Non-motor and neuropsychiatric features of Parkinson's disease

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Author Declaration

I, David Andrew Gallagher confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

This thesis focuses on non-motor symptoms (NMS) of Parkinson's disease (PD), particularly the neuropsychiatric symptoms of visual hallucinations, apathy and impulse control disorders. A clinical cohort study and pathology study were performed. PD patients (N=94) were recruited and each underwent neurological examination for motor aspects of the disease, detailed multi-domain cognitive assessment including executive and visuoperceptive function, and a battery of validated non-motor assessments for symptoms including mood, apathy, sleep, fatigue, psychosis, autonomic function, disability and health-related quality of life (QOL). A subgroup (N=50) also had detailed ophthalmological examination. In the autopsy study, the presence of ante-mortem visual hallucinations (VH) in PD donors was correlated with Lewy body (LB) density and distribution at different cortical locations. The clinical study examined the impact of NMS on QOL and found that NMS, particularly depression, had stronger association with QOL than motor scores, but despite this NMS were often under-reported by their treating neurologist. A significant proportion of pathologically confirmed PD patients presented exclusively with NMS and this led to misdiagnosis and, in some cases, inappropriate investigations and treatment. An aetiological model of VH was proposed and examined; factors investigated included dopaminergic medication, higher cortical function, sleep and ophthalmic pathology. Clinical associations of VH were rapid eye movement sleep behaviour disorder, autonomic function, and executive and visuoperceptive cortical function. There was however no clear association with co-existing ophthalmic pathology. In the post-mortem analysis, LB involvement at corresponding cortical areas was confirmed, including frontal (executive) and temporal and trans-entorhinal (visuoperception) cortices. A meta-analysis of studies reporting

pathological gambling was performed and an association with dopaminergic medication, particularly dopamine agonist therapy, and co-existing psychopathology was confirmed.

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Abbreviations

ACE	Addenbrooke's Cognitive Examination
ADL	Activities of Daily Living
ALDS	American Medical Center Linear Disability Score
AS	Apathy Scale
AUC	Area under the curve
BAI	Beck Anxiety Inventory
BORB	Birmingham Object Recognition Battery
BPRS	Brief Psychiatric Rating Scale
CI	Confidence Interval
CIT	Carbomethoxy-3β-4-Iodophenyltropane
CGI	Clinical Global Impression
CBD	Corticobasal Degeneration
DA	Dopamine Agonist
DAT	Dopamine Transporter
DDS	Dopamine Dysregulation Syndrome
DLB	Dementia with Lewy Bodies
DLPFC	Dorsolateral Prefrontal Cortex
DMV	Dorsal Motor Nucleus of Vagus

dPD	Depression in Parkinson's Disease
DSM	Diagnostic and Statistical Manual
ESS	Epworth Sleepiness Scale
FAB	Frontal Assessment Battery
FIM	Functional Independence Measure
fMRI	Functional Magnetic Resonance Imaging
FSS	Fatigue Severity Scale
FTD	Fronto-Temporal Dementia
HADS	Hospital Anxiety Depression Scale
HARS	Hamilton Anxiety Rating Scale
HDRS	Hamilton Depression Rating Scale
Hr-QOL	Health-Related Quality of Life
ICD	Impulse Control Disorder
ICSD-R	International Classification of Sleep Disorders - Revised
IPT	N-(3-iodopropen-2-yl)-2β-carbomethoxy-3β-(4-chlorophenyl) tropane
iRBD	Idiopathic Rapid Eye Movement Sleep behavioural disorder
LARS	Lille Apathy Rating Scale
LB	Lewy Body
LN	Lewy Neurite

LogMAR	Logarithm of Minimal Angle of Resolution
MDRS	Mattis Dementia Rating Scale
MDS	Movement Disorder Society
MIBG	Metaiodobenzylguanidine
MMSE	Mini Mental State Examination
MRD	Mean Radial Degrees
MRI	Magnetic Resonance Imaging
MSA	Multisystem Atrophy
MSLT	Multiple Sleep Latency Test
NCC	Nest Case Control
NMS	Non-Motor Symptoms
NMSQ	Non-Motor Symptoms Questionnaire
NPI	Neuropsychiatric Inventory
nM-EDL	Non-motor Experiences of Everyday Living
OFC	Orbitofrontal cortex
OR	Odds ratio
PANSS	Positive and Negative Symptom Scale
PDD	Parkinson Disease Dementia
PDQ-39	Parkinson's Disease Questionnaire – 39 Item Version

PDSS	Parkinson's Disease Sleep Scale
PET	Positron Emission Tomography
PG	Pathological Gambling
PPRS	Parkinsons Psychosis Rating Scale
PSP	Progressive Supranuclear Palsy
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
RBD	Rapid Eye Movement sleep behavioural disorder
REM	Rapid Eye Movement
RLS	Restless Leg Syndrome
ROC	Receiver Operating Characteristics
SCOPA	Scales for Outcome in Parkinsons
SCOPA-AUT	Scales for Outcome in Parkinsons – Autonomic Scale
SCOPA-COG	Scales for Outcome in Parkinsons – Cognitive Scale
SOREMP	Sleep Onset Rapid Eye Movement Periods
SPECT	Single Photon Emission Computer Tomography
UM-PDHQ	University of Miami Parkinson's Disease Hallucination Questionnaire
UPDRS	Unified Parkinson's Disease Rating Scale
UPSIT	University of Pennsylvania Smell Identification Test

VAS	Visual Analogue Scale
VH	Visual Hallucinations
VMPFC	Ventromedial prefrontal cortex
WAIS-R	Wechsler Adult Intelligence Scale – Revised
WCST	Wisconsin Card Sorting Task

Publications associated with this thesis

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Chapter 1

Introduction

1.1 Range of non-motor features of Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor phenotype of tremor, rigidity, bradykinesia and gait disturbance. However, an increasing number of non-motor symptoms (NMS) have been recognised to be of clinical importance. These include autonomic dysfunction (gastrointestinal, genitourinary, cardiovascular, pupillomotor, thermoregulatory and sexual), sleep disturbance (daytime hypersomnolence, nocturnal insomnia, vivid dreaming, and REM sleep behavioural disorder), neuropsychiatric complications (cognitive impairment, depression, anxiety, apathy, impulse control disorders and dopamine dysregulation, visual hallucinations [VH] and delusional thought disorder), pain and fatigue. NMS in PD are often under-recognized by treating physicians yet have significant impact on disability and health-related quality of life, particularly in advanced disease (Chaudhuri et al., 2006).

1.1.2 Determinants of quality of life in Parkinson's disease

Several clinical determinants of Health-Related Quality of Life (Hr-QOL) in PD have been evaluated. Whilst it is clear that severity of motor symptoms and their treatment are important predictors of Hr-QoL scores in PD (Global Parkinson's Disease Survey Steering Committee, 2002, Slawek et al., 2005), these factors may only explain a small proportion of Hr-QoL scores. Motor fluctuations (end of dose wearing-off, unpredictable "off" periods, morning akinesia, biphasic dyskinesia) (Chapuis et al., 2005), peak-dose dyskinesias (Chapuis et al., 2005, Pechevis et al., 2005), postural instability and falls (Michalowska et al., 2005), freezing of gait (Kuopio et al., 2000),

bradykinesia, limb rigidity, abnormal posture, impaired speech (Gomez-Esteban et al., 2007), and dysphagia (Miller et al., 2006) are all associated with reduced Hr-QOL. However, non-motor features, in particular depression (Schrag, 2006), but also cognitive impairment (Weintraub et al., 2004), fatigue (Yoshii et al., 2006, Martinez-Martin et al., 2006), sexual dysfunction (Bronner et al., 2004, Moore et al., 2002), sweating dysfunction (hypo/hyperhidrosis) (Swinn et al., 2003), sleep quality (Scaravilli et al., 2003), excessive daytime somnolence (Weintraub et al., 2004), bladder and bowel problems (Sakakibara et al., 2001), and weight loss (Kashihara, 2006) also contribute to reduced Hr-QOL in PD. In addition, patient rather than disease related features such as psychological adjustment to the disease (Suzukamo et al., 2006), poor patient education (Shimbo et al., 2004), and perception of how the diagnosis was told (Global Parkinson's Disease Survey Steering Committee, 2002) play an important role in patients self-rated Hr-QoL. Whilst studies differ in their methodology, multiple regression studies analysing the relative impact of different parameters on Hr-QOL in PD (Hobson et al., 1999, Global Parkinson's Disease Survey Steering Committee, 2002, Slawek et al., 2005, Chapuis et al., 2005, Kuopio et al., 2000, Gomez-Esteban et al., 2007, Weintraub et al., 2004, Karlsen et al., 1999, Schrag et al., 2000, Carod-Artal et al., 2007) have consistently demonstrated depression and disability as the major non-motor determinants of Hr-QOL in PD. Therefore clinical studies and drug trials in PD that typically use motor function as the primary outcome measure are unlikely to determine the effect on all non-motor aspects of disease or the overall impact on Hr-QOL, particularly in subjects where non-motor features predominate.

1.2 Assessment of non-motor features of Parkinson's disease

Research on effective treatment for PD has traditionally concentrated on motor control through replacement of nigrostriatal dopamine depletion (Lang & Obeso, 2004).

Currently motor function on the Unified Parkinson's Disease Rating Scale (UPDRS) Motor Score (Fahn et al., 1987) is the main outcome measure to determine efficacy of pharmacological agents as monotherapy in early PD, often supplemented by UPDRS activities of daily living (ADL) score, the Hoehn and Yahr staging system, the Schwab and England disability scale, assessment of time to adjunctive levodopa use, latency to development of motor complications and clinical global impression (CGI) indices (Wheatley et al., 2002). In addition, functional imaging of the dopaminergic system has been used as a potential marker of neuroprotection for pharmacological agents in early PD ([18]-fluorodopa positron emission tomography with ropinirole (Whone et al., 2003) and [123]-I β-CIT and single photon emission computer tomography with pramipexole, Parkinson Study Group, 2000). For adjunctive treatment in more advanced PD with motor fluctuations, reduction in "off" period (determined from patient diaries) is the most commonly used outcome measure. Other outcome measures in advanced disease, depending of the aim of the study and the population studied include the UPDRS motor score, UPDRS ADL score, L-dopa dose reduction, dyskinesia rating scales, CGI indices and health economic evaluations (Wheatley et al., 2002). In recent years, these observer-rated outcome measures have been supplemented by patient-rated health status scales, which are increasingly incorporated into clinical trials (Den Oudsten et al., 2007). They have the advantage of including the patients' perspective into the evaluation of newly available treatments, and incorporate multiple aspects of the disease for the patient's well-being, including motor and non-motor symptoms, adverse effects, overall disability and the importance in patients overall evaluation of their lives. In addition, there has also been more emphasis given to specifically measuring non-motor aspects of PD and scales for NMS are increasingly being used as primary or secondary outcome measures in clinical trial designs. This has involved revision of existing scales that measure overall motor and non-motor aspects of PD (for example, the UPDRS)

with more emphasis given to non-motor features of the disease, validation of existing non-motor symptom scales developed and used in other neurological and non-neurological disorders in PD and the development of PD specific non motor scales. For example, a substantial revision of the UPDRS (Movement Disorder Society [MDS] sponsored revision of UPDRS, MDS-UPDRS) has been developed and undergone validation (Goetz et al., 2007; Goetz et al., 2008), with additional emphasis on non-motor aspects of the disease that were not included in the original scale. Also, a specific non-motor scale, the Non-Motor Symptom Scale (NMSS) has been developed (Chaudhuri et al., 2006b) which contains nine dimensions covering the range of non-motor features found in PD; cardiovascular, sleep/fatigue, mood/cognition, perceptual problems, attention/memory, gastrointestinal, urinary, sexual function, and miscellaneous symptoms. Other groups have developed specific non-motor scales in PD, for example the Scales in Outcome of Parkinson's group (SCOPA) have validated scales for cognition (SCOPA-COG), autonomic function (SCOPA-AUT) and sleep (SCOPA-sleep).

1.2.1 Movement Disorder Society revision of UPDRS

The UPDRS has been the main outcome measure in clinical and pharmacological studies in PD and consists of four sections; Part I - mood, behaviour and mentation, Part II - activities of daily living, Part III - motor examination and Part IV - complications of therapy. However several criticisms of the UPDRS have been made based on limitations of scale structure and clinimetric properties, items encompassed in scale including motor and non-motor symptoms and instructions provided to facilitate scale administration and consistent scoring. The MDS sponsored a critique of the original UPDRS and an international task force was formed to develop and perform clinimetric testing of a novel scale (MDS-UPDRS) [Goetz et al., 2007]. Criticisms of the original

scale include: (1) Irregular placement of non-motor features throughout the UPDRS parts; mood, apathy and cognition in Part I; pain in Part II; and sleep and autonomic dysfunction in Part IV. The MDS-UPDRS retains the original four part structure however all non-motor items are included together in Part I (Non-motor experiences of daily living). These features are further subdivided into complex neuropsychiatric symptoms that require physician evaluation (cognition, psychosis, depression, anxiety, apathy and dopamine dysregulation), and other non-motor experiences which can be quantified using a patient questionnaire (sleep, staying awake during the daytime, pain and abnormal sensory sensations, urinary function, constipation, light-headedness on standing, and fatigue); (2) Structural inconsistencies in the UPDRS were identified, for example a combination of multiple item responses and yes/no answers are employed, and a given numeric answer did not always reflect same level of disability across scale items. In the MDS-UPDRS a consistent structure has been proposed throughout; all items scored 0 to 4 (normal, slight, mild, moderate, or severe), reflecting the impact of intensity and frequency of symptoms on everyday functioning; (3) Several important non-motor features are not included in the UPDRS and have been included in the revised version: anxious mood, impulse control disorders (ICD) and dopamine dysregulation syndrome (DDS), urinary problems, constipation problems, and impact on hobbies and other activities; (4) The UPDRS has particular emphasis on severe disability and is therefore unable to differentiate mild gradations in symptom severity, particularly in early disease. The MDS-UPDRS has more emphasis on rating mild disability or impairment, to reduce the liability to statistical floor effects; (5) The UPDRS was first published in book format, instructions for use were never readily available, and several items are ambiguous or are phrased in an unclear manner. To address these issues, the MDS-UPDRS will include instructions that guide raters on the overall scale, each section, and individual items with a short explanation for each

response that describes the exact criteria for that response. An effort was made to avoid medical jargon and the MDS-UPDRS questionnaire was reviewed for clarity by non-physicians, including patients and their carers. In order to ensure uniformity among raters, a MDS-UPDRS formal teaching tape and certification programme will be available and the scale will be translated into a range of different languages; (6) an MDS-UPDRS appendix of suggested and recommended clinical scales will be provided, which will be available online and continuously updated, to allow more in depth measurement of the motor and non-motor symptoms identified (Goetz et al., 2008).

1.3 Neuropathology of non-motor features of Parkinson's disease

The classical motor features of idiopathic PD result from depletion of dopaminergic neurons in the substantia nigra pars compacta. The pathogenesis of PD is complex and postulated mechanisms include involvement of ubiquitin proteasome system, mitochondrial dysfunction, oxidative stress and free radical mediated neuronal damage, excitotoxic cell damage, oligodendrocytic interaction and nerve trophic factor depletion (Olanow, 2007). Pathologically, PD is characterized the presence of ubiquitinated inclusions, Lewy bodies (LB) and Lewy neurites, which can also occur at a number at a number of extra-nigral locations and involve non-dopaminergic neurotransmitter systems (Braak et al., 2006). The exact role of LB in the pathogenesis of PD, whether toxic, neuroprotective or an epiphenomenon, remains unclear. Over 70 molecular constituents have been identified in LB, including alpha-synuclein, microtubule-associated proteins, cell cycle proteins, kinases and components of the ubiquitin proteasome system (Wakabayashi et al., 2007). However, alpha-synuclein has received closest attention and immunohistochemistry to alpha-synuclein has become an integral part of the neuropathological diagnosis of PD (Dickson et al., 2009). Evidence for a role for alpha-synuclein has been suggested by an association of synuclein gene (SNCA)

mutations or dysregulation of wild type SNCA gene expression (for example multiplications, Ross et al., 2008) with Parkinsonism. Potential mechanisms of alpha-synuclein-related toxicity include an effect on calcium homeostasis, cytoskeletal effects (including phosphorylation of tau), influence on lysosomal and mitochondrial function, including mitochondrial complex activity, mitochondrial lysis and fusion, and mitochondrial autophagy (mitophagy) (Vekrellis et al., 2011). LB are characteristically found in PD and related disorders, Dementia with Lewy Bodies (DLB) and Multisystem Atrophy (MSA). However LB pathology is not unique to these disorders and can occur in several other degenerative neurological conditions including Neurodegeneration with Brain Iron Accumulation (NBIA, Sneider et al., 2012), Subacute Sclerosing Panencephalitis (SSPE, Gibb et al., 1990), and Alzheimer's disease. Therefore LB may represent a non-specific downstream process, encountered in different neurodegenerative disorders. In addition, autopsy studies have demonstrated a high burden of incidental LB pathology in some elderly individuals with no clinical evidence of an extrapyramidal disorder (Lees, 2009). Also, in certain subtypes of genetic Parkinsonism, for example autosomal recessive juvenile Parkinsonism, LB pathology may not be found, demonstrating that degeneration of dopaminergic neurons and Parkinsonian phenotype can occur in absence of LB. In PD the presence of extra-nigral LB is not always associated with neuronal loss (Lees, 2009). However post-mortem studies have demonstrated a correlation between cortical Lewy body counts and some non-motor features, including cognitive impairment (Mattila et al., 2000) and visual hallucinations (Harding et al., 2002).

1.3.1 Braak staging hypothesis

Autopsy studies of the topographic distribution of α-synuclein pathology provide important insights into neuroanatomical correlates of NMS in PD and their temporal

relationship to onset of motor symptomatology. Braak and colleagues have proposed a sequential staging of LB pathology in PD (Braak et al., 2006). Stage 1 involves the anterior olfactory structures and dorsal motor nucleus of the vagus (DMV) in the lower medulla. Involvement of the olfactory bulb and vagal nucleus have been proposed as pathological correlates for olfactory impairment and autonomic dysfunction (particularly gastrointestinal) respectively, which occur commonly in early PD and during the pre-motor phase of the disease. Stage 2 involves LB deposition in a number of brainstem nuclei including the locus coeruleus, lower raphe nuclei and reticular formation but confined to the medulla and pontine tegmentum. These pathological changes have been implicated in the development of REM sleep behavioural disorder (RBD) and mood disorders in early PD. According to this hypothesis, it is only during stages 3 to 4 that LB appear in the substantia nigra, and motor symptoms become a prominent feature of the disease. In more advanced disease (stages 5 to 6) diffuse deposition of LB in neocortical structures occur and this is proposed to account for the cognitive, behavioural and neuropsychiatric features that are encountered particularly in advanced disease. However, methodological aspects of the detailed pathological study by Braak have been criticised. In particular, post-mortem cases that were included in the study were selected by the presence of LB in the dorsal motor nucleus of vagus and in patients in whom LB were present in the substantia nigra but absent DMV were excluded. This selection bias makes it difficult to make the assertion that pathology begins in the medulla, if cases without DMV involvement are excluded. In addition, the Braak hypothesis has been independently examined by pathologists at other research centres, and this staging scheme does not apply to all patients. For example, a study by Halliday and colleagues identified three clinicopathological phenotypes in PD; (1) a malignant syndrome characterised by early dementia and severe neocortical LB involvement at an early stage, consistent with DLB, (2) younger onset patients with a

more typical clinical PD course and slow progression of LB pathology in a distribution compatible with the Braak staging system and (3) an older onset group, with shorter survival, higher LB loads and more frequent co-existing (for example tau) neuropathology (Halliday et al., 2008). In another study, Kalaitzakis and others examined 71 autopsy specimens (Kalaitzakis et al., 2008) with PD. The substantia nigra and nucleus basalis of Meynert were most commonly affected (100% and 98.5% respectively) and in 53% of cases the pattern of LB pathology was consistent with Braak staging, whereas in the remaining 47% this pattern was not evident and in 7% there were no alpha-synuclein inclusions in the DMV. In another study (Attems and Jellinger, 2008) 18.3% did not conform to the Braak distribution and in 8.3% there was no LB pathology in the DMV despite higher brainstem and cortical involvement. These studies suggest that the caudal to rostral spread of LB pathology, according to Braak, does occur in a significant proportion of PD patients but other patterns can be found, including neocortical involvement in early disease. The exact role of LB in the pathogenesis of PD is not completely elucidated, however these studies demonstrate that pathology in PD is not confined to the substantia nigra or dopaminergic neurotransmitter systems, with widespread brainstem, limbic and cortical involvement and this may be basis for the diverse non-motor phenotype of the disease.

1.4 Early non-motor features of Parkinson's disease

1.4.1 Sleep disorders

REM sleep behavioural disorder (RBD) is a parasomnia commonly occurring in PD and characterized by dream enactment and loss of muscle atony during REM sleep. Insights into the pathophysiology of RBD have been gained from brainstem structural lesions in humans, post-mortem autopsy studies and animal models. RBD has been described in case reports in association with demyelination of the dorsal pontine tegmentum,

ischaemic pontine lesions, ponto-mesencephalic cavernoma and brainstem neurinoma (Boeve et al., 2007). Incidental brainstem LB pathology has been demonstrated in an autopsied case of idiopathic RBD (iRBD) (Uchiyama et al., 1995). Proposed anatomical loci of RBD in humans, extrapolated from animal models, include the pre-coeruleus, sublaterodorsal nucleus and lateral pontine tegmentum (Boeve et al., 2007). These topographical locations correspond to brainstem regions that are involved before the development of striatal LB pathology (stages 1 to 2) according to the Braak hypothesis. This may provide an explanation for the high prevalence of RBD in PD and its occurrence prior to motor impairment.

There have been a number of epidemiological studies showing an association between RBD and the development of PD or other neurodegenerative disorders. For example, in one study of 44 patients presenting to a sleep centre with iRBD confirmed by polysomnography, 20 (45%) subsequently developed a neurodegenerative disorder (PD in nine, DLB in six, and MSA in one) at a mean 11.5 years after symptom onset and 5.1 years after formal diagnosis of RBD (Iranzo et al., 2006). In a second study, 57% of patients presenting to a sleep clinic with RBD had an underlying neurological disorder, and of those with PD, 52% had symptoms of RBD preceding the development of motor symptoms (Olson et al., 2000).

Several imaging studies in iRBD have demonstrated early pre-motor basal ganglia changes. An imaging study assessing pre-synaptic dopamine transporter (DAT) using [123]IPT single photon emission computer tomography (SPECT) has revealed significantly reduced striatal uptake in iRBD patients compared with controls, but less than in symptomatic PD (Eisensehr et al., 2000). [13C]dihydrotetrabenazine positron emission tomography (PET) in patients with iRBD has demonstrated reduced binding in all striatal nuclei, particularly the posterior putamen (Albin et al., 2000), and a cerebral

perfusion study (99m-Tc ethylene cysteinate dimer, [ECD] SPECT) in iRBD has shown increased perfusion bilaterally in the pons and putamen with reduced perfusion of the frontal and temporo-parietal cortices, a metabolic picture consistent with that found in idiopathic PD (Mazza et al., 2006).

These studies suggest that there is a predisposition to future development of PD in patients with iRBD and that early striatal and cortical metabolic changes may already be present, even years before the appearance of motor symptoms or clinical presentation of PD. Other disorders of sleep may also predict subsequent development of PD. A large population-based study (Honolulu-Asia Aging Study, n = 3078) revealed that daytime excessive somnolence was a risk factor (odds ratio [OR] 2.8, p = 0.014) for development of PD (Abbott et al., 2005).

1.4.2 Neuropsychiatric illness and cognitive impairment

LB deposition occurs in brainstem loci implicated in affective disorders, such as the noradrenergic locus coeruleus and serotoninergic dorsal raphe nuclei, and this can precede basal midbrain involvement. This may explain the high prevalence of depression in early PD, often preceding the development of motor symptoms (Shiba et al., 2000). In a recent systematic review of psychiatric illness preceding motor symptoms in PD (Ishihara & Brayne, 2006), two cohort studies, one nested case-control (NCC) study and six case-control studies were identified for depression and PD. Five of six case-control studies, both cohort studies and the NCC showed a statistically significant association between a history of depression and subsequent development of PD. These studies included a large retrospective cohort study (NCC, N = 105 416) (Leentjens et al., 2003) using a general practice based register which found that at diagnosis of PD, 9.2% of patients had a history of depression compared with 4.0% of controls (odds ratio 2.4, 95% confidence interval [CI] 2.1 to 2.7).

The retrospective cohort study by Schuurman and colleagues found that compared with controls, depressed subjects had a relative risk of 3.13 (95% CI 1.95 to 5.01) of subsequently developing PD (Schuurman et al., 2002). Meanwhile, a similar study to assess the likelihood of developing PD found that depressed subjects had a relative risk of 2.20 (95% CI 1.70 to 2.84) and 2.24 (95% CI 1.72 to 2.93) compared with a diabetes cohort and osteoarthritis cohort respectively (Nilsson et al., 2001). A case-control study has identified increased prevalence of pre-morbid anxiety disorders in PD compared with controls (Shiba et al., 2000), and in a large prospective study (n = 35 815) using the Crown-Crisp phobic anxiety index there was an increased risk of developing PD (RR 1.5, 95% CI 1.0 to 2.1) in those with highest level of anxiety at baseline (Weisskopf et al., 2003).

Therefore, depression and anxiety may be predictive of future development of PD. Several functional imaging studies in PD have demonstrated signal change in the brainstem (corresponding to loci of early LB deposition), which correlate with clinimetric indices of mood. For example, in a study using 123I-βCIT SPECT, dorsal midbrain binding reflecting serotoninergic function, was significantly correlated with UPDRS mood and mentation scores but not motor function (Murai et al., 2001). Additionally, trans-cranial sonography (TCS) has shown hypo-echogenicity of the dorsal raphe in PD patients in whom depression preceded motor symptoms (Walter et al., 2007). These imaging studies suggest that degeneration of serotoninergic and noradrenergic brainstem nuclei can occur in parallel or precede substantia nigra degeneration leading to affective disorders in the early and pre-motor phase of PD.

Development of dementia is common in PD, particularly in the later stages. However, a number of studies using detailed neuropsychological assessments, including tests sensitive to frontal lobe function, have revealed that cognitive impairment, particularly

dysexecutive, can occur early in PD (Lees & Smith, 1983). PD dementia (PDD) and DLB are distinguished by whether dementia occurs within one year of onset of motor symptoms, but this is perhaps an arbitrary distinction given the common neuropathology (α-synuclein containing LB deposition) and overlapping non-motor symptomatology of the two diseases. Imaging studies in PD have revealed that disruption of frontal-striatal dopaminergic connections can occur early in PD and is associated with abnormalities in frontal executive cognitive function. In a study using [18F] fluorodopa PET in patients with early PD (mean disease duration 1.3 years) fluorodopa uptake was, as expected, decreased in the striatum compared with controls (Brück et al., 2005). However, in PD there was also increased cortical fluorodopa activity and uptake in the right dorsolateral prefrontal cortex (DLPFC) which was correlated with tests of sustained attention (vigilance test) and increased uptake in the medial frontal and anterior cingulate cortices which was negatively correlated with the Stroop test. In a functional magnetic resonance imaging (fMRI) study, comparing PD patients with and without selective executive impairment (Lewis et al., 2003), significantly more hypoactivation in the DLPFC, ventrolateral PFC and putamen during working memory testing was demonstrated in the executively impaired group. These cognitive changes may in part be L-dopa responsive given their associated with striatal changes on functional imaging, the association of cognitive and attentional deficits with 'on'/ 'off' motor fluctuations in some patients, and evidence of exacerbation of executive dysfunction secondary to L-dopa withdrawal in some studies (Lange et al., 1993). While there has been no systematic analysis of cognitive impairment in patients with PD susceptibility in the pre-motor phase, the association of cognitive impairment with striatal dopamine depletion and impairment of striato-frontal cortical projections, suggests executive function may be an early pre-motor feature of PD.

1.4.3 Olfaction

Several epidemiological studies have suggested that impaired olfaction is an early marker of idiopathic PD. In the Honolulu-Asia Aging Study, 2267 participants had olfactory testing at baseline and those in the lowest quartile of olfaction had a significantly increased age-adjusted risk of subsequently developing PD (OR 5.2, 95% CI 1.5 to 25.6) compared with the top two quartiles (Ross et al., 2008). In a two-year longitudinal study of first-degree relatives of patients with PD, olfactory testing was used to select normosmic and hyposmic individuals who then underwent DAT SPECT (Ponsen et al., 2004). At two years, 10% of the hyposmic group who had shown markedly reduced DAT binding on SPECT imaging at baseline had developed clinical PD. In the remainder of the hyposmic group, despite no clinical evidence of parkinsonism, DAT binding had decreased more than normosmic controls. In a further study of 30 subjects with idiopathic hyposmia, 11 demonstrated hyper-echogenicity of the substantia nigra on transcranial sonography (a potential diagnostic tool for early dopamine depletion in PD), yet the majority had no motor features or signs suggestive of PD. Despite this, DAT SPECT was abnormal in five and had borderline binding ratios in two (Sommer et al., 2004), suggestive of possible pre-motor PD.

The University of Pennsylvania Smell Identification Test (UPSIT), a 40-item odour identification test, has been extensively studied in PD. In a study of early PD (mean Hoehn and Yahr stage 1.4), a strong correlation between UPSIT scores and DAT SPECT imaging indices in the striatum as a whole (regression coefficient 0.66, $p = 0.001$), and particularly the putamen (0.74, $p < 0.001$) (Siderowf et al., 2005) was demonstrated. Extrapolation of these findings into the pre-motor phase of PD is consistent with epidemiological studies of smell loss antecedent to clinical PD, and is supported by the topographical distribution of LB in anterior olfactory structures in

autopsy studies of early PD, and suggests a potential role of smell testing in the early diagnosis of PD.

The use of self-administered smell identification kits (such as UPSIT) in the diagnosis of early or pre-motor PD, to differentiate PD from other extrapyramidal disorders, and to differentiate tremor-dominant PD from essential tremor has undergone extensive research. For example, olfactory function has been used to distinguish vascular parkinsonism (diagnosis based on localization of MRI lesions and vascular risk factors) and idiopathic PD (Katzenschlager et al., 2004). UPSIT scores were significantly lower in PD than in both vascular parkinsonism and controls. In a study where olfaction in PD was compared with atypical parkinsonian syndromes (Wenning et al., 1995), UPSIT scores were normal in progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) compared with controls, and there was only mild impairment in MSA. However, UPSIT scores were markedly reduced in the PD group and demonstrated good sensitivity (77%) and specificity (85%) in differentiating PD from atypical parkinsonism. Smell testing can be used to differentiate essential tremor and tremor-dominant PD, particularly in the early stages when other akinetic-rigid extrapyramidal features are not present (Ondo & Lai, 2005).

Methods of smell testing include smell identification (such as the UPSIT), threshold detection, smell discrimination and odour memory (Hawkes, 2003). Olfactory identification tests may have reduced diagnostic utility in those with cognitive impairment or depression, features which can occur commonly in early PD. Additionally, local nasal disease should be actively sought (tests do not discriminate between conductive and sensorineural olfactory loss), as should lifestyle factors such as smoking history. Olfactory loss also occurs in the context of other neurodegenerative disorders such as Alzheimer's disease (Hawkes, 2003). Nonetheless, given these

caveats, olfactory testing may provide an important screening tool in PD to allow risk stratification in combination with other pre-motor symptoms and direct use of diagnostic imaging (DAT SPECT scanning, transcranial sonography).

1.4.4 Autonomic dysfunction

Early and prominent autonomic dysfunction in the context of an akinetic-rigid syndrome (particularly if pyramidal or cerebellar features are also present) raises the possibility of MSA. However, autonomic features occur commonly in PD and often predate the onset of motor features. Epidemiological evidence suggests that constipation in particular may be an early pre-motor feature of PD. In the Honolulu Heart Program, 6790 subjects were questioned about their bowel habits and in a 24-year follow-up period fewer than one bowel movement per day was associated with greater risk of developing PD (Relative Risk 4.1, 95% CI 1.7 to 9.6, $p = 0.001$) compared with those whose bowels were opened twice per day (Abbott et al., 2001). In a retrospective study, 44.6% of respondents described onset of constipation preceding motor symptoms with a mean latency of 18.7 years (Ueki & Otsuka, 2004).

Sexual dysfunction is common in PD and includes difficulties with sexual arousal, reduced libido, erectile dysfunction, and anorgasmia (Bronner et al., 2005). In a large retrospective epidemiological study (32,616 participants), men with erectile dysfunction had increased risk of subsequently developing PD (Relative Risk 3.8, 95% CI 2.4 to 6.0, $p < 0.0001$) (Gao et al., 2007). In another study, 23.3% of men and 21.9% of women reported that pre-morbid sexual dysfunction contributed to cessation of sexual activity following diagnosis of PD (Bronner et al., 2004).

Orthostatic hypotension is common in PD, particularly in later disease, and can be a consequence of dopaminergic medication. However, in a study of patients with a

clinical diagnosis of PD, in whom MSA had been excluded using imaging of myocardial sympathetic function (cardiac [18F]-fluorodopa SPECT), orthostatic hypotension was of early onset (within 1 year of onset of motor symptoms) in 60% and in 13% preceded motor involvement (Goldstein, 2006). Autopsy examinations have revealed early involvement (LB deposition) of central (medulla oblongata) and peripheral (sympathetic and parasympathetic) neurons that control autonomic function in PD, which may represent a pathological basis for early autonomic symptoms (Braak et al., 2007).

1.4.5 Sensory disturbance and pain syndromes

Pain is a common and often early feature of PD. An autopsy study has demonstrated immunoreactive α-synuclein inclusion bodies in the spinal cord lamina I neurons in PD and these changes can occur early in the disease (Braak et al., 2007). These neurons are important in transmission of painful sensations and may represent a pathological basis for this pre-motor symptom. In addition, the emerging increase in tone that denotes substantia nigra par compacta cell loss often leads to pain, typically presenting as a 'frozen shoulder'.

1.5 Neuropsychiatric features of Parkinson's disease

1.5.1 Visual hallucinations

1.5.1.1 Epidemiology of visual hallucinations

VH are common in PD and can involve extracampine hallucinations (illusions of presence and passage), illusional misinterpretations and formed VH with or without retained insight. Cross-sectional estimates of VH prevalence in PD range from 16-75 percent (Goetz et al., 2009), with higher prevalence in studies using sensitive screening

questionnaires or structured psychiatric assessments (Williams et al., 2008). Lifetime prevalence of VH was a 50% in a large retrospective autopsy study in pathologically proven PD (445 patients) (Williams & Lees, 2005). The occurrence of VH may predict progression to more severe forms of psychosis including loss of insight and delusions, increased risk of nursing home placement and development of dementia (Fenelon and Alves, 2010). VH in PD have been associated with older age and longer disease duration (Fenelon and Alves, 2010, Papapetropoulos et al., 2005, Sanchez-Ramos et al., 1996) and greater disease severity (Holroyd et al., 2001, Papapetropoulos et al., 2005). The role of dopaminergic medication in development VH is unclear. A majority of cross-sectional studies have shown no clear association between L-dopa and development of VH (Aarsland et al., 1999, Fenelon et al., 2000, Holroyd et al., 2001, Merins et al., 2004, Papapetropoulos et al., 2005, Williams et al., 2005, Benbir et al., 2006, Fenelon and Alves, 2010). However in a large community based 12 year prospective study, development of VH was associated with higher L-dopa-equivalent doses at baseline (Forsaa et al., 2010). There is also stronger evidence for a positive association with dopamine agonist use than with levodopa preparations (Rascol et al, 2000; Holloway et al, 2004; Onofrj et al., 2006, Stowe et al., 2008, Baker et al., 2009, Williams et al., 2005). Anti-cholinergic drug use has been implicated in development and exacerbation of VH but this association has not been clearly confirmed in clinical studies (Williams et al., 2005, Benbir et al., 2006). Some studies have shown an association of VH with co-existing psychiatric disorders, including depression (Sanchez-Ramos et al., 1996, Holroyd et al., 2001, Marsh et al., 2004) and apathy (Reijnders et al., 2009, Mosimann et al. 2006); however results are inconsistent and when other factors are considered, co-existing psychiatric comorbidity appears less important (Fenelon et al., 2000). Autonomic dysfunction has also been associated with the presence of VH in PD (Kitayama et al., 2008, Oka et al., 2007, Williams and Lees,

2005). VH have been associated with cardiac sympathetic denervation on [123]-metaiodobenzylguanidine (MIBG) imaging (Kitayama et al., 2008, Oka et al., 2007) and with greater fall in systolic blood pressure and impaired norepinephrine response during tilt table testing (Oka et al., 2007).

1.5.1.2 Diagnosis and assessment

Psychotic features found in PD differ from those encountered in primary psychiatric conditions and other neurological disorders, for example visual illusions and hallucinations predominate whereas delusions and hallucinations in other modalities, such as auditory hallucinations, are less common. A number of rating scales are available to assess psychotic symptoms and many of these have been applied in PD. However the majority of scales were developed in general psychiatry populations and have not been validated specifically in PD and do not cover the range of psychotic features in PD. In a review of available rating scales, The Neuropsychiatric Inventory (NPI), Brief Psychiatric Rating Scale (BPRS), Positive and Negative Symptom Scale (PANSS) and the Schedule for Assessment of Positive Symptoms have been recommended as these scales have been applied in PD, have been used in studies other than by the original authors and have undergone successful clinimetric testing (Goetz, 2009). However, none of these scales has been validated in PD or cover the entire spectrum of PD psychosis. This highlights the importance of developing specific, well validated psychosis scales in PD.

Formal diagnostic criteria for psychosis in PD have been proposed (Ravina et al., 2007). These criteria include (1) presence of at least one characteristic symptom, including visual illusions, false sense of presence, hallucinations or delusions; (2) primary diagnosis of PD according to UK Brain Bank criteria; (3) symptoms occurring after the onset of PD; (4) symptoms that are recurrent or continuous for more than one month

and (5) exclusion of other causes, for example other causes of Parkinsonism such as DLB, psychiatric disorders such as schizophrenia, schizoaffective disorder, delusional disorder, or mood disorder with psychotic features, or a general medical condition including delirium (Ravina et al., 2007).

1.5.1.3 Pathophysiology

The exact aetiology of VH in PD is unknown but several factors have been implicated in the aetiopathogenesis in clinical, polysomnographic, functional imaging and histopathological studies. On the basis of these, attempts have been made to formulate an integrated model based on an imbalance of external and internal inputs (Diederich et al., 2005, Diederich et al., 2009, Goetz et al., 2009). This includes (a) impaired visual input and central visual processing through aberrant activation of primary and associative visual cortices, (b) impaired brainstem regulation of the sleep-wake cycle with fluctuating vigilance, intrusion of REM dream imagery into wakefulness and emergence of internally generated imagery, (c) cognitive dysfunction and (d) influence of dopaminergic drugs on mesolimbic and visual processing pathways (Goetz et al., 2009).

1.5.1.3.1 Visual input and central visual processing

Impaired visual input in PD can result from disease-related pathophysiological changes such as retinal dysfunction, diminished visual acuity, reduced contrast sensitivity, colour discrimination and motion perception, and impairment of central visual processing pathways (Archibald et al., 2009), or coexisting, particularly age-related, ophthalmic factors or environmental considerations such as poor luminance. Evidence for abnormal retinal processing in PD includes reduced visual acuity, delayed visual evoked potentials and abnormal pattern electroretinograms (Nightingale et al., 1986),

and decreased colour discrimination and contrast sensitivity (Pieri et al., 2000), and these ophthalmic factors have been reported to be associated with VH in PD (Matsui et al., 2006, Holroyd et al., 2001, Diederich et al., 1998, Matsui et al., 2005). VH in PD have also been associated with ophthalmological disease such as cataracts (Matsui et al., 2004) and retinitis pigmentosa (Hermanowicz, 2002) in a Charles Bonnet-type phenomenon (Schadlu et al., 2009).

Visual inputs project to multiple cortical areas specialized for different visual attributes (Zeki et al., 1991). The temporal lobe, particularly parahippocampal and entorhinal cortices and amygdala are thought to be important processing centres of the ventral visual processing stream (identification and discrimination) (Papapetropoulos, 2006a) and are involved in emotional visual processing (Morris et al., 2001). There is evidence of abnormal cortical visual processing in PD patients with VH from clinical, imaging and pathological studies: Neuropsychological studies of visuoperceptive function in PD patients with VH have demonstrated significantly slower image recognition (Meppelink et al., 2008), worse facial recognition and visual form discrimination (Ramirez-Ruiz et al., 2006, Ramirez-Ruiz et al., 2007) and abnormalities in subsets of the Visual Object Space Perception battery (Barnes et al., 2003). fMRI (Holroyd and Wooten, 2006, Meppelink et al., 2009), PET (Boecker et al., 2007), SPECT (Oishi et al., 2005) and MRI voxel based morphometry studies (Ramirez-Ruiz et al., 2007b) have also demonstrated abnormalities in areas involved in visual processing, and pathological studies have demonstrated high density of LB in the amygdala and temporal lobes, including parahippocampal cortex, in association with VH in LB disorders (Harding et al., 2002a, Kalaitzakis et al., 2009, Papapetropoulos et al., 2006). In addition significantly higher LB burden has been demonstrated in frontal, temporal and parietal cortices (Papapetropoulos et al., 2006).

1.5.1.3.2 Impairment of the brainstem-regulated sleep-wake cycle

It has been hypothesized that altered visual input is counterbalanced by increased internal inputs resulting from impaired regulation of the brainstem sleep-wake cycle and intrusion of episodes of REM sleep during wakefulness (Diederich et al., 2005, Goetz et al., 2009). Clinical studies have demonstrated that RBD is more frequent among PD patients with VH than without (Benbir et al., 2006, Pacchetti et al., 2005, Sinforiani et al., 2008, Onofrj et al., 2006), and daytime somnolence has been shown to be an independent predictor of VH in PD (Fenelon et al., 2000). In longitudinal studies, RBD has been associated with subsequent development of VH (Sinforiani et al., 2008, Onofrj et al., 2006, Onofrj et al., 2002). Polysomnography (PSG) studies in PD patients with VH have demonstrated significantly greater REM sleep aberration (Comella et al., 1993, Manni et al., 2002), significantly increased stage 1 REM sleep with tonic electromyogram (neurophysiological correlate of RBD) with these periods corresponding to occurrence of nocturnal hallucinations in most patients (Nomura et al., 2003) and increased sleep onset REM periods (SOREMP) on multiple sleep latency testing (MSLT), with dream content during MSLT similar to regular hallucinations (Nomura et al., 2003). It has been suggested that VH in PD resemble hypnogogic hallucinations in narcolepsy (Nomura et al., 2003). A narcolepsy type phenotype with reduced sleep latency and high frequency of SOREMP (Arnulf et al., 2002) has been demonstrated in PD patients referred for excessive sleepiness. Furthermore, in a study using wrist-worn actigraphy, subjects with VH demonstrated significantly altered rest-activity rhythms and unpredictable circadian patterns (Whitehead et al., 2008), implicating disruption of the brainstem-regulated sleep-wake cycle.

1.5.1.3.3 Cognitive Function

Global cognitive impairment and dementia have been consistently associated with VH in PD (Papapetropoulos et al., 2005, Merims et al., 2004, Fenelon and Alves, 2010, Goetz et al., 2009, Holroyd et al., 2001). Abnormal visuoperception and frontal cognitive dysfunction in particular have been hypothesized to predispose to VH in PD. VH are associated with impairment of frontal sensitive tasks, for example reduced verbal fluency (Santangelo et al., 2007, Ramirez-Ruiz et al., 2006, Ozer et al., 2007, Grossi et al., 2005), Stroop duration and errors (Ozer et al., 2007) and poorer scores on Wisconsin Card Sorting Task (Sinforioni et al., 2008). Functional imaging studies have also shown frontal cortical abnormalities in association with VH in PD (Nagano-Saito et al., 2004, Ramirez-Ruiz et al., 2008) and pathological studies have demonstrated significantly increased LB pathology in frontal cortical areas (Papapetropoulos et al., 2006). It has therefore been proposed that impaired visual input and central visuoperceptive processing disinhibit release of stored visual memories resulting in VH, and that cognitive impairment, reduced vigilance and sleep-wake cycle all contribute to impairment in filtering these external and internal perceptions (Goetz et al., 2009).

1.5.1.3.4 Dopaminergic transmission in limbic and visual processing pathways

Dopamine acts as a neurotransmitter in the retina at multiple levels. Dopaminergic amacrine cells receive input from rod and possibly cone bipolar cells, dopamine has a direct effect on gap junction permeability between rods and cones and horizontal cells, and a diurnal variation of retinal dopamine has been demonstrated (Archibald et al., 2009). The mesolimbic system is a dopaminergic pathway projecting from the midbrain ventral tegmental area via the striatal nucleus accumbens to the limbic system, amygdala and prefrontal cortex (Tisch et al., 2004). Dopaminergic neurotransmission in

these areas important for visual processing is a potential target for aberrant stimulation by dopaminergic drugs and this has been implicated in the pathogenesis of VH in PD

1.5.2 Impulse control disorders

ICD are manifest as reduced ability to resist pleasurable impulses and include pathological gambling, sexual dysfunction such as hypersexualtiy and paraphilia, excessive shopping and eating, and other compulsive activities such internet use. ICD have been estimated to occur in between 3.5 to 19% of PD patients (Weintraub et al., 2010, Lee et al., 2010, Fan et al., 2009, Verbaan et al., 2009, Voon et al., 2006, Weintraub et al., 2006). ICD in PD are associated with dopaminergic medication, particularly dopamine agonist use (Ambermoon et al., 2011, Weintraub et al., 2010, Fan et al., 2009), with a possible dose relationship in some studies (Ambermoon et al., 2011, Lee et al., 2010). Early onset PD and younger age, but not disease severity, have also been implicated (Ambermoon et al., 2011). Other associations include previous history of ICD, family or personal history of substance misuse, personality traits (impulsivity, novelty and risk seeking) (Voon et al., 2011a, Voon et al. 2011b), and in some studies male sex, (Ambermoon et al., 2011), suggesting that these are predisposing factors to develop ICD on dopaminergic medications.

1.5.2.1 Pathogenesis

Striatal dopaminergic transmission has an important role in novelty seeking and reward (Wittmann et al., 2008, Balleine et al., 2007, Bodi et al., 2009) and this has been demonstrated in imaging studies assessing ventral striatal dopamine release using the dopamine D2 ligand [(11)C] raclopride. For example, increased ventral striatal dopamine release has been shown in PD patients with ICD in response to reward related

cues [Steeves et al., 2009, O'Sullivan et al., 2011] and in patients with dopamine dysregulation in relation to L-dopa use [Evans et al., 2006].

More marked dopaminergic loss has been reported in the dorsal compared to the ventral striatum in PD (Kish et al., 1988), with dopaminergic replacement therapy leading to improved motor function but tonic stimulation of less affected brain regions, including the ventral striatum, limbic system and prefrontal areas (Cilia et al., 2011). Resting over activity in these brain areas has been demonstrated in functional imaging studies in pathological gambling (PG) (Cilia et al., 2008). The effect of dopaminergic medication may be particularly important for agonists such as pramipexole and ropinirole, with greater affinity for dopamine D3 receptors, which occur at higher density in the ventral striatum and limbic system (Sokoloff et al., 1990). Dopaminergic stimulation is proposed to facilitate learning from positive feedback (reward mechanisms, thus leading to increased novelty and reward seeking behaviour) and to disrupt negative feedback (punishment learning) (Bodi et al., 2009). In addition, genetic polymorphisms in dopaminergic neurotransmission (DAT and dopamine receptor genes) have been implicated in impulse control disorders and addiction in PD and non-PD subjects (Cilia et al., 2011).

1.5.3 Depression, anxiety and apathy

1.5.3.1 Prevalence

Establishing the prevalence of disorders of mood, motivation and anxiety in PD is complicated by the symptomatic overlap between the somatic features of the neuropsychiatric and underlying movement disorder, differences in the phenomenology of these disorders in PD (dPD) and the general population, frequently coexisting cognitive problems, psychiatric side effects of dopaminergic medication, the presence of

motor and non-motor fluctuations and the different diagnostic frameworks available (eg, Diagnostic and Statistical Manual [DSM], version IV [DSM-IV], applied with or without Structured Clinical Interview for DSM disorders and clinical rating scales) (Gallagher & Schrag, 2009). Thus estimates of prevalence of neuropsychiatric disorders in PD vary considerably in published studies (e.g. 2.7-90% for depression) (Reijnders et al., 2008). However, in a large systematic review of the prevalence of depression in PD, 36 studies met criteria for inclusion and the weighted prevalence of major depressive disorder was 17%, minor depression 22%, dysthymia 13% and clinically significant depression in 35% (Reijnders et al., 2008). The prevalence of anxiety disorders in cross-sectional studies has been estimated at between 20-49% (Chen et al., 2010, Dissanayaka et al., 2010, Riedel et al., 2010, Negre et al., 2010, Pontone et al., 2009, Kulisevsky et al., 2008, Nuti et al., 2004, Stein et al., 1990), with generalised anxiety disorder, panic disorder, agoraphobia and social phobia being most common. Apathy has an estimated prevalence of up to 60% in PD (Pedersen et al., 2009, Oguru et al., 2010). It frequently co-exists with depression, cognitive impairment, particularly dysexecutive syndromes, which may impact on motivation and make primary apathetic disorders difficult to differentiate.

1.5.3.2 Pathophysiology of depression, anxiety and apathy

Endogenous (e.g. involvement of monoamine neurotransmitter systems), environmental, genetic and psychological factors (e.g. personality, psychological adjustment to disease) are likely to be important in the development of mood disorders in PD (Schrag et al., 2001). Thus, rates of depression are increased in several neurological and other chronic conditions. However, they are higher in PD and may predate the onset of motor symptoms (Shiba et al., 2000), suggesting that depression is a manifestation of PD. Several endogenous neurobiological factors are thought to underlie the development of

psychiatric features of PD. The loss of dopaminergic neurons particularly in the substantia nigra underlies the motor phenotype of the disease (tremor, rigidity, bradykinesia and gait disturbance). However, the epidemiological association of PD with higher rates of depression and anxiety, the association of dopaminergic medication with improvement of mood disorders (including in non-PD subjects [Corrigan et al., 2000]) and the potential development of neuropsychiatric complications (mania, psychosis, ICD and DDS) on dopaminergic medication in some patients suggests a role of dopaminergic transmission in mood, motivation and reward (Voon et al., 2009). In a study using DAT SPECT in PD, anxiety and depression were correlated with left anterior putamen DAT availability (Weintraub et al., 2005), suggesting a role for dopaminergic pathways. This non-motor role of dopamine is also supported by experimental, pathological and functional imaging studies in neuropsychiatric disorders in non-PD subjects (Dunlop & Nemeroff, 2007). For example, post-mortem studies in depressed patients have demonstrated altered dopamine receptor gene expression in the amygdala and pre-synaptic DAT downregulation suggesting deficiency in mesolimbic dopamine (Klimek et al., 2002, Xiang et al., 2008), chronic antidepressant treatment may result in altered dopamine receptor gene expression (Lammers et al., 2000; Rocc et al., 2002) and polymorphisms in genes involved in dopamine metabolism and signalling, have been implicated in major depression (Opmeer et al. 2010). In addition, dopamine receptor polymorphisms have been implicated in anxiety disorders, including Obsessive Compulsive Disorder (Light et al., 2006), and fMRI has demonstrated striatal involvement in patients with generalized social phobia (Sareen et al., 2007).

The involvement of extra-striatal and non-dopaminergic neurotransmitter systems in the disease course of PD has also become increasingly recognized (Braak et al., 2006). LB deposition in brainstem areas implicated in depression, including the serotoninergic

raphe nuclei and the noradrenergic locus coeruleus (Lowry et al., 2008; Itoi K & Sugimoto N, 2010), can precede basal midbrain involvement in PD (Braak et al., 2006). This may explain the occurrence of depression and anxiety in PD occurring during the pre-motor phase (Shiba et al., 2000). A PET study using serotonin transporter specific ligands has shown reduced caudate and putaminal serotonin transporter distribution volumes, similar to reduced striatal DAT density, reflecting loss of both serotonergic and dopaminergic innervation in PD (Kerenyi et al., 2003). In another recent PET study, depressive symptoms in PD correlated with relatively higher serotonin transporter binding in the median raphe nuclei and limbic structures, interpreted as reflecting lower extracellular serotonin levels in these areas (Politis et al., 2010). However other studies have shown no correlation between depressive symptoms and serotonin transporter availability (Strecker et al., 2011). A study using trans-cranial sonography has shown hypo-echogenicity of the dorsal raphe to be associated with onset of depression preceding motor deficit in PD (Walter et al., 2007). These studies support the involvement of serotonergic systems in depression in PD. Other studies have implicated cholinergic and noradrenergic pathways. A PET study examining cortical acetylcholinesterase activity demonstrated that depressive symptoms in PD are associated with cortical cholinergic denervation (Bohnen et al., 2007). A pathological study in PD showed involvement of catecholamine areas of the brain, particularly neuronal loss and gliosis in the noradrenergic locus coeruleus (Frisina et al., 2009) and a PET study showed reduced dopaminergic and noradrenergic innervation in the locus coeruleus and limbic system in depressed PD patients (Remy et al., 2005).

A recent literature review examining the nosological validity of dPD (Even & Weintraub, 2011), identified three potential subtypes of depression in PD, (1) nonspecific casual comorbid dPD, patients who would have developed depression even

if they didn't develop PD, (2) nonspecific reactive comorbid dPD, patients who are likely to have become depressed if they had another chronic debilitating illness, not necessarily PD and (3) specific comorbid dPD, directly related to the pathophysiology of PD.

Reduced limbic and ventral striatal dopamine has been suggested a cause of apathy in PD, and there is evidence that apathetic symptoms may be at least partially responsive to dopaminergic medication (Czernecki et al., 2008). Imaging studies have shown reduced grey matter density in several cortical areas, including inferior frontal gyrus, insula and cingulate gyrus (Reijnders et al., 2010). Apathy is closely related to cognitive impairment, and may respond to cholinesterase inhibitors (McKeith et al., 2000a; McKeith et al., 2000b), suggesting cholinergic mechanisms are also important.

1.5.3.3 Assessment of psychiatric Disorders in PD

1.5.3.3.1 Depression

Diagnostic frameworks for depression include DSM criteria for major, minor or subsyndromal depression and the International Statistical Classification of Diseases and Related Health Problems (ICD) criteria for a mild, moderate or severe depressive episode. DSM-IV-R diagnosis of major depression requires one or more of the two core criteria (depressed mood, loss of interest or pleasure), and a total of five or more symptoms including significant weight change, insomnia or hypersomnia, psychomotor retardation or agitation, fatigue, expression of worthlessness or guilt, reduced concentration or decisiveness or recurrent thoughts of death, with exclusion of symptoms attributable to medication or an underlying medical condition. However the diagnosis of depression in PD provides conceptual difficulties (Gallagher & Schrag, 2009). A National Institute of Neurological Disorders and Stroke/ National Institute of

Mental Health working group examined the use of DSM-IV in PD (Marsh et al., 2006) and suggested that use of these criteria in PD may miss up to half of patients with clinically significant depression. Several recommendations were made: (1) the diagnosis should be made using an inclusive approach to include all symptoms, irrespective of potential aetiological basis, as it has the greatest sensitivity and reliability and does not require clinical judgment; (2) subsyndromal depression should be included as a diagnostic category in research studies; (3) the timing of assessment should be specified in patients with motor fluctuations, as a significant proportion of these patients describe prominent mood fluctuations; (4) informants should be used for cognitively impaired patients; and (5) anhedonia should only be diagnosed based on loss of pleasure rather than loss of interest for diagnosis of minor depression or subsyndromal depression, as it overlaps with apathy. In a recent large study there was a significant association between the severe depression and co-morbid apathy and anxiety and it has therefore been proposed that these features, particularly psychic anxiety, be added to the DSM diagnostic criteria but this will require further clarification (Starkstein et al, 2011). Some studies (Starkstein et al, 2011) reported that all items in the DSM-IV criteria identify severe depression with high statistical significance. However, others (Leentjens et al., 2003) reported that some somatic items (psychomotor slowing, tiredness, physical anxiety) are much poorer discriminators between depressed and non-depressed PD patients than core symptoms (low mood or loss of interest) or other non-somatic symptoms (guilt, suicidal ideation and psychic anxiety). Thus, whilst somatic symptoms are an important aspect of depression, particularly at the severe end, these may be less useful in distinguishing depressed from non-depressed patients with PD.

Clinimetric rating scales are often used in large epidemiological studies and as outcome measures in therapeutic trials because they are quantifiable and do not require clinical

judgment. A systematic review of depression rating scales in PD has highlighted their diverse properties and clinical applicability (Schrag et al., 2007). Diagnosis of depression should only be made using validated clinical criteria, and where possible using structured interview, as false negatives can occur in patients with low mood and anhedonia but with few somatic symptoms and conversely, false positives can occur in the absence of low mood but with a large number of overlapping somatic symptoms in PD. Additionally, depressive symptoms in PD that present in atypical circumstances, such as in the context of motor fluctuations or dysphoric episodes in DDS, are not suitable for assessment by rating scales. Similar caveats apply to other neuropsychiatric diagnoses in PD.

1.5.3.3.2 Anxiety

DSM-IV-R categories for anxiety include panic attacks, agoraphobia, specific phobias, social phobias, obsessive compulsive disorder, post-traumatic stress disorder, acute stress disorder and general anxiety disorder. The application and clinical validity of DSM-IV-R criteria for anxiety in PD has not undergone the same in depth analysis as depression but suffers the same conceptual difficulties, particularly somatic symptom overlap, for example, DSM-IV criteria for general anxiety disorder include fatigability, impaired concentration, sleep disturbance and muscular tension, which are all very common in PD. In addition autonomic dysfunction, including cardiac, respiratory and gastro-intestinal involvement, is common in PD and these phenomena have substantial overlap with diagnostic items on anxiety criteria and rating scales. Anxiety disorders are also often co-morbid with depression in PD and can occur in the context of motor and non-motor fluctuations.

1.5.3.3.3 Apathy

There is no definition or diagnostic framework for apathy in DSM-IV. Reduced interest and motivation can occur as a component of cognitive impairment or depression, and a full neuropsychological assessment should be made to exclude apathy in the context of cognitive impairment or depression. Diagnosis has previously been made using clinical judgement or rating scales, including the NPI and the Marin Apathy Evaluation Scale. More recently the Lille Apathy Rating Scale (LARS) has been developed and validated to assess apathy in PD (Sockeel et al., 2006). Two groups have recently proposed and validated diagnostic criteria that can be applied to PD. Diagnostic items include (1) diminished motivation compared to baseline level of functioning, (2) involvement of goal-directed behaviour, cognition and emotional domains, (3) symptoms sufficiently severe to cause significant impairment of personal, social or occupational function and (4) reduced motivation not attributed to the effects of physical disability, level of consciousness or medication (Robert et al., 2009, Starkstein et al., 2009). The first group formulated consensus criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders [Robert et al., 2009] and these have been validated in PD, showing good internal consistency, concurrent validity with the LARS and the apathy section of the NPI and discriminant validity against the depression section of the NPI (Drijgers et al., 2010). The second group performed a study to validate criteria specifically for diagnosis of apathy, based on modified Marin's criteria for apathy and validated in other neurodegenerative disorders, which showed high sensitivity and specificity compared to an expert neuropsychiatrist's clinical judgement (Starkstein et al., 2009). In this study 83% of patients with apathy had depression and 56% had dementia however 13% had neither depression or dementia, suggesting that apathy can exist as a distinct nosological entity (Starkstein et al., 2009).

1.6 General aims and objectives

The aim of this thesis is to examine important non-motor aspects in PD. The impact of NMS on quality of life and disability in PD patients overall, and in sub-groups based on disease duration and Hoehn-Yahr stage, using detailed clinical rating scales for each non-motor feature will be examined. The detection and documentation of individual NMS, in the same PD cohort, using retrospective case notes audit will be made and compared to their relative importance on quality of life. NMS at PD diagnosis will be assessed in pathologically proven PD cases from the UK Brain Bank, and patients presenting with classical motor features (tremor, rigidity, bradykinesia, and gait disturbance) versus predominantly non-motor symptoms will be compared to determine whether this has impact on diagnostic accuracy in primary care or hospital setting, or influence on disease treatment and outcome. This part of the thesis led by Dr Sean O'Sullivan and was done in collaboration with the UK Brain Bank research team (Dr David Williams, Dr Luke Massey and Dr Laura Silveira-Moriyama) and Brain Bank pathologists (Professor Tamas Revesz and Dr Laura Parkinnen). The clinimetric assessment of NMS in PD will also be examined, with particular reference to the MDS-UPDRS.

This thesis has particular emphasis on neuropsychiatric phenomena, including VH, ICD and DDS, and disorders of mood and apathy. A detailed study of the aetiology of VH in PD will be made with particular emphasis on cognitive and visuoperceptive cortical function (based on bedside psychometric evaluation), ophthalmic factors (examined by an ophthalmologist) and in a separate pathological study, LB distribution in different cortical areas implicated in visual processing and hallucinations will be examined. A detailed literature review and meta-analysis will be performed on pathological gambling in PD, the archetypal ICD in PD and be used to determine potential demographic,

pharmacological and clinical associations, and a further exploratory analysis will be performed in our PD cohort. An assessment of the clinical determinants of apathy in PD will be made, including the relationship of apathy with depression and cognitive factors.

1.7 Conclusion

NMS are common in PD and occur throughout the course of the disease, including in the pre-motor phase, and have consistently been shown to have a significant impact on Hr-QOL. The pathophysiology of these disorders is likely to relate to widespread brainstem and cortical LB deposition, with involvement of different neurotransmitter systems, including dopaminergic, serotonergic, cholinergic and adrenergic transmission. The pathology of non-motor features in PD appears to be distinct from other neurological or primary psychiatric disorders, and there are particular challenges in the diagnosis of these disorders due to the comorbid physical, cognitive and psychiatric features found in PD. Therapeutic options are available for most NMS in PD, mainly based on treatments used in the non-PD context, but these interventions will require further evaluation and may have different clinical efficacy, due to distinct pathophysiological mechanisms in PD.

Chapter 2

Data acquisition and clinical measures

2.1 Clinical Study

Patients with idiopathic PD attending out-patient clinics at University College London Hospital, The Royal Free Hospital and Luton and Dunstable Hospital were recruited into the clinical study. This study received ethical approval by The Royal Free Hospital and Medical School Research Ethics Committee, The National Hospital for Neurology and Neurosurgery and Institute of Neurology Joint Research Ethics Committee and Luton and Dunstable Research Ethics Committee. The research governance sponsor of this study was University College London Hospitals/University College London Joint Biomedical Research Unit, R&D Directorate. All patients fulfilled UK Brain Bank criteria for PD, and patients with other parkinsonian disorders were excluded. Any PD patient was eligible for inclusion, including those with cognitive impairment or dementia, provided they were felt able to complete the physician assessment, complete questionnaires at home, alone or with help from their partner or carer and to give consent for the study. All patients received a detailed patient information sheet and informed written consent was obtained. During the clinical interview assessments were performed in a standard sequence. Physician interview was performed in hospital or if there were mobility, transport or general medical issues, at the patients' request in their own homes. Arrangements were made to interview patients at a time when they were most likely to be in an "on" motor state in relation to the timing of their dopaminergic medication. In circumstances where there were cognitive or attentional difficulties, excessive somnolence or fatigue, or if during the interview the subject developed motor

or non-motor wearing "off" that had potential to compromise accurate scoring, interview was held over two or more separate sessions.

Patients underwent a detailed clinical interview to record demographic details (occupational history, handedness, educational attainments, marital status, domestic living arrangements [alone, with partner or family, warden controlled accommodation, residential home or nursing home]), smoking, alcohol and recreational drug use history, PD history (symptom onset date, laterality of onset, disease duration and predominant clinical phenotype [tremor dominant, akinetic-rigid or mixed]), PD medication history (start date, treatment duration, maximum dose of each potential medication [levodopa, ergot and non-ergot dopamine agonists, monoamine oxidase inhibitors, catechol-o-methyltransferase inhibitors, amantadine, or subcutaneous apomorphine], record of any neurosurgical interventions [for example, subthalamic nucleus or globus pallidus deep brain stimulation or pallidotomy], history of cardiac, respiratory, gastrointestinal, endocrine or other medical comorbidities and medication. Each patient underwent full neurological examination and a battery of clinimetric tests, which included physician-administered assessments and self-completed questionnaires, covering a wide range of motor and non-motor aspects of the disease. Non-motor assessments included cognitive scales (SCOPA-cognitive scale, SCOPA-COG, Marinus et al., 2003a, Addenbrooke's Cognitive Examination [ACE], Larner et al., 2007, Frontal Assessment Battery [FAB], Dubois et al., 2000, and Birmingham Object Recognition Battery [BORB]), assessment of mood, motivation and anxiety (Hamilton Depression Rating Scale [HDRS], Schwab et al., 1967, Hospital Anxiety Depression Scale [HADS], Upadhyaya & Stanley, 1993 and LARS, Sockeel et al., 2006), scales to assess nocturnal and daytime sleep and fatigue (Pittsburgh Sleep Quality Index [PSQI], Buysee et al., 1989, Epworth Sleepiness Scale [ESS], Johns et al., 1991, SCOPA-sleep scale, Marinus et al., 2003b, Fatigue

Severity Scale [FSS], Krupp et al., 1989, International Classification of Sleep Disorders, Revised (ICSD-R) diagnostic criteria for RBD, American Academy of Sleep Medicine, 2001, International Restless Leg Syndrome Study Group Criteria for the diagnosis of Restless Leg Syndrome, Walters et al., 2003), quality of life scale (Parkinson's Disease Questionnaire, 39 item version [PDQ-39], Fitzpatrick et al., 1997), assessment of autonomic function (SCOPA-autonomic scale [SCOPA-AUT], Visser et al., 2004), assessment of VH and psychosis (Parkinson's Psychosis Rating Scale [PPRS], Friedberg et al., 1998, University of Miami Parkinson's disease hallucinations questionnaire [UM-PDHQ], Papapetropoulos et al., 2008), Visual Analogue Scale [VAS] of Pain and Non-Motor Symptoms Questionnaire (NMSQ), Martinez-Martin et al., 2007. Motor measures were the UPDRS, Fahn et al., 1987, and MDS-sponsored revision of the UPDRS, Goetz et al., 2008.

2.1.1 Cognitive Assessments

2.1.1.1 Scales for Outcome in Parkinson's, cognitive scale

The SCOPA-COG is a cognitive scale developed specifically for use in PD (Marinus et al., 2003). In formulating this scale, the development team performed an extensive literature review of studies measuring cognitive function in PD and selected the cognitive domains most frequently affected in PD and within those domains selected items that most consistently distinguished PD from control subjects. Cognitive domains most frequently affected were attention, memory, executive and visuospatial function whereas verbal function and reasoning were excluded as these tended to be normal. The proposed scale items were applied to 85 PD patients and 75 age, sex and education matched controls. Items were selected based on reproducibility and tests that significantly discriminated between patients and controls ($P<0.05$). Ten items were

retained which fulfilled criteria of eligibility; (1) four items were included in the memory domain including tests for both visual memory (copying the order in which cubes are pointed to) and verbal memory (backward digit span; reading and recalling 10 words, with immediate and delayed recall), (2) two items in the attention domain were naming the months of the year in reverse order and counting backwards from 30 in steps of three, (3) the three items included in the executive domain were categorical verbal fluency (number of animals named in one minute), a set shifting task and test of motor planning (Luria sequencing task) and (4) one visuospatial test, figure assembly (patient asked to determine which shapes are needed to construct another figure). The maximum total scale score is 43 (Range 0-43), with lower scores indicating higher degrees of cognitive impairment. Individual domains are scored as follows: memory and learning 0-22, attention 0-4, executive functions 0-12 and visuospatial functions 0-5. The scale showed high test-retest reliability (intraclass correlation coefficient 0.78) and internal consistency (Cronbach's alpha 0.83). Convergent validity has been demonstrated by high correlation with the Cambridge Cognitive Examination (rho = 0.83, $p < 0.001$), Mini-Mental State Examination (MMSE, rho = 0.72, $p < 0.001$) (Marinus et al., 2003), and ACE (rho = 0.93, $p < 0.0001$) (Reyes et al., 2009). The SCOPA-COG had higher coefficient of variability than either Cambridge Cognitive Examination or MMSE, indicating better ability to detect cognitive differences between patients (Marinus et al., 2003). In another study, a higher coefficient of variability was also demonstrated compared to the Mini-Mental Parkinson (Serrano-Duenas et al., 2010). In a further analysis (Verbaan et al., 2007), SCOPA-COG was applied to a large cohort of PD patients (N=400) and age, sex and education matched controls (N=150). PD patients scored significantly lower compared to controls on all SCOPA-COG domains, particularly executive and memory subscores. The total SCOPA-COG score showed moderate correlation with motor function (rho = −0.35), psychotic symptoms (rho =

−0.33), autonomic function (rho = −0.28), and depressive symptoms (rho = −0.24). A regression analysis was performed to determine the influence of clinical and demographic variables on cognitive function and found that age and years of education had the largest effect (29% of variance), with levodopa dose and motor function (6%) and psychotic symptoms (6%) only having a small influence, suggesting that the scale is relatively independent of motor and other confounding neuropsychiatric features. In another study (Reyes et al., 2009), with receiver operating characteristic (ROC) analysis using The Mattis Dementia Rating Scale as a diagnostic reference, the area under the curve (AUC) was high, 0.92 (95% CI 0.83-1.00) demonstrating excellent discriminant validity, with high sensitivity (92%) and specificity (87%). Therefore the SCOPA-COG has been developed and validated specifically for patients with PD, has acceptable scale properties (high test-retest reliability and internal consistency), has demonstrated high convergent validity with currently available cognitive rating scales (Cambridge Cognitive Examination, MMSE, ACE), has shown excellent ability to detect cognitive differences between PD patients (high coefficient of variability), has high sensitivity and specificity to detect cognitive impairment in PD (discriminant validity), and in a logistic regression study only a small proportion of SCOPA-COG total score variance was accounted for by other disease-related factors, such as motor function, dopaminergic medication and psychosis.

2.1.1.2 Addenbrooke's Cognitive Examination

The ACE is a cognitive scale that was developed for use in Alzheimer's disease and Frontotemporal Dementia (total score 0-100), and contains six domains: (1) orientation (scored 0-10), testing orientation to time (5 items) and place (5 items); (2) attention/concentration (scored 0-8), testing three item registration and serial seven subtraction; (3) memory domain (scored 0-35) testing immediate and delayed

anterograde memory (recall of objects, and a fictional person's name and address) and retrograde memory (naming important historical and political figures); (4) verbal fluency (scored 0-14), testing phonemic (words beginning with the letter "P") and semantic (animals) verbal fluency; (5) language domain (scored 0-28) testing confrontational object naming, comprehension including three stage command and comprehension of complex grammar, single word and phrase repetition, reading regular (phonetic) and irregular (non-phonetic) words and writing, and (6) visuospatial function (scored 0-5) testing drawing of intersecting pentagons, Necker's cube (three dimensional representation of cube) and clock face task (Mathuranath et al., 2000). Use of the ACE as a cognitive measure in PD has been examined by several groups. For example, in one study (Chade et al., 2008) ACE was administered to 22 patients with PD, 53 with Alzheimer's disease, 24 with Frontotemporal dementia and 53 control subjects. PD patients scored significantly lower than controls on ACE total score, memory score, and verbal fluency (particularly semantic fluency). ACE total score demonstrated better sensitivity at detecting cognitive impairment than MMSE. Convergent validity of ACE has been demonstrated with high correlation with SCOPA-COG (rho = 0.93, $P < 0.0001$), MDRS (rho = 0.91 $P < 0.0001$) and MMSE (rho = 0.84, $P < 0.001$) in one study (Reyes et al., 2009) and significant correlation with MMSE (rho = 0.72, $P < 0.01$) and FAB (rho = 0.56, $P < 0.01$) in another study (Kaszás et al., 2012). In ROC analysis, using MDRS as the reference, the AUC was higher for ACE (0.97) than for SCOPA-COG (0.92) or MMSE (0.91) and ACE demonstrated high sensitivity (92%) and specificity (91%) for diagnosing dementia at the optimal cut-off score (Reyes et al., 2009). Therefore ACE is a cognitive scale which has been used in PD and has demonstrated high convergent validity with currently available cognitive rating scales (SCOPA-COG, MMSE, MDRS) and has high sensitivity and specificity to detect cognitive impairment in PD (discriminant validity).

2.1.1.3 Frontal Assessment Battery

The FAB is a short bedside test to examine frontal executive function (Dubois et al., 2000) and contains six domains: (1) Similarities task, testing conceptualization where patient is asked to provide categorical responses to objects presented (fruits, furniture and flowers); (2) Lexical fluency testing phonemic verbal fluency (words beginning with the letter "S"); (3) Motor series using Luria sequencing task ; (4) Conflicting instructions task testing sensitivity to interference on a tapping test (subject is asked to tap once when examiner taps twice and vice versa), (5) Go-No Go task, testing inhibitory control (withholding a response that was previously given to the same stimulus) and (6) Prehension behaviour testing response to environmental cues which are inhibited in normal individuals (utilization behaviour). Each item is scored 0-3, with total maximum score 18. The study authors (Dubois et al. 2000) administered their scale to patients with various neurodegenerative disorders, including PD (N=42), MSA (N=6), CBD (N=21), PSP (N=47) and Frontotemporal Dementia (N=23) and healthy controls (N=42). FAB scores had high correlation with MDRS scores (rho = 0.82) and with Wisconsin Card Sorting Task (WCST) correct categories (rho = 0.77) and perseverative error (rho = 0.68) scores. Convergent validity was further demonstrated in a study where the FAB was applied in MSA (N=11), PSP (N=17) and PD (N=12) (Paviour et al., 2005). This study included detailed neuropsychological assessments and FAB had high correlation with tests specific for executive function and also tests of general cognitive function. For example, FAB had significant correlation with frontal-executive scores, including Wechsler Adult Intelligence Scale – Revised (WAIS-R) similarities score (rho = 0.68), WCST correct categories score (rho = 0.48), phonemic (rho = 0.70), semantic (rho = 0.59) and alternating semantic (rho = 0.75) verbal fluency, Paced Auditory Serial Addition Test score (rho = 0.65), MDRS Initiation/Perseveration

(rho = 0.60) and conceptualisation (rho = 0.39) subscores. FAB also had significant correlation with scores for general cognitive function, including National Adult Reading Test (rho = 0.61), WAIS-R verbal IQ (rho = 0.71), WAIS-R vocabulary score (rho = 0.78), WAIS-R digit span (rho = 0.67), MMSE (rho = 0.62), and MDRS total (rho = 0.67) and initiation (rho = 0.60), construction (rho = 0.44), memory (rho = 0.36) and attention (rho = 0.33) subscores. This study also demonstrated that the FAB could differentiate between types of extrapyramidal disorder, with FAB score significantly lower in PSP compared to MSA (p=0.02) or PD (P<0.001) and significantly lower in MSA than in PD (P=0.047) (Paviour et al., 2005). In another study, FAB was administered to PD patients (N=50) and healthy controls (N=122) (Lima et al., 2008), and FAB had significant correlation with general cognitive scales, MMSE (rho = 0.50) and Raven's Coloured Progressive Matrices (a non-verbal test of reasoning, rho = 0.43) and executive scales, phonemic verbal fluency (rho = 0.41), WCST perseverative errors (rho = 0.43) and Trail Making Test parts A and B (rho = 0.41). FAB scores were significantly lower in PD, particularly the Similarities (P<0.02) and Go-No-Go (P<0.0001) subscales, and on discrimination analysis correctly classified PD and normal controls in over 70% of cases (P<0.00001) (Lima et al., 2008). Therefore, the FAB is a simple bedside test of executive cognitive functioning, which has been applied to PD and related neurodegenerative disorders, and has demonstrated high convergent validity with a number of executive and global cognitive scales, in several studies, and has potential to differentiate between extrapyramidal disorders.

2.1.1.4 Birmingham Object Recognition Battery

The BORB is a standardised set of psychological tests assessing visuoperceptive function. The elements include (1) Drawing from Memory; (2) Copying; (3) Length Match Task; (4) Size Match Task; (5) Orientation Match Task; (6) Position of Gap

Match Task; (7) Overlapping Figures; (8) Minimal Feature View Test; (9) Foreshortened View Task; (10) Object Decision Task; (11) Function Match Task; (12) Associative Match Task and (13) Picture Naming Task – short and long versions. Patients performed a large number of cognitive tests and other clinimetric measures and therefore for the purpose of this study an abbreviated set of tests was employed; tests were selected to cover the range of low to high level visuoperception, and included Length Match Task, Size Match Task and Orientation Match Task, which assess low level aspects of visual perception (same-different matching of elemental features such as orientation, length, and object size), Overlapping Figures Test, Minimal Feature View Test and Foreshortened View Task (higher level of visual perception assessing identification of overlapping images, identification of objects from minimal features and matching objects from usual and unusual viewpoints), Object Decision Task (test of stored perceptual knowledge assessing discrimination between pictures of real objects and non-objects made by combining parts of different real objects, Humphreys et al., 1997) and Associative Matching Task (semantic knowledge test where subject decides which of two reference pictures [e.g. a screw and a nail] is most associated with a target picture [a screwdriver], Humphreys et al., 1997). The BORB is a standardised set of neuropsychological tests to detect visual agnosia. Visual agnosia refers to impairment of visual object recognition, but with intact visual pathways (globe, retina, optic nerves, chiasm and optic tracts) and implicates involvement of cortical visual pathways, and is further divided into failure in interpretation of spatial and structural properties (apperceptive agnosia) or semantic context (associative agnosia) of visual stimuli. Visuoperceptive function has been explored much less in PD than other cognitive or high cortical modalities, in particular attention, memory and executive function and the BORB has not been specifically applied or validated in the PD population.

2.1.2 Assessment of mood, motivation and anxiety

2.1.2.1 Hamilton Depression Rating Scale

HDRS contains 21 items, of which 17 items are usually used in scoring. These items are (1) Depressed mood - feelings of sadness, hopelessness, helplessness or worthlessness, scored 0-4; (2) Feelings of guilt, scored 0-4; (3) Suicide - feelings, wishes, ideas or gestures of suicide and suicide attempts, scored 0-4, (4) Insomnia early - difficulty falling asleep; (5) Insomnia middle - disrupted nocturnal sleep; (6) Insomnia late - early morning wakening with difficulty getting back to sleep, with all insomnia items scored 0-2, (7) Work and activities - incapacity, loss of interest, decreased productivity, scored 0-4, (8) Psychomotor retardation - slowness of speech and thought, reduced concentration and decreased motor activity, scored 0-4; (9) Agitation, scored 0-4; (10) Psychological anxiety, scored 0-4; (11) Somatic symptoms of anxiety, particularly features of autonomic overactivity, scored 0-4; (12) Gastrointestinal somatic symptoms, scored 0-2; (13) General somatic symptoms, including heaviness in limbs, back, or head, diffuse backache, loss of energy and fatigability, scored 0-2; (14) Genital symptoms - loss of libido and menstrual disturbances; (15) Hypochondriasis - self-absorption, preoccupation with health, complaining attitude and hypochondrial delusions, scored 0-4; (16) Loss of weight and (17) Lack of Insight (Hamilton, 1960). The HDRS has been used extensively in non-PD subjects and has demonstrated high sensitivity, specificity and discriminant ability for DSM-IV diagnosis of depression and good test-retest and inter-rater reliability (Schrag et al., 2007). Studies of the HDRS in PD have concentrated on discriminant validity of the scale in relation to formal DSM-IV diagnostic criteria, to determine optimal cut-off scores with maximal sensitivity and specificity for diagnosis or screening of depression. There have been relatively few studies examining convergent validity in relation to other rating scales. The several

studies using ROC analysis, with DSM-IV as the diagnostic criterion have demonstrated good sensitivity and specificity and high AUC (Williams et al., 2012, Reijnders et al., 2010, Weintraub et al., 2006, Narding et al., 2002). In a study where The Geriatric Depression Scale and HDRS was applied to PD patients there was a moderately high correlation between the two scales (rho = 0.54; P < 0.001) (McDonald et al., 2006). HDRS has also demonstrated sensitivity to change over time in PD and correlation with biological markers of depression in PD (Schrag et al., 2007). The scale is freely available to the public and has been translated into a number of different languages. The MDS Task Force on Rating Scales for PD recommends HDRS scale to measure of severity of depressive symptoms in clinical studies and as adequate screening tool for depression in PD. Therefore, HDRS is a well validated scale in PD and non-PD subjects, and has demonstrated good discriminant validity with respect to DSM criteria, has good convergent validity compared to other depression rating scales (for example, GDS) and has shown good sensitivity to change in PD.

2.1.2.2 Hospital Anxiety Depression Scale

The HADS consists of fourteen items, seven dealing with anxiety (HADS-Anxiety) and seven with depression (HADS-Depression), with each item scored from 0 to 3. Use of HADS in PD has been examined in some studies. For example, in a large study to determine the convergent validity of HADS, 342 PD patients underwent detailed psychological assessments, including rating scales for anxiety and depression and DSM-IV diagnostic criteria for anxiety (Leentjens et al., 2011). HADS-D had significant correlation with NPI anxiety score (rho = 0.31), Hamilton Anxiety Rating Scale (HARS, rho = 0.32), Beck Anxiety Inventory (BAI, rho = 0.35), and HDRS total score (rho = 0.40) (all p < 0.002). HADS-Anxiety had significant correlation with NPI anxiety (rho = 0.19), HARS (rho = 0.25), BAI (rho = 0.36) and HDRS total score (rho = 0.27) (all p <

0.002). HADS-Total Score was significantly correlated with CGI (rho = 0.41), NPI anxiety score (rho = 0.47), HARS score (rho = 0.47), BAI (rho = 0.62) and HDRS (rho = 0.56) (Leentjens et al., 2011). In another study HADS-D (rho = 0.57) and HADS-A (rho = 0.60) had high correlation with NPI (Kulisevsky et al., 2008). In a longitudinal study, 67 patients were followed up for one year and score changes in the HADS-Anxiety and HADS-Depression correlated highly with SCOPA-Psychosocial change (rho = 0.50 and rho =0.58 respectively) (Martinez-Martin et al., 2008). In another study to assess the discriminant validity of HADS, the discrimination power of HADS-Total (AUC 0.75) and HADS-A (AUC 0.63) was relatively low, but statistically significant (Leentjens et al., 2011). Therefore, HADS total score and anxiety and depression subscores have demonstrated reasonable convergent validity with a wide variety of anxiety and depression scales in PD (although in some studies with only relatively low correlation coefficients) and sensitivity to change in a longitudinal study; however have only shown modest discriminant validity. HADS-Depression focuses on non-somatic features of depression, which may be advantageous in mild depression where the overlapping somatic symptoms of PD could lead to artificially high scores and false positive diagnoses. However, in moderate to severe depression somatic features have an important impact and contribution to severity rating. The MDS Task Force on Rating Scales for PD suggest HADS is moderately suitable as screening tool in PD but its role as a severity measure remains uncertain (Schrag et al., 2007). This study, by including both HDRS and HADS-Depression, therefore covered the entire range of depressive symptoms encountered in PD, including HDRS, which has a large focus on somatic symptoms and the predominantly non-somatic HADS-D.

2.1.2.3 Lille Apathy Rating Scale

The LARS was designed and validated specifically for use in PD and contains 33 items, divided into nine domains representing (1) everyday productivity; (2) lack of interest; (3) lack of initiative; (4) novelty seeking; (5) motivation; (6) emotional responses; (7) lack of concern; (8) social life and (9) self-awareness (Sockeel et al., 2006). In addition four factorial scores, (1) intellectual curiosity; (2) action initiation; (3) emotion and (4) self-awareness, can be calculated from these nine domains. In the original study, LARS showed high internal consistency (Cronbach alpha coefficient between items, 0.80, and between subscales, 0.74), test–retest reliability (correlation coefficient = 0.95) and inter-rater reliability (intra-class correlation = 0.98) (Sockeel et al. 2006). The scale ranges from −36 to +36, where higher scores represent a greater degree of apathy. A cut-off score of ≥−16 was calculated to have a high degree of accuracy (accuracy 91%, sensitivity 89% and specificity 92%) in discriminating an expert's dichotomous judgement of apathy (moderately/severely apathetic versus non-apathetic/mildly apathetic). In a further validation study with 71 PD participants (Zahodne et al., 2009), the convergent validity of LARS with the Apathy Scale (AS), a self-reported 14-item Likert based apathy scale, was high (Intraclass Correlation Coefficient 0.75) and AS also had significant correlation with three of four LARS factorial subscores; intellectual curiosity (rho = 0.61; $P < 0.001$), action initiation (rho = 0.42; $P < 0.001$), and emotion (rho = 0.33; $P < 0.01$) and a trend to correlation with self-awareness score (rho = 0.229; $P = 0.05$) (Zahodne et al., 2009). LARS has been validated against proposed diagnostic criteria for apathy in neuropsychiatric disorders (Robert et al., 2009; Drijgers et al., 2010). These proposed criteria (Robert et al., 2009) require (A) loss of or diminished motivation in comparison to the patient's previous level of functioning and which is not consistent with age or culture, (B) presence of at least one symptom in at least two of

the three domains: (B1) goal-directed behaviour, (B2) goal-directed cognition and (B3) spontaneous emotion, and (C) symptoms which cause clinically significant impairment in personal, social, occupational, or other important areas of functioning and (D) symptoms are not exclusively explained or due to physical disabilities, to motor disabilities, to diminished level of consciousness or to the direct physiological effects of a substance. LARS had high correlation with these diagnostic criteria for apathy, correlation coefficient 0.72, P = 0.01 (Drijgers et al., 2010). Goal-directed behaviour criterion (B1) had significant correlation with intellectual curiosity (rho = 0.56), emotion (rho = 0.24) and action initiation (rho = 0.32) factorial scores. Goal-directed cognition (B2) had significant correlation with intellectual curiosity (rho = 0.62), emotion (rho = 0.20), action initiation (rho = 0.47) and self-awareness (rho = 0.28). Spontaneous emotion (B3) had significant correlation with intellectual curiosity (rho = 0.35), emotion (rho = 0.33) and action initiation (rho = 0.20) (Drijgers et al., 2010). Therefore LARS has been developed and validated specifically for use in PD; the scale has demonstrated high internal consistency, test–retest and inter-rater reliability, high convergent validity with other apathy rating scales and good discriminant validity compared to proposed diagnostic criteria and experts' diagnostic opinion.

2.1.3 Sleep and fatigue scales

2.1.3.1 Pittsburgh Sleep Quality Index

The PSQI is a self-completed questionnaire assessing overall sleep and contains seven domains, each scored 0-3, and giving a total score 0-21, with higher scores indicating greater impairment of sleep. The seven domains are (1) sleep quality, overall subjective impression of quality of nocturnal sleep, (2) sleep latency, time to onset of sleep, (3) sleep duration, actual hours of sleep per night, as opposed to time spent in bed, (4) sleep

efficacy, proportion of time spent in bed actually asleep, (5) sleep disturbance, whether sleep is disturbed for various reasons including nocturia, breathing difficulties, coughing, snoring, feeling too hot or cold, dreaming or pain or any other reason, (6) sleep medication, how often over the previous month the subject has taken prescribed or over-the-counter medication for sleep and (7) daytime sleepiness (Buysee et al., 1989). The MDS Task Force on Rating Scales in PD commissioned a Sleep Scale Task Force to evaluate sleep scales in PD (Högl et al., 2010) and PSQI scale was recommended to screen and measure severity of overall sleep problems in PD. PSQI has been used to assess sleep function in PD in several studies and also in PD related complications, such as restless leg syndrome, mood disorders, dementia and hallucinations (Högl et al., 2010). The scale has demonstrated high internal consistency and test-retest reliability (Högl et al., 2010). In a study using PSQI, ESS, Parkinson's Disease Sleep Scale (PDSS) and polysomnography in PD (Uemura et al., 2009), the PSQI demonstrated good convergent validity. PSQI total score was significantly correlated with PDSS total score ($rho = -0.488$, $p < 0.001$), the overall quality of a night's sleep in the PDSS significantly correlated with PSQI sleep quality subscore ($rho = -0.482$, $p < 0.001$); the PDSS sleep onset and maintenance score correlated with PSQI sleep latency subscore ($rho = -0.361$, $p < 0.001$); Sleep disturbances in the PSQI were correlated with the nocturnal restlessness ($rho = -0.276$, $p = 0.001$), nocturnal psychosis ($rho = -0.338$, $p < 0.001$), nocturia ($rho = -0.243$, $p = 0.004$), and nocturnal motor symptoms ($rho = -0.309$, $p < 0.001$) in the PDSS (Uemura et al., 2009) and the PSQI daytime sleep score was correlated with the nocturia ($rho = -0.279$, $p = 0.001$), sleep refreshment ($rho = -0.272$, $p = 0.001$), and daytime dozing ($rho = -0.349$, $p < 0.001$) in the PDSS. In another study (Suzuki et al., 2012), PSQI summary index correlated significantly with PDSS total score ($rho = 0.46$), disturbed sleep ($rho = 0.48$), motor symptoms at night ($rho = 0.36$) and PD symptoms at night ($rho = 0.34$), all $P < 0.001$ (Suzuki et al., 2012).

In another study, PSQI had high correlation with SCOPA night time sleep score (rho = 0.83, P < 0.001) (Marinus et al., 2003b). Therefore PSQI has demonstrated adequate scale properties (internal consistency and test-retest reliability) and convergent validity with a number of other validated sleep scales in several studies.

2.1.3.2 Epworth Sleepiness Scale

The ESS is a clinical measure of daytime somnolence and asks the subject to indicate how likely they are to fall asleep in eight different circumstances, (1) sitting and reading, (2) watching television, (3) sitting inactive in a public place, (4) as a passenger in a car without a break for an hour, (5) lying down to rest in the afternoon, (6) sitting and talking to someone, (7) sitting quietly after lunch without alcohol, and (8) in a car while stopped for a few minutes in traffic. Each item is scored 0-3, with maximum score 24 and higher scores reflecting greater daytime somnolence. The MDS Sleep Scale Task Force (Högl et al., 2010) have recommended the ESS for evaluation of daytime sleepiness in PD, because the scale has good clinimetric properties (test-retest reliability and internal consistency), the scale has been validated for use in PD and is freely available in the public domain and has been translated into several languages. In studies in PD comparing ESS to objective measures of sleep, such as polysomnography, MSLT and actigraphy, there have been inconsistent results. For example, in one study (Valko et al., 2010), there was no correlation of ESS with any polysomnographic findings, including latency to stage 2 non-REM sleep and latency to REM sleep, arousal index, sleep efficacy and Periodic Limb Movements of Sleep index. In another study there was negative correlation of ESS with total sleep time (rho = –0.55; P = 0.041) but not with other quantitative polysomnography variables (Compta et al., 2009). However, in another study (Poryazova et al., 2010) there was a highly significant negative correlation between ESS total score and mean sleep latency (rho = -0.65, p < 0.001) on

MSLT, nocturnal sleep latency (rho = –0.60, p < 0.001) and apnoea/hypoxia index (rho = 0.392, p = 0.032) and trend to significant correlation with percentage REM sleep (rho = –0.345, p=0.062). Also, in a study using actigraphy (Stavitsky et al., 2010), there was significant correlation with total measured sleep time (rho = 0.537) and a trend for correlation with other measures, including actigraphic sleep efficacy (rho = 0.384) and sleep fragmentation (rho = 0.413).

In a validation study comparing clinical scales, there was significant correlation of ESS with PDSS daytime dosing (rho = 0.403), nocturnal restless (rho = 0.286), nocturnal psychosis (rho = 0.309), nocturnal motor symptoms (rho = 0.365) and sleep refreshment (rho = 0.272, all P < 0.001) subscores (Uemura et al., 2009). In another study (Wang et al., 2008), there were significant correlations between EES and PDSS total score (rho = 0.325, P < 0.01) and PDSS item 15, unexpectedly falling asleep during the day (rho = 0.478, P < 0.01). Therefore ESS has been used extensively in PD, has acceptable scale properties, good convergent validity with other available sleep scales, and some evidence of validity compared to objective Polysomnographic and MSLT measures of sleep.

2.1.3.3 SCOPA-Sleep Scale

SCOPA-Sleep scale has sections for night time and daytime sleep. There are five questions for night time sleep, (1) trouble falling asleep, (2) awakening during the night, (3) episodes lying awake too long at night, (4) early morning waking and (5) patient's impression whether they had adequate duration of sleep at night. There are six questions for daytime sleep, (1) falling asleep unexpectedly during the day or evening, (2) falling asleep while sitting peacefully, (3) while watching television or reading, (4) while talking to someone, (5) trouble staying awake during the day or evening, and (6)

experiencing falling asleep as a problem. The MDS Sleep Scale Task Force (Högl et al., 2010) have recommended SCOPA sleep for assessment of sleep in PD. SCOPA sleep has demonstrated good scale properties, internal consistency and test-retest reliability (Marinus et al., 2003, Martinez-Martin et al., 2008). In studies to assess convergent validity, SCOPA-sleep night time had high correlation with PSQI (rho = 0.63, $p < 0.01$, Setthawatcharawanich et al., 2011, and rho = 0.83, $p < .001$, Marinus et al., 2003) and PDSS (rho = 0.60, Martinez-Martin et al., 2008). SCOPA- sleep daytime had high correlation with ESS (rho = 0.59, $p < 0.01$, Setthawatcharawanich et al., 2011 and rho = 0.81, $p < .001$, Marinus et al., 2003). In the later study, the coefficient of variation of SCOPA-sleep night time and the daytime sleepiness was higher than PSQI and ESS respectively, indicating a better ability to detect differences between individuals (Marinus et al., 2003). Therefore SCOPA-sleep scale has good scale properties, high convergent validity with other sleep scales and high coefficient of variability.

2.1.3.4 REM sleep behavioural disorder

REM sleep behavioural disorder is characterised by loss of REM sleep electromyographic atonia, and clinically manifests as vocalisation and elaborate movement during dreaming. ICSD-R require that (A) the patient has a complaint of violent or injurious behaviour during sleep; (B) limb or body movement is associated with dream mentation; (C) at least one of the following occurs, (i) harmful or potentially harmful sleep behaviours, (ii) dreams appear to be "acted out" or (iii) sleep behaviours disrupt sleep continuity; (D) polysomnographic monitoring demonstrates at least one of the following electrophysiologic measures during REM sleep, (i) excessive augmentation of chin EMG tone, (ii) excessive chin or limb phasic EMG twitching, irrespective of chin EMG activity and one or more of the following clinical features during REM sleep, (a) excessive limb or body jerking, (b) complex, vigorous, or violent

behaviours, (c) absence of epileptic activity in association with the disorder; (E) the symptoms are not associated with mental disorders but may be associated with neurologic disorders and (F) other sleep disorders (e.g., sleep terrors or sleepwalking) can be present but are not the cause of the behaviour (American Academy Sleep Medicine, 2001). Therefore both clinical and polysomnographic features are included in the criteria, but ICSD-R also allows diagnosis to be made on clinical criteria only (termed minimal criteria), where patients fulfil parts (B) and (C) of the algorithm. Polysomnography was not available for this study and therefore diagnosis of RBD was based on ICSD-R minimal diagnostic criteria.

2.1.3.5 Fatigue Severity Scale

FSS is a self-completed scale with nine questions, each rated by the subject on a Likert scale ranging from 1 "completely disagree" to 7 "completely agree". The total FSS score is calculated by the average score of the nine items, giving a range of 1 to 7, with higher scores representing greater degrees of fatigue. The nine questions relate to (1) impact of fatigue on motivation, (2) influence of exercise on fatigue, (3) ease at which person becomes fatigued, (4) impact of fatigue on physical functioning, (5) how frequent fatigue causes problems for the patient, (6) impact of fatigue on sustained physical functioning, (7) how fatigue interferes with carrying out duties and responsibilities, (8) how disabling fatigue is in comparison to other (neurological or other) symptoms and (9) how fatigue interferes with work, family or social life (Krupp et al., 1989). The FSS has been examined in PD in several studies. For example, in a 118 patient study, FSS demonstrated good scale properties (high reliability with alpha coefficient >0.90, low floor and ceiling effects, and factor and Rasch analysis supported unidirectionality of scale) (Hagell et al., 2006). FSS showed high convergent validity with 13-item Functional Assessment of Chronic Illness Therapy-Fatigue Scale (rho =

0.77) and Energy subscale of the Nottingham Health Profile (rho =0.62). In a second study, the FSS was highly correlated with Parkinson's Fatigue Scale (rho = 0.84) and one question fatigue rating (rho = 0.80). MDS Task Force on Rating Scales for PD has given critique and recommendations on fatigue rating scales in PD (Friedman et al., 2010). The FSS was recommended in PD, for both screening and severity rating, because it has been shown to have good psychometric properties (including discriminant validity) in non-PD and PD patients and has been used by groups other than the original scale developers, and demonstrated excellent convergent validity (Friedman et al., 2010).

2.1.4 Quality of life

2.1.4.1 Parkinson's Disease Questionnaire

PDQ-39 is a 39 item health-related quality of life questionnaire developed and validated in PD (Peto et al., 1995). In stage one of development, 20 patients underwent in-depth semi-structured interviews, where they were asked to describe which areas of their life were adversely affected by the disease. Researchers then formulated a 65 item pilot questionnaire based on their recorded responses. The pilot questionnaire was administered in a postal survey, and based on eigenvalues and factor loading on factor analysis, item number was reduced to 39 questions, forming eight discrete scales, (1) Mobility (10 items) - problems getting around at home or in public places; (2) Activities of daily living (6 items) - difficulties with personal care; (3) Emotional well-being (6 items) - assessing aspects such as mood and expectations for the future; (4) Stigma (4 items) - exploring social difficulties related to PD such as concealing the diagnosis from others or avoiding eating, drinking or other activities in public; (5) Social support (3 items) - relationship with friends, family and carers; (6) Cognitions (4 items) - aspects

such as attention and memory; (7) Communication (3 items) - problems communicating with others and (8) Bodily discomfort (3 items). For the purposes of scoring, each scale is converted to a percentage (range 0-100) with higher scores representing poorer quality of life. PDQ-39 summary index is calculated from the mean of the eight scales. In this original study, Cronbach's alpha was satisfactory for the eight scales and test-retest correlation coefficients were all significant. Convergent validity was tested against the Short From (36 item) Health Survey (SF-36); PDQ-39 mobility score correlated with SF-36 physical functioning (rho = -0.80), PDQ-39 activities of daily living correlated with SF-36 limitation due to physical problems (rho = -0.36), PDQ-39 emotion well-being correlated with SF-36 mental health score (rho = -0.71), PDQ-39 social support correlated with SF-36 social function (rho = -0.34), and PDQ-39 bodily discomfort correlated with SF-36 pain (rho = -0.66) (Peto et al., 1995). The scale is freely available to the public and is the main health-quality of life index that has been used in clinical studies in PD. Therefore the PDQ-39 was specifically developed in PD that encompasses a wide range of symptoms that impact on quality of life, shows good scale properties and convergent validity with other Hr-QOL scales.

2.1.5 Autonomic function

2.1.5.1 Scales for Outcome in Parkinson's disease – Autonomic Scale

The SCOPA-AUT scale was specifically developed for use in PD (Visser et al., 2004). 45 questions were selected following an extensive literature search and consulting specialists in the field. The questionnaire was applied to patients with PD and MSA, and subjects were asked to rate both the frequency and burden of symptoms, and items were selected based on high frequency, high burden, or high clinical relevance judged by specialists. Redundant items with high inter-item correlation were removed. The final

SCOPA-AUT scale consisted of 25 questions assessing gastrointestinal symptoms (7 items), urinary symptoms (6 items), cardiovascular symptoms (3), thermoregulatory function (4), pupillomotor symptoms (1), and sexual function (2 items for men and 2 items for women) giving a total of 23 items for men or women. Each question had four responses to rate frequency from zero "never" to three "often", and total score ranging from 0-69, with higher scores representing increased autonomic dysfunction. PD patients had significantly higher scores on all autonomic domains compared to controls, suggesting good discriminant validity, except for sexual function in men and women, and there was also significant difference between mild, moderate and severe disease stages. The test-retest validity was high for scale total score and individual domain scores. An independent validation study (Rodriguez-Blazquez et al., 2010) assessed scale acceptability (completeness of data, data distribution including skewness and floor and ceiling effects), internal consistency, and construct validity. In terms of scale acceptability, computable data were obtained for 97% of the sample (however a high proportion of men and women reported the sexual domain as "non-applicable"), mean and median values were close, but floor effects (cardiovascular, thermoregulatory, pupillomotor and sexual domains) and ceiling effect (pupillomotor) were observed for parts of the scale. In terms of internal consistency, Cronbach's alpha for domains range from 0.69 to 0.95. SCOPA-AUT correlation with several non-specific scales for pain, anxiety, depression, fatigue and quality of life was calculated but not with specific measures of autonomic function, in order to assess genuine convergent validity. A further study (Forjaz et al., 2010) using Rasch analysis has identified some scale weaknesses including a redundant item (incomplete bladder emptying), disordered thresholds of response categories and lack of empirical evidence to support scale subscores. However, Rasch model of the shorter 22-item scale with simplified response scheme revealed strengths including high internal consistency, and it is a scale which is

unidimensional and can be transformed into a linear metric scale. Studies have not shown a clear correlation between SCOPA-AUT and objective measures of autonomic function, for example sympathetic skin response and the R-R interval variation test (Papapetropoulos et al., 2006) and composite autonomic scoring scale with elements including presence of orthostatic hypotension (on standing for 1,3,5 minutes after 20 minutes bed-rest), heart rate ratio during deep breathing, Valsalva ratio (maximal to minimal heart rate), and sweat response (Oh et al., 2007) or heart/mediastinal MIBG uptake ratio using cardiac SPECT (Berganzo et al., 2012). Therefore, the SCOPA-AUT is a comprehensive scale that rates a wide range of autonomic symptoms in PD and has demonstrated adequate scale properties. Correlation with objective measures of autonomic function has not yet been demonstrated and will require further assessment. Also convergent validity with other clinical scales has not been assessed.

2.1.6 Psychosis

2.1.6.1 Parkinson's Psychosis Rating Scale

The PPRS contains six items which are rated from absent, mild, moderate or severe (scored 1-4). The items are (a) visual hallucinations, (b) illusions and misidentification of persons, (c) paranoid ideation (persecutory and/or jealous type), (d) sleep disturbance, (e) confusion and (f) sexual pre-occupation. For each item, the rater is given a further explanation to assist accurate and consistent scoring. For example, "mild" visual hallucinations are classified as occasional, with complete or partial insight and non-threatening; "moderate" are frequent, with absence of full insight; patients can be convinced they are real and may be threatening and "severe" are persistent hallucinations, with no insight, associated with heightened emotional tone, agitation, and aggression. The scale total score ranges from 4-24, with higher scores reflecting

more psychotic phenomena. In a systematic review and critique of available psychosis scales in PD the PPRS was considered (Fernandez et al., 2008). The PPRS is short, easy to administer scale and does not require special training to use. The hallucinations item considers frequency of symptoms and retention of insight, which are important features of psychosis in PD. However, the PPRS does not include the full spectrum of PD psychotic symptoms, for example hallucinations in other modalities (auditory, olfactory, gustatory, or cutaneous). Also, there is only a single item for the visual hallucinations, illusions and delusions domains, which gives only a narrow range of potential scores, and limits the scales ability to measure change over time. The final three items of the scale; sleep disturbance, confusion and sexual preoccupation are features that are often associated with psychosis, rather than psychotic symptoms per se. Clinimetric testing in the original study showed inter-rater reliability for items and scale total was high, but internal consistently was variable, and poor for some items. On assessment of convergent validity, PPRS was correlated with Brief Psychosis Rating Scale (BPRS), rho = 0.92, and Nurses' Observation Scale for Inpatient Evaluation (NOSIE) Psychotic dimension score (rho = 0.48) (Fernandez et al., 2008).

2.1.6.2 University of Miami Parkinson's Disease Hallucination Questionnaire

The UM-PDHQ is a hallucination scale based on a structured clinical interview that was developed by a group of movement disorders specialists, a geriatric psychiatrist, neuropsychologist, nurse specialist and neuro-ophthalmologist (Papapetropoulos et al., 2008). It contains six quantitative and fourteen qualitative questions. The six quantitative items rate (1) hallucination modality – visual, auditory, somatic/cutaneous, gustatory or olfactory, (2) frequency of episodes, (3) duration of episodes, (4) presence of insight, (5) variety of sensations experienced and (6) emotional distress involved. Total score range is 0-14, with higher scores denoting more psychotic symptoms. The

qualitative items ask about (1) co-existing ophthalmic problems, (2) current medications, (3) recent changes in treatment, (4) relationship of changes in medication to characteristics of hallucinations, (5) relationship to "on"-"off" motor fluctuations, if present, (6) description of hallucination experiences, including familiarity or non-familiarity, (7) whether patient can do anything to make sensations disappear, (8) diurnal variation and relationship to lighting conditions, (9) whether hallucinations make noise, (10) movement of visual hallucinations, (11) hallucination size, (12) transparency, (13) colour and (14) onset of hallucinations. This is a relatively new hallucination scale in PD and has not undergone independent validation by other groups.

2.1.7 Pain scale

A specific scale to measure pain in PD was not available when this study was designed; however pain occurs throughout disease course (for example "frozen shoulder" if often a presenting of PD) and has an important impact of quality of life in PD. Consideration was given to the various types of pain that may be experienced by PD patients, and subjects were asked to rate each symptom from 0 (no pain at all) to 10 (worst possible pain) on a Visual Analogue Scale (VAS). The nine domains were musculoskeletal pain, radicular pain, restless leg pain, dystonic pain, dyskinetic pain, mouth pain, visceral pain, akinetic pain and headache. An overall pain score was calculated by adding the individual scales, with a total range 0-90.

2.1.8 Non-motor symptom questionnaire

The non-motor symptom questionnaire (NMSQ) was developed by a multi-disciplinary group of specialists as a screening tool for the range of non-motor symptoms encountered in PD, and consists of a binary "yes"-"no" response to thirty symptoms; 8

questions on gastrointestinal symptoms, 2 on urinary tract symptoms, 2 on sexual function, 2 on cardiovascular features, 3 for attention, apathy and memory, 2 questions on hallucinations and delusions, 2 questions on depression, anxiety, anhedonia, 5 questions on sleep and fatigue, 1 question on pain, and 3 other miscellaneous items (Chaudhuri et al., 2006). This questionnaire was not developed as a diagnostic instrument or rating scale but as an initial screening tool, to allow further exploration of symptoms identified.

2.1.9 Motor Scales

2.1.9.1 Unified Parkinson's disease Rating Scale

The UPDRS was developed in the 1980s and has been the primary outcome measure in clinical studies in PD. The UPDRS contains four parts: Part I, Mentation, behaviour and mood; Part II, Activities of daily living; Part III, Motor examination and Part IV, Complications of therapy. Part I contains four items: (1) Intellectual impairment, (2) Thought disorder, (3) Depression and (4) Motivation and Initiative, with each item scored 0-4, and total score range 0-16. Part II contains 13 items: (1) Speech, (2) Salivation, (3) Swallowing, (4) handwriting, (5) Cutting food and handling utensils, (6) Dressing, (7) Hygiene, (8) Turning in bed and adjusting bed clothes, (9) Falling, (10) Freezing when walking, (11) Walking, (12) Tremor and (13) Sensory complaints related to Parkinsonism, with each item scored 0-4, and total score range 0-52. Part III contains 27 items: (1) Speech, (2) Facial expression, (3-7) Tremor at rest, individual scores given for head, right and left arm, and right and left leg, (8-9) Action or postural tremor of hands, scored for right and left side, (10-14) Rigidity, at neck and four limbs, assessed on passive movement with the patient sitting in a relaxed position, (15-16) Finger taps, tapping thumb and index finger in rapid succession, scored for right and left side, (17-

18) Hand movements, opening and closing hands in rapid succession, scored for right and left side, (19-20) Rapid alternating movements of hands, pronation and supination, with as large amplitude as possible, both arms simultaneously, each side scored, (21-22) Leg agility, tapping heel on ground in rapid succession, each side scored, (23) Arising from chair, (24) Posture, (25) Gait, (26) Postural stability and (27) Body bradykinesia. Each item is scored 0-4, giving a total score range 0-108. Part IV is divided into three sections: (A) Dyskinesias, with three items: (1) Duration - what proportion of the day dyskinesias are present, (2) Disability, (3) Painful dyskinesias (each scored 0-4) and (4) Presence of early morning dystonia (binary "yes"-"no" response, scored 0-1); (B) Clinical fluctuations, with four items: (1) Predictable "off" periods, (2) Unpredictable "off" periods, (3) Sudden onset "off" periods, each of these items is a binary "yes"-"no" response, scored 0-1, (4) percentage of waking day in "off" state, scored 0-4; (C) Other complications, (1) Anorexia, nausea or vomiting, (2) Disturbances of sleep such as insomnia or hypersomnolence and (3) Symptomatic orthostasis, each of these items binary "yes"-"no" response, scored 0-1.

2.9.1.2 Movement Disorder Society-UPDRS

The MDS-UPDRS contains four parts. Part I, Non-motor aspects of experiences of daily living (nM-EDL) has two sections, Part IA, Complex neuropsychiatric behaviours, completed by rater, and Part IB which is assessed by patient questionnaire. Part IA has six items (1.1) Cognitive impairment, (1.2) Hallucinations and psychosis, (1.3) Depressed mood, (1.4) Anxious mood, (1.5) Apathy and (1.6) Features of dopamine dysregulation syndrome. Part IB has items (1.7) Sleep problems, (1.8) Daytime sleepiness, (1.9) Pain and other sensations, (1.10) Urinary problems, (1.11) Constipation problems, (1.12) Light headedness on standing and (1.13) Fatigue. Each Part I item is scored 0-4, with total score range 0-52. Part II, Motor aspects of experiences of daily

living (M-EDL) has 13 items, (2.1) Speech, (2.2) Saliva and drooling, (2.3) Chewing and swallowing, (2.4) Eating tasks, (2.5) Dressing, (2.6) Hygiene, (2.7) Handwriting, (2.8) Doing hobbies and other activities, (2.9) Turning in bed, (2.10) Tremor, (2.11) Getting out of bed, a car or a deep chair, (2.12) Walking and balance and (2.13) Freezing; each item is scored 0-4, with total Part II score range 0-52. All Part II questions are assessed together with Part IB as a 20-item patient questionnaire. Part III, Motor examination, has items (3.1) Speech, (3.2) Facial expression, (3.3) Rigidity, (a) neck, (b) right upper extremity (RUE), (c) left upper extremity (LUE), (d) right lower extremity (RLE) and (e) left lower extremity (LLE), (3.4) Finger tapping, (3.5) Hand movements, (3.6) Pronation-supination movements of hands, (3.7) Toe tapping, (3.8) Leg agility, (3.9) Arising from chair, (3.10) Gait, (3.11) Freezing of gait, (3.12) Postural stability, (3.13) Posture, (3.14) Global spontaneity of movement (body bradykinesia), (3.15) Postural tremor of the hands, (3.16) Kinetic tremor of hands, (3.17) Rest tremor amplitude, of (a) RUE, (b) LUE, (c) RLE, (d) LLE and (e) lip/jaw, (3.18) Constancy of rest tremor. Each item is scored 0-4, with total Part III score range 0-132. Part IV, Motor complications, has items (4.1) Time spent with dyskinesias, (4.2) Functional impact of dyskinesias, (4.3) Time spent in “off” state, (4.4) Functional impact of fluctuations, (4.5) Complexity of motor fluctuations, (4.6) Painful “off”-state dystonia, each item scored 0-4, with total Part IV score range 0-24.

The clinimetric properties of the MDS-UPDRS were validated in large international study in 39 centres (USA, 32; Canada, 2; UK 5), with 877 participating PD patients, from all Hoehn-Yahr stages, including drug naïve patients and those taking dopaminergic medication. 483 (55%) had motor fluctuations and 304 (35%) had dyskinesias (Goetz et al., 2008). Our site provided 45 patients’ UPDRS and MDS-UPDRS scores for this validation study (5% of total). Internal consistency, calculated

using Cronbach's alpha, was good for all parts: Part I (13 items) alpha = 0.79, Part II (13 items) alpha = 0.90, Part III (33 items) alpha = 0.93, Part IV (6 items) alpha = 0.79. Convergent validity was demonstrated, with high correlation between MDS-UPDRS and UPDRS total scores (rho = 0.96) and individual parts of the two scales (Part I, rho = 0.76; Part II, rho = 0.92; Part III, rho = 0.96; Part IV [including only items covering motor complications on the UDPRS], rho = 0.89) (Goetz et al., 2008). MDS-UPDRS Part I, II and III showed extremely low floor and ceiling effects, whereas Part IV showed a floor effect, as expected, but there was no ceiling effect.

2.2 Ophthalmological Assessment

A subgroup of patients underwent detailed ophthalmological assessment. The ophthalmological study received ethical approval by The Royal Free Hospital and Medical School Research Ethics Committee, The National Hospital for Neurology and Neurosurgery (NHNN) and Institute of Neurology (ION) Joint Research Ethics Committee. The research governance sponsor of this study was University College London Hospitals/University College London Joint Biomedical Research Unit, R&D Directorate. Ophthalmological study was done in collaboration with Mr Fion Bremner, Consultant Neuro-Ophthalmologist at The National Hospital for Neurology and Neurosurgery, Ms Clare Davey, Consultant Ophthalmologist at The Royal Free NHS Trust, and Mr Alexander Spratt and Mr Ameet Shah, Specialty Registrars in Ophthalmology. All patients provided written consent and underwent a standardised examination, including corrected and uncorrected visual acuity, visual field measurement and examination for structural optic pathology.

2.2.1 Visual acuity

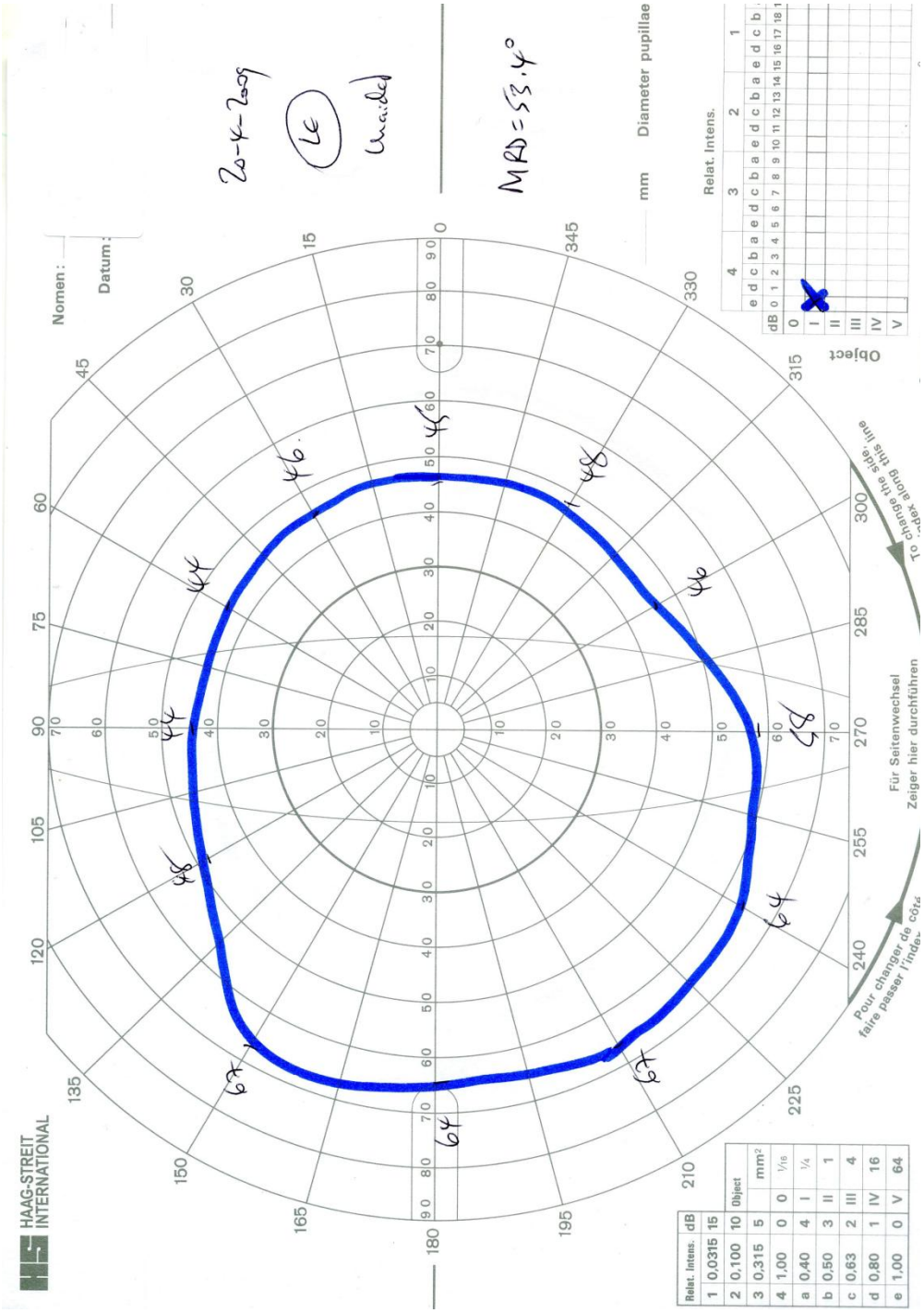
Visual acuity was assessed using Logarithm of Minimal Angle of Resolution (LogMAR) chart, which differs from the standard Snellen chart in that there are an equal number of optotypes (letters) per line (five) and there is regular spacing between lines and letters (spacing between letters is equal to individual letter width and space between rows is equal to height of letters in the row below). The Snellen chart is susceptible to spatial crowding, particularly in the lower rows where there are more optotypes. This can lead to increased errors, particularly with ophthalmic problems such as strabismic amblyopia and therefore the LogMAR chart is proposed to permit more accurate acuity measurement. Also on the Snellen chart there is a single optotype for the

lowest level of acuity (6/60) whereas on the LogMAR chart, there are a consistent five optotypes per row, allowing more accurate assessment in patients with poorer degrees of visual acuity. On the LogMAR chart, there is uniform progression in optotype size (each row corresponds to a logarithmic progression of 0.1 LogMAR). An acuity of 6/6 on the Snellen acuity chart corresponds to LogMAR score zero, with negative scores indicating better than normal visual acuity and positive score indicating power than normal visual acuity. Each line in the chart is scored 0.1 LogMAR and each individual letter is scored 0.02 LogMAR.

2.2.2 Visual fields

Visual field assessment was carried out using Goldmann kinetic perimetry, using standard calibrated equipment (Haag-Streit International), with close observation for correct fixation by the operator, and each eye tested individually (with the other eye covered) and using isopters of equal luminance during the examination and of standard luminance between all subjects tested at the different test sites (National Hospital for Neurology and Neurosurgery and Royal Free Hospital). To quantify visual fields, and allow statistical comparison between patients, Mean Radial Degrees (MRD) valve was determined for each eye, by calculating the average radial distance in degrees from the fixation point at 12 positions, 30 degrees apart (0-360 degrees) as per previously published methods (Newman et al., 2002) (Figure 2.1).

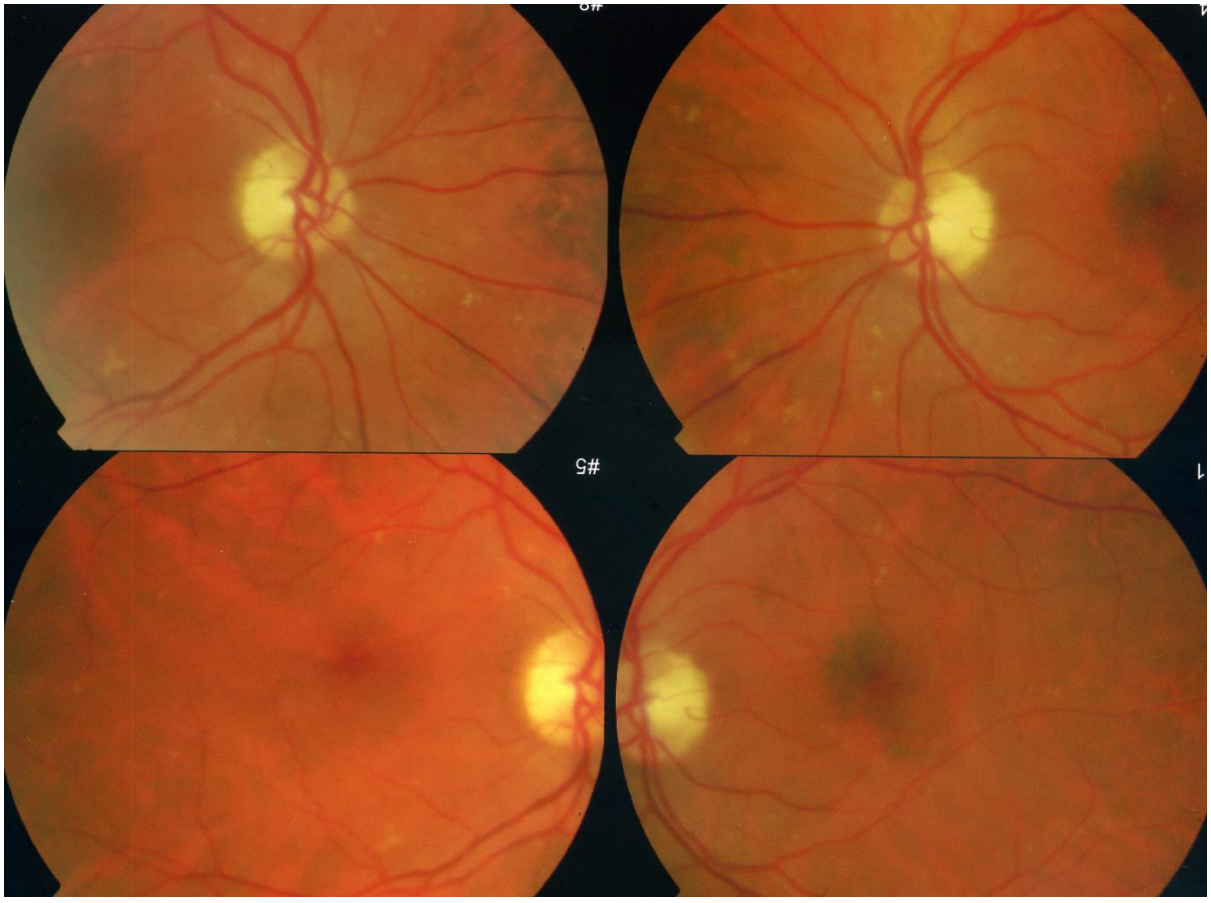
Figure 2.1 Goldmann Kinetic Perimetry: Example of Goldmann kinetic Perimetry from ophthalmology study patient, using isopters of equal luminance (4e) to calculate Mean Radial Degrees (MRD) field measurement from 12 positions at 30 degree intervals.



2.2.3 Ophthalmic examination

Each patient underwent standard ophthalmic examination by an experienced ophthalmologist, and fundal photography was performed (TOPCON Corporation) and images printed (IMAGEnet for Windows^{TM}) (Figure 2.2). Data recorded systematically included (1) presence or absence of corneal pathology; (2) presence or absence of lens pathology, including cataracts, and if present their location (nuclear, cortical or sub capsular) and opacity (semi-quantitative scale: mild, moderate or severe); (3) Retinal changes such as diabetic retinopathy (including grade), macular degeneration (including type) or other pathology.

Figure 2.2 Retinal photography was performed for each patient with optic disc and macula views, to allow standardised retinal assessment.



2.3 Pathological study

The London Multi-Centre Research Ethics Committee has approved procedures for the donation of brains to the Queen Square Brain Bank as well as retention of and access to clinical records. The Queen Square Brain Bank contains a large collection of donated brains, predominantly of subjects with neurodegenerative disorders, particularly extrapyramidal conditions (such as PD, DLB, MSA, PSP, and CBD) and other cognitive disorders (for example, Alzheimer's Disease and the Fronto-Temporal Lobar Degenerations). Each brain is carefully examined by a neuro-pathologist and given a primary diagnosis and where appropriate secondary diagnoses (for example PD, with co-existing Alzheimer's disease/tau pathology). The autopsy cases examined in this thesis have a pathological diagnosis of PD. The ante-mortem clinical records of the subjects are available, including in-patient notes, out-patient documentation and correspondence, and emergency room attendances. Demographic and clinical data has been systematically collected for each donor and includes age at onset of symptoms, age at death, disease duration, dopaminergic medication history (latency to use, duration of use and maximum dose of levodopa, dopamine agonists, mono-amine oxidase inhibitors and catechol-o-methyltransferase inhibitors), and other non-PD medication. Collation of clinical data from donors' medical records was done in collaboration with Dr Sean O'Sullivan, Dr David Williams, Dr Luke Massey and Dr Laura Silveira-Moriyama.

The examination of pathological material for this study was performed by Professor Tamas Revesz, Professor of Neuropathology and Lead of The Queen Square Brain Bank and Laura Parkinnen, Senior Research Fellow. Detailed analysis of LB distribution and density was made in different cortical and brainstem locations to determine whether there is an association with clinical features, such as visual hallucinations. Precise details of the brain locations sampled and methodology for

quantitative assessment of LB is given in Chapter 6, “Testing an aetiological model of visual hallucinations in PD”.

Chapter 3

Impact of non-motor symptoms on quality of life and disability

3.1 Introduction

NMS have long been recognised as an important part of PD (Bulpitt et al., 1985), but until recently have received relatively little attention (Chaudhuri et al., 2006a, O'Sullivan et al., 2008). Whilst many NMS occur in elderly patients without PD, the mean prevalence of NMS symptoms is significantly higher than controls (Chaudhuri et al., 2006b). Several studies have shown that many NMS, and particularly depression (Gallagher & Schrag, 2008), are important determinants of health-related quality of life (Hr-QoL). Despite this, patients' NMS are often under-recognised (Shulman et al., 2002). We therefore undertook a study to (1) assess the prevalence of self-reported NMS in a cross-sectional sample of PD patients, (2) examine the influence of individual NMS on Hr-QoL and disability, (3) determine the extent to which these self-reported NMS are reported in the medical case notes, and (4) to determine how well the NMS most strongly associated with impaired Hr-QoL and disability were detected.

3.2 Methods

3.2.1 Assessment

Consenting patients were assessed with the NMSQ (Martinez-Martin et al., 2007), a screening questionnaire which records the presence or absence of non-motor symptoms, and with scale for Hr-QoL (PDQ-39) and for individual NMS where validated clinimetric scales were available, and the UPDRS (assessed in optimal "on" state) (Fahn & Elton, 1987). The clinical measures used included cognitive scales, ACE (Larner, 2007), SCOPA-COG (Marinus et al., 2003a), and FAB (Dubois et al., 2000); an apathy

scale, LARS (Sockeel et al., 2006); psychosis scale, PPRS (Friedberg et al., 1998); scales to assess mood, HDRS (Schwab et al., 1967) and HADS (Upadhyaya & Stanley, 1993); an autonomic function scale, SCOPA-AUT (Visser et al., 2004), measures of nocturnal sleep and daytime hypersomnolence, PSQI (Buysee et al., 1989), ESS (Johns et al., 1991) and SCOPA-sleep scale (daytime and night time) (Marinus et al., 2003b); a fatigue scale, FSS (Krupp et al., 1989); Visual Analogue Scale of Pain (VAS); ICSD-R diagnostic criteria for RBD (American Academy of Sleep Medicine, 2001); International Restless Leg Syndrome (RLS) Study Group Criteria for the diagnosis of RLS (Walters et al., 2003) and the Parkinson's Disease Questionnaire (PDQ-39) (Fitzpatrick et al., 1997). Except for the NMSQ which is a binary response questionnaire (yes/no), all remaining measures are clinimetric scales with severity response options or formal diagnostic criteria (RBD and RLS). DDS and ICD were recorded and quantified (five point scale) using the structured question in the MDS-UPDRS, item 1.6 (Goetz et al., 2008). Percentage of daytime in the "off" state, "on" with dyskinesia and without dyskinesia was recorded to quantify motor complications.

3.2.2 Symptom Documentation Rate

Participants with the full set of clinical notes (including hand written notes, correspondence, requests and results of investigations) had their notes reviewed for documentation or action taken on non-motor and motor symptoms. The review included all documented patient contacts up to the neurology clinic visit at the date of completion of the NMSQ.

3.2.3 Statistical Analysis

Histograms of data were visually inspected for normality of distribution. Results were expressed as mean ± standard deviation or median and range. Comparison of PDQ-39

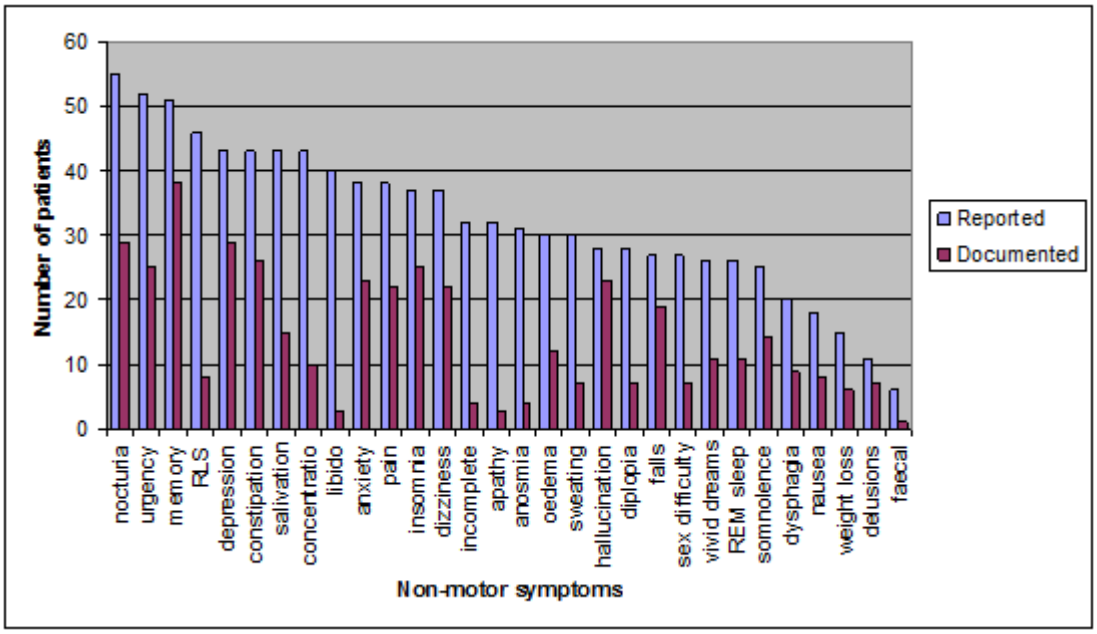
scores in patients with and without individual non-motor symptoms (identified on the NMSQ) was made using one–way analysis of variation (ANOVA) corrected for multiple comparisons using the Bonferroni correction. Symptom severity as assessed on specific scales was correlated with PDQ-39 and Schwab and England disability scores, using Spearman rank correlation. Stepwise multiple regression analysis was performed using SPSS (version 14.0). Assumption of linearity was confirmed using scatterplots. For collinear variables (e.g. HADS-depression scale and HDRS), clinimetric scales with higher Spearman regression coefficient in univariate analysis were chosen for regression analysis. Levodopa equivalent unit (LEU) was calculated based on theoretical equivalence used in previous reports (Evans et al., 2004).

3.3 Results

3.3.1 Prevalence of non-motor symptoms

In the 89 out of 94 patients (please see demographic details, table 6.1, page 144) in whom full notes were available, the most commonly reported non-motor symptoms on the NMSQ were nocturia (62%), urgency of micturition (58%), memory difficulties (57%), RLS (52%), hypersalivation (48%), constipation (48%), impaired concentration (48%), low mood (48%), changed libido (45%) and anxiety (43%) (table 3.1). Five of the 10 most prevalent symptoms on the NMSQ were autonomic. Overall patients reported a mean of 11.0 non-motor symptoms. In addition, 15/94 (16%) had evidence of DDS or ICD (score ≥ 1 MDS-UPDRS item 1.6) and 55/94 (59%) had significant fatigue (FSS≥4), both of which are not recorded on the NMSQ.

Figure 3.1: The prevalence of self-reported non-motor symptoms using the Non-Motor Symptom Questionnaire (NMSQ) in a cross-sectional sample of Parkinson's disease patients, given in order of prevalence and their documentation rate in a retrospective case-notes audit.



3.3.2 Impact of non-motor and motor symptoms on Hr-QoL

3.3.2.1 Patient completed and physician administered clinimetric scales

The severity of non-motor symptoms on most individual scales correlated more strongly with Hr-QoL than motor function on the UPDRS (table 3.1). The following were strongly correlated with PDQ-39: autonomic function on the SCOPA-AUT, including gastrointestinal, urinary and thermoregulatory domains; mood, fatigue, night-time sleep and daytime somnolence, psychosis and pain. Motor function (UPDRS part III) had a moderate correlation with PDQ-39, which was lower than all of the above non-motor clinimetric variables. Anxiety, apathy and global cognitive function had a weaker correlation with PDQ-39 than motor function (UPDRS). Neither frontal lobe cognitive function nor presence and severity of DDS/ICD score were correlated with PDQ-39

scores. Percentage daily “off”-time and dyskinesia time also correlated with PDQ-39 scores (table 3.1).

The mean PDQ-39 score of patients with and without each non-motor symptom on NMSQ was compared using one-way ANOVA and corrected for multiple comparisons (Bonferroni-corrected significant p-value <0.0017). 18 of 30 non-motor symptoms reached statistical significance (table 3.2). Presence of DDS/ICD (not included in the NMSQ) was not found to be significantly associated with lower Hr-QOL scores (DDS/ICD mean PDQ-39 =30.4±17.0 versus 24.4±16.9 for non-DDS/ICD, p=0.24).

Table 3.1 Correlation of the health related quality of life with non-motor and motor scores

Domains	Clinimetric Scale	Spearman's rank correlation coefficient with PDQ-39 subscales								
		Summary Index	Mobility	Activities Daily Living	Emotion	Stigma	Social	Cognitions	Communication	Bodily Discomfort
Non-Motor Scores										
Autonomic Function	SCOPA-AUT -Total	**0.84** [A]	**0.65** [A]	**0.71** [A]	**0.62** [A]	0.40 [A]	**0.58** [A]	**0.68** [A]	**0.72** [A]	**0.59** [A]
	-Gastrointestinal	**0.62** [A]	**0.51** [A]	**0.53** [A]	0.41 [A]	0.25 [C]	0.36 [B]	**0.52** [A]	**0.51** [A]	0.40 [A]
	-Urinary	**0.71** [A]	**0.61** [A]	**0.60** [A]	**0.55** [A]	0.28 [C]	0.45 [A]	**0.60** [A]	**0.62** [A]	0.47 [A]
	-Cardiovascular	0.41 [A]	0.31 [C]	0.42 [A]	0.30 [C]	0.21 [C]	0.36 [B]	0.42 [A]	0.42 [A]	0.18
	-Thermoregulatory	**0.57** [A]	0.34 [B]	0.46 [A]	0.48 [A]	0.41 [A]	0.42 [A]	0.41 [A]	0.38 [B]	**0.56** [A]
	-Sexual	0.48 [C]	0.37 [C]	**0.54** [B]	0.38 [C]	0.07	0.28	0.33 [C]	0.42 [C]	0.38 [C]
Pain	Visual analogue Scale	**0.56** [A]	0.40 [A]	0.36 [B]	0.47 [A]	0.35 [B]	0.39 [B]	0.40 [A]	0.36 [B]	**0.68** [A]
Sleep	PSQI	**0.55** [A]	0.44 [A]	0.37 [B]	0.46 [A]	0.26 [C]	0.43 [A]	0.39 [B]	0.33 [C]	**0.64** [A]
	ESS	**0.63** [A]	0.48 [A]	**0.53** [A]	0.40 [A]	0.30 [C]	0.39 [B]	**0.76** [A]	**0.54** [A]	0.40 [B]
	SCOPA sleep (night)	0.49 [A]	0.32 [C]	0.29 [C]	**0.57** [A]	0.34 [C]	0.45 [A]	0.30 [C]	0.28 [C]	**0.56** [A]
	SCOPA sleep (day)	**0.65** [A]	**0.53** [A]	0.45 [A]	0.40 [A]	0.29 [C]	0.36 [B]	**0.75** [A]	**0.52** [A]	0.44 [A]

Fatigue	FSS	**0.74** [A]	**0.69** [A]	**0.58** [A]	**0.56** [A]	0.36 [B]	0.43 [A]	**0.58** [A]	**0.51** [A]	**0.50** [A]
Apathy	LARS	0.35 [B]	0.25 [C]	0.39 [B]	0.31 [C]	-0.18	0.16	0.42 [A]	0.40 [A]	0.26 [C]
Psychosis	PPRS	**0.55** [A]	0.39 [B]	0.47 [A]	0.39 [B]	0.26 [C]	0.34 [C]	**0.62** [A]	**0.53** [A]	0.25 [C]
Mood	HDRS	**0.64** [A]	0.46 [A]	0.50 [A]	**0.65** [A]	0.33 [C]	0.37 [B]	0.42 [A]	0.41 [A]	**0.60** [A]
	HADS-Anxiety	0.44 [A]	0.23 [C]	0.24 [C]	**0.65** [A]	0.31 [C]	0.44 [A]	0.31 [C]	0.25 [C]	0.43 [A]
	HADS-Depression	**0.74** [A]	**0.58** [A]	**0.56** [A]	**0.65** [A]	0.33 [C]	0.49 [A]	**0.55** [A]	**0.55** [A]	**0.62** [A]
Cognition	ACE	-0.22 [C]	-0.25 [C]	-0.13	-0.18	0.01	-0.01	-0.32 [C]	-0.20	-0.08
	FAB	-0.15	-0.14	-0.19	-0.12	0.13	0.01	-0.32 [C]	-0.15	-0.10
	SCOPA-COG	-0.25 [C]	-0.21 [C]	-0.19	-0.24 [C]	0.01	-0.06	-0.35 [B]	-0.17	-0.19
DDS/ICD	Five-point scale (MDS-UPDRS)	0.14	0.02	0.05	0.24 [C]	0.02	0.26 [C]	0.09	0.19	0.16
Motor Scores										
Motor Function	UPDRS (III)	0.48 [A]	0.44 [A]	**0.55** [A]	0.28 [C]	0.06	0.24 [C]	0.41 [A]	0.42 [A]	0.30 [C]
Motor Complications	UPDRS (IV)	**0.66** [A]	**0.51** [A]	0.49 [A]	0.49 [A]	0.44 [A]	**0.57** [A]	**0.56** [A]	**0.51** [A]	0.47 [A]
Fluctuations	% daytime "off"	**0.57** [A]	0.47 [A]	0.41 [A]	0.41 [A]	0.37 [B]	0.47 [A]	0.46 [A]	0.39 [B]	0.48 [A]
Dyskinesia	% daytime with dyskinesia	0.43 [A]	0.27 [C]	0.34 [B]	0.36 [B]	0.41 [A]	0.41 [A]	0.40 [A]	0.32 [C]	0.21 [C]

Abbreviations SCOPA-AUT=Scales for outcome in Parkinson's disease, Autonomic scale, PSQI=Pittsburgh Sleep Quality Index, ESS=Epworth Sleepiness Scale, FSS=Fatigue Severity Scale, LARS=Lille Apathy Rating Scale, PPRS=Parkinson Psychosis Rating Scale, HDRS=Hamilton Depression Rating Scale, HADS=Hospital Anxiety Depression Scale, ACE=Addenbrooke's Cognitive Examination, FAB=Frontal Assessment Battery, SCOPA-COG=Scales for outcome in Parkinson's disease, cognitive scale, ICD=Impulse Control Disorder, DDS=Dopamine Dysregulation Syndrome, UPDRS=Unified Parkinson's Disease Rating Scale, Part III (motor score), Part IV (motor complications), MDS-UPDRS=Movement Disorder Society Sponsored Revision of the UPDRS.

Statistics High correlations (>0.50) given in bold. Statistical significance: ^{A} P<0.0001, ^{B} P<0.001 ^{C} P<0.05

Table 3.2 Impact of individual non-motor symptoms on quality of life. One way ANOVA with Bonferroni correction (n=30 comparisons, significance set at P<0.0017) of mean quality of life scores (Parkinson Disease Questionnaire – 39 item version, summary index, PDQ-39) in presence or absence of symptoms on the Non-Motor Symptom Questionnaire (NMSQ). Significant P values are given in bold. Documentation rate of individual non-motor symptoms, identified in retrospective case notes audit.

Non-motor symptom	Mean PDQ-39-SI (±SD)		P value	Detection (%)
	Present	Absent		
Hypersalivation	31.3 (17.3)	19.9 (14.8)	**0.0012**	34.9
Loss of taste/smell	30.5 (16.2)	22.4 (16.8)	0.027	12.9
Dysphagia	35.8 (15.9)	22.2 (16.1)	**0.0017**	45.0
Nausea	29.4 (19.2)	24.3 (16.4)	0.32	44.4
Constipation	33.0 (15.9)	18.3 (14.8)	**<0.0001**	60.5
Faecal incontinence	42.2 (18.9)	24.2 (16.3)	0.067	16.7
Incomplete bowel emptying	32.4 (11.3)	21.4 (18.3)	**0.0006**	12.5
Urgency	30.5 (17.3)	18.4 (14.0)	**0.0004**	48.1
Nocturia	29.5 (16.4)	18.5 (15.8)	0.0022	52.7
Pain	35.2 (16.8)	18.1 (13.1)	**<0.0001**	57.9
Weight change	33.9 (17.3)	23.5 (16.4)	0.038	40.0
Memory	30.5 (16.3)	18.3 (15.4)	**0.0004**	74.5
Apathy	38.4 (15.1)	18.7 (13.8)	**<0.0001**	9.4
Hallucinations	37.3 (16.9)	20.4 (14.4)	**<0.0001**	82.1
Concentration	34.7 (15.5)	17.1 (13.6)	**<0.0001**	23.3
Depression	32.6 (18.4)	18.9 (12.7)	**0.0001**	67.4
Anxiety	32.3 (17.1)	20.4 (15.2)	**0.0009**	60.5
Libido	31.2 (14.3)	20.6 (17.6)	0.0019	7.5
Sexual difficulty	28.8 (13.6)	23.8 (18.1)	0.15	25.9
Dizziness	33.0 (17.0)	20.4 (15.1)	**0.0006**	59.5
Falling	35.3 (15.2)	21.2 (16.0)	**0.0002**	70.4
Daytime somnolence	36.3 (17.3)	21.2 (15.0)	**0.0004**	56.0
Insomnia	30.4 (16.1)	21.9 (16.9)	0.018	67.6
Vivid dreaming	34.2 (17.6)	22.0 (15.6)	0.0041	42.3
REM sleep disorder	34.4 (13.9)	21.7 (16.8)	**0.0005**	42.3
Restless leg syndrome	31.9 (17.4)	19.1 (14.1)	**0.0002**	17.4
Leg swelling	31.9 (17.3)	22.0 (15.9)	0.010	40.0
Excessive sweating	33.0 (17.5)	21.6 (15.5)	0.038	23.3
Double vision	36.6 (16.5)	20.7 (14.9)	**<0.0001**	25.0
Delusions	38.7 (11.1)	23.7 (16.9)	0.0019	63.6

3.3.2.2 Early versus later Parkinson's disease

In the group with ≤5 years disease duration (table 3.3), depression, autonomic function, pain and fatigue had the highest correlation with PDQ-39, and in the group with > 5 years disease duration, autonomic function, fatigue, depression and daytime hypersomnolence had highest correlation with PDQ-39 scores. When individual subscales on SCOPA-AUT were considered, differences between ≤5 years and >5 years groups are evident (most marked for sexual dysfunction: $r=0.59$, $p<0.05$ in early PD versus $r=0.08$, not significant, in later PD). In the group with H&Y stage ≤ 2, fatigue, autonomic function, depression, and overall sleep had highest correlation with PDQ-39 and in group with H&Y >2 autonomic function, daytime hypersomnolence, depression and psychosis had highest correlation. In both early and later disease (determined by either disease duration or H&Y stage) NMS had higher correlations with Hr-QOL scores than motor scores (UPDRS part III), overall motor complications (UPDRS part IV), dyskinesias and "off"-time. UPDRS part IV had highest correlation with Hr-QOL in H&Y>2 group ($r=0.67$), but this was still less than non-motor symptoms (depression, autonomic function and daytime somnolence, table 3.3).

Table 3.3 Correlation of health-related quality of life with non-motor symptom and motor scores in patients with disease duration ≤ and >5 years or Hoehn-Yahr stage ≤2 or >2.

Domain	Clinimetric Scale	Correlation with PDQ-39 index			
		≤5 years (n=45)	> 5 years (n=47)	H&Y ≤2 (n=56)	H&Y >2 (n=36)
Non-motor scales					
Depression	HADS-Depression	0.81[A]	0.62[A]	0.74[A]	0.73[A]
Autonomic (Total)	SCOPA-AUT	0.79[A]	0.72[A]	0.82[A]	0.87[A]
Pain	VAS	0.66[A]	0.37[C]	0.61[A]	0.44[C]
Depression	HDRS	0.65[A]	0.49[B]	0.65[A]	0.57 [B]
Urinary	SCOPA-AUT-Urinary	0.64[A]	0.64[A]	0.73[A]	0.66[A]
Gastrointestinal	SCOPA-AUT-Gastrointestinal	0.63[A]	0.32[C]	0.60[A]	0.63[A]
Fatigue	FSS	0.60[A]	0.69[A]	0.82[A]	0.54[B]
Sexual	SCOPA-AUT-Sexual	0.59[C]	0.08	0.52[B]	0.57[C]
Psychosis	PPRS	0.49[B]	0.40[C]	0.47[B]	0.60[B]
Thermoregulation	SCOPA-AUT-Thermoregulatory	0.49[B]	0.54[A]	0.51[A]	0.67[A]
Sleep	SCOPA-day	0.47[C]	0.50[B]	0.55[A]	0.76[A]
Sleep	SCOPA-night	0.44[C]	0.45[C]	0.57[A]	0.37[C]
Anxiety	HADS-Anxiety	0.42[C]	0.39[C]	0.40[B]	0.51[C]
Apathy	LARS	0.39[C]	0.32[C]	0.43[B]	0.26
Sleep	PSQI	0.32[C]	0.45[C]	0.62[A]	0.37[C]
Sleep	ESS	0.32[C]	0.43[C]	0.56[A]	0.74[A]
Global cognition	SCOPA-COG	0.32[C]	0.21	0.20	0.14
Cardiovascular	SCOPA-AUT-Cardiovascular	0.30[C]	0.25	0.36[C]	0.39[C]
Global cognition	ACE	0.27	0.24	0.06	0.27
Frontal cognition	FAB	0.25	0.08	0.07	0.09
Motor scales					
Motor function	UPDRS part III	0.37[C]	0.35[C]	0.45[B]	0.40[C]
Motor complication	UPDRS part IV	0.49[B]	0.45[C]	0.60[A]	0.67[A]
"off" time	Percentage	0.34[C]	0.41[C]	0.56[A]	0.45[C]
Dyskinesia	Percentage	0.13	0.21	0.36[C]	0.47[C]

Abbreviations: H&Y=Hoehn & Yahr, SCOPA-AUT=Scales for outcome in Parkinson's disease, Autonomic scale, PSQI=Pittsburgh Sleep Quality Index, ESS=Epworth Sleepiness Scale, FSS=Fatigue Severity Scale, LARS=Lille Apathy Rating Scale, PPRS=Parkinson Psychosis Rating Scale, HDRS=Hamilton Depression Rating Scale, HADS=Hospital Anxiety Depression Scale, ACE=Addenbrooke's Cognitive Examination, FAB=Frontal Assessment Battery, SCOPA-COG=Scales for outcome in Parkinson's disease, cognitive scale, UPDRS (III) =Unified Parkinson's Disease Rating Scale, Part III (motor part).

Spearman Rank Correlation coefficients; [A] P<0.0001, [B] P<0.001 [C] P<0.05

3.3.2.3 Multiple Regression Analysis

Using multiple regression analysis with the PDQ-39 index score as the dependent variable, nine scales with the strongest, unrelated univariate association with PDQ-39 index scores were entered (SCOPA-AUT, HADS-depression, FSS, SCOPA-daytime sleep, PPRS, pain VAS, PSQI, HADS-anxiety and UPDRS part III). Significant predictors of PDQ-39 scores were SCOPA-AUT, SCOPA sleep daytime, HADS-depression and FSS (total adjusted R^2 change [R^2] 0.79, table 3.3). When individual SCOPA-subscores were entered (excluding sexual dysfunction due to number of missing data) together with SCOPA sleep daytime, HADS-depression and FSS, the results were similar with HADS depression as the main predictor of PDQ-39 scores, followed by the FSS, SCOPA-AUT thermoregulation, SCOPA-AUT gastrointestinal, SCOPA-AUT cardiovascular, SCOPA-sleep day-time and SCOPA-AUT urinary (R^2=0.77, table 3.4). Repeating the analysis with all of the above variables did not change this result. The additional binary variables (RBD, RLS) that were not covered by clinimetric scales individually added to this model had no significant predictive effect on the multiple regression model. Inclusion of additional motor variables (postural instability on the UPDRS, UPDRS part IV, percentage "off" time, percentage time with dyskinesia) also did not add to the predictive effect in the regression model. In the ≤5 years disease duration group, using multiple regression analysis, HADS-depression, SCOPA-AUT and FSS (R^2=0.81) were significant predictors of Hr-QoL. In the >5 years disease duration group SCOPA-AUT and FSS (R^2=0.64) were significant predictors of Hr-QoL. In the H&Y ≤2 group, FSS, SCOPA-AUT and PSQI (R^2=0.76) and in the H&Y >2 group, SCOPA-AUT, SCOPA-sleep daytime, HADS-depression (R^2=0.81) were significant predictors using multiple regression analysis. In all groups (≤5 or >5 years disease duration and H&Y stage ≤2 or 2) addition of UPDRS part IV, percentage "off" time or percentage dyskinesia time did not contribute to the regression model.

Table 3.4 Regression analysis of clinical determinants of quality of life in Parkinson's disease

Logistic regression model	Cumulative adjusted R^2	Standardized β coefficient	t value	p value
Clinical scale summary indices				
SCOPA-AUT	0.68	0.49	6.77	<0.001
SCOPA sleep (daytime)	0.74	0.17	2.61	0.011
HADS-depression	0.77	0.22	3.05	0.003
FSS	0.79	0.18	2.69	0.009
Including autonomic subscales				
HADS-depression	0.53	0.22	2.89	0.005
FSS	0.64	0.17	2.22	0.029
SCOPA-AUT thermoregulation	0.69	0.22	3.33	0.001
SCOPA-AUT gastrointestinal	0.73	0.18	2.85	0.006
SCOPA-AUT cardiovascular	0.75	0.15	2.77	0.007
SCOPA sleep (daytime)	0.76	0.16	2.27	0.026
SCOPA-AUT urinary	0.77	0.16	2.15	0.035

Abbreviations: SCOPA=Scales for Outcome in Parkinson's disease, SCOPA-AUT=SCOPA autonomic, HADS=Hospital Anxiety and Depression Scale, FSS=Fatigue Severity Scale.

3.3.3 Impact of non-motor and motor symptoms on disability

3.3.3.1 Univariate analysis

Motor function (UPDRS Part III) had the highest correlation with S&E disability scores. Motor fluctuations score (UPDRS Part IV) and the majority of non-motor scales also correlated significantly with disability, particularly autonomic symptoms, fatigue, depression, psychosis, pain, daytime somnolence, nocturnal insomnia, cognitive impairment and apathy (rho > 0.40) (table 3.5). In the ≤5 years disease duration group, motor function, depression, cognition, autonomic function, pain, and fatigue had highest correlation with S&E score, and in the >5 years disease duration group, motor function, cognition, psychosis, and apathy had highest correlation with S&E (rho > 0.40) (table 3.5). In the H&Y stage ≤ 2 group, fatigue, motor function, pain, autonomic function, insomnia, depression, motor fluctuations, apathy, and psychosis had highest correlation with S&E score, and in the H&Y>2 group, daytime somnolence, motor function, autonomic symptoms, psychosis, motor fluctuations, depression and apathy had highest correlation with S&E (rho > 0.40) (table 3.5).

Table 3.5. Correlation of Schwab & England disability score with non-motor symptom and motor scores in patients with disease duration ≤ and >5 years.

Domain	Clinimetric Scale	Correlation with S&E				
		Total (n=94)	≤ 5 years (n=46)	> 5 years (n=48)	H&Y ≤2 (n=57)	H&Y >2 (n=37)
Non-motor scales						
Autonomic	SCOPA-Autonomic	0.58 [A]	0.48 [B]	0.39 [C]	0.58 [A]	0.57 [A]
Pain	VAS	0.49 [A]	0.47 [C]	0.28	0.60 [A]	0.33 [C]
Sleep	PSQI	0.41 [A]	0.36 [C]	0.10	0.52 [A]	0.10
	ESS	0.47 [A]	0.12	0.18	0.35 [C]	0.63 [A]
	SCOPA-sleep-night	0.27 [C]	0.32 [C]	0.06	0.37 [C]	0.11
	SCOPA-sleep-day	0.46 [A]	0.34 [C]	0.18	0.35 [C]	0.53 [B]
Fatigue	FSS	0.55 [A]	0.47 [B]	0.31 [C]	0.65 [A]	0.32
Apathy	LARS	0.41 [A]	0.37 [C]	0.46 [C]	0.42 [C]	0.42 [C]
Psychosis	PPRS	0.50 [A]	0.35 [C]	0.49 [A]	0.40 [C]	0.51 [C]
Mood	HDRS	0.49 [A]	0.51 [A]	0.22	0.47 [A]	0.46 [C]
	HADS-Anxiety	0.30 [C]	0.28	0.19	0.29 [C]	0.27
	HADS-Depression	0.52 [A]	0.56 [A]	0.27	0.51 [A]	0.44 [C]
Cognition	ACE	0.38 [A]	0.48 [B]	0.39 [C]	0.28 [C]	0.30
	FAB	0.38 [A]	0.46 [C]	0.36 [C]	0.30 [C]	0.28
	SCOPA-Cognitive	0.45 [A]	0.47 [B]	0.51 [A]	0.35 [C]	0.35 [C]
Motor scales						
Motor function	UPDRS part III	0.68 [A]	0.63 [A]	0.57 [A]	0.64 [A]	0.61 [A]
Motor complication	UPDRS part IV	0.55 [A]	0.36 [C]	0.29 [C]	0.44 [B]	0.47 [C]
"off" time	Percentage	0.52 [A]	0.35 [C]	0.29 [C]	0.45 [A]	0.31
Dyskinesia	Percentage	0.37 [A]	0.40	0.18	0.27 [C]	0.36 [C]

Abbreviations: S&E=Schwab & England, H&Y=Hoehn-Yahr, SCOPA-AUT=Scales for outcome in Parkinson's disease, VAS=Visual Analogue Scale, PSQI=Pittsburgh Sleep Quality Index, ESS=Epworth Sleepiness Scale, FSS=Fatigue Severity Scale, LARS=Lille Apathy Rating Scale, PPRS=Parkinson Psychosis Rating Scale, HDRS=Hamilton Depression Rating Scale, HADS=Hospital Anxiety Depression Scale, ACE=Addenbrooke's Cognitive Examination, FAB=Frontal Assessment Battery, SCOPA-COG=Scales for outcome in Parkinson's disease, cognitive scale, UPDRS =Unified Parkinson's Disease Rating Scale.

Statistical significance: [A] P<0.0001, [B] P<0.001 [C] P<0.05

3.3.3.2 Multiple Regression Analysis

Using multiple regression analysis with the S&E score as the dependent variable, nine scales with the strongest, unrelated univariate association with S&E scores were entered (UPDRS Part III, SCOPA-AUT, UPDRS Part IV, FSS, HADS-D, PPRS, pain VAS, ESS, SCOPA-COG). Significant predictors of S&E scores were UPDRS Part III, UPDRS Part IV and SCOPA-COG, total adjusted R^2=0.58, (table 3.6). A regression analysis was also performed with the six clinically distinct factors identified for the UPDRS Part III (axial features/gait, right and left limb bradykinesia, rigidity, and rest and postural tremor) (Stebbins & Goetz, 1998). Axial bradykinesia (adjusted R^2 0.67, beta -0.82, t-score -13.84, $p < 0.001$) was significant predictor of disability in this model. Subgroup analysis was performed based on disease duration and H&Y stage. For each analysis, the five variables with highest univariate correlation were chosen, excluding collinear variables. In the ≤5 years disease duration group, using multiple regression analysis, UPDRS Part III, ACE, HADS-D (R^2=0.67) were significant predictors of disability and in the >5 years disease duration group UPDRS Part III, SCOPA-COG, and SCOPA-autonomic (R^2=0.54) were significant. In the H&Y ≤2 group, UPDRS Part III, FSS, Pain VAS were significant predictors of disability (R^2=0.56) and in the H&Y > 2 group ESS and UPDRS Part III were significant (table 3.6).

Table 3.6 Regression analysis of clinical determinants of Schwab & England disability score in Parkinson's disease

Logistic regression model	Cumulative adjusted R^2	Standardized β coefficient	t value	p value
Overall				
UPDRS Part III	0.40	-0.47	-6.18	<0.001
UPDRS Part IV	0.52	-0.33	-4.45	<0.001
SCOPA-COG	0.58	0.24	3.28	0.001
Disease duration ≤ 5 years				
UPDRS Part III	0.51	-0.38	-3.26	0.002
ACE	0.61	0.35	3.50	0.001
HADS-depression	0.67	-0.31	-2.86	0.007
Disease duration > 5 years				
UPDRS Part III	0.31	-0.43	-4.05	<0.001
SCOPA-COG	0.48	0.38	3.68	0.001
SCOPA-Autonomic	0.54	-0.25	-2.34	0.024
H&Y ≤ 2				
UPDRS Part III	0.42	-0.49	-4.68	<0.001
FSS	0.53	-0.29	-2.59	0.013
Pain (VAS)	0.56	-0.20	-2.02	0.049
H&Y > 2				
ESS	0.39	-0.45	-3.42	0.002
UPDRS Part III	0.52	-0.40	-3.02	0.005

Abbreviations: UPDRS =Unified Parkinson's Disease Rating Scale, ACE=Addenbrooke's Cognitive Examination, HADS=Hospital Anxiety Depression Scale, SCOPA-COG=Scales for outcome in Parkinson's disease, cognitive scale, SCOPA-AUT=Scales for outcome in Parkinson's disease, autonomic scale, FSS=Fatigue Severity Scale, VAS=Visual Analogue Scale, ESS=Epworth Sleepiness Scale.

3.3.4 Documentation rate of non-motor symptoms

A mean of 4.8 non-motor symptoms were documented per patient in the clinical notes, a detection rate of 44% (table 3.7). Cognitive and neuropsychiatric complications of PD were generally well documented: hallucinations (82%), memory loss (75%), mood alteration (67%), delusional thought disorder (64%) and anxiety (61%) (figure 3.1 and table 3.2). The NMSQ is divided into nine domains and detection of symptoms in the hallucination/delusions (77%) and depression/anxiety (64%) domains were highest. Except for cardiovascular symptoms (64%), autonomic symptoms and in particular sexual function were poorly documented (urinary symptoms 50%, digestive 35% and sexual problems 15%). Problems in the domains apathy/attention/memory were documented in 40% and sleep problems in 43% (table 3.7).

Table 3.7 Detection of non-motor symptoms: Number of self-reported symptoms on the non-motor symptom questionnaire (NMSQ) by domain, and detection rate calculated from documentation in the clinic notes and correspondence.

NMSQ Domain (items)	Symptoms (total, N=89)	Symptoms (mean per patient)	Detected (N)	Detected (mean per patient)	Percentage (%)
Digestive (7)	193	2.2	67	0.8	34.7
Urinary (2)	107	1.2	54	0.6	50.5
Apathy, Attention, Memory (3)	126	1.4	51	0.6	40.5
Hallucination/Delusion (2)	39	0.4	30	0.3	76.9
Depression/Anxiety (2)	81	0.9	52	0.6	64.2
Sexual (2)	67	0.8	10	0.1	14.9
Cardiovascular (2)	64	0.7	41	0.5	64.1
Sleep (5)	160	1.8	69	0.8	43.1
Miscellaneous (5)	141	1.6	54	0.6	38.3
TOTAL (30)	978	11.0	428	4.8	43.8

3.4 Discussion

3.4.1 Quality of Life

This study found that NMS are common (>10 per patient) and have a significant association with poor Hr-QoL of patients which, in patients in specialist care, exceeds the impact of motor dysfunction. This association was found in advanced disease where symptoms of autonomic dysfunction and fatigue had the strongest association with poorer Hr-QoL but also in early disease (<5 years disease duration), where depression, autonomic dysfunction and fatigue were the strongest predictors of PDQ-39 scores.

The prevalence of overall and individual NMS in PD in this study was similarly high as in other studies, including autonomic symptoms (particularly nocturia and urgency), impairment of cognition and concentration, and psychiatric features such as depression and anxiety (Martinez-Martin et al., 2007, Cheon et al., 2008, Barone et al., 2009). Numerous studies have also assessed the clinical determinants of Hr-QoL in PD (Gallagher & Schrag, 2008), but most have focused on motor symptoms (disease severity and motor complications), disability and depression. However, these studies have been limited by the clinical scales used and, except for neuropsychiatric symptoms (depression, anxiety, cognition, hallucinations) other NMS have been included inconsistently and often without validated scales. The present study provides the most comprehensive and in-depth assessment of the range of recognised NMS in PD and their relative relationship to patients' Hr-QoL as well as their recognition rate in clinical practice.

Depression has consistently been shown to be one of the most important determinants of Hr-QoL in PD in these studies (Gallagher & Schrag, 2008), with additional associations of Hr-

QoL with disability, disease severity, gait, postural stability, motor complications, levodopa medication, cognition, fatigue, sleep, and satisfaction with explanation of diagnosis (Karlsen et al., 1999, Gomez-Esteban et al., 2007, Schrag et al., 2000, Global Parkinson's Disease Survey Steering Committee, 2002, Martinez-Martin et al., 2006). Despite the high impact of fatigue and autonomic dysfunction on Hr-QOL in our study, these variables have been infrequently included in previous Hr-QOL studies. However fatigue (Martinez-Martin et al., 2006, Qin et al., 2009) and autonomic function (Visser et al., 2008) have been shown to contribute to overall Hr-QOL in some regression models. Cognitive impairment had a statistically significant but modest correlation of with Hr-QOL in univariate analyses (ACE, r=0.22 and SCOPA-COG, r=0.25). The strength of this association is of similar magnitude as the modest correlation in other studies in the literature (ranging from r=0.24 to 0.32 [Schrag et al., 2000, Visser et al., 2008, Carod-Artal et al., 2007, Slawek et al., 2005, Cubo et al., 2002]). However, when other confounding clinical variables were considered in this and other studies, cognitive scores did not (Visser et al., 2008, Slawek et al., 2005, Cubo et al., 2002, Kuopio et al., 2000) or minimally (Schrag et al., 2000) contribute to overall Hr-QOL prediction. Our results also confirm a moderately strong association between Hr-QOL and motor score (r=0.48), similar to regression coefficients reported in the literature (ranging from r=0.33 to 0.53 (Gomez-Esteban et al., 2007, Schrag et al., 2000, Visser et al., 2008, Carod-Artal et al., 2007, Slawek et al., 2005, Cubo et al., 2002). However, when other confounding variables are considered, UPDRS motor score has not been shown to be a major contributor to Hr-QOL (Slawek et al., 2005, Cubo et al., 2002, Greene & Camicioli, 2007).

3.4.2 Disability

As expected motor features (severity of motor symptoms and motor complications) had high correlation with disability score; however non-motor features also had significant association with disability. This association was found in advanced disease where motor impairment,

cognitive impairment and autonomic dysfunction had the strongest association with increased disability but also in early disease (<5 years disease duration), where motor function, cognitive impairment and depression, were the strongest predictors. Only a few previous studies have examined the influence of motor and non-motor symptoms on disability in PD and compared to our study, these have been more limited in terms of the number of predictive measures included. For example, one study assessed the influence of motor features (UPDRS), cognitive function (MMSE and a battery of neuropsychological tests to measure attention, psychomotor speed, memory, executive function and visuospatial function) and mood (HADS) on three disability measures (S&E, AMC [American Medical Center] -Linear Disability Score [ALDS] and Functional Independence Measure [FIM]) (Muslimovic et al., 2008). The motor features, axial impairment, bradykinesia and hypomimia contributed to S&E score in the regression analysis (35% of variance); axial impairment and medical comorbidity contributed to ALDS score (37% of variance) and axial impairment, comorbidity, hypomimia, and executive function (semantic verbal fluency) contributed to FIM score (45% variance). In each case axial UPDRS score was the strongest predictor. A longitudinal study examined determinants of progression of disability (Post et al., 2011). Age at onset and motor subscore were significant predictors of progression of S&E score and age at onset, motor subscore and comorbidities were significant predictors of ALDS. Our results are consistent with these findings, with motor severity and motor complications significant predictors in the regression model, and on separate analysis axial symptoms having a large influence on disability. However, the inclusion of other non-motor variables in this study demonstrated the impact of non-motor features, including cognitive impairment (overall regression model), depression (<5 years disease duration), autonomic symptoms (>5 years duration), fatigue and pain (H&Y stage $\leq$ 2) and daytime somnolence (H&Y stage >2) on disability in PD.

3.4.3 Documentation of non-motor symptoms

Whilst some of the NMS were well documented, others were poorly documented in clinic notes, particularly seemingly PD-unrelated ones, such as apathy, or potentially embarrassing ones, such as faecal incontinence, which patients may be unlikely to report spontaneously and may not be routinely enquired about. Depression, which has high impact on Hr-QoL in the multivariate analysis, and other neuropsychiatric complications (such as hallucinations and delusions) were generally well detected although documentation rate was less than 100%. A low detection rate of NMS has been reported in previous studies (Shulman et al., 2002, Sullivan et al., 2007). In one study (Sullivan et al., 2007) depression, anxiety and constipation were addressed and treated in only 50% of patients, with even lower detection rates for other NMS such as fatigue (6%), memory (9%), somnolence (16%), insomnia (30%), incontinence (35%) and pain (35%). Another study (Shulman et al., 2002) found a lower diagnostic sensitivity for fatigue (25%), depression (35%), anxiety (42%) and sleep disturbance (60%) by physicians' interview compared to patients' response using a screening questionnaire. However patients' responses were less specific with a higher rate of false positive responses, highlighting that self-reported symptom questionnaires are not diagnostic tools and require clinical validation in the consultation. Thus, the higher reports of self-reported symptoms than documented NMS may also partly result from false positive responses. Another explanation for low detection rates of NMS may be low patient awareness of NMS associated with PD, which was examined in one study (Cheon et al., 2008). Patients recognised on average only 5.2±6.8 NMS (of 30 symptoms on the NMSQ) as being related to PD, although this was higher (7.7±6.5) for carers and relatives. This may be analogous to the often seen unawareness of dyskinesias by patients. NMS which patients were least aware of being part of PD included delusions, faecal incontinence, RBD, weight change, hallucinations, nausea, unexplained pain, interest in sexual activity, sexual difficulty and incomplete bowel

emptying. This unawareness is likely to contribute to the low rate of documentation of at least some of the symptoms in this study, and highlights the importance of patient education and vigilance for NMS that patients may not be aware as symptoms of PD. Further explanations for under-recognition may be relatively low symptom severity, embarrassment, expectation that these cannot be dealt with and insufficient time for consultations.

3.4.4 Methodological considerations

There are some methodological considerations in this study. (1) Given that this study required completion of a large number of physician-assessments and self-completed questionnaires, it may not be fully representative, and patients with cognitive impairment and apathy may be under-represented. Cognitive symptoms could have a higher impact on Hr-QoL than detected by this analysis. However, we endeavoured to include patients in all stages of PD, from early untreated to advanced disease, which is reflected in the motor and cognitive scores of our patients. This included patients with a range of mild and sub-clinical cognitive impairment; (2) DDS/ICD and FAB scores correlated poorly with Hr-QoL. However, the lack of insight found in some these patients may obscure declines in Hr-QOL despite possible severe consequences on the social, familial and personal life of patients. In addition, consequences associated to these abnormalities are not represented in the PDQ39 questionnaire and their impact may be underrepresented; (3) Patients were seen in specialty movement disorder clinics and thus optimization of dopaminergic therapy may be better than for primary neurologists or patients in the community and therefore it is possible that NMS might be proportionately more troublesome in this study. However, this study included a high proportion of patients with marked motor symptoms despite maximal possible drug therapy, and mean UPDRS motor score in optimal state was 30, reflecting moderate to advanced disease. (4) Motor scores assessed in the “on” state may underestimate the impact of motor impairment on Hr-QoL as they are likely to have less variability between subjects than in the

"off" state, which could explain the lower correlation of motor function and Hr-QoL found in this study. However, patients were assessed on maximal motor and non-motor therapies as encountered in a naturalistic setting. Therefore our conclusions apply to patients as seen in clinical practice and highlight a possible inattention of treating physicians to non-motor features (44% from our data), disproportionate emphasis on motor symptoms or unavailability of treatment options for NMS. (5) Part of this study was based on a patient-reported measure with single questions without diagnostic clarification (NMSQ). It is therefore possible that some symptoms were misinterpreted (e.g. RLS may represent motor impatience, akathisia or non-specific sensory symptoms than classical RLS).

3.4.5 Conclusions

The results indicate that NMS are frequently under-recognised despite their importance for patients' subjective Hr-QoL and disability. In optimally treated patients from a motor point of view, particularly autonomic features, fatigue and daytime somnolence are correlated with poor Hr-QoL, in addition to the now well-recognised impact of depression. The detection of NMS has important consequences for the management of patients, as treatment options are available for many (Chaudhuri & Schapira, 2009), with potential for improvement of Hr-QoL. Clinicians should therefore try to elicit NMS more systematically, e.g. by the use of screening instruments. This may be particularly relevant for embarrassing or seemingly unrelated symptoms and for features of the disease that are not commonly included in PD evaluations, such as autonomic function and fatigue.

Chapter 4

Non-motor symptoms as presenting complaints in Parkinson's disease

4.1 Introduction

NMS are increasingly recognized as a significant cause of morbidity in later stages of PD. Prodromal NMS are also a well-recognized component of the clinical picture in some patients but the prevalence of NMS as presenting complaints, and their impact on clinical management, in pathologically-proven cases of PD is unknown. PD cannot be diagnosed until motor symptoms appear but many patients will in hindsight recall a prodromal phase including NMS (Wilson et al., 1954). It is also reported that more non-specific complaints are reported by PD patients to their general practitioners in the 5 years leading up to diagnosis than are reported by age matched controls (Gonera et al., 1997). The aims of this study were to review the prevalence of NMS as presenting complaints in pathologically-proven cases of PD.

4.2 Methods

4.2.1 Patients

A retrospective review of cases of pathologically-proven PD archived at the Queen Square Brain Bank for Neurological Diseases was made. Donors were from the UK and died between 1988 and 2005. Of the 543 cases identified 110 were excluded because of inadequate clinical detail of the presenting features. The London Multi-Centre Research Ethics Committee has approved procedures for the donation of brains to the Queen Square Brain Bank as well as retention of and access to clinical records.

4.2.2 Data Collection

A systematic chart review was performed paying particular attention to the case notes of the family doctor in the 3 years before the documentation of the first motor symptom definitively linked to progressive Parkinsonism. First and subsequent correspondence between the medical specialist and family doctor were also scrutinized. Hospital inpatient notes, inpatient consultations, and emergency room admission notes were also reviewed. The initial presenting complaint prompting patients to attend medical services was noted, and early diagnoses made were documented. The included symptoms or doctors' diagnoses were those considered retrospectively to be associated with PD. That is, they did not resolve or they were related to the eventual motor problems, for example; frozen shoulder or sensory disturbances with the later development of bradykinesia, tremor, or rigidity on that same side; depression that did not improve; urinary symptoms with subsequent autonomic dysfunction; new onset low back pain; personality or cognitive changes. Patients were compared according to two groups; those presenting with exclusively non-motor and those presenting with motor symptoms. In patients with more than one presenting complaint documented, if motor symptoms were present in addition to NMS as first complaints, these patients were included in the “motor symptoms” group for analysis. The latency from presenting complaint to final clinical diagnosis was reviewed. Other clinical features were recorded as present or absent early in the disease (within 2 years of first symptom onset) and at any time during the disease. These features included: age of onset (age at the time of the first reported symptom considered to be attributable to disease), disease duration (time from onset until death), falls, bradykinesia, cognitive dysfunction (reported by the family, patient, or physician, and not attributed to affective disorder), symmetry of disease at onset, tremor, rigidity, postural reflexes (reported by the physician), response to L-dopa (graded by patient or clinician from 1 to 4, 1 = nil or slight, 2 = moderate, 3 = good, or 4 = excellent), and autonomic dysfunction.

Abnormal autonomic function was recorded according to test results or reports of any two of these symptoms: urinary urgency, frequency, and nocturia without hesitancy; chronic constipation; postural hypotension; sweating abnormalities; erectile dysfunction. The presence and time of onset of hallucinations and dyskinesias were noted. Sleep disturbances were not included in the analysis. We recorded symptoms as absent if not reported and clinical signs as missing if they were not specifically mentioned in the notes. Where reports of clinical features conflicted, the findings of the neurologist were used. Complete drug history was obtained, including latency from symptom onset to initiation, and time from initiation to maximum dose of L-dopa.

4.2.3 Statistics

Comparison between groups was performed using the parametric (Student's t test) or non-parametric (Mann-Whitney U) tests as appropriate. Statistical analysis of difference in the frequency of categorical variables was performed using the chi square ($\chi 2$) test or Fisher Exact Tests as appropriate. Statistical analyses of data were performed with SPSS version 12.0 (SPSS, Chicago, IL).

4.3 Results

From the 433 cases with detailed histories of early symptoms, 91 (21%) had exclusively NMS at presentation to their general practitioner. Of the NMS, pain was the most frequent, seen in 48 (53%) of these cases, urinary symptoms were present in 15 (16.5%), depression or anxiety in 11 (12.1%). Other NMS included non-specific cognitive impairment without functional limitation or dementia (5.5%), lethargy (4.4%), sensory disturbances, and visual impairment (Table 4.1).

Table 4.1 Patient characteristics and presenting symptoms.

	Total cases (N = 433)	Cases with "motor symptoms" at presentation (N = 342)	Cases without "motor symptoms" at presentation (N = 91)	P value
Male: Female (%)	274:159 (63:37%)	215:127 (63:37%)	59:32 (65:35%)	NS[A]
Number of patients with a documented family history of PD (%)	31 (7%)	28 (8.2%)	3 (3.3%)	0.08[A]
Age of PD onset (mean ± SD)	60.9 ± 10.4 years	60.6 ± 10.6 years	61.9 ± 9.5 years	NS[B]
Interval between symptom onset and diagnosis of PD (median, interquartile range [years])	1.1 (0.9–2.4)	1.0 (0.8–2.2)	1.6 (1.0–3.0)	0.001[C]
Duration of PD before death (mean ± SD [years])	14.9 ± 6.9	15.3 ± 7.0	13.4 ± 6.6	0.016[B]
Age of death (mean ± SD)	75.8 ± 7.4	75.9 ± 7.6	75.3 ± 6.6	NS[B]
First symptoms including tremor	196 (45.3%)	196 (57.3%)	0	N/A
First symptoms including bradykinesia	136 (31.4%)	136 (39.8%)	0	N/A
First symptoms including rigidity	44 (10.2%)	44 (12.9%)	0	N/A
First symptoms including unspecified gait disturbance	51 (11.8%)	51 (14.9%)	0	N/A
First symptoms including pain	65 (15%)	17 (5%)	48 (52.7%)	N/A
First symptoms including urinary dysfunction	17 (3.9%)	2 (0.6%)	15 (16.5%)	N/A
First symptoms including depression or anxiety	11 (2.5%)	0	11 (12.1%)	N/A
Other symptoms	59 (13.6%)	34 (9.9%)	25 (27.5%)	N/A

Statistical analysis A= Chi square test, B= students t-test, C= Mann-Whitney U

Presenting with NMS is associated with a delayed diagnosis of PD, with a median interval of 1.6 years between first symptom and diagnosis of PD, compared with 1.0 years in those presenting with motor symptoms (Mann-Whitney U, P = 0.001). PD was the initial diagnosis made in only 15 (16.5%) of patients presenting with NMS, compared to 230 (67.3%) for

patients in the motor group ($\chi 2$, $P < 0.0001$). The non-motor cases were more likely to be diagnosed with osteoarthritis, degenerative spinal disease, frozen shoulder, depression, or anxiety. (Table 4.2) Correspondingly, patients presenting with NMS were significantly less likely to be initially referred to a neurologist by their general practitioner than the motor group (5.5% vs. 44.2%, $\chi 2P < 0.0001$). Patients in the non-motor group were more likely to be referred to orthopaedic and rheumatological services (29.7%), urological services (15.4%), general physicians (13.2%), and psychiatrists (11%) than a neurologist. In contrast, 26% of patients from the motor group were referred to general physicians and only 4.3% to orthopaedic or rheumatological services. A high proportion of patients presenting with NMS underwent surgical interventions prior to the diagnosis of PD, including steroid injections in 9 of 10 patients diagnosed with frozen shoulders, and five out of 12 patients diagnosed with degenerative spinal disease.

Table 4.2 Initial diagnoses following symptom onset

	Total cases (N = 433)	Cases with "motor symptoms" at presentation (N = 342)	Cases without "motor symptoms" at presentation (N = 91)	*P* value (Chi Square)
Parkinson's disease	245 (56.6%)	230 (67.3%)	15 (16.5%)	<0.0001
Osteoarthritis/degenerative vertebral disease	21 (4.8%)	9 (2.6%)	12 (13.2%)	<0.0001
Depression, anxiety or psychogenic causes	17 (3.9%)	7 (2%)	10 (11%)	0.0003
Frozen shoulder	14 (3.2%)	3 (0.7%)	11 (12.1%)	<0.0001
Stroke	9 (2.1%)	7 (2%)	2 (2.2%)	NS
Essential tremor	8 (1.8%)	8 (2.3%)	0 (0%)	NS
Other diagnoses	57 (13.2%)	23 (6.7%)	34 (37.4%)	
Unknown	62 (14.3%)	55 (16.1%)	7 (7.7%)	NS

A small percentage of patients from the non-motor group (4.4%) had no bradykinesia, rigidity, or tremor documented 2 years after symptom onset. After the same interval, only two of the 342 patients (0.6%) had none of the "classical parkinsonian triad" documented, both patients having presented with unspecified gait disturbances or writing difficulties (P = 0.02, $\chi 2$ analysis) (Table 4.3). Autonomic dysfunction was the only symptom that was more common in the non-motor group (P = 0.025, $\chi 2$ analysis). Tremor was more frequently documented throughout the disease in the motor group (P = 0.04, $\chi 2$ analysis). There were no other differences in the frequency of clinical features between the groups. Hallucinations were documented in 168 (52.2%) of the motor group and 46 (53.5%) of the non-motor group during their disease history. There was no difference in the mean latency from first symptom onset to the development of hallucinations between groups (motor group 131 ± 75 months, nonmotor 115 ± 81 months). Drug-induced dyskinesias were documented in 158 (53%) of the motor group, and 41 (50%) in the nonmotor group during the disease history. The mean latency to onset of dyskinesias from first symptom onset was similar in both groups (motor group 101 ± 52 months, nonmotor group 93 ± 45).

Table 4.3 Symptoms documented at 2 years from first symptom

	Total cases (N = 433)	Cases with "motor symptoms" at presentation	Cases without "motor symptoms" at presentation	P value*
Bradykinesia	354 (85.3%)	278 (85%)	76 (86.4%)	NS
Tremor	308 (73.9%)	251 (76.3%)	57 (64.8%)	0.04
Extra-axial rigidity	321 (78.3%)	254 (78.2%)	67 (78.8%)	NS
Postural instability	36 (9%)	25 (7.8%)	11 (13.9%)	NS
Falls	23 (5.5%)	17 (5.2%)	6 (6.7%)	NS
Cognitive impairment	42 (10%)	29 (8.8%)	13 (14.6%)	NS
Autonomic dysfunction	29 (7%)	15 (4.6%)	14 (16.1%)	0.001
Depression	97 (24.7%)	71 (22.9%)	26 (31.3%)	NS
Dysarthria	50 (12.3%)	39 (12.1%)	11 (13.4%)	NS
Hallucinations	12 (5.9%)	8 (5.0%)	4 (8.9%)	NS
Dyskinesia	7 (3.6%)	6 (3.8%)	1 (2.9%)	NS

*Chi Square test, NS= non-significant

The final clinical diagnosis before death was PD in 81 of 91 (89%) patients initially presenting with NMS, compared with 316 of 342 (92.4%) patients presenting with motor symptoms ($P > 0.05$). There were no significant differences in the latency to initiation of L-dopa, the maximum doses prescribed, or the response to this medication between these groups (Table 4.4). Similarly, no differences were seen between groups regarding the prescription of dopamine agonists (DA). DA were used in 52% of patients presenting with motor symptoms, compared to 46% of the patients presenting with NMS, ($P = 0.5$). Non-ergot agonists were prescribed in ~80% of these cases in both patient groups. Antidepressant medication prescription rates throughout the disease course were also similar between patient groups, at 29.2% of patients presenting with motor symptoms, compared to 29.7% of the patients presenting with NMS.

It is thought that by the time patients fulfil diagnostic criteria for the diagnosis of PD, there may be degeneration of ~50% of neurons in the substantia nigra (Greffard et al., 2006, Fearnley & Lees, 1991). The duration of the premotor phase following the onset of nigral loss is uncertain, but pathological and radiological estimates have suggested between 5 and 7 years (Fearnley & Lees, 1991, Morrish et al., 1998)

Table 4.4 History of L-dopa use and response

	Total cases	Cases with "motor symptoms" at presentation	Cases without "motor symptoms" at presentation	P value*
Latency from first symptom to L-dopa commencement (mean ± SD)	2.9 ± 2.8 years	2.9 ± 2.9	2.9 ± 2.2	NS
Maximum L-dopa dose (mg/day) (mean ± SD)	923 ± 499	947 ± 502	828 ± 478	NS
Response to L-dopa (%)	395 (96%)	299 (94.9%)	79 (98.8%)	NS
Grade of response to L-dopa (QSBB scale) (mean ± SD)	3.2 ± 0.9	3.2 ± 0.9	3.3 ± 0.9	NS

QSBB = Queen Square Brain Bank, *Student's t-test, NS = non-significant

4.4 Discussion

In this study 21% of people who went on to develop motor features of PD, described their initial symptoms in exclusively non-motor terms, and pain was seen as a presenting symptom in 15%. We acknowledge the retrospective nature of the study is a limiting factor and the recording and interpretation of non-specific non-motor symptoms in general practice may vary. General practitioners in the United Kingdom are however required to make a written entry of all symptom complaints for every consultation. We accept nonetheless that some physicians may be more aware and astute in suspecting early Parkinsonism when a non-motor presentation occurs. Hyposmia is rarely spontaneously reported by patients with PD and REM sleep disorder may be dismissed. Once the diagnosis of PD has been firmly established however direct enquiry about deterioration of olfaction frequently results in a positive response We also acknowledge that among the high percentage of pain as a presenting symptom, some could be pain related to bradykinesia in akinesia dominant PD, which would be more likely to be mechanical pain related to a rigid arm rather than the typical pain of PD. Nevertheless, we feel that this study is relevant as it is the first to assess

the prevalence and clinical characteristics of a subgroup of patients with pathologically proven PD who present with NMS.

Autonomic dysfunction has been described in up to 50% of patients with diagnosed PD (Magerkurth et al., 2005), and one study on constipation has been associated with an almost threefold increased risk of a subsequent diagnosis of PD after 12-year follow-up (Abbot et al., 2001). In our cohort, new urinary symptoms were found to be a presenting complaint in 3.9% of patients with PD. Autonomic dysfunction was found to be the only NMS that remained more prevalent throughout the course of the PD in the group of patients presenting initially with NMS, compared to those presenting with motor-related complaints. Shorter disease duration is found in patients presenting with NMS ($P = 0.0016$, t-test). Whether this is due to more frequent and severe autonomic dysfunction in this group is unclear, as in the majority of our cases formal autonomic function tests were not performed, and the specific cause of death is not documented.

Depression or anxiety was shown to be a presenting complaint in 2.5% of our PD cases, with ~25% developing these symptoms within two years of disease onset. These findings are in keeping with previous research showing that depression affects between 30 and 50% of people with PD (Slaughter et al., 2001, Dooneief et al., 1992). Studies have suggested that neuropsychiatric conditions may also be "preclinical" symptoms of PD, with strong associations between premorbid depression and subsequent development of PD (Schuurman et al., 2002, Ishihara & Brayne, 2006, Shiba et al., 2000). Similarly, anxiety has been associated with subsequent diagnoses of PD (Shiba et al., 2000, Weisskopf et al., 2003) although the evidence is not as strong as for depression (Ishihara & Brayne, 2006).

Hyposmia has been associated with PD for over 30 years, and has been widely studied with clinical and pathological evidence of olfactory dysfunction in a majority of patients (Ansari & Johnson, 1975). The presence of idiopathic hyposmia is thought to predict the development of clinical PD in around 10% of patients at 2-year follow-up (Ponsen et al., 2004). Sleep disturbance, including RBD precede the development of the classical parkinsonian symptoms in up to 38% of cases, with a latency of over 10 years between RBD onset and clinical Parkinsonism (Schenck et al., 1996, Iranzo et al., 2006). Excessive day-time sleepiness has also been shown to precede the diagnosis of PD, with a threefold increased risk demonstrated in one longitudinal study (Abbott et al., 2005). Unfortunately there was almost no documentation of the presence or absence of olfactory or sleep disturbances in patients we studied, possibly due to a lack of awareness of the clinical importance of these features during the period in which this cohort was treated.

Non-motor presentations of PD were frequently misdiagnosed initially by primary carers, leading to a high proportion of potentially inappropriate specialist referrals and treatments, including steroid injections for frozen shoulders and surgical interventions for degenerative spinal disease or carpal tunnel syndromes. Clearly, such interventions may have a deleterious effect on patients' quality of life, in addition to potentially increasing costs of health care. An increased latency between symptom onset and final diagnosis of PD was made in these patients. However, despite these early diagnostic difficulties, it has been shown that, after the first 2 years from symptom onset, these groups have similar symptoms and signs, and the rate of correct final clinical diagnoses did not differ. A good response to L-dopa therapy was seen in both subgroups, despite suggestions that NMS tend to respond less well than motor symptoms to dopaminergic treatments (Dhawan et al., 2006). However, the response rating to L-dopa is an overall clinical impression, and does not account for individual symptoms that may not be deemed significant by the treating clinicians. Furthermore the limitations of the

retrospective nature the data, and the selection bias that is expected in a brain bank post-mortem series, may account for the differences with previous studies (Maraganore et al., 1999). The large number of patients and the inclusion of patients that otherwise might not have been included in a prospective clinical study are relative strengths of this study.

Despite the increasing literature demonstrating that NMS are frequent and disabling features of more advanced PD (Witjas et al., 2002), they are still likely to be under-recognized by neurologists (Shulman et al., 2002). Our findings suggest that NMS may be significant features in earlier PD stages and that an increased awareness of these problems as manifestations of PD is also required at a primary care level. To minimize misdiagnoses and potentially harmful and inappropriate interventions in patients presenting without the typical motor symptoms, a clearer message about NMS of early PD in medical education is required. This may be facilitated by the development of clinical tools such as the validated Non Motor Questionnaire to aid clinicians in identifying, and managing, NMS in patients at earlier stages of PD (Chaudhuri et al., 2006).

Chapter 5

Assessment of non-motor symptoms in PD, including validation of the MDS-UPDRS Part I

5.1 Introduction

The UPDRS has been the main outcome measure in clinical trials in PD and a revision developed by the Movement Disorder Society (MDS-UPDRS) has recently been published (Goetz et al., 2008). Particular emphasis was placed on improving scale properties and representing the breadth of manifestations, including NMS of the disease. However, the convergent validity of the scale in comparison to validated scales for individual non-motor aspects of PD has not been demonstrated. We here present a validation of MDS-UPDRS Part I (nM-EDL).

5.2 Methods

5.2.1 Patients and assessments

Consenting patients were assessed with the MDS-UPDRS part I (Goetz et al., 2008), original UPDRS (Fahn et al., 1987), ACE (Larner, 2007), SCOPA-COG (Marinus et al., 2003), FAB (Dubois et al., 2000), PPRS (Friedberg et al., 1998), HDRS (Schwab et al., 1967), HADS-Anxiety and HADS-Depression (Upadhyaya & Stanley, 1993), LARS (Sockeel et al., 2006), PSQI (Buysse et al., 1989), ESS (John, 1991), SCOPA-sleep scale (daytime and night time) (Marinus et al., 2003), Visual Analogue Scale (VAS) of Pain, SCOPA-AUT (Visser et al.,

2004), and FSS (Krupp et al., 1989). 84% of questionnaires were completed by patients alone and 16% by both patients and their carers.

5.2.2 Statistical analysis

Statistical analysis was performed using SPSS version 17.0 (SPSS, Inc., Chicago, IL). Variables were expressed as mean and standard deviation (SD). In order to compare the scale scores in a common framework, standardized z-scores were calculated for MDS-UPDRS Part I and the non-motor scales from the raw scores. Cognitive impairment score was derived from ACE, SCOPA-COG and FAB; hallucinations and psychosis from PPRS; depressed mood from HDRS and HADS-D; anxious mood from HADS-A; apathy from LARS; sleep problems from PSQI and SCOPA-sleep-night; daytime sleepiness from ESS and SCOPA-sleep-daytime; pain and other sensations from VAS; urinary problems from SCOPA-AUT urinary; constipation problems from SCOPA-AUT gastrointestinal; light headedness on standing from SCOPA-AUT cardiovascular and fatigue from FSS. This study does not include a clinimetric assessment for dopamine dysregulation or impulse control disorders as no scale was available at the time of the study onset. Where there was more than one scale representing a non-motor symptom, a mean z-score was calculated from the individual z-scores (eg, cognition z-score = [ACE z-score + SCOPA-COG z-score + FAB z-score]/3). In addition composite z-scores were calculated for non-motor symptoms overall and the two non-motor sub-scores (depression/anxiety/apathy and other non-motor symptoms) identified in the MDS-UPDRS exploratory factor analysis (Goetz et al., 2008). Internal consistency was measured using Cronbach's alpha, for the MDS-UPDRS part I total score and the two factor sub-scores. Internal consistency, homogeneity of items in relation to the construct, was expected to be higher than 0.70. Floor and ceiling effects were assessed by calculating number of lowest and highest possible responses and acceptable values were expected to be

less than 3%. To assess concurrent validity, the MDS-UPDRS Part I was correlated with the original UPDRS Part I. Convergent validity was assessed by correlating standardized z-scores of MDS-UPDRS Part I, its two sub-scores previously derived from the original factor analysis of the MDS-UPDRS, and individual item scores with standardized scores of validated scales for each non-motor component. Correlation coefficients were calculated using Spearman rank analysis. The magnitude of correlation coefficients for MDS-UPDRS total score, factor sub-scores and individual items was expected to be at least moderate ($r > 0.40$) in order to demonstrate acceptable convergent validity.

5.3 Results

5.3.1 Clinimetric properties of MDS-UPDRS

All Hoehn and Yahr stages were represented with the majority (90%) being stages II and III. On cognitive assessment, 5/94 (5%) had evidence of mild dementia on the MMSE (24/30 or less) and none had MMSE <20. The internal consistency of MDS-UPDRS Part I total score (Cronbach's alpha) was 0.85, for the depression/anxiety/apathy factor score was 0.69 and other non-motor factor score was 0.82. MDS-UPDRS Part I had high concurrent validity with the original UPDRS part I (correlation, $r = 0.81$, $p<0.001$). Floor and ceiling effects were small (2% floor and 0% ceiling effect). In a sub-analysis that examined only the 54 subjects not included in the original MDS-UPDRS validation program, the analysis was repeated with similar results (correlation with original UPDRS, $r=0.84$, $p<0.001$).

5.3.2 Correlation of MDS-UPDRS items with validated non-motor clinimetric scales

The standardized z-score of MDS-UPDRS Part I had a high correlation with the composite z-score of non-motor scales ($r = 0.89$, $p < 0.0001$, figure 5.1). The two MDS-UPDRS part I standardized factor scores had high correlations with composite z-scores of corresponding non-motor features (depression, anxiety, apathy factor score, $r = 0.72$, $p < 0.0001$ and other non-motor features factor score, $r = 0.87$, $p < 0.0001$, figure 1). Amongst individual MDS-UPDRS items, scales for hallucinations and psychosis (PPRS), sleep problems (PSQI, SCOPA-sleep night-time and daytime), cardiovascular and gastro-intestinal autonomic symptoms (SCOPA-AUT), fatigue (FSS), pain and other sensations (VAS) and apathy (LARS) had high and significant correlations ($r \geq 0.60$) with the MDS-UPDRS items, and scales for depression (HDRS and HADS-D), anxiety (HADS-A), daytime sleepiness (ESS), and urinary autonomic symptoms (SCOPA-AUT-urinary) had moderate and significant correlations with corresponding scales ($r = 0.40$ to 0.60), The only MDS-UPDRS item with weak correlation with more detailed scales was Cognitive Impairment where r values for all three cognitive scales (ACE, SCOPA-COG and FAB) fell below 0.40 (Table 5.1).

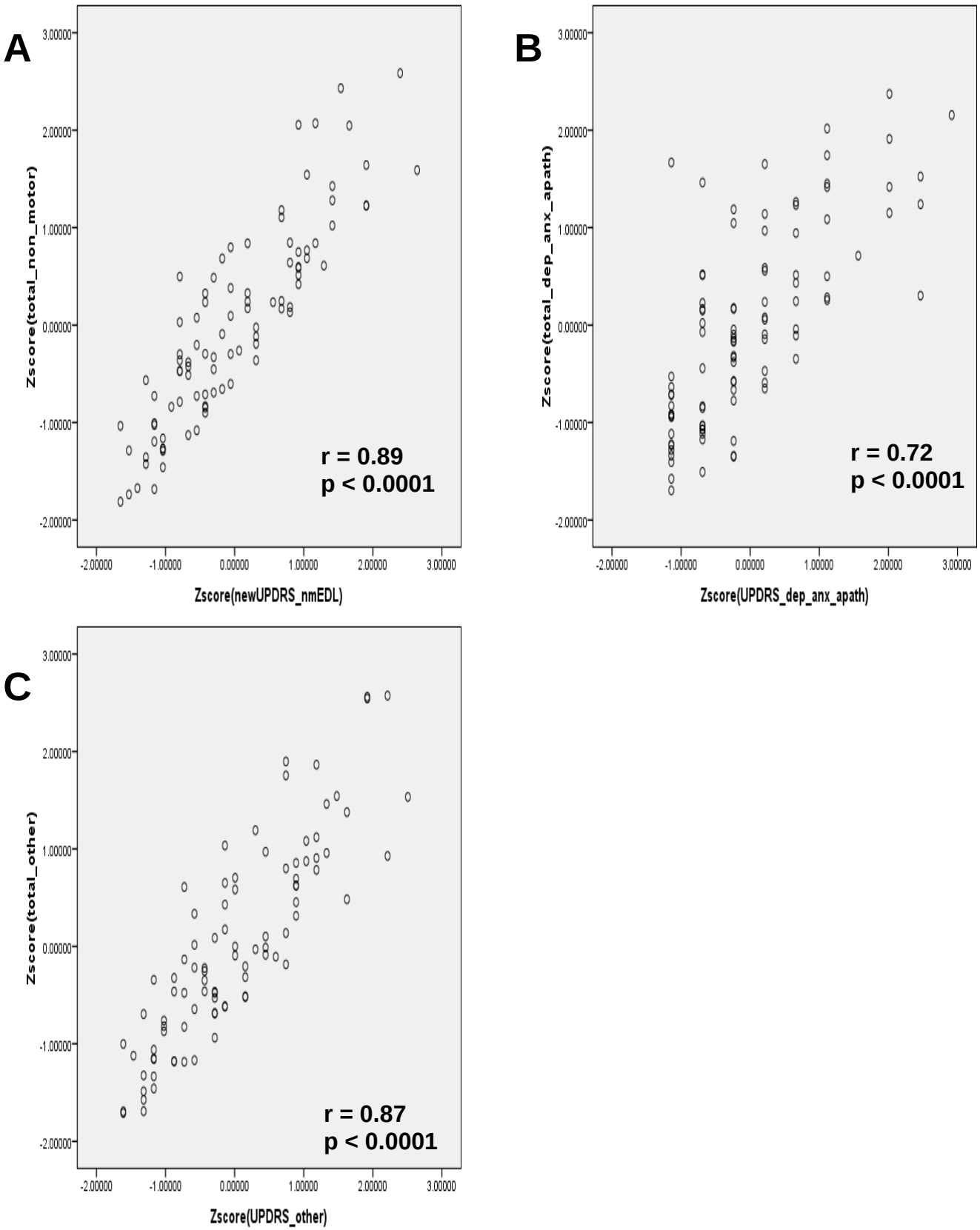


Figure 5.1 Validation of MDS-UPDRS Part I. Scatterplots and Spearman rank correlation coefficients for **(a)** standardized z-score of total MDS-UPDRS Part I (non-motor experiences of daily living) versus composite z-score of non-motor scales, **(b)** standardized z-score of MDS-UPDRS depression, anxiety and apathy factor score versus composite z-score of depression, anxiety and apathy scales and **(c)** standardized z-score of MDS-UPDRS other non-motor functions factor score versus composite z-score of other non-motor scales.

Table 5.1 MDS-UPDRS item correlations with individual corresponding clinical scales and with composite scores of corresponding scales (z-scores)

MDS-UPDRS item	Non-motor symptoms	Clinical scale	Mean (± standard deviation)	Correlation of MDS-UPDRS items with corresponding clinical scale	Correlation of MDS-UPDRS items with composite of corresponding scales
1.1	Cognitive impairment	ACE	89.0 ± 10.3	0.32[B]	0.29[B]
		SCOPA-COG	24.9 ± 7.0	0.26[C]	
		FAB	15.1 ± 2.8	0.33[B]	
1.2	Hallucinations and psychosis	PPRS	7.6 ± 2.3	0.86[A]	0.86[A]
1.3	Depressed mood	HDRS	4.1 ± 4.1	0.56[A]	0.53[A]
		HADS-D	5.8 ± 3.6	0.41[A]	
1.4	Anxious mood	HADS-A	6.0 ± 4.1	0.53[A]	0.53[A]
1.5	Apathy	LARS	-23.4 ± 8.4	0.67[A]	0.67[A]
1.7	Sleep problems	PSQI	6.9 ± 4.2	0.70[A]	0.80[A]
		SCOPA-night	5.1 ± 4.1	0.78[A]	
1.8	Daytime sleepiness	ESS	8.9 ± 5.2	0.56[A]	0.60[A]
		SCOPA-day	5.4 ± 4.3	0.62[A]	
1.9	Pain and other sensations	VAS	17.4 ± 16.9	0.64[A]	0.64[A]
1.10	Urinary problems	SCOPA-AUT-urinary	5.8 ± 3.7	0.55[A]	0.55[A]
1.11	Constipation problems	SCOPA-AUT-gastrointestinal	3.9 ± 3.0	0.68[A]	0.68[A]
1.12	Light headedness on standing	SCOPA-AUT-cardiovascular	1.0 ± 1.4	0.84[A]	0.84[A]
1.13	Fatigue	FSS	4.2 ± 1.7	0.61[A]	0.61[A]

Abbreviations, **MDS-UPDRS** - Movement Disorder Society sponsored revision of the Unified Parkinson's Disease Rating Scale (UPDRS), **ACE** – Addenbrooke's Cognitive Examination, **SCOPA-COG** - Scales for Outcome in Parkinson's disease (SCOPA), cognitive scale, **FAB** - Frontal Assessment Battery, **PPRS** – Parkinson Psychosis Rating Scale, **HDRS** – Hamilton Depression Rating Scale, **HADS-D** – Hospital Anxiety Depression Scale (HADS), depression score, **HADS-A** – HADS anxiety score, **LARS** – Lille Apathy Rating Scale, **PSQI** – Pittsburgh Sleep Quality Index, **ESS** – Epworth Sleepiness Scale, **VAS** – Visual Analogue Scale, **SCOPA-AUT** – SCOPA autonomic scale, **FSS** – Fatigue Severity Scale. *Statistical Analysis*, Spearman rank correlations with significance levels A, $p<0.001$, B, $p<0.01$, C, $p=0.01$. All MDS-UPDRS Part I items represented except dopamine dysregulation syndrome (item 1.6)

5.4 Discussion

Our data demonstrate that the MDS-UPDRS Part I total score has a strong and highly significant relationship with a composite score of non-motor aspects of PD, based on validated scales of individual non-motor symptoms. This observation suggests that the MDS-UPDRS Part I, with an application time of only 10 minutes, appropriately reflects the burden of NMS in PD patients and is indicative of performance on extensive battery of established scales with an application time over 2 hours. We have also demonstrated statistically significant correlations of individual MDS-UPDRS Part I items with corresponding clinical scales with moderate to high correlation for the majority of items despite their brevity. Only the MDS-UPDRS cognition item had weak correlation with the three corresponding cognitive scales. This problem is likely due to heterogeneity in cognitive profiles in PD including dysexecutive but also amnestic, visuoperceptive, visuospatial and global cognitive impairment; behaviours difficult to correlate with a single screening question. The MDS-UPDRS depression item was more highly associated with the HDRS than with the HADS-D. This discrepancy may be due to the differing content of these scales with greater in-depth assessment of depressive symptoms on the HDRS. Our analysis also confirmed the clinimetric properties of the scale in a new patient population. The MDS-UPDRS has undergone initial validation (Goetz et al., 2008) and has demonstrated high internal consistency, concurrent validity and internal validity. Our analysis of the non-motor part of the scale in another population has confirmed this initial validation. The internal consistency of the MDS-UPDRS Part I score was high for the total score and the first factor score with slightly lower consistency for the second factor measuring mood. This lower internal consistency is likely to reflect the low number of items (n=3) in this subscale rather than low correlation between items.

This study has some methodological considerations: (1) Scales at study onset were chosen to reflect the broad spectrum of non-motor features and have been at least partially validated in PD but many require further assessment. (2) Composite Z-scores are derived from a battery of individual scales and while most of the individual components of the composite may be validated measures in PD, the validity of the composite measure has never been established. (3) This study does not include an assessment for dopamine dysregulation or impulse control disorders as no scale was available at study onset. (4) The majority of patients in this study were Hoehn-Yahr stages II and III, with early and advanced stages under-represented. However studies suggest that clinic populations regardless of time frame are almost fully composed of patients in Hoehn-Yahr stages II and III (Sato et al., 2006). (5) MDS-UPDRS item 1.11 (constipation problems) was compared to SCOPA-AUT gastrointestinal score, which encompassed other aspects including swallowing, hypersalivation, early satiety and faecal incontinence. (6) Given the relatively small sample size and the distribution of patients by Hoehn and Yahr stages, these findings will require confirmation by future studies.

Overall our preliminary data demonstrate that the MDS-UPDRS Part I total score has a strong convergent validity with a composite score of scales for the non-motor aspects of PD and that the majority of MDS-UPDRS Part I items have at least moderate correlation with representative non-motor scales. Further studies to confirm the validity of the MDS-UPDRS in larger samples, including greater numbers of patients in higher Hoehn and Yahr stages, are required.

Chapter 6

Testing an aetiological model of visual hallucinations in Parkinson's disease

6.1 Introduction

6.1.1 Epidemiology of visual hallucinations in Parkinson's disease

Visual hallucinations (VH) are common in Parkinson's disease (PD) with estimates ranging from 16 to 75 percent (Goetz et al., 2009). The occurrence of VH may predict progression to more severe forms of psychosis, increased risk of nursing home placement and development of dementia (Fenelon and Alves, 2010). Previously reported risk factors include older age, longer disease duration, greater disease severity (Papapetropoulos et al., 2005, Fenelon and Alves, 2010), cognitive impairment (Papapetropoulos et al., 2005, Merims et al., 2004), particularly frontal lobe (Ozer et al., 2007, Grossi et al., 2005) and visuoperceptive function (Meppelink et al., 2008, Ramirez-Ruiz et al., 2006, Barnes et al., 2003). The role of dopaminergic medication and other PD treatments in the development of VH is unclear (Aarsland et al., 1999, Fenelon et al., 2000, Fenelon and Alves, 2010, Merims et al., 2004). Some studies have shown an association of VH with co-existing psychiatric disorders, including depression (Sanchez-Ramos et al., 1996, Holroyd et al., 2001, Marsh et al., 2004) and apathy (Mosimann et al. 2006), but when other factors are considered, co-existing psychiatric comorbidity appears less important (Fenelon et al., 2000). Autonomic dysfunction such as fall in systolic blood pressure and cardiac sympathetic denervation has also been associated with the presence of VH in PD (Kitayama et al., 2008, Oka et al., 2007, Williams and Lees, 2005). In addition, excessive daytime somnolence, sudden onset REM periods and intrusion of episodes of REM sleep during wakefulness have been shown to be associated

with VH in PD (Nomura et al., 2003, Diederich et al., 2005, Whitehead et al., 2008, Goetz et al., 2009).

6.1.2 Pathogenesis of visual hallucinations in PD

LB in PD are found in the substantia nigra in association with nigral cell loss but are also found in widespread extra-nigral cortical locations (Braak et al.,2003). A higher LB burden in the temporal lobe and amygdala (Harding et al., 2002a, Harding et al., 2002b, Kalaitzakis et al., 2009, Papapetropoulos et al., 2006b), and in the frontal and parietal cortices (Papapetropoulos et al., 2006b) has been associated with VH in PD in pathological studies. In addition several milestones of advanced disease, including dementia and the development of VH, have been associated with higher cortical LB scores (Kempster et al., 2010). Functional imaging studies also suggest involvement of these regions in PD patients with VH (Meppelink et al., 2009, Boecker et al., 2007, Oishi et al., 2005, Ramirez-Ruiz et al., 2007, Nagano-Saito et al, 2004). These areas are also thought to play an important role in visuoperception. The dual stream hypothesis of visual processing proposes a dorsal stream from the occipital to the parietal lobe specialized for spatial location and a ventral stream involving the temporal lobes and limbic structures for object recognition (Mishkin & Ungerleider, 1982), with white matter tracts projecting to the medial and lateral temporal cortices including the amydgala and parahippocampal gyrus (Catani et al., 2003). As a mechanism for the pathophysiology of VH in PD, it has been suggested that impaired object identification through pathology in temporal lobe and limbic structures can lead to disinhibition of internally generated imagery (Diederich et al., 2005, Goetz et al., 2009). Thus, there is evidence to suggest that hallucinations in other conditions as well as in PD are associated with impaired discrimination of external perceptions from internally generated

information, referred to as Reality Monitoring, and the medial temporal and frontal lobes have been implicated in this process (Henkel et al., 1998, Barnes et al., 2003).

6.1.3 Integrated hypothesis for VH in PD

Taking together the results from clinical, neuropsychological, imaging and pathological studies, a model of imbalance of external and internal inputs and impaired Reality Monitoring (Diederich et al., 2005, Diederich et al., 2009, Goetz et al., 2009) leading to the development of VH has therefore been suggested, including (a) impaired visual input and central visual processing, (b) impaired brainstem regulation of the sleep-wake cycle with fluctuating vigilance, intrusion of REM dream imagery into wakefulness and emergence of internally generated imagery, (c) cognitive dysfunction including areas implicated in discriminating internal and external generated information (reality monitoring), and (d) influence of dopaminergic drugs on mesolimbic and visual processing pathways (Goetz et al., 2009).

This study was undertaken to examine the in vivo and pathological validity of this proposed hypothesis, taking into account all clinical and pathological features that have been proposed to contribute to VH in PD. The aim was therefore (a) to determine the demographic and clinical variables associated with VH in PD including age, disease duration, dopaminergic medication, sleep disorders (daytime somnolence, nocturnal insomnia and RBD), current psychopathology (depression, anxiety and apathy), and presence of executive and global cognitive dysfunction, (b) to determine the relative importance of cortical visual processing and presence of ophthalmic pathology in the aetiology of VH in PD, (c) to validate an integrated model of VH in PD including abnormal visual processing, RBD and brainstem dysfunction, dysexecutive cognitive impairment and dopaminergic medication, (d) to determine the distribution of LB and Lewy neurite (LN) load as a marker of disease

involvement at different cortical regions involved in visual processing (temporal lobes and limbic structures including the amygdalae) and regions implicated in reality discrimination (medial temporal and frontal lobes).

6.2 Methods

6.2.1 Clinical study participants

Consecutive patients who fulfilled UK Brain Bank criteria for PD (Gibb and Lees, 1989) were recruited from PD outpatient clinics. Subjects underwent a face-to-face interview, comprising clinical examination and physician-administered questionnaires in clinic, and were given further questionnaires to complete at home. A subgroup of patients, who consented to an additional appointment, also had a full ophthalmological assessment. VH were defined as persistent formed visual hallucinations and illusions. Patients with brief episodes of hallucinations related to sepsis or alteration of medication were excluded.

6.2.2 Measures

(a) Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn et al., 1987), (b) non-motor scales and assessments including SCOPA-Sleep scale (Marinus et al., 2003a), ICSD-R minimal diagnostic criteria for RBD (American Academy of Sleep Medicine, 2001), LARS (Sockeel et al., 2006), HDRS (Schwab et al., 1967), FAB (Dubois et al., 2000), SCOPA-COG) (Marinus et al., 2003b), SCOPA-AUT (Visser et al., 2004), UM-PDHQ (Papapetropoulos 2008), (c) (in a subgroup) ophthalmological measures including LogMAR visual acuity testing (Sprague et al., 1989) (LogMAR of zero is equivalent to normal visual acuity [6/6] on Snellen chart, with negative scores representing better than normal acuity and positive scores poorer acuity), Goldmann kinetic perimetry (Niederhauser and Mojon, 2002), mean peripheral field diameter expressed as mean radial degrees (MRD), retinal

photography, descriptive assessment of cataract presence, location (nuclear, cortical, subcapsular) and degree of opacity, (d) (in a subgroup) tests for visual agnosia, the BORB (Riddoch and Humphreys, 1993) including low level aspects of visual perception (same-different matching of elemental features such as orientation, length, and object size), higher visual perception (identification of overlapping images, matching objects from usual and unusual viewpoints and identification of objects from minimal features) and stored perceptual knowledge (object decision tasks; discrimination between pictures of real objects and non-objects made by combining parts of different real objects, Humphreys et al., 1997) and semantic knowledge testing (associative matching; deciding which of two reference pictures [e.g. a screw and a nail] is most associated with a target picture [a screwdriver], Humphreys et al., 1997). Ethical approval for the clinical studies was obtained from the local research ethics committees.

6.2.3 Pathological Study

In a separate study, histological specimens were obtained from cases of pathologically-proven PD archived at the Queen Square Brain Bank for Neurological Diseases. A retrospective case notes review was made for reporting of persistent formed visual hallucinations. Demographic and disease characteristics including age, sex, disease duration, dopaminergic medication and documented presence of cognitive impairment were recorded. An approximation of the cumulative life-time L-dopa amount was made based on the information available in the patient records.

6.2.4 Neuropathological assessment

After fixation in 10% buffered formalin, the brains were examined by a neuropathologist and sampled in accordance with the standardised protocols of the Queen Square Brain Bank. In

compliance with established criteria for the neuropathological diagnosis of PD (Ince et al., 2008), brain samples from selected regions were embedded in paraffin. Eight µm-thick tissue sections were cut, deparaffinised and rehydrated, followed by pre-treatment with formic acid and pressure-cooking in citrate buffer at pH 6.0. Following epitope unmasking, monoclonal antibody to alpha-synuclein (αS) (clone KM51, dilution 1:1000; Novocastra; Newcastle upon Tyne, UK) was applied and incubated overnight at +4^{o}C. For detection, Histostain SP kit (Zymed, San Francisco, CA) was used with Romulin AEC chromogen (Biocare Medical, Walnut Creek, CA). Semiquantitative assessment of αS-immunoreactive (IR) LB-type pathology was carried out in five cortical regions, frontal (middle frontal gyrus, Brodmann's area [BA] 8/9), temporal (middle temporal gyrus, BA 21), parietal (inferior parietal lobule BA 40), entorhinal (parahippocampal gyrus, BA 28) and cingulate (anterior cingulate, BA 24) cortices as recommended by the consensus diagnostic criteria for DLB, (McKeith et al., 2005) and rated as follows: 1 = mild (sparse LBs at x100 magnification); 2 = moderate (1 to 3 LBs at x100 magnification); 3 = severe (≥ 4 LBs at x200 magnification); 4 = very severe (numerous LBs and LNs at x200 magnification). In addition, all LBs were systematically counted within the same five cortical areas of interest and these counts were adjusted to the surface area (LB/mm^2) using Image-Pro Plus software package (MediaCybernetics, UK). The "total cortical LB density" was determined as the sum of counts in the five cortical areas divided by a sum of respective surface areas. In addition, in the amygdala, the number of αS-IR LBs per x200 microscopic field (field diameter 1mm) was determined in the region with the greatest LB density. In the brainstem, αS-immunopositive LBs were counted unilaterally within entire nuclei and assessed following an arbitrary grading system: in SN, + ≤ 25 LBs; ++ 25-50 LBs; +++ ≥ 50 LBs, in LC and DMV, + = 1-9 LBs; ++ = 10-19 LBs, +++ = >20 LBs. The αS-IR LNs in each region were rated semi-quantitatively as: 0=absent, 1= sparse; 2= moderate; and 3= frequent. Finally, each case was also classified according to Braak PD

stage (ranging from 0 to 6) depending on the topographic distribution of αS-IR inclusions (Braak et al., 2002). All pathological analyses were done blinded to the clinical data.

6.2.5 Statistical Analysis

Data were entered into the statistical programme SPSS version 17.0 (SPSS, Inc., Chicago, IL) and inspected for normality of distribution. As the data were mostly not normally distributed, we used non-parametric tests for analysis. For comparison of VH and non-VH groups, data was expressed as median and inter-quartile range and non-parametric (Mann-Whitney U) analysis was performed. Categorical data was analysed using Chi-Square or Fisher exact test. The univariate analysis was used to select variables for inclusion in the multivariate regression analysis. A binary logistic regression analysis was performed to assess the effect of different clinimetric variables (treatment duration, UPDRS part III, UPDRS part IV, RBD, SCOPA-sleep daytime, HDRS, SCOPA-AUT, FAB, SCOPA-COG-executive score, BORB object decision, minimal feature match, association match and overlapping images) on the main dichotomous outcome measure (presence or absence of visual hallucinations).

6.3 Results

6.3.1 Clinical study

94 patients participated in the study, of whom five (5%) had evidence of global dementia (Mini-mental State Examination, MMSE≤24). No patient fulfilled clinical criteria for DLB (McKeith et al., 2005), with onset of dementia before or within one year of onset of parkinsonism. Thirty patients had experienced visual hallucinations and/or illusions (referred to as VH henceforth). Three of five patients with dementia had VH whereas the remainder with VH were non-demented (MMSE>24). The type of visual experiences reported by patients were (a) illusions of presence (N=18), (b) illusions of passage (N=26), (c) visual

illusions (N=27) and (d) formed visual hallucinations (N=22). 6 patients also reported acoustic, 5 tactile and 3 olfactory hallucinations. 27 of 30 patients with VH completed the UM-PDHQ hallucinations questionnaire. 14/27 (52%) had very frequent hallucinations (≥ once per day). In terms of VH content, 19/27 (70%) reported seeing animals, 18/27 (67%) saw people, 15/27 (56%) whole faces, 13/27 (48%) insects or reptiles, 13/27 (48%) objects and 6/27 (22%) fragmented faces. In only one patient were VH not formed or difficult to describe. In 23/27 (85%) the visual experience was familiar. Images were solid (rather than transparent) in 24/27 (89%), moving in 15/27 (56%), coloured in 15/27 (56%) and made a sound in 3/27 (11%).

After adjustment for multiple comparisons (N=29 comparisons, Bonferroni correction, significance $p<0.0017$) disease duration, treatment duration, dopaminergic medication dose (Levodopa Equivalent Units, LEU), motor function (UPDRS) and motor complications (UPDRS total part IV and percentage daily "off" time) were significantly associated with VH in PD (table 6.1). A higher proportion of patients with VH were taking levodopa (87% versus 58%, $p<0.009$) but this was not significant for multiple corrections and there was no association with other medication (ergot or non-ergot dopamine agonists, amantadine, catechol-O-methyl transferase inhibitors, monoamine oxidase-B inhibitors, anticholinergics, cholinesterase inhibitors or atypical antipsychotics). Significant associations with non-motor aspects of PD, after correction for multiple comparisons, included excessive daytime somnolence (SCOPA-sleep-daytime) and RBD, depression (HDRS) and overall autonomic dysfunction (SCOPA-AUT) (table 6.1) and gastro-intestinal, urinary and cardiovascular subscales (all $p\leq0.0001$). In addition, VH were associated with global cognitive impairment scores (SCOPA-COG total) but in particular frontal cortical dysfunction (FAB total score, FAB motor series and inhibitory control subscores, and SCOPA-COG executive subscore,

table 6.1). 81 of 94 (86%) patients were assessed using the BORB. Several tests of visuoperceptive cortical function including BORB object decision, overlapping images, minimal feature match and association match were associated with VH. In contrast, there was no clear association of VH with lower-level visuoperceptual tasks on the BORB and visuospatial tasks on the SCOPA-COG.

Table 6.1 Clinical findings of PD patients with and without visual hallucinations.

	VH (n=30) Median (interquartile range) or n (%)	Non-VH (n=64) Median (interquartile range) or n (%)	p-value (Mann-Whitney U or chi square test)
Demographics			
Age (years)	71.0 (65.5, 74.3)	66.5 (59.0, 74.0)	0.018
Sex (male)	24/30 (80%)	41/64 (64%)	0.15
Disease duration (years)	11.2 (5.3, 15.8)	3.4 (1.8, 7.7)	**0.0001**
Treatment duration (years)	10.5 (4.8, 15.4)	2.8 (0.2, 7.0)	**<0.0001**
LEU (mg)	750 (400, 1026)	300 (100, 739)	**0.0012**
UPDRS part III	38.0 (28.5, 48.0)	26.0 (17, 33.8)	**<0.0001**
UPDRS part IV	6.0 (3.0, 8.0)	1.0 (0.0, 4.0)	**<0.0001**
"off" (% of waking day)	18.0 (6.8, 31.3)	0.0 (0.0, 6.8)	**<0.0001**
Dyskinesia (%)	0.0 (0.0, 31.8)	0.0 (0.0, 3.0)	0.045
Non-motor Scales			
REM sleep disorder	16/30 (53%)	11/64 (17%)	**0.0005**
SCOPA-sleep-night	6.0 (3.0, 11.0)	3.0 (1.0, 7.0)	0.012
SCOPA-sleep-day	7.5 (4.0, 12.3)	3.0 (2.0, 6.0)	**<0.0001**
LARS-total	-21 (-27, -16.5)	-26.5 (-31.0, -22.0)	0.0096
HDRS	5.0 (2.0, 8.0)	2.0 (0, 5.0)	**0.0002**
SCOPA-AUT total	21.5 (16.8, 26.3)	11.0 (8.0, 17.0)	**<0.0001**
Cognition			
FAB total	14.0 (12.0, 16.0)	17.0 (15.0, 17.0)	**<0.0001**
SCOPA-COG total	22.0 (17.8, 25.5)	26.0 (23.0, 31.8)	**0.0004**
SCOPA-COG memory	7.5 (5.0, 9.3)	9.0 (7.0, 12.8)	0.017
SCOPA-COG attention	4.0 (3.0, 4.0)	4.0 (4.0, 4.0)	0.026
SCOPA-COG executive	7.0 (5.5, 9.0)	9.5 (8.3, 11.0)	**<0.0001**
SCOPA-COG visuospatial	3.0 (2.0, 5.0)	4.0 (3.0, 5.0)	0.13
Visuoperceptive function			
BORB size match	26.0 (23.5, 27.0)	27.0 (26.0, 28.0)	0.048
BORB length match	25.0 (23.0, 27.0)	26.0 (25.0, 27.0)	0.12
BORB orientation match	25.0 (23.0, 25.5)	26.0 (25.0, 27.0)	0.0064
BORB foreshortened	24.0 (22.0, 25.0)	24.0 (24.0, 25.0)	0.045
BORB minimal feature	24.0 (23.0, 25.0)	25.0 (25.0, 25.0)	**0.0006**
BORB overlapping	36.0 (32.0, 39.0)	40.0 (38.3, 40.0)	**<0.0001**
BORB association match	28.0 (26.0, 30.0)	30.0 (29.0, 30.0)	**0.0002**
BORB object decision	23.0 (21.5, 24.5)	26.0 (25.0, 28.0)	**<0.0001**

Abbreviations: VH – Visual Hallucinations, LEU – Levodopa Equivalent Units, UPDRS – Unified Parkinson's Disease Rating Scale, SCOPA – Scales for Outcome in Parkinson Disease, LARS – Lille Apathy Rating Scale, HDRS – Hamilton Depression Rating Scale, FAB – Frontal Assessment Battery, SCOPA-COG – SCOPA cognitive scale, BORB – Birmingham Object Recognition Battery. Variables that reach statistical significance when corrected for multiple comparisons (Bonferroni correction, n=29, $p<0.0017$) are given in bold. BORB scores based on subgroup, 81 of 94 (86%) patients.

6.3.2 Ophthalmological Assessments

Fifty out of 94 (53%) of participants underwent full ophthalmological assessment including 23 of the 30 (77%) of participants with visual hallucinations. There were no differences in disease duration, LEU, MMSE and UPDRS between participants and non-participants in ophthalmological substudy; however patients undergoing ophthalmological assessments were older ($p=0.01$). The ophthalmological and visuoperceptive variables were compared between patients with VH and those without. There were no differences in the ophthalmological parameters tested between the VH and non-VH group (table 2). However, in this smaller subgroup several of the visuoperceptive variables (minimal feature match, overlapping images, object decision, association match, size match and orientation match) were still more impaired ($p<0.05$) in the group of patients with hallucinations, with minimal feature match and overlapping images scales meeting significance for multiple comparisons (Bonferroni correction, 21 comparisons, $p<0.0024$, table 6.2).

Table 6.2 Ophthalmological findings and visuoperceptive measures in Parkinson's disease patients with or without visual hallucinations.

	VH (n=23) Median (interquartile range) or n (%)	Non-VH (n=27) Median (interquartile range) or n (%)	p value (Mann-Whitney U or chi square)
Ophthalmology findings			
VA right uncorrected	0.27 (0.14, 0.55)	0.28 (0.10, 0.46)	0.69
VA left uncorrected	0.25 (0.12, 0.48)	0.20 (0.10, 0.40)	0.61
VA right corrected	0.16 (0.04, 0.30)	0.14 (0.02, 0.22)	0.46
VA left corrected	0.20 (0.06, 0.30)	0.08 (0.0, 0.20)	0.076
Fields right (MRD)	46.8 (41.7, 48.9)	46.3 (37.9, 49.7)	0.80
Fields left (MRD)	45.5 (39.5, 49.3)	46.9 (40.5, 50.5)	0.44
Cataract right	14/23 (61%)	14/27 (52%)	0.58
Cataract left	14/23 (61%)	14/27 (52%)	0.58
Macular degeneration R	1/22 (5%)	5/27 (19%)	0.20
Macular degeneration L	1/22 (5%)	5/27 (19%)	0.20
Corneal pathology R	1/23 (4%)	1/27 (4%)	1.00
Corneal pathology L	1/23 (4%)	0/27 (0%)	0.46
Optic pathology (any)	17/23 (74%)	17/27 (63%)	0.55
Visuoperceptual function*			
BORB object decision	23.0 (21.0, 25.0)	26.0 (23.0, 27.0)	0.0026
BORB length match	25.0 (23.0, 27.0)	26.0 (25.0, 27.0)	0.072
BORB foreshortened	24.0 (22.0, 25.0)	24.0 (24.0, 25.0)	0.23
BORB minimal feature	24.0 (23.0, 25.0)	25.0 (25.0, 25.0)	**0.0011**
BORB association	28.0 (26.0, 30.0)	30.0 (28.0, 30.0)	0.008
BORB size match	26.0 (23.0, 27.0)	27.0 (26.0, 28.0)	0.026
BORB orientation	25.0 (23.0, 25.0)	26.0 (25.0, 27.0)	0.022
BORB overlapping	36.0 (33.0, 39.0)	40.0 (38.0, 40.0)	**0.0014**

Abbreviations, VA = Visual Acuity (Logarithm of Mean Angular of Resolution [logMAR]), MRD = Mean Radial Degrees, BORB = Birmingham Object Recognition Battery. Bonferroni correction for multiple comparisons, significance set at $p < 0.0024$

*only includes those patients who had ophthalmological assessments

6.3.3 Multivariate Analysis of clinical, cognitive and ophthalmological variables and visual hallucinations

All variables that were associated with VH in the univariate analyses (excluding collinear variables where scale with highest statistical significance was chosen) were added to the regression analysis (treatment duration, UPDRS part III, UPDRS part IV, RBD, SCOPA-sleep daytime, HDRS, SCOPA-AUT, FAB, SCOPA-COG-executive score, BORB object decision, minimal feature match, association match and overlapping images). The four independent determinants of VH in PD were RBD (p=0.026), SCOPA-AUT (p=0.004), SCOPA-COG executive (p=0.020) and BORB object decision (p=0.031) (table 6.3), and overall predicted 67% of the variability in the regression model.

Table 6.3 Factors associated with visual hallucinations in a multiple regression analysis

	Odds ratio	95% CI	P value
RBD	6.18	1.24-30.78	0.026
SCOPA-AUT	1.16	1.05-1.28	0.004
SCOPA-COG-Executive	0.63	0.43-0.93	0.020
BORB-object decision	0.66	0.46-0.96	0.031

Abbreviations CI – Confidence Interval, RBD - REM sleep behavioural disorder, SCOPA - Scales for Outcome in Parkinson Disease, SCOPA-AUT - autonomic scale, SCOPA-COG – cognitive scale, BORB – Birmingham Object Recognition Battery.

6.3.4 Clinico-pathological analysis of visual hallucinations

Post-mortem analysis was performed in 91 subjects. Amygdala analysis was performed in a subset of 68 patients (43 with and 25 without hallucinations) where pathological samples were adequate. On retrospective case notes examination, persistent formed VH were found in 57/91 (63%). The VH and non-VH did not differ in terms of demographic characteristics, including age and disease duration (table 4) however VH patients were significantly more likely to be cognitively impaired (p=0.004). Patients with VH had significantly higher LB densities particularly in the middle frontal gyrus and transentorhinal cortices with higher counts also in the total, middle temporal gyrus and anterior cingulate cortices but not inferior parietal cortex (table 4). Semi-quantitative LN density scores did not differ in any of the cortical locations sampled, although there was a trend for higher LN density in the temporal cortex (p=0.056). There was no significant difference in semi-quantitative LN or LB scores in the brainstem nuclei assessed (substantia nigra, locus coeruleus and dorsal motor nucleus of vagus). In the VH group, the majority were Braak stage 6 (72%) whereas in non-VH group the majority were Braak stage ≤5 (65%), p=0.002. In the subgroup with amygdala analysis, there was no difference in amygdala LB density between the VH (N=43) and non-VH (N=25) groups (p=0.69); however there was significantly higher total cortical (p=0.027) and particularly middle frontal gyrus LB density (p=0.006) in association with VH in this subgroup.

Table 6.4 Difference in clinical and pathological features of patients with and without visual hallucinations in the pathological study

	VH (N=57)	Non-VH (N=34)	P value (Mann-Whitney U or Chi square)
	Median (interquartile range) or number (%)	Median (interquartile range) or number (%)	
Medication use and cognitive impairment			
Cumulative levodopa dose (x10^6 mg)	2.5 (1.1-5.3)	2.5 (0.8-5.3)	0.71
Maximum levodopa dose (mg)	700 (500-1050)	750 (500-1000)	0.95
Ergot agonist use	18/57 (32%)	13/34 (38%)	0.52
Non-ergot agonist use	32/57 (56%)	18/34 (53%)	0.77
Apomorphine use	16/57 (28%)	6/34 (18%)	0.26
COMT inhibitor use	9/57 (16%)	6/34 (18%)	0.82
Selegiline use	31/57 (54%)	21/34 (62%)	0.49
Amantadine use	12/57 (21%)	7/34 (21%)	0.96
Anti-cholinergic use	29/57 (51%)	16/34 (47%)	0.73
†Cognitive impairment	45/52 (87%)	16/32 (50%)	0.0004
Pathological data – Lewy body density			
Parietal cortex (LB/mm^2)	0.00 (0.00-0.06)	0.00 (0.00-0.00)	0.22
Frontal cortex (LB/mm^2)	0.08 (0.00-0.43)	0.00 (0.00-0.07)	0.002
Temporal cortex (LB/mm^2)	0.15 (0.04-0.43)	0.06 (0.00-0.22)	0.033
Cingulate cortex (LB/mm^2)	0.82 (0.23-2.02)	0.38 (0.07-0.98)	0.020
Entorhinal cortex (LB/mm^2)	0.85 (0.28-2.74)	0.27 (0.06-1.00)	0.005
Total cortex (LB/mm^2)	0.40 (0.16-0.86)	0.17 (0.03-0.43)	0.004

Abbreviations VH = visual hallucinations, LB = Lewy body, COMT = catechol-O-methyl transferase. †Smaller sample (N=84, 92%) in whom reliable impression of cognitive status could be made on retrospective case notes review.

6.4 Discussion

This study supports an integrative model of pathogenesis of VH in PD, examining the diverse abnormalities reported in clinical, neurophysiological and imaging studies of VH in PD. In keeping with previous work, we found that VH in our PD population were associated with older age and longer disease duration (Fenelon and Alves, 2010, Papapetropoulos et al., 2005, Sanchez-Ramos et al., 1996) and greater disease severity (Holroyd et al., 2001, Papapetropoulos et al., 2005). Using a comprehensive assessment of the clinical, demographic, ophthalmological and pathological correlates of VH in PD, the combined data support a model of impaired visual processing, sleep-wake dysregulation and brainstem dysfunction and cognitive impairment.

6.4.1 Visual pathways

Examining different aspects of the visual pathways, we did not find evidence to support ophthalmic factors such as impaired visual acuity, reduced visual fields, cataracts, macular degeneration, and corneal or other optic pathology contributing to VH in PD overall. This is in contrast to previous studies of VH associated with poor visual acuity (Matsui et al., 2006, Holroyd et al., 2001) and ocular pathology (Fenelon et al., 2003). We did not examine subtle retinal abnormalities using contrast sensitivity or colour discrimination, which has been shown in previous studies to be more prevalent in patients with VH than without (Diederich et al., 1998), but visual acuity, visual fields and standard optic examinations did not show any differences in this study. Visuospatial tasks which are processed through the parietal lobes (Parks et al., 2010) and lower level visuoperceptive tasks related to posterior temporal lobe areas (Bright et al., 2005) did also not differ between patients with and without VH in PD. However, several higher level visuoperceptive tasks, which implicate the anteromedial temporal cortex, including the entorhinal cortex (Bright et al., 2005), were significantly

different even when corrected for multiple comparisons. This is consistent with neuropsychological studies demonstrating impaired visuoperceptive function in PD patients with VH (Meppelink et al., 2008, Ramirez-Ruiz et al., 2006, Barnes et al., 2003) and functional imaging studies demonstrating involvement of extrastriate visual processing pathways (Meppelink et al., 2009, Boecker et al., 2007, Oishi et al., 2005, Ramirez-Ruiz et al., 2007). These data suggest that impairment of cortical visuoperceptive function is more likely to be involved in the pathogenesis of VH in the majority of patients with PD than optic pathology, although this may be relevant in individual patients where this has been reported (Matsui et al., 2006, Holroyd et al., 2001, Fenelon et al., 2003). Our logistic regression results also support the importance of associative visuoperceptive dysfunction, rather than constructional visuospatial dysfunction or lower level apperceptive visual agnosia in the development of VH.

The findings of impairment of higher cortical function in visual pathways in neuropsychological testing were also supported by results of the pathological study. VH patients demonstrated higher overall cortical LB density with significantly increased LB density in the middle temporal gyrus, anterior cingulate gyrus and particularly the middle frontal gyrus and transentorhinal cortices consistent with previous pathological studies showing higher LB counts in temporal lobe structures in VH (Harding et al., 2002a, Papapetropoulos et al., 2006a). Additionally there was a trend to higher LN density in the temporal cortex. On the other hand, in contrast to previous studies, no increased LB density was found in patients with VH in the amygdala (Harding et al., 2002a, Harding et al., 2002b, Kalaitzakis et al., 2009, Papapetropoulos et al., 2006b) or parietal cortex (Papapetropoulos et al., 2006b). Kalaitzakis and colleagues found αS burden in the amygdala to be strongly

related to VH but only in those PD cases with concomitant dementia, implicating that αS pathology in this region is not related to the presence of VH per se but moreover to dementia.

6.4.2 Sleep-wake regulation and brainstem function

This study also demonstrated significant impairment of the brainstem-regulated sleep-wake cycle with excessive daytime somnolence and increased prevalence of RBD in PD patients with VH. This is consistent with previous studies showing higher prevalence of polysomnographic abnormalities and RBD in VH (Comella et al., 1993, Manni et al., 2002, Nomura et al., 2003). Brainstem locations implicated in REM sleep include the dorsolateral tegmental and pedunculopontine nuclei (Kalia, 2006). We have also shown that VH are associated with autonomic dysfunction including gastro-intestinal, urinary and cardiovascular function. This is consistent with previous studies, where autonomic function has been associated with VH (Kitayama et al., 2008, Oka et al., 2007, Williams and Lees, 2005). Autonomic impairment in PD can be mediated by central brainstem (LB deposition in and degeneration of brainstem nuclei, such as the dorsal vagal nucleus) and peripheral (i.e., cardiac sympathetic denervation) mechanisms. Autonomic dysfunction is associated with RBD, for example abnormal cardiac scintigraphy has been demonstrated in idiopathic RBD (Mitra & Chaudhuri, 2009) and these functions co-localise to similar brainstem locations. In our clinical study, presence of RBD and autonomic impairment were significant independent predictors in a regression model and this is supportive of greater involvement of brainstem function in PD patients with VH. Furthermore, VH in PD resemble the complex peduncular (Lhermitte's) hallucinations (colourful images of people or animals with clear sensorium), which have been described secondary to lesions of the rostral brainstem, the thalamus and striatocapsular regions (Benke, 2006), particularly cerebrovascular events, and are associated with disrupted sleep architecture. Peduncular hallucinations are thought to result from

disruption of ascending reticular systems and thalamocortical circuits involved in sleep-wakes cycle and alertness (Benke, 2006). In our pathological study higher LB or LN densities were not demonstrated in the brainstem nuclei sampled (substantia nigra, locus coeruleus and dorsal nucleus of the vagus). However, other brainstem nuclei which may be relevant to sleep-wake cycle pathology such as lateral tegmental and pedunculopontine tegmental nuclei were not examined in this study and further pathological studies in these areas will be required to clarify to the role of brainstem LB in the pathogenesis of VH in PD.

6.4.3 Cognitive impairment

Global cognitive impairment, in the clinical study and retrospective record analysis in the pathological study, was associated with VH, consistent with previous literature (Papapetropoulos et al., 2005, Merims et al., 2004). In addition, frontal lobe function was significantly worse in the group with VH, and was an important contributory factor in a regression model to predict presence of VH. This is in keeping with previous neuropsychological (Ozer et al., 2007, Grossi et al., 2005), functional imaging (Nagano-Saito et al., 2004, Ramirez-Ruiz et al., 2008) and pathological (Papapetropoulos et al., 2006b) studies which showed impairment in frontal lobe function in hallucinating patients compared to those without VH. Furthermore, the pathological data in this study confirmed higher LB density in the frontal cortex in patients with VH than without, as well as higher total cortical LB density.

6.4.4 Integrated hypothesis

In an integrated analysis of all factors studied in the clinical sample, VH in PD were associated with, and independently predicted by, impaired higher visuoperceptive function, particularly implicating the ventral visual pathway, sleep-wake cycle disruption and

autonomic dysfunction implicating brainstem dysfunction, and dysexecutive cognitive dysfunction. Similar to previous cross-sectional studies, medication did not contribute further to prediction of occurrence of VH (Aarsland et al., 1999, Fenelon et al., 2000, Holroyd et al., 2001, Merins et al., 2004, Fenelon and Alves, 2010), suggesting that other factors modify the impact of dopaminergic medication on VH or that this effect is small compared to other factors. The pathological study also supported the important role of frontal and temporal cortical dysfunction, and particularly the involvement of the areas in the ventral visual pathways and areas implicated in reality discrimination.

There are some methodological limitations to this study. The pathological study is limited by the retrospective nature the clinical data, and a selection bias is expected in a brain-bank post-mortem series. However, cases were chosen based on the availability of adequate clinical data regarding the presence or absence of VH. Pathological data were not available for all areas implicated in visual processing; in particular there was no assessment of retinal pathology or regions such as the primary visual cortex. The role of LB deposition in the pathogenesis of PD remains unclear. The proposed sequential staging of topographical involvement of LB pathology in PD (Braak et al., 2003) has not been uniformly confirmed in pathological series and widespread cortical LB pathology has been demonstrated in elderly individuals without neuropsychiatric correlates (Jellinger, 2009, Parkkinen et al., 2008). Attributing non-motor symptoms such as VH in PD to regional cortical LB distribution and density, in the absence of clearly demonstrated cell death, should be interpreted cautiously and requires further clarification (Jellinger, 2009, Parkkinen et al., 2008). VH are associated with advanced disease and therefore in the clinical study participants could not be matched for disease duration or severity. In order to reduce possibility of alpha errors, strict

Bonferroni correction was made in making statistical comparisons. This correction may however discount valid weaker associations.

In conclusion, the results support the proposed integrated model of pathogenesis of VH through dysregulation in gating of external perception and internal image production, aberrant activation of associative visual and frontal cortex, lack of suppression or spontaneous emergence of internally generated imagery, intrusion of rapid eye movement dreaming imagery into wakefulness and dysfunction of the brainstem filtering capacities (Diederich et al, 2005, Goetz et al., 2009). Whilst in individual patients ophthalmic abnormalities and medication-related factors may play a role, these were not found to make a major contribution to this overall model of VH in PD.

Chapter 7

Pathological Gambling and Impulse Control Disorders in Parkinson's Disease.

7.1 Introduction

PG is defined by DSM IV criteria (American Psychiatric Association, 2004) as a persistent and recurrent maladaptive behaviour. It is classified as an ICD and often leads to severe financial embarrassment and breakdown of interpersonal relationships. It occasionally occurs in PD and has been associated with its treatment with dopaminergic drugs. PG together with hypersexuality, and other impulse control behaviour and stereotyped repetitive activities known as punding (Evans et al., 2004) are recognised components of DDS. DDS is characterised by the overuse of additional non-prescribed dopaminergic medication despite an adequate motor response ("on" state) and is frequently complicated by marked dyskinesia and "off" state dysphoria (Giovannoni et al., 2000). The central role of dopaminergic drug therapy in these disorders suggests that they share a common neurobiology and that these may be different manifestations of an underlying vulnerability to developing an ICD. Specific differences in relation to use of dopamine agonists (DA) and demographic characteristics of patients with PG compared to those with DDS may provide important insights. The first part of this study examined the published literature to determine the demographic characteristics and medication profiles of PD patients who pathologically gamble and examined the prevalence of other DDS behaviours in this group. In addition, we assessed how the overall frequency of each DA used in the PG group related to the prescription of each drug overall and specifically whether any particular DA is more implicated in this maladaptive behaviour. In the second part of the study, the detailed demographic data, dopaminergic medication profile and clinimetric measures available from our cohort of PD patients were used. For each

patient the presence or absence of impulse control behaviour or DDS had been recorded on the MDS-UPDRS (Part 1.6). Predictive variables for ICD/DDS identified in the initial meta-analysis (age, sex, dopaminergic medication, and co-morbid psychopathology) and other associated features predicted from the literature (for example cognitive impairment and sleep disorders) were examined.

7.2 Methods

7.2.1 Literature review and meta-analysis

PubMed literature search using term "gambling" and "Parkinson's disease" or "dopamine agonist" or any of individually named DAs was carried out for the period up to March 2007. Additional relevant case series referenced by these publications were included (Tyne et al., 2004, Serrano-Duenas, 2002, Antonini et al., 2006). Sex, age at presentation of PG, age at onset of PD, disease duration, type of DA used, total daily levodopa equivalent units (LEU), and presence of co-morbid psychopathology, including DDS behaviour, was recorded for each. LEU was calculated based on theoretical equivalence used in previous reports (Evans et al., 2004). Categorical data were compared using the Chi-squared test and continuous numerical data using the unpaired t-test. Odds ratio (OR) and confidence intervals (CI) were calculated from available data in retrospective database reviews (Driver-Dunckley et al., 2003) and prospective screening studies (Antonini et al., 2006, Weintraub et al., 2006, Voon et al., 2006, Grosset et al., 2006, Pontone et al., 2006), where overall prescription rates of individual DA in the screened population were known (Bland & Altman, 2000), using STATA® software (StataCorp LP, USA).

7.2.2 Clinical study on dopamine dysregulation

Each patient was assessed on the MDS-UPDRS. The MDS-UPDRS Part 1.6 encompasses

DDS and gives instructions to the examiner to consider "involvement in a variety of activities including atypical or excessive gambling (e.g. casinos or lottery tickets), atypical or excessive sexual drive or interests (e.g. unusual interest in pornography, masturbation, sexual demands on partner), other repetitive activities (hobbies, dismantling objects, sorting or organizing), or taking extra non-prescribed medication for non-physical reasons (i.e. addictive behaviour)" (Goetz et al., 2008). The examiner is also asked to rate the impact of these behaviours on the patient's personal life, family and social relations. For the purposes of analysis, patients who scored ≥ 1 on MDS-UPDRS item 1.6 were considered to have DDS and were compared with non-DDS group in terms of demographics (age, sex, smoking history), dopaminergic medication, disease characteristics (PD duration, motor severity and motor complications [UPDRS]), psychiatric symptoms (HDRS, HADS), cognition (ACE, FAB, SCOPA-COG) and sleep (PSQI, ESS, SCOPA-sleep), using non-parametric (Mann-Whitney) statistical analysis.

7.3 Results

7.3.1 Prevalence of PG in PD compared to the general population

Two large North American epidemiological studies using structured interviews based on the DSM-IV criteria show a prevalence of PG in the general population of 0.42% (USA national survey, N=43,093) (Petry et al., 2005) and 1% (Ontario, Canada, N= 1,030) (Ferris et al., 1996) respectively. In PD, the prospective screening studies for PG that replicate this strict methodology and adherence to DSM-IV criteria, including use of an experienced psychiatrist to interview patients (Voon et al., 2006), revealed higher rates of PG than the general population. In one study, 4.4% of patients on PD medication and 8.0% on DA fulfilled DSM-IV criteria for PG (Grosset et al., 2006) and in another, the lifetime prevalence of PG in PD was 7.2% in patients using a DA (Voon et al., 2006).

7.3.2 Patient characteristics

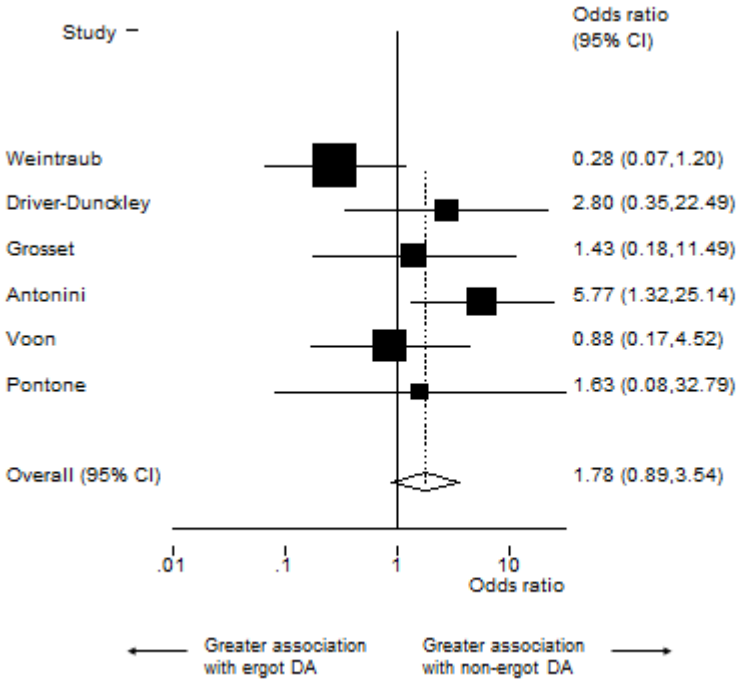
28 case series were identified with a total of 177 patients, dating from July 2000 to March 2007 (Tyne et al., 2004, Serrano-Duenas, 2002, Antonini et al., 2006, Dodd et al., 2005, Driver-Dunckley et al., 2003, Weintraub et al., 2006, Voon et al., 2006, Grosset et al., 2006, Pontone et al., 2006, Larner, 2006, Seedat et al., 2000, Gschwandtner et al., 2001, Avanzi et al., 2004, Bandini et al., 2006, Spengos et al., 2006, Nirenberg & Waters, 2006, Montastruc et al, 2003, Ardouin et al., 2006, Kurlan, 2004, Imamura et al., 2006, Drapier et al., 2006, Avanzi et al., 2006, Lu et al., 2006, Sevincok et al., 2007, Wong et al., 2007, Voon et al., 2007, Garcia et al., 2007, Smeding et al., 2007). There was a male preponderance of 118/156 (75.6%) cases, mean age at diagnosis of PG of 57.3 years (±9.9, range 30-78, N=80), mean age at onset of Parkinson's disease of 49.5 years (±10.3, range 18-72, N=80) and a disease duration of 7.8 years (±4.9, range 2-22, N=80). Other psychopathology was reported in 45/70 (64.3%) with depression in 38/91 (41.8%). Absence or presence of previous gambling behaviour was reported in 8 series. The majority, 23/31 (74.2%) did not gamble before diagnosis of PD. Previous substance misuse was reported in 6 series. A minority, 14/38 (36.8%) had previous substance misuse, predominantly alcohol. Information on pre-morbid smoking and caffeine use was not given. Previous impulse control disorder (ICD) was reported in one series (Weintraub et al. 2006). 36.4% of patients with active ICD had ICD behaviour prior to PD compared to 3.5% of controls.

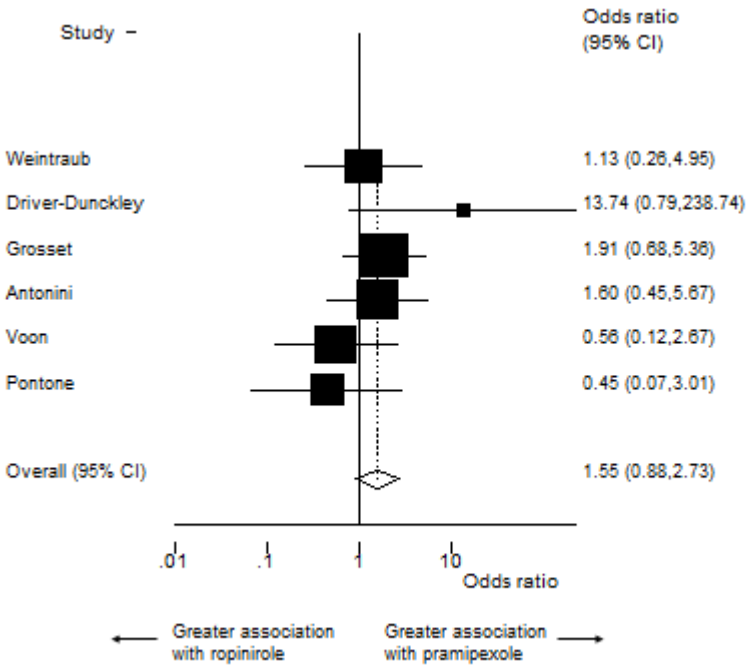
7.3.3 Medication use

DAs were used in 174/177 (98.3%) of cases, with DA monotherapy in 17/130 (13.1%). This included two patients using a combination of two different DA. The three exceptions were a case of PG related to use of selegiline (Drapier et al., 2006) and two cases related to the use

of L-DOPA monotherapy (Ardouin et al., 2006, Avanzi et al., 2006). L-DOPA was the most frequently co-prescribed agent, 110/130 (84.6%). Overall, pramipexole was the most commonly prescribed DA 78/177 (44.1%). Other agents were ropinirole in 42/177 (23.7%), pergolide in 32/177 (18.1%), bromocriptine in 13/177 (7.3%) and cabergoline in 8/177 (4.5%). In six series, the number prescribed each individual DA in the screened population group was given; overall, pramipexole was the most commonly used DA (43.6%), followed by ropinirole (28.9%). In five prospective screening studies, the prevalence of PG in patients taking DA ranged from 2.3 to 8.0% (>6% in four series). In one paper (Driver-Dunckley et al., 2003), pramipexole was significantly more frequently associated with occurrence of PG, compared to ropinirole (P=0.01). However, overall the difference between treatment with individual DA does not reach statistical significance. The pooled OR of PG associated with pramipexole compared to ropinirole is 1.55, CI 0.88-2.73, P=0.13 (heterogeneity χ^2 P=0.32, fixed effects model) (figure 7.1) and the OR comparing total non-ergot and ergot DA is 1.78, CI 0.89-3.54, P=0.10 (heterogeneity χ^2 P=0.088, fixed effects model). The latter calculation very nearly approaches statistical heterogeneity, but if a random effects model is applied the OR is less statistically significant (OR 1.38, CI 0.49-3.93, P=0.55).

Figure 7.1: Meta-analysis to determine influence of dopamine agonists on prevalence of pathological gambling: (a) ergot versus non-ergot dopamine agonists and (b) pramipexole versus ropinirole. Forest plots are shown with pooled odds ratio and 95% confidence ratios.





The mean latency of onset of PG from DA initiation was 23.0 months (±24.6, range 1-84 months, N=30) and from L-DOPA initiation 86.9 months (±65.1, range 12-216 months, N=13). Some patients had been on DA therapy for relatively long periods (18/30 ≥ 1 year and 12/30 ≥ 2 years) with their problem of gambling not becoming clinically evident until dopaminergic treatment was increased. In 7/9 cases in one paper (N=9) (Driver-Dunckley et al., 2003) PG started within one month of increasing the dose of a DA, which had previously been initiated.

The mean total LEU was 909.2 (±621.1) mg and the mean DA LEU was 308.9 (±146.6) mg, equivalent to 4.6mg of pramipexole salt content (= 3.1 mg base) or 15.4 mg of ropinirole. The pramipexole equivalent of 4.6 mg (salt) exceeds the maximum recommended dose for this drug. In cases where individual doses of pramipexole were provided (N=41), 26/41 (63.4%) were taking ≥ 4.5mg. In cases where individual doses of ropinirole were provided (N=23), none exceeded the recommended maximum (24mg) with one patient was taking 24mg. In total for ropinirole and pramipexole (the two most commonly prescribed non-ergot DA) 27/64 (42.2%) were taking the maximum recommended dose or more. In papers where individual doses of L-DOPA were recorded (N=74), 38/74 (51.4%) were using <500mg, 28/74 (37.8%) 500-1000mg and 8/74 (10.8%) >1000mg, the dose range typical of DDS.

7.3.4 Dopamine dysregulation syndrome and psychiatric comorbidity

In case series on PG, DDS was explicitly reported in 18 patients, specifically excluded in 53 patients and in the remaining 106 cases DDS was not specifically reported (table 7.1). In those with PG, the DDS and no DDS groups were similar in terms of their predominantly male sex (P=0.62), early onset of PD (P=0.26), high DA LEU (P=0.42) and overall history of psychiatric disorders (P=0.47). However, the DDS group had significantly longer disease

duration (P=0.05), and higher total LEU (P=0.003). Directly comparing the non-DDS PG group (N=50) with a larger (N=25) representative group of DSS (Evans et al., 2005), disease duration was significantly longer in patients with DDS (P<0.0001), DA were used less frequently (P=0.001) and L-DOPA more frequently (P=0.003). Both DA LEU (P<0.0001) and total LEU (P<0.0001) were significantly more in DDS than non-DDS PG (table 7.2). The non-ergot DA (P<0.0001) were significantly less associated with DDS behaviour than ergot DA. Gambling in the context of an episode of mania is an exclusion criterion in DSM-IV criteria for PG. However, cases of hypomania (Voon et al., 2006, Seedat et al., 2000) and psychotic symptoms, such as delusional thought disorder (Dodd et al., 2005) developing after the onset of PG were reported, although this was uncommon.

7.3.5 Type of Gambling

Preferred gambling activities are listed in 17 series (N=75). These include slot machines in 25/75 (33.3%), casino attendance (activities unspecified) in 16/75 (21.3%), lottery/scratch cards in 12/75 (16%), internet gambling in 15/75 (20%), horse/greyhound racing 10/75(13.3%), bingo in 4/75 (5.3%), interactive television in 2/75 (2.7%) and stock market in 1/75 (1.3%). This is consistent with previous reports of a predilection for activities which are repetitive, require little higher cortical processing and have high reward uncertainty.

Table 7.1 Characteristics of patients with pathological gambling (PG) compared to a representative sample of patients with dopamine dysregulation syndrome (DDS). Figures given as mean (±SD)

	Patients with pathological gambling (PG)				Patients with dopamine dysregulation syndrome (DDS) Evans et al. (Previously unpublished data)	Statistical comparison between patients with DDS and non-DDS PG group.
	TOTAL	No DDS	DDS	Statistical comparison of PG patients with and without DDS		
Number (N)	177	50	13	-	25	-
Sex (males)	118/156(75.6%)	35/50(70%)	10/13 (76.9%)	NS	19/25 (76.0%)	NS
Age (years)	57.3 (±9.9)	56.2 (±9.3)	61.5 (±7.5)	**P=0.04**	55.4 (±8.1)	NS
PD Onset (years)	49.5 (±10.3)	49.9 (±8.9)	53.0 (±8.1)	NS	42.4 (±8.7)	NS
Duration (years)	7.8 (±4.9)	6.3 (±3.8)	8.5 (±3.4)	**P=0.05**	13.1 (±5.9)	**P<0.0001**
All dopamine agonists(DA) (N)	174/177(98.3%)	50/50 (100%)	12/13 (92.3%)	**P=0.05**	20/25 (80.0%)	**P=0.001**
All non-ergot DA (N)	120/177(67.8%)	42/50 (84%)	5/13 (38.5%)	**P=0.0008**	1/25 (4%)	**P<0.0001**
Pramipexole (N)	78/177 (44.1%)	24/50 (48%)	2/13 (15.4%)	**P=0.03**	0	**P<0.0001**
Ropinirole (N)	42/177 (23.7%)	18/50 (36%)	3/13 (23.1%)	NS	1/25 (4%)	**P=0.003**
All ergot DA (N)	53/177 (30.0%)	8/50 (16%)	7/13 (53.8%)	**P=0.004**	7/25 (28%)	**P=0.004**
Apomorphine (N)	0	0	0	NS	14/25 (56%)	**P<0.0001**
L-DOPA (N)	110/130 (84.6%)	36/50 (72%)	12/13 (92.3%)	NS	25/25 (100%)	**P=0.003**
Total levodopa equivalent daily dose (LEDD) (mg)	909.2 (±621.1)	710.4 (±424.2)	1,581.7 (±857.5)	**P=0.003**	1,993 (±833)	**P<0.0001**
DA LEDD(mg)	308.9 (±146.6)	307.0 (±105.9)	361.2 (±224.9)	NS	706 (±309)	**P<0.0001**
Ψ history (N)	45/70 (64.3%)	19/33 (57.6%)	9/13 (69.2%)	NS	20/25 (80%)	NS
Depression (N)	38/91 (41.8%)	12/33 (36.4%)	9/13 (69.2%)	**P=0.04**	12/25 (48%)	NS

7.3.6 Management

Patient management was detailed in 18 case series (N=72). Improvement of PG was reported with decrease or discontinuation of DA dose in 29 patients (40.3%), four of whom required concomitant increase in L-DOPA to control parkinsonian symptoms. Decrease of both L-DOPA and DA was required in 5 patients. In three patients L-DOPA was decreased with increase of the concomitant DA (cabergoline) in one and with switch from ropinirole to pramipexole in another. Eight others improved after switching to an alternative dopamine agonist (in 6 cases from pramipexole to ropinirole). In patients that responded to dopaminergic dose reduction, 9 needed concomitant psychotherapy and 5 antidepressant prescription. One responded to stopping selegiline. Overall 22 (30.6%) had psychiatric input, of whom 17 had counselling/psychotherapy, 10 were prescribed antidepressants, and three an atypical neuroleptic. One did not respond to psychotherapy and SSRI, ultimately committing suicide (Driver-Dunckley et al., 2003). Ten patients required subthalamic nucleus (STN) stimulation because dopaminergic medication reduction was not tolerated or unsuccessful (N=9), there was no response to behavioural therapy (N=4), no response to SSRI (N=2) or clozapine (N=1). PG resolved spontaneously in one person. Of the remainder, there was no response to treatment in one (decrease in both L-DOPA and pramipexole, Kurlan, 2004), no attempted treatment intervention in three (Nirenberg & Waters, 2006, Avanzi et al., 2006, Wong et al, 2007) and no information on management in 5 patients.

7.3.7 Clinical study

15/94 (16%) scored ≥1 on the MDS-UPDRS Part 1.6, indicating ICD or DDS behaviour. The majority exhibiting this behaviour were male, although this did not reach statistical significance (table 7.3). As in the published literature, patients with ICD/DDS were younger and had significantly earlier age at diagnosis of PD. This was a cross-sectional study and

patients were not specifically asked about the onset and duration of their abnormal behaviours, however ICD/DDS patients had longer disease duration, consistent with finding in the meta-analysis that patients with PG have usually been exposed to dopaminergic medication for several years. ICD/DDS was associated with overall DA use, and in particular ergot DA use. In this study there was only a trend for higher non-ergot DA use ($p = 0.19$) but patients had significantly higher total LEU and DA LEU doses (table 7.3), suggesting that it is not only DA use *per se* that is important, but there is also a possible dose effect, as demonstrated in the meta-analysis. ICD/DDS was also associated with amantadine use. Alcohol and smoking history was similar in the two groups. Patients with ICD/DDS were more anxious (HADS-anxiety), had a trend to more depression (HDRS), significantly more sleep disruption (PSQI and SCOPA-sleep-night) and more drug-related motor complications (UPDRS Part IV). There was however no difference in scores on the cognitive scales (ACE, FAB, and SCOPA-COG).

Table 7.2 Demographic and clinical features associated with Impulse Control Disorders and Dopamine Dysregulation Syndrome in PD.

	ICD/DSS (n=15) Median (IQR)	Non-ICD/DDS (n=79) Median (IQR)	P value
Demographics			
Age (years)	64 (57-71)	69 (62-75)	0.076
Age at diagnosis (years)	50 (46-59)	63 (54-71)	0.007
Disease duration (years)	10.8 (6.6-17.9)	4.2 (2.3-11.3)	0.020
Sex (male)	13/15	52/79	0.11
Smoking (pack years)	1 (0-5)	0 (0-14.5)	0.80
Alcohol (units/week)	5 (0-10)	5 (0-16)	0.37
Medication			
Levodopa	13/15	50/79	0.078
All dopamine agonists	14/15	39/79	0.002
Non-ergot agonists	10/15	38/79	0.19
Ergot dopamine agonists	4/15	1/79	<0.001
MAO inhibitor	3/15	8/79	0.28
COMT inhibitor	7/15	19/79	0.073
Amantadine	5/15	7/79	0.009
Total LEDD	901.5 (601.5-1034.7)	360.0 (100.5-800.0)	<0.001
Dopamine agonist LEDD	268.0 (201.0-320.0)	0.0 (0.0-201.0)	<0.001
Psychiatric co-morbidity			
HDRS	5 (2-8)	2 (1-6)	0.071
HADS-Anxiety	8 (5-10)	5 (2-8)	0.007
HADS-Depression	7 (3-10)	5 (3-8)	0.34
Cognition			
ACE	94 (90-99)	92 (85-96)	0.088
FAB	16 (15-18)	16 (14-17)	0.51
SCOPA-COG	28 (22-32)	24 (21-30)	0.18
Sleep			
PSQI	10 (6-13)	6 (3-8)	0.003
ESS	12 (9-14)	7 (4-13)	0.051
SCOPA-Sleep-Night	8 (4-12)	4 (2-7)	0.008
SCOPA-Sleep-Day	6 (3-8)	4 (2-8)	0.23
UPDRS			
Part I	4 (2-5)	3 (1-5)	0.20
Part II	16 (12-22)	14 (8-20)	0.20
Part III	27 (21-35)	31 (20-38)	0.51
Part IV	6 (3-10)	2 (1-6)	0.003

7.4 Discussion

There are certain major caveats in this type of review and meta-analysis that limit generalization of results. These include lack of robust selection criteria and therefore over-reliance on case studies rather than systemic analyses. This is likely to result in selection bias for young male PD patients, who are felt most likely to exhibit PG. In addition, retrospective identification of mood disorders, substance misuse and previous gambling may be biased in case control studies, and underestimated in studies where these behaviours are not actively sought. Only large prospective studies can overcome these limitations.

7.4.1 Risk factors of Pathological Gambling in Parkinson's disease

PG occurs as a rare side effect of treatment of PD in up to 8% of patients on DA. This prevalence is considerably higher than in the general population, where the prevalence of PG is around 1% (Ferris et al., 1996). Patients are predominantly male and young. Psychiatric co-morbidity was often present but as many studies were retrospective it is not clear whether this is a predisposing factor or consequence of the condition. These findings are consistent with population-based observations that link PG to younger age, male gender and high rates of psychiatric problems (Potenza et al., 2001). However substance misuse appears to be a less frequent risk factor in PD patients compared to PG in the general population. The majority of patients have no history of gambling or substance misuse. This may however be an underestimate as the majority of studies did not actively screen for these pre-morbid risk factors.

7.4.2 Relationship to dopaminergic treatment

With the exception of one patient on selegiline and two on L-DOPA alone, all the affected patients in the meta-analysis were on DA (98.3%). An initial case series of 12 patients

(Molina et al., 2000) implicated L-DOPA as a potential aetiological agent for PG, however other dopaminergic drugs used (particularly DA) were not listed. Subsequently, several series reporting the phenomenon of DA-associated PG were published. Results of this meta-analysis confirm treatment with this drug group as the largest independent risk factor. It has been suggested that the DA pramipexole is associated with a particularly increased risk of PG. Evidence for this includes a high adjusted reporting ratio compared to other DA in an FDA audit of adverse events (Szarfman et al., 2006). However, the increased reporting ratio may reflect reporting bias in the FDA audit as the first large case series implicated pramipexole as the main aetiological agent (Driver-Dunckley et al., 2003). The difference may also reflect the relative prescription frequency of pramipexole (overall 43.6%, and >50% of DA prescriptions in several reported series (Weintraub et al., 2006, Pontone et al., 2006). Comparison of the risk of PG on different DA did not reach statistical significance, comparing pramipexole to ropinirole and comparing non-ergot and ergot DA. With further prospective studies these differences may become significant; however the OR is likely to remain small.

The doses of DA were generally large, with a large proportion of patients taking higher than the recommended maximum dose, particularly of pramipexole. The use of L-DOPA in the majority of PG patients may suggest cross-sensitization of brain systems mediating reward. This is further supported by the observation that many individuals with PG had been on stable doses for many months before PG evolved. However, many patients with PD are exposed to a large variety of different dopaminergic drugs and only a relative minority develop compulsive behaviours indicating that individual factors, including a neurobiological predisposition, are highly relevant.

The clinical study in the PD patient cohort confirmed an association of DDS with dopaminergic medication, and in particular high dopamine equivalent doses of L-dopa and DAs. The median DA LEU was 268 mg, equivalent to pramipexole 4 mg (salt) dose. Patients with DDS had significantly longer disease and treatment duration (median 10.8 years since diagnosis), consistent with the finding in the meta-analysis that patients exhibiting this behaviour had been exposed to dopaminergic medication for some time.

7.4.3 Neurobiological Predisposition

Ventromedial prefrontal cortex (VMPFC) involvement has been implicated in ICD from imaging studies. These include an fMRI study of individuals with PG (non-PD) compared to controls which showed negative correlation between activation of the VMPFC and ventral striatum (an area implicated in drug addiction) and gambling severity (Reuter et al., 2005). PET studies in PD patients, un-medicated and with early stage disease, showed significantly lower activation in the orbitofrontal cortex (OFC) and amygdala, as well as striatum (Ouchi et al., 1999) and a further PET study in medicated PD patients performed whilst doing the Iowa Gambling task (Bechara et al., 2005) showed reduced activity in the mesial-frontal areas (Thiel et al., 2003). Decreased activity of the OFC has been consistently reported in imaging studies of drug-addicts (Volkow et al., 2005) and is consistent with evidence that the prevalence of PG is higher in addicts in general (Toneatto & Brennan, 2002). In DDS, PET studies have demonstrated sensitization of ventral striatum to dopaminergic transmission, which correlates with the trait of L-DOPA "wanting" (Evans et al., 2006). VS sensitization is replicated in PET studies after amphetamine administration (Boileau et al., 2006). PG and chemical addiction share many similarities, which include difficulty in controlling the impulse to gamble/overuse medication and the persistence in these behaviours despite negative consequences. Investigation into the biological features of both PD and non-PD

subjects with impulse control behaviour provide support for at least an overlapping biological substrate.

7.4.4 Relationship to impulse control disorders and dopamine dysregulation syndrome

The patient characteristics of PG in PD are comparable to case series of other impulse control disorders in PD such as hypersexuality (Klos et al., 2005). PG also shares a number of characteristics of DDS, such as male sex, early age of onset of PD, higher prevalence of depression than controls and intake of relatively high doses of DA. However, a number of patients with PG have been specifically reported not to have DDS and, conversely, not all patients with DDS have PG as part of the syndrome. PG also differs from DDS in that DA use is almost invariably associated (98.3%), whereas DDS is associated with high doses of L-DOPA. In patients with PG, those with DDS have longer disease duration and higher total LEU.

There are various hypotheses for the aetiology of dopaminergic medication associated compulsive behaviours in PD. It may be speculated that differences between occurrence of DDS and PG are due to the shorter duration of action of L-DOPA producing more instant effects than DAs in DDS, whereas PG may be an adverse effect relating to more continuous dopamine receptor stimulation. However, it is possible that PG represents a dose dependent side effect of DA treatment with a different pathophysiology to DDS and overlap with the DDS phenotype may represent DA co-prescription in this group. The relative selectivity of DA for D3 dopamine receptors, including in mesolimbic areas of the brain, has been postulated as a mechanism for their association with impulse control disorders (Dodd et al., 2005). The differential receptor profile of L-DOPA and DA (including differences between

ergot and non-ergot DA) may influence the type of compulsive behaviour that manifests.

7.4.5 Management

A large proportion of patients with PG were taking higher than the maximum licensed dose of DA. This should clearly be avoided, even with good antiparkinsonian benefit. Pre-morbid gambling, drug use histories and impulsive sensation seeking personality traits may be relevant in identifying at risk individuals. The onset of PG may also occur after the introduction of new dopaminergic medications (particularly DA) or dose increases, and at these times, and especially in young male patients, particular attention should be given to the possibility of this syndrome, although overall only a relatively small minority of patients will be affected. In the non-PD population, there is evidence of benefit from cognitive behavioural therapy (Sylvain et al., 1997), however long term compliance with self-help groups (Stewart & Brown, 1988), particularly in those with co-morbid psychopathology or drug dependency is poor. SSRI use has also been shown to be potentially beneficial (Hollander et al., 2000). In PD several treatment strategies have been reported to be beneficial but no prospective study has been conducted to date. Reduction of DA dose, possibly with increase in L-DOPA to alleviate worsening PD symptoms, reduction of all dopaminergic treatments, or switching from one DA to another may be successful. However, changes to dopaminergic treatment are often not well tolerated and the psychological/cognitive treatments and psychotropic medication, used in the non-PD PG population may prove beneficial.

Chapter 8

Clinical Features associated with Apathy in Parkinson's Disease.

8.1 Introduction

The clinical syndrome of apathy is found in up to 60% of patients with Parkinson's disease (Oguru et al, 2010). Diagnostic criteria for apathy in PD (Starkstein et al., 2009) include loss of motivation relative to pre-morbid function, diminished goal-directed behaviour and cognition, and flattened affect and lack of emotional responses, that are severe enough to result in significant distress or impact on social or occupational function. Apathy may be associated with depressive disorders (Reijnders et al., 2010; Starkstein et al., 2009) or cognitive impairment (Reijnders et al., 2010, Dujardin et al., 2007, Butterfield et al., 2010), particularly executive dysfunction (Varanese et al., 2011, Zgaljardic et al., 2007, Dujardin et al., 2009), but it can exist as a distinct neurological entity (Kirsch-Darrow et al., 2006). However, few data exist on the relative contribution of each of these factors to apathy and its relationship with other non-motor features that may influence its occurrence has not been examined in detail. We here examined the role of other factors that may lead to reduced goal-directed behaviour and cognition, loss of motivation, flattened affect and lack of emotional responses such as impaired night time sleep, excessive daytime somnolence, fatigue, anxiety, motor severity and motor complications ("off" fluctuations and dyskinesias) in addition to impaired cognition and depression.

8.2 Methods

8.2.1. Patients and clinical measures

The Lille Apathy Rating Scale (LARS) was administered to all patients (Sockeel et al., 2006). The LARS is a 33-item apathy rating scale based on structured clinical interview with several

domains (everyday productivity, interests, initiative, novelty seeking, motivation, emotional response, concern, social life and self-awareness) which has been validated for use in PD and has shown high internal consistency, test-retest reliability and inter-rater reliability (Sockeel et al., 2006). A cut-off score of ≥ -16 (scale range: -36 to +36, where higher scores represent a greater degree of apathy) had a high degree of sensitivity and specificity in discriminating an expert's judgement of apathy in the original validation study in PD cohort (n=159) and healthy controls (n=58) (Sockeel et al., 2006). The LARS has also shown good concurrent validity with proposed consensus criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders (Robert et al., 2009). Other clinical measures included the HDRS (Schwab et al., 1967), HADS (Upadhyaya and Stanley, 1993), ACE (Larner, 2007), FAB (Dubois et al., 2000), SCOPA-COG (Marinus et al., 2003), UPDRS (Fahn et al., 1987), SCOPA)-Sleep scale (Marinus et al., 2003b), and FSS (Krupp et al., 1989),

8.2.2. Statistical analysis

Based on established cut-off scores on clinical scales, patients were classified as apathetic (LARS score ≥ -16 [Sockeel et al., 2006]) and/or depressed (HDRS score ≥ 10, cut-off score for screening in PD [Schrag et al., 2007]) and/or cognitively impaired (SCOPA-COG ≤ 24, optimal cut-off for screening for PD dementia [Verbaan et al., 2011]). Scores on clinical rating scales for motor and non-motor features of PD in apathetic and non-apathetic groups were compared using Mann-Whitney U analysis. Multiple regression analysis was performed separately with the LARS total score and the four subscores (intellectual curiosity, emotion, action initiation and self-awareness) as the dependent variables and clinical factors in the univariate analysis ($P<0.05$), excluding collinear variables, as the independent variables. Regression analysis was performed with backward selection, with probability criteria for variable removal $P>0.10$.

8.3 Results

8.3.1 Clinical features associated with apathy

15 of 94 (16%) patients were defined as apathetic using the LARS cut-off score. Only one of 15 (7%) had pure apathy, the remainder having depression (5 of 15, 33%) and/or cognitive impairment (12 of 15, 80%), with 3 (19%) having both (fig 8.1). In comparison, in the non-apathetic patients, 6 of 79 (8%) had depression and 34 of 79 (43%) had cognitive impairment. There was no significant difference between the apathetic and non-apathetic groups in age, disease duration or dopaminergic medication (Levodopa equivalent units, LEU) (table 8.1). Patients with apathy had significantly more depression (HDRS, HADS-depression score), fatigue (FSS), cognitive impairment (ACE, SCOPA-cognition, FAB), daytime somnolence (SCOPA-sleep-daytime), severity of motor symptoms (UPDRS motor score, Part III) and motor fluctuations (UPDRS Part IV, table 8.1). In the regression analysis five variables were independently associated with apathy in PD: greater depression (HDRS), daytime somnolence (SCOPA-sleep-daytime), cognition (SCOPA-cognition), and motor severity (UPDRS Part III) and lower motor complications scores (UPDRS Part IV) (table 8.2). Predictive variables for the LARS intellectual curiosity subscore were greater depression (HDRS), cognitive impairment (SCOPA-cognitive), daytime somnolence (SCOPA-sleep-daytime) and lower motor fluctuation scores (UPDRS Part IV). Predictive variables for the action initiation subscore were greater daytime somnolence, cognitive impairment and motor function (UPDRS Part III) scores. Predictive variable for self-awareness subscore was fatigue (FSS). No variables allowed significant prediction of the LARS emotion subscore in this study.

Figure 8.1 Apathy, Depression and Cognition in Parkinson's Disease

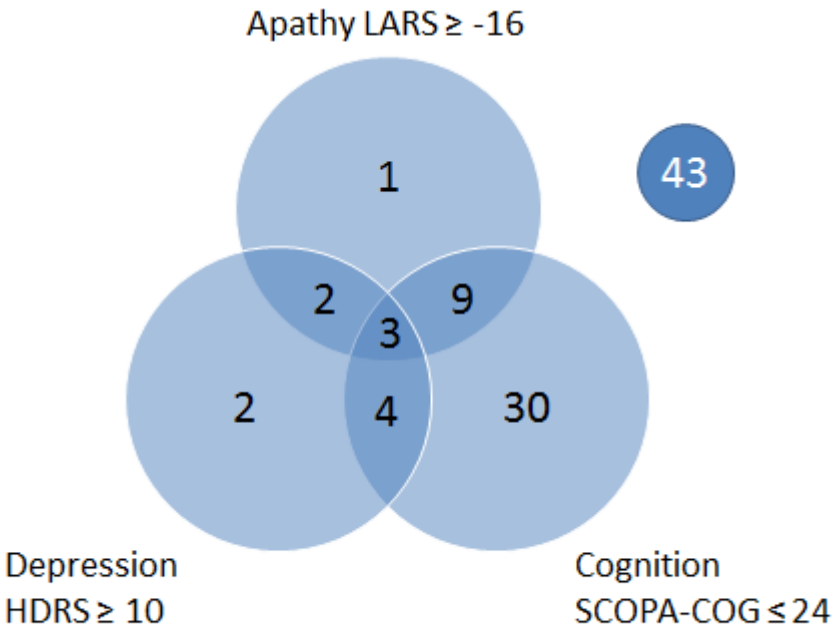


Table 8.1 Clinical findings of PD patients with and without apathy

	Apathetic (N=15) Median (Interquartile range)	Non-Apathetic (N=79) Median (Interquartile range)	P value
Demographics			
Age (years)	71.0 (62.0-75.0)	68.0 (62.0-74.0)	0.55
Disease duration (years)	6.7 (3.1-15.9)	4.8 (2.3-11.6)	0.19
LEU (mg)	626.7 (300.0-883.5)	400 (100.5-900.0)	0.14
Sleep and fatigue			
SCOPA-Sleep-Night-time	3.0 (1.0-11.3)	4.0 (2.0-8.0)	0.76
SCOPA-Sleep-Daytime	8.0 (3.0-12.5)	4.0 (2.0-6.0)	0.021
FSS	5.7 (4.5-6.6)	4.1 (2.8-5.2)	0.008
Depression and anxiety			
HDRS	8.0 (6.0-11.0)	2.0 (1.0-5.0)	<0.001
HADS-Anxiety	3.5 (1.8-7.5)	5.0 (3.0-9.0)	0.20
HADS-Depression	8.5 (6.0-11.3)	5.0 (2.0-8.0)	<0.001
Cognition			
ACE	85.0 (77.0-94.0)	93.0 (87.0-96.0)	0.021
FAB	13.0 (12.0-17.0)	16.0 (15.0-17.0)	0.031
SCOPA-Cognition	20.0 (18.0-23.0)	25.0 (22.0-31.0)	0.003
-memory	6.0 (5.0-8.0)	9.0 (7.0-12.0)	0.003
-attention	4.0 (2.0-4.0)	4.0 (4.0-4.0)	0.28
-executive	8.0 (6.0-9.0)	9.0 (8.0-10.0)	0.038
-visuospatial	3.0 (2.0-4.0)	4.0 (3.0-5.0)	0.076
Motor function			
UPDRS Part III	38 (29-48)	28 (19-37)	0.020
UPDRS Part IV	4 (3-9)	2 (1-6)	0.031

Abbreviations LEU – Levodopa Equivalent Units, SCOPA – Scales for Outcome in Parkinson's disease, FSS – Fatigue Severity Scale, HDRS – Hamilton Depression Rating Scale, HADS – Hospital Anxiety and Depression Scale, ACE – Addenbrooke's Cognitive Examination, FAB – Frontal Assessment Battery, UPDRS – Unified Parkinson's Disease Rating Scale.

Table 8.2: Multiple regression analysis of clinical features associated with apathy subscores in Parkinson's disease

	β-coefficient	T score	P value
LARS total score			
SCOPA-sleep-daytime	0.59	3.00	0.004
HDRS	0.73	3.70	<0.001
SCOPA-cognition	-0.27	-2.44	0.017
UPDRS Part III	0.12	1.99	0.050
UPDRS Part IV	-0.47	-2.08	0.041
			Model R^2 = 0.39
LARS intellectual curiosity			
SCOPA-sleep-daytime	0.09	3.08	0.003
HDRS	0.12	4.48	<0.001
SCOPA-cognition	-0.04	-2.74	0.007
UPDRS Part IV	-0.06	-1.98	0.051
			Model R^2 = 0.38
LARS emotion			
Nil significant			
LARS action initiation			
SCOPA-sleep-daytime	0.10	3.60	0.001
SCOPA-cognition	-0.06	3.26	0.002
UPDRS Part III	0.02	2.32	0.023
			Model R^2 = 0.37
LARS self-awareness			
FSS	0.14	1.77	0.080
			Model R^2 = 0.03

Abbreviations, LARS = Lille Apathy Rating Scale, SCOPA = Scales for Outcome in Parkinson's disease, HDRS = Hamilton Depression Rating Scale, UPDRS = Unified Parkinson's Disease Rating Scale, FSS = Fatigue Severity Scale.

8.4 Discussion

Our finding that apathy in PD is strongly and independently associated with higher depression scores and cognitive impairment is consistent with previous studies (Reijnders et al., 2010; Reijnders et al., 2010, Dujardin et al., 2007, Butterfield et al., 2010; Starkstein et al., 2009). We could also confirm that considerable overlap exists between these three syndromes, although in some patients apathy is not associated with either of these comorbidities. Apathy was also significantly associated with fatigue and daytime somnolence, which was not fully explained by greater cognitive impairment and depression, and not associated with poor night-time sleep, suggesting that this non-motor feature additionally contributes to patients' loss of motivation, and addressing this separately may improve patients' apathy. Greater motor impairment, as measured by UPDRS motor score, further contributed mildly to higher apathy scores. This is in contrast to previous studies where there was no difference in motor scores between apathetic and non-apathetic patients (Starkstein et al., 2009) or this variable did not contribute to the regression model once other variables had been accounted for (Oguru et al., 2010). As this was primarily seen in the action initiation subscale, this may reflect patients' difficulty in physically initiating activities due to immobility. Finally, there was a significant greater apathy score in those with lower motor complications subscores on the UPDRS, which may reflect lower responsiveness to medications. In conclusion, apathy in PD is frequently associated with depressive symptoms and cognitive impairment and with greater motor impairment and fewer motor complications but also independently with increased daytime somnolence/fatigue, which can potentially be addressed directly in clinical practice to improve apathy.

Chapter 9

Conclusions

9.1 Quality of life

PD is a multisystem neurodegenerative disorder, characterised by dopaminergic neuronal loss in the substantia nigra pars compacta. However, a number of other neurotransmitter systems are involved and detailed pathology studies have demonstrated involvement of widespread extra-nigral locations. The development and widespread introduction of Levodopa therapy for PD in the 1970s resulted in a dramatic change in the prognostic outcome and quality of life for PD patients with improvement in the characteristic motor features of the disease. In subsequent decades, research and development into pharmacological therapies has focused on drugs that act on dopaminergic pathways, for example synthetic dopamine agonists and medication to potentiate L-dopa function, such as mono-amine oxidase inhibitors (selegiline and rasagiline) and catechol-o-methyl transferase inhibitors (entacapone and tolcapone). The majority of primary care physicians are able to recognise the typical motor features of PD (tremor, rigidity, bradykinesia, and gait disturbance) and have good knowledge of the dopaminergic drug therapies available, and feel confident to prescribe and adjust doses in the primary care setting. In addition, many patients have access to specialist hospital based care (geriatricians, general neurologists and movement disorder specialists), and in many cases are seen in clinics with multi-disciplinary input (PD nurse specialists, occupational therapists and occupational therapy). Therefore in most cases dopaminergic drug therapy has been optimised depending on motor severity and within limits of associated motor complications (motor fluctuations and dyskinesias). However, until relatively recently, there has been little research into the prevalence of NMS or into the development of novel drug therapies for these symptoms; but despite this, NMS have been shown to influence Hr-QOL. Previous

studies that have examined the influence of different clinical factors on quality of life have concentrated on motor severity and motor complications; where non-motor features have been included, this has generally been limited to cognitive function and mood. Cognitive scales used have often been generic (for example MMSE) rather than scales specifically developed in PD, or scales more sensitive to detect dysexecutive or subcortical cognitive function. Depression has consistently been shown to have a significant impact on quality of life however other important neuropsychiatric features such as anxiety, apathy and psychosis have not been extensively examined. This study aimed to examine a very broad range of motor and non-motor symptoms, and to quantify these accurately with validated clinical scales. Where possible, scales were used that had been developed specifically for PD, rather than generic scales, and also scales that had undergone independent validation by other groups and had demonstrated adequate clinimetric scales properties, and good convergent and discriminant validity, were used, although this was not possible in all cases. A wide range of NMS were assessed including autonomic function, neuropsychiatric features (depression, anxiety, apathy, hallucinations and delusions), sleep (nocturnal and daytime sleepiness), cognition (including a scales specifically measuring frontal cognitive function), pain, and fatigue. This study confirms that NMS are frequent in PD (mean of 11 symptoms per patient, on the NMSQ screening questionnaire). As expected, motor features (severity, fluctuations and dyskinesia), depression and cognition had statistically significant univariate correlation with Hr-QOL scales. The correlation coefficients for these variables, was similar to the published literature, with cognition in particular having only modest correlation with quality of life indices. However, in this study, autonomic function, sleep, fatigue, pain and psychosis also had high univariate correlation with quality of life, and the multivariate analysis demonstrated that in optimally treated patients from a motor perspective, depression, autonomic features, fatigue and daytime somnolence were most highly correlated with poor

Hr-QoL, and motor features were excluded in the final regression analysis. Therefore emphasis on the optimisation of motor symptoms is unlikely to be sufficient to have maximal impact on Hr-QOL. Treatment options are not available for all non-motor symptoms in PD, or have been developed for use in other neurological or non-neurological disorders rather than in PD, and therefore these treatments will require further validation in well-designed studies. A challenge for the future will be determine the exact role of extra-nigral dopaminergic transmission and other non-dopaminergic neurotransmitter systems in the aetiopathogenesis of the wide spectrum of motor and non-motor features of PD and the development of novel pharmacotherapies to improve debilitating non-motor features. When proven therapies for NMS become available, they should have significant impact on patients' functioning.

9.2 Detection of non-motor symptoms

This thesis has examined two aspects of physicians' awareness and recognition of NMS in PD. A retrospective case notes analysis of donors with pathologically proven PD, from the UK Brain Bank, revealed that the presenting feature in PD can often be non-motor, with pain, autonomic symptoms, and disorders of mood being the most common presenting features. This is consistent with autopsy studies that have proposed that the pathological changes in PD (LB deposition) can begin in extra-nigral locations, particularly brainstem areas implicated in mood and autonomic function. This study has demonstrated that primary care physicians are less adept at making an early and confident diagnosis of PD, when non-motor features predominate, and this has often led to misdiagnosis as musculoskeletal disorders ("frozen shoulder", osteoarthritis, or degenerative disc-vertebral disease), psychiatric problems (depression and anxiety), cerebrovascular disease or other non-neurological diagnoses. Many patients are thus referred to inappropriate specialists (rheumatology, orthopaedics, psychiatry, urology, or stroke) and may undergo unnecessary investigations or interventions. This study

highlights the importance of educating primary care and hospital general physicians in the recognition and use of NMS, in the early diagnosis of extra-pyramidal disorders; this will be of greater importance if disease-modifying therapies in PD are developed, that could impact on disease progression, rather than the currently available symptomatic therapies.

In addition, this thesis examined the documentation of non-motor features in a cross-sectional sample of PD patients in specialist movement disorders clinics, using a screening questionnaire and compared this to a retrospective case notes audit. Our study found that under half of NMS reported in the screening questionnaire had not been documented in the medical notes, particularly potentially embarrassing bowel, bladder and sexual dysfunction. The majority of NMS however were shown in our analysis to have significant impact on disability and Hr-QOL, and specific enquiry for these issues in PD patients and implementation of management strategies is likely to result in significant improvement in quality of life.

9.3 Measurement of non-motor symptoms in PD

PD is a complex disorder and in the time and resource pressures of the out-patient setting it would be virtually impossible to question patients on all NMS, assess their severity and clinical significance, and to counsel and instigate multi-disciplinary management strategies. The MDS-UPDRS has been developed as a global PD scale, and is a substantial revision of the original UPDRS, designed to encompass the complete range of motor and non-motor symptoms and to quantify their severity, and is an objective measure of change over time or response to drug therapies. The MDS-UPDRS consists of a physician's assessment of neuropsychiatric features (cognition, mood, anxiety, apathy, hallucinations and DDS) and a detailed examination of motor features and also a patient (or carer) completed questionnaire dealing with other motor or non-motor experiences of daily living. We have demonstrated

that the MDS-UPDRS Part I (nM-EDL), which normally takes less than ten minutes to complete, has high convergent validity with a battery of detailed clinimetric scales for non-motor features.

9.4 Neuropsychiatric symptoms

Psychiatric phenomena are common in PD. VH, in particular, have been proposed as a diagnostic marker of LB pathology and already form part of the formal diagnostic criteria for DLB. This thesis examined the pathogenesis of VH in PD. Based on an extensive review of clinical, psychometric, pathological, functional imaging and polysomnographic studies, an integrated hypothesis was proposed implicating altered visual processing, disorder of sleep-wake cycle and REM sleep dream mentation, cognitive function, and dopaminergic medication. In this study, a multiple regression analysis supported this hypothesis, with RBD (ICSD-R minimal diagnostic criteria), executive cognitive function (SCOPA-COG-executive score) and a measure of higher order cortical visual processing (BORB object decision task) identified as independent determinants of VH in our cohort of PD patients. SCOPA-AUT score also contributed significantly to the model and is a marker of brainstem dysfunction, which is consistent with the integrated hypothesis. As with, previous cross-sectional studies, dopaminergic medication did not make a significant contribution to the regression model. A post-mortem study was also performed which demonstrated increased LB density in several cortical areas (frontal, temporal, cingulate and entorhinal cortices), including areas implicated in visuoperception and cognitive function. This study has potential therapeutic implications for the treatment of VH. For example, further analysis of the brainstem nuclei involved in the sleep-wake cycle and dreaming, and identification of specific neurotransmitters involved, and development of drugs that act on these transmitter systems, will help in the development of effective treatments for VH. Similarly, development of medication that can improve cognitive function (executive and visuoperceptive) is likely to be important.

In this thesis, a meta-analysis of published case series of PG, the archetypal ICD in PD, was performed and identified characteristic clinical features, including younger age, male sex, psychiatric co-morbidity such depression, and in particular dopaminergic medication. ICD was highly associated with DA use, particularly at higher doses, and L-dopa has also been implicated in the majority of PG patients, suggesting cross-sensitization of brain systems mediating reward. In our PD cohort, patients with ICD/DDS had younger age at diagnosis of PD, longer disease duration (suggesting more prolonged exposure to dopaminergic medication) and were significantly more likely to use DA medication, and had higher doses of dopaminergic medication. It was also demonstrated that psychiatric co-morbidity (particularly anxiety), disordered sleep (nocturnal insomnia) and motor complications (higher UPDRS part IV scores) are associated with DDS.

This study also examined the relationship of apathy with depression and cognitive impairment. Apathy in PD was strongly and independently associated with higher depression scores and cognitive impairment, consistent with previous studies. Considerable overlap exists between these three syndromes, although in some patients apathy exists as a distinct clinical feature. Apathy was also significantly associated with fatigue, increased daytime somnolence, higher motor scores (UPDRS Part III) but also fewer motor complications (UPDRS Part IV), which may reflect lower responsiveness to medication. These identified features could potentially be addressed directly in clinical practice to improve apathy.

9.5 Conclusions

This thesis has demonstrated the importance of NMS in PD. NMS can occur in the early stages of PD, and their identification can aid early and accurate diagnosis of the disease, but alternatively misattribution of these symptoms to other neurological or non-neurological disorders, can lead to misdiagnosis, inappropriate specialty referrals or therapeutic

interventions. I have also demonstrated that NMS have a significant impact on Hr-QOL and disability, in early and late disease, but can be under-recognised by neurologists. This study has also specifically examined neuropsychiatric features of PD, with particular reference to VH, apathy, ICD and DDS.

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