.1)	24.7 (2.6)
P-value for main effect of Group		F(1,37)=16.6, *P*<0.001	F(1,37)=1.2, *P*=0.279	F(1,37)=10.7, *P*=0.002	F(1,35)=12.7, *P*=0.001	F(1,37)=8.7, *P*=0.006	F(1,37)=4.3, *P*=0.046
P-value for main effect of L-DOPA		F(1,38)=129.1, *P*<0.001	F(1,38)=15.4, *P*<0.001	F(1,38)=32.4, *P*<0.001	F(1,37)=0.4, *P*=0.542	F(1,38)=48.9, *P*<0.001	F(1,38)=8.9, *P*=0.005
P-value for interaction between Group and L-DOPA		F(1.38)=18.2, *P*<0.001	F(1,38)=0.2, *P*=0.675	F(1,38)=6.3, *P*=0.016	F(1,37)=6.3, *P*=0.017	F(1,38)=9.0, *P*=0.005	F(1,38)=3.3, *P*=0.075

Means calculated at the average age of 57.5

*N=15 due to patients' inability to perform motor requirements of the task, DDS – Dopamine Dysregulation Syndrome, UPDRS – Unified Parkinson's Disease Rating Scale

5.4.2 Non-motor scores

The results of a paired-samples test in all 40 participants for the 31 non-motor item scores in off- compared to "ON"-state are given in Appendix A. The interaction between GROUP and L-DOPA was significant for the number of affective items endorsed [$F(1,38)=6.34$; $p=0.016$], (Table 5-2). This was largely accounted for by a higher number of affective items endorsed in "OFF" in the DDS group ($t=-4.43$, $p<0.0001$). The number of affective items endorsed in "ON" was not different ($t=-1.68$, $p=0.101$). The interaction between GROUP and L-DOPA was not significant for number of somatic items endorsed [$F(1,38)=0.18$; $p=0.675$] and there was no significant between GROUP effect on the number of somatic items endorsed [$F(1,37)=1.21$; $p=0.279$], although the main effect of L-DOPA on the number of somatic items endorsed was significant [$F(1,38)=15.44$; $p<0.001$].

Table 5-3: A. Paired-samples Wilcoxon signed rank test of autonomic symptoms in 40 participants of difference between symptom ratings in "OFF" minus symptom ratings in "ON" and B. Paired sample nonparametric Mann Whitney tests between control PD group and DDS patients of the difference between the "ON"- and "OFF"-state scores.

	A. Difference from "OFF" to "ON" N=40				B. Between group difference			
Symptom	Median	Range	*Z*	*p*	Median	Range	*W*	*p*
Autonomic								
Sweats	0.0	-4.0 – 1.0	-2.67	0.008	0.0	-4.0 – 2.0	442.5	0.387
Feeling Hot	0.0	-4.0 – 2.0	-1.35	0.176	0.0	-4.0 – 3.0	397.0	0.735
Flushing of face	0.0	-3.0 – 3.0	-1.32	0.188	0.0	-3.0 – 3.0	431.5	0.570
Dry mouth	0.0	-4.0 – 2.0	-2.37	0.018	0.0	-5.0 – 2.0	447.0	0.288
Choking feeling	0.0	-3.0 – 2.0	-2.58	0.010	0.0	-3.0 – 3.0	446.5	0.240
Abdominal discomfort	0.0	-3.0 – 2.0	-2.67	0.008	0.0	-3.0 – 3.0	445.5	0.228
Cold hands/feet	0.0	-4.0 – 4.0	-2.00	0.046	0.0	-4.0 – 4.0	477.0	0.030
Drooling	0.0	-2.0 – 4.0	-1.47	0.142	0.0	-3.0 – 4.0	439.5	0.433
Need to pass urine	0.0	-4.0 – 3.0	-2.50	0.012	0.0	-6.0 – 2.0	418.0	0.839
Visual blurring	0.0	-4.0 – 1.0	-2.62	0.009	0.0	-4.0 – 3.0	452.0	0.229
Racing heart	0.0	-4.0 – 1.0	-2.00	0.046	-1.0	-4.0 – 3.0	410.0	1.000
Chest tightness	0.0	-1.0 – 2.0	-2.89	0.004	0.0	-4.0 – 3.0	420.0	0.797
Difficulty breathing	0.0	-1.0 – 2.0	-2.85	0.004	0.0	-1.0 – 2.0	437.0	0.375
Feverish	0.0	-4.0 – 0.0	-1.51	0.132	0.0	-2.0 – 4.0	394.5	0.561
Sensory								
Tight feelings	-1.0	-4.0 – 3.0	-3.00	0.003	-1.0	-4.0 – 2.0	464.0	0.148
Tingling sensations	0.0	-4.0 – 3.0	-2.10	0.036	0.0	-4.0 – 3.0	398.5	0.766
Pain or cramping	-2.0	-4.0 – 3.0	-2.82	0.005	-0.5	-7.0 – 3.0	470.5	0.095

Affective								
Anxious	0.0	-3.0 – 3.0	-3.45	0.001	0.0	-2.0 – 4.0	471.5	0.079
Tired	1.0	-2.0 – 4.0	-2.55	0.011	1.0	-3.0 – 4.0	449.0	0.298
Irritable	-1.0	-4.0 – 2.0	-3.21	0.001	-1.0	-4.0 – 2.0	505.0	0.011
Withdrawn	-1.5	-4.0 – 1.0	-4.09	<0.001	-1.0	-4.0 – 2.0	530.0	0.001
Weary	0.0	-4.0 – 2.0	-2.31	0.021	-1.0	-5.0 – 2.0	469.5	0.110
Pessimism	0.0	-4.0 – 2.0	-2.09	0.037	-1.0	-4.0 – 5.0	471.0	0.102
Apathy	0.0	-4.0 – 2.0	-3.00	0.003	0.0	-4.0 – 2.0	496.5	0.020
Panicky	-1.0	-4.0 – 2.0	-3.88	<0.001	0.0	-4.0 – 2.0	529.0	0.001
Angry	0.0	-4.0 – 1.0	-2.05	0.040	-0.5	-4.0 – 1.0	456.0	0.128
Cognitive								
Slowness of thinking	0.0	-2.0 – 2.0	-4.17	<0.001	-1.0	-3.0 – 2.0	451.0	0.256
Memory problems	0.0	-4.0 – 3.0	-3.33	0.001	-1.0	-5.0 – 2.0	416.0	0.882
Mental emptiness	0.0	-4.0 – 2.0	-3.85	<0.001	-0.5	-4.0 – 2.0	515.0	0.005
Racing thoughts	-1.0	-4.0 – 1.0	-2.36	0.018	-1.0	-4.0 – 2.0	455.5	0.121
Poor concentration	-1.0	-4.0 – 2.0	-3.97	<0.001	-0.5	-3.0 – 3.0	469.5	0.110

Non-motor item scores were compared using the Mann Whitney U test between the DDS and control PD patients in the "OFF"- and "ON"-medication states. In the "OFF"-state, DDS patients had higher ratings of "anxious" (Z=-2.31, p=.021), "tired" (Z=-2.20, p=.028), "irritable" (Z=-3.01, p=.002), "withdrawn" (Z=2.86, p=.004), "weary" (Z=-2.19, p=.029), "apathy" (Z=-2.76, p=.006), "panicky" (Z=-3.23, p=.001), "angry" (Z=-2.35, p=.019), "slowness of thinking" (Z=-2.25, p=.024), "mental emptiness" (Z=-3.17, p=.002), "poor concentration" (Z=-2.97, p=.003), and "tight feelings" (Z=-2.95, p=.003). In the "ON"-state, DDS patients had higher ratings of "feeling hot" (Z=-2.37, p=.018), and "weary" (Z=-1.99, p=.047) only.

5.4.2.1 Positive and Negative Affect

For PA, there was a significant interaction between L-DOPA and GROUP [$F(1,38)$=9.02; p=0.005]. For NA, there was a trend for an interaction between L-DOPA effect and GROUP

[$F(1,38)=3.34$; $p=0.075$]. However, there was a significant main effect of L-DOPA on NA [$F(1,38)=8.91$; $p=0.005$] and a between-GROUP difference in ratings of NA [$F(1,37)=4.26$; $p=0.046$]. The differences were largely due to reduced scores of PA ($t=4.93, p<0.0001$) and higher scores of NA ($t=-2.76, p=0.009$) in the DDS group compared to controls in "OFF" (Table 5-2). There were no between group differences in PA ($t=0.95, p=0.347$) or NA ($t=-1.39, p=0.172$) in "ON".

5.4.2.2 Reward responsivity

There was an interaction between L-DOPA effect and GROUP for reward responsivity [$F(1,37)=6.26$; $p=0.017$] (Table 5-2). Means show RR went up from "OFF" to "ON" in DDS group but down in control group. Reward responsivity was not different between the groups in "OFF" ($t=-0.579, p=0.566$).

5.4.2.3 Drug "wanting" and Drug Effects

In "ON", DDS patients had higher ratings of drug "wanting" but there was no difference in ratings of "feel" drug, "like" drug, or drug "high" compared to control PD patients (Table 5-4).

Table 5-4: Linear mixed model for dyskinesia scores, and drug effects questionnaire ratings in "ON" in control PD patients versus patients with Dopamine Dysregulation Syndrome adjusted for age.

Ratings in "ON"	**Control PD mean (SE)**	**DDS mean (SE)**	Wald statistic; P-value
Goetz dyskinesia score	**0.9 (0.2)**	**2.0 (0.2)**	W=14.56, P<0.001
"Want" drug	**7.6 (5.7)**	**43.6 (5.7)**	W=19.33, P<0.001
"Feel" drug	**65.4 (6.3)**	**74.9 (6.3)**	W=1.02, P=0.314
"Like" drug	**65.7 (7.2)**	**65.9 (7.2)**	W=0.00, P=0.977
drug "High"	**26.0 (7.1)**	**37.0 (7.1)**	W=1.22, P=0.269

* Means calculated at the average value of age

Variables independently associated with DDS were worse UPDRS part 3 in "OFF", increased expressions of drug "wanting" in "ON", and novelty seeking and these accounted for a large degree of the variance (Table 5-5).

Table 5-5: Logistic regression analysis examining the influence of age, disease duration, NS, GDS, UPDRS part 3, PA, NA, number of affective and somatic symptoms in "OFF" and drug "wanting" in "ON" on the dependent binary variable: PD patients with DDS vs PD fluctuating controls using a forward selection procedure

Variable	Model R^2	p value on entry to model
UPDRS part 3 in "OFF"	**0.579**	**0.001**
Drug "wanting" in "ON"	**0.746**	**0.034**
Novelty seeking	**0.819**	**0.070**

Hosmer-Lemeshow goodness-of-fit statistic=2.9; 8 *df*; p=0.942.

5.4.3 Correlations

In the DDS group, change in PA correlated with NS (r=0.461, p=0.041, n=20) and change in NA with GDS (r=0.473, p=0.035, n=20). The correlation between change in NA and GDS remained significant even when the severity of UPDRS in "OFF" was partialled out (r=0.456, p=0.049, n=20). In DDS patients reward responsivity in "ON" correlated with punding severity (r=0.452, p=0.044, n=20). In the control PD group, change in NA correlated with GDS (r=0.483, p=0.031, n=20).

5.5 Discussion

Following overnight withdrawal of medications, DDS patients had more motor parkinsonism, reduced positive affect, and reported a broader range of affective non-motor symptoms compared to control patients. With the L-dopa challenge, DDS patients had a greater reduction in the motor UPDRS, number of affective non-motor symptoms, and positive affect due to their relatively lower baseline scores. They displayed generally enhanced reward responsivity and had significant L-dopa induced increases in reward responsivity. In "ON", DDS patients reported increased drug

"wanting" but did not "feel" or "like" drug effects more than controls and they had more disabling dyskinesias.

Treatment for the motor disability of PD may reduce depressive symptomatology (Burn, 2002b) even though dopaminergic drugs have limited or no hedonic effects at their initiation (Maricle *et al.* 1998). With time, medication-responsive affective states may emerge and include anhedonia, allodynia, anxiety, fatigue, irritability lassitude, sadness and panic (Witjas *et al.* 2002). Patients with DDS, frequently complaint of disabling "OFF"-state symptomatology (Bearn *et al.* 2004). In this study, a broad range of non-motor symptoms were found to fluctuate in both groups of PD patients in response to an acute L-dopa challenge. Affective fluctuations do not simply reflect a psychological reaction to worsening motor disability or changing brain catecholamine levels. Blinded cessation of a L-dopa infusion quickly leads to deterioration in affective states before any changes in motor function can be detected (Maricle *et al.* 1995). Dissociation between mood and motor states is also evident when comparing effects of stimulation of the subthalamic nucleus to the effects of L-dopa (Funkiewiez *et al.* 2003). Moreover some DDS patients have distressing non-motor "OFF" periods even when their motor symptoms are well controlled (Lawrence *et al.* 2003). Imaging data suggest that mood fluctuations result from dopaminergically mediated functional changes within limbic cortices (Black *et al.* 2005).

Negative reinforcement accounts of addiction propose that escape from or avoidance of *negative affect* is the principal motive for addictive drug use. The initially rewarding effects of drugs of abuse are later followed by opposing longer-lasting emotional states during withdrawal as the body seeks to restore its "hedonic equilibrium". Persistent plasticity is proposed to occur in the activity of neural circuits mediating two different motivational systems: recruitment of "anti-reward" systems (i.e. brain systems that limit reward) that drive aversive states, and decreased function of brain reward systems driven by natural rewards (or reduction in baseline pleasure levels (Barr *et al.* 2002)). This is hypothesized to ultimately sustain compulsive drug use.

In this study, DDS patients reported a "withdrawal" state characterised by a global reduction in positive affect, a trend to increased negative affect, a broader range of negative affective symptoms and worse motor function. The withdrawal state in DDS resembles the withdrawal state of psychostimulant addiction (Barr *et al.* 2002). Although "Somatic" withdrawal symptoms differ greatly between different drugs of addiction, emotional withdrawal symptoms in particular seem to underpin drug dependence (Koob and Le, 2008).

DDS patients also had higher depression scores despite having comparable "ON" motor disability to the PD fluctuators group. Higher depression scores correlated with greater reductions of negative affect from L-dopa. In psychostimulant addiction, the severity of the withdrawal symptoms predict the presence of depressive symptoms (Sofuoglu *et al.* 2003) and greater severity of drug dependence. Thus, in DDS patients, negative reinforcement might not only represent self-medication of a drug-generated aversive state (such as withdrawal) but could also include self-medication of an existing aversive state (such as depressive symptoms). The latter proposal is in keeping with observations in untreated PD patients where depressive symptomatology has been found to predict greater need for symptomatic therapy (Ravina *et al.* 2007). However, in treating DDS, treatment of depression alone is not effective in reducing compulsive drug use or its behavioral consequences (Lawrence *et al.* 2003).

Individual differences, either via genetic or environmental factors, at critical periods may cause a predisposition develop addiction disorders. In this study, greater drug-induced improvement in positive affect did occur in DDS patients from "OFF"- to "ON"-medication and greater change in PA was predicted by higher novelty-seeking personality traits. Yet, PA in "OFF" (and thus the change in PA) did not independently predict DDS in the regression model. In human studies of psychostimulants, higher novelty-seeking traits have also been found to predict greater subjective psychostimulant effects (Hutchison *et al.* 1999). Moreover, higher novelty-seeking traits are an independent risk factor for the development of DDS (Evans *et al.* 2005) and the emergence of impulse control disorders with dopamine agonist treatment (Voon *et al.* 2007).

Negative reinforcement models also propose that there is a reduction of brain reward function during acute withdrawal (Koob and Le Moal, 2001). The CARROT is a behavioral measure of responsiveness to financial incentive, in which participants sort cards under conditions of nonreward and reward (Powell *et al.* 1996). Normal subjects show a significant increase in sorting speed when rewarded of about 4%. In a previous study with heavy smokers, reward responsiveness was impaired during abstinence and restored after a single cigarette (al-Adawi and Powell, 1997). In contrast to the predictions of negative reinforcement models of addiction, there did not appear to be a "reward" deficit in the "OFF" state, in control PD patients or DDS patients as measured by performance on the CARROT. Others have even suggested that drug seeking in humans comes at the expense of natural rewards (Cardinal and Everitt, 2004) implying that reduced incentive processing is causally related to anhedonia (Baker *et al.* 2004). Instead, we found that DDS patients showed even greater reward responsivity with a L-dopa challenge.

The finding that DDS patients have higher reward responsivity is relevant to clinical observations that link both DDS (Evans and Lees, 2004) and the dopaminergic drugs used in PD with a variety of impulse control disorders (Driver-Dunckley *et al.* 2003) and punding. Moreover, we observed that emotional and motivational states in "ON" and "OFF" in DDS patients appeared to be independent. This indicates that anhedonia may not necessarily result from reduced incentive processing. Heightened responsivity to nondrug (monetary) rewards in DDS patients may relate to a global effect of dopaminergic drugs on sensitizing incentive motivational systems and may share the same substrates as those mediating drug-primed craving. Further, these systems may also overlap with those that mediate the expression of drug-induced complex repetitive stereotypies (punding) due to the correlation between punding severity and reward responsiveness.

Appetitive motivation may also have a role in compulsive drug use in DDS. Incentive-motivational accounts of addiction assume that the withdrawal state enhances the incentive value of the drug to such an extent that drug-seeking becomes the dominant behavior (Hutcheson *et al.* 2001). Drug absorption, distribution, and elimination kinetics produce innumerable spikes and troughs in drug levels in the body over the course of drug use. The addicted individual develops interoceptive cues of the negative affect that occur whenever drug levels begin to fall and this biases a proceduralised drug motivational processing routine. Similarly, in PD, repeated experience with end-of-dose wearing-off and co-existence of a chronic depressive state may further enhance the incentive value of the drug to such an extent that dopaminergic drug seeking becomes the over-riding behavior. Many DDS patients use idiosyncratic internal symptoms to herald impending "OFF"-states and cue stereotyped drug dosing schedules despite the external appearance of adequate parkinsonian motor control (Giovannoni *et al.* 2000). However, both groups of PD patients in this study reported at least one "withdrawal" symptom and experienced some hedonic impact of L-dopa. Moreover, DDS patients in "ON" did not '*like*' the effects of their medications any more or experience greater '*highs*'.

Drug-induced neuroadaptations in the dopaminergic ventral striatum (VS) and related circuitry may play a pivotal role in the development of DDS (Evans *et al.* 2006b). In "ON" DDS patients had comparable motor function, had comparable ratings of PA and NA and drug "liking" but had greater expressions of drug "wanting" despite more disabling dyskinesias. The VS and related circuitry are proposed by some authors to mediate a subcomponent of reward termed incentive salience (or drug "wanting") (Robinson and Berridge, 2000). With repeated drug taking, brain reward systems mediating drug "wanting" are proposed to become hyperresponsive (sensitized)

to dopaminergic drugs and drug-associated stimuli. At the same time, individuals are thought to become tolerant to the hedonic impact of drugs (i.e. drug "liking" is reduced). Drugs become compulsively "wanted" or craved even when the drug's pleasurable effects are diminished (Robinson and Berridge, 2000). L-Dopa primed craving (increased drug "wanting" in "ON") in DDS is more easily explained by these "proponent" neural processes and has been found to correlate with drug-induced neuroadaptations in the nucleus-accumbens in individuals with DDS (Evans *et al.* 2006b).

We conclude that a harmful pattern of compulsive dopaminergic drug use in PD is associated with an aversive medication-withdrawal state, consistent with some predictions of negative reinforcement models of compulsive drug use. However, "OFF" period motor disability alone cannot be the only factor in the driving compulsive drug use in these individuals. Patients in both groups of this study experienced some sort of aversive "OFF" symptoms and all patients had motor fluctuations. Moreover, the affective aspects of medication-withdrawal appeared to be less important than "OFF" period motor disability in predicting DDS and some aspects of motor function were in fact worse in the "ON" state of DDS patients. Medication-responsive affective states, in general, appeared to relate more to depressive symptomatology and individual personality traits rather than mechanisms that mediate general incentive arousal or motor function. Incentive learning processes associated with repeated experience with the aversive "OFF" state may also contribute the development or maintenance of DDS although we did not specifically test whether DDS patients experienced "OFF" symptoms more frequently than controls. Consistent with the incentive sensitisation theory of addiction (Robinson and Berridge, 2000), patients' ratings of drug "wanting" in "ON" were independently associated with DDS – despite DDS patients having more "ON" period motor disability due to dyskinesia.

Chapter 6

COMPULSIVE DRUG USE LINKED TO SENSITISED VENTRAL STRIATAL DOPAMINE NEUROTRANSMISSION

Summary

Objective: Sensitisation of dopamine neurotransmission is a consistently found neuroadaptation in animals repeatedly exposed to stimulant drugs. The aim was to evaluate L-dopa induced dopamine neurotransmission in the striatum of patients with DDS compared to PD controls.

Methods: A two-scan PET protocol was used to calculate the percentage change in ^{11}C-raclopride binding potential (BP) from a baseline withdrawal ("off" drug) state to the BP after an oral dose of L-dopa. The subjective effects of L-Dopa were related to the effects on endogenous dopamine release of a pharmacological challenge with L-Dopa in 8 control PD patients and 8 patients with DDS.

Results: PD patients with DDS exhibit enhanced L-dopa induced ventral striatal-dopamine release compared to L-dopa treated patients with PD not compulsively taking dopaminergic drugs. The sensitised ventral striatal-dopamine neurotransmission produced by L-dopa in these individuals correlated with self-reported compulsive drug "Wanting" but not "liking" and was related to heightened psychomotor activation (punding).

Interpretations: This provides evidence that links sensitisation of VS-circuitry in DDS patients to compulsive expressions of drug "Wanting".

6.2 Introduction

Dopaminergic drug therapy is a highly effective symptomatic treatment for the motor disability of PD (Hoehn, 1992). However, anti-Parkinson dopaminergic medications have the potential to be compulsively used (Evans and Lees, 2004; Giovannoni *et al.* 2000; Lawrence *et al.* 2003). In animal models, L-dopa and dopamine agonists appear to share some of the psychomotor activating properties of commonly abused drugs (van der Kooy *et al.* 1983; Katajamaki *et al.* 1998; Bardo and Bevins, 2000). It has been posited that the addictive liability of anti-Parkinson dopaminergic medications may be mediated by alterations in ventral striatal dopamine neurotransmission and related neural circuitry

(Lawrence *et al.* 2003) – a system that evolved to mediate aspects of "natural" rewards such as food, water and sex (Wise and Bozarth, 1987; Di Chiara and Imperato, 1988).

Early experiences with high doses of L-dopa without peripheral dopa decarboxylase inhibition in PD and bipolar depressive disorder highlighted the frequent occurrence of neuropsychiatric disturbance; including hypomania, psychosis, insomnia, aggression, impulsive behavioural disturbances, and intermittent "mood spells" in which patients would develop sudden feelings of intense exhilaration (Damasio *et al.* 1971; Murphy, 1972). More recently, it has become apparent that dopaminergic medications may also potentiate the appearance of drug-responsive compulsive behaviours (Evans and Lees, 2004; Giovannoni *et al.* 2000; Lawrence *et al.* 2003) (pathological gambling, hypersexuality and food bingeing (Giovannoni *et al.* 2000)) and the development of punding, a form of complex behavioural stereotypy (Evans *et al.* 2004). These drug-responsive behaviours frequently complicate DDS and may be implicated in a common neurobiological process.

The aim of this study was to evaluate L-dopa induced dopamine neurotransmission in the ventral striatum of patients with DDS compared to PD controls using molecular imaging with positron emission tomography (PET) and the dopamine D2/3 receptor ligand ^{11}C-raclopride (RAC). Differences in L-dopa induced endogenous dopamine release in DDS patients were correlated with the hedonic (i.e. pleasurable, euphoric) effects of L-dopa (drug "liking"), and a subcomponent of reward termed incentive salience (drug "Wanting") (Robinson and Berridge, 1993; Robinson and Berridge, 2000).

6.3 Methods

Eight non-demented patients with DDS and eight non-demented control PD patients (Table 6-1) gave written informed consent for protocols approved by local ethics committees. Permission to administer RAC was obtained from the Administration of Radioactive Substances Advisory Committee of the UK. Patients were asked to withhold all anti-Parkinson medication for 12 hours prior to scanning. A two-scan protocol was used to study the effects of the pharmacological challenge on endogenous dopamine levels that were estimated using percentage change in RAC binding potential (BP) relative to a baseline withdrawal ("off" drug) state. Each patient received two RAC-PET scans on separate mornings after overnight drug withdrawal; under baseline conditions and then after an oral dose of Sinemet-275 (L-dopa 250mg, carbidopa 25mg). The characteristics of the PET

scanner are described elsewhere (Piccini *et al.* 1999). Dynamic emission scans were initiated at the beginning of administration of a slow IV bolus of a mean 183 MBq dose of RAC. Patients also had volumetric brain magnetic resonance imaging. Two methods of analysis were employed: 1. a Region of Interest (ROI) approach focusing on the ventral and dorsal striatum and 2. Statistical Parametric Mapping (SPM), allowing exploratory voxel-by-voxel group comparisons throughout the entire brain volume.

Table 6-1: Patient characteristics

	Control PD group mean (range)	**DDS PD group mean (range)**	
Age (years)	60.0 (45 - 70)	51.2 (42.5 - 61)	Z= -2.10, p=0.038
Symptom duration (years)	12.1 (7 - 17)	12.4 (5-20)	NS
Mini-Mental Parkinson (Mahieux *et al.* 1995)	29 (27-32)	28.6 (25-31)	NS
motor UPDRS "off"-medication	37.1 (20 – 64)	52.7 (21 – 81)	Z=0.71, p=0.721
motor UPDRS "on"-L-dopa	27.1 (10 – 43)	23.1 (8 – 59)	Z=0.71, p=0.721
Daily L-dopa equivalent unit*	848 (267-1287)	1517 (700-2200)	Z= -2.20, p=0.027

UPDRS – Unified Parkinson's Disease Rating Scale, DDS – dopamine dysregulation syndrome, *L-dopa equivalent unit was defined according to (Evans *et al.* 2004)

6.3.1 Region of interest analysis

Parametric images of RAC-BP for each patient were generated from the dynamic RAC scans using a BASIS function implementation of the simplified reference region compartmental model with the cerebellum as the reference tissue (Gunn *et al.* 1997) and were anatomically co-registered (Studholme *et al.* 1997) with their respective volumetric T1-weighted MRI. Values of BP for caudate, putamen, and VS were obtained by defining on the co-registered magnetic resonance images ROI that were subsequently applied to the parametric images similar to the method reported by Leyton and colleagues (Leyton *et al.* 2002) and averaged values of the right and left sides were calculated for each region. Percentage change in RAC-BP was calculated using the formula: 100 x [(value when "off" L-dopa) - (value when "on" L-dopa)] ÷ (value when "off" L-dopa). Percentage change in motor UPDRS scores was calculated as follows: 100 x [(value when "off" L-dopa) - (value when "on" L-dopa)] ÷ (value when "off" L-dopa).

6.3.2 Statistical parametric mapping

Parametric images of RAC-BP were interrogated to localise significant differences of ligand BP at a voxel level using SPM99 software (Wellcome Department of Imaging Neuroscience, Institute of Neurology, London UK). Stereotaxic transformation of the parametric images involved spatially normalizing the individual RAC-BP image to an in-house RAC template in Montreal Neurological Institute space and subsequently spatial smoothing as previously described (Piccini *et al.* 2003). A between-group comparison localised clusters of voxels showing significant differences in mean RAC-BP after L-dopa between these two patient groups. An appropriately weighted contrast to localise significant decreases in mean voxel BP was used to derive *Z* scores on a voxel-wise basis using the general linear model. Regional brain differences were considered significant when maps of *Z* scores exceeded a threshold of 2.33 ($p<0.01$) after correction for cluster size ($p<0.05$). No global BP normalisation was applied. Statistical analyses of data were performed with SPSS version 11.0 (SPSS Inc., Chicago, IL, USA).

6.3.3 Clinical evaluations

The positive affect and negative affect schedule (PANAS) (Watson *et al.* 1988) was administered to measure the affective state prior to scanning on both scanning days, immediately before tracer injection and 15 and 30 minutes after tracer injection. Change in PA and NA was determined by comparing baseline ratings prescan to peak PA scores and trough NA scores during both the "off"-state scan and the L-dopa scan. The percentage changes in PA and NA were calculated with the following formula: [(peak or trough affect scale score during the scan) - (prescan affect scores obtained in the "off" medication state)] ÷ (prescan affect scores obtained in the "off" medication state) *x* 100. To control for the effects of scanning on affect, a summary measure was obtained by subtracting the percentage change in PA and NA during the "off"-medication scan from the percentage change in PA and NA during the "on" L-dopa scan. Motor disability was assessed in a baseline "off"-medication state with the Unified Parkinson's Disease Rating Scale (Fahn *et al.* 1987) (UPDRS) and then again immediately after the "on"-drug L-dopa scan. Percentage change in motor UPDRS scores was calculated as follows: 100 *x* [(value when "off" L-dopa) - (value when "on" L-dopa)] ÷ (value when "off" L-dopa).

6.3.4 Drug effects questionnaire

After overnight medication withdrawal, patients underwent a challenge with L-dopa in a similar manner to the challenge conducted on the day of PET. Patients' ratings of subjective L-dopa effects (drug "Wanting" and drug "liking") were evaluated using the DEQ (de Wit *et al.* 1987). In the "on" state, patients rated drug effects (Leyton *et al.* 2002; de Wit *et al.* 1987) on two 100mm VAS, anchored at 0="not at all" and 100="very much", with two questions: "Do you like the effects you are feeling right now?"; and "Do you want more of what you consumed, right now?". The patient's reward responsivity, as measured by speeding of responses in the presence of a small monetary reward, was assessed using the Card Arranging Reward Responsivity Objective Test (CARROT) (Powell *et al.* 1996).

Punding behaviours were rated by the examining physician (Evans *et al.* 2004) and patients completed questionnaires assessing novelty (Cloninger *et al.* 1993) and BAS fun-seeking (Carver and White, 1994) personality traits. To minimise potentially confounding influences of stress during the PET scan on these assessments, DEQ, punding, the CARROT and personality scores were rated during a separate L-dopa challenge prior to undergoing PET scanning.

6.4 Results

Using *a priori* defined dorsal- and VS-ROIs, no significant differences in "off-drug" RAC-BP were found between the PD groups (ROI RAC-BP mean values ±SEM; control PD caudate 1.95 ±0.1, putamen 3.08 ±0.2, VS 2.01 ±0.1; DDS caudate 1.95 ±0.1, putamen 2.98 ±0.1, VS 2.07 ±0.1 p values $\geq$0.72). Following L-dopa administration, both groups showed significant decreases in all regional striatal RAC-BPs compared to the "off-drug" scan. L-dopa had an equal effect on percentage reduction in dorsal putaminal RAC-BP in control and DDS groups. In marked contrast, there was significantly greater percentage reduction in VS RAC-BP in response to L-dopa in the DDS group (Figure 6-1) indicating higher drug-induced extracellular dopamine levels than controls. These findings were corroborated using voxel-based SPM analysis which confirmed the ROI findings of higher extracellular dopamine levels in the VS of the DDS group (Figure 6-2).

Figure 6-1: Effect of a single dose of L-dopa on percentage reduction in striatal RAC BP (mean ±SEM) in control PD versus DDS patients indicating a significantly greater generation of dopamine in VS regions in the DDS group (putamen, controls 11.5 ±3.3, versus DDS patients 11.6 ±2.0, p=0.88; VS, controls 3.6 ±1.5, versus DDS patients 14.4 ±2.7, p=0.003).

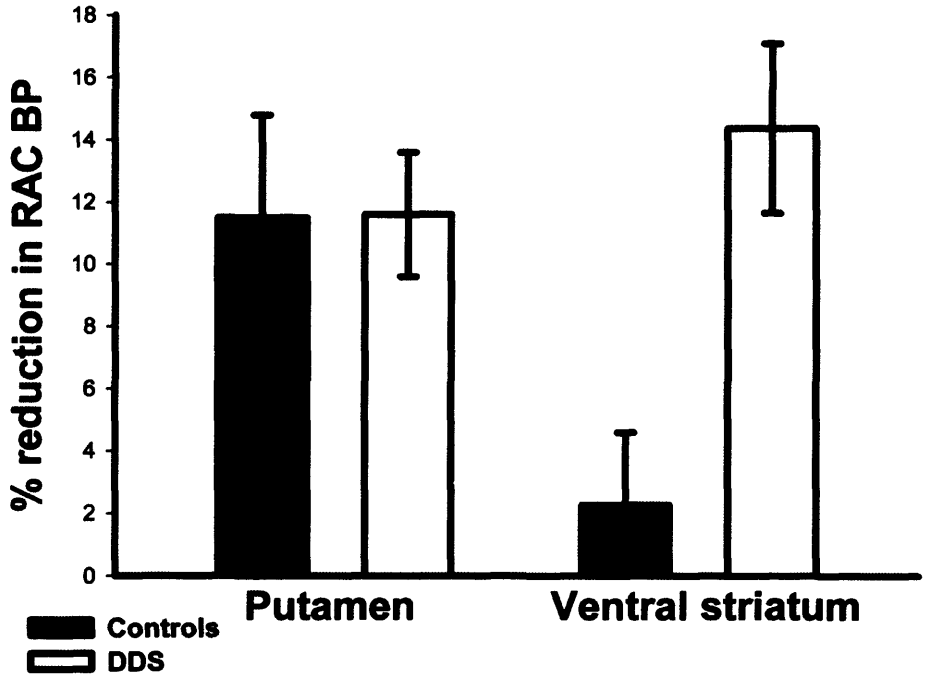
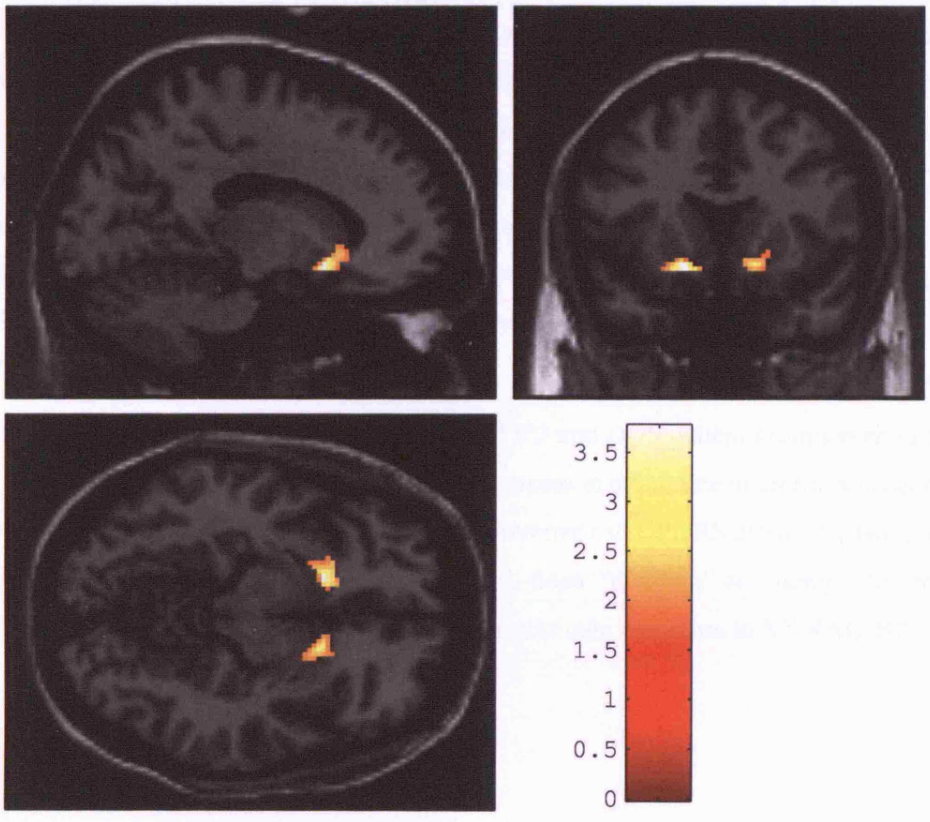


Figure 6-2: Sagittal (x=17.40), coronal (y=14), and transaxial (z= -9.85) projections of statistical parametric maps superimposed on a standardised MRI template. The figure shows the localisation of significant differences (in orange/yellow) in altered ^{11}C-raclopride (RAC) binding potential after a single dose of L-dopa between control PD and DDS groups. These areas were identified as right and left ventral striatum using Montreal Neurological Institute coordinates (right $x/y/z$ 18/12/-8, p=0.049, z=3.22; left $x/y/z$ -14/14/-8 p=0.048, z=3.38) confirming the region of interest findings of higher dopamine release in ventral striatum in the DDS group.

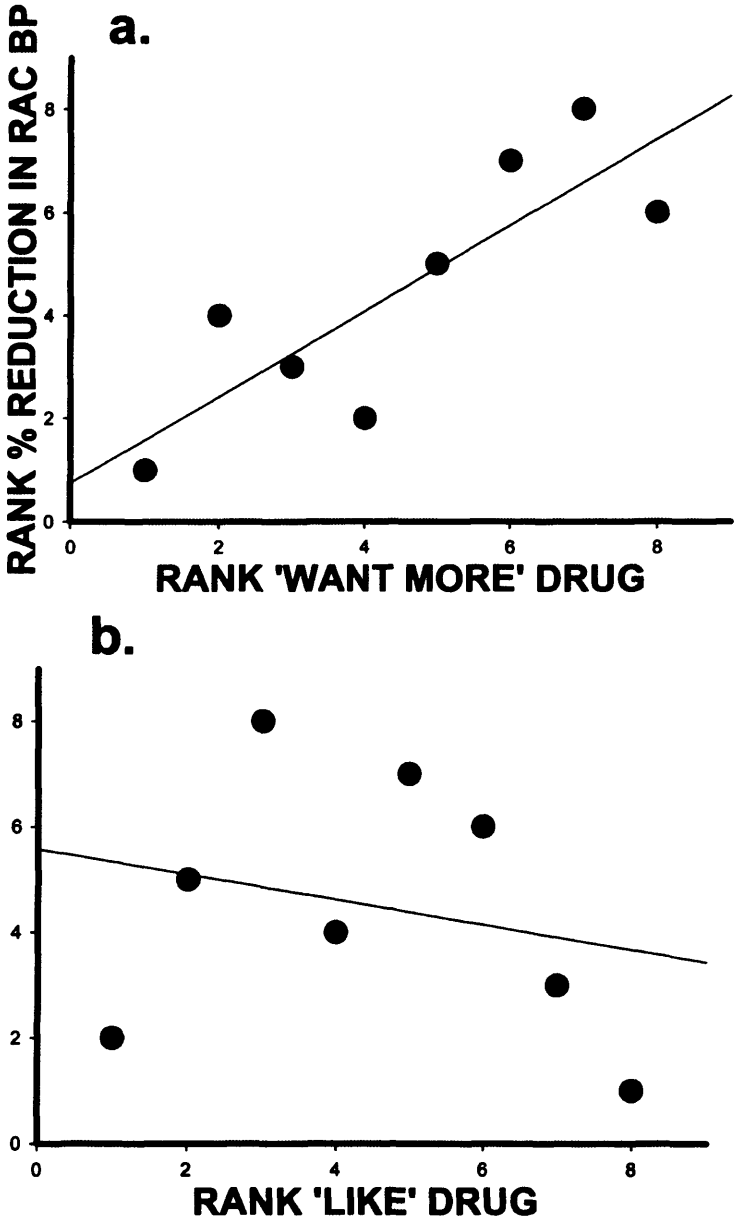


A strong representation of punding behaviour was found in the DDS group (controls 1/8 punders, versus, DDS patients 8/8, p=0.001). If the patients are divided along lines of punders versus nonpunders, the percentage reduction VS RAC-BP in punders was markedly higher (punders 14.1 ±2.4, nonpunders 0.83 ±2.1, Z= -3.23, p<0.001), however, the dorsal striatal release was no different between the groups.

In the DDS group L-dopa "Wanting" was higher than in the control group and significantly correlated with L-dopa induced dopamine levels in the VS (Figure 6-3A). In contrast, there was no significant association with L-dopa "liking" (Figure 6-3B). Self-reported drug effects were related to daily medication intake and a positive trend, although not significant, was found between daily dopaminergic drug intake and drug "Wanting" (r_s=0.627, $p < 0.10$, N=8) conversely "liking" was negatively correlated (r_s= -0.771, p=0.025, N=8). In the "off"-medication state, DDS patients had lower PA (t= -2.46, p=0.027) and showed a trend towards a higher NA (t=1.84, p=0.087) than controls. Ratings of state affect "on"–L-dopa were comparable between the groups (data not shown). Only a weak trend was observed for an association between L-dopa induced VS dopamine increases and change in PA (r_s=0.690, p=0.058, N=8) and no association with change in NA. The relationship between ratings of drug "Wanting" and L-dopa induced dopamine levels in the VS was only mildly weakened by partialling out the effects of changes in self-reported affect (r_s=0.682, p=0.092). DDS patients also showed an increased willingness to work for a small financial reward "on-L-dopa" (DDS patients mean "reward responsivity" on CARROT testing 12.3% SD 8.8, vs. control PD patients -1.9%, SD 8.8, Z= -2.94 p=0.003). Reward responsivity correlated with punding severity (r_s=0.873 p=0.005, N=8).

UPDRS motor scores were comparable in control PD and DDS patient groups both in the "on" and "off" L-dopa states (Table 6-1). L-dopa induced increases in dopamine neurotransmission in the putamen positively correlated with percentage improvement in UPDRS across the two groups (r_s=0.59, p=0.017, N=16) but did not correlate with L-dopa "Wanting" or "liking". Percentage change in UPDRS motor scores did not correlate with the percentage reduction in VS RAC-BP.

Figure 6-3: Rank correlation between rank percentage reductions in ventral striatal (VS) RAC BP induced by a single dose of L-dopa in DDS patients and: A. "Wanting" more L-dopa (r_s=0.833, p=0.010, N=8) B. "liking drug" (r_s= -0.238, p=0.570, N=8). "Wanting" and "liking" ratings were obtained "on" dopa.



DDS patients had increased novelty (Cloninger *et al.* 1993) and fun-seeking (Carver and White, 1994) traits (BAS Fun seeking mean (range); controls 9.5 (7-12), DDS 12.5 (8-16), Z= -2.34, p=0.021. NS1-Exploratory Excitability; controls 1.4 (0-3), DDS 2.6 (2-4), Z= -2.14, p=0.050). Neither of these traits correlated with L-dopa induced VS dopamine release.

6.5 Discussion

Using RAC PET, an enhanced or sensitised drug-induced VS dopamine neurotransmission was demonstrated in PD patients compulsively using dopaminergic drug therapy despite its adverse consequences. Basal levels of dopamine D2 receptor availability were comparable between the groups. Other clinical studies have linked compulsive drug use to reductions in striatal D2 receptor binding. However, in those individuals, the findings may be explained by past chronic drug exposure or possibly represent a premorbid susceptibility factor for compulsive drug use (Volkow *et al.* 1993; Martinez *et al.* 2004). The control group in this study had been exposed to chronic intermittent dopaminergic drug schedules for a similar duration to DDS patients. Therefore, the sensitised VS dopamine response that was found in the DDS group would not be the result of drug exposure *per se* but must be related to the development of a compulsive pattern of drug use.

Progressive augmentation of drug-induced VS dopamine release, measured after a period of drug withdrawal, is a consistently reported neuroadaptation associated with repeated psychostimulant drug administration in rodent microdialysis studies (Robinson and Berridge, 1993; Robinson and Berridge, 2000; Vanderschuren and Kalivas, 2000). Basal dopamine levels, however, remain largely unaltered (Vanderschuren and Kalivas, 2000). Some have proposed that compulsive drug seeking results from neuroadaptations that lead to persistent hypersensitivity (neural sensitisation) of ventral striatal dopaminergic circuitry, a circuit that mediates certain aspects of reward (Robinson and Berridge, 1993; Robinson and Berridge, 2000).

In animals, expressions of drug-induced stereotypies are influenced by drug dose (Samaha *et al.* 2002; Robinson and Berridge, 2000; Robinson and Berridge, 1993) and are hypothesised to index the neuroadaptive changes that occur in the VS in response to compulsive drug self-administration, as the neural substrate that mediates drug-induced stereotypies overlaps with the neural substrate responsible for the rewarding effects of drugs (Robinson and Berridge, 2000; Wise and Bozarth, 1987). In PD, drug-induced complex stereotyped behaviour has been called punding. The results of

the current study provide further evidence that punding may be homologous to drug-induced motor stereotypies in laboratory animals studies (Robbins *et al.* 1990) as the VS dopamine levels that were generated after oral L-dopa ingestion was even more striking in punders than nonpunders.

DDS patients frequently demand more medication and quickly complain of tolerance to the beneficial effects of treatment. However, spiralling dopaminergic drug intake tends to worsen drug tolerance and lead to an increased frequency of distressing "off" (medication withdrawal) periods. In the DDS patients enhanced L-dopa induced dopamine neurotransmission in the VS positively correlated with L-dopa "Wanting" but not L-dopa "liking". Further, drug "Wanting" predicted levels of drug use in DDS patients. Moreover, with increasing dopamine neurotransmission there was an increasing dissociation between L-dopa "Wanting" and its subjective pleasurable effects (L-dopa "liking") – potentially reflecting the concurrent development of tolerance. In these individuals the hedonic impact of the L-dopa, as measured by drug "liking", was negatively related to the patients' daily amount of L-dopa intake. Consequently, L-dopa "Wanting" appears to be directly related to compulsive use of that drug, even when its effects become less pleasant. The dopaminergic ventral striatum and related circuitry is proposed to mediate a specific reward process called "Wanting" or incentive salience (Robinson and Berridge, 1993; Robinson and Berridge, 2000). With repeated drug taking, brain reward systems mediating drug "Wanting" become hypersensitive (sensitised) to drugs and drug-associated stimuli. At the same time, individuals are thought to become tolerant to the hedonic impact of drugs so drugs become compulsively "Wanted" or craved even when the drug's pleasurable effects become diminished. These conceptualisations of compulsive drug use (the Incentive Sensitisation Theory) may be directly relevant to understanding compulsive use of dopaminergic drugs in PD patients with DDS. For instance, dopaminergic agonists have also been shown to induce the neural and behavioural phenotypes induced by psychostimulant drugs (Capper-Loup *et al.* 2002).

Animal data investigating the behavioural effects of drug sensitisation have found enhanced responding for natural reward related stimuli such as sugar, food, sex and conditioned stimuli for such rewards (Fiorino and Phillips, 1999; Wyvell and Berridge, 2001; Nocjar and Panksepp, 2002). By contrast, a proposed characteristic of human addiction is that responding for non-drug reinforcement decreases relative to that for drug reinforcement. It has been suggested that motivation for non-drug rewards may actually be decreased in humans (Cardinal and Everitt, 2004), although there are

anecdotal reports of hypersexuality in cocaine addicts (Robinson and Berridge, 2000) and some substance-dependent individuals may be hyper-responsive to money rewards (Bechara *et al.* 2002). The increased responsivity to nondrug (monetary) reward found in DDS patients is consistent with clinical observations that link the dopaminergic drugs used in PD and DDS (Evans and Lees, 2004) with other addictive behaviours such as hypersexuality and compulsive gambling (Driver-Dunckley *et al.* 2003; Dodd *et al.* 2005), and is relevant to the debate as to whether or not behavioural and chemical addictions share the same substrates. The correlation between punding severity and reward responsivity may reflect a relationship between the reward-enhancing and stereotypical effects of psychomotor stimulant drugs (Robbins, 1976) or relate to a global increase in wanting for conditioned rewards (Wyvell and Berridge, 2001).

A clear general relationship exists between novelty (Cloninger *et al.* 1993) and fun-seeking (Carver and White, 1994) personality traits and addiction proneness (Cloninger *et al.* 1988; Johnson *et al.* 2003; Zuckerman, 1994). These traits mediate biological responses to novelty (Bardo *et al.* 1996) and individual variability of drug-induced dopamine neurotransmission in the VS (Leyton *et al.* 2002). In adolescence, high novelty seekers are more likely to experiment with drugs (Zuckerman, 1994) and develop harmful patterns of drug (Sher *et al.* 2000) and alcohol use (Cloninger *et al.* 1988). In individuals with substance dependence, novelty-seeking traits also influence craving (Zilberman *et al.* 2003), vulnerability to relapse (Meszaros *et al.* 1999) and social influences on drug taking (Audrain-McGovern *et al.* 2003). Higher novelty-seeking traits independently predict the presence of DDS in PD (Evans *et al.* 2005). In this study, these trait scores did not correlate with L-dopa induced VS dopamine release, suggesting they may be independent predisposing risk factors for DDS.

These findings offer a unique insight into how exposure to a drug, even for therapeutic purposes, can subvert brain reward systems and lead to enduring susceptibility to compulsively use a drug. The findings of the present study may also be relevant to understanding the neurobiological processes that lead to other forms of addiction and to the development of management strategies for the disorder. For instance, the persistence of drug-induced neuroadaptive changes in many laboratory models suggests that once features of DDS are present, management can be difficult and relapse of the disorder common. Reduction in dopaminergic drug therapies can reduce the disability caused by the behavioural disorders associated with DDS. However, individuals may remain sensitised to the drug's

rewarding effects and in time, relapse may occur with smaller drug dosages. Identifying patients diagnosed with PD prospectively who may be vulnerable to developing a pattern of compulsive dopaminergic drug use may be a critical step in preventing the physical, social and financial impact of DDS.

Chapter 7
DISCUSSION

Summary

Compulsive dopaminergic drug use, a newly described phenomenon, can have devastating financial, social and legal consequences in a few patients whose motor handicap has been successfully treated with dopaminergic therapy. Recognition, understanding, and prompt effective treatment are important and hopefully prediction of those at greatest risk from the dopamine dysregulation syndrome and impulse control disorders will become possible. Further study of these phenomena also has an exciting potential to yield important insights into the neurobiological process that are relevant to addiction in general.

7.1 Summary of work undertaken

The main aims of this work were to delineate the phenomenology associated with compulsive drug use in PD, understand the factors that may lead to its genesis, and examine the neurobiological processes that mediate its expression.

7.1.1 Study of various forms of behavioural sensitisation in early Parkinson's disease

All the patients studied were attending Parkinson's disease clinics at the Middlesex Hospital and the National Hospital for Neurology and Neurosurgery in London. The study presented in Chapter 2 was carried out on 15 patients with newly diagnosed PD who underwent blinded L-dopa and methylphenidate challenges to assess their psychomotor and cardiovascular effects. With repeated drug dosing, individuals were predicted to develop tolerance to some drug effects whereas other drug effects may result from sensitisation. To assess whether this is the case, the challenges were repeated in all but one patient after 18 months regular treatment with dopaminergic drug therapy. A variety of psychomotor and drug effects were found most notably euphoriant effects to an acute dose of methylphenidate and the motoric effects of L-dopa were enhanced by regular dopaminergic therapy in PD.

These findings indicate that the psychomotor effects, possibly mediated by striatal monoaminergic systems, may be sensitised by sustained intermittent dopaminergic drug therapy a finding which may

be of particular importance in those individuals who are at risk of compulsively overusing their medication.

7.1.2 Characterisation of punding, a form of behavioural sensitisation in late Parkinson's disease

Animal models have provided considerable insight into the neurobiological substrate for the psychomotor effects of addictive drugs but translational research is generally lacking. It was posited that complex repetitive stereotypies, behaviours known to index the neuroadaptive changes of sensitisation in animal models, were demonstrable in PD outpatients and linked with DDS. Punding is a term that was coined originally to describe complex prolonged, purposeless and stereotyped behaviour in chronic amphetamine users and is homologous to the psychostimulant-induced behavioural stereotypies in animal models. The study presented in Chapter 3 presents the findings of a semi-structured interview of a selected group of 50 patients with higher dopamine replacement therapy requirements (>800LEU/day) from 123 unselected patients with PD. Seventeen patients (14%) exhibited punding which was associated with either high doses of dopaminergic drug therapy or prolonged repeated dosing. Punders also showed a high incidence of appetitive behavioural disorders such as hypersexuality, and gambling. The findings indicate that punding is an under-reported, socially disabling phenomenon which is commonly associated with the syndrome of dopamine dysregulation and is phenomenologically distinct from both obsessive-compulsive disorder and mania. The frequent concurrence of punding with compulsive dopaminergic drug use suggests that punding might represent an important step in the eventual progression to a form of automatic behaviour in which voluntary control over drug use is lost.

7.1.3 Examination of the factors which may influence the development of DDS

Personality and physiological traits differentially affect the various stages of addiction, defined chronologically as initiation of drug use, regular drug use, addiction/dependence and potential relapse. The predictive relationship between traits characterised by impulsivity and a tendency to seek new or varied experiences (ISS traits) and addiction vulnerability purportedly reflect some rewarding aspect of experiencing novelty and suggests that novelty-elicited exploration and drug stimuli may interact in biologically and behaviourally meaningful ways. Other factors such as exposure to drugs capable of cross-sensitising brain reward systems to the effects of dopaminergic drugs and stress and genes may also be relevant.

In the study presented in Chapter 4, predisposing factors to DDS were sought in a population of PD outpatients. Clinical features, ISS personality traits, past experimental drug use, alcohol consumption, smoking behaviours and depressive symptoms in 25 DDS patients were compared to an outpatient sample of 100 PD patients who were not compulsively overusing dopaminergic medication. DDS patients had a significantly younger age of disease onset, higher dopaminergic drug intake, greater past experimental drug use, more depressive symptoms, scored higher on ISS ratings and tended to have higher alcohol intake. Using logistic regression analysis, novelty seeking personality traits, depressive symptoms, alcohol intake and age of PD onset were significant predictors of DDS. These factors may help to identify early patients who are more vulnerable to developing a pattern of compulsive dopaminergic drug use and help minimise its consequences.

7.1.4 Characterisation of an aversive withdrawal state in DDS

PD patients with DDS commonly identify dysphoric "off" mood-states as the primary motivation to compulsively use their drugs. Several notions of addiction claim that the motivational force for compulsive drug-taking arises from the need to alleviate the negative emotional state of drug abstinence.

In the study presented in Chapter 5, affective state, motor function and incentive motivational state was assessed after withdrawal and then in response to L-dopa in 20 patients with DDS and 20 control PD patients. The effect of depressive symptoms and personality traits on the response to L-dopa was assessed. In the "off"-state, DDS patients reported lower PA, higher NA and more motor and non-motor disability in the "off"-state. However, reward responsivity (implicit reward processes) was not different between the groups in withdrawal. In "on", DDS patients had higher expressions of drug "Wanting", reward responsivity, and dyskinesias. Positive and negative affect, non-motor symptomatology and motor disability were comparable in both groups in the "on"-state.

These data suggest that the same neurobiological mechanisms that mediate the transition to compulsive drug use in individuals with DDS are implicated in the development of a broad range of affective, motivational and cognitive disorders.

7.1.5 ^{11}C-Raclopride study of neuroplastic changes in dopaminergic brain reward systems induced by compulsive dopaminergic drug use

A major theme underlying the development of addictions is the neuronal and behavioural plasticity induced by addictive drugs. In humans, the neurobiological substrate that is responsible for the transition

from drug use to drug addiction is poorly understood and little is known about why some individuals are more susceptible to this transition than others. This novel clinical paradigm of drug dependence in patients with PD was studied in Chapter 6. The effects of a pharmacological challenge on ^{11}C-Raclopride binding potential in 8 individuals with DDS were compared to a control group of PD patients who had been exposed to chronic intermittent dopaminergic drug regimens for a similar duration to DDS patients but were not using them compulsively. PD patients with DDS exhibit enhanced L-dopa induced VS-dopamine release compared to L-dopa treated patients with PD not compulsively taking dopaminergic drugs. This finding would not be the result of drug exposure *per se* but must be related to the development of a compulsive pattern of drug use. The sensitised VS-dopamine neurotransmission produced by L-dopa in these individuals correlated with self-reported compulsive drug "Wanting" but not "liking" and was related to heightened psychomotor activation (punding). Therefore drug-induced sensitisation of VS-circuitry, mediating compulsive drug "Wanting", is sufficient for the development of substance dependence in humans. These findings are relevant to a broad range of compulsive disorders.

7.2 Conclusion

The dopamine dysregulation syndrome is characterised by a disabling cluster of psychomotor, associative, cognitive, and emotional symptoms. The similarity of the symptomatology of DDS with that seen in psychostimulant abuse also provides support for a role of dopamine in these addictions. Nearly all patients diagnosed with PD are treated with dopaminergic drugs, but only a minority compulsively use them. Abuse of other anti-Parkinsonian drugs in PD has been rarely, if ever, described. Thus, extrinsic factors influencing addictive susceptibility may be less influential in predicting vulnerability to compulsive dopaminergic drug use in PD patients. These patients therefore represent an opportunity to understand individual factors that may predispose to addiction.

The brain region found to be involved in mediating the transition to compulsive drug use was the mesolimbic dopaminergic projections and the nucleus accumbens. Neuroadaptive changes within the nucleus accumbens were linked to a subcomponent of reward, drug "Wanting", or incentive salience. These findings provide support for Robinson and Berridge's IST of addiction. IST assumes that over the course of iterative drug use, there are progressive and persistent neuroadaptations induced in dopamine projections to the nucleus accumbens-related circuitry. These critical neuroadaptations are proposed to sensitise neural systems that mediate the incentive motivational or rewarding effects of drugs. The transition to compulsive drug use is posited to involve excessive salience attribution to drugs activating

this circuitry making them pathologically "Wanted" or craved. In these accounts, the process of incentive salience attribution is thought to be dissociated from neural systems mediating the hedonic impact of drugs.

Similar neuroadaptive changes were also linked to punding and heightened reward responsivity in DDS patients. The latter is thought to represent a form of motivational spillover in which sensitisation of brain systems of drug-reward can also involve brain systems mediating nondrug reward. This is consistent with observations described in Chapter 3 in which a link was found between punding and a variety of impulse control disorders (hypersexuality, pathological gambling, binge eating and so on). In the 5th Chapter, these behavioural expressions of sensitisation were further linked to the development of an aversive withdrawal state "off"-medication. This has relevance to theories of addiction that emphasise the role of the withdrawal syndrome as a critical motivator in compulsive expressions of drug use. These data suggest that the withdrawal syndrome and possibly depressive symptoms in general, represent another form of behavioural sensitisation phenomenon.

7.3 Future work

7.3.1 Validation of factors that predict DDS

Why exposure to dopaminergic drugs affects only a minority of individuals remains unresolved. The results presented in Chapter 4 should form the foundation for ongoing research project to follow a cohort of recently diagnosed PD patients throughout the progression of their disease. This may provide useful information about the prognostic implications attached to the syndrome, which in turn may influence clinical decisions taken by those managing PD patients.

7.3.2 Dopamine dysregulation syndrome and Impulse control disorders – part of the same spectrum or mediated by separate but overlapping neurobiological systems?

There is considerable overlap between individual vulnerability factors for DDS and ICDs in PD and similarities with susceptibility factors for PG in the general population. As in the general population PG in PD is linked to being male, having comorbid psychiatric,(Gallagher *et al.* 2007) or alcohol use disorders, and having higher ISS traits (Voon *et al.* 2007). However, there are important differences. Depressive symptomatology may not be a strong factor for PG (Voon *et al.* 2007). A number of patients with PG have been specifically reported not to have DDS and, conversely, not all patients with DDS have PG or another ICD as part of the syndrome. Pathological gambling and DDS, but not hypersexuality, have been

associated with alcohol use. Moreover, DDS is associated with high doses of L-dopa and higher total daily L-dopa equivalent doses compared to ICDs that appear to be highly influenced by agonist dose (Gallagher *et al.* 2007).

7.3.3 Identification of criteria for impulse control disorders in Parkinson's disease

An association between PD and impulse control disorders (ICDs) and DDS and ICDs is likely linked to the pathophysiology of PD, and interventions used to treat PD. Many studies have noted onset of ICD behaviours particularly with dopamine agonist onset or dose increase and a remission or reduction in ICD behaviours with reductions or cessations of dopaminergic therapies (Gallagher *et al.* 2007). This raises the possibility that different dopaminergic drugs may sensitise different aspects of brain dopamine function. Research gaps therefore exist in the definition, knowledge of prevention and treatment strategies related to impulse control disorders in PD and the relationship with dopaminergic drugs.

7.3.4 Determination of why dopaminergic agonists preferentially sensitise behaviours mediated by ventral striatal systems and L-dopa preferentially sensitises behaviours mediated by dorsal striatal systems

There is a strong and dose-dependent association between DA therapy and ICDs (Courty *et al.* 1997; Klos *et al.* 2005; Nirenberg and Waters, 2005; Uitti *et al.* 1989; Voon *et al.* 2006a); and daily L-dopa equivalent dose and DDS. However, PG differs from DDS in that DA use is almost invariably associated (98.3%), whereas DDS is associated with high doses of L-dopa and higher total daily L-dopa equivalent doses (Gallagher *et al.* 2007).

Disabling punding has also been linked to higher daily requirements of dopaminergic drugs (Evans *et al.* 2004) and punding-like behaviour has been linked to concomitant daily medication dosage from dopamine receptor agonists (Lawrence *et al.* 2007). Cases series also highlight improvement in punding behaviour after reduction or cessation of DA therapy (Kimber *et al.* 2008; Miyasaki *et al.* 2007).

In contrast, L-dopa is associated with the earlier appearance of motor fluctuations and dyskinesias (Hubble, 2002), proposed to reflect sensitisation phenomena of the dorsal striatal system (Pavese *et al.* 2006).

It is interesting to speculate why the uncontrolled effects of dopaminergic agonism via oral dopamine agonists might be linked to enhanced gambling behaviour, hypersexuality, and punding. Dopamine D3 receptors are localised to limbic regions. Additionally, orbitofrontal cortex dysfunction has been

implicated in ICDs from imaging studies (Reuter *et al.* 2005). Subsequently, D3 preferring dopaminergic agents have been demonstrated to have an inhibitory influence on orbitofrontal cortex function – potentially contributing to aspects of behavioural disinhibition (Black *et al.* 2002). However, receptor activation profile alone is not enough to explain the dissociated effects of agonists and L-dopa as the association between PG and agonists appears to be a class effect (Gallagher *et al.* 2007) and some agonists have relative little D3 activation.

7.3.5 Histopathological correlates

Behavioural sensitisation following repeated intermittent psychostimulant administration in animals involves alterations in neural activity within the accumbens and caudate brain regions. In humans, *Fos* immunohistochemistry, *c-fos in situ* hybridisation and morphological examination of striatal medium spiny neurons might be used to assess changes in dopaminergic drug-induced neural activity following compulsive dopaminergic drug use in behaviourally sensitised individuals.

7.3.6 Longitudinal treatment studies

Some of the manifestations of behavioural sensitisation with dopaminergic drugs (i.e. dyskinesias) have been demonstrated to reverse through therapies that involve continuous dopaminergic stimulation (such as with continuous subcutaneous apomorphine infusions) and surgical therapies. However, there is little data on what effect these therapies might have on individuals with DDS. Moreover, other features of behavioural sensitisation have not been examined in the context of these therapies.

7.3.7 Clinicogenetic studies

A specific predisposition to the addictive effects of dopaminergic therapy is probably present in affected patients. They may be genetically predisposed to addiction and efforts to characterise their unique genetic constitutions may provide an important insight into the neurobiological basis of addiction in general. These patients may represent a natural experiment in which a pharmacological probe has disclosed a unique genetic predisposition that can be identified with results that may be generalisable to other addiction disorders.

7.3.8 Cognitive and behavioural correlates

The behavioural profile of DDS patients is similar to that seen with substance dependence in individuals without PD. Cognitive studies might explore the nature of the decision-making impairments in

PD that may either predispose to developing DDS in the course of treatment (i.e. certain cognitive profiles in early disease may predispose to the genesis of the disorder) or arise from DDS and lead to further loss of inhibitory control on drug taking. Further study of these individuals may provide insight into other neuropsychiatric features of DDS including depression, psychosis, mania, hallucinations, gambling disorders, sexual deviations, and aggression. Longitudinal studies of the nature of the study in Chapter 2 could be particularly relevant in studying the various changes in drug effects that occur after initiation of sustained drug therapy for motor symptom control.

7.3.9 Neuroimaging studies

fMRI of DDS patients in dopaminergic withdrawal and in response to a drug challenge may yield significant findings about the underlying neural correlates of changes in motivation for natural and drug rewards, and neural circuitry mediating aversive "off"-symptoms in these individuals. This type of study is likely to reveal the role of non-frontostriatal circuitry, such as the cerebellum, in these processes. However, this can be problematic as DDS patients can be intolerant of prolonged drug withdrawal.

This research also provided a hint that compulsive dopaminergic drug use in DDS patients may contribute to a further worsening of frontal cognitive functions. Further dynamic studies using raclopride to explore the release of dopamine during cognitive tasks might form the basis of a future study to directly determine the role that dysregulation of dopaminergic systems play in the cognitive impairment observed in DDS. Additionally, DDS patients would be predicted to show changes in brain glucose metabolism in withdrawal that may relate to aversive "off"-symptoms and frontal cognitive deficits.

7.4 Summary

PD is a progressive condition that often requires specialist care for a variety of motor and non-motor symptoms due to the disease process and also the medications used to manage the disease. Dopaminergic drugs used to treat Parkinson's disease improve quality of life, reduce motor handicap and prolong survival (Hoehn, 1992). In addition to commonly reported motor drug side-effects, a small group of patients appear to compulsively use dopaminergic medications well beyond the dose needed to optimally control their motor disability. This destructive behaviour occurs in the face of a mounting number of resulting harmful physical, psychiatric and social sequelae. Hedonistic homeostatic dysregulation was first used to describe this uncommon complication but the term dopamine dysregulation syndrome is now preferred.

Although compulsive dopaminergic drug use is a relatively uncommon side-effect of drug management in PD, many of the behavioural associations of the disorder such as punding, and ICDs such as gambling and hypersexuality have been linked to dopamine agonist use in particular, in the absence of compulsive dopaminergic drug use. This suggests two things; firstly, dopamine has a pivotal role in behavioural addictions, drug-induced stereotypies and drug addiction; and secondly, the brain systems that mediate the transition from drug-use to compulsive drug-taking and craving would be expected to overlap with those systems that mediate behavioural addictions and the development of drug-induced stereotypies. Consistent with this, chronic treatment with dopaminergic drugs in PD was able cross-sensitisation to the euphoriant effects of methylphenidate and L-dopa as well as generally enhance reward responsivity. Moreover, regular dopaminergic drug therapy led to sensitisation to the motor effects of L-dopa.

Psychostimulant drugs and dopaminergic agonists induce complex motor stereotyped behaviour in animals. A study to identify similar behaviours in patients with PD was carried out and identified a group of patients with complex stereotyped motor behaviours similar to those previously described in amphetamine and cocaine addicts (punding).These were often socially disabling and the chosen activity tended to reflect the premorbid interests of the patient. They were more common in patients exhibiting other core features of the DDS.

This research was driven by the need for more accurate patient characterisation and it proposes mechanisms by which patients with the syndrome may be identified early. This disorder and the accompanying phenomenology can lead to potentially devastating consequences. This increases the need for further improvements in understanding the aetiology of the syndrome and finding tailored approaches to its management. The relative rarity of DDS provides testament to the low addictive liability of dopaminergic drugs used to treat PD but also suggests that it should be possible to identify which individuals about to start dopaminergic therapy are vulnerable to becoming addicted to it. Since nearly all Parkinson's patients are exposed to dopaminergic drugs in the course of management of their symptoms, individual susceptibility factors are less likely to be subject to the confounding effects of environment, and social influences. Impulsive sensation seeking personality traits relevant to epidemiological studies of substance dependence and other substance use were found to be highly predictive in the DDS patients as well as an independent association of depressive mood symptoms. Impulsive sensation seeking traits have subsequently been demonstrated to be relevant to individual susceptibility to the emergence of ICDs with treatment with dopamine agonists.

DDS patients report and were found to display an aversive drug withdrawal state akin to the withdrawal state with drugs of addiction. The nature of the medication-withdrawal state was characterised in a group of DDS patients after drug withdrawal after an overnight fast. Following overnight withdrawal of medications, DDS patients had more motor Parkinsonism, reduced positive affect, and reported a broader range of affective non-motor symptoms compared to control patients. With the L-dopa challenge, DDS patients had a greater reduction in the motor UPDRS, number of affective non-motor symptoms, and a greater increase in reward responsivity and positive affect. In "ON", DDS patients reported increased drug "wanting" but did not "feel" or "like" drug effects more than controls. They had more disabling dyskinesias and showed enhanced reward responsivity.

A novel clinical paradigm of drug dependence was investigated using a two-scan ^{11}C-Raclopride protocol. The results of this study have provided the first human evidence that drug-induced sensitisation of ventral striatal-circuitry mediates compulsive drug "wanting" and is sufficient for the development of substance dependence in humans. These findings are relevant to a broad range of compulsive disorders in general.

Appendix A
PUNDING QUESTIONNAIRE

Appendix A: Questionnaire

Do you have any hobbies or pastimes?

If yes, when did you become interested in your hobby (years)?

How do you feel when you are engaged with your hobby and why do you do it? (i.e. do you find it soothing? calm? fascinating? or are you driven to it in response to obsession? fear? anxiety?).

How many hours per day do you spend on the hobby?

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

Do you ever do it if you can't sleep at night (e.g. between midnight and 5:30?)?

If yes, have you ever missed a whole night's sleep because of it?

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

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

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

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

Do you have difficulties in finishing projects?

How many hours per day do you spend on the following?

- Cleaning/tidying
- Do-it-yourself
- Gardening
- Collecting things

- Repairing/dismantling – computers, television, radios, apomorphine pump (If yes, were you able to put them back together)
- Sorting – papers, through drawers/handbag?
- On the computer?

What is your past occupation? When did you retire and why?

Do you use rescue medications? If yes, how often per day and do you ever use them after 11pm or before 6am?

Other questions:

Insomnia – How many hours do you sleep per night on average? If you cannot sleep, do you ever get up and continue with your pastime or hobby?

Spending excessive amounts of money or money on unnecessary things for your hobby or pastime?

Do you gamble? Have you ever gambled and lost too much money?

Has your libido changed with the introduction of medications for Parkinson's disease?

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