

# Nonmotor Symptoms of Parkinson's Disease

Guest Editors: Irena Rektorova, Dag Aarland, K. Ray Chaudhuri,  
and Antonio P. Strafella





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## Editorial

# Nonmotor Symptoms of Parkinson's Disease

**Irena Rektorova,<sup>1</sup> Dag Aarsland,<sup>2,3</sup> K. Ray Chaudhuri,<sup>4</sup> and Antonio P. Strafella<sup>5</sup>**

<sup>1</sup> Movement Disorders Center, First Department of Neurology, Medical Faculty, St. Anne's University Hospital and Applied Neuroscience Research Group, Central European Institute of Technology CEITEC, Masaryk University, 625 00 Brno, Czech Republic

<sup>2</sup> Department of Neurobiology, Care Sciences and Society, Alzheimer's Disease Research Center, Karolinska Institute, 141 86 Stockholm, Sweden

<sup>3</sup> Centre for Age-Related Medicine, Stavanger University Hospital and Institute of Clinical Medicine, Akershus University Hospital, University of Oslo, 4005 Stavanger, Norway

<sup>4</sup> National Parkinson Foundation Centre of Excellence, King's College Hospital, King's College, London SE5 9RS, UK

<sup>5</sup> Movement Disorder Unit and E. J. Safra Parkinson Disease Program, Toronto Western Hospital, UHN and Imaging Research Centre, Centre for Addiction and Mental Health, University of Toronto, Toronto, ON, Canada M5T 2S8

Correspondence should be addressed to Irena Rektorova, irena.rektorova@fnusa.cz

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The nonmotor symptoms (NMSs) of Parkinson's disease (PD) have received a lot of attention in the last few years. Despite this fact, they have still been underrecognized and undertreated [1, 2]. NMS may include cognitive problems, apathy, depression, anxiety, hallucinations, and psychosis as well as sleep disorders, fatigue, autonomic dysfunction, sensory problems, and pain [1]. Since these symptoms substantially contribute to patients' quality of life and are a frequent cause of hospitalization and institutionalization, the NMSs and their management have been recognized by the UK National Institute for Clinical Excellence as an important unmet need in PD [3]. Besides dopamine and Lewy-type pathology involving both striatal and extrastriatal brain regions, deficits in other neurotransmitter systems and/or other types of brain pathologies seem to play a key role in the pathogenesis of NMS in PD [4–6].

It has been clearly shown that dopaminergic treatment improves motor symptoms and the quality of life in patients with PD. However, it only partly improves some features of the NMS, and it is not free from nonmotor side effects such as hallucinations and other psychotic symptoms, irritability, sleep attacks, and impulse control disorders. Furthermore, one study found that the patients who survived at 20 years from PD diagnosis suffered mainly from the non-dopaminergic symptoms including falls, choking, dysarthria, but also dementia, visual hallucinations, daytime somnolence, symptomatic postural hypotension, and urinary

incontinence [7]. Therefore, the management of these non-dopaminergic symptoms is a priority for research in the near future.

In addition to pharmacotherapy, high-frequency deep brain stimulation of the subthalamic nucleus (STN DBS) is a powerful surgical treatment in well-selected candidates with advanced PD. STN DBS leads to improvements in dopaminergic drug-sensitive symptoms and reductions in subsequent drug dose and dyskinesias [8]. Although quality of life improves substantially, the procedure cannot be recommended for the treatment of NMS, and it may even cause specific cognitive side effects and may increase the risk for suicide. Skilled speech and physical therapy with cueing to improve gait, cognitive therapy to improve transfers, exercises to improve balance, and training to build up muscle power and increase joint mobility are efficacious. Regular physical and mental exercise is therefore recommended for all PD patients [9].

As outlined above, multidisciplinary approach including both pharmacological and nonpharmacological treatment of PD is essential; however, the current delivery of allied healthcare services is inadequate, and many people who require such care are not being referred to the relevant specialist. Parkinson's Standards of Care Consensus Statement will soon be released by the European Parkinson's Disease Association and should be implemented in Europe in the near future.

Besides symptomatic treatment, search for the disease-modifying, neuroprotective, and restorative treatment of PD is ongoing. Despite many so far unresolved issues, gene- and stem-cell-based therapies as well as immunotherapy targeting alpha-synuclein might become treatment options in the future. Development of these therapies is dependent on an accurate and comprehensive understanding of the pathogenesis and pathophysiology of PD and on the ability of very early diagnosis of premotor stages of PD. Therefore, a search for specific biomarkers (clinical, neuroimaging, biochemical, genetic) for early (premotor) diagnosis and for the disease progression is essential and large multicenter trials are underway.

This special issue is dedicated to nonmotor symptoms of PD and focuses on the above-mentioned “old-new” topics. We sincerely hope that it will provide readers with interesting new data as well as with comprehensive up-to-date reviews. We wish our readers pleasant and inspiring reading.

*Irena Rektorova  
Dag Aarsland  
K. Ray Chaudhuri  
Antonio P. Strafella*

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## Clinical Study

# The Possible Clinical Predictors of Fatigue in Parkinson's Disease: A Study of 135 Patients as Part of International Nonmotor Scale Validation Project

**Vinod Metta,<sup>1,2,3</sup> Kartik Logishetty,<sup>1</sup> P. Martinez-Martin,<sup>4</sup> Heather M. Gage,<sup>3</sup> P. E. S. Schartau,<sup>2</sup> T. K. Kaluarachchi,<sup>2</sup> Anne Martin,<sup>1</sup> Per Odin,<sup>5,6</sup> P. Barone,<sup>7</sup> Fabrizio Stocchi,<sup>8</sup> A. Antonini,<sup>9</sup> and K. Ray Chaudhuri<sup>1,2</sup>**

<sup>1</sup> National Parkinson Foundation Centre of Excellence, King's College Hospital, King's College London, Denmark Hill Campus, 9th Floor, Ruskin Wing, London SE5 9RS, UK

<sup>2</sup> University Hospital Lewisham, London SE13 6LH, UK

<sup>3</sup> University of Surrey, Surrey GU2 7XH, UK

<sup>4</sup> Alzheimer Disease Research Unit, CIEN Foundation, Carlos III Institute of Health, Alzheimer Center Reina Sofia Foundation, Madrid, Spain

<sup>5</sup> Department of Neurology, University Hospital, Lund University, Lund, Sweden

<sup>6</sup> Department of Neurology, Central Hospital, Reinkenheide, Bremerhaven, Germany

<sup>7</sup> Department of Neurological Sciences, University of Naples Federico II, Via S. Pansini 5, 80131 Naples, Italy

<sup>8</sup> Department of Neurology, IRCCS San Raffaele, 00163 Rome, Italy

<sup>9</sup> Department of Neurology, IRCCS San Camillo Venice and University of Padua, 35122 Padua, Italy

Correspondence should be addressed to K. Ray Chaudhuri, [chaudhuriray@hotmail.com](mailto:chaudhuriray@hotmail.com)

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Fatigue is a common yet poorly understood and underresearched nonmotor symptom in Parkinson's disease. Although fatigue is recognized to significantly affect health-related quality of life, it remains underrecognised and empirically treated. In this paper, the prevalence of fatigue as measured by a validated visual analogue scale and the Parkinson's disease nonmotor symptoms scale (PDNMS) was correlated with other motor and nonmotor comorbidities. In a cohort of patients from a range of disease stages, occurrence of fatigue correlated closely with more advanced Parkinson's disease, as well as with depression, anxiety, and sleep disorders, hinting at a common underlying basis.

## 1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder which is known to be associated with nonmotor symptoms (NMS) including dribbling of saliva, constipation, depression, sleep disorders, apathy, hallucinations, and dementia [1]. NMS of PD contributes significantly to health-related quality of life (HrQoL) and some NMS such as constipation, hyposmia, rapid eye movement behavior disorder (RBD), fatigue, and depression may be markers of a preclinical stage of PD [2, 3]. In spite of its clinical and patient-related importance, NMS remain undeclared and often undertreated in primary or secondary care [4].

Fatigue is now recognized as a key NMS in PD. It may be present at diagnosis and can complicate late disease and become an overwhelming problem for patients and relatives [5–7]. Indeed, fatigue impacts most dimensions of HrQoL even as a factor independent of depression and disability [8–10]. The largest holistic study of NMS in PD, the PRIAMO study, reported fatigue to be prevalent in 58.1% of a population sample of 1072 patients ranging from 37.7% in early (Hoehn and Yahr (HY) stage 1) PD to 81.6% in advanced (HY stage 5) [11]. Other studies have suggested a prevalence between 33% to 58%, although the method of diagnosis and definition of “fatigue” is heterogeneous [7, 12–16]. However, there is a poor correlation between the severity of mental

and physical fatigue suggesting independent aetiologies [17]. Since there is as yet no biomarker of fatigue, patient-reported questionnaires remain the mainstay of measuring and diagnosing fatigue. Specific scales for clinical assessment of fatigue have now been validated for PD and can be used in the clinic while “holistic” nonmotor scales can be used to explore the relationship of other key NMS of PD such as depression, apathy, excessive daytime sleepiness, and fatigue. The Parkinson's nonmotor group (PDNMG) led pivotal studies validating the first nonmotor questionnaire (NMSQuest) and subsequently, the nonmotor scale (NMSS) for PD [18–20]. Fatigue is a key component of domain 2 of the NMSS. It is scored based on the multiplication of its severity and its frequency—a measure that was validated based on the collection of data from an unselected cohort of PD patients from a number of international centers.

Fatigue in PD occurs independent of motor severity. There is a paucity of research exploring the treatment of fatigue in PD. There is conflicting evidence regarding the efficacy of levodopa in treating fatigue [21, 22] while it may be alleviated using methylphenidate [23]. Independent of PD, large cohort [24–26] studies have associated fatigue with a more sedentary lifestyle. Only one study, which evaluated patients with PD, found that lower levels of physical activity, poorer physical function, and less frequent strenuous exercise were associated with increased fatigue (see the work of Garber and Friedman [27]). A study on rats which had 6-OHDA lesioning [28] has suggested a link between increased exercise and reduced loss of striatal dopamine concentrations, with another study showing that later intervention with exercise did not improve deficits [29]. However, no animal studies to date have demonstrated an improvement of fatigue with exercise, and there is no evidence yet to recommend the efficacy of exercise therapy on fatigue in PD in humans.

In this study, we have analysed the prevalence of fatigue from the composite data set used to validate the nonmotor symptom scale. We attempted to explore if other measures used in the study contributed or could be marked as “predictors” of fatigue in this population. We also aimed to discern whether disease severity or pharmacological treatment of PD affected the prevalence of fatigue. An improved understanding of this poorly researched area of nonmotor symptoms in PD could then guide a holistic treatment strategy.

## 2. Methods

*2.1. Design.* This data is obtained from the database related to the validation study of the NMSS [18] which was an international, cross-sectional, open, multicentre, one point-in-time evaluation with retest study. Details of the administration of the scales have been published previously.

*2.2. Patients.* Consecutive patients with PD (patients with Parkinsonism were excluded), of all age groups and disease severity, satisfying the UK PD Brain Bank criteria for diagnosis of idiopathic PD were included after attending

relevant outpatient clinics [30]. Patients with a diagnosis of parkinsonism due to alternative causes were excluded.

Patients were recruited from specialist movement disorder clinics at the National Parkinson Foundation centre of excellence at King's College and Lewisham Hospitals (UK) and also local Care of the Elderly clinics. This ensured that we recruited a range of patients from the composite group. Cases with disease severity spanning Hoehn and Yahr (HY) stages 1 to 5 were studied, and we also attempted to include a proportion of untreated cases. Datasets were included where fatigue data was available and computable.

Only patients able to provide informed consent were selected for the study and demented patients were excluded. The latter would mean that the clinician would exclude patients with significant cognitive impairment that

- (i) affected their ability to provide informed consent,
- (ii) affected their ability to complete self-reported items.

The data presented relates to 135 patients included largely from the King's/Lewisham, German and Italian sites.

## 3. Ethical Approval

Central ethical approval for the full study was initially obtained via the research ethics committee at University Hospital Lewisham and subsequently all centres obtained site specific ethical approval.

## 4. Procedure

The scales (listed below) and the nonmotor symptom questionnaire used in the study were applied following a standardized protocol, always in the same order, and there was no reported patient fatigue while completing the scales [3, 18]. Patient and carers took approximately 25 minutes to complete the questionnaire while the investigator-led instruments took 40 minutes to complete.

## 5. Assessments

The researcher then completed the following battery of standard assessment measures:

- (i) standard demography form,
- (ii) unified Parkinson's disease rating scale (UPDRS) [31],
- (iii) cumulative illness rating scale-geriatrics [32] (CIRS-G to measure physical comorbidity),
- (iv) Hoehn and Yahr scale [33],
- (v) frontal assessment battery [34] (FAB),
- (vi) nonmotor symptom scale [18].

Sections 3 and 4 of the UPDRS were applied. These domains evaluate motor examination and complications of therapy, respectively. The frontal assessment battery is a short scale exploring assessing cognitive and behavioural function, as a measure of executive capacity in PD.

In addition, the patient (assisted by the research nurse if necessary) completed the following self-assessments:

- (i) PDQ-8 [35] (a specific instrument for assessment of health-related quality of life in PD),
- (ii) a fatigue-visual analogue scale (VAS-F) [36],
- (iii) hospital anxiety and depression Scale (HADS) [37] (a self-administered instrument developed for the detection of mood disorders in nonpsychiatric outpatients attending hospital consulting rooms).

The total time required for a single assessment was approximately 65 minutes per patient.

**5.1. Fatigue.** For this study the VAS was used as a measure of convergent validity with the fatigue section of the NMSS. Fatigue was assessed using the fatigue VAS validated specifically for PD. Patients were asked about the severity of perceived fatigue by means of visual analogue scale (VAS) where 0 represented the worst imaginable fatigue state to 100 representing no fatigue at all [37].

**5.2. The NMS Scale.** The NMS scale is composed of 30 items grouped in 9 domains: cardiovascular, sleep/fatigue, mood/apathy, perceptual problems, attention/memory, gastrointestinal, urinary, sexual function, and miscellaneous. Each item is scored for frequency (ranging from 1 (rarely) to 4 (very frequent)) and intensity (ranging from 0 (none) to 3 (severe)). The product of these scores gives the item severity score (0 to 12). Domains and NMSS total scores are obtained by the sum of items scores. The scale has been extensively validated in two large international studies exceeding 700 patients [3, 18].

**5.3. Inclusion/Exclusion Criteria.** All patients with established diagnosis of PD satisfying the UK Brain bank criteria were included while all cases of Parkinsonism due to other causes were excluded [13]. Additionally, after data had been collected, patients whose clinical assessments indicated dementia, severe depression (HADS > 13), or major sleep disturbances were excluded as these factors may confound assessment of fatigue.

**5.4. Statistics.** Descriptive statistics were used for the study variables as needed. For comparisons, the Pearson's chi-squared, Mann-Whitney test (to test between two groups), and Kruskal-Wallis test (to compare more than two groups) were applied, as the variables did not meet the assumptions for use of parametric statistics. Looking for a balance between error types I and II adjustment for multiple comparisons, the Benjamini-Hochberg method was applied. Association of nonlinear relationships was analyzed by Spearman rank correlation coefficient ( $r_s$ ) with an alpha level set at 0.0001 but with a Bonferroni downward adjustment for multiple comparisons. The statistical software SPSS 19.0 (IBM, USA) was used for data analysis.

## 6. Results

A total of 135 patients met eligibility criteria with complete datasets. Demographic details and summary of measures are shown in Tables 1–5. Patients had a mean age of  $69.7 \pm 10.52$  years and an age range of 35 to 88 yrs (24.4% TD, 28.9% AD, 46.6% mixed). However, as this was a clinic-based study, only 2% were HY stage 5 while the majority were between HY stages 2–3 (Table 4). The breakdown of NMSS scores in each domain is shown in Table 6.

Data from the application of the fatigue-specific visual analogue scale showed no significant differences between males (1) and females (2) using the Mann-Whitney test (male  $62 \pm 20.4$  versus female  $63.1 \pm 19.2$ ). Analysis of fatigue scores (grouped as mild, moderate, or severe) using HY staging of disease progression (HY 1–2.5 = 7 (mild fatigue); HY 3 = 8 (moderate fatigue); HY 4–5 = 9 (severe fatigue)) showed a significant correlation ( $P = 0.004$ ) using the Kruskal-Wallis test as seen in Table 3. No significant differences were observed in fatigue scores between the different drug treated and drug naive patients using the Mann-Whitney test. Correlation measures using Spearman rank correlation coefficient were used between the various variables and fatigue scores and are listed in Table 7.

Correlation measures using the Spearman rank correlation coefficient associating measured variables from UPDRS, CIRS, HADS, FAB, PDQ-8, Hoehn & Yahr, NMSQuest, and NMSS instruments are also shown in Table 7. Increased fatigue was independently correlated strongly ( $r < -0.30$ ,  $P < 0.0001$ ) with HADS anxiety and depression domains, FAB score, total NMSQuest score, total NMSS score, HRQo measured by PDQ-8, and NMS sleep and mood domains.

## 7. Discussion

Fatigue was noted by James Parkinson (1817) in his original description of the disorder, but it is only in 1993 that studies began describing its prevalence, progression, and impact and characterising fatigue [7].

Studies since then have suggested that sleep disorders, medications, and depression may be possible secondary causes of fatigue in individuals with PD [6]. The prevalence of autonomic impairment, nocturnal sleep disturbances, and depression have been found to exacerbate the subjective perception of fatigue. However, fatigue occurs in patients with PD independent of sleep dysfunction and in nondepressed patients, suggesting that these factors may not be the only contributors to the high prevalence of fatigue in PD patients. Indeed, population-based studies in PD report that sleep disorders and in particular excessive daytime somnolence (EDS) do not account for fatigue in the majority of PD subjects. This relationship is, however, clouded by evidence showing that certain medications used to treat PD are associated with EDS [6].

The PRIAMO study showed that fatigue is present in patients presenting at Hoehn and Yahr stage 1 of the disease while the percentage of patients with fatigue rises as the disease progresses to stage 5 [11]. It is likely that in the majority of PD patients, fatigue is intrinsic to the disease.

TABLE 1: Distribution of disease severity as measured by Hoehn and Yahr stage (H &amp; Y stage).

H & Y stage	Patients ( <i>n</i> )	Percent (%)
1	16	11.85
1.5	17	12.59
2	22	16.30
2.5	20	14.81
3	42	31.11
4	15	11.11
5	3	2.22

TABLE 2: Distribution of patients after H &amp; Y stage grouped by severity.

H & Y categories	Patients ( <i>n</i> )	Percent (%)
Mild	75	55.56
Moderate	42	31.11
Severe	18	13.33

Subdivisions: H & Y 1–2.5 = (mild); 3 = (moderate); 4 + 5 = (severe).

TABLE 3: Analysis of fatigue scores using Hoehn and Yahr staging of disease progression showed a significant correlation ( $P = 0.004$ ) using the Kruskal-Wallis test.

H & Y categories	Mean fatigue score	Std. Dev.
Mild	67.52	18.33
Moderate	56.83	17.16
Severe	54.94	26.44

TABLE 4: The distribution of antiparkinsonian therapy used in the patients studied.

Therapies	Patients ( <i>n</i> )	Percent (%)
Drug naïve	12	8.89
Levodopa monotherapy	50	37.04
DA monotherapy	11	8.15
Levodopa + DA	61	45.19
Others	1	0.74

DA: dopamine agonists.

Our current study was aimed at exploring these various issues, in particular by using PD-specific fatigue measures which were used as secondary variable measure in the original validation study of NMSS, and employing correlation measures with seemingly confounding variables. The patient base was “real life” and representative of a PD population.

We found no difference in fatigue scores between subtypes of PD. Akinesia dominant cases had similar levels of fatigue compared to tremor dominant types, and fatigue levels were similar between male and female patients. However, using Kruskal-Wallis comparative measures, fatigue levels worsened significantly with worsening disease severity as measured by HY stage and graded as mild, moderate, and

TABLE 5: A unified table showing demographic values and assessment scores in this study.

Variable	Patients ( <i>n</i> )	Mean	SD	Minimum	Maximum
Age	135	69.74	10.52	25	88
Duration	135	5.78	5.19	0	32
Agedx	135	63.88	11.34	29	65
UPDRS 3	130	16.13	8.01	2	44
UPDRS 4	132	2.92	3.03	0	13
Dysk & Flct	132	2.32	2.74	0	12
CIRS Total	135	4.74	2.84	0	15
VAS-F	135	62.52	19.90	10	100
HADS Anx	135	10.73	4.79	0	21
HADS Dep	135	10.19	4.62	1	21
FAB Total	134	14.79	2.83	3	18
PDQ-8	134	28.19	17.82	0	78.13

SD: standard deviation, duration = duration of disease, agedx: age at diagnosis. Dysk & Flct: dyskinesia and fluctuation, UPDRS 3 and 4: unified Parkinson's disease rating scale domains 3 & 4, CIRS: cumulative illness rating scale, VAS-F: fatigue-specific visual analogue scale, HADS Anx & Dep: hospital anxiety and depression rating scale anxiety and depression domains, FAB: frontal assessment battery.

TABLE 6: Table showing nonmotor scale (NMSS) data distribution including subitem scores.

Variable	Patients ( <i>n</i> )	Mean	Std. Dev.	Min	Max
GI	135	4.38	5.14	0	23
Urinary	135	6.44	7.01	0	36
CV	133	2.60	4.04	0	21
Sexual function	135	3.08	5.66	0	24
Sleep/fatigue	135	11.11	9.03	0	48
Perception	135	1.81	4.43	0	36
Mood	135	10.56	14.34	0	72
Attention/memory	135	5.97	8.03	0	36
Misc.	135	6.66	7.38	0	36
NMSS total	133	52.96	41.52	0	243

GI: gastrointestinal, CV: cardiovascular, Misc.: miscellaneous, NMSS total: total score on NMSS.

severe (Table 2). This observation is in line with the recently reported PRIAMO study where fatigue levels were reported incrementally as HY stages increased [11]. However, it is to be noted that a substantial proportion of mild PD cases, including drug naïve PD patients, experienced some level of fatigue.

The level of fatigue between drug naïve cases and those treated with either mono or combination therapy of antiparkinsonian agents were similar and provides an indirect support for the observation that fatigue in PD appears to be unaffected by conventional PD therapy. However, we observed a trend (although nonsignificant) of better fatigue scores in those treated by combined levodopa and dopamine agonists (fatigue score of  $71.3 \pm 19.1$  in untreated PD versus fatigue score of  $60.6 \pm 20.6$  in combined therapy). At least one study has suggested that pergolide, an

TABLE 7: Correlation measures using Spearman rank correlation coefficient measures between the various variables and fatigue scores.

Variable	<i>r</i>	<i>P</i>
Age	—	N.S.
<b>UPDRS domain 3</b>	<b>- 0.2380</b>	<b>=0.0064</b>
UPDRS domain 4	- 0.1968	0.0237
CIRS total	—	N.S.
CIRS domain 1	—	N.S.
<b>HADS anxiety domain</b>	<b>- 0.3948</b>	<b>&lt;0.0001</b>
<b>HADS depression domain</b>	<b>- 0.4171</b>	<b>&lt;0.0001</b>
<b>Frontal assessment battery</b>	<b>0.3374</b>	<b>=0.0001</b>
<b>NMSQuest total</b>	<b>- 0.3122</b>	<b>=0.0003</b>
NMSQuest sleep domain	- 0.2823	=0.0009
Other NMSQuest domains	—	N.S.
Hoehn & Yahr staging	- 0.2882	=0.0007
<b>PDQ-8</b>	<b>- 0.367</b>	<b>&lt;0.0001</b>
<b>NMSS total</b>	<b>- 0.3924</b>	<b>&lt;0.0001</b>
NMSS cardiovascular domain	- 0.2985	=0.0004
NMSS sexual function domain	- 0.2576	=0.003
<b>NMSS sleep domain</b>	<b>- 0.3908</b>	<b>&lt;0.0001</b>
<b>NMSS mood domain</b>	<b>- 0.3766</b>	<b>&lt;0.0001</b>
NMSS attention/memory domain	- 0.2574	=0.003
NMSS misc. domain	- 0.2666	0.002
Other NMSS domains	—	N.S.

The key correlations ( $P < 0.0001$ ) are highlighted (N.S.: not significant, UPDRS: unified Parkinson's disease rating scale, CIRS: cognitive impairment rating scale, HADS: hospital anxiety and depression scale, NMSQuest: nonmotor symptom questionnaire, NMSS: nonmotor symptom scale).

ergot dopamine agonist may improve fatigue in PD although controlled studies are lacking [38].

Finally, in an attempt to unravel the positive correlations of fatigue and other measures in PD, a detailed correlation analysis was undertaken (Table 7). The key findings were that anxiety and depression as measured by the HADS anxiety and depression subscales, and the mood domain of NMSS showed a robust association with fatigue scores on VAS. Sleep dysfunction was also associated highly significantly with fatigue while HY score also registered a significant association. All together this translated to a robust association with health-related quality of life as measured by PDQ-8.

The association of fatigue with sleep dysfunction and anxiety and depression appears confirmatory with other observations as quoted previously while the lack of association with age, sex, and pattern of PD is also in line with established views on fatigue [6]. Statistically the dominant predictive factors of fatigue emerging from this study are depression, anxiety, and sleep dysfunction. This was our a priori hypothesis and may support a view held by Shulman et al. who suggested that nonmotor symptoms of PD such as fatigue, depression, and pain could share the same pathogenic origin [39].

Indeed, a recent study suggests that reduced serotonin (and perhaps dopamine) in certain areas of the brain may provide the pathophysiological basis of fatigue in

PD [40]. Pavese et al. [40] used  $^{11}\text{C}$ -DASB imaging to demonstrate reduced serotonin transporter binding in the caudate, putamen, ventral striatum, and thalamus in PD patients with fatigue. Although there was no difference between nigrostriatal dopamine levels as measured by  $^{15}\text{F}$ -dopa values, reduced uptake in the insular cortex of PD patients with fatigue points to a link between fatigue and loss of extrastriatal dopaminergic function. Methylphenidate, a dopamine transporter blocker, has been shown to be effective in improving fatigue in PD patients [23]. While SSRIs have been used to treat chronic fatigue, and anecdotally to address fatigue in PD, the  $^{11}\text{C}$ -DASB findings suggest that treatment strategy should aim to restore serotonin levels rather than inhibit its transport (via the serotonin transporter, SERT).

Although it is clinically difficult to separate fatigue and sleep given the difficulty a patient may have in distinguishing the two, several studies have suggested that fatigue is an independent nonmotor symptom unrelated to sleepiness [7, 16]. Sleepiness in PD has been associated to damage to central arousal systems by neuronal loss and Lewy bodies in several areas including serotonergic neurons in the raphe median nucleus.

Isolating depression from fatigue in PD can also be challenging. Although it has been shown that fatigue occurs more in the depressed patient than in the general population [41, 42], this relationship is obscured by varying definitions of "fatigue" in the literature. More so, symptoms of fatigue and anergia contribute to the disability of depression. However, there are reports demonstrating that PD patients may experience depression and/or sleepiness without fatigue [5]. Depression has long been associated with widespread serotonergic loss [43, 44]. One small study has shown that nortriptyline, a tricyclic antidepressant with moderate antiserotonin receptor effects, improved symptoms of fatigue [45].

Although it is unlikely that one neuronal hormone, be it serotonin or dopamine, is responsible for fatigue, sleepiness, anxiety, or depression in PD, this study shows a commonality between these nonmotor symptoms, and is thus consistent with the hypothesis proposed by Shulman et al. Less robust association was observed for instance with cardiovascular NMS such as orthostatic tolerance, sexual function, pain, hyperhidrosis, attention, and memory functions (Table 7). Further studies must be designed to disentangle the specific relationship of these issues with fatigue, including the role of sleep pattern in fatigued PD patients, and explore alternative strategies to target the role of low central serotonin levels in these patients.

In conclusion, this study suggests that fatigue is an important independent nonmotor symptom of PD and is associated with depression, anxiety, and sleep disorders. Fatigue appears to be widespread irrespective of the motor stage of PD and has a close correlation with quality of life in people with Parkinson's.

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## Case Report

# Dementia after DBS Surgery: A Case Report and Literature Review

**I. Rektorova,<sup>1,2</sup> Z. Hummelova,<sup>1</sup> and M. Balaz<sup>1,2</sup>**

<sup>1</sup> 1st Department of Neurology, St. Anne's University Hospital, Medical School of Masaryk University, Pekarska 53, 656 91 Brno, Czech Republic

<sup>2</sup> Applied Neuroscience Research Group, Central European Institute of Technology, Masaryk University, 602 00 Brno, Czech Republic

Correspondence should be addressed to I. Rektorova, irena.rektorova@fnusa.cz

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We report the case history of a 75-year-old woman with Parkinson's disease who developed severe cognitive problems after deep brain stimulation (DBS) of the bilateral subthalamic nuclei (STN). After a brief cognitive improvement, the patient gradually deteriorated until she developed full-blown dementia. We discuss the case with respect to the cognitive effects of STN DBS and the possible risk factors of dementia after STN DBS surgery.

## 1. Introduction

Parkinson's disease (PD) is a degenerative disorder. Clinical heterogeneity, progressive motor pattern changes, and variations in the course of the disease are well known [1, 2]. The disease process continues throughout life as there is no spontaneous or treatment-induced remission. PD subtypes change with time, and the progression is nonlinear [3]. The point-prevalence of dementia in PD is close to 30%, and the incidence rate is 4- to 6-times greater than that of age-matched controls. The cumulative prevalence of dementia is at least 75% for PD patients who survive for more than 10 years [4–6].

Although there is no causal treatment for PD, deep brain stimulation (DBS) of the bilateral subthalamic nuclei (STN) has been shown to be surgically safe in well-selected candidates, and subsequent improvements in dopaminergic drug-sensitive symptoms and reductions in drug doses and dyskinesias are well documented. However, the procedure is associated with adverse effects, mainly neurocognitive and neuropsychiatric, and with side effects created by the spread of stimulation to surrounding structures, depending on the precise location of electrodes [7–9]. The morbidity rates associated with invasive surgery can also be significant, including particularly intracranial bleeding [10, 11].

## 2. Case History

A 61-year-old woman was diagnosed with PD in 1991. She had no family history of PD and she had not been chronically treated for any other medical condition. She worked as a high school teacher until the age of 65.

The first symptoms of PD included hyposmia, fatigue, and tremor and rigidity of the left lower extremity (LLE). She was first put on selegiline. In 1994, she started L-dopa treatment, which had an excellent effect on the motor symptoms of PD. In 1995, while the daily dose of L-dopa was 500 mg, the first choreodystonic peak-dose dyskinesias appeared on the LLE. After that, different therapies were prescribed as add-on treatments to the L-dopa, including dopamine agonists (pergolide, ropinirole), amantadine, and entacapone. These therapies had transient effects in the alleviation of both the motor symptoms of PD and the motor complications.

In 2005, the patient was on a stable antiparkinsonian medication therapy consisting of ropinirole 5 mg tid and L-dopa plus entacapone in alternating doses of 100 mg and 50 mg in six 3-hour intervals starting at 7 am (altogether, six doses; total daily L-dopa dose 450 mg). At that time, the patient suffered either from generalised tremor and rigidity accompanied by severe pain of the whole body or

from severe choreodystonic involuntary movements. She stopped leaving her house and was unable to take full care of herself. We examined the patient using the Core Assessment Program for Surgical Interventional Therapies in PD (CAPSIT-PD) [12]. At that time, the patient experienced no falls, no postural instability, no freezing of gait, and there was no history of depression, hallucinations, or delusions. According to a detailed neuropsychological examination in October 2005, she was declared cognitively normal in all domains including memory (as measured by the Wechsler Memory Scale III), executive functions (as assessed by Mattis Dementia Rating Scale, semantic and phonological verbal fluency, Tower of London Task, Stroop test), visuospatial and visuoconstructive abilities (as assessed by Rey-Osterrieth Complex Figure Test), and speech [13]. The Mattis Dementia Rating Scale score was 144 points, and her IQ as measured by the Wechsler Adult Intelligence Scale-revised (WAIS-R) was 129 [13]. No symptoms of behavioural or affective disorders were present. The brain MRI was normal for age. Except for PD, the patient was otherwise healthy. She was very motivated for PD surgery. The L-dopa test was clearly positive: the Unified Parkinson's Rating Scale (UPDRS, [14]) III subscore dropped from 44 to 22 points. Despite her high age (75 years), she was considered a good candidate for the procedure.

Bilateral STN electrodes were implanted in December 2005. The stereotactic procedure was performed using the Leibinger open frame with the Praezis Plus software and the Talairach diagram. We used the standard tungsten microelectrode 291A (Medtronic, Inc., Denmark) with an impedance of 0.5–1.5 M $\Omega$  for the intraoperative microrecording and microstimulation. Once the target coordinates were determined, a permanent quadripolar DBS electrode (Medtronic, model 3389 with 0.5 mm intercontact distance and 1.5 mm electrode contact width) was implanted. The electrode position was verified by the intraoperative use of fluoroscopy to compare the position of the trajectories of the microrecording electrodes with the definitive trajectory of the quadripolar macroelectrode [15]. The final coordinates of electrode tips within the STN ( $x, y, z$ ) were 11.5 mm anteriorly, 3 mm posteriorly, 5 mm caudally from AC-PC midpoint. The position of the electrode was confirmed by postoperative CT scan and X-ray with a stereotactic frame still mounted.

No complications were observed at the time of surgery; the patient remained conscious, alert, and cooperative during all stages of the procedure. Nevertheless, on the day after the electrode implantation, a transient somnolence, disorientation in time and space, and retrograde amnesia occurred. This acute confusion regressed within 4 days. The electrode cables were internalized, and a neurostimulation device (Kinetra, Medtronic Inc., Minneapolis, USA) was implanted. The patient was released from the hospital. She was rehospitalized one month later in order to start the stimulation.

In January 2006, a neuropsychological examination was performed with the stimulation off while the patient was on stable dopaminergic medication. It revealed a moderately intense organic psychosyndrome and a marked dysexecutive

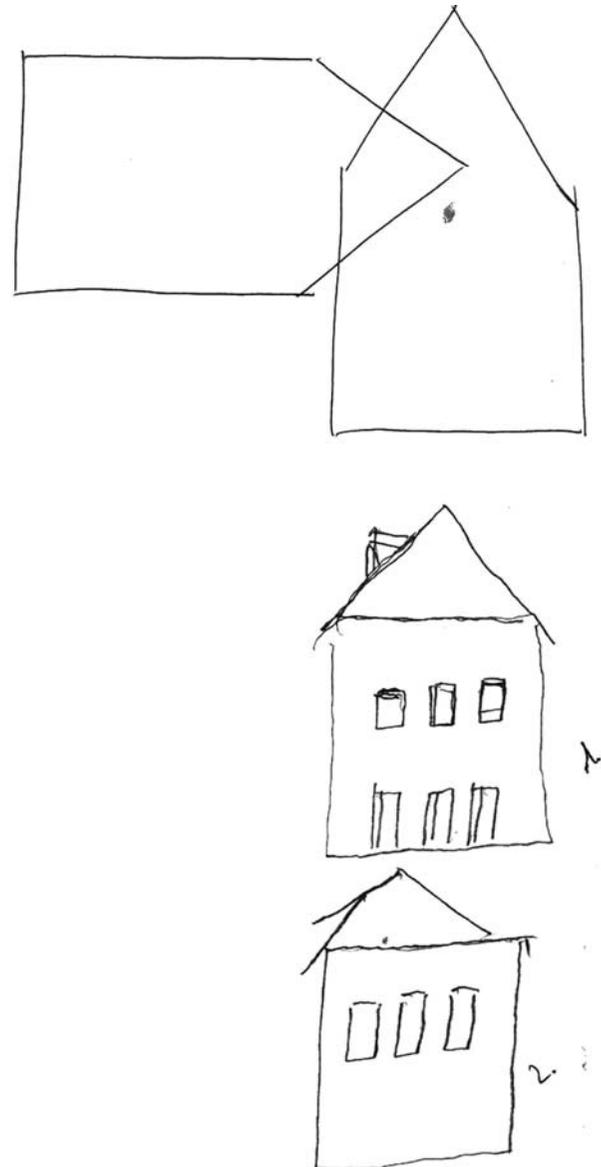


FIGURE 1: Intersecting pentagons drawing from the Mini-Mental State Examination reflects patient's disinhibition.

syndrome with a major impact on other cognitive functions and instrumental activities of daily living. It manifested symptomatically by decreased psychomotor speed, flexibility, spontaneity, and concentration, as well as attention deficits and disinhibition (see Figure 1 for the intersecting pentagons drawing from the Mini-Mental State Examination (MMSE, [13])). Mild memory impairment was also identified, affecting primarily recent episodic and semantic memory. Visuospatial deficits, dyscalculia, and deficits in time orientation were also reported, and the patient became negativistic and dysphoric. Her MMSE score was 14 points and the Montgomery-Asberg Depression Rating Scale (MADRS) score was 24 [13]. We performed brain MRI and FLAIR sequences to verify the electrode location and to rule out possible adverse effects of implantation. The electrode

location was correct; however, mild oedema and bleeding were found in the anterior limb of the left internal capsule, spreading to the putamen and caudate head (see Figure 2(a)).

The stimulation had been started very slowly. By March, the stimulation parameters were set at intensities of 2.0 and 2.7 V, for the left and right sides, respectively, with a 130 Hz frequency, and 90  $\mu$ sec pulse width. The stimulated contacts were 2 and 6, respectively. The patient's motor symptoms of PD and motor complications improved significantly. The Unified Parkinson's Rating Scale (UPDRS, [15]) III subscore in the off medication state improved from 44 to 21 points. The UPDRS IV subscore decreased from 4 to 0 points. Ropinirole was decreased to 7.5 mg/day, L-dopa was decreased to 300 mg/day (administered in 6 doses), entacapone was 1200 mg/day (6 doses taken together with L-dopa), and citalopram was started (20 mg per day). Cognitive functions had improved slightly from the cognitive outcomes of January 2006.

Mild cognitive impairment, with the predominant involvement of the frontal lobes, was reported during neuropsychological testing in June 2006 (see Table 1), affecting verbal fluency, motor sequential tasks, and strategic planning. Mild dyscalculia, recent memory, and visuospatial memory impairments were also identified, but the global cognitive performance was within the normal range; the MMSE score was 27. At that time, the previously described pathology observed on the brain MRI had partially regressed. However, the MRI results in May 2006 still demonstrated hyperintensity changes along the left electrode trajectory in the area of the genu of internal capsule, and the medial edge of the lentiform nucleus reaching to the left thalamus (see Figure 2(b)). On the whole, the clinical status of our patient improved from the motor, behavioural, and cognitive points of view. In June 2006, the stimulation intensity was 3.3 and 3.7 V, for the left and right sides, respectively, while the antiparkinsonian medication remained stable with no changes. We tried to introduce acetylcholinesterase inhibitors (rivastigmine, donepezil) but the patient did not tolerate any of the drugs because of nausea and vomiting.

During the summer of 2006, the patient's medical condition again started to gradually deteriorate, with episodes of freezing of gait and postural instability, visual hallucinations, and delusions. The behavioural disturbances were worse in the morning. The patient experienced no tremor. Sometimes she had very mild dyskinesias on the left side, but no motor fluctuations were present. She left the house and got lost repeatedly, and she became partially dependent on the caregiver (her husband). Quetiapine was started at that time with a dose titration up to 75 mg per day; this was later exchanged for clozapine in low doses (50 mg per day). All other medications except L-dopa (550 mg/day) and citalopram (20 mg/day) were withdrawn. Cognitive testing in March 2007 confirmed the cognitive decline, with a Mattis Dementia Rating Scale score of 116 points and an IQ score measured at 90. In addition to dysexecutive syndrome, memory functions, and praxis, visuoconstructive, visuospatial, and other cognitive functions were impaired, including writing and picture drawing.

In 2008, full-blown dementia was reported, which progressed over time. Memantin (20 mg per day) was introduced, but no visible effect on slowing the dementia course was detected. In December 2008, a marked overall brain atrophy was depicted in brain MRI, including both hippocampi. White matter hyperintensities along the electrode trajectories (possible gliosis) were also visible (see Figure 2(c)). In 2009, the MMSE score was 19, and according to the 7-min subtests [13], orientation in time score was 74, enhanced cued memory score was 8, the clock test score was 1, and semantic verbal fluency was 5. In February 2010, the stimulation battery was changed, with the last stimulation parameters being as follows: amplitude 3.6 V and 3.8 V for the left and right sides, respectively, stimulation frequency 130 Hz, pulse width 90  $\mu$ sec. The MMSE was 14. The patient suffered from hallucinations, delusions, and postural instability with occasional falls. She had severe aphasia and dysarthria with telegraphic slurred speech and moderately severe motor and ideomotor apraxia. She became incontinent, and fully dependent on her husband. She died in April 2010. The probable cause of death was pneumonia. No brain biopsy was performed.

### 3. Discussion

Our patient suffered from intracranial bleeding as a consequence of the STN electrode implantation. Intracerebral hemorrhages (ICHs) have been known to occur as possible adverse effects of DBS surgery in 1 to 4% of cases, according to literature reports of case studies, large studies, and meta-analyses [10, 11, 16–21]. These manifest as transient neurological symptoms, some with complete recovery and others with long-term deficits. In our patient, the specific location of the ICH including the left striatum and thus involving the frontostriatal circuitry could have explained an abrupt cognitive deterioration and marked dysexecutive syndrome in particular [22–24]. The possible risk factors of ICH include particularly arterial hypertension. The impact of the use of microelectrode recordings and of an increased number of microelectrode trajectories have been rather controversial [17–19, 25]. Older age and male sex have also been associated with hemorrhage, according to some studies [19, 26]. Our patient had normal blood pressure; however, her advanced age might have played a role.

Interestingly, our patient partially recovered, but approximately 8 months after the surgery she again started to deteriorate cognitively until full-blown dementia developed within 2.5 years after the DBS surgery. Although the vast literature on cognitive short-term as well as long-term outcomes after bilateral DBS surgery of the STN varies and remains rather controversial, mild to moderate decreases in verbal fluency have been reported as the most common after-effects of the procedure (e.g., [7–9, 27–32]). The exact mechanisms of possible cognitive effects of STN DBS are not known. The precise location of the active electrode contact and the spatial extent of the effects of stimulation as well as the frequency, voltage, and amplitude of STN stimulation, or patient variables such as degree of dopaminergic denervation could be involved (e.g., [33, 34]).

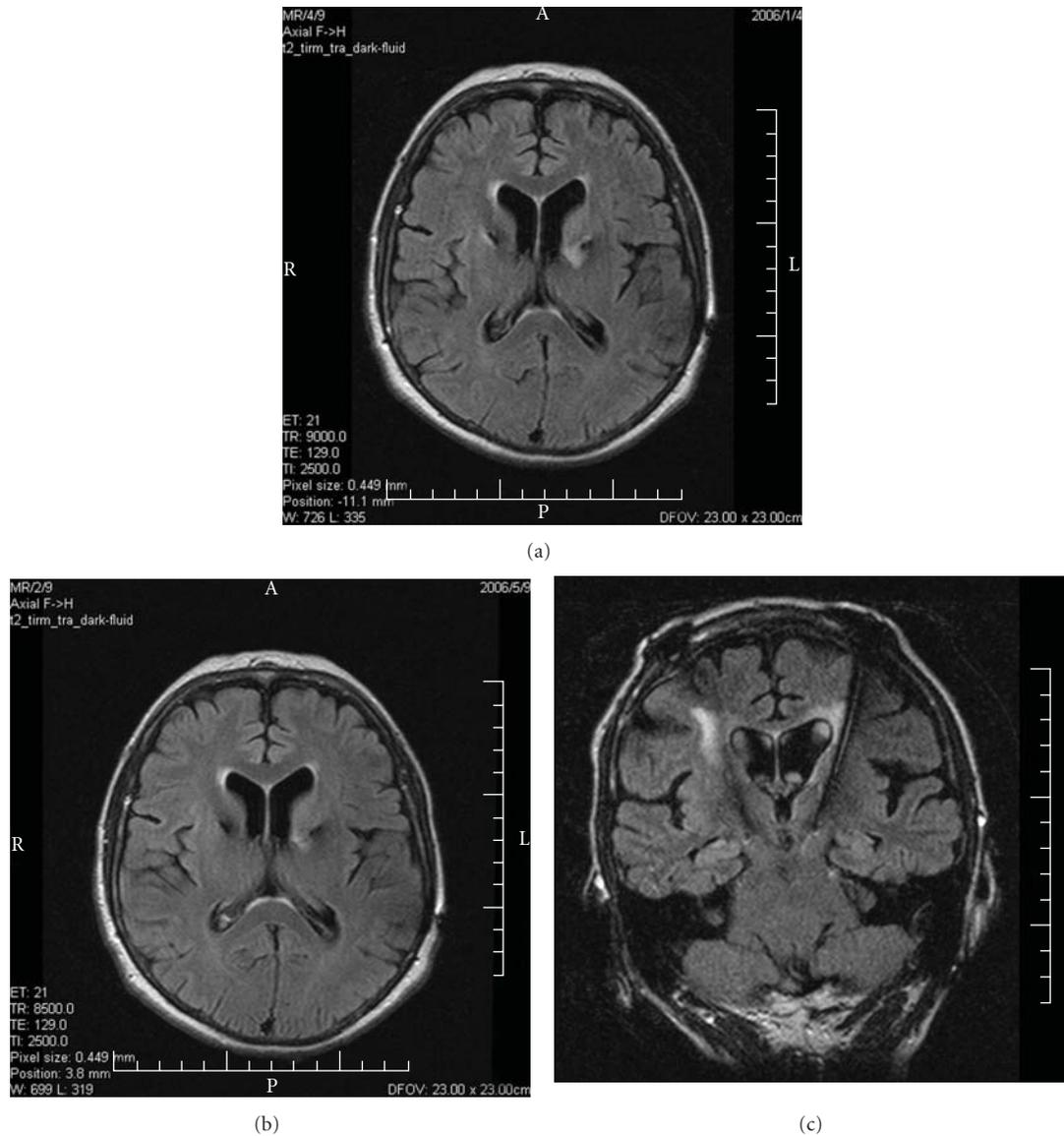


FIGURE 2: (a) Fluid-attenuated inversion recovery magnetic resonance imaging (FLAIR MRI) in January 2006 shows mild edema and bleeding in the anterior limb of the left internal capsule and left striatum. (b) FLAIR MRI in May 2006 still depicts signal changes along the left electrode trajectory in the internal capsule, medial edge of the lentiform nucleus reaching to the left thalamus. (c) FLAIR MRI in December 2008 demonstrates marked brain atrophy and white matter hyperintensities along the electrode trajectories.

Conversely, development of dementia has been generally related to the PD progression itself [30–32]. According to a Sydney study, 48% of PD patients had dementia after 15 years of the disease progression and 83% after 20 years of having PD [5, 35]. Other studies have reported the cumulative prevalence of dementia to be least 75% among PD patients who survive for more than 10 years [36]. The most established risk factors for dementia in PD (PDD) are higher age, severity of motor symptoms, in particular postural and gait disturbances, cognitive impairment at baseline, and visual hallucinations. Other risk factors, such as lower education and socioeconomic status, later disease onset, longer disease duration, positive family history, depression, and REM sleep

behavioural disorder have also been reported (e.g., [4–6, 35, 36]). Of all the above-mentioned factors, old age (75 years at the time of DBS and 78 years at the time of dementia diagnosis) and long disease duration (17 years at the time of dementia diagnosis) were the most marked risk factors to take into account in our patient.

The time from onset of PD to dementia varies considerably [36, 37]. There is a growing body of evidence derived from clinicopathological studies to suggest that there are different PDD subtypes depending on the age at PD onset and the disease duration. A less malignant type with a long time to dementia onset is characterized by Lewy body distributions consistent with the Braak staging of disease

TABLE 1: Neuropsychological test battery results.

Psychological test	Examination date						
	10/2005	1/2006	3/2006	6/2006	11/2006	3/2007	7/2008
WAIS-R (IQ)	129	14 MMSE only	102	27 MMSE only	97	90	
Mattis DRS (raw/maximum score)							
Total score	144/144					116/144	84/144
Attention	37/37					35/37	31/37
Initiation	37/37					29/37	14/37
Construction	6/6					5/6	2/6
Conceptualization	39/39					30/39	26/39
Memory	25/25					17/25	11/25
WORD-LIST WMS III (raw/scaled score)							
1st trial	5/12		3/7			2/6	2/6
Immediate recall	29/11		22/7			13/4	15/4
Delayed recall	4/11		4/11			1/8	0/6
Recognition	22/10		23/11			18/7	15/4
Verbal fluency tests (raw score)							
Category (animal)	20		1	14	7	4	6
letter (N, K, P)	45		19	6	10	7	5
Rey-Osterrieth CFT (raw/T score)							
Copy (raw)	36		33		32.5	28	4.5
Immediate recall	21/67		10/43		15/57	12.5/52	1.5/25
Delayed recall	18.5/62		13/49		13.5/54	9/43	failed
Recognition	29/49		20/49		21/56	20/50	14/20
Stroop test (raw/T score)							
Word	98/45			97/45	103/47	93/43	56/24
Color	73/45			61/37	65/40	34/20	31/20
Word/color	49/54			33/38	39/44	25/30	failed
Interference (T score)	57			50	49	55	—
Tower of London (raw/maximum score)	33/36					8/36	failed
MADRS	4	24		9	5	3	8

1/2006: very poor compliance—only screening; 3/2006: still poor compliance, but much better than during the previous examination in 1/2006; WAIS-R: Wechsler Adult Intelligence Scale—Revised; Mattis DRS: Mattis Dementia Rating Scale; WMS III: Wechsler Memory Scale III; Rey-Osterrieth CFT: Rey-Osterrieth Complex Figure Test; MADRS: Montgomery-Asberg Depression Rating Scale.

[37, 38], while a more malignant course occurs in people with older age at PD onset and shorter survival shows more brain atrophy and both higher Lewy body and Alzheimer's disease plaque pathology [37]. In our case, the major brain atrophy also seen in the hippocampus, that is, a finding typical of Alzheimer's disease, could have been related to possible coincidence of PD dementia and Alzheimer's pathology and could at least in part explain the malignant course. Unfortunately, the brain biopsy was not performed since the family did not approve it.

Another interesting issue that has to be taken into consideration relates to possible gliosis along the electrode trajectories. It has been shown by others [39] that DBS electrodes may cause a giant cell reaction or gliosis around them when implanted in the brains of patients with PD. This reaction is present from 3 months to at least 31 months onwards after implantation, and may possibly represent a response to the polyurethane component of the electrodes' surface coat. The accumulation of inflammatory tissue

occurs predominantly around the electrode sheath rather than tip, and it is conceivable that on the whole it plays only a small role in maintaining benefit or causing side effects of DBS [39].

Finally, we indeed cannot exclude a possibility that the ICH as an adverse event of the STN implantation might not only have caused an acute cognitive and behavioural impairment after the procedure but might also have accelerated the development of dementia in our patient, probably as a result of collapsed brain reserve and disturbed compensatory mechanisms caused by the electrode implantation and IHC. Age was probably the major contributor and risk factor for the intracranial bleeding, postoperative confusion, and later dementia development [26, 40, 41].

Despite many unresolved questions, this has taught us not to include PD patients above 70 years of age for the DBS surgery. In addition, the length of PD duration should also be taken into consideration, and the question remains as to what the best time for considering DBS in PD would be. Further

research should focus on potential biological markers such as specific brain imaging techniques and cerebrospinal fluid examination that would better predict the disease prognosis and that might help to better select good candidates for DBS surgery in PD patients.

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## Research Article

# A Perfusion MRI Study of Emotional Valence and Arousal in Parkinson's Disease

Sunsern Limsoontarakul,<sup>1,2</sup> Meghan C. Campbell,<sup>3</sup> and Kevin J. Black<sup>1,3,4,5</sup>

<sup>1</sup> Department of Psychiatry, Washington University School of Medicine St. Louis, St. Louis, MO 63110, USA

<sup>2</sup> Department of Neurology, University of British Columbia, Vancouver, BC, Canada V6T 2B5

<sup>3</sup> Department of Neurology, Washington University School of Medicine St. Louis, St. Louis, MO 63110, USA

<sup>4</sup> Department of Radiology, Washington University School of Medicine St. Louis, St. Louis, MO 63110, USA

<sup>5</sup> Department of Anatomy & Neurobiology, Washington University School of Medicine St. Louis, St. Louis, MO 63110, USA

Correspondence should be addressed to Kevin J. Black, kevin@wustl.edu

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**Background.** Brain regions subserving emotion have mostly been studied using functional magnetic resonance imaging (fMRI) during emotion provocation procedures in healthy participants. **Objective.** To identify neuroanatomical regions associated with spontaneous changes in emotional state over time. **Methods.** Self-rated emotional valence and arousal scores, and regional cerebral blood flow (rCBF) measured by perfusion MRI, were measured 4 or 8 times spanning at least 2 weeks in each of 21 subjects with Parkinson's disease (PD). A random-effects SPM analysis, corrected for multiple comparisons, identified significant clusters of contiguous voxels in which rCBF varied with valence or arousal. **Results.** Emotional valence correlated positively with rCBF in several brain regions, including medial globus pallidus, orbital prefrontal cortex (PFC), and white matter near putamen, thalamus, insula, and medial PFC. Valence correlated negatively with rCBF in striatum, subgenual cingulate cortex, ventrolateral PFC, and precuneus—posterior cingulate cortex (PCC). Arousal correlated positively with rCBF in clusters including claustrum-thalamus-ventral striatum and inferior parietal lobule and correlated negatively in clusters including posterior insula—mediodorsal thalamus and midbrain. **Conclusion.** This study demonstrates that the temporal stability of perfusion MRI allows within-subject investigations of spontaneous fluctuations in mental state, such as mood, over relatively long-time intervals.

## 1. Background

Even though Parkinson's disease (PD) is a neurodegenerative disease defined by motor features [1], psychiatric sequelae are common such as depression, anxiety, and apathy [2, 3]. Previous studies have shown alteration of emotional processing in PD including reduced emotional physiologic response [4], impaired emotional word recognition [5], and impaired arousal judgment but normal valence [6]. The bulk of the evidence suggests that these changes result primarily from the degenerative process in the brain, and are not merely psychological reactions to disability [3]. Pathologically, Braak and Del Tredici [7] found that in PD clinical stages 1–3 (stage 4–5 pathologically), neurodegeneration could be seen in almost all areas of the brain including prefrontal cortex (PFC) and limbic system. Brain areas affected by PD that

are hypothesized to cause emotional dysfunction including raphe nuclei, locus ceruleus, amygdala, mesolimbic, mesocortical, mesothalamic dopaminergic systems, and cingulate cortex [8]. Furthermore, neuroimaging studies have shown that a decrease in dopamine transporter availability in left putamen was associated with a reduction of ventrolateral prefrontal cortex activity during emotional gesture recognition tasks [9]. Lack of amygdala activation was observed by visual event-related potentials (ERPs) during facial expression recognition [4]. Based on these data, emotional processing in PD may differ from that of healthy controls.

Most fMRI experiments on emotional processing used a variety of validated affective stimuli to elicit changes in mood; stimuli included pictures [10], sounds [11], and words [12]. These studies have identified various brain regions involved in the emotional responses to these stimuli,

depending partly upon the type of stimulus [13, 14]. However, studies designed in this manner may identify brain regions involved in affective perception or naming rather than those that produce internal emotional states. Alternatively, the emotional states transiently induced by these artificial stimuli may be pale shadows of the emotional states people experience in response to spontaneous thoughts, real-life events, idiopathic mood disorders, or the cellular and pharmacological pathology of PD.

We studied self-rated emotional valence and arousal in patients with PD on several occasions per subject, without attempting to induce specific emotional states. These patients were participating in a pharmacological perfusion MRI study of an adenosine A2a receptor antagonist and the dopamine precursor levodopa, but emotional ratings were obtained in the same drug and placebo conditions in each subject, allowing us to separate the effects of drug from spontaneous variance in emotional state across participants. The objective was to describe brain areas associated with naturalistic emotional state in PD. We hypothesized that spontaneous variation in self-rated emotional state would be accompanied by statistically significant changes in brain activity, as indexed by regional cerebral blood flow (rCBF) measured with perfusion MRI.

## 2. Materials and Methods

These data were collected during the course of a Phase IIa clinical and brain imaging study of the investigational adenosine A2a receptor antagonist SYN115, and the primary analyses of those data are reported elsewhere [15, 16]. The results presented here have not been previously reported except in abstract form [17].

*2.1. Regulatory Approvals, Registrations, and Patient Consents.* This study was approved by the Washington University Human Research Protection Office. Written documentation of informed consent was obtained in advance from each subject. Levodopa and SYN115 were given under US FDA Investigational New Drug application (IND) number 78,230.

*2.2. Study Participants.* Further details appear in Black et al. [15]. Briefly, 21 patients with Parkinson's disease (Hoehn and Yahr stages 1–3) on a stable dose of levodopa for 30 days were studied. Exclusion criteria included cognitive impairment indicated either by MMSE score <23 or estimated premorbid IQ <70 [18, 19], neurological diseases other than PD, self-reported history of psychosis or mania, current depression indicated by Geriatric Depression Scale Short Form [20] score >7, or current use of a dopamine agonist. All were Caucasian and right-handed, and 13 were male. Mean age was 60.8 years (range 44–73 years), mean duration of PD symptoms was 5.3 years (range 0.9–10.8 years), mean “off” UPDRS (placebo day, before levodopa) was 22.5 (range 7–51), and half had ever experienced dopa-induced dyskinesias.

*2.3. Study Protocol.* Participants were randomly assigned either (a) to take SYN115 twice daily for a week, wait 1

week (washout period), then take a matching placebo twice daily for a week, or (b) the reverse order. For 14 participants, each dose of active drug contained 60 mg of SYN115, whereas 12 subsequent subjects (5 of whom had participated in the 60 mg placebo study) received 20 mg at each dose. Participants and staff were blind to assignment.

On the last day of each treatment week, participants abstained from food, caffeine, and antiparkinsonian medication overnight, but took the last dose of SYN115 or placebo at 6 am at home. At the imaging center, they took 200 mg carbidopa, and then underwent a set of clinical and MRI assessments. An intravenous levodopa infusion was then begun, dosed in such a way as to rapidly produce and then maintain a steady plasma concentration [21], with a target concentration of 600 ng/mL. At least 25 minutes after the levodopa infusion started, all MRI and clinical assessments were repeated while the levodopa infusion continued.

Participants rated their emotional state in each of four conditions: (1) before and (2) during levodopa infusion (after carbidopa) while taking oral SYN115, and (3) before and (4) during levodopa infusion while taking placebo pills. In each of these 4 conditions, 8 perfusion MRI (CBF) scans were acquired. In 4 of the 8 scans in each condition, the participant fixated on a crosshair throughout the entire 2.73 minutes of each scan; half of these were white on black and half were black on white. In 2 scans, an 8 Hz reversing circular checkerboard pattern surrounded the fixation crosshair, and in 2 scans the participant performed a 2-back letter working memory task for the entire scan.

*2.4. Visual Analog Scale (VAS) and Scoring of Emotional Valence and Arousal.* The circumplex model of emotion [22] describes human emotional states in terms of two independent constructs called valence and arousal (also called valence and “activation,” a term avoided here due to potential confusion with the homonymous word as used in the neuroimaging literature). The original model suggests but does not specify a numerical coordinate system for valence and arousal scores. For this study they were computed as follows. Participants rated various antipodal pairs of emotional descriptors from the circumplex model using VAS [23] displayed on a computer. They were instructed to freely self-evaluate their current feelings by clicking on the scale for each pair of emotional descriptors. The VAS ratings were recorded on 100 mm scales with anchor terms chosen from the original item set for 4 categories, that is, (a) negative valence, neutral arousal versus positive valence, neutral arousal (sad-happy, grouchy-cheerful); (b) negative valence, high arousal versus positive valence, low arousal (nervous-calm, distressed-relaxed); (c) negative valence, low arousal versus positive valence, high arousal (sluggish-lively, dull-excited); (d) neutral valence, high arousal versus neutral valence, low arousal (intense-tranquil, aroused-passive). For each VAS, the left item anchor was scored as 0 and the right anchor as 100. Subjects were advised to use the full 100 mm VAS range for each item and to score how they felt “at this moment.” Valence and arousal scores were computed from the VAS-item scores by the following formulae:

- (1) valence score = [average (a, b, c)/50] - 1; possible range - 1 to +1;
- (2) arousal score = 1 - [average (b, 100 - c, d)/50]; possible range - 1 to +1.

2.5. *MRI Methods.* All MRI data were acquired on the Siemens 3T Tim Trio with matrix head coil. ASL images were acquired with the commercial Siemens pulsed arterial spin labeling (pASL) sequence [24]; the center-to-center slice distance was 7.5 mm. Details of image acquisition and transformation to scaled CBF images in atlas space are given elsewhere [15].

2.6. *Statistical Analysis.* Only those voxels were analyzed, that were represented in every EPI image in every subject. Statistical analysis of the CBF data was done via a two-level, random effects model using SPM8 software (<http://www.fil.ion.ucl.ac.uk/spm/>). First, a voxelwise general linear model (GLM) was computed for each subject. This first-level GLM followed the method of Henson and Penny [25] by including factors coding for each of the 16 possible combinations of drug (SYN115 or placebo), levodopa (before versus during infusion), and task (the 4 behavioral conditions described in Study Protocol, above). The GLM also included 3 covariates, representing the pertinent valence and arousal scores and their interaction. This approach partitions the variance from each subject's CBF data at a given voxel into components representing valence, arousal, and their interaction, plus components representing the nuisance variables drug, levodopa, task, and all their interactions. The  $\beta$  (model coefficient) images from each subject for the valence and arousal covariates became the input data for the final, second-level analysis.

The second-level (across-subjects) analysis was a voxel-wise general linear model (GLM) that tested whether, across subjects, the mean  $\beta$  value for valence was significantly greater than zero, after controlling for sex, age, and dose group (60 versus 20 mg SYN115 b.i.d. during the active drug week). A corresponding analysis tested whether mean  $\beta$  was significantly less than 0. The same analyses were done for arousal. Multiple-comparisons correction was performed at the cluster level with the false discovery rate (FDR) set at  $P = 0.05$ . Approximate anatomical locations were provided by the Talairach Daemon client (<http://www.talairach.org>) [26], with corrections by reference to the study-specific MRI template atlas image.

### 3. Results

3.1. *Valence and Arousal, and Their Association with Subject Characteristics.* The mean value for each VAS item and for the emotional valence and arousal scores are given in Table 1 and depicted on a diagram of the circumplex model of emotion (Figure 1). Across conditions, participants tended to have positive valence, mean  $0.375 \pm 0.339$ , and low arousal, mean  $-0.199 \pm 0.254$  (in other words, they tended to be closer to cheerful and calm than to the opposite). Valence and arousal scores correlated negatively with each other

TABLE 1: Visual analog scale scores for each emotion item pair.

Visual analog scale	Mean, mm (range)
(1) Sad-happy	72.721 (8–100)
(2) Grouch-cheerful	77.471 (19–100)
(3) Nervous-calm	72.000 (5–100)
(4) Distressed-relaxed	74.731 (11–100)
(5) Sluggish-lively	55.010 (7–100)
(6) Dull-excited	60.529 (23–96)
(7) Intense-tranquil	67.375 (0–100)
(8) Aroused-passive	61.038 (1–100)
<i>Valence score</i>	0.375 (– 0.333 to 0.967), SD 0.339
<i>Arousal score</i>	– 0.199 (– 0.673 to 0.423), SD 0.254

( $r = -0.31, P < .01$ ); that is, subjects who were less aroused (more tranquil) tended also to be happier.

Table 2 shows associations of valence and arousal with pharmacological status and demographic variables. SYN115 increased valence ( $t(25) = 2.57, P = 0.02$ ) and valence decreased from before to on levodopa ( $t(25) = -2.26, P = 0.03$ ), though the mean change in valence score with either drug was less than 5% of the available range. Demographic variables and PD factors were not significantly associated with emotional valence or arousal (Table 2).

#### 3.2. Perfusion MRI Data

3.2.1. *Correlations of rCBF with Valence.* Random-effects analysis revealed significant positive correlations of rCBF with valence across subjects. We found significant areas in prefrontal-subcortical circuits; that is, bilateral dorsolateral PFC, bilateral anterior cingulate cortices (ACCs), orbital frontal cortex, striatum, and thalamus. Other significant clusters were observed in cortical areas including left and right ventral frontotemporal regions, lateral parietal cortex, insula, right motor, and premotor areas (see Table 3(a) and Figures 2(a)–2(c).

Areas whose rCBF correlated negatively with valence included a part of ACC, bilateral subcallosal cingulate cortex (SCC), along with parts of caudate and putamen, bilateral inferior frontal gyri, bilateral superior parietal lobule (SPL), inferior parietal lobule, precuneus, and PCC (see Table 3(b) and Figures 2(d)–2(f)).

3.2.2. *Correlations of rCBF with Arousal.* Random-effects analysis of rCBF-arousal correlations found no voxels whose  $t$  value exceeded our predetermined voxel-level threshold corresponding to uncorrected  $P = 0.001$ . However, as an exploratory analysis, relaxing that initial threshold to a value corresponding to uncorrected  $P = 0.005$  revealed several clusters that were significant after correction for multiple comparisons (Table 4 and Figures 3(a)–3(b)).

3.2.3. *Correlations of rCBF with the Interaction of Valence and Arousal.* A random-effects analysis of the valence  $\times$  arousal interaction found no activated clusters significant at  $P < 0.05$  after correction for multiple comparisons.

TABLE 2: Associations of valence and arousal with pharmacological status and demographic variables.

	Valence	Arousal	<i>P</i> (valence)	<i>P</i> (arousal)	<i>N</i> <sup>†</sup>
Effect of SYN115 (mean difference [unitless])	+0.08	+0.05	0.02	0.08	26
On levodopa minus pre-levodopa (mean difference [unitless])	- 0.06	- 0.04	0.03	0.18	26
Age (correlation, <i>r</i> )	0.09	0.18	0.70	0.43	21
Hoehn and Yahr stage (correlation, <i>r</i> )	0.22	- 0.03	0.34	0.89	21
UPDRS (correlation, <i>r</i> )	0.08	0.08	0.42	0.41	104
Sex ( <i>t</i> -test)			0.82	0.92	
Male (mean)	0.33	- 0.22			13
Female (mean)	0.30	- 0.20			8
PD symptoms worse on which side of body? ( <i>t</i> -test)			0.25	0.34	
Right (mean)	0.26	- 0.17			13
Left (mean)	0.43	- 0.28			7 <sup>‡</sup>

<sup>†</sup> *P* 0.05.

<sup>†</sup> 21 people, 26 experiments (5 people participated twice, once for the 20 mg b.i.d. study, once for the 60 mg b.i.d. study), 4 UPDRS measurements per experiment (26 × 4 = 104).

<sup>‡</sup> One subject was equally affected on left and right and was excluded from this analysis.

TABLE 3: CBF correlates with emotional valence.

(a) Clusters in the brain in which CBF correlates positively with valence

FDR-corrected <i>P</i> value	Number of voxels <sup>a</sup>	Peak <i>T</i> value (22 d.f.)	Coordinates of peak <i>T</i> value	Side of brain	Anatomical description of cluster
<10 <sup>-15</sup>	674	3.86	28.5, 21, 18	Right	Middle frontal gyrus (BA 8, 9), precentral gyrus, anterior cingulate (BA 32), insula, putamen, caudate
0.001	76	3.86	4.5, 57, 18	Bilateral	Medial and superior frontal gyri (BA 10, 9)
0.001	97	3.86	- 58.5, 3, 21	Left	Precentral gyrus (BA 6)
0.002	87	3.86	16.5, - 3, - 3	Right	Medial globus pallidus, ventrolateral thalamus, amygdala, frontal prepiriform cortex ventral to accumbens
0.002	82	3.86	- 16.5, 6, - 18	Left	Olfactory area, parahippocampal gyrus, medial globus pallidus/thalamus border, thalamus, hypothalamus, substantia nigra
0.053	36	3.85	28.5, 42, - 9	Right	Middle frontal gyrus (BA 11)
0.010	56	3.84	- 46.5, - 60, 33	Left	Angular gyrus and inferior parietal lobule (BA 39, 40)

<sup>a</sup> Each voxel contained 0.027 mL.

(b) Clusters in the brain in which CBF correlates negatively with valence

FDR-corrected <i>P</i> value	Number of voxels	Peak <i>T</i> value (22 d.f.)	Coordinates of peak <i>T</i> value	Side of brain	Anatomical description of cluster
<0.0002	117	3.86	- 34.5, - 42, 66	Left	Superior parietal lobule and precuneus (BA 7), postcentral gyrus (BA 5), posterior cingulate cortex (BA 31)
<10 <sup>-5</sup>	178	3.86	- 13.5, 12, 3	Bilateral	Subcallosal gyrus (BA 25), left caudate and putamen
0.007	67	3.86	4.5, - 75, 54	Right	Superior parietal lobule and precuneus (BA 7), postcentral gyrus (BA 5)
0.020	46	3.86	- 34.5, - 15, 57	Left	Precentral gyrus (BA 6), postcentral gyrus (BA 3)
0.014	54	3.86	43.5, - 39, 63	Right	Inferior parietal lobule (BA 40), superior parietal lobule (BA 7), postcentral gyrus (BA 5)
0.008	63	3.85	43.5, 39, - 6	Right	Inferior frontal gyrus (BA 47)—lateral frontal part
0.020	46	3.85	25.5, - 63, 6	Right	Lingual gyrus (BA 18, 19)
0.036	39	3.85	- 37.5, 33, - 6	Left	Inferior frontal gyrus (BA 47)
0.043	36	3.83	25.5, 24, - 6	Right	Inferior frontal gyrus (BA 47)

Note: Only clusters significant after correction for multiple comparisons are shown here.

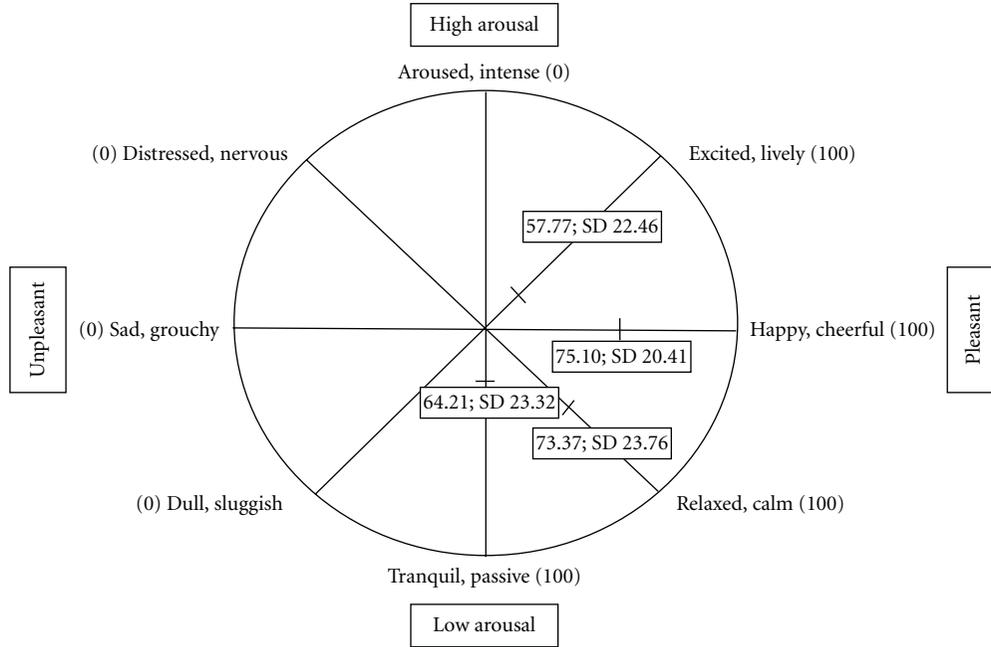


FIGURE 1: Score of visual analog scale on circumplex model of emotion. The 4 diameters shown represent the 8 pairs of adjectives used for the VAS items that generated the valence and arousal scores. The short perpendicular mark on each diameter represents the mean value for the corresponding VAS items in this sample.

TABLE 4: CBF correlates with emotional arousal.

(a) Clusters in the brain in which CBF correlates positively with emotional arousal<sup>†</sup>

FDR-corrected <i>P</i> value	Number of voxels	Peak <i>T</i> value (22 d.f.)	Coordinates of peak <i>T</i> value	Side of brain	Anatomical description of cluster
0.039	84	3.00	31.5, -9, -6	Right	Putamen, thalamus (ventrolateral), hippocampus
0.039	85	3.00	-34.5, -75, 6	Left	Middle temporal gyrus (BA 39), middle occipital gyrus (BA 19)
<0.0005	231	3.00	-37.5, -57, 45	Left	Inferior parietal lobule (BA 40), superior occipital gyrus (BA 19)
0.039	100	3.00	34.5, -57, 39	Right	Inferior parietal lobule (BA 40), superior parietal lobule and precuneus (BA 7)

(b) Clusters in the brain in which CBF correlates negatively with emotional arousal<sup>†</sup>

FDR-corrected <i>P</i> value	Number of voxels	Peak <i>T</i> value (22 d.f.)	Coordinates of peak <i>T</i> value	Side of brain	Anatomical description of cluster
0.001	216	3.00	-34.5, -27, 27	Left	Striatum and nearby white matter, thalamus (medial dorsal), insula (BA 13)
0.015	110	3.00	-34.5, -60, 57	Left	Precuneus and superior parietal lobule (BA 7)
0.005	139	3.00	-25.5, -6, -9	Left	Putamen, claustrum, insula (BA 13), amygdala-striatal transition area, superior temporal gyrus (BA 22, 38), inferior frontal gyrus (BA 47)—ventral frontal part
<10 <sup>-7</sup>	577	3.00	13.5, -45, -6	Right	Superior and middle occipital gyrus, cuneus (BA 17, 18, 19), posterior cingulate cortex (BA 23), thalamus (medial dorsal), midbrain (central portion and red nucleus)
0.005	149	3.00	34.5, -81, 39	Right	Superior parietal lobule and precuneus (BA 7)

<sup>†</sup> No voxels passed the predefined voxel-level threshold of  $P < 0.001$ . For hypothesis generation, we repeated our analysis using a voxel-level threshold of  $P < 0.005$ , and those results are shown here.

Note: only clusters significant after correction for multiple comparisons are shown here.

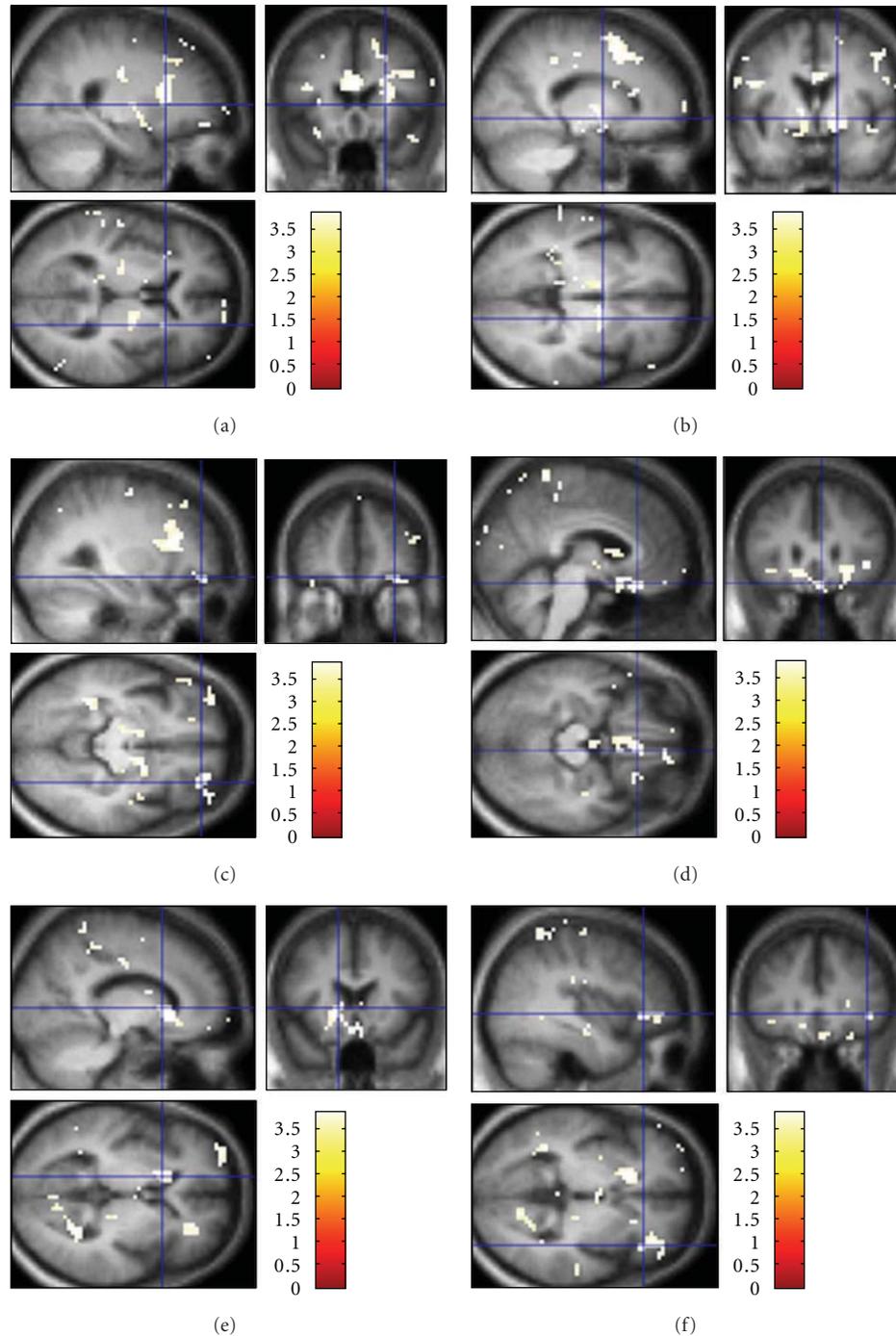


FIGURE 2: Statistical parametric (T) maps for correlations with valence. (a–c) Positive correlation with valence in (a) right putamen (22.5, 15, 6); (b) right medial globus pallidus (16.5, -3, -3); (c) right middle frontal gyrus (28.5, 42, -9) (BA 11). (d–f) Negative correlation with valence in (d) right subcallosal gyrus (4.5, 24, -15) (BA25); (e) left caudate (-13.5, 12, 3); (f) right inferior frontal gyrus (38, 27, 0) (BA47).

#### 4. Discussion

This study found a number of brain regions whose activity increased or decreased with changes in self-rated current mood state. Emotional state ratings, drawn on the face validity and experimental history of the circumplex model of emotion [22], augmented here by a numerical implementation

of the valence and arousal constructs. The conservative statistical approach employed for this analysis lends credence to the results and uses general linear modeling to minimize the potential confounds of demographic variation (age and sex) and unrelated experimental manipulations (such as medication status). Additionally, the study design allowed us to study ecologically valid or “real,” that is, spontaneously

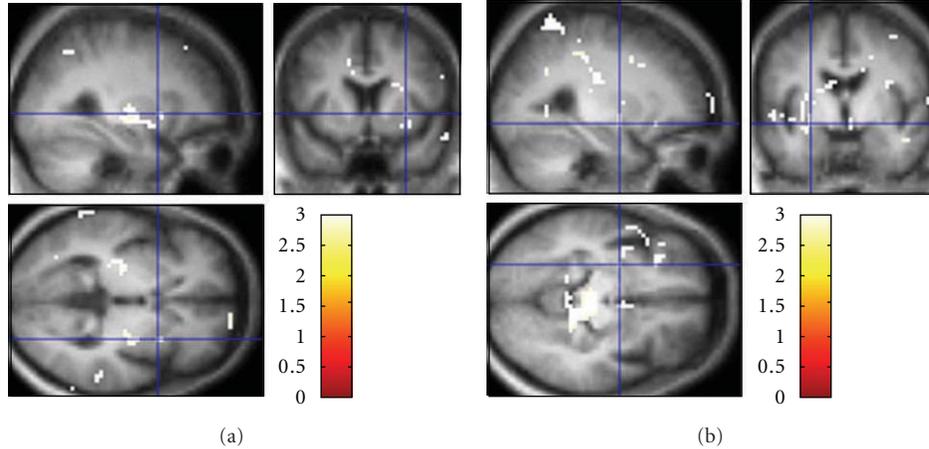


FIGURE 3: Statistical parametric (T) maps for correlations with arousal. (a) Positive correlation with arousal in right putamen (28.5, 6, 0). (b) Negative correlation with arousal in left amygdala-striatal transition area (-25.5, -6, -9).

experienced, internal emotional state, which may more faithfully reflect patients' day-to-day experiences.

On the other hand, the study has a number of limitations, most of which derive from the fact that correlation of rCBF with current emotional state was not a primary goal of the data collection. Mood ratings were not done within the scanning session itself, but rather within a half hour or so, under broadly similar physiological conditions. This may have added noise to our results, so that we may have failed to detect some true correlations. Second, valence and arousal scores were (inversely) correlated, interpretation of results related to one emotional dimension might also be a result of changes in the other. However, the inclusion in our SPM model of a valence-arousal interaction should help disentangle their relation to rCBF. The correlation also tends to restrict the range of emotional states sampled. For that and perhaps other reasons, the range of emotional states reported by the subjects in our data did not equally sample all quadrants of emotional experience. Specifically, there was a bias of positive over negative valence, and low over high arousal. As a consequence, negative correlations with valence came primarily from data with positive values. Additionally, we cannot comment conclusively on whether regions identified as correlating with self-rated mood in this study are specific to PD, since we did not include healthy control subjects.

**4.1. Nonimaging Results.** Emotional rating in our participants tended towards positive valence and low arousal (Table 1, Figure 1). We did not test whether this differed from a control group. However, Drago et al. [6] show that nondemented PD patients under-rate arousal in others' facial expressions, compared to healthy control subjects, and that their spatial judgments are less affected than controls' by emotional stimuli. Imaging studies have shown decreased activation of emotional regions to emotional faces or gestures [9]. These findings may correspond to observations that PD patients actually experience lower emotional arousal, along with other manifestations of apathy [3, 4].

The slight improvement in mood with SYN115 is not surprising given that it is an adenosine 2a antagonist (caffeine is a nonspecific adenosine antagonist). The small decrease in valence on levodopa may seem counterintuitive, depression and anxiety commonly attend wearing off of individual levodopa doses in PD [27]. However, on-levodopa data were always collected a few hours after the off-levodopa data, and if subjects were merely less enthusiastic later in the study day, as one might expect, then valence and arousal would be lower, causing an apparent association with levodopa.

The lack of correlation of UPDRS with mood ratings may be a Type II error, but is consistent with other data suggesting that, contrary to common expectation, motor impairment is at best a modest predictor of mood state in PD [3].

#### 4.2. Regions Associated with General Emotional Processing.

Our study revealed a number of neural substrates associated with naturalistic emotional state; that is, (a) medial frontal PFC/ACC—subcortical circuit—medial PFC/ACC, basal ganglia, and thalamus; (b) limbic and paralimbic—amygdala, hippocampus and parahippocampal gyrus, thalamus, mamillary body, and PCC, insula, parietal, and lateral PFC; (c) visual system—occipital and temporal cortex. These regions are generally in line with previous studies in healthy controls.

In a meta-analysis of functional neuroimaging studies of human emotions by Phan et al. [28, 29], medial frontal PFC (BA 9, 10) was activated in response to nonspecific emotion. In other words, this region was involved in emotional processing regardless of valence, arousal, or induction method. In the present study, we found some brain regions that contained activations associated with either arousal or valence, such as basal ganglia (BG), thalamus, and parietal lobe. Basal ganglia were correlated with happiness induction in 70% of the studies, and disgust induction in 60% [28] as well as responded to arousal stimuli evidenced by fMRI and skin conductance response (SCR) [30]. The thalamus is connected to BG, ACC, medial frontal PFC, orbital PFC, and dorsolateral PFC, forming several frontal-subcortical circuits

[31]. The ACC is also closely interconnected to medial PFC. Lesions in the anterior cingulate—subcortical circuit can produce apathy [31], and the apathy experienced by PD patients who undergo subthalamic (STN)—deep brain stimulation (DBS) has been attributed to dysfunction of medial PFC [32, 33]. In addition, the thalamus links other structures in the limbic system, which is responsible for fundamental instinctive behaviors, cognition, and emotion, by receiving input from amygdala, basal forebrain, cerebellum, hippocampus, and septal nuclei, and projecting to prefrontal, cingulate, and parietal cortex [34]. Therefore, the BG, thalamus, and parietal cortex might be related to general emotion processing as a part of this network.

*4.3. Associations between Valence and rCBF.* We found regions in limbic and paralimbic structures—amygdala, medial PFC/rostral ACC, lateral PFC, and insula—that were positively correlated with valence; whereas subcallosal and posterior cingulate cortex (SCC and PCC) were negatively correlated with valence.

*4.3.1. Positive Correlation with Valence.* Amygdala responses to valence or arousal stimuli have varied. Although amygdala response was related to arousal stimuli [35], and over 60% of studies reported amygdala activation in response to fear induction [28, 29], other studies have found activation to happy faces [36] or have linked amygdala activity to both valence and arousal [37, 38]. Thus, it may respond to salient characteristics of emotion. However, we found amygdala rCBF positively related only to valence. According to the neuropathological staging of PD (stages 1–6) proposed by Braak and colleagues [39], amygdala dysfunction first appears in presymptomatic stage 3 in a particular region. In addition, dopamine is lost in the amygdala due to degeneration of the ventral tegmental area in PD. In fact, loss of dopaminergic innervation of amygdala and other limbic structures were observed in PD subjects diagnosed with major depression [40], and dopamine modulates the response of amygdala to fearful stimuli in PD patients with depression [41].

The ACC is known to be involved in a form of attention that serves to regulate both cognitive (dorsal) and emotional (ventral) processings [42]. Valence perception has been reported to be normal in nondemented and nondepressed PD patients [6], thus, the activity in medial frontal PFC might reflect activation of circuits involved in valence-related attention or decision making.

*4.3.2. Negative Correlation with Valence.* Subcallosal cingulate cortex was associated with sadness in about 46% studies [29], in line with our results. Clinically, patients with more than 3 episodes of untreated MDD had smaller SCC volume than controls [43, 44], and DBS of SCC may benefit treatment resistant depression [45].

Posterior cingulate cortex was also negatively correlated with valence. PCC has been linked to emotional processing and is thought to enhance memory for emotional stimuli [46]. A study that controlled for nonemotional, memory

enhancing stimulus features suggested that this region might mediate interactions of emotional and memory-related processes [47]. Activity in PCC has also been reported to correlate with severity of anxiety symptoms in major depression and obsessive-compulsive disorder [48, 49] and was associated with levodopa dose-related mood fluctuations in PD patients [50].

*4.4. Associations between Arousal and rCBF.* We adopted a more permissive first-stage threshold to find any regions in which rCBF correlated with emotional arousal. The approach is reasonable, but as this threshold differs from the prespecified methods, the arousal results should be taken with a grain of salt.

The rCBF in hippocampus and middle temporal gyrus correlated positively with arousal in the present study, consistent with the study of Nielen et al. [51]. The connection with hippocampus may relate to observations that arousal can modulate memory [52].

Results from prior studies were arguable whether occipital lobes actually responded to valence or to arousal. The studies of Mourão-Miranda et al. [53] and Lane et al. [54] found that visual processing could vary with either valence or arousal, consistent with our findings, in which lingual gyrus was also associated negatively with valence, whereas others found occipital activation only when participants were presented stimuli of negative valence [51, 55]. The activation of the visual system with emotional valence and arousal may be that both can increase attentional processing. Emotional and attentional processings both involve medial frontal PFC, and a variety of functional neuroimaging studies have suggested that attention modulates activity of extrastriate visual cortex [55]. Moreover, threat stimuli lead to increased perceptual processing [56]. Our data might extend prior knowledge that current internal emotion, and not just visually presented emotional stimuli, may enhance visual system activity.

## 5. Conclusion

Emotions are usually regarded as brief but intense responses to changes in the environment featuring a number of subcomponents: (a) cognitive appraisal, (b) subjective feeling, (c) physiological response, (d) expression, (e) action tendency, and (f) regulation [57]. In addition, emotional stimulation can be of an interoceptive or exteroceptive nature. Different methods used to provoke emotional state changes can activate different systems. For example, the recall method activated mostly ACC and insula, whereas amygdala and occipital lobe were activated by visual induction [28].

Many neuroimaging studies of emotion in healthy volunteers have used clever methods to transiently stimulate emotional perception or attempt to quickly induce a given emotional state. Some experimental designs were chosen in part due to the limitations of blood oxygen level dependent (BOLD) fMRI, namely, its nonquantitative nature and the marked decline in signal-to-noise ratio of BOLD signal at time intervals greater than a few minutes.

The use of ASL perfusion fMRI enabled us to study within-subject fluctuations of internal mood states over relatively long periods of time (hours to weeks), a study design that is not possible with BOLD fMRI. Since we studied self-perceived emotional state without intentional provocation of a specific emotion, we could examine the effect of “subjective feeling” while being minimally confounded by other emotional processes. Furthermore, the rated emotion might be as a result of both “interoceptive” and “exteroceptive” natural stimulation that might result in stronger and more regions emotional stimulation, as compared to only one induction method alone. Despite the limitations of this study, it may demonstrate the potential utility of perfusion fMRI in the study of emotion.

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## Review Article

# Bladder, Bowel, and Sexual Dysfunction in Parkinson's Disease

**Ryuji Sakakibara,<sup>1</sup> Masahiko Kishi,<sup>1</sup> Emina Ogawa,<sup>1</sup> Fuyuki Tateno,<sup>1</sup> Tomoyuki Uchiyama,<sup>2</sup> Tatsuya Yamamoto,<sup>2</sup> and Tomonori Yamanishi<sup>3</sup>**

<sup>1</sup>Neurology Division, Department of Internal Medicine, Sakura Medical Center, Toho University, 564-1 Shimoshizu, Sakura 285-8741, Japan

<sup>2</sup>Department of Neurology, Chiba University, Chiba 263-8522, Japan

<sup>3</sup>Department of Urology, Dokkyo Medical University, Tochigi 321-0293, Japan

Correspondence should be addressed to Ryuji Sakakibara, sakakibara@sakura.med.toho-u.ac.jp

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Bladder dysfunction (urinary urgency/frequency), bowel dysfunction (constipation), and sexual dysfunction (erectile dysfunction) (also called “pelvic organ” dysfunctions) are common nonmotor disorders in Parkinson's disease (PD). In contrast to motor disorders, pelvic organ autonomic dysfunctions are often nonresponsive to levodopa treatment. The brain pathology causing the bladder dysfunction (appearance of overactivity) involves an altered dopamine-basal ganglia circuit, which normally suppresses the micturition reflex. By contrast, peripheral myenteric pathology causing slowed colonic transit (loss of rectal contractions) and central pathology causing weak strain and paradoxical anal sphincter contraction on defecation (PSD, also called as anismus) are responsible for the bowel dysfunction. In addition, hypothalamic dysfunction is mostly responsible for the sexual dysfunction (decrease in libido and erection) in PD, via altered dopamine-oxytocin pathways, which normally promote libido and erection. The pathophysiology of the pelvic organ dysfunction in PD differs from that in multiple system atrophy; therefore, it might aid in differential diagnosis. Anticholinergic agents are used to treat bladder dysfunction in PD, although these drugs should be used with caution particularly in elderly patients who have cognitive decline. Dietary fibers, laxatives, and “prokinetic” drugs such as serotonergic agonists are used to treat bowel dysfunction in PD. Phosphodiesterase inhibitors are used to treat sexual dysfunction in PD. These treatments might be beneficial in maximizing the patients' quality of life.

## 1. Introduction

Parkinson's disease (PD) is a common movement disorder associated with the degeneration of dopaminergic neurons in the substantia nigra. In addition to the movement disorder, patients with PD often show nonmotor disorders. The non-motor problems of PD include neuropsychiatric disorders, sleep disorders, sensory symptoms, and autonomic disorders [1]. Bladder, bowel, and sexual dysfunction (also called “pelvic organ” dysfunctions) is one of the most common autonomic disorders [2, 3]. Studies have shown that the pelvic organ dysfunctions have great significance in relation to quality-of-life measures, early institutionalization, and health economics [4, 5]. It is particularly important to note that, unlike motor disorder, pelvic organ dysfunctions are often nonresponsive to levodopa, suggesting that they occur

through a complex pathomechanism [6]. This is because pathology of PD is not confined to the degeneration of dopaminergic neurons in the substantia nigra, and involves other locations in the brain and other neurotransmitter systems than the dopaminergic system. For this reason, add-on therapy is required to maximize patients' quality of life. This article reviews pelvic organ dysfunctions in PD, with particular reference to neural control of the bladder [2], bowel [2], and genital organs, symptoms, objective assessment, and treatment.

## 2. Bladder Dysfunction in PD

*2.1. Neural Control of Micturition: Normal Micturition and Detrusor Overactivity.* The lower urinary tract (LUT) consists of two major components, the bladder and urethra.

The bladder has abundant muscarinic M2, 3 receptors and adrenergic beta 3 receptors, and is innervated by cholinergic (parasympathetic) and noradrenergic (sympathetic) fibers for contraction and relaxation, respectively [7]. The urethra has abundant adrenergic alpha 1A/D receptors and nicotinic receptors, and is innervated by noradrenergic (sympathetic; contraction) and cholinergic (somatic; contraction) fibers (Figure 1). The LUT performs two opposite functions, storage and emptying of urine, both of which require an intact neuraxis that involves almost all parts of the nervous system [8]. This is in contrast to postural hypotension, which arises due to lesions below the medullary circulation center in humans [9].

Normal urinary storage is dependent on the sacral autonomic reflex [7, 10]. The storage reflex is thought to be tonically facilitated by the brain, particularly the pontine storage center [11, 12]. The pontine storage center lies just ventrolateral to the pontine micturition center (PMC). In addition to the pontine storage center, the storage function is facilitated by the hypothalamus, cerebellum, basal ganglia, and frontal cortex. These areas have been shown to be activated during urinary storage by functional neuroimaging in humans [13]. Normal micturition is dependent on the spino-bulbo-spinal autonomic reflex [7], which particularly involves the midbrain periaqueductal gray matter (PAG) [14–17] and the PMC [7, 11]. The PAG is thought to be central in regulating micturition and has a range of inputs from the higher structures. The PMC is located in or adjacent to the locus coeruleus [18–20]. The PMC is thought to project spinal descending fibers containing glutamate as a facilitatory neurotransmitter, which activates the sacral bladder preganglionic nucleus [21]. PMC also projects fibers containing  $\gamma$ -amino-butyric acid (GABA) and glycine as inhibitory neurotransmitters, which suppresses the sacral urethral motor nucleus (the Onuf's nucleus) [22]. The voiding function seems to be initiated and facilitated by the higher brain structures, for example, the hypothalamus and prefrontal cortex, which seem to overlap in the storage-facilitating area [13, 23]. Bladder (detrusor) overactivity (DO) is the major cause of urinary urgency/frequency and incontinence [24]. In lesions above the brainstem, the micturition reflex arc is intact, where DO is considered an exaggerated micturition reflex [24–26]. The exaggeration of the micturition reflex might be brought about by more than simply the decreased inhibition of the brain, and might be further facilitated by glutamatergic and D2 dopaminergic mechanisms [27].

**2.2. Basal Ganglia Circuit and Dopamine.** The net effect of the basal ganglia on micturition is thought to be inhibitory (Figure 2) [7, 28–30]. Functional neuroimaging during bladder filling results in activation in the globus pallidus of normal volunteers [31] and in the putamen in patients with PD [32]. In contrast, dopamine transporter imaging was lower in PD patients with urinary dysfunction than in those without it [33, 34]. Electrical stimulation of the substantia nigra pars compacta (SNc) inhibited the micturition reflex [35, 36], and striatal dopamine levels *in situ* significantly

increased in the urinary storage phase in experimental animals [37]. The micturition reflex is under the influences of dopamine (both inhibitory in D1 and facilitatory in D2) and GABA (inhibitory) [7, 28]. Both the SNc neuronal firing and the released striatal dopamine seem to activate the dopamine D1-GABAergic *direct pathway* (Figure 2), which not only inhibits the basal ganglia output nuclei, but also may inhibit the micturition reflex via GABAergic collateral to the micturition circuit [37–40]. In patients with PD, disruption of this pathway may lead to DO and resultant urinary urgency/frequency. In addition to the nigrostriatal fibers, the ventral tegmental area (VTA)-mesolimbic dopaminergic fibers are thought to be involved in the control of micturition [36, 41, 42] (Figure 1).

### 2.3. Bladder Dysfunction in PD

**2.3.1. Lower Urinary Tract Symptom.** The reported prevalence of LUT symptoms (LUTS) in patients with PD ranges from 38% to 71% [43–48]. However, it has been difficult to determine to what extent PD contributes to LUTS. Men older than 60 years of age may have bladder outlet obstruction due to prostate hyperplasia. Women may have stress urinary incontinence. “Idiopathic DO” [10] may occur in men and women older than 65 years due in part to latent brain ischemia [49]. Some of the studies were published before the diagnosis of multiple system atrophy (MSA) [50] was recognized. In recent studies of PD patients who were diagnosed according to modern criteria [5, 51–53], the prevalence of LUTS was found to be 27–63.9% using validated questionnaires [51–53], or 53% in men and 63% in women using a nonvalidated questionnaire that includes a urinary incontinence category [5], with all of these values being significantly higher than the incidence rates in healthy controls. The majority of patients had onset of bladder dysfunction after appearance of motor disorder. Correlations have been shown between bladder dysfunction in patients with PD and neurological disability [51], and bladder dysfunction and stage of disease [5], both suggesting a relationship between dopaminergic degeneration and LUTS. However, Campos-Sousa and colleagues did not find such a correlation [53].

**2.3.2. Storage Symptoms.** LUTS are divided majorly into two; storage symptoms and voiding symptoms. Storage symptoms are the most common of the LUTS symptom types in PD. Storage symptoms include nocturia (nighttime urinary frequency), which is the most prevalent symptom reported by patients with PD (>60%) [5, 51–53]. Patients also complain of urinary urgency (33–54%) and daytime frequency (16–36%). Urinary incontinence was present in 26% of male and 28% of female patients with PD [5].

**2.3.3. Voiding Symptoms.** Although less common than storage symptoms, voiding symptoms also occur in PD patients. In the study by Sakakibara and colleagues, PD patients had significantly higher rates of retardation in initiating urination (44% of men only), prolongation/poor stream



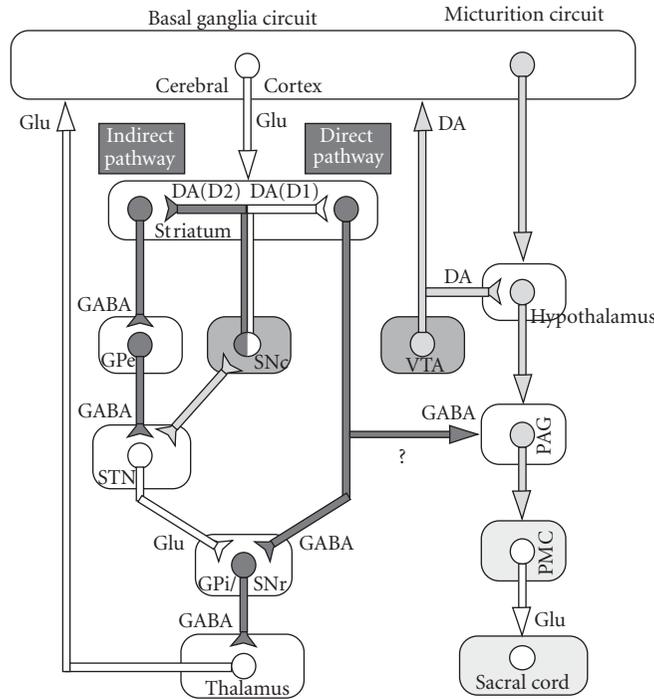


FIGURE 2: Possible relationship between basal ganglia circuit (left side) and micturition circuit (right side; modified from Sakakibara et al. [39]). DA, dopamine; GABA, gamma-aminobutyric acid; SNc, substantia nigra pars compacta; GPi, globus pallidus internus; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; GPe, globus pallidus externus; VTA, ventral tegmental area; PMC, pontine micturition centre; Glu, glutamate; black line, inhibitory neurons; white line, excitatory neurons; hatched line, neurons of undetermined property. The micturition reflex (right-side pathway) is under the influences of dopamine (DA; both inhibitory in D1 and facilitatory in D2) and gamma-aminobutyric acid (GABA; inhibitory). The substantia nigra pars compacta (SNc) neuronal firing and the released striatal dopamine seem to activate the dopamine D1-GABAergic *direct pathway*, which not only inhibits the basal ganglia output nuclei (e.g., the globus pallidus internus (GPi), substantia nigra pars reticulata (SNr)), but also may inhibit the micturition reflex via GABAergic collateral to the micturition circuit. High-frequency stimulation (leading to inhibition) in the subthalamic nucleus (STN) also results in bladder inhibition. See text.

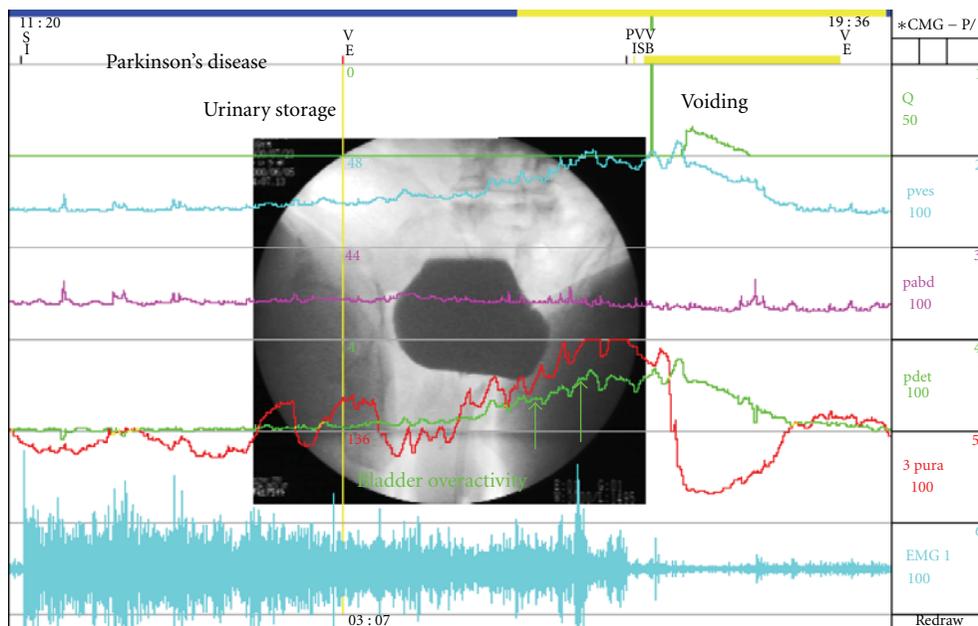


FIGURE 3: Detrusor (bladder) overactivity by urodynamic measurement.

symptoms in PD, the average volume of postvoid residuals in PD was as small as 18 mL [56].

*Differential Diagnosis of Parkinsonism by Bladder Dysfunction.* In the differential diagnosis of PD and parkinsonian-type MSA, large postvoid residuals, open bladder neck, and neurogenic change in sphincter motor unit potentials are all common in MSA [56, 63] whereas they are rarely seen in clinically typical PD. However, recent evidence suggests that PD with dementia, or dementia with Lewy bodies [64], may have large postvoid residuals and neurogenic change in the sphincter motor unit potentials [65], thereby mimicking MSA.

#### 2.4. Treatment of Bladder Dysfunction in PD

*2.4.1. Dopaminergic Drugs.* It is possible that levodopa and other antiparkinson medication may affect bladder function in PD. Aranda and Cramer [66] studied the effects of 3–8 mg apomorphine injection on the storage function in 2 *de novo* PD patients, and found that the bladder capacity increased. They gave oral levodopa to one of the patients, and the bladder capacity increased. We compared the frequency of bladder dysfunction in *de novo* PD and PD with levodopa. In that study, LUTS was less frequent than in the treated group [59]. In another study, after 3 months of treatment with levodopa, the storage urodynamic parameters were slightly improved in *de novo* PD [67].

In contrast, in treated patients, studies concerning the effect of dopaminergic drugs on micturition have produced conflicting results. Regarding overactive bladder, some reports have shown a storage-facilitating effect of dopaminergic drugs [5]. In contrast, Kuno and colleagues showed that a change in medication from bromocriptine (D2 selective agonist) to pergolide (D1 < 2 agonist) brought lessening of nocturia [68], and Yamamoto described improvement of DO by pergolide [69]. Benson and colleagues [70] gave 2000 mg of levodopa in 2 longstanding PD patients, and bladder capacity increased in both patients. After discontinuation of levodopa, the bladder capacity further increased in one of the patients, but decreased in the other. Other reports have shown a voiding-facilitating effect of dopaminergic drugs [71]. Fitzmaurice and colleagues [72] have described that, in advanced PD with the on-off phenomenon, DO worsened with levodopa in some patients and lessened in others. Winge and colleagues [73] found that the effect on micturition of treatment with dopaminergic drugs in PD was unpredictable. Recent studies have shown that in early PD [74] and advanced PD with the on-off phenomenon [6], a single dose of levodopa exacerbates DO in the filling phase. We still do not know the exact reasons for the discrepancy.

There are several factors underlying the complex bladder behavior in treated PD patients [75]. Postsynaptic dopamine D1 (excitatory) and D2 (inhibitory) receptors have a millimolar affinity to dopamine whereas dendritic D2 (inhibitory) autoreceptors have a picomolar affinity to

dopamine [76]. Therefore, levodopa may first stimulate dendritic D2 autoreceptors, which might suppress the dopaminergic cells and facilitate the micturition reflex. In cases of PD under long-term treatment with levodopa, dopamine receptors are downregulated and potential hypersensitivity might occur [77]. The A11 dopaminergic cell group lies in the dorsal-posterior hypothalamus, which is affected in marmosets with MPTP-induced parkinsonism [78]. This cell group descends as the sole source of spinal dopamine [79], which might also involve in generating bladder overactivity [80]. Peripheral dopamine D1 and D2 receptors also exist in the bladder [81], although their exact role has not been delineated.

*2.4.2. Cholinergic Drugs.* Anticholinergics [82] are generally used as a first-line treatment for overactive bladder. However, it is important to balance the therapeutic benefits of these drugs with their potential adverse effects. When the dose of drug increases, postvoid residuals may appear [75]. Dry mouth and constipation are common [83]. Cognitive adverse events by anticholinergics are a concern particularly in the elderly. For example, trihexyphenidyl (for PD) and oxybutynin (for overactive bladder) have been shown to have central side effects [84, 85]. Factors contributing to the central effects of drugs may include blood-brain barrier (BBB) penetration [86]. Among the factors of BBB penetration, diffusion is facilitated by lipophilicity [87]. Particularly in elderly patients who have hallucinations or cognitive decline (PD with dementia/dementia with Lewy bodies) [64, 65], anticholinergics should be used with extreme caution.

*2.4.3. Other Treatments.* When a first-line treatment fails or is contraindicated, a second-line treatment might be considered. The main action of central 5-hydroxytryptamine- (5-HT, or serotonin-) ergic neurons on the LUT is facilitation of urine storage [88]. In PD, neuronal cell loss in the raphe nucleus has been documented [89]. Therefore, serotonergic drugs, such as duloxetine and milnacipran [90] can be a choice to treat overactive bladder in PD. Nocturnal polyuria should be distinguished from overactive bladder. In patients with PD, the imbalance between diurnal and nocturnal production of urine can be observed in the course of the disease [91]. Treatment with desmopressin proved to be effective in reducing nocturia in PD [92], although this medication needs caution of water intoxication. The subthalamic nucleus (STN) is regarded as the key area in the *indirect* pathway, which is dominant in the parkinsonian state [93]. Deep brain stimulation (DBS) in the STN inhibits many cells within the STN, probably due to depolarization block and release of GABA from activation of inhibitory afferent terminals [94]. In the STN, neuronal firings related to the micturition cycle have been observed in cats [39]. DBS in the STN proved to have an inhibitory effects on the micturition reflex in animals [39, 40] and in patients with PD [95–97]. DBS in the STN also increased bladder capacity and facilitated bladder afferent pathways in the brain of PD patients [98, 99].

### 3. Bowel Dysfunction in PD

**3.1. Neural Control of Defecation: Enteric Nervous System and Dopamine.** The enteric nervous system (ENS) plays the most important role in regulating the peristaltic reflex of the lower gastrointestinal (GI) tract (LGIT) [100]. Slow phasic pressure waves are the most common manometric phenomenon [101], and are measured in the colon and rectum (spontaneous phasic rectal contraction) in humans [102–105]. The origin of the slow wave rhythmicity in LGIT has been identified in the myenteric (Auerbach's) and submucous (Meisner's) plexuses, where interstitial cells of Cajal (ICC) exist [106]. The peristaltic reflex consists of two components: ascending contraction oral to, and descending relaxation caudal to, the site of stimulus (Figure 4). The reflex can be evoked by surface stroking or by circumferential stretch [100], in which 5-HT stimulates the sensory nerve terminals [107]. The oral excitatory component is mediated by cholinergic fibers whereas the aboral inhibitory component is mediated by nonadrenergic, noncholinergic fibers. Thus, local neuronal circuits and ICCs, together with appropriate external stimuli, might bring about the peristaltic reflex. Other types of pressure changes in the colon include giant motor complexes [100], which is perhaps analogous to the migrating motor complex of small intestine [100, 101]. After a meal, the motility index increases for 20 to 30 min and remains elevated for up to 3 hours. A combination of slow waves and giant motor complexes is thought to promote bowel transport, which is measured by colonic transit time (CTT) in humans [107, 108].

The strength of cholinergic transmission in the ENS is thought to be regulated by opposing receptors; serotonin 5-HT<sub>4</sub> receptor-mediated excitation [109, 110] and dopamine D<sub>2</sub> receptor-mediated inhibition [111, 112]. Endogenous 5-HT may facilitate intestinal motility [109], as colorectal motility is greater than normal in 5-HT transporter knockout mice with elevated extracellular 5-HT levels. Reports using dopamine transporter knockout mice have indicated that endogenous dopamine may inhibit intestinal motility [113, 114]. However, a number of studies have also demonstrated increased motility in the colon (scarce in dopamine receptors) in response to dopamine [115, 116], presumably mediated by other receptor populations such as adrenergic or serotonergic receptors, or by central mechanisms [116]. It is uncertain whether MPTP-induced parkinsonian animals might have enteric dopaminergic pathology as seen in PD [117–121]. Nevertheless, MPTP/salsolinol-induced parkinsonian animals showed decreased GI motility [122] and decreased c-Kit expression in the ICC [123]. More recently, Dorolet and colleagues found myenteric plexus alpha-synuclein aggregate pathology, neuron loss, and slowing of gastrointestinal motility in rotenone-induced parkinsonian animals [124].

**3.2. Extraenteric Nervous System and Dopamine.** Whereas small intestine and ascending colon are innervated by the vagus nerves originating in the medulla, extraenteric innervation of descending colon, sigmoid colon, and rectum primarily shares that of the LUT (Figure 5) [7, 102]. LUT

and LGIT perform the similar function of storage and emptying. However, there are also profound differences with regard to physiology (dysfunctional transport, rare ureter versus common bowel; smooth muscle contraction, only on emptying bladder contraction versus persistent spontaneous phasic rectal contraction; abdominal strain, minimum versus large, resp.) [102]. In addition, while the LUT requires intact neuraxis for storage and emptying [7], it has not been entirely clear to what extent LGIT needs extra-ENS.

Acute transection of the pelvic plexus shows slowed transit and abolishes the defecation reflex [125]. Six months later, the transit and defecation reflex are recovered [125]. In contrast, chronic replacement of esophagus [126] or bladder [127] by a colonic segment preserves colonic motility. Pathological studies in PD have shown a degenerative lesion in the spinal parasympathetic PGN [128], although the degree is much less than that in MSA. No Lewy bodies were found in the Onuf's nucleus innervating the anal sphincter [128]. Both the sacral cord and the vagus nuclei receive projecting fibers from Barrington's nucleus (identical to the PMC) in the pons. The spinal descending pathway for defecation is located in the lateral columns in humans [129, 130]. In the acute stage of spinal cord injury [131] or multiple sclerosis [132], CTT is significantly prolonged. In the chronic phase, prolonged CTT of the proximal colon returns to normal whereas that of the distal colon persists [133, 134]. Abdominal strain and cough are accompanied by sphincter contraction, which is called the guarding reflex [135]. However, when the sphincter contraction is large enough, defecation becomes unsuccessful as commonly seen in spinal cord injury (paradoxical sphincter contraction on defecation (PSCD) or anismus) [136]. In the brainstem, lesion in the vagus nuclei causes intestinal pseudo-obstruction [137, 138]. In PD, neuronal cell loss [139] and the appearance of Lewy bodies [128] in the vagus nuclei have been documented. Barrington's nucleus is thought to be critical to eliciting migrating motor complex [140, 141]. In PD, involvement of the Barrington's nucleus has also been documented [139].

The basal ganglia modulate the bowel motility [142, 143], with the main action apparently being inhibitory [142, 143]. However, under stress conditions, facilitatory responses were also observed [144, 145]. Although the connection is not fully clarified, bowel function seems to be modulated by the higher brain structures [146]. Most areas activated in functional neuroimaging by bowel distention [147] strikingly overlap the area activated by bladder distention [148].

#### 3.3. Bowel Dysfunction in PD

**3.3.1. Lower Gastrointestinal Tract Symptoms.** In PD there is dysfunction along the entire length of the GI tract. Therefore, while we focus on the colon and rectum, we refer to stomach and small intestine when necessary. The reported prevalence of LGIT symptoms in PD is mostly more than half [149–151]. However, it has been difficult to determine the extent to which PD is contributing to the LGIT symptoms. This difficulty occurs because not only PD but also idiopathic constipation may occur in the elderly due in part to dietary

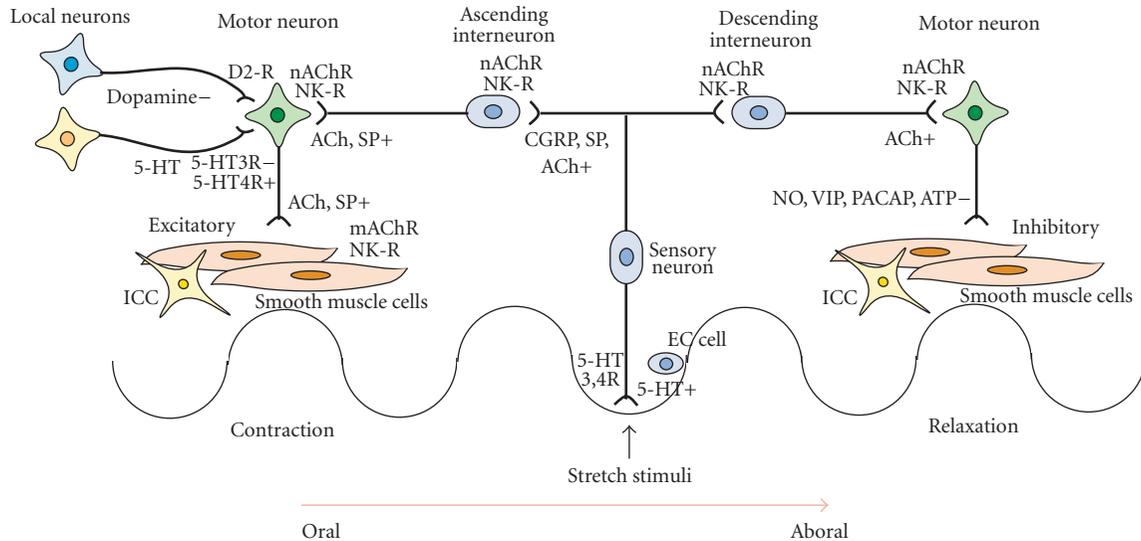


FIGURE 4: Enteric neural circuitry relevant to peristaltic reflex. Following mucosal stimulation, 5-HT is released from enterochromaffin cells to intrinsic primary sensory neurons (with 5-HT<sub>3</sub> and 5-HT<sub>4</sub> receptors) and extrinsic vagal and spinal sensory neurons (with 5-HT<sub>3</sub> receptors). Sensory neurons release calcitonin gene-regulated peptide (CGRP), substance (SP), and acetylcholine (ACh) to interneurons. Interneurons release ACh and SP orally to excitatory motorneurons while ACh is released aborally to inhibitory motorneurons. Excitatory motorneurons release ACh and SP to smooth muscle cells while inhibitory motorneurons release nitric oxide (NO), vasoactive intestinal peptide (VIP), pituitary adenylate cyclase-activating polypeptide (PACAP), and adenosine triphosphate (ATP) to smooth muscle cells. 5-HT also acts as an excitatory modulator on motor neurons (with 5-HT<sub>3</sub> and 5-HT<sub>4</sub> receptors) whereas dopamine seems to be an inhibitory modulator on motor neurons (with D<sub>2</sub> receptor). Interstitial cells of Cajal (ICC) interact with smooth muscle cells for generating rhythmicity (with Ach, VIP, and NO receptors).

habit [151], exercise [152], or age-related ENS degeneration [153]. Controlled studies [5, 149, 154, 155] could overcome these problems, in which the incidence rate of decreased stool frequency (<3 times a week) in PD patients ranges from 20% to 81%, that of difficulty in stool expulsion in 57–67%, and that of diarrhea in 21%. All of these values are significantly higher than in the normal population (range, decreased stool frequency, 0–33%; difficulty in stool expulsion, 26–28%; diarrhea, 10%) [5, 149, 154, 155]. Fecal incontinence has been reported to be 10–24% in PD [5, 149]. Therefore, constipation is the most prominent LGIT symptoms in patients with PD. Indeed, PD is a risk factor for elderly nursing home residents to have constipation [156]. Of particular importance is that bowel dysfunction affects the quality of life in patients with PD [5].

There is no significant difference in the use of dopaminergic or anticholinergic drugs and bowel dysfunction [5, 149]. Difficulty in expulsion, and diarrhea are more common in the higher grade of Hoehn and Yahr staging [5, 149, 150], suggesting a relationship between dopaminergic degeneration and LGIT symptoms. However, there are also studies in which no such relationship was found [157]. Constipation in PD occurs commonly with a low coefficient of variation in electrocardiographic R to R intervals [158]. The findings indicate that parasympathetic dysfunction might underlie these abnormalities. A recent epidemiological study revealed an association between the frequency of bowel movements and the future risk of developing PD [159]. From a clinical perspective, it is of particular importance that patients

with PD see gastroenterologists or physicians first because of their bowel dysfunction before a diagnosis of PD is made.

A more severe and often acute presentation of bowel dysfunction is intestinal pseudo-obstruction [160], also called paralytic ileus. Yokoyama and Hasegawa [161] have recently reported the frequency to be 7.1% among 112 patients with PD. Radiographical features of intestinal pseudo-obstruction are dilatation of colon and small intestine [160, 162–164]. True obstruction due to volvulus in PD also occur [161, 163, 164]. Intestinal pseudo-obstruction also occurs insidiously [165, 166]. In such patients, histology specimens may reveal Lewy body disorder.

**3.3.2. Lower Gastrointestinal Tract Function Tests.** LGIT function primarily consists of (1) colonic transport of the bowel content to the anorectum [107, 108], (2) transient anorectum reservoir, and (3) defecation from the anorectum with the aid of strain [102]. In PD, constipation results primarily from decreased transport and/or disturbed anorectal evacuation. Fecal incontinence may result from disturbed anorectal reservoir, or overflow secondary to constipation.

**3.3.3. Transit Time Study.** Previous reports have shown that total CTT is increased beyond the normal threshold in 80% of PD patients [167], which translates into an increased average CTT ranging from 44 hours to 130 hours in PD [167, 168], and in 89 hours in de novo PD patients [167], all of which are significantly longer than those of controls

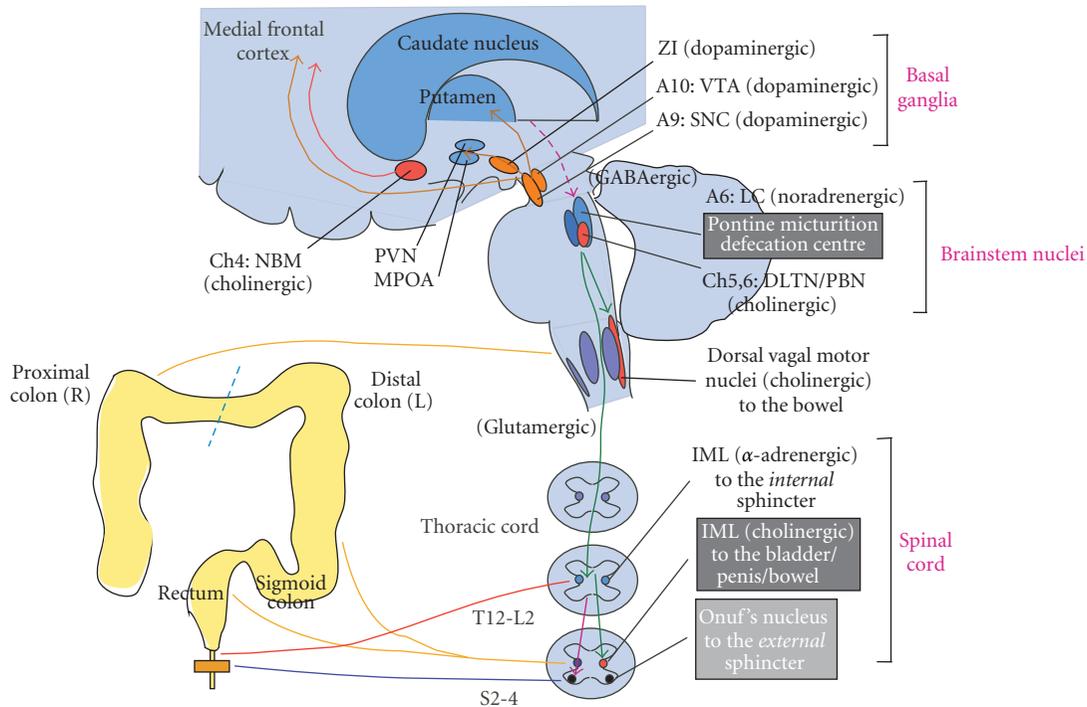


FIGURE 5: Neural circuitry relevant to defecation. Although less significantly than the lower urinary tract (LUT) does, it is thought that function of the lower gastrointestinal tract depends on the brain and the spinal cord. Whereas small intestine and ascending colon are innervated by the vagus nerves originating in the medulla, descending colon, sigmoid colon, and rectum primarily share sacral innervation of the LUT (Figure 1). Both the sacral cord and the vagus nuclei receive projecting fibers from Barrington's nucleus (the pontine micturition/defecation center). Bowel function seems to be modulated by the higher brain structures; including the frontal lobe, the hypothalamus, and the basal ganglia; the main action of the latter on the bowel seems to be inhibitory. NBM: nucleus basalis Meynert, Ch: cholinergic, PVN: paraventricular nucleus, MPOA: medial preoptic area, ZI: zona incerta, A: adrenergic/noradrenergic, VTA: ventral tegmental area, SNC: substantia nigra pars compacta, LC: locus ceruleus, DLTN: dorsolateral tegmental nucleus, PBN: parabrachial nucleus, PAG: periaqueductal gray, IML: IML cell column, GABA:  $\gamma$ -aminobutyric acid, T: thoracic, L: lumbar, S: sacral.

(range, 20–39 hours) [160, 167, 168]. Prolonged CTT has also been documented in PD patients without subjective constipation [169]. Slow colonic transit is the major cause of decreased stool frequency. The slow colonic transit is likely to reflect a decrease in slow waves and spike activities of the colon, which may reflect the ENS pathology, and to a lesser extent, the CNS pathology in PD. Among right, left, and rectosigmoid segments of the CTT, the rectosigmoid CTT is significantly prolonged in PD patients [160, 167, 169]. Several explanations for this finding can be hypothesized. It is possible that the ENS innervated by the sacral cord is more severely affected than that innervated by the DMV in PD [160]. Oro-caecal transit time in PD is also prolonged [170].

Pathological studies have demonstrated that PD affects the ENS [117–121]; showing decrease in dopaminergic myenteric neurons and the appearance of Lewy bodies along the proximal-distal axis, for example, they were most frequent in the lower esophagus, but scarce in the rectum. Presumably, degeneration of not only the inhibitory (dopaminergic) fibers, but also of facilitatory (cholinergic and serotonergic) fibers might contribute to the slow colonic transit in PD.

### 3.3.4. Rectoanal Videomanometry and Sphincter Electromyography

**Resting State.** Anal function at the resting state is measured by anal manometry and analysis of the external sphincter motor unit potentials. At the resting state, the anal pressure of PD patients is low or normal [160, 171]. The resting anal pressure may reflect sympathetic innervation in the internal anal sphincter, since lesions or anaesthetic blocks at T12-L3 (where the sympathetic PGN is located) substantially lessen the anal pressure [172]. Similarly, PD patients have low [173] or normal [160, 171] anal pressure increase on squeezing. However, neurogenic changes in motor unit potentials of the external sphincter muscles occur in only 0–15% of PD patients [174, 175]. This negative finding may correspond to the result of pathological studies indicating that the sacral Onuf's nucleus is spared in the majority of PD patients [128]. Nevertheless, the latent anal sphincter dysfunction may explain the fecal incontinence that occurs in most advanced cases. The rectoanal inhibitory reflex comprises a slow anal pressure decrease following a rapid distention of the intra-rectal balloon [176]. This reflex might be appropriate for evacuation. In PD, the threshold of the rectoanal inhibitory

reflex is reduced [168, 171, 177] or normal. Although this reflex is thought to be mediated by the intrinsic ENS [178], the exact reflex arc is not entirely clear.

**3.3.5. Filling Phase.** Rectoanal videomanometry measures functions of the anorectum reservoir and evacuation. During slow rectal filling, PD patients have a slightly but not significantly larger rectal volume at first sensation and a maximum desire to defecate compared with control subjects [160, 171]. The PD patients had the same rectal compliance as control subjects using the slow-liquid-filling method [102, 160], which is in accordance with the studies using the balloon-inflation method. However, the amplitude of the spontaneous phasic rectal contraction in the PD patients is significantly less than that in control subjects [102, 160]. The decreased spontaneous phasic rectal contraction may share the same aetiology with the decrease in CTT.

In normal subjects, anal pressure not only varies during the storage phase, but also shows a close relation with spontaneous phasic rectal contraction, for example, when the rectal pressure increases, the anal pressure tends to decrease [102]. The concurrent sphincter relaxation with the spontaneous phasic rectal contraction resembles the rectoanal inhibitory reflex [176]. The concurrent sphincter relaxation might be appropriate for the following evacuation phase [102]. However, in the PD patients, both rectal and anal pressures tend to increase together [160]. This phenomenon during filling resembles the paradoxical sphincter contraction on defecation, as described below.

**3.3.6. Defecation Phase.** In addition to slow transit constipation, anorectal (outlet type) constipation is a common feature in PD. Indeed, most PD patients could not defecate completely and had postdefecation residuals, the volume of which were significantly larger than those in a control group [160]. During defecation, it has remained a subject of controversy whether true rectal contraction occurs, since abdominal strain is large enough to mask the rectal contraction if present. Only a few studies have measured the differential rectal pressure component [179] and not found rectal contraction on defecation. In recent studies, healthy control subjects had a moderate rectal pressure increase on defecation, for example, the healthy subjects utilized the final wave of spontaneous phasic rectal contractions for defecation [102]. However, rectal contraction on defecation in PD patients is smaller than that in controls [160].

The abdominal straining in PD patients is less than that in control subjects [160]. Straining plays a physiological role in both coughing and defecation, which is achieved by cocontraction of the glottis, diaphragm, and abdominal wall [180]. Straining is associated with activation in brainstem nuclei such as the Kolliker-Fuse nucleus and medullary respiratory neurons [180]. However, PD patients show a less pronounced increase in abdominal pressure on coughing [160, 181] and Valsalva maneuver [160, 182] before starting rectal filling, and in the defecation phase [160, 182], than do control subjects. The mechanism of the impaired straining in PD may include rigidity and reduced contractility of the

axial muscles, and a failure of coordinated glottis closure [181]. However, neuronal degeneration in the CNS relevant to straining is yet to be clarified in PD.

During defecation, the anal pressure increase on defecation in patients is significantly larger than that in control subjects, with an increase in the sphincter electromyography (EMG) activity. This finding in PD has been described as paradoxical sphincter contraction on defecation (PSCD), or anismus [118, 160, 167, 171, 182, 183]. During fictive defecation (straining), a lack of anal inhibition has also been reported in 65% of PD patients. Although PSCD can also be seen in patients with idiopathic constipation [184], the frequent occurrence of PSCD in PD suggests that PSCD is a disease-related condition. The frequency of PSCD is almost the same in early and late PD [185], indicating that PSCD is an early defecatory abnormality. Mathers and colleagues [182] consider PSCD a focal dystonia. PSCD also occurs in spinal cord-injured patients [136], suggesting that dysfunction in the suprasacral descending pathway to the external sphincter is a contributing factor. Apomorphine is shown to lessen PSCD [182, 183]. This effect was not antagonized by domperidone, which did not penetrate the BBB, suggesting that the CNS pathology may produce PSCD. Both weak abdominal strain and PSCD seem to be the major causes of difficulty in stool expulsion in PD patients.

### 3.4. Treatment of Bowel Dysfunction in PD

**3.4.1. Dietary Fibers.** Although it is not certain whether exercise may facilitate bowel habit in PD, in the healthy population, moderate exercise is reported to shorten mouth-to-anus transit time [186] and improve overall wellbeing [152]. Water content is an important determinant to make stools normal (70% water) or hard (40–60% water) [184]. PD patients are reported to have reduced water intake [187]. Diet and laxatives are the first-line treatment for constipation [188]. Dietary fibers such as psyllium produced an improvement in stool consistency and an increase in stool frequency in healthy population [189] and PD [169, 190]. Polyethylene glycol 3350 [191], or bulking and highly hydrophilic agent polycarbophil [192], improve constipation in PD.

**3.4.2. Cholinergic Drugs.** A prior report has shown that pyridostigmine bromide, an acetylcholinesterase inhibitor, is effective in the amelioration of constipation in PD [193].

### 3.4.3. Dopaminergic Drugs

**Levodopa and Other Dopaminergic Agonists.** Dopamine is used as a peripheral vasoactive drug in intensive care units, in which dopamine is shown to reduce gastric migrating motor complex [194]. Dopamine also decreases gastric motility in normal volunteers [195] whereas it increases motility of the duodenum and sigmoid colon. Similarly, dopamine administration increases colonic motor activity in irritable bowel syndrome [196]. Unlike dopamine, levodopa penetrates the BBB [197]. However, it is possible that

levodopa acts on the ENS and affects bowel function in PD, since levodopa can also be metabolized in the periphery. A modern formula utilizes levodopa in combination with peripheral dopa-decarboxylase inhibitor. This regimen could possibly reduce GI side effects [198]. However, no reports are available to see whether levodopa might change gut function in untreated PD patients. As for somatic sphincter function, levodopa improves voluntary anal squeezing in fluctuating PD patients, which parallels an improvement in gait difficulty from “off” to “on” stage [177]. Apomorphine, a dopaminergic agonist, has also been shown to lessen PSCD [182, 183]. This effect is not antagonized by domperidone, suggesting that apomorphine might act on the CNS dopaminergic pathways.

**3.4.4. Dopaminergic Blockers.** Dopaminergic blockers (domperidone, etc.) are widely used as GI prokinetics by means of antagonizing dopamine's inhibitory effects on the GI motility, particularly D2 receptor blockade [199]. The pharmacological profiles of the compounds differ in terms of their molecular structure, affinity at D2 receptors, and ability to interact with other receptor systems (5-HT<sub>3</sub> and 5-HT<sub>4</sub> receptors for metoclopramide; 5-HT<sub>4</sub> receptors for levosulpiride). Since domperidone does not cross the BBB, it can be used as GI prokinetics for constipation in PD [200], although the effect of domperidone on constipation is minimal. In contrast, dopaminergic blockers that could penetrate the BBB (metoclopramide, levosulpiride, etc.) may potentially worsen extrapyramidal motor disorder in PD [199]. Since levodopa is absorbed from the small intestine [201], bowel dysfunction in PD may interfere with levodopa absorption, worsen the motor disorder, or even lead to malignant syndrome [202, 203]. Gastric emptying of an isotope-labeled solid meal becomes significantly faster during domperidone therapy in PD [200]. In addition, domperidone pretreatment causes a mean 12% increase in peak plasma levodopa concentrations that occurs a mean of 10 min earlier than when levodopa is given alone [202]. Peak plasma levodopa concentrations are reported to be greater on levodopa-domperidone than on levodopa-carbidopa [204].

**3.4.5. Serotonergic Drugs.** Cisapride, a selective 5-HT<sub>4</sub> receptor agonist, has significantly shortened CTT in PD [205], although after 1 year, only a small effect could be demonstrated [206]. Of particular importance is that cisapride add-on therapy improved the “on-off” phenomenon in advanced PD [203]. However, some reports indicated cisapride's D2 dopaminergic receptor blocking property [207]. Cisapride also blocks K<sup>+</sup> channels and leads to cardiotoxicity. Mosapride is a novel selective 5-HT<sub>4</sub> receptor agonist that lacks a D2 receptor or K<sup>+</sup> channel blocking property [208]. Mosapride is shown to ameliorate delayed gastric emptying [209] as well as constipation in PD [210], by shortening of total CTT (particularly the caudal segment), and by augmenting the amplitude in rectal contraction during defecation [210]. Improvement of parkinsonism is more significant with pergolide-mosapride than with pergolide-domperidone [211]. Tegaserod, a selective 5-HT<sub>4</sub>

agonist, is also effective in ameliorating constipation in PD [212].

**3.4.6. Other Drugs.** Although prior reports have indicated the effectiveness of motilides (erythromycin, etc.) [213], neurotrophin-3 [214] and colchicine [215] on constipation in PD, their use remains limited. Type A botulinum toxin injection into the puborectalis muscle [216, 217] and biofeedback [218] ameliorates anismus in PD.

## 4. Sexual Dysfunction in PD

**4.1. Neural Control of Erection: Normal Erection in Men.** Sexual dysfunction is not uncommon in PD [5, 219–223]. Studies have shown that sexual dysfunction has great significance in relation to quality-of-life measures. However, the detailed mechanism of sexual dysfunction in PD has not been well known.

The genital organ primarily shares lumbosacral innervation with the lower urinary tract. Erection is a vascular event [224]; occurring secondarily after dilatation of the cavernous helical artery and compression of the cavernous vein to the tunica albuginea [224]. Helical artery dilatation is brought about by activation of cholinergic and nitrenergic nerves; this activation facilitates nitric oxide secretion from the vascular endothelium. Ejaculation is brought about by contraction of the vas deferens and the bladder neck, in order to prevent retrograde ejaculation, by activation of adrenergic nerves (Figure 6). Sexual intercourse in healthy men can be divided into 3 phases [225]: (a) desire (libido), (b) excitement and erection, and (c) orgasm, seminal emission from the vas deferens, and ejaculation from the penis. Erection can be further classified into 3 types by the relevant stimulation: (1) psychogenic erection (by audiovisual stimulation), (2) reflexive erection (by somatosensory stimulation), and (3) nocturnal penile tumescence (NPT; associated with rapid eye movement (REM-) sleep). “Morning erection” is considered the last NPT in the nighttime.

**4.2. Hypothalamic Neurons and Dopamine in Men.** Among the 3 types of erection, reflexive erection requires an intact sacral cord, particularly the intermediolateral (IML) cell columns. Pathology studies have shown that involvement of the IML nucleus is common in MSA, whereas it is uncommon in PD. Therefore, reflexive erection can be affected in patients with MSA. In patients with a supra-sacral spinal cord lesion, reflexive erection might be preserved, whereas psychogenic erection is severely disturbed because of a lesion in the spinal pathways to the sacral cord. Libido and erection are thought to be regulated by the hypothalamus; particularly the medial preoptic area (MPOA) and the paraventricular nucleus (PVN) (Figure 4) [226, 227]. Electrical or chemical stimulation in the MPOA/PVN evoked erection and mating behaviors in experimental animals, both of which were abolished by destruction of these areas. Somatosensory inputs from the genitalia ascend in the anterior spinal cord, and project to the MPOA/PVN via the thalamic nuclei. Erotic visual inputs from the retina are thought to reach the

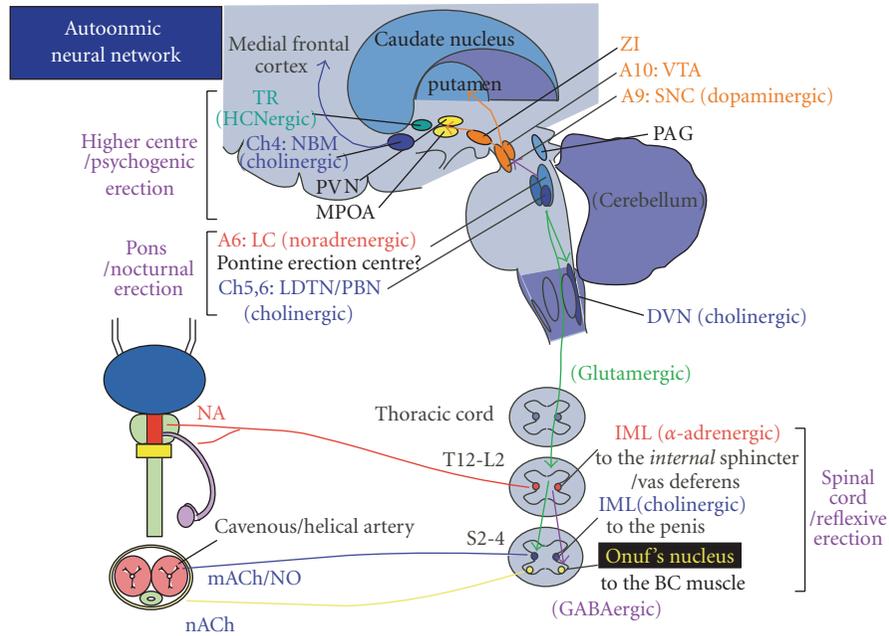


FIGURE 6: Neural circuitry relevant to erection. PAG, periaqueductal gray; LC, locus coeruleus; NBM, nucleus basalis Meynert; PVN, paraventricular nucleus; MPOA, medial preoptic area; A, adrenergic/noradrenergic; ZI, zona incerta; VTA, ventral tegmental area; SNC, substantia nigra pars compacta; DLTN, dorsolateral tegmental nucleus; PBN, parabrachial nucleus; IML, intermediolateral nucleus; GABA,  $\gamma$ -aminobutyric acid; T, thoracic; L, lumbar; S, sacral; NA, noradrenaline; Ach, acetylcholine; NO, nitric oxide. See text.

MPOA via the mamillary body. Recent neuroimaging studies have shown that penile stimulation or watching pornography activated these areas in humans [228]. NPT [229] seems to be regulated by the hypothalamic lateral preoptic area [230].

The raphe nucleus and the locus ceruleus are candidate areas participating in the regulation of NPT. Oxytocinergic neurons in the hypothalamic PVN are thought to facilitate erection by projecting directly to the sacral cord, and by projecting to the midbrain periaqueductal gray and the Barrington's nucleus (identical to the PMC). Serum oxytocin concentration increases during masturbation in healthy men.

In experimental animals, dopamine is known to facilitate erection and mating behaviors. The MPOA/PVN receives projections from the nigral dopaminergic neurons [231]. A microdialysis study showed that the dopamine concentration in the MPOA was increased by sexual stimulation. It is reported that dopamine D1/D2 receptors in the hypothalamus participate in erection whereas only D2 receptors participate in ejaculation. Pathology studies have shown that the hypothalamus is affected in PD [231]. Recently, polymorphism in the dopamine D4 receptor gene is shown to contribute to individual differences in human sexual behavior [232]. Prolactinergic neurons are thought to be inhibitory in sexual function. Serum prolactin levels increase after orgasm in healthy men. Prolactin-producing pituitary tumors often cause gynecomastia and erectile dysfunction in male patients. Hyperprolactinemia occurs after the use of sulpiride, metoclopramide, and chlorpromazine (all dopamine receptor antagonists). Therefore, dopaminergic neurons seem to facilitate oxytocinergic neurons whereas they inhibit prolactinergic neurons. Some *de novo* PD

patients have hyper prolactinemia [233], which may contribute to erectile dysfunction in those patients.

4.3. *Female Sexual Function and Dopamine.* As compared with male genitalia, studies of female genital organs are limited. Vulva [234], clitoris [235] and vagina [236] primarily shares lumbosacral innervation with the lower urinary tract. Sexual arousal in women is a vasocongestive and neuromuscular event through these organs, paralleling genital lubrication, controlled by facilitatory parasympathetic (by vasoactive intestinal peptide, nitric oxide, and to a lesser extent acetylcholine, via the pelvic nerves from S2–4 intermediolateral (IML) cell column) and inhibitory sympathetic (by noradrenaline, via the hypogastric nerves from T12–L3 IML cell column,) inputs. Some information is thought to travel the vagal nerves. Activity of these spinal nuclei is controlled by sensory afferents from the genitalia and descending projections from the brain.

Like men, libido in women is thought to be regulated by the hypothalamus. The neural circuit for lordosis in animals involves a supraspinal loop, which is controlled by an estrogen- and progesterone-dependent signal, presumably at the ventromedial hypothalamus (VMH), medial preoptic area (MPOA), and paraventricular nucleus (PVN) in the hypothalamus. Lordosis is facilitated by luteinizing hormone-releasing factor (LHRH), alpha-melanocyte stimulating hormone (alpha-MSH), and methionine-enkephalin whereas suppressed by corticotrophin-releasing factor and beta-endorphin [237, 238]. Recent neuroimaging studies have shown that vaginal self-stimulation with/without orgasm

activated these areas in humans [239]. Oxytocinergic neurons in the VMH and the MPOA are thought to facilitate vagino-clitoral sexual arousal and lordosis by projecting directly to the sacral cord [238, 240]. Role of dopamine in female sexual function remains not completely clear [241]. It is reported that lordosis was increased in female animals by microinjection of apomorphine (D1, 2 agonist) and quinpirole (D2 agonist) in the MPOA whereas it decreased by SKF 38393 (D1 agonist) [242]. This was counteracted by chemical inhibition of dopaminergic neurons in the ventral tegmental area (VTA) [243].

**4.3.1. Male Sexual Symptoms.** The reported prevalence of sexual symptoms in men with PD ranges from 37% to 65% [234–239]. Only few previous studies have looked at sexual symptoms in PD and control subjects. Jacobs et al. [244] studied 121 men with PD (mean age 45 years) and 126 age- and sex-matched community male controls. Patients were more dissatisfied with their present sexual functioning and relationship whereas no differences were found for the frequency of sexual intercourse itself. Erection and ejaculation were not inquired. Sakakibara et al. [5] analyzed sexual function of 46 men with PD (age 35–70 years old) and 258 healthy male control subjects (age 30–70 years old) [5]. As compared with the control group, the frequency of dysfunction in PD patients was significantly higher for decrease of libido (84%), decrease of sexual intercourse (55%), decrease of orgasm (87%), and decrease of erection (79%) and ejaculation (79%). Therefore, sexual dysfunction is significant in PD. The majority of patients had onset of the sexual dysfunction after the appearance of the motor disorder. This is in contrast to patients with MSA, who often have sexual dysfunction before the onset of motor disorder.

Comparing the results between four age subgroups (subjects in their 30s, 40s, 50s, and 60s) in the control group, the frequencies of sexual intercourse and of orgasm were significantly lower in older individuals [5]. In the PD group, only the frequency of orgasm was lower in older men ( $P < 0.05$ ). Comparing the results between both sexes in the control group, decrease of libido and orgasm were more common in women ( $P < 0.01$ ). In the PD group, there was no significant difference in sexual function items. Bronner et al. [245] reported that use of medications (selective serotonin reuptake inhibitors used for comorbid depression), and advanced PD stage contributed to the development of ED.

**4.3.2. Rigiscan.** In healthy men, sexual intercourse is thought to be carried out by integrating affective, motor, sensory, autonomic, and other factors. In male patients with PD, depression, motor disorder, and pain inevitably lead to sexual dysfunction. In contrast, it has been difficult to determine to what extent autonomic factors contribute to the sexual dysfunction in PD. However, erectile dysfunction often precedes motor disorder in MSA, and abnormal NPT is not uncommon in PD. These findings strongly suggest that the disorder does in fact contribute to sexual dysfunction in PD. Rigiscan is an objective measure for erectile dysfunction,

which allows both tumescence and rigidity measurement, and is suitable for assessing NPT.

Only few data have been available concerning the relationship between NPT and dopamine. However, in experimental animals, administration of levodopa elicited erection and yawning together. Animals with experimental parkinsonism showed fewer REM stages during sleep than control animals did.

**4.3.3. Female Sexual Dysfunction.** As compared with men, few studies are available concerning female sexual dysfunction in PD. Further, only few previous studies have looked at female sexual symptoms in PD and control subjects. Sakakibara et al. [5] analyzed sexual function of 38 women with PD (age 35–70 years old) and 98 healthy control women (age 30–70 years old) [5]. As compared with the control group, the frequency of dysfunction in women with PD was significantly higher for decrease of libido (83%) and decrease of sexual intercourse (88%) while decrease of orgasm was not different between women with PD and control. The majority of patients had onset of the sexual dysfunction after the appearance of the motor disorder. Welsh et al. [246] studied 27 women with PD (mean age 67 years) and community healthy controls, and in both groups 50% were sexually active. As compared with control, women with PD had more common decrease of libido, vaginal tightness, involuntary urination, and dissatisfaction in sexual intercourse. There was no difference in terms of sexual arousal, sexual intercourse, and orgasm. Without control, in young PD patients (36–56 years) women had more common sexual problems (decrease of libido, 70%, decrease of sexual intercourse, 80%) than men (40%, 33.4%, resp.) [247, 248]. Other domains, such as loss of lubrication and pain, are not clearly known.

#### 4.4. Treatment of Sexual Dysfunction in PD

##### 4.4.1. Male Sexual Dysfunction

**Dopaminergic Drugs.** It is possible that levodopa and other antiparkinson medication may affect sexual function in PD. However, it is not entirely clear to what extent levodopa ameliorates sexual dysfunction in PD. In contrast, subcutaneous apomorphine injection is used to ameliorate fluctuating symptoms in PD. It has also been used to treat erectile dysfunction in the general population [247, 248] and in patients with PD [249], although the dose is different (general population, initial 2 mg and up to 3 mg [247, 248], PD, 4 mg [250]). Apomorphine is thought to stimulate dopamine D2 receptors, and activate oxytocinergic neurons in the PVN. Nausea is a common side effect of this drug. Cabergoline [251] and pergolide [252] are also reported to improve sexual dysfunction in PD. In contrast, pathological hypersexuality may occur together with [253] or without delirium [254], which is attributed to the dopamine dysregulation syndrome in this disorder. DBS in the STN has produced either improved sexual wellbeing [255] or transient mania with hypersexuality [256] in patients with PD.

*Phosphodiesterase-5 Inhibitors.* When dopaminergic drugs did not help, phosphodiesterase-5 inhibitors, for example, sildenafil, vardenafil, and so forth, become the first line treatment in PD [257, 258]. These drugs inhibit nitric oxide degradation and facilitate smooth muscle relaxation in the cavernous tissue. When treating PD patients with postural hypotension, these drugs should be prescribed with extreme caution [258].

*Other Drugs.* When phosphodiesterase-5 inhibitors did not help, recent trials of melanocortin, for example, melanotan-II, bremelanotide, and so forth, showed that these drugs might become a choice for treating erectile dysfunction. A group of pro-opio-melanocortin (POMC) gene products include adrenocorticotrophic hormone (ACTH),  $\alpha$ -melanocyte stimulating hormone ( $\alpha$ -MSH),  $\beta$ -MSH, and  $\gamma$ -MSH. It is known that the arcuate nucleus of the hypothalamus projects POMC-containing neurons to the lateral hypothalamus, dorsal medial nucleus, MPOA, and PVN [22].  $\alpha$ -MSH as secreted in the MPOA and PVN participates in the central control of sexual function [21]. Bremelanotide is a melanocortin receptor agonist, and is reported to be effective for treating erectile dysfunction as compared with placebo [259].

*4.4.2. Female Sexual Dysfunction.* There is no established regimen to treat sexual dysfunction in women with PD. PDE5 inhibitors, such as sildenafil, tadalafil, and vardenafil, has become the first choice in the treatment of erectile dysfunction in men. Whereas sildenafil facilitated clitoral engorgement in women with sexual dysfunction [260], clinical efficacy of this drug in women with PD awaits further clarification [261]. Bremelanotide, a melanocortin receptor agonist, is applied to female sexual dysfunction, and is reported to be effective [262].

## 5. Conclusions

This article reviewed the current concepts of bladder, bowel, and sexual dysfunction (pelvic organ dysfunctions) in PD. Central nervous system pathology is clearly associated with bladder (urinary urgency/frequency) and sexual dysfunction (decrease in libido, erection, and overall dissatisfaction) in PD. In contrast, both central (weak strain and anismus) and peripheral myenteric pathology (slow colonic transit and loss of rectal contraction) are associated with bowel dysfunction. Anticholinergic agents are generally used to treat bladder dysfunction while phosphodiesterase inhibitors are used to treat sexual dysfunction. Dietary fibers, laxatives, and serotonergic agents are used to treat bowel dysfunction. These treatments are beneficial in maximizing patients' quality of life.

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## Review Article

# Sleep Disturbances Associated with Parkinson's Disease

**Keisuke Suzuki, Masayuki Miyamoto, Tomoyuki Miyamoto,  
Masaaki Iwanami, and Koichi Hirata**

*Department of Neurology, Center of Sleep Medicine, Dokkyo Medical University School of Medicine, 880 Kitakobayashi,  
Mibu, Shimotsuga, Tochigi 321-0293, Japan*

Correspondence should be addressed to Keisuke Suzuki, keisuke@dokkyomed.ac.jp

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Sleep disturbances are common problems affecting the quality life of Parkinson's disease (PD) patients and are often underestimated. The causes of sleep disturbances are multifactorial and include nocturnal motor disturbances, nocturia, depressive symptoms, and medication use. Comorbidity of PD with sleep apnea syndrome, restless legs syndrome, rapid eye movement sleep behavior disorder, or circadian cycle disruption also results in impaired sleep. In addition, the involvement of serotonergic, noradrenergic, and cholinergic neurons in the brainstem as a disease-related change contributes to impaired sleep structures. Excessive daytime sleepiness is not only secondary to nocturnal disturbances or dopaminergic medication but may also be due to independent mechanisms related to impairments in ascending arousal system and the orexin system. Notably, several recent lines of evidence suggest a strong link between rapid eye movement sleep behavior disorder and the risk of neurodegenerative diseases such as PD. In the present paper, we review the current literature concerning sleep disorders in PD.

## 1. Introduction

Parkinson's disease (PD) is a movement disorder characterized by bradykinesia, resting tremors, rigidity, and impaired postural reflexes, which are caused by the degeneration of dopaminergic neurons in the substantia nigra. However, the pathological course of PD has been recognized to be much more extensive, involving the serotonergic, noradrenergic, and cholinergic systems [1]. These systems may play a role in the development of the nonmotor symptoms commonly observed in PD such as sleep disturbances, depression, olfactory dysfunction, cognitive impairments, fatigue, and autonomic dysfunctions. In a recent large study comprising 1,072 patients with PD, almost all of the patients exhibited at least one type of nonmotor symptoms [2].

Sleep disturbances are among the most common nonmotor symptoms, with a prevalence ranging from approximately 40% to 90%, and these disturbances can interfere with patients' quality of life [2–5]. Various factors, including nocturnal motor symptoms, psychiatric symptoms, dementia, dopaminergic medications, and circadian cycle disruptions, cause sleep disturbances [6]. Comorbidity with sleep apnea syndrome (SAS), restless legs syndrome (RLS), and rapid

eye movement sleep behavior disorder (RBD) is often observed, complicating the sleep disturbances related to PD. The orexin system may be involved in PD, contributing to the daytime sleepiness independent of impaired sleep conditions. RBD preceding or coexisting with PD has received attention, but whether RBD and PD are caused by a similar neurodegenerative process remains unknown. The evaluation and treatment of sleep disorders in PD are of great importance because of their negative impact on quality of life. A "sleep benefit" of improved early-morning motor function before medication intake is often reported by some PD patients [7]. Högl et al. reported that levodopa concentrations and polysomnographic findings were similar between PD patients with and without the sleep benefit but that PD patients with the sleep benefit exhibited a different response profile to levodopa; the magnitude of motor deterioration after levodopa intake was greater in PD patients with the sleep benefit than in patients without it [8]. Subjective perceptions or sensory mechanisms may play a role in the sleep benefit in PD. In contrast, the effect of sleep deprivation on motor performance is controversial [9]. In this paper, we review and discuss the current literature concerning sleep disorders in PD.

## 2. Pathophysiology of Insomnia and Excessive Daytime Sleepiness

As a result of an examination of polysomnography (PSG) recordings, altered sleep structure has been observed in PD, namely, a decrease in the quantity of nonrapid eye movement (NREM) sleep stages 3 and 4 and REM sleep [10]. The degeneration of cholinergic neurons in the basal forebrain and brainstem including the pedunculopontine nucleus and noradrenergic neurons in the locus coeruleus results in disorders of REM sleep, and a loss of serotonergic neurons in the raphe nucleus is associated with a reduction in the amount of slow-wave sleep [11]. In addition to the orexin and histamine systems, these serotonergic, noradrenergic, and cholinergic neurons in brainstem serve as arousal systems that maintain wakefulness, and disturbance of these neurons leads to excessive daytime sleepiness. In patients with PD, a loss of orexinergic neurons in the posterior portion of the lateral hypothalamus [12] and a reduction in the number of A10 dopaminergic neurons in the ventral tegmental area [13] have been implicated in impaired wakefulness. The histaminergic neurons in the hypothalamus appear intact in patients with PD. Orexin/hypocretin may promote wakefulness by upregulating monoaminergic neuronal populations [14]. Wake-active dopaminergic neurons in the ventral periaqueductal gray matter have been identified [15] but seem to be intact in patients with PD [16]. In animal models, D2 receptors exhibit a biphasic response, with sedating effects occurring after low-dose stimulation of the presynaptic receptors and awakening effects occurring after high-dose stimulation of the postsynaptic receptors [17]. The ventral tegmental area and the mesolimbic and mesocortical dopaminergic circuits are crucial sites for the action of dopamine in the sleep-wake cycle [18]. In humans, low doses of dopaminergic stimulation may result in sleepiness, and high doses of stimulation may induce wakefulness, resulting in insomnia [19]. A placebo-controlled, randomized, double-blind, crossover study performed in 20 healthy volunteers using the multiple sleep latency test indicated that low-dose ropinirole reduces the time to sleep onset in humans [20]. By contrast, in a study of 54 consecutive levodopa-treated patients with PD referred for sleepiness, a positive correlation between mean daytime sleep latency and the daily administration of levodopa was observed, even after accounting for controlling factors, indicating that levodopa may have alerting effects in some groups of patients [21]. Nevertheless, all dopaminergic drugs can have sedating effects on patients with PD, and the mechanism of this discrepancy has not been fully elucidated [22].

## 3. Insomnia

Insomnia is defined as a complaint of one or more of the following symptoms: difficulty falling asleep, difficulty staying asleep, early awakening, or nonrefreshing sleep that occurs despite adequate opportunities for sleep. Daytime impairments related to nighttime sleep difficulties have also been reported. In a community-based survey, sleep initiation

was reported to be similar in all groups, but the PD patients complained of greater sleep fragmentation compared with diabetic patients or healthy control subjects [5]. In patients with PD, sleep maintenance insomnia (difficulty staying asleep) appears to be a common form of insomnia that is frequently caused by nocturnal motor disturbances [23, 24]. Figure 1 represents the major causes of insomnia observed in patients with PD. Insomnia is attributable to these various causes, but the prevalence of insomnia increases as the disease progresses along with the aging process, suggesting that disease severity has an impact on sleep disturbances [3, 23, 24]. Insomnia is probably correlated with depression, disease duration [24–26], or motor symptoms [3]. In contrast, the prevalence of insomnia was 54%–60% over an eight-year period in a prospective study, but the data showed no linear increase over an eight-year followup period [26]. This finding indicates that sleep disorders can occur during an early stage of PD.

Identifying the factors contributing to insomnia can result in an improvement in sleep. Melatonin administration to PD patients led to a significant improvement in subjective sleep disturbances, sleep quantity, and daytime sleepiness [27]. Using short-acting hypnotic drugs such as zolpidem [28], which have less impact on muscle relaxation, is recommended to prevent falls associated with sleep aids, especially in elderly subjects.

*3.1. Nocturnal Disturbances.* Lees and colleagues [4] have reported nocturnal disturbances in 215 of 220 PD patients, including nocturia (79%), difficulty turning over in bed (65%), painful muscle cramps (55%), nightmares (48%), limb or facial dystonia (34%), leg jerks (33%), and visual hallucinations (16%). Stack and Ashburn [29] studied impaired bed mobility in patients with PD and determined that approximately 80% of the patients turned in bed successfully but exhibited difficulty turning in bed, suggesting that identifying the least disruptive turning strategy may be useful.

Chaudhuri et al. [23] developed the Parkinson's disease sleep scale (PDSS), a visual analogue scale that includes 15 PD-related nocturnal symptoms for assessing nocturnal disability in patients with PD. Their study showed that patients with an advanced level of the disease had impaired scores compared with those with early or moderate levels of the disease. The PDSS was described in a recent review [30] as a recommended, reliable scale, except that it may not be sufficient for screening for sleep apnea, RBD, or RLS. This scale has been validated and employed extensively in a number of countries and was reported to exhibit high reliability [24, 31–34]. Our multicenter study also found more severe nocturnal disturbances in patients with an advanced stage of PD, as measured by the PDSS, (Hoehn & Yahr (H&Y) stage IV) compared with those with early and moderate stages of the disease (H&Y I–III). These disturbances were associated with disease duration, depressive symptoms, and complications of dopaminergic treatments (such as dyskinesia and wearing-off symptoms) [24]. By contrast, Dhawan et al. [35] reported that nocturnal

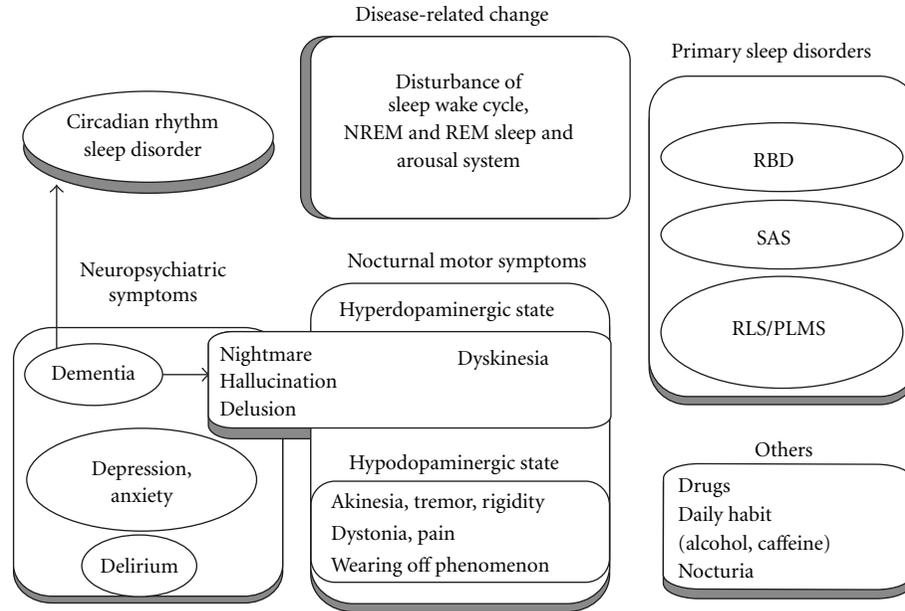


FIGURE 1: The major causes of insomnia and its contributing factors. RBD: rapid eye movement sleep behavior disorder; SAS: sleep apnea syndrome; RLS: restless legs syndrome; PLMS: periodic limb movement during sleep.

symptoms such as nocturia, nocturnal cramps, dystonia, and tremors were observed in untreated PD patients with short disease durations. PDSS-2, a new version of PDSS, has been developed, and its total and three domain scores, including disturbed sleep, motor symptoms at night, and PD symptoms at night, have been shown to correlate with patients' quality of life, the Unified Parkinson's Disease Rating Scale (UPDRS) motor scores, and disease severity in different patterns [36].

Nocturia is a common nighttime problem; 80% of PD patients exhibited two or more episodes of nocturia per night caused by overflow incontinence and a spastic bladder [4]. If the nocturia is found to be related to wearing-off symptoms, then changing medications to administer a long-acting dopamine agonist before bedtime can be beneficial. A urologic examination is recommended because nocturia may also be associated with the normal aging process or underlying urological diseases.

Nocturnal motor symptoms are caused by a hypodopaminergic state, such as akinesia and increased tremor and rigidity, and a hyperdopaminergic state, such as levodopa-related dyskinesia. The inability to turn in bed and difficulty in rising to pass urine during the night due to nocturnal akinesia are significant disabling symptoms. Increasing the dose of a dopamine agonist or levodopa or adding these drugs to the regimen of medications administered at bedtime should be considered. A double-blinded, placebo-controlled trial with 287 PD patients demonstrated the efficacy of 24-h rotigotine on daytime motor function (UPDRS part III) and nocturnal disabilities, as evaluated by the PDSS-2 [37]. In addition, subcutaneous overnight apomorphine infusion led to a dramatic reduction of nocturnal awakenings, nocturnal-off periods, pain, dystonia, and nocturia in patients with PD [38]. Arnulf et al. reported that high-frequency subthalamic nucleus stimulation in 10 PD patients with insomnia reduced

nighttime akinesia by 60% and completely suppressed axial and early-morning dystonia [39].

By contrast, a reduction in the dose of dopaminergic drugs may be effective for the symptoms associated with a hyperdopaminergic state. If patients with frequent nocturnal awakenings have taken amantadine or selegiline, which have potential alerting effects, then a reduction in the dose of these drugs, discontinuation of the administration of these drugs, or a change in the time of administration of these drugs from evening to morning may reduce the number of nocturnal awakenings.

**3.2. Assessment Tools for Sleep Disturbances in PD.** PSG is the "gold standard" method used to evaluate sleep disorders and provides detailed information about actual sleep status, including sleep efficiency, sleep latency, and sleep structure. PSG can detect the cooccurrence of SAS, RBD, and periodic limb movements. However, the use of PSG is limited because of its cost and requirement for special equipment. As an alternative, questionnaire-based sleep studies have been widely conducted. The application of several scales for sleep disturbances has recently been reviewed [30]. The Pittsburgh Sleep Quality Index [40] is recommended to assess overall sleep abnormalities, and the Epworth sleepiness scale (ESS) is suggested for use in evaluating daytime sleepiness [41]. However, prior studies have reported that ESS score was correlated with multiple sleep latencies, but the correlation was weak and false negatives were detected, suggesting that a normal ESS score does not exclude the sleepiness observed in PD [21]. The Parkinson's disease sleep scale (PDSS) [23], a visual analogue scale including 15 PD-related nocturnal symptoms for assessing nocturnal disability in PD, is now a recommended, reliable scale [30]. The scale includes the following items: overall quality of nighttime sleep (item 1),

sleep onset and maintenance insomnia (items 2 and 3), nocturnal restlessness (items 4 and 5), nocturnal psychosis (items 6 and 7), nocturia (items 8 and 9), nocturnal motor symptoms (items 10-13), sleep refreshment (item 14), and daytime dozing (item 15). For further improvement, the PDSS-2, a modified version of the PDSS that assesses the frequency of nocturnal symptoms and includes the screening of SAS, has been published with an excellent level of validity and reliability [36].

#### 4. Excessive Daytime Sleepiness

After a report in 1999 stated that sudden-onset sleep episode is associated with motor vehicle accidents in PD patients who take nonergot dopamine agonists (either ropinirole or pramipexole) [42], the association of excessive daytime sleepiness (EDS) or sleep episodes with dopaminergic medications has become a focus of attention. Approximately 15%–50% of PD patients have been reported to show EDS [43–45]. A high Epworth sleepiness scale (ESS) score, male gender status, longer disease duration, and high-disease severity have also been observed to be associated with EDS [43, 44, 46]. Similar to the insomnia observed in patients with PD, multiple factors are associated with EDS: impaired arousal systems in addition to the disease process, dopaminergic medication, nocturnal disturbances, and concurrent primary sleep disorders such as SAS, RBD, and RLS are thought to be contributing factors. In addition, narcolepsy-like symptoms have been observed in patients with PD. Daytime sleepiness or sleep episodes exhibiting a short sleep latency, short sleep onset REM period, and decreased orexin levels are independent of the patients' nighttime sleep conditions. These symptoms are similar to those observed in narcolepsy, which is a sleep disorder characterized by severe daytime sleepiness and caused by loss of orexin neurons. However, cataplexy is lacking in patients with PD [47], and the role of orexin levels in PD patients with EDS is still controversial. Studies in PD patients with EDS have not observed a reduction in orexin concentrations in the cerebrospinal fluid [48, 49]. However, while markedly decreased orexin levels in the hypothalamus and a loss of orexin neurons have been observed in PD patients and were significantly correlated with clinical disease progression, no description was provided for EDS [12, 50]. The lumbar cerebrospinal fluid may not reflect the orexin cell loss reported in the hypothalamus of patients with PD. Further research is needed to determine whether a decrease in the number of orexin neurons in the hypothalamus or other systems, in addition to orexin dysfunction, accounts for EDS in PD patients. Additional work is also required to determine whether decreased orexin levels reflect disease-related changes or secondary, compensatory changes that result from dopaminergic dysfunction [51, 52].

Several studies have demonstrated that taking dopamine agonists or levodopa is associated with increased daytime sleepiness in patients with PD [43, 44, 46, 53, 54]; however, several other studies have failed to confirm this significant association [55, 56]. To date, whether specific dopamine

agonists are associated with sleepiness is still unclear [43, 44, 54]. Sudden onset sleep episodes while driving have been reported in 3.8%–22.8% of PD patients and are associated with a high score on the ESS [43, 46, 56]. This finding suggests that PD patients with high ESS scores are at risk for experiencing sleep episodes while driving.

### 5. Comorbid Sleep Disorders

*5.1. Rapid Eye Movement Sleep Behavior Disorder.* Rapid eye movement sleep behavior disorder (RBD) is characterized by a loss of muscle atonia during REM sleep that results in dream-enacting behavior, which often leads to injury to the individual or bed partner [57]. RBD tends to affect older individuals and has a higher prevalence in males [58].

Lesions of the locus coeruleus perialpha in cats and the sublateralodorsal nucleus in rats have been suggested to cause REM sleep without atonia and with complex movements [59, 60]. Involvement of subcoeruleus-coeruleus complex was found in cases with incidental Lewy body disease (preclinical stages of PD) [61]. This brain region may be crucial for RBD pathophysiology in addition to the cholinergic nuclei, pedunculopontine nucleus, and laterodorsal tegmental nucleus, which play a role in regulating REM sleep. A flip-flop switch model for the control of REM sleep has been proposed: GABAergic REM-on neurons located in the sublateralodorsal nucleus inhibit GABAergic REM-off neurons located in the ventrolateral periaqueductal gray matter and lateral pontine tegmentum, and vice versa [62].

RBD was considered to be an idiopathic, isolated disorder until a study in 1996 by Schenck demonstrated that 38% of 29 patients with idiopathic RBD developed PD after a mean followup of  $3.7 \pm 1.4$  years [63]. Subsequently, a positive association has emerged between RBD and neurodegenerative disorders, particularly synucleinopathies such as PD, multiple system atrophy, and dementia with Lewy bodies [58, 64, 65]. Early manifestations of PD preceding the onset of typical motor symptoms, such as impaired visual and olfactory discrimination, cardiac sympathetic denervation, and cognitive impairment, have been observed in idiopathic RBD patients [66–70]. As a possible prodromal phase of neurodegenerative diseases, a diagnosis of RBD is crucial for early intervention to treat neurodegenerative disorders. Therefore, to establish an accurate diagnosis, a quantitative visual scoring of the electromyographic (EMG) data in REM sleep may be necessary [71]. In a recent report, RBD preceded the onset of synucleinopathies by up to 50 years [72], indicating that if idiopathic RBD patients lived long enough, the underlying cause of the neurodegenerative disease would be unveiled [73].

Recently, Iranzo et al. [74] conducted a study measuring PSG at baseline and after a mean followup of five years; this study revealed that excessive tonic and phasic EMG activity occurs during REM sleep and is increased over time in patients with RBD. This finding suggests that an underlying progressive process affects the brainstem in patients with RBD. Even though as many as half of RBD patients will develop neurodegenerative diseases, a wide variability is

observed in the incidence rates of PD development, and no method exists to predict which patients will develop PD. We cannot currently predict why some idiopathic RBD patients develop PD and others do not. However, a recent study by Postuma et al. has helped elucidate this subject. Their results indicate that in subjects with idiopathic RBD initially free of neurodegenerative disease, the severity of the REM atonia loss on the baseline PSG findings can predict PD development [75].

In terms of the comorbidity of PD and RBD, PD patients with RBD exhibited a predominantly nontremor phenotype, an increased frequency of falls, and a poor response to dopaminergic medications, which were associated with orthostatic hypotension and impaired color vision. However, overall disease severity, quantitative motor testing, and motor complications did not differ between PD patients with RBD and those without RBD [76, 77]. Interestingly, restored motor control (movements, speech, and facial expressions) has been observed during REM sleep with enacted dreams in PD patients who had RBD [78].

RBD can be triggered by antidepressants, such as tricyclics, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors; by beta-blockers; by states of barbiturate and alcohol withdrawal [79]; however, whether the subjects who develop RBD are susceptible to drugs or whether they have underlying diseases has not been fully elucidated. Clonazepam (0.5 to 1.5 mg) at bedtime is effective for decreasing the frequency and severity of RBD; however, it has little effect on EMG tone [80]. Melatonin has been indicated to ameliorate RBD symptoms [81] and improve EMG tone during REM sleep [82]. Levodopa and pramipexole also reduce the clinical manifestations of RBD [80], although in a prospective study of 11 consecutive PD patients with RBD, pramipexole improved parkinsonism but did not modify RBD [83]. The administration of the herbal medication Yi-Gan San at 2.5 g three times a day, alone or in conjunction with 0.25 mg clonazepam, has been reported to be effective in treating RBD [84]. However, there have been no randomized, double-blind, placebo-controlled trials on the treatment for RBD in the PD population.

RBD may be a prodrome of neurodegenerative disorders, including PD, and this notion is a topic of great interest. As a result, the following questions are under investigation: what factors can determine who will develop neurodegenerative disorders? who will remain free of symptoms during life? what neuroprotective strategy is effective for patients who are susceptible to neurodegenerative disorders? and when should this strategy be employed?

**5.2. Restless Legs Syndrome.** Restless legs syndrome (RLS) and PD are considered to share pathophysiological characteristics, given that both neurological disorders exhibit favorable responses to dopaminergic medications; however, RLS usually responds to lower doses than those required for PD. In addition, several studies have demonstrated a higher rate of comorbidity of RLS and PD compared with the prevalence of idiopathic RLS in the general population [3, 85], while other studies have reported no difference in

the prevalence of RLS when comparing PD patients with the general population [86, 87]. However, one should note that daytime dopaminergic medications for PD may unmask subclinical RLS by augmentation, resulting in an increased prevalence of RLS in PD [88]. Patients with PD may not report RLS symptoms unless asked because they regard RLS as a part of the PD symptom complex [89].

In PD patients, nonmotor symptoms related to non-dopaminergic systems, such as cognitive impairments, autonomic dysfunction, depression, and sleepiness, but not motor symptoms were observed to be associated with RLS [90]. Gómez-Esteban et al. [85] reported a high prevalence of RLS (21.9%) in PD patients but determined no difference in disease severity, UPDRS scores, or quality of life between PD groups with or without RLS. Caution must be taken for RLS mimics in PD. Peralta et al. [91] described a positive association between motor fluctuations, the wearing-off phenomenon, and RLS symptoms in PD patients but suggested that off-period restlessness can be an "RLS mimic."

Autopsy studies have revealed increased substantia nigra (SN) iron levels in PD patients [92] and decreased SN iron levels in RLS patients [93]. A recent study by Kwon et al. [94] employing transcranial sonography demonstrated no significant differences in SN echogenicity, which is considered to reflect the quantity of tissue iron, between PD patients with and without RLS, whereas the idiopathic RLS patients demonstrated significant SN hypoechogenicity. This finding suggests that the pathogenesis of PD with RLS and idiopathic RLS may involve different mechanisms.

Caffeine, alcohol, and several medications, including antihistamines, dopamine antagonists, tricyclic antidepressants, and serotoninergic reuptake inhibitors, can exacerbate RLS [95]. Although the pathophysiology of RLS is not fully understood, a central dopaminergic dysfunction has been implicated based on the findings that dopamine agonists relieve patients' symptoms and that decreased dopamine D2 receptor binding is observed in the striata of RLS patients by SPECT [96]. The A11 hypodopaminergic theory, which involves spinal cord positive feedback mechanisms that mediate dopamine, has been proposed using an animal model [97]. Dysfunctions of the A11 dopaminergic diencephalospinal pathways, which innervate the preganglionic sympathetic neurons and dorsal horn of the spinal cord, lead to an increased sympathetic drive that results in the occurrence of RLS [98]. An iron deficiency can also contribute to impairments in dopamine signaling in the brain. Low iron and ferritin levels in the cerebrospinal fluid have been observed in patients with RLS [99, 100]. Iron replacement therapy should be considered when serum levels of ferritin are below 50  $\mu\text{g/L}$ . When taken at bedtime, dopamine agonists such as pramipexole and ropinirole are an effective treatment for RLS.

RLS and PD may share a pathogenesis; however, the pathogenic link between RLS and PD should be investigated further.

**5.3. Sleep Apnea Syndrome.** Previous studies have reported a high incidence of sleep apnea syndrome (SAS) in PD patients

(approximately 20%–60%) compared with age- and sex-matched control patients [21, 101, 102]. In these studies, the body mass index of patients with PD was similar to or even lower than that of control patients, suggesting that upper airway muscle dysfunction caused by nocturnal akinesia or dyskinesia of the respiratory muscle may play a role in the development of obstructive sleep apnea (OSA) in PD [103]. By contrast, a study measuring PSG over three consecutive nights found that the apnea-hypopnea index (AHI) was not different between PD patients and control patients and that the rate of OSA in PD patients was similar to that observed in the general population [104]. Another study reported that sleep apnea, defined as an AHI >5, was less frequent in the PD group compared with an in-hospital control group who exhibited daytime sleepiness (27% versus 40%) and that daytime sleepiness was caused by other, nonapneic, mechanisms [105]. The relationship between OSA and PD requires further investigation.

Nocturnal stridor, a life-threatening event caused by vocal cord abductor dysfunction, has been observed in patients with PD but occurs more frequently in patients with multiple system atrophy [106]. It is important to screen for vocal cord abductor dysfunction using laryngoscopy during sleep. Adequate treatments, including continuous positive airway pressure therapy, noninvasive positive pressure ventilation, or tracheotomy, can prevent sudden death in patients.

**5.4. Circadian Rhythm Sleep Disorders.** In PD, circadian rhythm during sleep, blood pressure, heart rate, and levels of cortisol and melatonin hormones may be altered, possibly due to autonomic dysfunction, changes in sleep structure, and dopaminergic treatments [107–110]. In addition, PD patients with dementia may exhibit sundowning [111]. The suprachiasmatic nucleus (SCN) is the crucial center responsible for generating the circadian rhythm. The SCN is included in the paraventricular zone of the hypothalamus, which is a component of the central autonomic network (CAN) that controls autonomic functions in a state-dependent manner [112]. The SCN seems to be intact in PD patients, but the reported involvement of the hypothalamus and brainstem in PD patients [113, 114] appears to be associated with the CAN.

In animal models of PD, significant decreases in midline estimating statistics of rhythm and phase advances were observed for heart rate, locomotor activity, and core body temperature (CBT) [115]. Pierangeli et al. [116] have demonstrated that a nocturnal fall in CBT was attenuated in multiple system atrophy compared with PD. Similarly, in a small cohort study of progressive supranuclear palsy patients, a decreased circadian amplitude of CBT was observed compared with that of PD patients [117]. In our previous study of 24 nondepressed PD patients and six depressed PD patients, we demonstrated that nondepressed patients exhibited a circadian rhythm of CBT, but two out of six of the depressed patients exhibited an infradian rhythm as a predominant rhythm in CBT. The remaining depressed patients demonstrated a decreased circadian amplitude of CBT compared with that of the nondepressed PD patients [118]. Our results suggest that PD patients with depression

can exhibit circadian rhythm abnormalities compared with PD patients without depression. Further research, including a larger number of PD patients and control subjects, is needed to confirm this finding.

**5.5. Depression.** The reported prevalence of depression in PD patients varies, ranging from 2.7% to 89% [119]. This variation may be due to the population studied or methods employed for diagnosis. Depression is associated with sleep disorders, nocturnal motor symptoms, and poor quality of life [120–123]. Depression is also related to motor fluctuations, such as wearing-off symptoms [124]. In a recent randomized, double-blinded, placebo-controlled trial, pramipexole, which has a higher affinity for D3 than D2 or D4 receptors, significantly improved the depressive symptoms of PD patients, suggesting that this drug is useful for treating depression in addition to the selective serotonin reuptake inhibitors and tricyclic antidepressants often used for treating depression [125]. Hence, identifying and treating depression or depressive symptoms can be beneficial in ameliorating sleep disorders and nocturnal motor dysfunctions in PD patients.

## 6. Conclusion

Sleep disorders can occur in the early stages of PD and worsen as the disease progresses. The worsening of sleep disturbances occurs in a manner similar to the progression of motor dysfunctions, cognitive impairments, and depression, which supports the idea that complex mechanisms and impairments of the arousal system and sleep structure play a role. Sleep disturbances can be underestimated if the patients, their families, and their physicians do not investigate the possibility of impaired sleep.

Active intervention for sleep disturbance is of great importance, as sleep disturbances can significantly impair the quality of life of patients with PD.

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## Research Article

# The On-Freezing Phenomenon: Cognitive and Behavioral Aspects

**Rita Moretti, Paola Torre, Rodolfo M. Antonello, Francesca Esposito, and Giuseppe Bellini**

*Medicina Clinica, Ambulatorio Complicanze Internistiche Cerebrali, Dipartimento Universitario Clinici di Scienze Mediche Tecnologiche e Traslazionali, Università degli Studi di Trieste, Ospedale di Cattinara, Strada Fiume 447, 34149 Trieste, Italy*

Correspondence should be addressed to Rita Moretti, moretti@univ.trieste.it

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Freezing of gait is a warning sign of Parkinson's disease. One could distinguish off-freezing, which is associated with dopaminergic therapy and to its titration, and it is clinically related to wearing-off phenomenon. Differently, the on-freezing phenomenon seems to be related to a neural disruption of the frontal-parietal-basal ganglia-pontine projections; clinically, it does not respond to therapy modifications or to different drug titration. In a group of patients with on-freezing, we have detected an alteration of focusing attention, an impairment of set-shifting, in addition to poor abstract reasoning and a reduction of planning. These aspects have been even more evident, when compared with the results obtained by a group of PD patients, without freezing.

## 1. Introduction

Freezing of gait (FOG) refers to transient episodes, usually lasting seconds, in which a patient is unable to initiate or continue locomotion, especially while turning, in stressful time-constrained situations and upon entrance into and through confined spaces such as doorways occurring on a background of relatively good ability to move [1–3] and is best described by patients as “feet get glued to the ground.” FOG typically appears when a patient is forced to change his normal, automatic gait pattern or speed (at tight quarters, reaching destination) or when responding to stressful situations [4].

Freezing of gait is common in Parkinson's disease (PD), with increasing prevalence as the disease progresses [1, 2, 5–7], but it has been commonly reported in pathologically proven progressive supranuclear palsy (PSP) and vascular parkinsonism [8, 9]. Although not present in all patients, freezing is perhaps the most debilitating symptom of Parkinson's disease as it may lead to falls, a decrease in quality of life, and loss of independence. Nearly one third of Parkinson's disease patients experience some type of freezing episode [1, 10].

To be precise, two types of freezing of gait have been recognized in patients affected by Parkinson's disease, taking L-Dopa. The most common is an “off-”freezing of gait, which can be improved with L-Dopa or dopaminergic treatment,

such as apomorphine [4, 11]. “Off-”freezing appears during an “off” state, when the patient is generally bradykinetic and rigid.

In contrast, “on-”freezing is characterized by a worsening of symptoms as the dose of L-Dopa is increased and by a general improvement as the dose is decreased or, better said, modulated. Patients who experience “on-”FOG frequently report that they walk better before the first morning dose of L-Dopa, or at their “off” state. On-freezing lasts for short times: generally few seconds, at most several minutes. The on-freezing of gait is related to abnormal execution of complex motor tasks such as repetitive, simultaneous, or sequential motor acts [12–14]. Recent evidence has suggested other possible factors that may contribute. In their more recent work, Giladi et al. [15] argue that FOG must have a different pathophysiology than typical motor symptom, since other motor issues are positively influenced by dopaminergic medication, while freezing remains unresponsive.

Different authors suggested that the primary underlying abnormality might be related to the inability to deliver or hold a preprogrammed, continuous, and complex motor act, in response to an established and correct internal plan of action [12, 13]. Increased stride-to-stride variability has recently been identified before FOG (compared with Parkinson's disease patients without FOG) during a 20 m

TABLE 1: (a) Specific scores of the two groups, (b) specific scores of the two groups.

(a)					
	Group A	Group B	Group A	Group B	
	in on		in off		
Freezing when walking (UPDRS II)	2.7 ± 1.2	1.2 ± 0.4	2.9 ± 0.7		3.1 ± 0.3
Walking (UPDRS II)	2.4 ± 0.5	0.9 ± 0.7	2.5 ± 0.2		2.7 ± 0.1
Gait (UPDRS III)	2.5 ± 0.3	1.1 ± 0.9	2.6 ± 0.2		2.9 ± 0.4

(b)					
	Group A	Group B	Group A	Group B	
	in on		in off		
Hohen and Yahr, Goetz et al. [14, 26]	2.5 ± 0.1	2.2 ± 0.7	3.5 ± 1.1		3.9 ± 0.2
(UPDRS II) [27]	18.4 ± 0.5	17.9 ± 5.7	20.5 ± 1.2		23.7 ± 0.1
(UPDRS III) [27]	28.5 ± 1.3	29.1 ± 0.9	34.6 ± 1.5		37.9 ± 1.4

“stand up and go” walking task [16]; in this work, it has been demonstrated that the ability to regulate stride-to-stride timing during gait is severely impaired in FOG patients compared with other individuals with Parkinson's disease [16]. Parkinson's disease patients with FOG also display altered timing and, specifically, premature muscle activation and termination patterns before a freezing episode, leading to an abnormally long stance phase [17–19]. Perception may be the most important alternate mechanisms to consider. While perceptual influences associated with freezing are rarely considered, Parkinson's disease patients are profoundly influenced by awareness of their body (relative to environment) [10, 16, 20, 21] and by space perception [22, 23]. Impaired integration of vision with spatial memory altered recovery might help FOG patients in adapting to confined spaces [24].

Considering that the “on-FOG” is a complex phenomenon, with an obscure pathogenesis and an even obscurer clinical history [4, 25], we hypothesized that PD patients, presenting the on-freezing, might be cognitively well differentiated from the other clinical subtypes of PD, without on-FOG.

Therefore, several patients were chosen, presenting on-freezing as an early manifestation of PD, and their cognitive and behavioral scores on different specific tasks were compared with those obtained by patients with PD, without on-freezing, but manifesting off-freezing. The clinical and neuropsychological followup was done in 12 months.

## 2. Method

**2.1. Subjects.** The study included 73 patients (40 men and 33 women) suffering from idiopathic PD [29]. Three patients did not want to be tested and therefore did not participate to the followup. All the other patients could be fully studied (mean age  $68.4 \pm 7.12$  years, range = 60–78 years; average age at onset =  $63.22 \pm 3.12$  years, range = 62–67 years). The patients suffered for a mean of  $3.56 \pm 2.75$  years from PD and had been treated with dopaminergic preparations (L-Dopa and dopamine-agonists).

All the patients fulfilled the criteria of idiopathic PD [29].

Group A enclosed 38 cases of PD, who presented on-freezing, as referred by caregivers, and confirmed by personal trainers and by their neurologist (three patients of this group refused to complete the study). On-freezing was verified historically and by an actual gait assessment at on and at off (see Table 1(a)). Group B was composed by 35 Parkinson's disease patients, without on-freezing (but with off-freezing).

Patients were evaluated in off- and on-pharmacological states (see Table 1(b)). All the patients responded to L-Dopa. The mean L-Dopa equivalent dosage was  $1215 \pm 321.34$  mg/day. 43 patients received dopamine agonists during their cure; only 27 began their therapy with dopamine-agonists.

All the subjects were right handed ( $+22.34 \pm 1.32$ ) according to the Briggs' and Nebes' handedness test [28]. Their average educational levels, represented by school years, are of  $11.34 \pm 5.67$  years.

Patients were divided into two homogenous groups, matched for age and education levels. Patients have been followed for one year. 33 patients of Group A and 29 patients of Group B completed the followup.

Neuroimaging studies were assessed, including magnetic resonance imaging (in 32 patients, 17 in group A and 15 in group B) and CT scans (in all the patients). Neither signs of normal pressure hydrocephalus, nor ischemic infarctions or lacunar infarcts have been found.

The trial was conducted in accordance with the Declaration of Helsinki and with the Ethics Guidelines of the Institute.

**2.2. Outcome Measures.** The general cognitive profile was tested by this battery of tests: Stroop Test [30], considering as subscores the time of execution and the number of mistakes, Raven Standard Progressive Matrices [31], considering as sub-scores the time of execution and the number of correct answers, Digit span backwards and forwards [32], the oral version of the Trail Making, part A [33] considering as subscores the time of execution and the number of mistakes, word fluency, considering three minutes of phonological task [32], Proverbs' Interpretation Test [34], Ten-Point Clock

TABLE 2: Synopsis of the baseline characteristics of the two groups.

	Group A	Group B
Age	68.31 ± 4.12	65.45 ± 1.23
Average age at onset	63.78 ± 1.56	63.01 ± 1.21
Illness duration	3.12 ± 1.12	3.87 ± 3.5
Mean L-Dopa equivalent dosage	1212 ± 121.34 mg/day	1200 ± 621.45 mg/day
Handedness test [28]	+23.10 ± 1.50	+20.50 ± 2.30
Average educational levels (school years)	11.11 ± 3.45 years	13.11 ± 5.20 years

Test [35], verbal retrieval [36], and Clinical Insight [37]. The patients underwent a Cornell evaluation for depression [38]. In particular, we employed the item: “anxiety” from the Cornell’s scale, with a maximum score of 8, which indicate a maximum degree of anxiety, as an adjunctive informative parametric score, of mood.

All the patients have been tested (as far as neuropsychological measures are concerned) in on-pharmacological state; so far, all the patients should have the most convincing performances; in fact, no off-freezing has been detected. On the contrary, on-freezing, in group A, appears frequently during the test.

**2.3. Statistical Analyses.** Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 13.0). Within-group changes from baseline to 12 months were tested using the Wilcoxon Signed Ranks test, due to the small number of patients enrolled. Between-group comparisons of changes from baseline were tested using the Wilcoxon two-sample test. This was done for the overall scores for each efficacy variable. Spearman’s rho correlation, 2-tailed analyses were performed among digit span (forward and backward), phonological fluency, proverbs’ interpretation and clock execution, and between clinical insight and depression scores. Results are presented as mean changes from baseline with standard deviations, and *P*-values are presented where appropriate.

### 3. Results

A synopsis of the characteristics of the two groups has been reported in Table 2. Table 3 reports the results obtained at baseline by the two groups. Group A manifested transient episodes, usually lasting seconds. During this kind of episode, a patient is unable to initiate a sentence or talk as he did before. At the end of the episode, usually after few seconds, he starts again to talk and to express his opinions, beginning from the point when he was interrupted. We define these episodes as “freezing of thought or freezing of speech.”

According to a Wilcoxon two-sample test, Group A (on-FOG PD) had lower scores than Group B (PD patients) in the digit span forward task ( $P < 0.05$ ); they made more mistakes in the Trail Making test ( $P < 0.01$ ), in Proverbs’ Interpretation task ( $P < 0.01$ ), in the Stroop Test ( $P < 0.01$ )

(execution time and number of mistakes), and in the Ten-Point Clock Test ( $P < 0.01$ ). However, Group A scored higher than Group B in the phonological task ( $P < 0.01$ ). The two groups did equally well in the digit span backward task, in the Trail Making Test (considering time of execution), in the Raven Matrices (time and number of correct answers), and in the memory recall tasks. Group B scored as more depressed than Group A on the Cornell’s Score ( $P < 0.01$ ), but patients from Group B reported greater introspection in their clinical situation ( $P < 0.01$ ) on the Cornell’s Score subitem. There was no difference among the two groups, when considering the anxiety scores (subitem of the Cornell’s Score).

Table 4 reports the results obtained at 12 months by the two groups. Within-group changes from baseline to 12 months were tested using the Wilcoxon Signed Ranks test; between-group comparisons of changes from baseline were tested using the Wilcoxon two-sample test. Group A (on-FOG PD) scored worse, over baseline according to a Wilcoxon Signed Ranks test, in the digit span backward ( $P < 0.05$ ), in Proverbs’ Interpretation Test ( $P < 0.05$ ) and in the Stroop test ( $P < 0.05$ ) (time of execution and number of mistakes). Group B (PD) scored worse over baseline in the digit span backward test ( $P < 0.05$ ) and in the Cornell’s Scale ( $P < 0.01$ ). Group B improved in the Proverbs’ Interpretation Test ( $P < 0.05$ ). Group A scored worse than Group B, according to a Wilcoxon two-sample test, in the digit span forward task ( $P < 0.05$ ) and made more mistakes in the Trail Making test ( $P < 0.01$ ), in Proverbs’ Interpretation task ( $P < 0.01$ ); they scored more poorly in the Stroop Test ( $P < 0.01$ ) (execution time and number of mistakes) and in the Ten-Point Clock Test ( $P < 0.01$ ). Like at baseline, Group A scored better than Group B in the phonological task ( $P < 0.01$ ). Group B reported being more depressed than Group A, as demonstrated by the Cornell’s Score ( $P < 0.01$ ), and continued to show greater introspection in the clinical situation ( $P < 0.01$ ), on the Clinical insight rating Scale (CIR). The anxiety score for Group A was lower than that of group B ( $P < 0.05$ ).

Only Group A patients manifested freezing of thought, freezing of speech, or both.

Spearman’s rank correlation analyses indicated that there was a significant correlation between the digit span scores and the proverbs’ interpretation scores ( $r = 0.78$ ,  $P < 0.01$ ;  $r = 0.81$ ,  $P < 0.01$ , resp.) and between the digit span scores and the Ten-Point Clock Test ( $r = 0.69$ ,  $P < 0.05$ ;  $r = 0.72$ ,  $P < 0.01$ , resp.); no correlation was found between digit span scores and the phonological fluency. A positive correlation between CIR and Cornell’s Scale ( $r = 0.88$ ,  $P < 0.01$ ) was found.

### 4. Discussion

Freezing of gait (FOG), as stated previously, is a complication of PD. Ianssek et al. [39] suggested that FOG during walking was possibly due to the presence of the “sequence effect” (gradual step to step reduction), in combination with an overall reduced step length which, if small enough, would eventually lead to freezing. That hypothesis was based on the duality of basal ganglia function and malfunction in

TABLE 3: A comparison between the two groups, at baseline.

Items	Group A	Group B	<i>P</i>
Phonological fluency	23.12 ± 9.10	12.12 ± 2.11	<i>P</i> < 0.01
Intrusion mistakes	8.90 ± 2.34	2.34 ± 0.12	<i>P</i> < 0.01
Digit span forward	3.34 ± 0.50	4.75 ± 1.12	<i>P</i> < 0.05
Digit span backward	3.20 ± 1.07	3 ± 0.76	ns
Trail making oral; time (sec.)	37.33 ± 6.33	34.65 ± 3.98	ns
Trail making oral; mistakes	7.98 ± 3.4	4.10 ± 0.40	<i>P</i> < 0.01
Freezing of thoughts	1 ± 0.0	0.0	
Freezing of language	1 ± 0.0	0.0	
CIR	3.23 ± 0.43	0.98 ± 0.12	<i>P</i> < 0.01
Proverbs' Interpretation (correct answers)	4.76 ± 2.65	14.23 ± 2.45	<i>P</i> < 0.01
Raven; time (min.)	35.53 ± 4.30	34.12 ± 7.20	ns
Raven; (correct answers)	21.34 ± 4.24	21.5 ± 4.04	ns
Stroop; time (sec.)	57.91 ± 39.56	22.38 ± 10.53	<i>P</i> < 0.01
Stroop; mistakes	5 ± 4.23	1.23 ± 2.25	<i>P</i> < 0.01
Retrieval of a story; (correct answers)	9.38 ± 5.60	10.13 ± 4.64	ns
Ten-Point Clock Test	1.88 ± 1.25	3.5 ± 0.53	<i>P</i> < 0.01
Cornell's Scale	7.75 ± 2.76	12.5 ± 3.59	<i>P</i> < 0.01
Anxiety score	3.2 ± 1.71	2.93 ± 2.78	ns

TABLE 4: A comparison between the two groups, at 12 months.

Items	Group A	Over baseline	Group B	Over baseline	<i>P</i> A versus B
Phonological fluency	- 1.23 ± 0.20	ns	+2.70 ± 0.40	ns	<i>P</i> < 0.01
Intrusion mistakes	+3.45 ± 0.34	<i>P</i> < 0.05	+0.23 ± 0.20	ns	<i>P</i> < 0.01
Digit span forward	- 0.40 ± 0.10	ns	- 0.50 ± 0.10	ns	<i>P</i> < 0.05
Digit span backward	- 1.10 ± 0.20	<i>P</i> < 0.05	- 1.23 ± 0.10	<i>P</i> < 0.05	ns
Trail making oral; time (sec.)	+3.20 ± 1.10	ns	+3.10 ± 1.80	ns	ns
Trail making oral; mistakes	+1.80 ± 0.20	<i>P</i> < 0.05	+0.70 ± 0.20	ns	<i>P</i> < 0.01
Freezing of thoughts	1 ± 0.0		0.0		
Freezing of language	1 ± 0.0		0.0		
CIR	+0.70 ± 0.91	ns	+0.69 ± 0.39	ns	<i>P</i> < 0.01
Proverbs' Interpretation (correct answers)	- 1.30 ± 0.50	<i>P</i> < 0.05	+2.30 ± 0.50	<i>P</i> < 0.05	<i>P</i> < 0.01
Raven; time (min.)	+1.50 ± 0.30	ns	+1.70 ± 0.30	ns	ns
Raven (correct answers)	+1.40 ± 0.24	ns	- 0.50 ± 0.04	ns	ns
Stroop; time (sec.)	+7.20 ± 0.50	<i>P</i> < 0.05	+2.90 ± 4.20	ns	<i>P</i> < 0.01
Stroop; mistakes	+2.10 ± 0.40	<i>P</i> < 0.05	+1.70 ± 0.90	ns	<i>P</i> < 0.01
Retrieval of a story (correct answers)	+1.30 ± 0.20	ns	- 0.98 ± 0.60	ns	ns
Ten-Point Clock Test	- 0.20 ± 0.50	ns	+0.40 ± 0.20	ns	<i>P</i> < 0.01
Cornell's Scale	+1.20 ± 0.60	ns	+4.50 ± 0.90	<i>P</i> < 0.01	<i>P</i> < 0.01
Anxiety score	+0.10 ± 0.21	ns	+1.20 ± 0.12	<i>P</i> < 0.05	<i>P</i> < 0.05

Parkinson's disease in the elaboration of automatic movement in conjunction with the supplementary motor area. It has been suggested (see data and Literature in [40]) that the basal ganglia maintains cortically selected motor set, in the supplementary motor area, and provides internal cues to the supplementary motor area, in order to enable each sub-movement, to be correctly linked together [41]. Iansek et al. [39] examined the sequence effect in FOG subjects and found that, contrary to hypokinesia, the sequence effect did not

respond to medication or attention strategies. It did disappear with the use of external cues in that study; however, no evidence was provided to support the hypothesis that FOG was due to the presence of the sequence effect (gradual step to step reduction) in combination with an overall reduced step length.

FOG leads to difficulties in set shifting [42] while other executive domains, such as working memory, verbal fluency, and planning/organization abilities have weaker

associations [43–47]. Thus, it would appear that the neural network underlying FOG in PD may overlap with the network controlling processes of set shifting [47].

The results obtained in our work can be summarized as follows: two homogenous groups of patients, with Parkinson's disease, followed for three years by a dedicated neurologist, have been compared. There is overall PD duration of 3–4 years since diagnosis. Patients have been tested in on-pharmacological state; in this condition, only Group A manifested on-freezing, Group B did not evidence it. Effectively, Group A (and therefore the matched cases selected for Group B) had high UPDRS and *H* and *Y* scores and L-Dopa equivalent dose over 1000 mg/day, clear hallmarks of advanced stage PD, which does not usually correspond to 3–4 year PD duration. It was not our intention to select a subgroup of patients with a worse form of PD, but in fact, that it is the result: it seems that on-freezing and off-precocious phenomena [46] are selected forms of an intriguing and rather complicated form of PD; the former case is not sensitive to dopamine adjustment; the latter has good response to therapy modulation, almost in precocious time.

Our study demonstrated that the cognitive and behavioral profile of these patients vary from those of patients with Parkinson's disease, who did not suffer from on-freezing of gait. The results indicated that patients with Parkinson's disease and who did present freezing of gait could not focus their attention on a given task, as indicated by the worse scores obtained in the digit span forward task and in the Trail Making test. They could not implement a correct verbal logical judgment (as showed by the low score obtained in the Proverbs' Interpretation task). They showed worse performances in executive function (as demonstrated by the Stroop test and by the Ten-Point Clock test). Contradictorily, our patients with on-freezing produced much more words in the phonological task than patients who suffered from Parkinson's disease without freezing. When examined more closely, their verbal production contained a higher percentage of intrusion words (semantically related to the produced words, most of the time) than that of Parkinson's patients without freezing. Patients with off-freezing are more depressed and with major introspection and insight than patients with on-freezing.

Our results indicate that “induced” verbal fluency is qualitatively compromised in on-freezing patients with Parkinson's disease. Moreover, these patients altered the focusing mechanism of selective attention, of the abstract reasoning, judgment, and of the executive function, as well as they showed a lack of insight in their clinical situation. In our study, we observed that while the patients with the on-freezing phenomenon manifest sudden brisk interruption of thought or of speech, a simple provoked noise (even a question formulated by the investigator) shortens the time of them and accelerates the “rescue” of the cognitive process. These considerations support what has been said about motor blocks in PD. The novel external stimulus, represented by the noise or by the examiner's voice, seems to “oblige” the cortex to process the novel stimulus. The consequential results are the prosecution of the task.

Anatomical localization of the processes underlying attentive control, utilizing functional magnetic resonance imaging in PD patients, has identified that attentive control is related to increased activation of the ventrolateral prefrontal cortex [48]. In addition, works in healthy controls have proposed that the reward feedback mechanisms involved in switching attention relate to regions within the orbitofrontal cortex [49]. On-freezing (motor aspects, of course) has been reported to improve with the applications of external rhythmic stimuli, including metronome stimulation or application of weak electromagnetic fields [50]. Thereby, the use of external attentive strategies may allow movement to be mediated by less automatic and more conscious attentive motor control processes (frontal cortical regions), which may be less impaired than the automatic process (subcortical basal-ganglia-frontal neural pathway) ([39, 51, 52]). Chronic on-line control exerted by the subcortical circuits might be disrupted in on-freezing of gait patients, with an alteration of a presumed “salient map” representation as a consequence. Attention should be elicited with novel external stimuli, in order to implement the cortical parietal circuits: when the cortex actively participates, the patient can reapproach the task and the stop is abolished [53–55]. We hypothesize that the control exerted by the frontal-caudate-pulvinar circuits might be disrupted in on-freezing; this circuit is mainly involved in verifying the semantic acceptability of the linguistic production and in the so-called language planning loop [56, 57]. This hypothesis might explain the intrinsic difficulty showed by on-FOG patients to suppress their “intrusive verbal thoughts” in phonological tasks [58].

To speculate, one might say that on-freezing is not at all a motor variance of Parkinson's disease, but rather a complex, wide-extended, syndrome, that involves gait (as one of the most evident aspects), as well as cognition and behavior.

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## Research Article

# Impact of External Cue Validity on Driving Performance in Parkinson's Disease

**Karen Scally,<sup>1</sup> Judith L. Charlton,<sup>2</sup> Robert Iansek,<sup>3</sup> John L. Bradshaw,<sup>1</sup> Simon Moss,<sup>4</sup> and Nellie Georgiou-Karistianis<sup>1</sup>**

<sup>1</sup> *Experimental Neuropsychology Research Unit, School of Psychology and Psychiatry, Faculty of Medicine, Nursing and Health Sciences, Monash University, Clayton Campus, VIC 3800, Australia*

<sup>2</sup> *Monash Accident Research Centre, Monash University, Clayton Campus, VIC 3800, Australia*

<sup>3</sup> *Clinical Research Centre for Movement Disorders and Gait, Kingston Centre, Warrigal Road, Cheltenham, VIC 3192, Australia*

<sup>4</sup> *School of Psychology, Deakin University, 221 Burwood Highway, Burwood, VIC 3125, Australia*

Correspondence should be addressed to Nellie Georgiou-Karistianis, [nellie.georgiou-karistianis@monash.edu](mailto:nellie.georgiou-karistianis@monash.edu)

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This study sought to investigate the impact of external cue validity on simulated driving performance in 19 Parkinson's disease (PD) patients and 19 healthy age-matched controls. Braking points and distance between deceleration point and braking point were analysed for red traffic signals preceded either by Valid Cues (correctly predicting signal), Invalid Cues (incorrectly predicting signal), and No Cues. Results showed that PD drivers braked significantly later and travelled significantly further between deceleration and braking points compared with controls for Invalid and No-Cue conditions. No significant group differences were observed for driving performance in response to Valid Cues. The benefit of Valid Cues relative to Invalid Cues and No Cues was significantly greater for PD drivers compared with controls. Trail Making Test (B-A) scores correlated with driving performance for PDs only. These results highlight the importance of external cues and higher cognitive functioning for driving performance in mild to moderate PD.

## 1. Introduction

In addition to its cardinal motor signs (bradykinesia, postural instability, resting tremor, cogwheel rigidity), a distinctive profile of cognitive deficits has been well documented in Parkinson's disease (PD) [1–10]. Although primarily dysexecutive in origin, cognitive impairment has been observed across a range of domains including attention, working memory, verbal and visual memory, visuoperception, visuospatial functioning, verbal fluency, planning, and organizational abilities [11–17].

PD has been characterised by a particular deficit in the volitional control or internal cueing of movement, with patients typically demonstrating significantly slower initiation and execution times as well as reduced accuracy of movement compared to age-matched controls [18–22]. This internal cueing deficit is also present on tasks that primarily

demand cognition rather than motor performance, with impairment observed in the ability to use advance information to internally cue responses on Stroop colour naming and cognitive set-shifting tasks [23, 24]. Importantly, research findings have further demonstrated that provision of valid external cues compensates for defective internal initiation and improves performance on both motor and cognitive tasks in PD relative to controls [19, 20, 25–35]. Although invalid cues—providing incorrect information about the task requirements—have been found to prolong response times in neurologically normal subjects, the impact of invalid cues on performance in PD has generated conflicting results: some studies have reported greater performance costs in PD relative to controls [35–39], whereas other studies have found the opposite pattern of results or no group differences [25, 40, 41]. These inconsistent findings may be ascribed to

differences across studies particularly in the timing of the invalid cue relative to the contradictory task demand.

Because of the range of motor and cognitive impairments observed in PD, the potential impact on driving performance has become a topical issue with critical implications for safety [42, 43]. Driving is a time-pressured activity that imposes constant demand on an individual's attentional resources, requiring simultaneous processing of different stimuli, prompt responding to environmental cues, anticipation of potential hazards, and the ability to plan and execute movement in a continually changing environment [44–46].

Investigations of on-road driving ability in PD have consistently reported significantly higher incidence of at-fault safety errors for patients relative to controls [47–54]. The type of errors most commonly reported across studies involved visual scanning and checking behaviours prior to lane changing and pulling out into traffic as well as unspecified difficulties negotiating T-intersections, traffic light intersections, and roundabouts [48, 50, 51]. More recent research has further highlighted particular areas of difficulty during on-road driving performance in PD. Uc et al. [54] found that PD drivers exhibited significant difficulty visually scanning and verbally reporting landmarks and road signs compared with controls. Moreover, in another study, PD drivers committed significantly more incorrect turns and became lost more often than control drivers during a route-finding task [55].

Simulator studies have also documented significant deficits in specific driving skills of PD drivers relative to age-matched controls, including delayed reaction time in response to both traffic signal change [56, 57] as well as simple auditory and visual cues [58]. Similarly, PD drivers demonstrate a reduced ability to stop at red lights [56, 57], poor detection of imminent collisions [59], and have significantly more collisions [60].

Stolwyk et al. [57] further investigated the impact of internal and external cues on simulated driving performance. Results indicated that, consistent with numerous previous findings of dependence on external cues to generate action, drivers with PD relied heavily on late-occurring external cues to initiate driving responses at traffic signals even when they had acquired internal knowledge of the upcoming events. When external cueing was unavailable, driving performance of the control group significantly benefitted from internalised advance information. In contrast, PDs were unable to utilise internal knowledge to improve driving performance in the absence of external cues. The findings of this study indicate that a persistent dependence on the external environment to guide driving behaviours, in addition to well-documented prolonged reaction times, could compromise safe driving in Parkinson's disease, generating important implications for driving assessment outcomes such as the use of licence restrictions to limit driving to a familiar locale.

Given the dependence of PD drivers on external guidance for initiating driving responses, even when anticipatory action is possible and safer, the utilisation of external cues during driving warrants further investigation. Driving occurs in a continually changing environment with many dynamic cues that can change quickly and unpredictably and may

be valid, invalid, or contradictory. For example, a green light, but a pedestrian crossing against signal represents a contradictory cue. Drivers must be able to adapt and change to a new course of action quickly, depending on the environmental demands.

The research on driving in PD to date has primarily utilised driving scenarios with clear and predictable task demands. One study [57] showed that due to impaired internal cueing, PD drivers were overreliant on external pre-warning cues to initiate driving responses, but it remains unknown how PD drivers respond to a variety of dynamic cues that are more representative of the range of task demands in real driving. The purpose of the current study was to investigate driving performance of PD drivers and healthy controls in response to Valid Cues, Invalid Cues, and No Cues. Examining the impact of cue validity on driving performance will give some insight into PD driver's ability to respond to changing task demands. It will also reveal the potential costs and benefits of this overreliance on external cues to guide driving behaviour.

Because the sole driving event utilised was a traffic signal, the driving performance variables of interest were approach speed, braking point, and deceleration-to-brake point distance in response to *red traffic signals* preceded either by No Cue, a Valid Cue (Correct), or an Invalid Cue (Incorrect), which advised participants of the upcoming traffic signal phase (red or green). Only red signal events were analysed, because green lights did not necessitate a braking response. Other driving performance measures such as deceleration point, stopping point, and mean speed were not selected for analysis because of poor sensitivity for this particular experiment.

It was hypothesised that patients would brake significantly later than controls in the Invalid and No Cue conditions. It was further hypothesised that patients' mean braking point would benefit to a greater extent from Valid Cues relative to No Cues, whereas controls would demonstrate less difference between their braking points under Valid and No Cue conditions. It was hypothesized that Invalid Cues would produce later mean braking points relative to the other cue conditions for both groups although specific predictions were not formed about group differences in the response cost of Invalid Cues. Finally, it was predicted that patients would demonstrate greater deceleration to braking point distance across all cueing conditions compared to controls.

## 2. Method

*2.1. Participants.* Nineteen mild to moderately affected individuals with PD voluntarily participated. PD participants consisted of 4 females and 15 males whose age ranged from 52–81 years ( $M = 68.74$ ,  $SD = 6.72$ ). All patients were clinically diagnosed by a neurologist (R.I.) with age at onset ranging from 51 to 77 years ( $M = 62.32$ ,  $SD = 8.19$ ) and disease duration ranging from 1 year to 17 years ( $M = 6.58$ ,  $SD = 4.51$ ). PD motor symptom severity was assessed using the motor subscale of the Unified Parkinson's Disease Rating Scale (UPDRS: scores ranged from 0 to 37,

$M = 15.37$ ,  $SD = 9.86$ ). All PD participants were on an established levodopa medication regime (Madopar, Sinemet or Stalevo) and were tested in the morning when they were optimally medicated. In addition, 5 participants were also on agonist medication (Cabergoline/Dostinex) and another 5 patients were on comt Inhibitors (Tasmar or Comtan). Nineteen matched, neurologically healthy control subjects also participated. Control participants consisted of 6 females and 13 males whose age ranged from 56 to 78 years ( $M = 68.05$ ,  $SD = 7.20$ ). There was no statistical difference in age between the two groups,  $t(36) = .30$ ,  $P > .05$ .

All participants held a valid driver's license and were driving on a regular basis—at least once a week. A brief interview and screening tests were administered to ensure that no participant demonstrated any uncorrected visual or hearing impairment or any history of debilitating physical conditions, drug or alcohol dependence, psychiatric illness, dementia, or head injury. All participants scored 23 or above on the Mini-Mental State Examination (MMSE) [61] and no significant difference was noted between PDs ( $M = 29.21$ ,  $SD = 1.23$ ) and controls ( $M = 29.37$ ,  $SD = 1.12$ ),  $t(36) = -.42$ ,  $P > .05$ . Depressive symptoms were evaluated using the Montgomery and Asberg Depression Rating Scale (MADRS). No significant difference was found in MADRS scores between PDs ( $M = 3.37$ ,  $SD = 3.02$ ) and controls ( $M = 2.58$ ,  $SD = 2.61$ ),  $t(36) = .86$ ,  $P > .05$ . Moreover, there was no significant difference in level of education (years) between patients ( $M = 14.16$ ,  $SD = 3.06$ ) and controls ( $M = 13.63$ ,  $SD = 4.32$ ),  $t(36) = .43$ ,  $P > .05$ . Also, no significant difference was found in the number of years of driving experience between the PD ( $M = 48.74$ ,  $SD = 7.13$ ) and control groups ( $M = 49.11$ ,  $SD = 7.84$ ),  $t(36) = -.15$ ,  $P > .05$ .

No participants reported taking any medication known to impair driving performance, other than the medications used to treat PD symptoms. Table 1 contains a summary of group characteristics and neurocognitive scores. The study was approved by the Monash University Human Ethics Committee, and written informed consent was obtained from all participants.

**2.2. Procedure.** All participants completed testing in one session of approximately 2.5 hours duration at the Monash University Accident Research Centre (MUARC). Screening tasks were then completed (MMSE and MADRS), followed by a written questionnaire regarding demographics and driving history. Prior to commencing the experimental driving scenarios, participants were informed about all aspects of participation including the possibility of experiencing motion sickness, basic mechanics and capabilities of the simulator, breakdown of the testing session, process for communication during testing, and procedures for discontinuation. Participants then completed the baseline Current Well-Being Questionnaire in which they rated the degree of motion sickness symptoms currently present.

Participants first undertook a familiarisation drive for approximately 3 minutes in which the investigator sat in the passenger seat and explained the simulator controls

including steering, acceleration, and braking. A practice drive was then undertaken by participants alone but with two-way communication available between control room and the car. Participants were allowed to practice until they reported that they felt competent and comfortable enough with the simulator controls to proceed to the first experimental task (usually around 5–10 minutes). The experimental driving scenario was split into two drives, each approximately 15 minutes. Participants were granted rest breaks in between these drives to minimise fatigue and simulator discomfort. Participants were also monitored for signs of simulator discomfort during the driving tasks via a camera mounted on the dashboard. If participants displayed any of the signs, such as increased swallowing, licking lips, yawning or sweating, they were advised to stop the driving task immediately.

The experiment consisted of a straight arterial drive with 26 traffic signals in total across the two drives (13 Red; 13 Green). The speed limit was set at 50 km/hr for this experiment to minimise the risk of simulator sickness as a consequence of the frequent stopping in the task. On approach to each traffic signal, participants either encountered no warning cue or one of two Warning Cues informing them about the phase of the upcoming traffic signal: Red or Green. The Warning Cue utilised was a modified version of the "Prepare to Stop" signal used on Australian roads, in which flashing amber lights indicate that the imminent traffic light is about to change from Green to Red. The warning cue was placed 70 metres prior to the traffic signal in accordance with its real world use. However, the sign was altered slightly for this experiment. Instead of amber lights that flashed or did not flash, the sign utilised flashing red lights to indicate a change to Red and flashing green lights to indicate an upcoming Green light. Therefore, the Warning Cue was either *Valid* (congruent with traffic signal) or *Invalid* (incongruent with traffic signal). Intersections were placed approximately 700 metres apart to allow participants time to accelerate up to 50 km/hr before approaching the next intersection. A diagram of the driving event is shown in Figure 1

Participants were advised of the starting speed limit for the drive and instructed to pay attention to their speed, remain within 10 km of the speed limit, and respond as appropriate to traffic signals throughout the drive. At the end of the second drive, participants completed the questionnaire to reassess well-being.

### 2.3. Apparatus

**2.3.1. Driving Simulator Performance.** The MUARC Advanced Driving Simulator consists of a Silicon Graphics Indy (for development and running of driving scenarios), a Silicon Graphics Onyx (for graphics generation, vehicle data inputs and outputs, control of audio system and vehicle dynamics), and a personal computer (for generating sounds). The simulator interface comprises a GM Holden sedan with normal interior appearance and controls; a curved projection screen in front of the vehicle, which provides a 180 degree field of view; a quadratic sound system producing realistic

TABLE 1: Means (and SDs) of demographic and neurocognitive information for PD and control groups.

	PD ( <i>n</i> = 19)		Control ( <i>n</i> = 19)	
Age at testing (yrs)	68.74	(6.72)	68.05	(7.20)
Years since diagnosis	6.74	(4.51)	—	—
Age at disease onset	62.58	(8.19)	—	—
UPDRS motor score	15.37	(9.86)	—	—
Driving experience (yrs)	48.74	(7.13)	49.11	(7.84)
Education (yrs)	14.16	(3.06)	13.63	(4.32)
MMSE score (max 30)	29.21	(1.23)	29.37	(1.12)
MADRS score (max 60)	3.37	(3.02)	2.58	(2.61)
Digit Span (SS: WMS-III)	11.74	(3.38)	12.42	(2.71)
Mental Control (SS: WMS-III)	12.21	(2.88)	13.42	(2.29)
Trails A (time in seconds)	43.05	(20.20)	35.74	(11.56)
Trails B (time in seconds)	106.16	(63.76)	73.63	(24.63)
Trails B-A (time in seconds)	63.11	(50.44)	37.89	(20.26)
Hayling (SS)	4.42	(1.77)	5.21	(1.81)
Brixton (SS)	4.74	(2.13)	5.84	(1.50)

UPDRS: Unified Parkinson's Disease Rating Scale (Max score 108); MMSE: Mini Mental State Exam (Max score 30, cutoff score 23); MADRS: Montgomery and Asberg Depression Rating Scale (Max score 60); Trails B-A: Score derived from subtraction of score for Trails A from Trails B; SS: Scaled score; WMS-III: Wechsler Memory Scale—Third Edition. : Sig Group difference at 0.05 level.

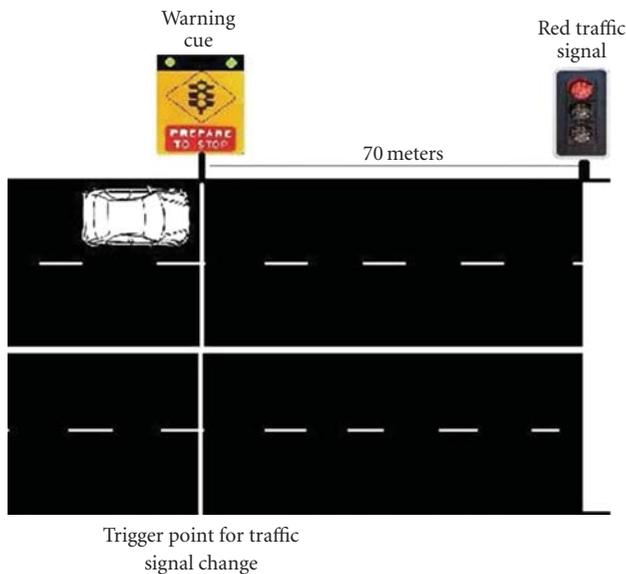


FIGURE 1: Example of the Cueing Driving Event. Warning cue was either Valid (red flashing lights) or Invalid (green flashing lights).

traffic sounds and low-frequency vibrations; and a motion platform underneath the vehicle to simulate the feel of the road and allow up-down movement, and pitch and roll rotations. The MUARC Advanced Driving Simulator has been validated against on-road driving for research on speed-related variables [62].

2.3.2. *Data Analysis.* Group means of the driving performance variables (approach speed, deceleration point, braking point) were calculated for each of the red light signals

across each of the three Cueing conditions (Valid, Invalid, and No Cue). All statistical comparisons were conducted on these group means using various Analysis of Variance (ANOVA) techniques. A series of Pearson's product moment correlations were also performed to examine associations between driving performance measures and scores on clinical indices and screening tasks. One-way MANOVAs were used to compare groups on approach speed and braking point. The relative distance of deceleration point and braking point was compared across groups within each of the cueing conditions using one-way ANCOVAs.

### 3. Results

Means and standard deviations of approach speed, deceleration point, and braking point for each of the cueing conditions are presented in Table 2.

#### 3.1. Differences in Driving Performance across Groups within Cueing Conditions

3.1.1. *Approach Speed.* Mean approach speeds indicate that both patients (Valid  $M$  48.30 SD 4.86; Invalid  $M$  47.85 SD 5.25; No-Cue  $M$  47.19 SD 5.42) and controls (Valid  $M$  48.88 SD 2.69; Invalid  $M$  50.67 SD 3.76; No-Cue  $M$  49.39 SD 2.91) were able to maintain a steady speed across the cueing conditions and remain within the speed limit (50 km/hr) as instructed. No statistically significant difference was found in approach speed between groups for any of the cueing conditions (Valid-Cue,  $(1, 36) = 0.20, P = .66$ ; Invalid-Cue,  $F(1, 36) = 3.64, P = .07$ ; No-Cue,  $F(1, 36) = 2.43, P = .13$ ).

3.1.2. *Braking Points.* Both patients and controls braked within 70 metres of the traffic signal when no cue was

TABLE 2: Red traffic signal means (and SDs) of driving variables for each group across the three cueing conditions.

Driving Variable	Group	Cueing Condition					
		Valid		Invalid		No Cue	
Approach Speed (km/h)	PD	48.30	(4.86)	47.85	(5.25)	47.19	(5.42)
	Control	48.88	(.901)	50.67	(3.76)	49.39	(2.91)
Deceleration Point (m to signal)	PD	117.70	(15.19)	119.79	(18.96)	101.76	(22.84)
	Control	119.20	(24.41)	113.92	(34.09)	107.54	(30.76)
Brake Point (m to signal)	PD	62.56	(18.21)	50.64	(18.99)	41.65	(9.64)
	Control	72.52	(33.89)	74.56	(39.10)	61.66	(35.37)
Decel to Brake Pt Distance (m) (se)	PD	62.10	(5.64)	51.36	(7.00)	40.30	(5.28)
	Control	72.98	(5.64)	73.85	(7.00)	63.02	(5.28)

present. For the Valid Cue condition, in which the cue correctly predicted a red signal, the difference in braking points between patients ( $M = 62.56$ ,  $SD = 18.21$ ) and controls ( $M = 72.52$ ,  $SD = 33.89$ ) was not statistically significant,  $F(1,36) = 1.86$ ,  $P = .181$ . However, for the Invalid Cue condition, in which the cue incorrectly predicted a green signal, patients with PD ( $M = 50.64$ ,  $SD = 18.99$ ) braked significantly later than did controls ( $M = 74.56$ ,  $SD = 39.10$ ),  $F(1,36) = 6.95$ ,  $P = .012$ . Likewise, in the No-Cue condition, patients with PD ( $M = 41.65$ ,  $SD = 9.64$ ) also braked significantly later than did controls ( $M = 61.66$ ,  $SD = 35.37$ ),  $F(1,36) = 12.81$ ,  $P = .001$ .

### 3.2. Effect of Cues on Braking Performance for Each Group.

For each group, the effect of cueing condition on braking points was examined. Analyses for the control group found no significant main effect of cue type on braking point (Valid  $M = 72.52$ ,  $SD = 33.89$ ; Invalid  $M = 74.56$ ,  $SD = 39.10$ ; No Cue  $M = 61.66$ ,  $SD = 35.37$ ). Conversely, analyses for the PD group did find a significant main effect of cue type on braking point,  $F(2) = 12.56$ ,  $P = .00$ . The results of post hoc tests showed a significant difference between patients' braking points under Valid ( $M = 62.56$ ,  $SD = 18.21$ ) and No Cue ( $M = 41.65$ ,  $SD = 9.64$ ) conditions ( $M_{diff} = -20.91$ ,  $S.E. = 3.66$ ,  $P = .00$ ). Moreover, a significant difference was also found between patients' braking points for Valid ( $M = 62.56$ ,  $SD = 18.21$ ) and Invalid ( $M = 50.64$ ,  $SD = 18.99$ ) cue conditions ( $M_{diff} = 11.92$ ,  $S.E. = 3.90$ ,  $P = .02$ ). However, the mean difference between patients' braking points under Invalid Cue and No Cue conditions ( $M_{diff} = -8.99$ ,  $S.E. = 4.89$ ) was not statistically significant ( $P = .23$ ).

### 3.3. Relative Distance between Deceleration Point and Braking Point.

The relative points at which deceleration and braking occurred were compared between the groups for each of the cueing conditions. Separate ANCOVAs were conducted for each condition, with braking points designated as the dependent variables and corresponding deceleration point designated as the covariates. Under Valid Cue conditions, mean braking point for patients ( $M = 62.56$ ,  $SD = 18.21$ ) occurred on average 55.14 meters after their first deceleration point ( $M = 117.70$ ,  $SD = 15.19$ ), whereas braking point for controls ( $M = 119.20$ ,  $SD = 24.41$ ) occurred on average 46.68 meters after their first deceleration point ( $M = 72.52$ ,

$SD = 33.89$ ). The distance between deceleration and braking points for Valid Cue conditions did not differ significantly between patients and controls,  $F(1,36) = 1.859$ ,  $P = .18$ .

Under Invalid Cue conditions, patients' mean braking point ( $M = 50.64$ ,  $SD = 18.99$ ) occurred 69.15 meters after their initial deceleration point ( $M = 119.79$ ,  $SD = 18.96$ ), whereas controls' mean braking point ( $M = 74.56$ ,  $SD = 39.10$ ) occurred just 39.36 meters after their first deceleration point ( $M = 113.92$ ,  $SD = 34.09$ ). Statistical analysis revealed that the distance between deceleration and braking points for Invalid Cue conditions was significantly greater in patients than in the controls,  $F(1,36) = 5.134$ ,  $P = .03$ .

Finally, for No-Cue conditions, braking point in the patient group ( $M = 41.65$ ,  $SD = 9.64$ ) occurred 60.11 meters after initial deceleration point ( $M = 101.76$ ,  $SD = 22.84$ ). In contrast, braking point for the control group ( $M = 61.66$ ,  $SD = 35.37$ ) was 45.88 meters after their initial deceleration point ( $M = 107.54$ ,  $SD = 30.76$ ). The difference between deceleration and braking points under No-Cue conditions was significantly greater in the PDs compared to the controls,  $F(1,36) = 9.21$ ,  $P = .005$ .

### 3.4. Correlations between Driving Performance and Cognitive and Clinical Indices.

Correlations between driving variables and neurocognitive measures for the patient and control groups are presented in Table 3.

The screening tasks and neurocognitive measures that were found to differ between groups were correlated with the driving performance variables, namely, braking point and deceleration-to-brake point distance for each cueing condition. Results of correlations for the PD group will be discussed first. UPDRS motor scores and MADRS scores did not significantly correlate with any of the driving performance variables under any of the Cueing conditions in the PD group. However, it was found that patients who scored better on the MMSE tended to brake later in the absence of external cues ( $r = -.50$ ,  $P < .05$ ). Scores on part A of the Trail Making Test (TMT-A), a measure of psychomotor speed involving focused attention, visual scanning, and motor planning, were positively correlated with earlier braking point during invalid cue conditions ( $r = .60$ ,  $P < .01$ ) for the PD group: slower psychomotor speed was therefore associated with earlier braking in response to invalid cues. Likewise, completion time on part B of the Trail Making Test

TABLE 3: Correlations between driving performance variables and Trail Making Test scores (part B and B-A).

Driving performance measures	Trails B		Trails B-A	
	PD	Control	PD	Control
Valid Cues Braking Point (m)	.288	.581	.197	.379
Invalid Cues Braking Point (m)	.606	.592	.524	.435
No Cues Braking Point (m)	-.152	.373	-.163	.211
Valid Cues Deceleration to Brake Point Distance (m)	-.092	-.541	-.014	-.357
Invalid Cues Deceleration to Brake Point Distance (m)	-.399	-.432	-.337	-.281
No Cues Deceleration to Brake Point Distance (m)	.414	-.215	.351	-.071

Sig 0.05. Sig 0.01.

(TMT-B), which imposes the same psychomotor demands as TMT-A with an additional working memory and set-switching component, also showed a significant positive correlation with invalidly cued braking point ( $r = .61$ ,  $P < .01$ ). This indicates that poorer psychomotor speed and set-shifting ability was associated with earlier braking under invalid cue conditions. Moreover, TMT (B-A), which reflects the attention, and set-switching component of TMT-B, independent of psychomotor speed, showed a positive correlation with invalidly cued braking point ( $r = .52$ ,  $P < .05$ ), indicating that with the contribution of psychomotor speed removed, poorer attention and set-switching was associated with earlier braking in response to invalid cues.

In the control group, scores on the MADRS and MMSE did not correlate with any driving performance measures. However, TMT-A performance was positively correlated with braking point under valid ( $r = .58$ ,  $P < .05$ ) and invalid ( $r = .50$ ,  $P < .05$ ) cue conditions and was negatively correlated with deceleration to brake point distance for valid cues ( $r = -.54$ ,  $P < .05$ ). This indicates that slower psychomotor speed was associated with earlier braking under valid and invalid cue conditions and shorter distance travelled between deceleration and braking points in response to valid cues. Similarly, TMT-B was also positively correlated with braking point for valid cues ( $r = .58$ ,  $P < .01$ ) and invalid cues ( $r = .59$ ,  $P < .01$ ) and negatively correlated with deceleration to brake point distance under valid cue conditions ( $r = -.54$ ,  $P < .05$ ). Together these indicate that slower psychomotor speed and attention switching abilities were related to earlier braking points under valid and invalid cue conditions and shorter distance travelled between deceleration and brake point when validly cued. However, with the psychomotor speed component removed, TMT (B-A) failed to correlate with any driving performance variables in the control group.

#### 4. Discussion

This study sought to further investigate cue utilization by examining the impact of cue validity on simulated driving performance in PD. External cue validity was manipulated to examine how PD drivers adjust to different and changing environmental cue demands, reflecting the dynamic nature of the real driving environment. Approach speed, braking point, and deceleration-to-brake point distance were evaluated in response to three Cueing conditions throughout the simulated drive: Valid Cueing, Invalid Cueing, and No Cueing. We also explored correlations between the driving performance measures found to be significantly different between groups and scores on neurocognitive measures. It was first hypothesised that patients would brake significantly later than controls for both the Invalid and No Cue conditions. Consistent with this prediction, patients were found to brake significantly later than controls under Invalid and No-Cue conditions, yet braked comparably to controls under Valid Cue conditions. This pattern of findings reinforces the purported benefits of valid external cues on motor and cognitive performance in PD [19, 20, 24–29, 31–35, 63].

Importantly, under both Cueing conditions, the warning Cue was placed 70 metres prior to the traffic light, consistent with VicRoads regulations for the State of Victoria, Australia. Moreover, traffic signal change was triggered by driver presence at the 70 meter mark across all conditions, at which point the light then changed from green, to amber followed by red over a two-second timeframe. Thus, any braking points occurring before the 70 meter mark could not have been informed by traffic signal change, although the traffic light itself was minimally visible through a fog screen from approximately 200 meters and easily visible within 100 meters. Accordingly, although control participants initiated braking a few meters prior to passing the Cue

under both Valid and Invalid Cueing conditions, patients braked eight meters beyond the Cue during Valid conditions and 20 meters beyond the Cue during Invalid conditions. This observation implies that, although controls' braking responses reflected anticipatory action in response to the warning Cue, patients' braking responses showed delayed initiation, occurring after both the warning Cue and the onset of traffic signal change. Nevertheless, the finding that PD patients braked earlier under Valid Cue conditions compared to Invalid Cue conditions, and in Cued conditions compared to No-Cue conditions, indicates that the presence of cues and, particularly Valid Cues, improved driving performance perhaps by triggering preparatory motor action and thereby facilitating earlier braking responses. This supposition accords with previous research, showing that control drivers were able to internally generate deceleration and braking responses prior to the display of external cues, whereas PD drivers were dependent on the appearance of late occurring external cues to initiate driving responses [57].

Our second hypothesis predicted a greater facilitatory effect of Valid Cues relative to No Cues on mean braking point for patients compared with controls. Consistent with this prediction, patients benefitted to a significantly greater extent (20.91 m gain in brake point) than controls (10.86 m gain) from the provision of Valid Cues relative to noncued conditions. This finding is also consistent with results from peripheral cueing tasks that report greater effects of Valid cueing for patients compared with controls [41].

We further hypothesised that Invalid Cues would elicit significantly later braking points for PDs and Controls relative to braking points under Valid and No-Cue conditions. While patients' braking points showed a significant advantage in response to Valid Cues relative to Invalid Cues, controls were found to brake similarly during Valid and Invalid Cueing conditions. This result contrasts to findings of studies using central cueing paradigms that reported similar effects of Valid Cueing relative to Invalid Cueing on task performance of patients and age-matched controls [41] and may simply reflect the relatively low demands of the driving task which did not sufficiently challenge the control participants. Interestingly, results further indicated that, compared with the No Cue condition, Invalid Cues did not incur any significant response cost to braking point for either group. Indeed compared to the No Cue condition, braking points were similarly facilitated by the presence of Invalid Cues with an 8.99 meter advantage noted for patients and 12.9 meter advantage found for controls. This benefit contradicts typical findings from cueing studies utilizing various experimental paradigms and likely reflects the limitations of driving simulator studies to sufficiently replicate the cognitive demands and experimental control of discrete psychophysical tasks within a simulated drive that alone presents a challenging trade-off between maximizing ecological validity, participant well-being and experimental control. Alternatively, the mere presence of the flashing light may have a high level of salience for driving safety, and therefore even the invalid cues may have augmented arousal, facilitating performance on this functional task.

Our final hypothesis concerned deceleration to brake point distance which is measured in meters but essentially reflects the time elapsed between the initial point of deceleration on approach to the warning sign and the affirmative action of applying the brake pedal. We predicted that deceleration to brake point distance would be significantly greater for patients relative to controls across all cueing conditions. Consistent with the results for braking point, but against expectations, no significant difference was observed between the groups in deceleration-to-brake point distance for Valid Cues. In contrast, and in line with our predictions, deceleration-to-brake point distance was significantly greater for patients compared with controls under both Invalid Cue and No Cue conditions. This measure essentially reflects a combination of decision and movement time between the point drivers initially began to decelerate on approach to the warning sign and the point they actually applied the brake, although unfortunately this measure cannot be parsed into the separate component processes.

Nevertheless, although the time course of approach to the intersection at the outset, as represented by approach speed and deceleration point, was similar in patients and controls, as the event drew closer, driving performance in these groups began to diverge, except when Valid Cues were provided. This pattern of observations is consistent with previous findings of significantly delayed reaction time on various tasks in PD, particularly under circumstances of increased complexity: a delay that is successfully ameliorated by Valid Cues. Determining the extent to which decision time and reaction time contribute to driving performance output measures will have important implications for clinical estimation of driver safety particularly with regard to hazard perception and time-to-collision judgments. Theoretically, given the evidence of impairments in visuo-perceptual and visuospatial processes, attention and executive functions, delayed responses are likely to reflect inefficiencies in cognitive information processing that informs responses, in addition to slowness in initiating the motor response itself. Indeed, performances on both Trails A and Trails B were significantly positively correlated with invalidly cued braking point in both patients and controls, such that slower psychomotor speed and set-shifting abilities corresponded with earlier braking point in both groups. Moreover, driving performance remained significantly positively correlated with TMT (B-A), a measure of cognitive set switching with the psychomotor speed component removed, in patients only, further highlighting the pertinence of information processing. Surprisingly, higher scores on the MMSE were significantly negatively correlated with braking point under noncued conditions in the patient group only indicating that superior cognitive ability was associated with later braking in the absence of external cues. Collectively, these findings suggest that perhaps those with poorer cognitive functioning and/or cognitive inflexibility adopt a more cautious driving style as a compensatory mechanism.

The significant correlations between driving performance and scores on the Trail Making Test are consistent with those of previous PD driving studies [48, 54, 55, 64, 65] although such studies rarely report significant correlations

with the MMSE and typically implicate several independent areas of cognition, visual, and/or motor function as potential contributors to impaired driving ability in PD. Such functions include but are not limited to contrast sensitivity [47, 66, 67], information processing speed [49, 67], visuospatial and planning abilities [47, 48, 65], attention [54, 55], motor dexterity [48, 50], and both visual and verbal memory [49, 50, 55]. The general lack of consensus in the literature as to the particular functions likely to impact on driving ability in PD may reflect differences in the driving measures used for correlation and in the size and disease characteristics of the samples utilized across studies. It may also be indicative of an inherent difficulty in identifying independent predictors of impaired functioning on a multifactorial task within a heterogeneous clinical population. Nevertheless, in contrast to previous studies, with one notable exception [59], the current sample of PD drivers performed comparatively to controls on all cognitive tasks except for the Trail-Making Test perhaps highlighting the importance of higher cognitive information processing and set-shifting abilities for driving performance in the mild to moderate stages of PD. While the Trail Making Test seems to have a unique value in correlating with driving performance measures, further research with larger samples and perhaps clinical subtypes of PD is required to determine whether this test is a suitable screening tool for fitness to drive. Moreover, such a study would need to go beyond correlational analyses and be designed specifically for predictive analyses in order to address issues of sensitivity and specificity.

There are many advantages to using a driving simulator, including increased safety, greater experimental control, and reduced costs; however, it should be borne in mind that simulated driving performance does not fully equate to on-road driving performance. In addition, a relatively small sample size was utilised in this study. Future research should employ larger sample sizes with greater variation on disease indices to explore the effects of PD heterogeneity and associated cognitive function on driving performance. The current results are particularly noteworthy given the largely comparable cognitive functioning of the two groups and despite the relatively low demands of the simulated driving task which utilized a conservative speed limit (50 km/hr), straight road, simple visual environment and use of a single driving event that differed only in terms of the cue and response requirement. Hence, contrary to the general consensus in the PD literature that cognitive and motor difficulties are most likely to arise in complex and cognitively demanding situations; it has been shown that patients may experience difficulties with driving even at low speeds in which rapid reaction times are not as crucial. Overall, the present results indicate that patients drive significantly worse than healthy age-matched controls under both noncued and invalidly cued conditions and that driving performance is significantly improved with provision of valid warning cues. It is anticipated that these and future results will assist in developing compensatory strategies and thereby improving driver safety for individuals with PD.

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## Review Article

# The Role of Cognitive-Behavioural Therapy for Patients with Depression in Parkinson's Disease

Andreas Charidimou,<sup>1</sup> John Seamons,<sup>1</sup> Caroline Selai,<sup>1</sup> and Anette Schrag<sup>2</sup>

<sup>1</sup>*Institute of Neurology, The National Hospital for Neurology and Neurosurgery, University College London (UCL), Queen Square, London WC1N 3BG, UK*

<sup>2</sup>*Department of Clinical Neurosciences, Institute of Neurology, University College London, Royal Free Campus, London NW3 2PF, UK*

Correspondence should be addressed to Anette Schrag, a.schrag@medsch.ucl.ac.uk

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Depression is a common complication of Parkinson's disease (PD) with considerable impact on patients' quality of life. However, at present the most appropriate treatment approach is unclear. There are limited data on antidepressant medications in PD-associated depression (dPD) and those available suggest limited efficacy and tolerability of these drugs. Cognitive behavioural therapy (CBT) has been shown to be an effective treatment of depressive disorders. Treatment of dPD with CBT may pose particular challenges, including possible different pathophysiology, physical and mental comorbidities, and barriers to treatment through disability, which do not allow simple transfer of these results to patients with dPD. However, a number of case reports, case series, and small pilot studies suggest that this is a promising treatment for patients with PD. We here summarise the published evidence on this treatment in dPD.

## 1. Introduction

Although Parkinson's disease (PD) is diagnosed on the basis of the classic features of motor disturbance [1, 2], it is now widely recognised that nonmotor symptoms are common, and occur across all stages of the disease [3]. Depressive disorders affect approximately 40% of patients with PD [4–7]. They are linked to functional impairment, cognitive decline, and faster disease progression and are the main determinant for poor quality of life in PD [8–12]. They are also associated with increased health care costs in the population, raising both direct and indirect costs [13, 14].

Despite this established negative impact, depressive symptoms in PD are underrecognised and undertreated in clinical practice [15]. Additionally, there is a lack of well-designed studies that can guide clinical management of these patients. So far, only a few double-blind, placebo-controlled trials have specifically assessed antidepressant use for PD patients [16, 17], and even fewer research data exist on

nonpharmacological approaches for PD-associated depression [18, 19]. As a result, evidence-based recommendations and consensus on the best treatment choice for this patient population are scarce [20].

The previous pharmacological studies have shown that medication traditionally used for depression in older people (e.g., SSRIs) may not be more effective than placebo in PD, or may be difficult to utilise in this age group due to the aggravation of orthostatic hypotension, constipation, and cognitive impairment (e.g., tricyclic antidepressants) [21–23]. In addition, depressive symptoms in PD often do not fulfil the criteria for major depression, and it may therefore not be appropriate to treat such cases with medication.

Cognitive behaviour therapy (CBT) is well established for the treatment of depression, and there is considerable evidence from depression without PD that CBT in this patient group is effective. This has recently been shown to include older patients [24]. However, it is recognised that dPD may differ from depression without PD, both

in terms of aetiology and patient characteristics. Patients with PD are typically older, have physical impairment and subtle cognitive deficits, and therefore delivery, feasibility, and outcome of CBT may be different in patients with PD.

In this paper we consider the role of cognitive-behavioural therapy (CBT) as a potential approach for patients with PD and associated depression, based on a systematic review of published studies in the area.

## 2. Methods: Scope of This Review, Search Strategy, and Selection Criteria

We included all types of studies of CBT for depressive symptoms in PD patients (including single case studies, case series, and pilot studies of any duration), and systematically reviewed the evidence for effectiveness of CBT in dPD.

References for this review were identified by searching PubMed for the last 40 years using the search terms “Parkinson's disease” or “Parkinsonism” or “Parkinsonian” and “Depression” or “affective disorders” or “mood disorders”; these results were cross-referenced with the search terms “CBT” or “cognitive therapy” or “psychotherapy”. In addition, the following databases were searched using the same strategy: MEDLINE (1950 to November 2010), EMBASE (1980 to November 2010), EMBASE Classic (1947 to 1979), PsychINFO (1806 to November 2010), PsycEXTRA (1908 to November 2010), PsycBOOKS (1806 to November 2010), Web of Science (January 1981 to November 2010), and AMED (January 1985 to November 2010). All abstracts were read, and the articles found were further screened and selected as follows: only articles in the English language were selected, and only those articles reporting data on adults using cognitive or cognitive behavioural therapy for dPD. We also searched the Cochrane Library for systematic reviews. The reference lists of the selected articles with the above strategy were checked for additional materials when appropriate. Hand searching of neurologic, psychiatric, and related literature was also performed. Moreover, online resources were searched systematically, including Medscape, NICE clinical guidelines, Department of Health publications, and registers of upcoming trials.

All the selected studies were assessed for their methodological quality. Key areas of evaluation included the accuracy/robustness of the diagnoses of depressive symptoms and idiopathic PD, the outcome measures used and their validity in PD and PD depression (with a special attention on the rating scales for evaluating changes in depression severity), the accurate description of the intervention used, and quantification of cognitive impairment and other comorbidities.

## 3. Results

We screened 1579 article abstracts in total; the search yielded a number of review articles and 15 studies of CBT for depression in PD patients. Of these, 2 were single case studies, and the rest were cases series and pilot studies, which are depicted in Table 1 and presented and discussed in the rest of this review.

*3.1. Pilot Studies and Case Series.* Dreisig et al. [25] reported a pilot study to explore the effects of CBT in 9 patients with PD compared to 70 matched control subjects who received treatment as usual. The 3-month CBT program included self-help and individual sessions. After this period, based on the Psychological Profile Questionnaire (including depression scores), the group receiving CBT showed significantly more improvement ( $P < .01$ ) compared to the control group. However, this study was not aimed specifically at depression in PD. Overall, the percentage of moderate or major depression amongst PD patients was low (10%), and no PD patients in the CBT group had major depression. Methodological problems also include lack of randomisation, small sample size, and choice of instrument (not a validated depression scale). The study was also limited to young PD patients, which were self-referred, which could have led to selection bias. It is also important to note that the content of CBT was not described in detail making evaluation difficult. Nevertheless, the study by Dreisig et al. provided data in a small series of patients in a naturalistic setting with some control data and suggests that CBT might be effective for patients with PD.

Dobkin et al. explored the feasibility of using CBT to treat depression in an open study in 15 PD patients [26]. All patients had major depression based on DSM-IV and no evidence of dementia, psychosis, or significant motor fluctuations. The content and delivery of treatment was developed via a previous case series [35]. Patients received 10–14 sessions of personalized CBT incorporating relaxation techniques and sleep hygiene education. Treatment delivery was modified to aid memory retention, and caregivers attended separate educational sessions. The Hamilton Rating Scale for Depression (HAM-D) and the Beck Depression Inventory (BDI) were used as the primary outcome measures, while negative thoughts (Inference Questionnaire; IQ), anxiety (State Trait Anxiety Inventory; STAI), and perception of social support (Adaptive Inferential Feedback Questionnaire, AIFQ) were evaluated as secondary outcome measures. Of the 13 patients who completed the study, 80% experienced significant reductions in depressive symptoms (HAM-D; BDI,  $P < .0001$ ). A significant decrease was also noted in negative inferences (IQ,  $P < .001$ ), while the perception of social support was increased significantly (AIFQ,  $P < .001$ ). Despite the methodological limitations of this study (lack of control group, small sample size, and no formal assessment of the contribution of caregivers), the detailed study design, inclusion of qualitative methods, involvement of caregivers, exclusion of patients with motor fluctuations and the delivery of treatment by a trained CBT therapist, provide good preliminary evidence as to the feasibility and potential effectiveness of this treatment modality for dPD.

Another uncontrolled study of CBT in targeting depression within the context of PD was recently reported recently by Farabaugh et al. [27]. Eight depressed patients were enrolled into an open study of 12-week individually tailored CBT treatment. The authors reported a significant linear decrease in mean Hamilton Rating Scale for Depression (HAM-D) scores over the treatment period. At the study

TABLE 1: Summary of studies reviewed focusing on CBT for patients with PD and depression.

Study	Sample size	Intervention	Delivery	Outcome measures
Dreisig et al. [25]	79 PD; 9 CBT; 70 control	Self-help & tailored CBT	Author (trained)	Psychological Profile Questionnaire, SDS
Dobkin et al. [26]	15 PD; 15 caregivers	Tailored CBT & caregiver program	Clinical psychologist	HAM-D, BDI, IQ, STAI, AIFQ
Farabaugh et al. [27]	8 PD	Individual CBT treatment	Author (trained)	HAM-D
Veazey et al. [28]	10 PD; randomized into CBT group or support group (control)	Telephone-administered CBT	Author (trained)	MMSE, PHQ-9, BAI, PDQ-39, SCID
Leroi and King [29]	8 PD	Individual CBT treatment	Consultant clinical psychologist	GAS, unreported scales
Simons et al. [30]	22 PD; 14 Caregiver	Educational program with CBT elements	Not reported	SDS, PDQ39, participant evaluation
A'Campo et al. [31]	64 PD; 46 Caregiver	Educational program with CBT elements	Not reported	Dutch version of PDQ-39 and EQ-5D, SDS, VAS
Macht et al. [32]	151 PD	Educational program with CBT elements	Author (trained)	Patients' ratings of the comprehensibility and feasibility of the programme as well as mood ratings before and after each session
Cole and Vaughan [33]	5 PD	CBT	Author (trained)	BDI-II, GDS15, PDQL
Feeney et al. [34]	4 PD	CBT	Not reported	BDI-II
Dobkin et al. [35]	3 PD; 3 caregivers	Tailored CBT & caregiver program	Not reported	HAM-D, BDI, IQ, STAI, AIFQ
Macht et al. [36]	3 PD	Tailored CBT	Author (trained)	Clinician's Assessment
Fitzpatrick et al. [37]	12 PD	MBCT	Author	Not formal outcome measures; Interpretative phenomenological analysis
Gupta and Bhatia [38]	1 PD	CBT	Author (trained)	Clinician's Assessment
Laidlaw et al. [39]	1 PD	CBT	Author (trained)	Clinician's Assessment

Studies with a control group.

AIFQ: Adaptive Inferential Feedback Questionnaire; BDI: Beck Depression Inventory; CBT: Cognitive Behavioural Therapy; CES-D: Centre for Epidemiologic Studies Depression Scale; GAS: Global Assessment Scale; GDS: Geriatric Depression Scale; HAM-D: Hamilton Rating Scale for Depression; HRQL: Health Related Quality of Life; IQ: Inference Questionnaire; MBCT: mindfulness-based cognitive therapy; MMSE: Mini-mental State Examination; PD: Parkinson's Disease; PDQL: Parkinson's Disease Quality of Life Questionnaire; PDQ39: Parkinson's Disease Questionnaire 39; PHQ-9: Patient Health Questionnaire-9; SCID: Structured Clinical Interview for DSM-IV; SDS: Zung Self-Rating Depression Scale; STAI: Spielberger State-Trait Anxiety Inventory; VAS: Visual Analogue Scale.

endpoint more than half of the patients (57%) met the criteria for complete remission. With the same limitations as the above studies, this pilot study also adds to the suggestion that CBT may be beneficial in this population of patients and may be an alternative or adjunct to pharmacological treatment strategies.

Veazey et al. [28] reported a controlled study of telephone-administered CBT for PD patients with depression and anxiety. At baseline, the ten patients who took part were assessed using MMSE, Patient Health Questionnaire-9 (PHQ-9), Beck Anxiety Inventory (BAI), Parkinson's Disease Questionnaire-39 (PDQ-39), and the Structured Clinical Interview for DSM-IV (SCID). Based on BAI and PHQ-9, half of the patients had anxiety and depression, 4 (40%) had only anxiety and 1 had only depression. Study participants

were randomized into either a CBT group or a support group (control). The CBT groups received 1 in-person CBT session, followed by 8 weekly telephone-delivered CBT sessions. Sessions covered depression and anxiety education, relaxation training, cognitive therapy, problem solving, activity scheduling, and sleep-management skills. The support group received 8 weekly phone calls from a therapist, during which the therapist followed a script including questions about the patient's general wellbeing; psychotherapy elements were not included. Whilst this was a pilot study on the feasibility of CBT with descriptive data, there was an improvement in depression (based on changes in PHQ-9 scores) for both groups following treatment and at 1-month followup. The CBT group was more improved, but with a small difference, compared to the support group. Similarly, anxiety

improved for both groups, with a greater improvement in the CBT group. The study is the first to use remote-delivered CBT for PD patients and to use a control group with a nonspecific “talking therapy”. Delivering CBT by telephone allows participants more flexibility in scheduling and keeping weekly appointments than in-person meetings. However, this approach also poses a number of problems; in particular, it may be more difficult to keep patients motivated and active, to ensure that patients complete homework and understand treatment sessions. Thus, it may be preferable to test the efficacy of CBT for PD-associated depression using standard therapy protocols (i.e., face-to-face) before using modified approaches with potential confounders.

In an abstract, Leroi and King [29] reported an uncontrolled pilot study to evaluate the feasibility of modified CBT for PD patients with depression and/or anxiety based on DSM-IV and Geriatric Depression Scale (GDS). The study included 5 patients with idiopathic PD, two of whom had major depressive disorder, one nonmajor depression, and two mixed anxiety and depression at study start. CBT (6–10 sessions) was delivered by a consultant clinical psychologist and relevant changes in depression/anxiety were measured using the Global Attainment Scale (GAS) and other unreported scales. Depression and anxiety scores improved in all participants, with 100% reaching subthreshold levels for clinical significance. The mean GAS score reflected moderate to marked improvement on pretreatment self-selected outcome goals, while the therapy was found to be well-tolerated and feasible. Conclusions from this study are difficult to draw as there were only overall 5 patients, no control group and the validity of the GAS in this patient group has not been tested. In addition, the authors reported modifications to the standard CBT protocol, but these were not detailed in the abstract.

Simons and colleagues [30] reported an eight-session group educational program, called the EduPark, that was developed to promote coping strategies and address common psychosocial problems in PD patients and caregivers. EduPark covers many of the skills included in standard CBT [36] and was evaluated in a pilot study of 36 participants. Patients completed a self-rating depression scale (SDS) before and after the program [40]. EduPark yielded short-term improvements in visual analogue ratings of mood and was favorably evaluated by participants. However, no significant effects on quality of life or depression as assessed on the SDS were found in patients or caregivers [30]. Studies from other participating countries reported similar findings in overall 151 patients with improvement of psychosocial functioning and mood assessment on a visual analogue scale but not on the SDS [32]. The limitations of this study, in addition to the lack of control group, include uncertainty whether any of the enrolled patients had a formal diagnosis of depression at baseline. In addition, although educational programs are of great importance, by definition they are more disperse and less intensive than individually tailored CBT. Achievement of significant changes in depression may require a more intensive and/or longer period of treatment.

The two uncontrolled studies conducted during the development of EduPark [30, 32] were more tailored to

evaluate its feasibility rather than its effectiveness. A'Campo et al. recently described a RCT which evaluated the effectiveness of this educational programme in PD patients and their caregivers from The Netherlands [31]. Sixty-four PD patients and 46 caregivers participated and were allocated to either the intervention group (receiving eight weekly, 90-minute duration sessions) or the control group (receiving usual care). The primary outcomes measure of this trial were psychosocial burden, depression and QoL of both patients and caregivers and depression (using the SDS). Participants in both groups were also asked to rate their present mood before and after each individual session on a 100-point visual analogue scale (VAS). No significant effects on the primary outcome measures of the patients were found after the completion of the programme. A marginally significant trend of improvement was only observed in the PDQ-39, favouring the intervention group ( $P = .015$ ). However, based on the VAS, patients' mood was found to be significantly improved from before to after sessions ( $P < .001$ ). Moreover, concerning the caregivers, psychosocial problems and need for help of the intervention group were significantly improved compared to the control group. The improvements on mood as highlighted by the VAS indicate that the patients in the intervention group felt better after the session. However, this scale represents an oversimplification of mood measuring and there was no comparison to a control group. Despite the randomised controlled nature of this trial, the methodological weaknesses of this trial include the fact that the participants had no or only minimal depressive symptoms, which were assessed by a relatively insensitive instrument (SDS). Moreover, the authors do not report how the diagnosis of the depressive disorders was made in this patient population (apart from the depression rating scale score) and how PD was diagnosed.

Cole and Vaughan [33] reported a case series where brief home-based CBT was used to treat depression in the context of PD. Five patients aged 54–82 years were referred for treatment from a movement disorders clinic following a diagnosis of possible depression (based on Geriatric Depression Scale-GDS). Three out of 5 patients had Beck Depression Inventory (BDI) scores indicating major depression, and none of them had dementia. CBT was protocol driven and based on a self-help booklet. One 60-minute CBT session per week was allocated for each section of the booklet, over 7 weeks. Following treatment, there were reductions in depression scores. However, these were marginal in the patients with less severe depression and changes in depression scores were not accompanied by changes in QoL. Lack of meaningful improvement in two patients was felt to be at least partly related to intervening illness and personal factors. This study is one of the few which reported how PD was diagnosed (UK Parkinson's Disease Society Brain Bank). However, diagnosis of depressive disorder was not made based on DSM-IV criteria. It is possible that the small patient number and the short baseline durations hamper the sensitivity of detecting an effectiveness of CBT. However, the results may indicate that less severe depression may be less responsive to this intervention.

The effects of group CBT for depression and anxiety in PD were also assessed in a small case series of 4 patients aged 56–81 years [34]. Participants were not cognitively impaired (based on Mini-mental Mental State Examination-MMSE), three of them had major depression [41], while one had a dysthymic disorder based on the Mini-International Neuropsychiatric Interview (MINI) [42]. Minor adaptations to the delivery of CBT were made, such as a reduction on the amount of writing to account for motor difficulties. Treatment resulted in a clinically significant improvement in depression in 3 out of 4 patients according to the BDI. This case series is documenting the feasibility of CBT for patients with PD and depression with maintenance of gains at the 1-month followup. Again, the small sample size, the lack of control, and exclusion criteria make the applicability of these findings to other patients with PD-associated depression uncertain. One other disadvantage of this particular study is that it does not report who delivered CBT, or whether a CBT protocol was used; therefore, the content of treatment is uncertain. One patient in this study had been diagnosed with PD 12 years ago, compared with 1–3 years for the rest of the participants, and this patient did not show improvement. At present it is unclear whether more advanced PD is a predictor of nonresponse to CBT.

Dobkin et al. [35] reported a case series of 3 patients with PD meeting the DSM-IV criteria for major depression (and with no evidence of dementia or psychosis). The primary outcome measure used was Hamilton Rating Scale for Depression (Ham-D). Patients received 12–14 sessions of individually tailored CBT. After identifying stressors that appeared to contribute to depressed mood, short and long-term plans were developed to minimize stress and maximize QoL by emphasizing behavioural activation and problem-solving strategies around physical limitations. All patients were experiencing sleep difficulties, so sleep hygiene techniques were incorporated. In parallel, relaxation techniques, such as diaphragmatic breathing, were also incorporated to address anxiety and somatic complaints. Treatment delivery was modified when necessary to aid memory retention. Patients and caregivers evaluated positively the overall treatment program. All patients achieved 50% reduction in depression based on HAM-D and BDI, maintained at 1-month follow-up. HAM-D and BDI endpoints for two patients indicated only mild depression, and all participants demonstrated decreased negative cognitions based on IQ and BDI. The authors later reported the results of a large pilot study based on these results (see above).

Another case series of 3 self-referred PD patients treated with CBT were reported by Macht and colleagues [36]. The patients differed in age, disease duration, disease severity, and disability, whilst none showed signs of cognitive impairment. CBT was tailored to each patient via formulation, and adjunctive techniques were used, such as strategies to cope with motor fluctuations. Notably, only one patient was reported to have depressive symptoms, although their pre/posttreatment severity was not reported. The authors reported that all patients improved in their ability to cope with their disease following CBT, but this effect was not quantified. The limited information provided in this study

regarding the CBT intervention, the patient group and aim of the study (improving coping with PD), combined with the small sample size make it difficult draw conclusions regarding the effect of CBT of dPD in this population.

An exploratory study was recently reported by Fitzpatrick and colleagues which analysed the experiences of 12 PD patients after an 8-week course of mindfulness-based cognitive therapy (MBCT) [37]. This type of psychological therapy combines elements of both cognitive therapy and mindfulness technique originating from Eastern spiritual and philosophical tradition. Mindfulness prioritizes learning how to pay attention on purpose, in the present moment and without judgement. In this framework MBCT is built around accepting thoughts and feelings in a nonjudgemental way with the aim of correcting cognitive distortions (rather than trying to suppress and avoid them) [43]. The authors of this study made it clear that they did not intend to assess the effectiveness of MBCT using formal outcome measures, but to gather preliminary evidence of its acceptance and perceived helpfulness from patients with PD [37]. Interpretative phenomenological analysis was the qualitative approach chosen for the analysis of emerging themes in this study (summarised from author's transcripts, compared against all cases, and also analysed by a second author). The analysis of both pre- and postcourse interviews, yielded 4 major themes including changing patterns of coping, the role of this intervention in consolidating already existing coping skills in the context of loss, the importance of group support effects and the dualism of experience between PD and mindful meditation. The results of this study should be evaluated under the framework of its original purposes, design, and methodology. Overall, it demonstrated the acceptability of MBCT in a group of patients with PD (based on the positive/supportive informal feedback from the participants and the well attendance of subsequent "catchup" groups). Moreover, this study analysed in depth what were the key factors making this course successful. Unfortunately, there is little information of the depressive symptomatology of the participants. Nine patients were found to have clinical levels of distress in one or more of the subscales of depression, anxiety, and stress evaluated by the Depression Anxiety and Stress Scales (DASS). This is the first study of MBCT in the context of PD suggesting this intervention may be useful in future intervention studies, and the emerging themes of this intervention can also help understand and enhance patterns of coping with PD.

*3.2. Case Studies.* Gupta and Bhatia [38] treated a 90-year-old PD patient with depression and suicidal ideation using home-based CBT. The focus of CBT was in reinforcing the patient's positive interactions with his daughter (the caregiver) and increasing his participation in enjoyable activities. CBT indeed decreased the patient's depressive symptoms, improved interactions with his caregiver, and increased activity levels. Laidlaw et al. [39] reported the effect of CBT in a patient with anxiety, depression, and insomnia following his diagnosis with PD. The patient had marked resting tremor in his right hand, reduced pleasurable activities and he had stopped going out unaccompanied.

Antidepressant medication had little effect; in contrast CBT reduced depression, anxiety, and insomnia, but the largest gains were in activity levels. The authors emphasise the importance of making interventions addressing the specific difficulties of the patients. For example, the patient in this paper became embarrassed and his mood dropped when his tremor prevented him from performing motor tasks. By the end of treatment, the patient was more willing to confront embarrassing situations and use CBT techniques to challenge negative thought patterns [39].

#### 4. Discussion

We identified and described 15 studies on the application of CBT in depressed PD patients. The majority of the studies reported functionally important improvements using this treatment strategy to target depressive symptoms in patients with PD, some with large effect sizes. Whilst these data are encouraging, at present there are no large randomised control trials (RCTs) in this area and the largest study included overall 15 patients (excluding the studies using education programmes rather than CBT *ipse*) [26]. Due to the small patient sample sizes, the results from these pilot studies and case series may overstate the effect of this intervention. Conclusions from these trials therefore have to be cautious, particularly given the large placebo effects known to exist in both depression and PD. Interpretation of the above studies should also take into account the following considerations.

The evaluation of CBT studies poses particular challenges. CBT is not a single, standard form of therapy, but, whilst including a core CBT strategy, incorporates a collection of different psychotherapeutic approaches and components. This makes it difficult to compare different studies, as they may have used different CBT approaches. In addition, many published studies do not provide adequate details of the CBT intervention complicating comparison further. For example, the intervention may not have contained the same noncore aspects of CBT; and treatment outcomes may be attributable to adjunctive techniques such as exercise or relaxation. However, despite this variation, all studies focusing on the application of CBT incorporate the same core elements. CBT is defined as a form of therapy that focuses on the relationship between thoughts, feelings, and behaviours. As such, even with many variations in its application from person to person, CBT is distinct and very distinguishable from other psychotherapeutic approaches (e.g., interpersonal, psychodynamic, etc.). In this context, the aspects and elements of CBT that are most beneficial are likely to vary for each individual patient.

Thus, treatment is typically tailored to patients. In clinical practice, CBT often uses protocols which have been developed for specific disorders (e.g., depression, anxiety, etc.). However, the first stage of CBT is patient assessment and the development of a formulation—a working model of the patient's problems. How the patient is treated, and the selection of therapeutic interventions, depends upon this formulation. Formulation allows CBT theory to be applied to unique individuals with distinct patterns of thoughts and

emotions. In this manner, CBT may be based on a protocol, but it is tailored to each patient. As new information emerges during treatment the formulation continues to evolve. The formulation informs the selection of specific cognitive, behavioural, and physical interventions. Whilst this introduces a certain variability, this is also one of the advantages of CBT. Other advantages of CBT include its structured, time-limited, and goal-oriented approach, the lack of medication side effects and long-term effects even after the treatment has been completed [44, 45].

Further methodological considerations in evaluation of the available data include the variation in reporting PD diagnosis and few studies used the UK Parkinson's Disease Society Brain Bank or other standardized criteria. In addition, current studies are likely to have been included in highly motivated, cognitively relatively intact and less disabled patients. However, it is currently unclear whether and to what extent severity of PD or other disease variables such as mild cognitive impairment influence the feasibility or effectiveness of this intervention, and whether this treatment approach is suitable across disease stages. Several studies report excluding patients with diagnoses of dementia, but do not report levels of cognitive impairment [26, 33, 35]. It is possible that subtle cognitive impairments could affect treatment outcomes. However, the exclusion of cognitively impaired patients also limits the applicability of studies to PD populations, where rates of cognitive impairment are high. A further important consideration is the inclusion of motor fluctuations. Only one study excluded patients with motor fluctuations [26]. "Off" periods are associated with acute episodes of depression and anxiety and could therefore confound treatment outcomes [46]. If not excluded, patients with motor fluctuations should be assessed during "on" periods [47].

Whilst diagnosis of depression in PD patients was generally made based on standard criteria (with their limitations for use in PD) rather than rating scales, severity varied and a wide range of depression rating scales were used as outcome measures in the different studies. Given the significant symptom overlap between depression, parkinsonism, and apathy in these patients, it is currently unclear which scale is the best choice in a trial of CBT in dPD [47]. However, given that CBT is unlikely to influence underlying parkinsonism, this treatment is less likely than some medications to improve depression rating scale scores through improvement of nondepression features of PD. At present it is also unclear whether CBT may be useful for major depression or depressive disorders not fulfilling these criteria.

#### 5. Conclusions

In summary, whilst additional data from large RCTs are needed to establish the efficacy of CBT in the management of depression in patients with PD, the available evidence, even with the above limitations, is encouraging for the effectiveness of CBT as an option in this patient population. In addition to establishing feasibility and efficacy of CBT in dPD in large RCTs, there are a number of questions remaining to be unanswered in future studies, including to

what extent the results of these studies can be translated and applied to the PD patients with cognitive impairment, whether this type of treatment is feasible in patients with motor and nonmotor complications, how to best assess outcome, patients of what severity of depression should be included and whether CBT needs to be modified for patients with PD. If shown to be effective in large RCTs, CBT could potentially provide a better possible nonpharmacologic treating option for clinicians for the treatment of depression in PD, either when pharmacotherapy fails, in combination or as an alternative to pharmacological treatment of dPD.

## Conflict of Interests

The authors declare that there is no conflict of interests.

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A. Charidimou and J. Seamons are joint first authors, and they have contributed equally to this paper.

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## Review Article

# Imaging Impulsivity in Parkinson's Disease and the Contribution of the Subthalamic Nucleus

Nicola Ray,<sup>1,2</sup> Francesca Antonelli,<sup>1,2</sup> and Antonio P. Strafella<sup>1,2</sup>

<sup>1</sup> Toronto Western Research Institute and Hospital, UHN, University of Toronto, Toronto, ON, Canada M5T 2S8

<sup>2</sup> PET Imaging Centre, Centre for Addiction and Mental Health, University of Toronto, Toronto, ON, Canada M5T 2S8

Correspondence should be addressed to Antonio P. Strafella, astrafel@uhnres.utoronto.ca

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Taking risks is a natural human response, but, in some, risk taking is compulsive and may be detrimental. The subthalamic nucleus (STN) is thought to play a large role in our ability to inhibit responses. Differences between individuals' ability to inhibit inappropriate responses may underlie both the normal variation in trait impulsivity in the healthy population, as well as the pathological compulsions experienced by those with impulse control disorders (ICDs). Thus, we review the role of the STN in response inhibition, with a particular focus on studies employing imaging methodology. We also review the latest evidence that disruption of the function of the STN by deep brain stimulation in patients with Parkinson's disease can increase impulsivity.

## 1. Introduction

Some of us are more impulsive than others, more likely to take risks and suffer the consequences or reap the rewards. Taking risks is a natural human response; we would not be flying through the skies and sailing across oceans without it. However, in some, risk taking is compulsive and damaging. Risk taking that is detrimental may take the form of, for example, pathological gambling, where sufferers are unable to withhold from placing bets even after losses have become unmanageable. Other examples include hyper-sexuality, compulsive eating, and compulsive shopping, all of which can be described as impulse control disorders (ICDs). ICDs have been likened phenomenologically, epidemiologically, and neurologically with substance addiction, and may therefore be thought of as behavioral addictions [1].

In individuals with substance or behavioral addictions, impulsiveness is a common personality trait and may be associated with a vulnerability for addiction [2]. This vulnerability will likely have roots in individuals' socioeconomic background, and be heavily influenced by behaviors prevalent within one's family and peer group. By cause or consequence, vulnerability to addiction is also associated with particular patterns of brain chemistry, most notably in the dopaminergic systems of the basal ganglia [3]. However,

these chemical differences may not be pathological, but only normal deviation. For example, in individuals without addiction, the same chemical differences are associated with the impulsive personality trait [4]. Thus, when such chemistry is combined with a lifestyle in which addictive stimuli are present and often available, addiction is more likely to ensue.

It may not be possible to "treat" vulnerability for addiction if it is based in the normal variation of brain transmitter systems. Instead, how those vulnerabilities affect how a person is able to control one's responses may be targeted. Response inhibition, and deficits thereof, is a subject of increased debate in the neuroscientific community. In particular, how the frontal cortex and basal ganglia, most notably the subthalamic nucleus (STN), act to allow the fast and effective inhibition of inappropriate responses is an area of research currently revealing some interesting findings.

The STN is one node within multiple, segregated cortico-basal ganglia-thalamo-cortical circuits subserving motor, cognitive, and affective functions. Dorsal and lateral regions of the STN connect with sensorimotor areas of the basal ganglia and thalamus, premotor, and motor cortical areas. On the other hand, ventro-medial STN regions communicate with higher-order cortical regions subserving response inhibition, such as the anterior cingulate cortex (ACC) and inferior frontal gyrus (IFG) [5–7].

In this paper, we provide an overview of the current knowledge of how the STN is involved in response inhibition, and therefore how disruption to its function, for example, during deep brain stimulation in Parkinson's patients, might contribute to pathologically impulsive behaviors.

## 2. Imaging of the STN during Impulsivity Tasks

Impulsivity in the motor domain can be measured via the stop-signal paradigm [8] and the go/no-go paradigm, in which a "stop" response is pitted against a "go" response. In a typical experiment, choice reaction times to an imperative go-stimulus are measured and are followed on a proportion of trials, after a variable delay (or no delay in the go/no-go tasks), by a stop-stimulus instructing participants to withhold their response. Individuals with behavioral and chemical addictions have been found to perform poorly on tasks such as these [9–11]. Thus, as mentioned above, impulsive behavior may be rooted in impaired response inhibition.

In healthy controls response inhibition, as measured in stop-signal and go/no-go tasks, is found to be dependent on activity in the right inferior frontal cortex (IFC) [12–14], and, more recently, the subthalamic nucleus [12, 15, 16]. It has been proposed that, during stopping, the right IFC sends a signal via the "hyperdirect" pathway [17] to the right STN. The STN then expedites the inhibition of activity in thalamocortical loops related to the action to be inhibited [12]. In the later paper, the authors found support for this hypothesis in that there was a blood oxygen level-dependent (BOLD) response in the STN to stop-signals. Further, participants with faster reaction times to the stop-signals showed larger responses than those with shorter reaction times in both the IFC and the STN, and there was a significant correlation between stop-signal reaction times and BOLD responses in these areas across subjects. Importantly, these authors confirmed that activity during the stop-signals was located in the STN using high-resolution structural and functional imaging in a second experiment within the same paper [12].

Alternatively, Li et al. [16], also measuring BOLD responses using fMRI during a stop-signal task in healthy participants, separated stop-trials in which inhibition was successful from those in which the participant was unable to withhold from performing the go-response. It was found that STN activity is the greatest during unsuccessful compared with successful inhibition. It was also greatest in those individuals who took longer to respond, or rather, not respond, to a stop-signal. These findings suggest that the role of the STN in response inhibition may be to process attentional aspects of the stop-signal and/or monitor performance, and not to act as a pathway for faster inhibition of the go-response. Supporting an attentional role, lesions of the STN produce attentional deficits in rats [18]. That said, activity in the STN, recorded in PD patients after deep brain stimulation surgery, during stopping in a go/no-task [19], has been shown to increase within frequency bands known to be associated with a lack of movement in the negative symptoms of PD [20–23].

Clearly, whatever the STNs' role in response inhibition, it must work in tandem with cortical and other brain areas in order that the conditions of stopping can be incorporated into the stop response. For example, Aron et al. [15] used diffusion-weighted imaging (DWI) tractography to show that the IFC and the STN region are connected. They were also able to report that both the inferior frontal cortex (IFC) and the STN region are connected with the presupplementary motor area (preSMA). The authors then found, using functional magnetic resonance imaging (fMRI) during a conditional stop-signal paradigm to study the neural control of slowing of go-responses in the presence of conflict, that the preSMA, IFC, and STN region were activated more when conflict-induced slowing was the greatest. Further, as discussed in more detail below, the anterior cingulate and its communication with the STN has been implicated in processes related to response inhibition.

## 3. Imaging and Behavioral Studies on DBS of the STN during Measures of Response Inhibition

Deep brain stimulation of the STN improves the motor symptoms of Parkinson's disease. It has also allowed us to, theoretically, interrupt function of the STN for experimental means. In the next section, we discuss how DBS of the STN might increase impulsiveness in PD patients; here, we discuss how this impulsiveness might be brought about via interrupted response inhibition.

A prominent paper on the effects of STN DBS on impulsivity compared decision making under conflict after DBS and after dopamine replacement therapy in PD patients [24]. It was found that each of these interventions had their own effect on impulsiveness during the task. While medication was shown to impair learning from negative outcomes, DBS was shown to impair patients' ability to slow down when faced with conflict, an ability that serves to allow us time to settle on the decision most likely to yield positive outcomes. Thus, both STN DBS and medication may incur impulsive behavior, but do so via different routes.

It must be noted, however, that measuring response inhibition while patients receive DBS has yielded conflicting results. Response inhibition is shown to improve, remain unaffected, or worsen during DBS [25–30]. Such results may be due to a marginal role played by the STN in response inhibition. However, Ray et al. [31], Wylie et al. [32], and Hershey et al. [33] provide possible explanations for these discrepancies. Ray et al. describe deficits in inhibitory control only when improvements on the task due to improved motor control more generally are controlled for. Wylie et al. describe dissociable temporal effects of STN DBS in that stimulation increased impulsive responding, but also improved the proficiency with which inhibitory control was engaged. Finally, Hershey et al. discovered differences in the effect of STN DBS on inhibitory control depending on whether the ventral or dorsal STN is stimulated.

That said, imaging the brain during response inhibition tasks has revealed interesting results. For example,

Cambell et al. [29] used PET and [(15)O]-water to measure STN DBS-induced variability in cognitive performance, focusing on working memory and response inhibition. They found that STN DBS-induced blood flow changes in the dorsolateral prefrontal cortex, that correlated with a change in working memory performance. On the other hand, STN DBS caused blood flow changes in the anterior cingulate cortex, that correlated with a change in response inhibition. This suggests that stimulation of the STN may induce changes in the cortical (ACC) control of response inhibition, and the more it does so in individual patients, the greater the impairment in response inhibitions.

A later PET and [(15)O]-water measured blood flow during a Go/NoGo and a control (Go) task to study response inhibition deficits associated with STN-DBS [30]. They found that STN DBS improved motor scores on the Unified Parkinson Disease Rating Scale, but impaired response inhibition, measured as a greater number of errors during NoGo trials. The PET results revealed that changes on the task were accompanied by reduced activation in the left PMC, pre-SMA, dorsal ACC, and IFC, areas thought to subserve retroactive response inhibition in which a stimulus to stop must be processed and acted upon in order that inhibition is successful. The authors also found reduced activation in the precuneus and left inferior parietal cortex, which they argue play an important role, via interaction with the medial prefrontal cortex, in proactive (preparing to stop) inhibitory processes.

Given the data above, it seems that the STN plays a large role in response inhibition via its connections within the basal ganglia as well as areas of cortex involved in the cognitive aspects of controlling actions, such as the ACC, IFC, the medial prefrontal cortex, and dorsolateral prefrontal cortex. Thus, it is interesting to note that altered activity in some of these areas is found to be associated with the development ICDs in both the general population [34] and in PD patients who develop an ICD subsequent to dopamine replacement medications [35].

#### **4. Does DBS of the STN Induce Impulsive Control Disorders?**

Given the research discussed above, the question of whether DBS of the STN can alter patients' tendency to be impulsive one way or the other must be asked. Up to now, several conflicting reports have stressed a direct correlation between STN-DBS and impulse control disorders (ICDs). In some reports, patients with preoperative ICDs significantly improved after surgery [36–38]. However, in all cases, the phenomena was accompanied by a significant reduction of dopaminergic therapy. It was argued, therefore, that this improvement may be explained by pharmacological therapy reduction rather than the introduction of STN DBS [37]. In other reports, however, the development of an ICD was reported to occur secondary to STN-DBS [38–43]. In these cases, the disorder appeared a few months after surgery and was transient, resolving within a year of its development [42, 43]. Some authors suggest that psychosocial factors, such

as male gender and patient compliance, might influence the potential for the development of an ICD after STN DBS [38].

A behavior closely related to ICDs is the development of excessive or inappropriate levodopa use, or drug hoarding, described as a symptom of hedonistic homeostatic deregulation by Giovannoni et al. [44]. This condition has been described postoperatively in one patient treated with STN DBS [44]; however, most of the time this behavior develops preoperatively [43, 45].

More recently, a few prospective, but more frequently retrospective, trials were conducted in order to better understand the incidence and prevalence of ICDs in DBS STN patients and to confirm a possible direct role of STN surgery in inducing impulsive behaviors. However, to date, a scarcity of data precludes our ability to make any firm conclusions regarding the causal role of STN DBS in the development of ICDs. That said, a recent cross-sectional study assessed the degree of trait impulsivity in a group of 16 PD patients with STN DBS and a group of 37 PD patients without DBS, matched for levodopa equivalent doses (LEDD). The evaluation, performed only postoperatively, observed ICDs in 19% of DBS PD patients (3/16) and in 8% (3/37) of the non-DBS PD patients. The authors concluded that STN DBS might induce ICDs in PD. However, such inferences are limited without a preoperative evaluation [46]. Lim et al. [38], following a series of 21 patients with ICDs and dopamine dysregulation syndrome (DDS) at some stage after the onset of PD, found, from 17 patients with preoperative problems, 10 who experienced a worsening or no improvement of their ICDs after STN DBS, 5 who improved or resolved and 3 who developed ex novo DDS and ICDs after the surgery. Further, the authors noted that the behavioral response to STN DBS might be predicted by the vigilance of the physician, the motor outcome and patient compliance. Finally, in a recent study on punding (the appearance of repetitive, complex, and stereotypical behaviors), using a patient and relative completed survey of 24 consecutive PD patients with STN DBS [47], 20.8% (5/24 in a group of PD DBS) were identified as punders, a higher percentage than the 14% (17/123 in a group of PD) previously found by Evans in a subgroup of PD on dopaminergic therapy, or 1.4% (4/291 in a group of PD) recently identified by Miyasaki in the same group. The higher ratio might be due to differences in the population studied.

While the studies above seem to suggest more impulsive behavior after STN DBS, Houeto et al., in a retrospective study on 24 patients, using a rating scale of personality change, found no differences in impulsivity pre- versus postoperatively in STN DBS PD patients [43].

As discussed above, many studies have attempted to test some of the underlying constructs of impulsive disorders, that is, using tasks that measuring motor and cognitive impulsivity. The majority of these studies have shown impairment while STN stimulation is on versus off [25, 27, 47–50]. However, Pillon et al. [50] found no differences on a gambling task in patients with STN DBS turned on versus off.

In conclusion, although these studies suggest overall that impulsive disorders may be related to STN DBS, we would like to stress the need for larger, prospective, controlled

trials to better understand the role of DBS in inducing ICDs. Recently, it has been proposed that impulsive patients might be at greater risk for postoperative suicide attempts [51]; however so far, there is no evidence supporting the presence of preoperative ICDs as a criterion of exclusion for surgery [51]. Neither do we have much inclination how to manage impulsive disorders that may appear postoperatively. In the case of ICDs occurring preoperatively, Voon et al. [52] have suggested that the relationship between ICDs and medication should be assessed before proceeding with surgery. If the problem persists, surgery should only be an option after an evaluation of the patients' cognitive status, their support, the intensity of the disorder and the patients' capacity for behavioral control. In the case of postoperative ICDs, Voon suggests medication reduction should be tried before considering a decrease in the intensity of the stimulation. Finally, she suggests that patients may benefit from the addition of an atypical antipsychotic to their regular medication, and from a multidisciplinary approach to managing the problem.

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## Research Article

# Visual Symptoms in Parkinson's Disease

**R. A. Armstrong**

*Department of Vision Sciences, Aston University, Birmingham B4 7ET, UK*

Correspondence should be addressed to R. A. Armstrong, r.a.armstrong@aston.ac.uk

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Parkinson's disease (PD) is a common disorder of middle-aged and elderly people in which degeneration of the extrapyramidal motor system causes significant movement problems. In some patients, however, there are additional disturbances in sensory systems including loss of the sense of smell and auditory and/or visual problems. This paper is a general overview of the visual problems likely to be encountered in PD. Changes in vision in PD may result from alterations in visual acuity, contrast sensitivity, colour discrimination, pupil reactivity, eye movements, motion perception, visual field sensitivity, and visual processing speeds. Slower visual processing speeds can also lead to a decline in visual perception especially for rapidly changing visual stimuli. In addition, there may be disturbances of visuospatial orientation, facial recognition problems, and chronic visual hallucinations. Some of the treatments used in PD may also have adverse ocular reactions. The pattern electroretinogram (PERG) is useful in evaluating retinal dopamine mechanisms and in monitoring dopamine therapies in PD. If visual problems are present, they can have an important effect on the quality of life of the patient, which can be improved by accurate diagnosis and where possible, correction of such defects.

## 1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder affecting middle aged and elderly people. It is a disease characterised by deficiency of dopamine in areas of the midbrain causing a variety of movement problems such as akinesia, rigidity, and tremor. Despite the emphasis on motor function in PD, nonmotor symptoms may also play a significant role in determining the general quality of life of the patient. Hence, the symptoms of PD can include depression, apathy, sleep problems, cognitive impairment, dementia, and autonomic, gastrointestinal, and sensory problems [1]. Sensory problems may include visual loss, loss of smell, auditory problems, and "restless legs" syndrome (RLS). Visual signs and symptoms of PD may include defects in eye movement, pupillary function, and in more complex visual tasks involving the ability to judge distance or the shape of an object [2, 3]. The symptoms of PD can be treated successfully using drug therapy or surgery, and these treatments may also have visual side effects. Hence, this paper provides a general overview of (1) the visual signs and symptoms of PD, (2) the areas of the eye and brain which may be affected by

the pathology of PD, and (3) the adverse ocular reactions to treatment.

## 2. Visual Symptoms in Parkinson's Disease

PD is associated with a variety of visual problems and these are summarised in Table 1.

*2.1. Visual Acuity.* PD patients often complain of poor vision especially as the disease progresses resulting, in part, from poor visual acuity [4], low contrast acuity being especially affected [5, 6]. Impaired visual acuity also appears to be a risk factor for the development of chronic hallucinations in PD [7]. Poor visual acuity may be caused by lack of dopamine in the retina, abnormal eye movements, or poor blinking and is only marginally improved by drug therapy [6].

*2.2. Colour Vision.* Vision has been reported to be blurred in PD to coloured stimuli [8] with reduced colour fusion times [9] which indicate the accuracy of perception of monochromatic contours. A progressive deterioration of colour

TABLE 1: Visual signs and symptoms of Parkinson's disease (PD).

Ocular aspect	Change in PD	References
Visual acuity	Poor, especially at low contrast	[6]
		[4]
Colour vision	Vision blurred for coloured stimuli	[8]
	Shortened colour fusion time	[9]
	Progressive deterioration	[10]
Visual fields	Increase in glaucomatous visual field defects	[13]
	Side effects of surgery	[14]
	Reaction time and max. velocity of horizontal gaze slower	[15]
Saccadic eye movement	Hypometria	[16]
	Amplitude increased after cued saccades	[17]
	Affected early in disease process	[20]
Smooth pursuit movement	Superimposed saccades	[15]
	Reduction in response magnitude	[15]
Optokinetic Nystagmus	Abnormal in some patients	[15]
Convergence	Impaired, associated with large exophoria, diplopia	[21]
		[22]
Blink frequency	Reduced, causing abnormal tear film, dry eye and reduced vision	[23]
Blink reflex	Habituation not observed	[24]
Pupil diameter	Larger after light adaptation with anisocoria	[26]
Light reflex	Longer latency	
Constriction time	Increased	[26]
Contraction amplitude	Reduced	[23]
Contrast sensitivity (CS)	Abnormal in some cases, intermediate to high frequencies	[28]
Temporal processing	Impaired ability to track rapid fluctuations	[32]
	Duration perception affected	[33]
Flash ERG	Reduced amplitude of "b" wave	[35]
	Reduced amplitudes.	[35]
PERG	Specific defect at medium SF	
	Delayed P50	[36]
Cortical VEP	Delayed P100	[45]
		[46]
Chromatic VEP	Increased latency and reduced	[44]
	Amplitude (esp. blue-yellow)	
ERP	Abnormal. Delayed reaction times	[42]
		[41]
Visuo-spatial	Difficulty in judging verticals,	[48]
	position of body parts, and in route-walking tasks	[49]
Orientation and motion discrimination	Impaired	[50]
Facial perception	Impaired ability to perceive and imagine emotional faces	[51]
Visual hallucinations	Chronic in 30–60% of treated cases	[54]

Abbreviations: ERG: Electroretinogram, ERP: event-related potentials, PERG: Pattern electroretinogram, SF: Spatial frequency, VEP: Visual evoked potentials.

discrimination is also evident and is often associated with impairments of higher motor function [10]. Using the Farnsworth-Munsell 100-hue test, however, colour visual discrimination does not appear to be consistently impaired in the early stages of PD [11].

**2.3. Visual Fields.** There have been few studies of visual field defects in patients with PD [12]. Retrospective analysis of ophthalmic charts from PD patients, however, using a cup-to-disc ratio of 0.8 or greater to define glaucoma, revealed glaucomatous visual field defects in approximately 24% of

patients suggesting there may be an increased rate of glaucoma in PD [13]. In addition, intraocular pressure (IOP) was slightly higher in PD patients with glaucoma compared with glaucoma patients without PD (mean 18.9 compared with 16.0). Of eight PD patients with glaucoma, five were considered to have low tension glaucoma. In one study, visual fields were investigated in patients undergoing posterior pallidotomy, a procedure which risks damaging structures such as the optic tract [14]. Of 40 such patients, three had visual field defects likely to be attributable to the surgery, namely, contralateral superior quadrantanopia, associated in two patients with small paracentral scotomas.

**2.4. Saccadic and Smooth Pursuit Eye Movements.** Assessment of oculomotor function in PD can be made clinically or by using electro-oculography (EOG). EOG responses are often normal in PD patients when the eyes are in the primary position or when resting. Abnormal saccadic and smooth pursuit eye movements, however, have been reported in about 75% of patients [15]. Both reaction times and the maximum saccadic velocity of horizontal gaze are slower in PD [15]. Saccadic eye movements may exhibit hypometria, that is, “under reaching of task” [16] while smooth pursuit movements may be interrupted by small saccades [15]. In addition, the amplitude of saccadic eye movements are increased in normal subjects when there is a change from externally cued saccades to self-paced saccades and this effect is often greater in PD [17]. In a study in which the delay of remembered (imagined) saccades was gradually increased in untreated PD patients, there was a marked hypometria of saccadic gain at all delays suggesting a dysfunction of the striatocollicular inhibitory pathways in PD attributable to dopamine deficiency in the basal ganglia [18]. In a further experiment, spatial working memory was studied in relation to eye movements [19]. A sequence of four targets was memorised by the patient and then the eyes were moved to fixate the targets in their correct order. In PD, several discrete saccadic eye movements of reduced amplitude were necessary before reaching the final eye position, and the patients also exhibited an increasing proportion of errors in remembering the target sequence. The results suggested that memory representation was disrupted early in the development of PD.

EOG recordings have been made before and after apomorphine treatment in patients with early-stage disease and have confirmed that smooth pursuit movements are affected during the initial stages of the disease [20]. In addition, patients with PD often have difficulty in sustaining repetitive actions and hence, smooth pursuit movements exhibit a reduction in response magnitude and a progressive decline of response with stimulus repetition.

**2.5. Nystagmus and Convergence.** Abnormal optokinetic nystagmus “train nystagmus” [15] and convergence [21] have been reported in PD patients. Further abnormalities that have been observed include “jerkiness”, “cogwheeling”, and limitation of eye movement. Vertical eye movements are

often more impaired than horizontal movements. Convergence can be associated with relatively large exophoria (outward deviation of the eye), and the result is often diplopia (double vision) [22].

**2.6. Blink Reflex.** Patients with PD exhibit a reduced frequency of blinking leading to a staring appearance [23]. Reduced blink rate can cause an abnormal tear film, dry eye, and reduced vision. A characteristic ocular sign may be the blink reflex, elicited by a light tap above the bridge of the nose, successive taps in normal individuals producing less and less response as the reflex habituates [24]. In PD, the blink reflex may not disappear on repeated tapping. In addition, blink duration may be increased in PD reflecting the loss of dopamine neurons [25].

**2.7. Pupil Reactivity.** Significantly larger pupil diameters, with anisocoria (unequal pupil sizes) after light adaptation, have been reported in PD [26], no differences being observed after dark adaptation. In addition, longer light reflex latencies and constriction times have been observed while contraction amplitudes may be reduced [23]. These results suggest that there is an autonomic imbalance in PD patients involving the parasympathetic system.

**2.8. Psychophysics.** Contrast sensitivity (CS) is affected in a proportion of PD patients especially at the high or intermediate frequencies [27–29]. In some individuals, a substantial decrease in CS can be demonstrated as the disease progresses and could be a contributory cause of poor vision in PD. Abnormalities in CS are likely to be related to dopamine dysfunction and are often orientation specific suggesting cortical involvement [30]. L-dopa therapy generally improves CS performance close to that of healthy control patients without any neurological dysfunction. In addition, apomorphine significantly improves achromatic spatial CS at all spatial frequencies but appears to have minimal effects on colour vision [31].

There may be decreased sensitivity to temporally changing stimuli in PD which have been well demonstrated by studies of the auditory system. Hence, in psychophysical tests assessing auditory processing, bilateral subthalamic nucleus stimulation caused dysfunction in ability to track rapid fluctuations in sound intensity [32]. In addition, in motor tasks involving finger tapping, a PD group were impaired both in the motor task itself and in assessing duration implicating the basal ganglia and thalamocortical connections in timing [33]. Subsequently, the substantia nigra, an important site of PD pathology, was shown to be involved in temporal processing involving motor and perceptual tasks [34]. Problems in the visual perception of rapidly moving stimuli are likely to cause problems in tracking fast moving targets.

**2.9. Electrophysiology.** Significant changes in the electroretinogram (ERG) have been found in PD. Studies show that the amplitude of the ERG “b” wave may be reduced in PD patients under a variety of light conditions [35]. Since

the amplitude of the “b” wave may be a diagnostic indicator of the functioning of the inner nuclear layer, the reduction may reflect defects in visual processing involving dopamine neurons. In addition, the amplitude of the pattern ERG (PERG) to a checkerboard stimulus is decreased [35] and the latency of the P50 component delayed [36] in PD patients. Subsequent studies have suggested that retinal dopamine depletion may result in attenuated ERG responses to peak stimuli [37]. Two dopamine sensitive pathways have been postulated: (1) involving the D1 receptors which primarily affect the “surround” organisation of ganglion cells with large centres and (2) the D2 postsynaptic receptors which contribute to the “centre” response amplification of ganglion cells with smaller centres. In addition, steady-state pattern PERG to sinusoidal gratings was studied over a range of spatial frequencies [38]. Aging affected responses at all spatial frequencies but the pattern of age-related loss was different in PD. In PD, there was a specific deficit at medium spatial frequencies accompanied by a distorted PERG spatial frequency response function. PERG is also sensitive to dopamine manipulation in the monkey retina [39]. In a further experiment involving the use of the selective D2 blocker l-sulpiride, treatment affected the PERG to a sinusoidal vertical grating presented at four spatial frequencies [39]. The data suggested that dopamine is involved in retinal processing in primates and that the D2 receptor is necessary for spatial-temporal tuning of pattern vision. Subsequently it was shown that the two dopamine receptors play different roles in retinal function and therefore in the different visual alterations in PD [40]. Hence, PERG is useful in evaluating retinal dopamine mechanisms and in monitoring dopamine therapies in PD.

Event-related potentials (ERP) employing various “odd-ball” tasks have been used to study the sensory and cognitive processing in PD. Abnormal ERP responses in PD often correlate with worsening Wechsler and motor dysfunctional scale scores [41]. In a study of the P300 response, believed to reflect orientation, attention, stimulus evaluation, and memory, reductions in reaction time were actually less in PD than in other “parkinsonian syndromes” such as progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) [42].

Evoked responses to coloured stimuli are also affected in PD [43] supporting the hypothesis that dopamine modulates the retinal colour system. In idiopathic PD, for example, amplitude is decreased and latency increased for all chromatic stimuli and especially for those using blue-yellow (B-Y) horizontal gratings [44], and this test may be a simple tool for distinguishing different parkinsonian syndromes. Increased latency of the visually evoked potential (VEP) P100 peak to a checkerboard stimulus has been reported in a proportion of patients suggesting a delay in visual processing at one or more stages of the visual system [45–47].

**2.10. Complex Visual Functions.** There are prominent deficits in PD involving neuropsychological tests requiring self-motivation and a demanding response from the patient [1]. PD patients may exhibit a variety of deficits in visuo-spatial

orientation [48, 49] including difficulty in judging verticals and the position of body parts, and in carrying out a route-walking task. Visuo-spatial working memory appears to be selectively impaired early in PD which probably reflects degeneration of the basal ganglia, the dorsal visual stream, and the frontal-prefrontal cortex [1]. Patients may also have problems with memory tasks involving spatial orientation. PD patients often show an impairment of orientation and motion discrimination [50] suggesting that the visual pathway beyond the retina may be affected since these tasks are most likely to involve the visual cortex. In addition, impairments in the ability to perceive and imagine faces have been reported in PD [51]. Medicated and unmedicated patients exhibit facial recognition problems but these deficits are most frequently present in the untreated group [52]. Normal subjects contract their facial muscles while imaging faces, a process which is often impaired in PD patients. In a problem solving task involving arranging coloured balls in pockets on a computer screen, PD patients made more errors on the task than controls and also did not show any dissociation in the amount of time fixating the two halves of the display [53]. The results suggested difficulties in encoding and/or maintaining current goals during problem solving in PD.

**2.11. Visual Hallucinations.** Visual hallucinations are a chronic complication of PD [54, 55] and especially in patients treated with L-dopa and dopamine agonists. In a large study of PD patients, hallucinations occurred in the previous three months in 40% of patients examined. Hallucinations were visual in 22% and auditory in approximately 10% of patients [55]. Patients with minor hallucinations had higher depression scores than those without. Three factors were the best predictors of hallucinations, namely, severe cognitive defects, daytime somnolence, and longer duration of disease. Hallucinations in PD are often complex with flickering lights, and illusionary misconceptions often preceding the most common manifestation, namely, stereotypical colourful images. Visual hallucinations may involve a disturbance in the regulation of the gating and filtering of external perception and internally generated visual images. Risk factors for hallucinations in PD patients include poor primary vision and reduced activity of the primary visual cortex (area V1).

### 3. Pathological Changes Affecting the Visual System

**3.1. Eye Pathology.** Few pathological changes have been reported in the eye in PD with the exception of the retina [56]. However, the maximum contraction ability of the iris muscle measured *in vitro* is greater in PD than in controls suggesting that the muscle may have acquired adaptive sensitivity changes [57].

Dopamine is an important neurotransmitter in the retina and is present in amacrine cells and along the inner border of the inner nuclear layer [58] (Figure 1). In addition, dopamine may be accumulated by interplexiform cells [59]. Two types of amacrine cells appear to be involved. Type

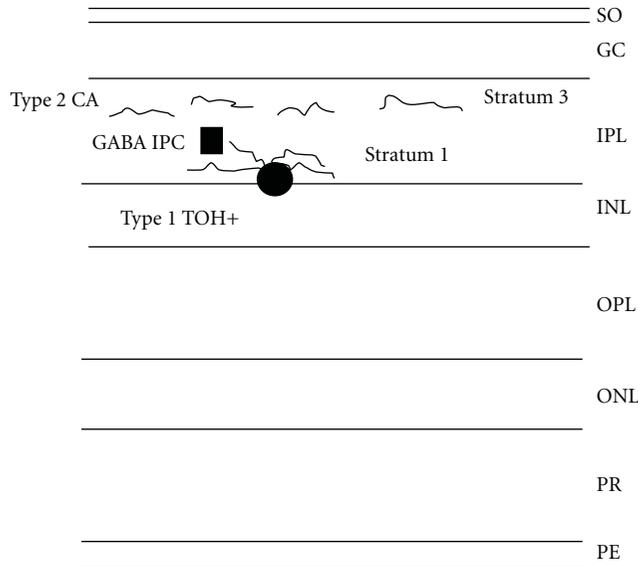


FIGURE 1: The layers of the retina (PE: pigment epithelium, PR: visual receptors, ONL: outer nuclear layer, OPL: outer plexiform layer, INL: internal nuclear layer, IPL: internal plexiform layer, GC: ganglion cell layer, and SO: Stratum opticum). Dopamine neurons (TOH+: Tyrosine hydroxylase positive neurons, Type 1 cells and Type 2 amacrine cells) are primarily concentrated in the INL and dopamine positive neurites (Type 1 in stratum 1 and type 2 ramify above stratum 1) in the IPL. Type 1 cells may synapse onto GABA interplexiform cells (IPCs). Some dopamine activities may also be observed in the ganglion cell layer.

1 cells send ascending processes to the outer plexiform layer where they synapse with  $\gamma$ -aminobutyric acid (GABA) interplexiform cells in stratum 1, whereas type 2 cells have their dendrites stratifying above those of the type 1 cells of the inner plexiform layer (Figure 1). Dopamine may be involved in the organisation of the ganglion cell and bipolar cell receptive fields and appears to modulate the physical activity of the photoreceptors [60]. In addition, dopamine is involved in the coupling of the horizontal and amacrine lateral system [61].

Pathological changes which have been observed in the PD retina include cell losses, which often affect the peripheral segments of the retina more severely and reductions in retinal dopamine [62]. In addition, the thickness of the circum-papillary retinal nerve fibre layer was studied using optical coherence tomography (OCT) [63]. The inferior quadrant layer, and especially the inferior temporal region, was significantly thinner in PD than in controls. In normal subjects, the foveola contains no dopamine neurons, innervation being achieved by processes originating in the avascular zone. In PD, swelling and loss of these processes has been observed. These observations are consistent with the ERG data and support the hypothesis that at least some of the cortical VEP changes could be retinal in origin.

3.2. Brain Pathology. The surviving neurons of the substantia nigra and cerebral cortex often contain inclusions called

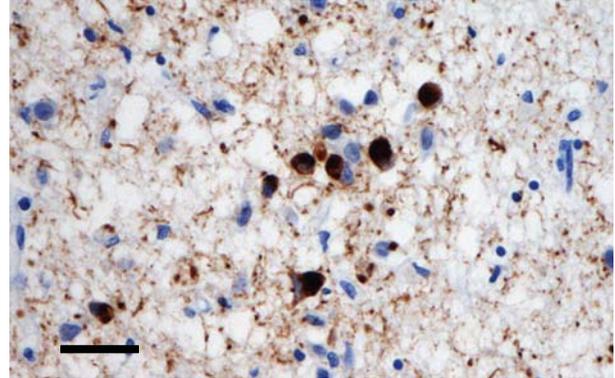


FIGURE 2: Cells from the cerebral cortex showing the presence of Lewy bodies ( $\alpha$ -synuclein immunohistochemistry, haematoxylin stain, bar = 25  $\mu$ m).

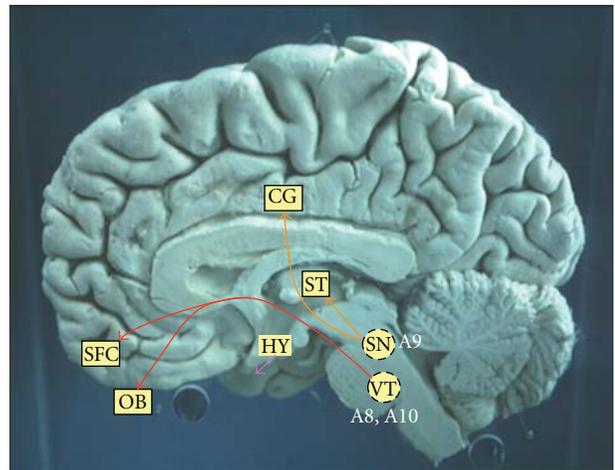


FIGURE 3: The dopamine projections of the central nervous system (OB: Olfactory bulb, SFC: superior frontal cortex, CG: Cingulate gyrus, ST: Striatum, HY: Hypothalamus, VT: Ventral tegmentum, SN: Substantia nigra).

Lewy bodies (LB) (Figure 2). LB are found in the cytoplasm of the cell and may be derived from cytoskeletal filaments. Recent research suggests that LB differ significantly from other neurofibrillary pathologies in neurodegenerative disease, for example, the neurofibrillary tangles (NFT) found in AD [64], in that they contain abnormal aggregates of the protein  $\alpha$ -synuclein [65].  $\alpha$ -Synuclein is a small presynaptic protein and the entire molecule undergoes a conformational change to result in the insoluble protein that forms a major component of the LB.

There are two major dopamine pathways in the brain (Figure 3). First, there is the striatonigral pathway from the substantia nigra (cell group A9) to the cortex and striatum. Second, a major pathway originates in the ventral tegmentum (cell groups A8, A10) and projects to the amygdala, septum, nucleus accumbens, olfactory tubercle, and frontal cortex. There are also dopamine pathways within the hypothalamus. Hence, within the brain significant dopamine activity is limited to the frontal and limbic areas of

TABLE 2: Adverse ocular reactions to treatment for Parkinson's disease.

Treatment	Examples	Ocular side effects
Anticholinergics	Benzhexol, Diphenhydramine	Mydriasis, photophobia, dry eyes, decreased accommodation, anisocoria, blurred vision, anterior angle closure
Dopamine agonists	Bromocriptine	May exacerbate visual hallucinations
	Pramipexole	May exacerbate visual hallucinations
	Ropinirole	May exacerbate visual hallucinations
L-dopa	L-dopa/carbidopa	Mydriasis, miosis, blepharospasm eyelid ptosis, may prolong latency of saccades
MAO inhibitors	Selegiline	May cause loss of visual acuity and blurred vision
Antiviral	Amantadine	Mydriasis, superficial keratitis, reduced accommodation, hallucinations
Antidepressant	Imipramine	Mydriasis, cycloplegia, dry eyes, ocular muscle paresis, nystagmus

the cerebral cortex with significantly less activity in the visual cortex [62]. Cerebral metabolic rates for glucose, however, are reduced by up to 23% in the primary visual cortex of PD patients [66]. Reductions in dopamine levels in the basal ganglia and frontal cortex may also deplete levels in the superior colliculus and thus could be a factor in the production of defective saccades [16].

Within the cerebral cortex, functional MRI (fMRI) and EEG studies have both revealed the essential role of the occipital cortex in producing saccadic eye movements while PET studies have revealed occipital hypometabolism in these areas in PD. In addition, in a study using "event-related" fMRI and which utilised a visual attention/motor inhibition task, during motor inhibition there was activation of the prefrontal cortex and basal ganglia [67]. In addition, there was a reduced and less coherent haemodynamic response in the occipital cortex. Hence, specific functional changes involving the frontostriatal network and temporal-occipital cortex were present in the early stages of PD. PD patients with damage to the medial temporal lobe perform the poorest in all explicit memory tasks and memory problems are often apparent in this group in early stage disease [68].

In subcortical regions, areas of the basal ganglia appear to be the most affected by the developing pathology. Within the basal ganglia, the substantia nigra pars reticulata, the subthalamic nucleus, and the caudate nucleus are all involved in saccadic eye movements [69]. There is, however, an overlap in the anatomical pathways involved in saccadic and smooth pursuit movements which may explain why both are affected in PD. Dopamine also has a peripheral role in sympathetic ganglia, visceral ganglia, and in all artery walls. Hence, reductions in dopamine in some of these areas could be a factor contributing to eye movement problems and defects in pupil reactivity.

#### 4. Adverse Ocular Reactions to Treatment

There are several drugs given alone or in combination used to treat PD (Table 2). Most act on the brain either by reducing cholinergic activity or by encouraging dopamine activity in the basal ganglia [70].

Anticholinergic drugs such as benzhexol and diphenhydramine act to decrease acetylcholine levels, the effect of which is enhanced by the lack of dopamine. Benzhexol may have a significant mydriatic effect and therefore, should not be given to patients with anterior angle closure and should be used with caution in those with a narrow anterior chamber angle. Prolonged exposure to this drug in a few patients may cause an angle closure of gradual onset but without acute symptoms. Optometrists may be the only health practitioners aware of this risk, that is, it is always important to assess anterior chamber depth in PD patients. In addition, photophobia and decreased accommodation can occur resulting in blurred vision [71].

Dopamine agonists such as bromocriptine, pramipexole, and ropinirole enhance the effect of dopamine by directly stimulating dopamine receptors. Pramipexole and ropinirole are often indicated as a treatment for early stage PD and RLS. These drugs may cause less motor complications and dyskinesia than L-dopa but are often given in combination with the latter. Use of dopamine agonists may exacerbate visual hallucinations in PD.

L-dopa is a precursor of dopamine and can penetrate the blood-brain barrier more successfully than dopamine itself. It is often given with a peripheral decarboxylase inhibitor, for example, carbidopa, to reduce the breakdown of L-dopa outside the brain. Mydriasis may occur at first, and this may be followed by miosis. Lid ptosis and blepharospasm have been reported in a few patients [72]. In addition, L-dopa may prolong the latency of saccades [73].

Monoamine oxidase B (MAO-B) inhibitors, such as selegiline, slow down the breakdown of dopamine at the synapse. Patients treated with MAO-B inhibitors and multiple ergotamine-derived dopamine agonists may exhibit blurring of vision [74].

The antiviral drug amantadine appears to have a beneficial effect on many of the symptoms of the disease. A few adverse reactions have been reported including a superficial keratitis, mydriasis and reduced accommodation while in some patients visual hallucinations may occur [75]. By contrast, imipramine has antidepressant and anticholinergic properties and acts by inhibiting the reuptake of dopamine. Ocular side effects include mydriasis, cycloplegia, dry eyes, nystagmus, and the paresis of ocular muscles.

## 5. Discussion and Conclusions

Patients who have been diagnosed as having PD may develop a range of visual problems during the course of the disease. Hence, changes in vision in PD may result from alterations in visual acuity, contrast sensitivity, colour discrimination, pupil reactivity, eye movements, motion perception, visual field sensitivity, and visual processing speeds. Slower visual processing speeds can also lead to a decline in visual perception especially for rapidly changing visual stimuli. In addition, there may be disturbances of visuo-spatial orientation, facial recognition problems, and chronic visual hallucinations. Some of the treatments used in PD may also have adverse ocular reactions. Visual deficits in PD are important in influencing overall motor function [10], are a risk factor for developing hallucinations [7] and are important in influencing general quality of life [7]. Hence, identifying and correcting the visual problems as far as possible can significantly benefit a PD patient.

Clinical examination of the patient by eye practitioners requires sensitivity to both the physical disability and mental state of the patient and the problems involved have been described in detail by Naylor [70]. Some of the visual problems may be adverse reactions to treatment. Side effects may occur relatively rapidly at the beginning of, or after a change, in drug treatment, but can also occur after a long latent period. It is important that those symptoms due to adverse reactions are distinguished from those due to the disease process itself. If ocular side effects are identified and become severe, then it is essential that these are monitored and the patient referred back to their physician for further clinical assessment.

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## Clinical Study

# Nonmotor Symptoms Groups in Parkinson's Disease Patients: Results of a Pilot, Exploratory Study

**Santiago Perez Lloret,<sup>1,2</sup> Malco Rossi,<sup>2</sup> Marcelo Merello,<sup>2</sup> Olivier Rascol,<sup>1</sup> and Daniel P. Cardinali<sup>3,4</sup>**

<sup>1</sup> *Department of Clinical Pharmacology and Neurosciences, Faculty of Medicine, Paul Sabatier University, and NSERM CIC9023 and UMR 825 Allées Jules Guesde, 31000 Toulouse, France*

<sup>2</sup> *Movement Disorders Section, Raul Carrea Institute for Neurological Research (FLENI), Buenos Aires, Argentina*

<sup>3</sup> *Departamento de Docencia e Investigación, Facultad de Ciencias Médicas, Pontificia Universidad Católica Argentina, 1107 Buenos Aires, Argentina*

<sup>4</sup> *Departamento de Fisiología, Facultad de Medicina, Universidad de Buenos Aires, 1121 Buenos Aires, Argentina*

Correspondence should be addressed to Santiago Perez Lloret, splloret@fleni.org.ar

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Nonmotor symptoms (NMS) like neuropsychiatric symptoms, sleep disturbances or autonomic symptoms are a common feature of Parkinson's disease (PD). To explore the existence of groups of NMS and to relate them to PD characteristics, 71 idiopathic non-demented PD out-patients were recruited. Sleep was evaluated by the PD Sleep Scale (PDSS). Several neuropsychiatric, gastrointestinal and urogenital symptoms were obtained from the NMSQuest. Sialorrhea or dysphagia severity was obtained from the Unified PD Rating Scale activities of daily living section. MADRS depression scale was also administered. Exploratory factor analysis revealed the presence of 5 factors, explaining 70% of variance. The first factor included PDSS measurement of sleep quality, nocturnal restlessness, off-related problems and daytime somnolence; the second factor included nocturia (PDSS) and nocturnal activity; the third one included gastrointestinal and genitourinary symptoms; the fourth one included nocturnal psychosis (PDSS), sialorrhea and dysphagia (UPDRS); and the last one included the MADRS score as well as neuropsychiatric symptoms. Sleep disorders correlated with presence of wearing-off, nocturia with age >69 years, and nocturnal psychosis with levodopa equivalent dose or UPDRS II score. Neuropsychiatric symptoms correlated with UPDRS II+III score and non-tricyclic antidepressants. These results support the occurrence of significant NMS grouping in PD patients.

## 1. Introduction

Nonmotor symptoms (NMSs) are a frequent feature of Parkinson's disease (PD), affecting up to 60% of patients [1, 2]. These symptoms are usually underrecognized and undertreated, thus leading to a reduced quality of life, to comorbidities, and to precocious institutionalization or hospitalization [2]. Recently, NMS management has been recognized as an important unmet need in PD [3].

NMSs comprise a large variety of symptoms including, among others, neuropsychiatric and sleep disturbances, autonomic dysfunction, and gastrointestinal or sensory symptoms [1, 4]. NMSs can be assessed by several tools

specifically designed for these symptoms, including the NMS questionnaire (NMSQuest) [4], the unified PD rating scale (UPDRS) [5] and the PD sleep scale (PDSS) [6].

Pathophysiologically, NMS may be related to both dopaminergic and nondopaminergic alterations. For example, PET studies reported dopamine dysfunction at the hypothalamus [7]. Degeneration of cholinergic, adrenergic, or serotonergic pathway could also contribute to NMS genesis [8]. Moreover, NMS can precede motor symptoms and thus PD diagnosis [2].

Several studies have suggested that NMS coexist, thus highlighting the possibility of NMS grouping [1, 4, 9]. Identification of such groups can be important for research

on underlying disease mechanisms, since homogeneous groups of patients are more likely to share pathological and genetic features [10]. Therefore, we conducted the present pilot study to explore the existence of NMS groups as well as to relate them to PD characteristics or pharmacological treatment.

## 2. Methods

**2.1. Study Sample.** PD patients were recruited from a tertiary outpatient clinic to conduct a study to validate sleep logs use in PD [11]. To be included, the subjects had to fulfill the United Kingdom Parkinson's Disease Society Brain Bank criteria [12]. Patients with minimal state examination (MMSE) score <25 points [13] were excluded.

The protocol conformed the principles enumerated in the Helsinki Declaration and was approved by the Institutional Review Board. All subjects signed an informed consent after full explanation of the procedures.

**2.2. PD and NMS Evaluation.** PD patients were subjected to cognitive, psychiatric, and motor evaluation including an MMSE [14], a Montgomery-Asberg Depression Rating scale (MADRS) [15], and UPDRS [5]. Medication records were used to calculate levodopa equivalent daily dose (LDED) according to the usual formula [16]. Severities of sialorrhea or dysphagia were obtained from items no. 6 or no. 7 of the UPDRS II (activities of daily living) section.

Presence of sleep disturbances was evaluated by the PDSS [6]. PDSS items were grouped according to domain: sleep quality (items 1 to 3); nocturnal restlessness (items 4 and 5); nocturnal psychosis (items 6 and 7), nocturia (item 8); nocturnal motor symptoms (items 9 to 13) and daytime somnolence (items 14 and 15) (25).

NMSQuest was also administered to patients [1]. Questions were grouped according to the following domains: gastrointestinal motility problems (items 5–7); urinary dysfunction (items 8–9) or neuropsychiatric disorders (i.e., apathy, memory, or attention disorders, items 12–15). Other domains were not included in the analysis.

All participants were instructed to wear an actigraphy device during 7 days (MicroMini-Motionlogger, Ambulatory Monitoring Inc, NY, USA) which served for the calculation of nighttime activity.

**2.3. Statistical Analysis.** Categorical data were compared using chi-square and numerical variables by an analysis of variance (ANOVA). Exploratory factor analysis (EFA) (with principal components as extraction methods followed by oblique rotation) was first employed to build NMS factors, since between-factor correlations could not be ruled out a priori [17]. The number of factors was determined by inspection of the screen plot and Kaiser's criterion (i.e., eigenvalue >1), and factor scores were calculated. Between-factors correlations were calculated and if all of them were <0.35 (i.e., a determination coefficient < 15%), independency was concluded. In this case, EFA was repeated but employing varimax rotation, which allows better factor definition.

TABLE 1: Patients characteristics.

Males/Females (%)	36 (51)/35 (49)
Age (Mean $\pm$ SD)	68.5 $\pm$ 8.7
UPDRS II+III in ON (Mean $\pm$ SD)	29.1 $\pm$ 14.1
Hoehn&Yahr score	
I	10 (14)
I.5	13 (18)
II/II.5	23 (32)
III	16 (23)
IV/V	9 (13)
PD duration (Mean $\pm$ SD)	7.7 $\pm$ 5.7 years (range: 1–20)
No dopaminergic therapy (%)	15 (21)
Levodopa (%)	45 (63)
Dopamine agonists (%)	42 (60)
LDED (Mean $\pm$ SD)	596 $\pm$ 462
Dyskinesias (%)	34 (47)
Wearing off (%)	35 (49)

LDED: levodopa equivalent daily dose; PD: Parkinson's Disease; SD: standard deviation.

Sampling adequacy was evaluated by Kaiser-Meyer-Olkin (KMO) score, which had to be >0.600. For the evaluation of model validity, communalities were calculated, which had to be >0.50 for all variables. Finally, bivariate and multivariate analyses were employed to disclose the independent variables related to factor scores. For these analyses, factor scores were categorized to their medians. The following independent variables were considered: age, sex, PD duration, UPDRS II total score, UPDRS II+III score, presence of dyskinesias or motor fluctuations (UPDRS IV), administration of levodopa and intake of dopamine agonists, monoamine oxidase inhibitors, catechol-O-methyl transferase inhibitors, antimuscarinics, amantadine, tricyclic or nontricyclic antidepressants, benzodiazepines, and hypnotics.

Bivariate analyses were carried out with chi-square statistic. A multivariate model with factor scores as dependent variables was constructed by forward logistic regression. Only correlates with a significance level in the bivariate analyses were included as explanatory variables in the models. These variables were dichotomized to their medians to help interpretation. Goodness of fit was explored by the Hosmer and Lemeshow score, which was >0.70 in all cases. Potential interactions and multicollinearity were tested for the models, and none was found. All analyses were performed by SPSS v.15 (SPSS Inc. Chicago, Ill).

## 3. Results

Seventy-one patients were included in this study. A summary of their characteristics is shown in Table 1. EFA revealed the presence of 5 factors with eigenvalues >1 and that explained 70% of variance. KMO score was 0.620. All communalities were >0.50. These results support the validity of the model.

TABLE 2: Results of the exploratory factor analysis.

Items	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
Sleep quality (PDSS)	0.789				
Noct. restlessness (PDSS)	0.839				
Off-related problems (PDSS)	0.636				
Daytime somnolence (PDSS)	0.538				
Nocturia (PDSS)		0.839			
Noct. Activity (actigraphy)		0.654			
GU symptoms (NMSQ)			0.935		
GI Motility disorders (NMSQ)			0.939		
Noct. Psychosis (PDSS)				0.572	
Sialorrhea (UPDRS)				0.809	
Dysphagia (UPDRS)				0.668	
MADRS					0.911
NPS symptoms (NMSQ)					0.866
Variance explained by factor	27.6	13.2	11.9	9.8	8.0

GU: genitourinary; GI: gastrointestinal; MADRS: montgomery-Asberg depression Rating scale; NPS: neuropsychiatric symptoms.

Factors loadings are shown in Table 2. The first factor included PDSS measurement of sleep quality, nocturnal restlessness, off-related problems, and daytime somnolence and was thus named “sleep disorders.” The second factor included nocturia (PDSS) and nocturnal activity and was named as “nocturia.” The third one included gastrointestinal and genitourinary symptoms (“autonomic disturbances”). The fourth one comprised nocturnal psychosis (PDSS), sialorrhea, and dysphagia (UPDRS) and was named as “nocturnal psychosis.” The fifth one included MADRS score as well as neuropsychiatric symptoms, being labeled as “neuropsychiatric symptoms.” Only the latter factor score showed some statistically significant correlations with sleep disorders factor score ( $r = 0.26$ ) or with autonomic disturbances factor score ( $r = 0.29$ ). As all correlation coefficients were below 0.35, EFA with varimax rotation was employed, which confirmed the factor structure.

Females showed lower scores for nocturnal psychosis ( $F = -0.26 \pm 0.11$ ,  $M = 0.27 \pm 0.20$ ,  $P < .05$ ) or higher for NPS symptoms ( $F = 0.27 \pm 0.17$ ,  $M = -0.27 \pm 0.15$ ,  $P < .05$ ). Subjects over 69 years old had higher nocturia scores ( $0.41 \pm 0.16$  versus  $-0.39 \pm 0.14$ ). Subjects with UPDRS II+III in ON-state  $>26$  had higher scores for NPS symptoms factor ( $0.34 \pm 0.19$  versus  $-0.33 \pm 0.12$ ,  $P < .01$ ). Subjects with UPDRS II in ON-state  $>9$  had higher NPS symptoms factor score ( $-0.33 \pm 0.19$  versus  $0.32 \pm 0.11$ ,  $P < .01$ ). Subjects with time from PD onset  $>7$  years had higher scores sleep disorders factor ( $0.26 \pm 0.17$  versus  $-0.25 \pm 0.15$ ,  $P < .05$ ), for nocturnal psychosis ( $0.37 \pm 0.19$  versus  $-0.36 \pm 0.11$ ,  $P < .05$ ) or for NPS symptoms ( $0.25 \pm 0.18$  versus  $-0.24 \pm 0.15$ ,  $P < .05$ ). Subjects with wearing-off had higher sleep disorders factor ( $0.34 \pm 0.17$  versus  $-0.31 \pm 0.14$ ,  $P < .01$ ). Subjects with levodopa equivalent dose  $>625$  mg/day had higher scores on sleep disorders ( $0.21 \pm 0.20$  versus  $-0.18 \pm 0.10$ ,  $P < .05$ ) or on nocturnal psychosis ( $0.36 \pm 0.19$  versus  $-0.31 \pm 0.19$ ). Subjects on antipsychotics had higher scores on nocturnal psychosis factor ( $1.16 \pm 0.41$  versus  $-0.66 \pm 0.12$ ,  $P < .05$ ). Subjects on nontricyclic antidepressants had

higher scores for NPS symptoms score ( $0.35 \pm 0.14$  versus  $-0.15 \pm 0.10$ ,  $P < .05$ ).

Variables independently related to categorized factor scores were then analysed by logistic regression. Results are shown in Table 3. Sleep disorders correlated with the presence of wearing-off, nocturia with age  $>69$  years, nocturnal psychosis with levodopa equivalent dose, or UPDRS II score, while neuropsychiatric symptoms correlated with UPDRS II+III score, or non-tricyclic antidepressants. Autonomic disturbance symptoms did not show any correlation with other factors.

#### 4. Discussion

The present pilot exploratory study suggests the existence of significant NMS grouping in PD. Such groups, which are usually named “factors” included sleep disorders, nocturia, autonomic disturbance symptoms, nocturnal psychosis, and neuropsychiatric symptoms. These results can contribute to the understanding of NMS underlying mechanism. Indeed, based on the herein reported correlations of NMS with PD characteristics or pharmacological treatments some pathophysiological considerations can be entertained.

Before further discussion, the limitations of the present study must be mentioned. Firstly, the sample size was small, although it included a wide range of subjects and was sufficient to allow sampling adequacy for factor analysis. While grouping of motor symptoms in PD has been extensively explored in the past years [18], to the best of our knowledge, there are no such studies focusing on NMS. Our study, which was conducted in a small precollected database, provides a preliminary impression on the subject, which should be confirmed in larger studies. We believe that they can be useful for generating hypothesis as well as for planning and interpreting future studies.

Secondly, evaluation of NMS was performed only by subjective scales which in some cases have only received partial validation, for example, PDSS or NMSQuest. Moreover,

TABLE 3: Variables independently related to categorized factor scores.

Factor	Independent variables	OR (95% CI)	P value
Sleep disorders	Wearing-off	4.18 (1.54–11.34)	.005
Nocturia	Age >69 years	5.45 (1.96–15.17)	.001
Autonomic disturbances	—	—	—
Nocturnal psychosis	LDED >625 mg/day	3.99 (1.39–11.38)	.01
	UPDRS II >9	2.91 (1.02–8.27)	.045
NPS symptoms	UPDRS II+III >26	4.07 (1.44–11.49)	.008
	Non-tricyclic antidepressants	5.85 (1.08–31.53)	.04

LDED: levodopa equivalent daily dose. 95% CI = 95% confidence interval.

dichotomous variables, such as those produced by the latter, cannot be included in factor analysis as such. Thus, proxy variables depicting numbers of neuropsychiatric, genitourinary, or gastrointestinal symptoms had to be employed, which may not reflect the true nature of these symptoms. In addition, some important and frequent NMS such as orthostatic hypotension, sexual dysfunction, leg swelling, olfactory dysfunction, visual problems, sweating, pain and fatigue, or weight loss could not be included in the analysis because of the aforementioned reason. Moreover, many factors were formed by less than 3 items, which could affect their stability. Future studies should therefore include disaggregated items (i.e., not the number of gastrointestinal symptoms but a measure of the intensity of each one of them). It should be noted that the present study was conducted before NMS development [19]. As this scale can capture frequency and severity of NMS in PD, its use should be important in future NMS grouping studies.

Keeping in mind these limitations, some theoretical hypotheses about the different NMS factors found can be entertained. Subjective complaints of troubled sleep, such as the ones captured by PDSS, have been related mainly to PD severity or depression [6, 10, 20, 21]. In our study, presence of wearing-off was the only variable independently related to troubled sleep factor, which is consistent with previous findings [21, 22]. Progressive neurodegeneration causing loss of long-term response to levodopa would lead to insufficient nighttime dopaminergic tone [23] thus providing a suitable explanation for the findings. In turn, this suggests that nighttime administration of controlled-release levodopa or dopamine agonists or COMT inhibitors could constitute an effective treatment for sleep disorders in PD [24]. Indeed, controlled-release ropinirole has been shown to increase PDSS score [25].

Nocturia has been considered in the past to be related to PD. Our results indicate that this may not be the case and that nocturia is a consequence of normal aging and thus should not be considered within the constellation of NMS in PD. Indeed previous studies did not disclose any difference between PD and healthy controls in this domain [26, 27].

Nocturnal psychosis, as subjectively evaluated by PDSS, was closely related to sialorrhea and dysphagia. It is not the first time that such an odd correlation is reported, and it has been previously related to antipsychotics intake [28]. This appears not to be the case in the present study, as antipsychotics were not statistically related to nocturnal psychosis

in the logistic analysis, while dopaminergic stimulation and disease severity were. It can be possible that increased disease severity is the underlying cause of both oral symptoms and increased dopaminergic stimulation which in turn would lead to psychotic symptoms [29].

Neuropsychiatric symptoms such as depression, apathy, memory, or attention disorders were significantly related to disease severity, in line with previous findings [29]. The detected relationship with non-tricyclic antidepressants can be explained by the fact that they are usually used to treat depression, thus probably revealing a protopathic bias. Finally, gastrointestinal and genitourinary symptoms loaded in the same factor, thus revealing a common origin, probably autonomic dysfunction [30].

In conclusion, EFA found 5 groups of NMS, including troubled sleep, nocturia, gastrointestinal/genitourinary symptoms, sialorrhea/psychotic symptoms, and NPS symptoms, which were related to some PD characteristics. These preliminary findings, resulting from a pilot exploratory study, can be useful for hypothesis generation as well as for planning of future studies.

## Conflict of Interests

S. P. Lloret, M. Rossi, M. Merello and D. P. Cardinali have no proprietary, financial, professional, nor any other personal interest of any kind in any product or services and/or company that could be construed or considered to be a potential conflict of interests that might have influenced the views expressed in this paper. O. Rascol has acted as an advisor for most drug companies developing antiparkinsonian medications and has received unrestricted scientific grants from GSK, Novartis, Boehringer-Ingelheim, Faust Pharmaceuticas, Eisai, Lundbeck, TEVA, Euthérapie, and Solvay.

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## Research Article

# Influence of Different Cut-Off Values on the Diagnosis of Mild Cognitive Impairment in Parkinson's Disease

Inga Liepelt-Scarfone,<sup>1,2</sup> Susanne Graeber,<sup>1</sup> Anne Feseker,<sup>1</sup> Gülsüm Baysal,<sup>1</sup>  
Jana Godau,<sup>1</sup> Alexandra Gaenslen,<sup>1</sup> Walter Maetzler,<sup>1</sup> and Daniela Berg<sup>1,2</sup>

<sup>1</sup>Department of Neurodegeneration, Hertie Institute for Clinical Brain Research, University of Tuebingen,  
72076 Tuebingen, Germany

<sup>2</sup>German Center of Neurodegenerative Diseases (DZNE), University of Tuebingen, 72076 Tuebingen, Germany

Correspondence should be addressed to Inga Liepelt-Scarfone, inga.liepelt@uni-tuebingen.de

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Comparable to Alzheimer's disease, mild cognitive impairment in Parkinson's disease (PD-MCI) is associated with an increased risk for dementia. However different definitions of PD-MCI may have varying predictive accuracy for dementia. In a cohort of 101 nondemented Parkinson patients who underwent neuropsychological testing, the frequency of PD-MCI subjects and PD-MCI subtypes (i.e., amnesic/nonamnesic) was determined by use of varying healthy population-based cut-off values. We also investigated the association between defined PD-MCI groups and ADL scales. Varying cut-off values for the definition of PD-MCI were found to affect frequency of PD-MCI subjects (9.9%–92.1%) and, maybe more important, lead to a “shift” of proportion of detected PD-MCI subtypes especially within the amnesic single-domain subtype. Models using a strict cut-off value were significantly associated with lower ADL scores. Thus, the use of defined cut-off values for the definition of PD-MCI is highly relevant for comparison purposes. Strict cut-off values may have a higher predictive value for dementia.

## 1. Introduction

Parkinson's disease (PD) is increasingly recognized as a multidimensional disorder compromising motor but also a wide range of nonmotor features, including cognitive functions [1–3]. There is evidence that already a slight deterioration of cognition may enhance the risk of conversion to dementia in PD [4, 5]. However, not all PD patients with such a cognitive profile develop dementia (PDD), and early identification of these patients with particularly increased risk is still not possible with sufficient accuracy [5–7]. Therefore, a lot of effort has been put on the identification of a clinical risk profile and especially in the characterization of mild cognitive deficits in patients who are later on developed dementia [8].

The current classification of mild cognitive impairment (MCI) in PD (PD-MCI) refers to the classification of Petersen and coworkers [9]. Here, the cognitive profile of MCI is basically defined by (i) the number of domains

affected (single-/multiple-domain MCI) and (ii) the involvement of memory function (amnesic/nonamnesic MCI). Thus, for PD-MCI diagnosis, one needs to consider two main aspects. First, assessments covering all relevant cognitive domains associated with PD must be included in a considerable test battery. Therefore, the Movement Disorder Society (MDS) Task Force recommended neuropsychological tasks for the assessment of major areas of subcorticofrontal and cortically mediated functions [10]. Second, a cut-off value to define cognitive impairment leading to the diagnosis of PD-MCI must be defined. In previous studies, dealing with this topic, different cut-off values ( $-1$ ,  $-1.5$ , or  $-2$  standard deviations (SD)) below the mean of a healthy control group have been used to classify a cognitive test performance as relevantly impaired [11–13]. In large cohorts, this means that deficits occur in less than 16% ( $-1$  SD), 7% ( $-1.5$  SD), or 2% ( $-2$  SD) of the subjects in the healthy population. Presently, a single test performance of  $-1.5$  SD below the population mean is increasingly

accepted as the best cut-off value for PD-MCI [8, 14]. So far, it is not known whether this cut-off value has a high predictive value for PDD. In research studies, standard scores could be determined to assess individual neuropsychological performance delineating specific cognitive domains [8]. However, this method is not easy to implement in clinical praxis due to the lack of appropriate reference groups which are necessary for the evaluation of cognitive performance over a repertory of neuropsychological tasks. For clinical purpose, one rather needs to define how many tests characterize one cognitive function and to what degree this function needs to be affected to make the diagnosis of PD-MCI. Therefore, to define a cut-off value for PD-MCI for clinical use, the level of impairment in both a single test as well as within a cognitive domain has to be considered.

The clinical profile of PD-MCI patients who are supposed to be at higher risk for PDD has been investigated in various studies, but these studies differ regarding the cut-off values used to define PD-MCI [12, 15–17]. Besides the fact that it is not known yet which PD-MCI subjects have the highest risk for conversion to PDD, it is not evaluated whether the choice of different cut-off values might have an impact on the interpretation of the PD-MCI phenotype.

The aim of this study was twofold: first, to compare the frequency of PD-MCI and subtypes of PD-MCI by use of varying cut-off values, and second, to analyse how this variation of cut-off values might affect the interpretation of the clinical profile investigated in the PD-MCI group.

## 2. Methods

**2.1. Subjects.** A nondemented group of 107 patients with idiopathic PD according to the UKPD Brain Bank criteria [18] was recruited from the Outpatient Clinic of the Department of Neurodegenerative Disorders, University of Tuebingen. Only patients older than 50 years, with adequate or corrected hearing/visual abilities and German as mother tongue, were investigated. Exclusion criteria were other neurological diseases affecting the central nervous system, prior surgery for PD and a Mini-Mental State Examination (MMSE [19]) score < 26, to exclude patients with possible dementia [8]. In addition, exclusion of patients with higher MMSE scores but diagnosis of probable dementia based on level II criteria of the MDS Task Force [10] was made. Hence, six patients with a performance (i) below a standard ( $z$ ) score of  $-1.5$  in at least two of the following cognitive domains: attention, executive functions, praxis and perception, memory or fluency, and naming abilities, (ii) self-report of cognitive decline with insidious onset and slow progression, and (iii) self-reported significant impact on instrumental activities of daily living functions fulfilling the recommended MDS dementia criteria were further excluded from data analysis [14, 20]. The data sets of 101 nondemented PD patients were analyzed. The study was approved by the Local Ethical Committee, and all participants gave written informed consent.

**2.2. Neuropsychological Assessment.** Cognitive and motor assessments were carried out on medication. Neuropsychological testing was conducted within two weeks of motor assessment. A comprehensive test-battery was composed to assess the major areas of subcortico-frontal and cortically mediated functions known to be affected in PD [10]. Different domains were theoretically specified and, composition was evaluated by internal consistency analysis. Cronbachs alpha coefficients indicated moderate to high consistency structure of the scales (0.52 Cronbachs  $\alpha$ -coefficient 0.86), except for the attention domain ( $-0.33$ ). For the attention domain, the Go-Nogo condition as well as the Alertness test, which are commonly used paradigms to assess different aspects of attention, were applied [21]. Two memory domains (list learning and memory recall, logical memory) and four nonmemory domains were defined (see below and Table 1 for details).

The domain “*Executive function*” (5 test scores) was assessed as follows: planning ability was tested by the Tower of London (TL-D) test [22], the trail-making test B [23], and the figure test of the NAI- (Nuernberger Altersinventar-) quantified set-shifting and set-maintenance abilities [23]. Working memory performance was assessed by the digit span part (forward and backward) of the NAI [24]. Ideomotor apraxia (primarily characterized by spatial postural and movement errors) is reported even in nondemented PD patients [25]. This symptom is known to be also caused by frontal lobe dysfunction [26, 27]. In corticobasal degeneration, rather frontal lobe damage than parietal or temporal lobe damage is proposed to account for this symptom [28]. In our cohort, performance in the ideomotor part of the Berlin-Apraxia test (BAXT) [29] was found to be predominately associated with tests measuring executive function.

Performance in the domain “*attention*” (2 test scores) was recorded by using the subtests “Alertness” and “Go-Nogo” of the test for attentional performance (TAP) [30]. The value of phasic alertness expressing the subject’s ability to increase attention processes in expectation of important stimuli and the median reaction time for the Go-Nogo test was analyzed.

The domain “*Praxis and visual function*” was investigated by 3 test scores: two praxis subtests of the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) [23], that is, copying of line drawings and the delayed recall of these drawings, as well as the object decision part of the Visual Object and Space Perception Battery [31].

The trail-making test (TMT) part A [23], the Boston Naming Test, and the semantic verbal fluency part of the CERAD were used to cover the domain “*psychomotor speed and naming ability*.” This test composition showed an acceptable internal consistency structure, and imaging studies support the assumption of a partly overlapping functional brain network activated by the tasks included [32, 33].

The memory domain “*list learning and memory recall*” was evaluated using three test scores of the German version of the CERAD [23], word-list memory, word-list recall after delay, word-list recognition, and the amount of incorrect responses concerning the word list memory recall (word-list intrusion).

TABLE 1: Overview of the cognitive domains.

	Nonmemory domains				Memory domains	
	Executive function	Attention	Praxis and visual function	Psychomotor speed and naming ability	List learning and memory recall	Logical memory
Trail making test, part B	63.2 ± 35.1					
Tower of London test	47.4 ± 26.4					
NAI: Digit span	60.4 ± 30.0					
NAI: Figure test	58.6 ± 22.5					
Berlin Apraxia test	37.5 ± 4.1					
TAP: Value of phasic alertness		49.7 ± 29.2				
TAP: Go-Nogo, median RT		48.9 ± 32.1				
CERAD: Constructional praxis			46.3 ± 33.8			
CERAD: Constructional praxis delayed recall			42.7 ± 36.6			
VOSP: Object decision			49.7 ± 29.1			
CERAD: Verbal fluency				44.1 ± 27.6		
CERAD: Boston Naming Test				55.5 ± 31.5		
Trail-making test, part A				56.9 ± 32.3		
CERAD: Word-list memory					36.4 ± 26.5	
CERAD: Word-list recall					41.6 ± 28.8	
CERAD: Word-list recognition					48.6 ± 33.4	
CERAD: Word-list intrusion					48.5 ± 31.6	
WMS-R: Logical memory I						31.8 ± 28.9
WMS-R: Logical memory II						33.0 ± 27.9
Cronbachs alpha coefficient	0.52	-0.33	0.61	0.58	0.72	0.86

All values are given as mean percentile rank scores ± standard deviation, except for the Berlin Apraxia test for which raw values are presented. CERAD: Consortium for the Registry for Alzheimer's Disease, German version; WMS-R—Wechsler Memory Scale: revised; NAI—Nuernberger Alters Inventar; VOSP—Visual Object and Space Perception Battery; TAP—Testatterie zur Aufmerksamkeitspruefung; RT—Reaction time.

The memory domain “*Logical memory*” (2 test scores) was assessed by the logical memory I and II of the Wechsler Memory Scale—Revised [34].

German norm data (percentile rank scores, PR) provided in the test manuals of the neuropsychological assessments, referring to an age-matched healthy population corrected for age or both age and education (CERAD, TAP, TMT, and TL-D), were used to compare test performance, except for the BAXT. For the BAXT tests, information of the PR was not available, but mean and SD of an age-matched healthy control group was available, so that a standard score could be calculated [29].

**2.3. Neurological Scales.** Neurological assessment included the Hoehn and Yahr stage, the Unified Parkinson Disease Rating Scale motor part (UPDRS-III) [35], and patient's history of medication.

**2.4. Nonmotor Symptoms and Activities of Daily Living Function.** The Neuropsychiatric Inventory (NPI), which evaluates different behavioural domains (e.g., delusions, hallucinations, depression, and apathy), was used for evaluation of psychiatric disturbances [36]. The NPI total score was applied to investigate the severity of abnormal behaviour. The Parkinson's Disease Questionnaire—PDQ-39 [37] and

the Beck Depression Inventory (BDI) [38] served as self-rating scales measuring health-related quality of life and mood.

The Nuernberger-Alters-Alltagsaktivitäten-Skala (NAA), a patient 15-item self-questionnaire focussing on different aspects of the activities of daily living (ADL) functions that is management of the financial situation and social independence, was performed. In addition, its equivalent was also assessed from the caregivers (Nuernberger-Alters-Beobachtungsskala, NAB) [24].

**2.5. Definition of PD-MCI.** Standard ( $z$ ) scores of  $-1$ ,  $-1.5$ , and  $-2$  were defined as cut-off values for the definition of PD-MCI. These cut-off values indicate that less than 16% ( $z < -1$ ), 7% ( $z < -1.5$ ), or 2% ( $z < -2$ ) of the healthy population score was below these criteria. We also differentiated whether a subject scored low in at least 1 ( $_{oneT}$ ) or at least 2 test scores ( $_{twoT}$ ) per cognitive domain. The six resulting diagnostic criteria ( $z < -1_{oneT}$ ,  $z < -1.5_{oneT}$ ,  $z < -2_{oneT}$ ,  $-z < 1_{twoT}$ ,  $z < -1.5_{twoT}$ , and  $z < -2_{twoT}$ ) were then applied to identify the frequency of PD-MCI subjects within the cohort. We specified cut-off values of a varying continuum, some of which are supposed to be more liberal ( $z < -1_{oneT}$ ), and some being assumed to be more strict ( $z < -2_{twoT}$ ) as diagnostic criteria for PD-MCI. Patients with

TABLE 2: Percentage (including 95% confidence interval, 95% CI) of Parkinson patients with minimal cognitive impairment (PD-MCI) and without (PD-noMCI) in regard to varying cut-off values.

	PD-noMCI			PD-MCI		
	N	%	95% CI	N	%	95% CI
<i>One test per domain below cut-off</i>						
$z < -1$	8	7.9	3.7–15.5	93	92.1	84.5–96.2
$z < -1.5$	28	27.7	19.5–37.7	73	72.3	62.3–80.5
$z < -2$	67	66.7	56.2–75.3	34	33.7	25.2–43.3
<i>Two tests per domain below cut-off</i>						
$z < -1$	44	43.6	33.8–53.9	57	56.4	46.2–66.2
$z < -1.5$	70	69.3	59.3–77.9	31	30.7	22.1–40.8
$z < -2$	91	90.1	82.1–94.9	10	9.9	5.1–17.9

PD-MCI were further classified into one of the following four subtypes: (1) amnesic single-domain PD-MCI (affection of one of the two memory domains); (2) nonamnesic single-domain PD-MCI (affection of one of the four non-memory domains); (3) amnesic multiple-domain PD-MCI (affection of at least two domains including one memory domain); or (4) nonamnesic multiple-domain MCI (affection of at least two domains excluding memory domains) [39].

2.6. *Statistics.* Frequencies of PD-MCI patients and PD-MCI subtypes are reported as proportion of patients with impairment in any cognitive domain referring to each of the six diagnostic scores, including 95% confidence intervals (95% CI; Vassar online program, <http://faculty.vassar.edu/lowry/VassarStats.html>) [8]. Performance in the demographical (e.g., age) data are descriptively shown with median and range. Post hoc explorative analysis of PD-noMCI and PD-MCI groups referring to clinical data (e.g., motor performance) were computed with nonparametric statistics, for example, Mann-Whitney  $U$  test or  $\chi^2$  test (e.g., gender). Differences were assumed to be significant at  $P < .05$  (two sided). Statistical analyses were done with SPSS 17.0 for Windows (SPSS Inc, Chicago, ILL, USA).

### 3. Results

3.1. *Patients' Characteristics.* Median age of all 101 patients was 67 (51–79) years, and 60 (59.4%) patients were males. Median disease duration was 5 years (0.3–19 years). Sixty-one volunteers (60.4%) received both levodopa and dopamine agonists, 12 (11.9 %) were treated with levodopa alone, 22 (21.8%) with dopamine agonists alone, and one (1.0%) with amantadine alone. Four patients (3.9%) were treated with either levodopa or dopamine agonists in combination with entacapone or amantadine. One subject (1.0%) received no anti-Parkinsonian medication. Twenty-five patients (24.8%) received antidepressants.

Mean performance of all patients for each test is reported in Table 1. PD patients scored lowest on both logical memory performance tests. In general, large standard deviations indicate a heterogenic test performance.

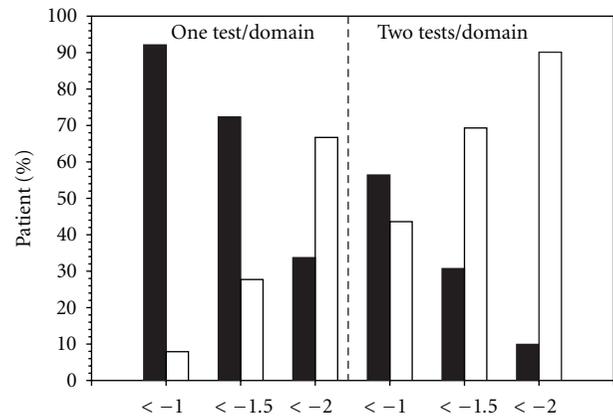


FIGURE 1: Distribution of both Parkinson's disease patients with mild cognitive impairment (PD-MCI, black bars) and without (PD-noMCI, white bars) by use of varying diagnostic criteria. Cognitive impairment was chosen to be present in less than 16% ( $z < -1$ ), 7% ( $z < -1.5$ ) ( $PR < 7$ ), or 2% ( $z < -2$ ) of healthy controls in at least one or two tests per cognitive domain. This demonstrates that the frequency of PD-MCI was highly influenced by the selection of the cut-off values.

### 4. Frequency of PD-MCI

Nearly all patients (92.1%, 95% CI [84.5–96.2]) scored below the most liberal cut-off value ( $z < -1_{\text{oneT}}$ , see Table 2 for details). Ten patients (9.9%, 95% CI [5.1–17.9]) scored below the strictest cut-off value ( $z < -2_{\text{twoT}}$ ). Frequency of PD-MCI was highly influenced by the selection of the classification criteria (Figure 1). In summary, the association between the number of patients defined as PD-MCI was as follows: the stricter a cut-off was defined (e.g.,  $z < -2_{\text{twoT}}$ ), the less patients were categorized as PD-MCI. However, there was an overlap between the 95% CI of the defined PD-MCI frequency by application of either of the following cut-offs: " $z < -2_{\text{oneT}}$ " (PD-MCI: 33.7%, 95% CI [25.2–43.2]) or " $z = -1.5_{\text{twoT}}$ " (PD-MCI: 30.7%, 95% CI [22.1–40.8]) as well as either " $z < -1.5_{\text{oneT}}$ " (PD-MCI: 72.3%, 95% CI [62.3–80.5]) or " $z < -1_{\text{twoT}}$ " (PD-MCI: 56.4%, 95% CI [46.2–66.2]).

TABLE 3: Percentage (including 95% confidence interval, 95% CI) of Parkinson patients with minimal cognitive impairment (PD-MCI) and without (PD-noMCI) in regard to different PD-MCI subtypes.

	PD-MCI total	Single				Multiple			
		Amnestic		Nonamnestic		Amnestic		Nonamnestic	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI
<i>One test per domain below cut-off</i>									
$z < -1$	93	9.7	4.8–18.0	16.1	9.6–25.5	68.8	58.3–77.8	5.4	2.0–12.7
$z < -1.5$	73	21.9	13.4–33.4	21.9	13.4–33.4	48.0	36.3–59.8	8.2	3.4–17.7
$z < -2$	34	41.2	25.1–55.2	41.2	25.1–55.2	11.8	1.0–21.1	5.8	3.8–28.4
<i>Two tests per domain below cut-off</i>									
$z < -1$	57	36.8	24.8–50.1	12.3	5.5–24.3	43.9	31.0–57.6	7.0	2.3–17.8
$z < -1.5$	31	54.8	36.3–72.2	19.4	8.1–38.1	22.6	10.3–41.5	3.2	0.2–18.5
$z < -2$	10	80.0	44.2–96.5	20.0	3.5–38.1	0	0.0–34.5	0	0.0–34.5

Thus, frequency of subjects having more severe cognitive impairment in *at least one* test score tended to overlap with the frequency of patients having less severe cognitive deficits in *at least two* test scores per domain.

## 5. Characterization of PD-MCI Subtypes

The proportion of subjects defined as amnestic multiple-domain PD-MCI tended to be higher when using a more liberal classification cut-off value ( $z < -1_{\text{oneT}}$ , 68.8% 95% CI [58.3–77.8] of PD-MCI patients) compared to a more stringent cut-off ( $z < -2_{\text{twoT}}$ , 0% 95% CI [0.0–34.5] of PD-MCI patients, see Table 3 for details).

In general, the frequency of amnestic PD-MCI subtypes was more heterogeneous (amnestic single domain: 9.7%–80.0%; amnestic multiple domain: 0.0%–68.8%) with regard to varying cut-off values than the frequency of nonamnestic subtypes (nonamnestic single domain: 12.3%–41.2%; nonamnestic multiple domain: 0.0%–8.2%). Less subjects tended to be classified as having nonamnestic multiple-domain PD-MCI than amnestic multiple domain PD-MCI irrespective of the chosen cut-off value. The ratio “frequency of amnestic single-domain PD-MCI over frequency of nonamnestic single domain PD-MCI” was highly influenced using either *one* (e.g.,  $z < -1_{\text{oneT}}$ : amnestic single-domain 9.7% versus nonamnestic single-domain 16.1%) or *two test scores* (e.g.,  $z < -1_{\text{oneT}}$ : amnestic single-domain 36.8% versus nonamnestic single domain 12.3%) per domain to define cognitive impairment.

## 6. Post Hoc Comparison of PD-noMCI with PD-MCI

Results of the explorative post hoc mean group analysis must be interpreted with caution due to variations of sample size and number of comparisons which may lead to compromising power.

The following cut-offs: “ $z < -2_{\text{oneT}}$ ” (PD-MCI = 33.7%) or “ $z < -2_{\text{twoT}}$ ” (PD-MCI = 9.9%) were associated with higher PDQ-39 total score ( $P < .05$ ) and with caregiver’s perception of lowered patients ADL functions (NAB  $P < .03$ ). Lower values for the NAB total score within the

PD-MCI group could also be demonstrated by using “ $z < -1.5_{\text{oneT}}$ ” ( $P = .03$ ) or “ $z < -1_{\text{twoT}}$ ” ( $P = .08$ ) as diagnostic criteria for PD-MCI. In addition, self-reported reduction of ADL function was only significantly associated with PD-MCI ( $P = .02$ ) when the strictest cut-off value was applied ( $z < -2_{\text{twoT}}$ ). This shows that ADL function scores were significantly associated with MCI occurrence only when strict cut-off values were taken. Interpretation of differences between PD-MCI and PD-noMCI patients related to the following variables were influenced by using varying cut-off values in our cohort: disease duration ( $z < -1_{\text{twoT}}$ ,  $P = .009$ ), MMSE score ( $z < -1.5_{\text{oneT}}$ ,  $P < .001$ ;  $z < -2_{\text{oneT}}$ ,  $P = .01$ ;  $z < -1_{\text{twoT}}$ ,  $P < .001$ ;  $z < -1.5_{\text{twoT}}$ ,  $P = .003$ ), and the BDI score ( $z < -1.5_{\text{oneT}}$ ,  $P = .006$ ;  $z < -2_{\text{oneT}}$ ,  $P = .03$ ,  $z < -2_{\text{twoT}}$ ,  $P = .03$ ). Thus, interpretation of group differences concerning these variables did not seem to be systematically related to the chosen cut-off value.

The interpretation of the following demographic/clinical variables was independent of the cut-off values applied: male gender, age at evaluation, age at onset, UPDRS-III motor score, and the NPI total score ( $P > .05$ ).

## 7. Discussion

In our nondemented PD cohort, both frequency and clinical profile of PD-MCI patients were relevantly dependent on the cut-off value used for the definition of cognitive impairment. However, disparities in the evaluated number of PD-MCI were not unexpected as they reflect divergent levels of severity of neuropsychological test impairment. It is interesting that, by use of the most liberal cut-off value, nearly all (92%) of our nondemented PD patients were defined as cognitively impaired, compared to less than 16% of subjects in the healthy population (by definition). This result confirms previous findings demonstrating that slight cognitive impairment is frequent in PD, affecting also patients at very early disease stages [13]. Severe cognitive deterioration (reflected by  $z$ -scores  $< -2$  in at least two test scores per domain) was found in less than 10% of our patients. In newly diagnosed PD patients, Williams-Gray and colleagues [11] reported a prevalence rate of 62% of PD-MCI after defining a value below 1 SD of the normative means

in age and IQ-matched samples as “cognitively impaired.” In contrast, Muslimovic and colleagues [13] used a value of 2 SD below the normative mean of healthy controls and found only 23.5% of PD patients to score below these cut-off values in standardized cognitive tasks. Although other variables such as age or education may have contributed to the difference between these two studies, our data make it intriguing that in particular the definition of the threshold for MCI explains this large divergence in prevalence of PD-MCI patients. This effect was also seen in our cohort by using either a more liberal or a more stringent criterion to define PD-MCI. In addition, both authors used different numbers of neuropsychological test scores for the classification of PD-MCI, which has been shown to also affect prevalence of PD-MCI as well as sample size and inclusion criteria [20]. Recently, the authors of a multicentre study including eight centres in Europe [8] evaluating the prevalence of PD-MCI concluded that MCI is a common syndrome affecting about 25% of PD patients. In this study, a standard score for each domain was calculated. Regarding our cohort, a performance below a z-score of  $-1$  in at least two test scores per domain seems to be closest to the population-based prevalence reported in this study. Results from our study lead to the assumption that the application of different diagnostic criteria affects the sensitivity of the detection of PD-MCI. Comparing our data and data from other studies, one may conclude that a unique PD-MCI profile does not exist. Rather, studies using different criteria for the classification of PD-MCI seem to characterize subgroups in varying disease stages of cognitive deterioration. Therefore, varying studies may differ concerning the clinical profile of PD-MCI patients identified [4, 12]. Different cut-off values may primarily represent a continuous deterioration of cognitive functions in our study population to which both severity of errors and/or the number of cognitive scores affected may contribute. Therefore, it is intriguing to hypothesize that deterioration within a cognitive domain is paralleled by a spreading of cognitive dysfunction throughout other cognitive domains. This hypothesis may offer an alternative model for the classification of mild to moderate cognitive impairment in PD as cognitive dysfunction is known to be heterogeneous in these patients [40]. According to our findings, we suggest the use of neuropsychological test batteries for future clinical or research application to (i) define a unitary cut-off value and (ii) standardize how many test scores within a cognitive domain need to be below this defined cut-off value for the diagnosis of PD-MCI.

In our cohort, varying cut-off values for the definition of PD-MCI not only affect frequency of PD-MCI subjects but, maybe more important, lead to a “shift” of the proportion of detected MCI subtypes especially within the amnesic single-domain subtype. Amnesic PD-MCI was more frequent when we used more stringent criteria (i.e., if more than one test score was required to be below the defined cut-off value for the diagnosis of PD-MCI). This means that patients with more severe cognitive dysfunction had an increased probability to suffer also from memory dysfunction. Amnesic PD-MCI has already been described to be a frequent syndrome in other studies [4, 12]. Based

on these findings, we conclude that for investigations dealing with PD-MCI subtypes, rigorous classification standards must be applied. The high frequency of amnesic MCI can not be explained by the number of test scores used per domain (it is suggestive that a higher number of scores assessed per domain increases the probability to detect a deficit), as we used a smaller number of test scores for the diagnosis of amnesic PD-MCI than for the diagnosis of nonamnesic PD-MCI (Table 1).

As limitation of the study presented here, it has to be kept in mind that interpretation of the post hoc comparison of PD-MCI and PD-noMCI patients must be taken with caution as discrepancies of sample size may compromise statistical power. Therefore, we may have not detected differences in other variables known as potential risk markers for dementia in PD such as demographical variables (e.g., age), motor performance and/or behavioural abnormalities between PD-MCI and PD-noMCI patients [1]. However, especially in our PD-MCI groups with smallest sample size, we found the strongest effect concerning to lower ADL functions.

In summary, our data supports the suggestions that a more liberal diagnostic criterion might be helpful for investigating even subtle cognitive impairments or minor changes in the course of PD. Application of a stricter cut-off value might increase specificity and/or the positive predictive value to detect patients at high risk for dementia. This hypothesis, however, needs to be verified in future longitudinal studies. A first corroboration of this hypothesis may be derived from the fact that a relevant association of both reduction of ADL function and lowered self-esteemed health-related quality of life—both parameters are relevantly associated with PDD [41]—was only observable in the PD-MCI group that was classified by the strictest criterion. As, in PD, cognitive dysfunction is most probably progressive [42]; we speculate that patients meeting the strictest criteria for MCI will show a higher conversion rate to dementia within a shorter time period. This hypothesis will be tested in an ongoing longitudinal study.

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## Research Article

# Traditional Chinese Medicine Improves Activities of Daily Living in Parkinson's Disease

Weidong Pan,<sup>1,2</sup> Shin Kwak,<sup>2</sup> Yun Liu,<sup>1</sup> Yan Sun,<sup>1</sup> Zhenglong Fang,<sup>1</sup> Baofeng Qin,<sup>1</sup> and Yoshiharu Yamamoto<sup>3</sup>

<sup>1</sup>Department of Neurology, Shuguang Hospital, Shanghai University of TCM, 185, Pu-An Road, Shanghai 200021, China

<sup>2</sup>Department of Neurology, Graduate School of Medicine, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

<sup>3</sup>Educational Physiology Laboratory, Graduate School of Education, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Correspondence should be addressed to Weidong Pan, panwd@medmail.com.cn

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We evaluated the effects of a traditional Chinese medicine (TCM), named Zeng-xiao An-shen Zhi-chan 2 (ZAZ2), on patients with Parkinson's disease (PD). Among 115 patients with idiopathic PD enrolled (mean age,  $64.7 \pm 10.2$  years old), 110 patients (M = 65, F = 45; mean age,  $64.9 \pm 10.7$  years old) completed the study. Patients took either ZAZ2 ( $n = 59$ ) or placebo granule ( $n = 56$ ) in a blind manner for 13 weeks while maintaining other anti-Parkinson medications unchanged. All participants wore a motion logger, and we analyzed the power-law temporal autocorrelation of the motion logger records taken on 3 occasions (before, one week, and 13 weeks after the drug administration). Drug efficacy was evaluated with the conventional Unified Parkinson Disease Rating Scale (UPDRS), as well as the power-law exponent  $\alpha$ , which corresponds to the level of physical activity of the patients. ZAZ2 but not placebo granule improved the awake-sleep rhythm, the UPDRS Part II, Part II + III, and Part IV scores, and the  $\alpha$  values. The results indicate that ZAZ2 improved activities of daily living (ADL) of parkinsonism and, thus, is a potentially suitable drug for long-term use.

## 1. Introduction

Conventional anti-parkinsonism drugs effectively ameliorate the symptoms of patients with Parkinson's disease (PD) during the initial several years of onset, but become increasingly less effective and induce motor fluctuations including wearing-off, on-off, dopa-induced dyskinesia, and agonist-induced sleep attack [1–5]. PD patients not infrequently suffer from nonmotor symptoms, such as neuropsychiatric symptoms, autonomic symptoms, gastrointestinal symptoms, sensory symptoms, nonmotor fluctuations (autonomic symptoms, cognitive or psychiatric symptoms, sensory symptoms including pain), fatigue, and sleep disturbance [6–8], and these nonmotor symptoms may be intrinsic to the disease pathology or may be the result of treatment with dopaminergic agents. Several studies have established that the nonmotor symptoms of PD are common, occur

across all stages of PD, and are a key determinant of quality of life [7].

Herbal remedies have a long history of use (particularly in East Asian countries) for alleviating various symptoms and have been increasingly used as alternative medicines worldwide, including the United States [9]. Traditional Chinese medicines (TCMs) ameliorate various symptoms, particularly the ageing-related symptoms [10, 11], and hence are likely to be beneficial for chronic diseases such as PD [12–14]. Good compliance for long-term use with few side effects may be another merit of TCM suitable for patients with PD [12–14].

In order to evaluate the effects of TCM on symptoms of parkinsonism, we used Zeng-xiao An-shen Zhi-chan 2 (ZAZ2) in this study. In addition, we adopted a recently developed method analyzing the power-law temporal autocorrelation of wrist activity measured with a motion logger

[15–17] in order to evaluate the efficacy of ZAZ2 on parkinsonism. Pan et al. showed that the power-law exponent ( $\alpha$ ) for higher levels or at the so-called local maxima of coefficients of the wavelet transform significantly and in correlation with the symptom severity of PD patients [15]; hence analysis of  $\alpha$  is likely to be useful for evaluating the effects of TCM on parkinsonism as a whole. The aim of the present study was to evaluate the ameliorating effects of ZAZ2 on impaired motor and nonmotor symptoms of PD patients using the UPDRS scores, secondary symptoms scores [18], and also by analyzing the mean activity levels and the power-law temporal exponents of *MicroMini-Motionlogger*, Ambulatory Monitoring Inc. (AMI) scores.

## 2. Methods

**2.1. Subjects.** Of the 140 PD patients who visited the clinic at the Department of Neurology of Shuguang Hospital Affiliated to Shanghai University of TCM between July 2008 and April 2010, 115 patients with idiopathic PD (mean age  $\pm$  SD, 64.7  $\pm$  10.2 years old, mean duration of illness, 5.5  $\pm$  7.3 years) who fulfilled the inclusion criteria, were invited to participate in the study. The UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria were used [19]. PD was defined by the presence of at least two of the four cardinal features (bradykinesia, tremor, rigidity, and postural reflex abnormality). Other forms of parkinsonism based on laboratory tests such as MRI were excluded. All the patients were at least 40 years of age and were evaluated in the middle of their levodopa dose cycle at maximal mobility (on) for the severity of parkinsonism, and signed informed consent before participation. Next, the patients were double blindly grouped into the TCM group ( $n = 59$ , 64.27  $\pm$  11.8) or the placebo group ( $n = 56$ , 63.91  $\pm$  13.9) (Table 1). Patients were randomly assigned to the ZAZ2 or placebo group and given random numbers by a study coordinator, who also encoded the drugs with matching random numbers. Neither the patients nor the researchers monitoring the outcome knew which patient was receiving which treatment, until the study was over and the random code was broken. Anti-parkinsonism drug administration was not changed throughout the experiment. The study was approved by The Ethics Committee of Shuguang Hospital Affiliated to Shanghai University of TCM, and performed under the principles outlined in the Declaration of Helsinki; all subjects provided informed consent in accordance with institutional requirements prior to participation in the study.

**2.2. Additional Treatment.** Zeng-xiao An-shen Zhi-chan 2 (ZAZ2), the TCM used in this study, is a granule made up of 14 kinds of herbs: *Uncaria rhynchophylla* 10 g, *Rehmanniae radix* 10 g, *Cornus officinalis* 8 g, *Asnaragus cochinchinensis* 10 g, *Paeonia lactiflora* 10 g, *Desertliving cistanche* 10 g, *Puerariae radix* 10 g, *Arisaema consanguineum* Schott 10 g, *Salviae Miltiorrhizae radix* 10 g, *Acorus tatarinowii* 10 g, *Curcuma longa* Linn 12 g, *Morindae officinalis radix* 10 g, *Rhizoma gastrodiae* 10 g, and *Rhizoma chuanxiong* 10 g. ZAZ2 is commonly used in “insufficiency of Kidney yang” in China. Placebo granules were made up of 5 kinds of herbs:

TABLE 1: Patient characteristics.

	Placebo ( $n = 54$ )	ZAZ2 ( $n = 56$ )
Age (yr)	63.1 $\pm$ 10.2	62.82 $\pm$ 10.31
Men/Women	32/22	34/22
Disease duration (yr)	5.81 $\pm$ 3.24	5.73 $\pm$ 4.81
Hoehn & Yahr stages	2.35 $\pm$ 1.33	2.37 $\pm$ 1.13
Levodopa/DCI (mg/day)	396.61 $\pm$ 159.24	390.59 $\pm$ 164.71
Pramipexole (mg/day)	1.03 $\pm$ 0.69	1.00 $\pm$ 0.79
Selegiline Hydrochloride (mg/day)	8.97 $\pm$ 5.66	9.28 $\pm$ 4.95

DCI: decarboxylase inhibitor.

*Largehead atractylodes rhizome* 10 g, *Poria cocos* (Schw.) wolf 10 g, *Jobstears seed* 10 g, *Malt* 10 g, and *Chinese date* 10 g. These 5 herbs have no activity in terms of traditional Chinese medicine [13]. Patients were instructed to take one package (8 g) of ZAZ2 or placebo soluble granule three times a day at least 30 min before or after the ingestion of other drugs for three consecutive months (13 weeks). The shape and color of ZAZ2 and the placebo soluble granule are very alike and cannot be distinguished from one another by appearance or aqueous solution taste. ZAZ2 and the placebo granule were made by the manufacturing laboratory of Shuguang Hospital Affiliated to Shanghai University of TCM. The trial was carried out as a randomized, double-blind, parallel group study.

**2.3. Equipment.** All patients wore a small watch-type activity monitor equipped with a computer (*MicroMini-Motionlogger*, Ambulatory Monitoring, Inc, Ardsley, New York) on the wrist of their nondominant hand for seven consecutive days before taking test granule (week 0), one week (week 1), and 13 weeks (week 13) after taking test granule. Zero-crossing counts were recorded every one minute to register and quantify human physical activity [15], and the data was stored in internal memory. After recording, data were transmitted to an external computer by software installed on the device.

**2.4. Assessments.** Daily profiles and mean counts: We plotted the activity scores for 7 consecutive days to see the daily profiles and biological rhythms of each patient (Figure 1). The records acquired during awake times and sleep times were separated with Action-W, Version 2 (Ambulatory Monitors Inc., Ardsley, NY, USA). The mean counts during awake times and sleep times were separately calculated for each record (Table 2 and Figure 2(a)).

**UPDRS Scores.** The UPDRS of all patients were evaluated at week 0, week 1, and week 13 by neurologists who were blinded to the test granule.

**Secondary Symptom Score [18].** This score is conventionally used in China to evaluate the effects of anti-parkinsonism drugs and consists of 8 parts, including the assessments of nonfluent speech, vertigo, insomnia/nightmares, headache,

TABLE 2: Results of clinical evaluation between before and after test granule administration.

	Placebo ( $n = 54$ )			ZAZ ( $n = 56$ )		
	Week 0	Week 1	Week 13	Week 0	Week 1	Week 13
UPDRS total score	46.6 ± 16.3	44.7 ± 15.3	45.9 ± 18.1	46.3 ± 17.1	37.1 ± 11.2 ##	40.7 ± 15.1 #
UPDRS I	2.5 ± 0.7	2.3 ± 1.1	2.4 ± 1.2	2.6 ± 0.8	2.1 ± 0.7	2.3 ± 0.9
UPDRS II	15.7 ± 9.3	14.8 ± 11.2	15.3 ± 11.6	15.9 ± 11.3	12.5 ± 4.6 #	13.4 ± 9.8 #
UPDRS III	25.5 ± 12.9	23.8 ± 10.6	24.9 ± 12.7	25.4 ± 10.1	19.3 ± 9.8 #	21.6 ± 10.4
UPDRS IV	3.1 ± 1.1	2.9 ± 1.6	3.0 ± 1.4	3.2 ± 1.4	2.6 ± 0.8 #	2.7 ± 1.3 #
Awake time (counts/min)	98.5 ± 14.1	102.6 ± 18.9	100.7 ± 16.9	99.8 ± 17.8	126.7 ± 13.4 ##	118.4 ± 11.8 ##
Sleep time (counts/min)	42.9 ± 17.1	38.8 ± 15.6	40.1 ± 14.8	43.2 ± 11.6	35.6 ± 13.6 #	32.8 ± 13.6 #
$\alpha$ (awake time)	0.97 ± 0.21	0.95 ± 0.28	0.96 ± 0.18	0.97 ± 0.24	0.88 ± 0.21 #	0.86 ± 0.19 ##
$\alpha$ (sleep-time)	1.19 ± 0.28	1.16 ± 0.27	1.15 ± 0.29	1.18 ± 0.26	1.04 ± 0.22 #	1.02 ± 0.18 ##

Data presented are mean ± SD.  $P < .05$ ;  $P < .01$  compared to week 0 (repeated-measure ANOVAs); # $P < .05$ ; ## $P < .01$  compared to placebo (Bonferroni test); UPDRS: Unified Parkinson's Disease Rating Scale;  $\alpha$ : power-law exponent.

sweating or night sweats, tiredness, sense of cold, and dysuria. In this study, the secondary symptom scores were evaluated in week 0, week 1, and week 13 for all participants by the same neurologists, and it reflects the opinion of PD patients (Table 3).

**Power-Law Temporal Analysis  $\alpha$ .** The methods for power-law temporal analyses were the same as those described in Pan et al. [15]. The awake time and sleep time data were used separately for the power-law temporal analyses. After integrating the time series, the data were wavelet-transformed using the third derivative of the Gaussian function as the so-called "mother wavelet." The wavelet coefficients ( $W(S)$ ) at each point along the time series and at different timescales ( $S$ ) were obtained by convolving the mother wavelet with the time series. This approach facilitates the probing of transient increases or decreases in detrended activity records at different timescales. The transient increases (low-high-low level activity patterns) yielded local maxima of the wavelet coefficients at their time points, while the decreases (high-low-high level activity patterns) yielded local minima of the wavelet coefficients. Next, the squared wavelet coefficients at the local maxima or minima were averaged for all the data points, and the power-law exponent ( $\alpha$ ) was obtained separately for local maxima and minima as the slope of a straight line fitted in the double-logarithmic plot of  $S$  versus  $W(S)^2$  in the range of  $S$  corresponding to 8 to 35 min. The power-law exponent of maxima has been successfully used for the assessment for PD in previous studies [15, 20]. In this study, we analyzed the local maxima separately for the awake time and sleep time of each record (Table 2 and Figure 2(b)).

For the safety assessments, each patient underwent a physical examination by a physician and laboratory tests for blood counts and biochemistry, and urinalysis at each visit.

**2.5. Statistical Analysis.** Repeated-measure ANOVAs were conducted to test the differences among week 0, week 1, and week 13 in the ZAZ2 and placebo groups. When a significant difference was detected, a post-hoc test (Bonferroni test) was conducted between the ZAZ2 and placebo groups compared for the UPDRS total score, UPDRS Part I, Part II, Part III,

Part II + Part III, and Part IV, mean values, and the power-law temporal  $\alpha$  in awake time and sleep time. A significant difference was defined as  $P < .05$ . SPSS windows Version 17.0 was used for statistical analyses. All data are expressed as the mean ± standard deviation.

### 3. Results

Five patients dropped out of the study; one patient in the ZAZ2 group was unable to tolerate the bitter taste of ZAZ2, while two in the ZAZ2 group and two in the placebo group dropped out due to a conflict with other TCM prescribed for concomitant diseases. Neither physical examination nor laboratory tests revealed any adverse changes after additional treatment in either group.

The post-hoc test revealed no significant differences in baseline (week 0) UPDRS scores, Hoehn & Yahr stages, mean counts, and power-law temporal exponent  $\alpha$  values, or in the dosage of L-dopa/DCI, Dopamine agonist or monoamine oxidase B, between the ZAZ2 and placebo groups (Tables 1 and 2).

Daily profiles of AMI counts clearly demonstrated improvement of the biological rhythm after the additional treatment in the ZAZ2 group (Figure 1(a)) but not in the placebo group (Figure 1(b)). Patients in the ZAZ2 group showed a more frequent switch from high activity to low activity in awake time and lower activity during sleep time after ZAZ2 than before ZAZ2 (Figures 1(a) and 2(a), Table 2,  $P < .05$ , Bonferroni test). Such changes were not observed after placebo granule intake (Figures 1(b) and 2(a), Table 2).

When the effects of ZAZ2 were evaluated with UPDRS scores, significant and persistent improvements were found in the part II, parts II + III, and part IV scores (Table 2). Although some parts of UPDRS improved in week 1 in both the ZAZ2 and placebo groups, the improvement did not persist until week 13 (repeated-measure ANOVAs Table 2). There were significant differences in UPDRS Part II, Part II + Part III, and Part IV scores at week 13 between the ZAZ2 group and placebo group ( $P < .05$ , Bonferroni test; Table 2).

The local power-law exponent  $\alpha$ , given by a slope of the log  $S$  versus log  $W(S)^2$  relationship, characterizes the nature

TABLE 3: Effects on secondary symptoms of PD.

Group	Time	Nonfluent speech	Vertigo	Insomnia/ nightmare	Headache	Sweating or night sweats	Tiredness	Sense of cold	Dysuria
Placebo	0 weeks	1.12 ± 0.59	1.31 ± 0.97	2.67 ± 0.87	1.03 ± 0.75	2.13 ± 1.32	1.70 ± 0.97	1.78 ± 0.39	2.29 ± 1.02
	1 weeks	0.69 ± 0.32	1.12 ± 0.69	2.40 ± 0.69	0.96 ± 0.36	1.87 ± 0.58	1.35 ± 0.69	1.39 ± 0.81	1.69 ± 0.92
	13 weeks	1.02 ± 0.36	1.28 ± 0.53	2.45 ± 0.38	0.99 ± 0.65	2.18 ± 0.56	1.58 ± 0.66	1.64 ± 0.58	2.18 ± 1.30
ZAZ2	0 weeks	1.08 ± 0.74	1.33 ± 0.83	2.77 ± 0.98	0.92 ± 0.56	2.11 ± 0.68	1.66 ± 0.57	1.90 ± 0.67	2.23 ± 0.69
	1 weeks	0.56 ± 0.28	0.84 ± 0.26 #	2.03 ± 0.78	0.64 ± 0.28 ##	1.38 ± 0.69 #	1.21 ± 0.46	1.48 ± 0.57	1.43 ± 0.31 #
	13 weeks	0.65 ± 0.33 ##	0.95 ± 0.37 #	1.73 ± 0.38 #	0.63 ± 0.19 #	1.48 ± 0.28 ##	1.27 ± 0.51 #	1.58 ± 0.61	1.46 ± 0.36 ##

Data presented are mean ± SD;  $P < .05$ ;  $P < .01$  compared with 0 weeks (repeated-measure ANOVAs). # $P < .05$ ; ## $P < .01$  compared to placebo (Bonferroni test).

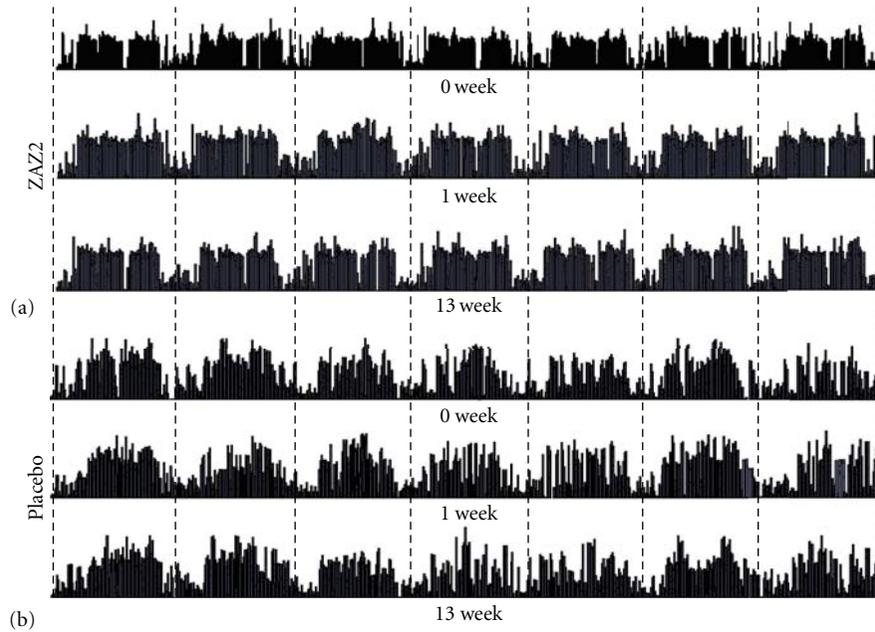


FIGURE 1: Daily profiles of AMI counts demonstrated the biological rhythm after granule ingestion in the ZAZ2 group (a) and in the placebo group (b). Each dash in the recordings represents midnight.

of “switching” patterns between high and low values in a statistical sense. The average wavelet coefficients exhibited linear relationships in the range of scales from 8 min to 35 min both for the ZAZ2 and placebo groups (Figure 2(b)). The local power-law exponent  $\alpha$  values during both awake time and sleep time were significantly decreased both 1 week and 13 weeks after taking ZAZ2, but not after taking placebo granule (Table 2 and Figure 2(c),  $P < .01$ ; Bonferroni test).

As the exploratory outcome of this study, most of the secondary symptoms were improved by the ZAZ2 treatment, whereas only a few symptoms in the placebo group were transiently improved in week 1 (Table 3).

#### 4. Discussion

In this study, we demonstrate that ZAZ2, a TCM, ameliorates the disability of PD patients using the analysis of power-law temporal autocorrelation of the AMI records together with conventional UPDRS. Because a recent study indicated that

improvement of the scores in UPDRS Part II reflect the long-term outcome of the patients [21], improvements of scores in UPDRS Part II, II + III, and IV likely reflect the beneficial effects of ZAZ2 on the patients’ overall ADL as an endpoint of the treatment. ZAZ2 induced no significant adverse effects and was tolerable by more than 98% of the participants.

We previously demonstrated that the change in the local power-law exponent  $\alpha$  is a quantitative predictor for evaluating the akinesia changes in PD [15, 20]. Because the  $\alpha$ -values indicate persistency, lower  $\alpha$ -values correspond to more frequent switching of behavior or higher physical activity [15, 20]. Therefore, the significant reduction in the  $\alpha$ -values after ZAZ2 likely represents the improvement of motor function of the patients as a whole, which is in accordance with the improvement of scores of UPDRS Part II and Part II + Part III.

The effects of ZAZ2 are also demonstrated by the improvement in the scores for the secondary symptoms (Tables 2 and 3) and in the wake-sleep cycle (Figure 1) as

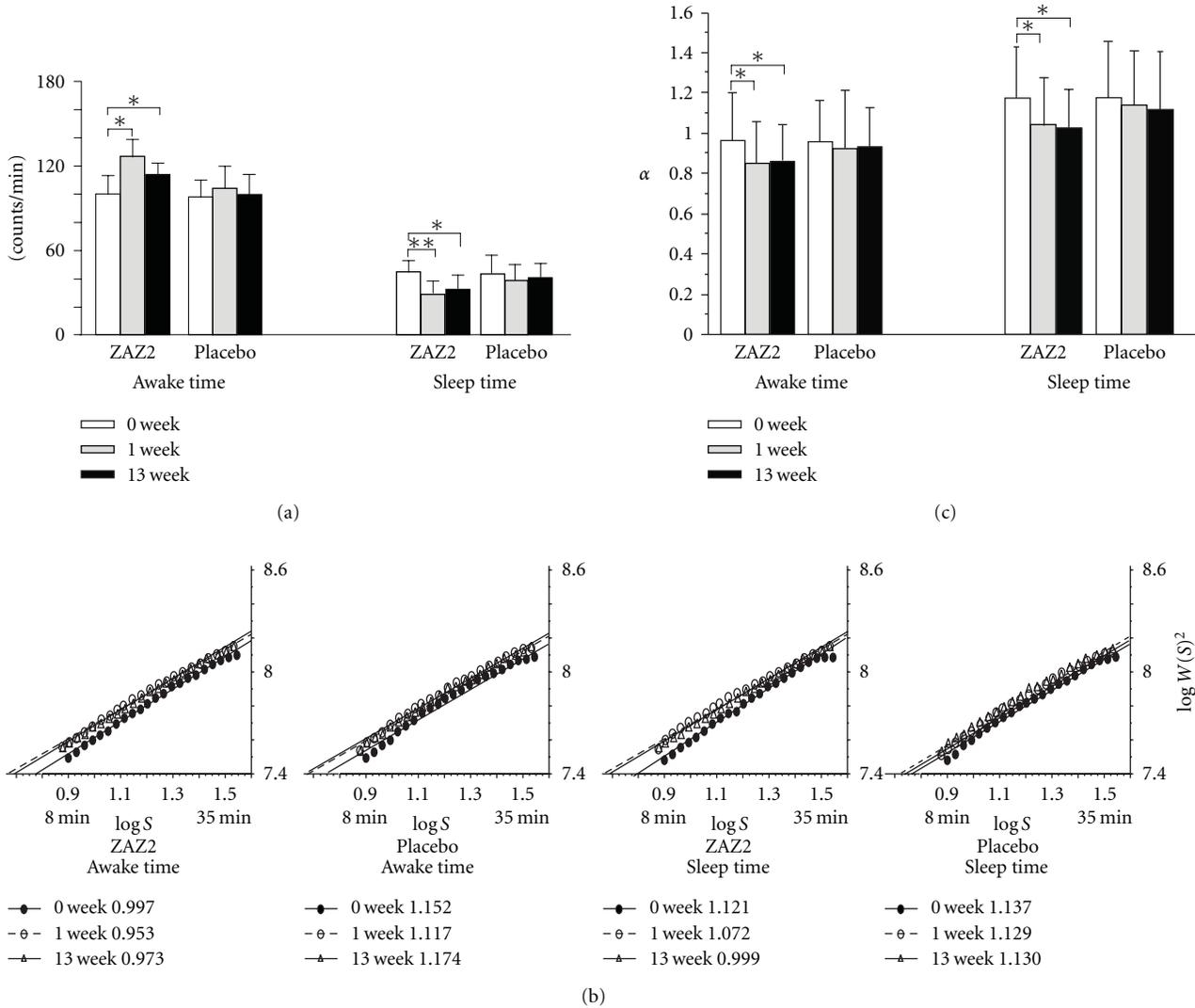


FIGURE 2: Before and after administration of granules of ZAZ2 and placebo for mean counts of physical activity (a), average wavelet coefficients, as a function of the wavelet scale for awake time and sleep-time, the slopes are power-law exponents,  $\alpha$  (b), and comparisons of the mean  $\alpha$  (c).

exploratory outcomes of this study. Indeed, activity during sleep time was markedly decreased and the local power-law exponent  $\alpha$  was significantly decreased during sleep time as well as during awake time (Figures 2(a) and 2(c)). Because sleep disturbance, which is frequent among patients with PD, is thought to be due to disruption of the nighttime effects of levodopa [22], improvement of wake-sleep rhythm is likely a reflection of an improvement in parkinsonism. ZAZ2 may have beneficial effects on ADL by ameliorating the symptoms resulting from parkinsonism without exacerbating the L-dopa-induced adverse effects, as demonstrated in the improvement in scores of UPDRS Part IV.

TCM ameliorates various symptoms, particularly the ageing-related symptoms that are called *shen xu* (kidney deficiency) in Chinese [10, 11]. *Shen* (the kidney) denotes a functional visceral system (*zang*) that plays a central role in the regulation of growth, maturation, and ageing, and

is subdivided into *shen yang* (kidney yang) and *shen yin* (kidney yin). Kidney yang can be described as the driving forces of all metabolic processes that improve the movements of the body. The production of kidney yin is considered to be effective at increasing nutrition to the muscles and improving the smoothness of the movements of the body by constituting the structive potential for the production of kidney yang. Based on this concept, TCM aims to potentiate a diminishing vitality of this transformative cycle caused by a decline of the essence (*jing*), which is stored in the kidneys and underpins the functions of both kidney yin and yang [23, 24].

Among the 14 components of ZAZ2, *Morindae officinalis radix* and *Desertliving Cistanche* might strengthen the “kidney yang” while *Asnaragus cochinchinensis*, *Cornus officinalis*, and *Rehmanniae radix* might increase the “kidney yin.” The other components ameliorate secondary symptoms such as

headache, vertigo, and tinnitus (*Uncaria rhynchophylla* and *Rhizoma gastrodiae*), enhance the strength of the “kidney” (*Paeonia lactiflora*, *Puerariae radix*, *Salviae Miltiorrhizae radix*, *Curcuma longa* Linn, and *Rhizoma chuanxiong*), or increase blood circulation in the brain (*Arisaema consanguineum* Schott and *Acorus tatarinowii*). In addition, the inhibitory effects of TCM on fibril formation and inhibited A $\beta$  aggregation (*Uncaria rhynchophylla*) [25], and on apoptosis and the neurobehavioral impairment of 1-methyl-4-phenylpyridinium ion (MPP<sup>+</sup>)-induced PD model mice (*desertliving Cistanche*) [26, 27] and rats (*Uncaria rhynchophylla*, *Cornus officinalis*, *Rehmanniae radix*, and *Paeonia lactiflora*) [28] have been reported. Whether the herbs in ZAZ2 contain L-dopa or anticholinergic agents has not been demonstrated. Therefore, ZAZ2 may be potentially effective in the regulation of motor and various nonmotor symptoms of patients with PD without inducing the adverse effects of conventional anti-parkinsonism drugs. ZAZ2 is tolerable for long-term administration, and hence is likely a suitable choice as an additional drug for long-term control of the symptoms of PD.

### Authors' Contribution

Weidong Pan participated in the entire study, formulated the study concept and design, provided statistical expertise, and assisted with drafting of the manuscript; Shin Kwak participated in the entire study and assisted with concept and design, and drafting of the manuscript; Yun Liu participated in part of content and data compilation; Yan Sun participated in part of content and data compilation; Zhenglong Fang participated in part of content and data compilation; Baofeng Qin participated in part of content and data compilation; Yoshiharu Yamamoto participated in part of content and critical revision of the manuscript for important intellectual content.

### Disclosure

All authors have no stock ownership in medically related fields, no consultancies, no advisory Boards, no partnerships, no grants, no intellectual property rights, no expert testimony, no employment, or no contracts as well as no royalties.

### Conflict of Interests

The authors declared that there is no conflict of interest.

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## Review Article

# Olfactory Loss in Parkinson's Disease

**Antje Haehner,<sup>1</sup> Thomas Hummel,<sup>2</sup> and Heinz Reichmann<sup>3</sup>**

<sup>1</sup> Department of Otorhinolaryngology and Department of Neurology, Medical School, Dresden University of Technology, Fetscherstraße 74, 01307 Dresden, Germany

<sup>2</sup> Department of Otorhinolaryngology, Medical School, Dresden University of Technology, Fetscherstraße 74, 01307 Dresden, Germany

<sup>3</sup> Department of Neurology, Medical School, Dresden University of Technology, Fetscherstraße 74, 01307 Dresden, Germany

Correspondence should be addressed to Antje Haehner, antje.haehner@uniklinikum-dresden.de

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Impairment of olfaction is a characteristic and early feature of Parkinson's disease. Recent data indicate that >95% of patients with Parkinson's disease present with significant olfactory loss. Deficits in the sense of smell may precede clinical motor symptoms by years and can be used to assess the risk for developing Parkinson's disease in otherwise asymptomatic individuals. This paper summarizes the available information about olfactory function in Parkinson's disease, indicating the advantageous use of olfactory probes in early and differential diagnosis.

## 1. Prevalence and Character of Olfactory Loss in PD

According to a recent study by Politis et al. [1], olfactory loss belongs to the top-five most prevalent motor and nonmotor symptoms in early stage PD patients that have affected their quality of life. Only pain is referred to as a more prevalent troublesome nonmotor problem in this patient group.

In line with this result, virtually all studies performed since the 1970s have shown olfactory disturbances in PD patients. Published data on the prevalence of olfactory dysfunction in PD range from 45% and 49% in the pioneering studies of Ansari and Johnson [2], and Ward et al. [3], respectively, up to 74% in the work of Hawkes et al. [4], or as high as 90% in a study published by Doty et al. [5]. In our recent multicentre study [6] using a comprehensive testing method (see chapter 2) in a large sample of PD patients ( $n = 400$ ) from 3 independent populations, the prevalence of olfactory dysfunction in people with PD was greater than previously reported with regard to norms obtained in healthy young subjects. More than 96% of PD patients were found to present with olfactory dysfunction. When using age-dependent normative criteria, 74.5% of this study population was diagnosed with olfactory loss (Figure 1). Furthermore, more than 80% of PD patients with

smell loss were functionally anosmic or severely hyposmic regardless of the olfactory test being used for diagnosis. Only very few patients present with accompanying parosmia, or phantosmia.

Our data also confirmed numerous previous studies with regard to the lack of olfactory improvement after therapy with dopaminergic agents [5, 7] and the missing correlation between olfactory loss and both duration of disease [4, 5, 8] and the clinical severity of PD as measured by means of the Hoehn and Yahr scale and the UPDRS (compare [9])—although some studies found a correlation between the severity of PD and certain measures of olfactory function, namely, latencies of olfactory event-related potentials [10] or results from an odor discrimination task [11]. With regard to olfactory function, we did not find major differences between subtypes of PD, namely, tremor-dominant PD, akinetic-rigid PD, and mixed-type PD. While this confirms previous observations in a small sample size of 37 patients [7] (Figure 2), the present findings are in contrast to reports by Stern and colleagues [8] who reported significantly better odor identification scores in patients with tremor-predominant PD than in cases with postural instability-gait disorder-predominant PD. While differences between studies may be due to the type of olfactory test used, sample size, normative data, and age distribution (which varied between

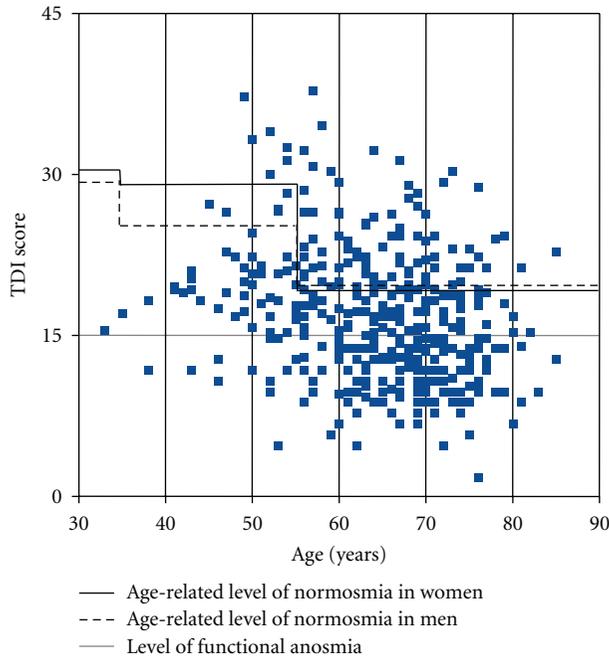


FIGURE 1: Olfactory function of the total number of 400 PD patients. Results are shown as a composite TDI score (sum of odor threshold, odor discrimination, and odor identification score) adjusted to age-related norms [6].

these investigations), available data allow the conclusion that olfactory dysfunction is a highly reliable symptom of the disease. This concurs with the results of a case-control study on 90 PD patients and healthy controls by Bohnen et al. [12] who found that the accuracy of smell testing in PD diagnosis outweighs the accuracy of motor test batteries, and also other nonmotor tests of, for example, depression and anxiety.

## 2. Testing Methods

As the olfactory loss in PD has a general character, all three olfactory qualities (threshold, discrimination, identification) are involved. Therefore, different subtests of olfactory function may reflect smell loss in PD patients and may be used as single measurement. Only a comprehensive approach, however, allows a precise evaluation of olfactory function, that is, that it would be best to perform all 3 subtests to obtain a maximum of reliable information.

Psychophysical assessment of olfactory function is based on the presentation of odors and the recording of the subjects' response. Advantage of this "low-tech" approach include the speed of testing, allowing for rapid screening of olfactory function [13, 14]. While screening tests only differentiate between normal and pathologic states, more extensive tests allow for a reliable discrimination between anosmic, hyposmic, and normosmic subjects, respectively. Good tests have to be based (1) on normative data acquired and validated in (2) large samples (e.g., [15, 16]). Many tests are based on a forced choice verbal identification of

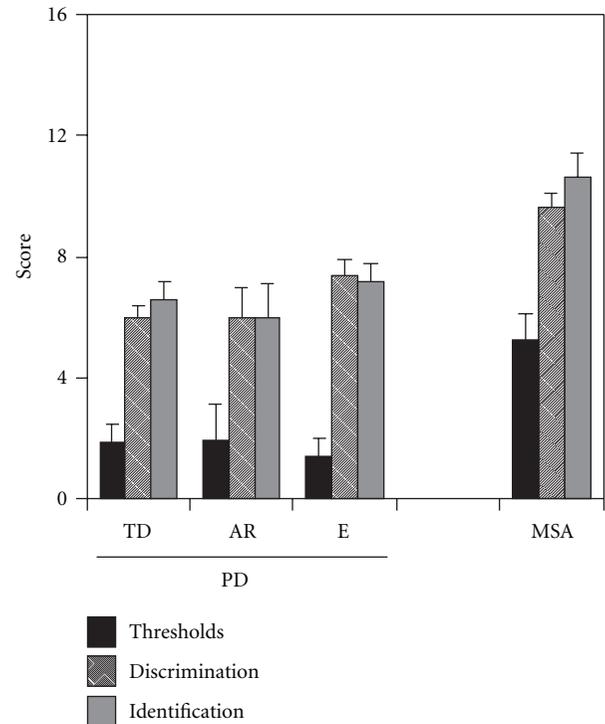


FIGURE 2: Olfactory function in PD subtypes (TD: tremor-dominant, AR: akinetic-rigid, e: equivalent type) and multiple system atrophy (MSA) [7].

odors while others also include results from odor discrimination and odor threshold measurements (comprehensive approach; Figure 3).

Most tests are based on the identification of odors. In odor identification tasks, an odorant is presented at a suprathreshold concentration and subjects are required to identify the odor from a list of descriptors. This forced-choice procedure controls the subjects' response bias. A major problem of odor identification is, however, that it strongly relies on the verbal abilities of the subject. Consequently, on average, this enables female subjects to outperform men [17]. In addition, odor identification tests have a strong cultural precondition as not all odors are known equally well in various cultural groups.

The concept embedded in threshold tests is that a subject is repeatedly exposed to ascending and descending concentrations of the same odorant and is required to identify the least detectable concentration for this individual odor ([18]; see also [19]).

Other measures assessing olfactory loss may include investigation of the patient's quality of life, for example, the "Questionnaire for Olfactory Dysfunction" [20], or the recording of olfactory event-related potentials (for review, see [21]).

In the near future, immunohistochemical, volumetric, and functional neuroimaging studies of the olfactory system might become relevant for PD diagnosis. There is still little information about PD-specific changes of the olfactory epithelium and their diagnostic use. In a recent study, we

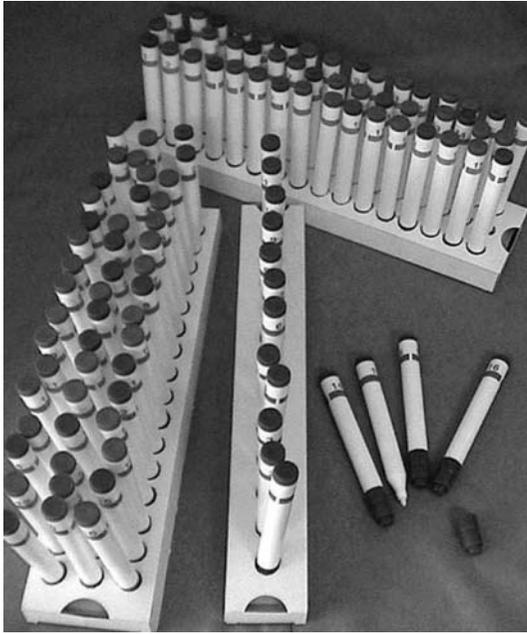


FIGURE 3: “Sniffin’ Sticks” test kit which is comprised of 3 individual tests of olfactory function (phenyl ethyl alcohol odor threshold, odor discrimination, and odor identification). The scores of the individual tests are summated to the so-called “TDI score” which is a reliable means to estimate the degree of olfactory function.

compared bioptic material from PD patients for histological/histochemical changes with that from patients with olfactory dysfunction due to other reasons [22]. However, we found no specific changes in the nasal mucosa of PD patients. Further, it could be assumed that loss of olfactory bulb volume would be a reliable finding in PD which, to some degree, might be helpful in differential and early diagnosis of PD. Results from a recent study [23] indicated that there is little if any difference in OB volume between PD patients with anosmia/hyposmia and healthy, normosmic controls. In another effort to identify brain structures responsible for smell loss in PD, functional magnetic resonance imaging (fMRI) was used to investigate brain activity related to olfactory processing in PD. Overall, the results of these studies [24, 25] indicate that neuronal activity in the amygdala and hippocampus is reduced in PD patients which may specifically impact on olfactory sensitivity. In addition, neuronal activity in components of corticostriatal loops appears to be upregulated indicating compensatory processes involving the dopaminergic system.

### 3. Olfactory Dysfunction as a Prodromal Symptom

Support for the existence of a prodromal phase comes from imaging, neuropathology, and various clinical or epidemiological surveys. The best evidence that derives from large prospective studies relates to disorders affecting olfaction, the enteric nervous system, and depression [26–28]. Estimates for the duration of the prodrome range from 2 to 50 years

depending on the symptom, duration of followup, accuracy of diagnosis, and individual variation.

PD patients frequently report reduction in their sense of smell that occurs a few years prior to the onset of motor symptoms. However, patients’ unawareness of smell deficits may account for the inconsistent results described in retrospective surveys. In a small study [29], upon questioning prior to olfactory testing, 9 out of 37 patients (24%) indicated an awareness of a decrease of olfactory function which actually preceded their diagnosis of PD.

A plethora of evidence from recent studies supports the view that deficits in the sense of smell may precede clinical motor symptoms by years. A study by Ponsen et al. [30] on 361 asymptomatic relatives of PD patients selected 40 relatives with the lowest olfactory performance. Within 2 years of followup, 10% of these first-degree relatives of PD patients with significant olfactory loss developed clinical PD. In a followup study, five years from baseline testing [31], five relatives had developed clinical PD as defined by the United Kingdom Parkinson’s Disease Society Brain Bank Diagnostic Criteria for Parkinson’s Disease. Initial clinical (motor) symptoms appeared 9 to 52 months (median 15 months) after baseline testing. Poorer performance on each of three olfactory tasks was associated with an increased risk of developing PD within 5 years. In 2007 [32], we published data on a clinical followup of a previous investigation [33], in which 30 patients diagnosed with idiopathic olfactory loss participated. Four years from baseline, 7% ( $n = 2$ ) of the individuals with idiopathic olfactory loss who were available for followup examination ( $n = 24$ ) had newly developed clinical PD symptoms. Altogether, 13% ( $n = 4$ ) of the patients presented with PD-relevant abnormalities of the motor system. The results indicated that unexplained olfactory loss may be associated with an increased risk of developing PD-relevant motor symptoms.

This is in accord with the results of a large longitudinal study by Ross and colleagues [34]. They assessed olfactory function in 2267 elderly men in the Honolulu Heart Program and found an association between smell loss and future development of PD. They came to the conclusion that impaired olfaction can predate PD by at least 4 years and may be a useful screening tool to detect those at high risk for development of PD in later life. However, this relationship appears to weaken beyond the 4-year period.

Along with quantitative smell loss, such as hyposmia, idiopathic phantosmia has also been suggested to herald PD. A number of case reports could show that some patients have experienced phantosmia very early in the course of the disease [35–37]. According to a recent study by Landis et al. [38], however, idiopathic phantosmia as an early sign of PD remains probably a rather exceptional presentation whereas the overwhelming majority of people with idiopathic phantosmia will not develop PD.

Recent data on olfactory loss as a PD symptom that is present at the earliest stages of the disease are compatible with predictions made on the basis of neuropathological investigations. Braak et al. [39] describe involvement of olfactory pathways and lower brainstem before nigrostriatal pathways are affected which might cause early nonmotor

symptoms. Huisman et al. [40] found an increase of (inhibitory) dopaminergic neurons in the olfactory bulb in PD patients. They interpreted their finding within the context of a possible compensatory mechanism in response to the loss of dopaminergic neurons in the basal ganglia. This concurs with their observation that dopaminergic neurogenesis in the glomerular layer tripled after nigrostriatal lesioning and, consistent with this finding, the total number of tyrosine hydroxylase- (TH-) positive cells increased [41]. However, results of a followup study [42] indicated a gender-related change, that is, that the number of dopaminergic cells in the olfactory bulbs of both male and female Parkinson's patients equals that of healthy males of the same age group. Authors, therefore, concluded that the hyposmia in Parkinson's disease patients cannot simply be ascribed to dopamine in the olfactory bulb.

Regardless the small number of prospective studies in this field, olfactory loss should be considered a promising contribution to the early diagnosis of PD. For instance, the current Parkinson's associated risk syndrome (PARS) study [43] will advance our understanding of early PD presentation.

#### 4. Olfaction in Differential Diagnosis

Numerous studies suggest that olfactory disturbances in PD may have diagnostic utility for the differentiation of PD from other movement disorders. Wenning et al. [44] presented data suggesting that olfactory function is differentially impaired in distinct Parkinsonian syndromes. They reported a preserved or mildly impaired olfactory function to be more likely for atypical parkinsonism such as multiple system atrophy, progressive supranuclear palsy, or corticobasal degeneration whereas markedly pronounced olfactory loss appeared to suggest PD. Similar to the results of Wenning et al., in a study on 50 Parkinsonian patients [29], we also found evidence for olfactory loss in MSA, but little or no olfactory loss in (the few investigated) patients with PSP and CBD. With regard to the differentiation between MSA and PD (Figure 3) at a cutoff of a TDI score (combined results for odor thresholds, odor discrimination, and odor identification; see also [15]) of 19.5, psychophysical testing had a sensitivity of 78% and a specificity of 100%. When the cutoff TDI score was increased to 24.8, sensitivity in this sample was 100% while specificity fell to 63%. This moderate specificity seems to be the limiting parameter for diagnostic purposes. A recent American Academy of Neurology practice parameter on the diagnosis and prognosis of PD concluded that olfactory testing "should be considered" to differentiate PD from PSP and CBD but not from MSA [45]. Furthermore, Liberini et al. [46] reported a significant olfactory impairment in Lewy body disease (LBD) which does not allow differentiation from PD. In a sample of 116 patients with mild LBD, mild Alzheimer's disease, mild cognitive impairment, and controls, Williams et al. [47] describe even more marked olfactory impairment in patients with mild dementia with Lewy bodies than present in those with mild Alzheimer's disease. This lends significance to the role of

Lewy body pathology in olfactory dysfunction [48] which would be in line with the observation that patients with nondegenerative causes of parkinsonism such as vascular parkinsonism [49] present with preserved smell function. There is also evidence for less olfactory disturbance in familial parkinsonism. In PARK2, the olfactory sense is relatively well preserved whereas PARK1 subjects are mildly hyposmic. Recent data [50] suggest that PARK 8 individuals present with impaired olfactory identification whilst asymptomatic carriers show normal olfactory performance.

In secondary parkinsonism, study results also indicate a relationship between Parkinsonian symptoms and olfactory dysfunction. We found an association between medication-induced parkinsonism and olfactory dysfunction in patients with psychotic depression treated with D2-blocking neuroleptic drugs [51]. Here, the severity of motor symptoms was positively correlated with the degree of olfactory dysfunction which might indicate patients with a latent basal ganglia dysfunction. Similar to the results seen in drug-induced parkinsonism, data from a recent study reveal that Wilson's disease patients with neurological symptoms show a significant olfactory dysfunction compared to hepatic-type patients [52]. Individuals who are more severely neurologically affected also present with more pronounced olfactory deficits. Based on these observations, olfactory testing should not be considered to differentiate PD from these specific conditions. However, olfactory testing has been shown to be important in cases where patients present with Parkinsonian features but with preserved olfaction. Here, it appears valid to question a diagnosis of PD.

#### 5. Conclusions

Recent data suggest that inexpensive olfactory probes improve the diagnostic process in patients with PD. In contrast to imaging procedures, olfactory testing is quick and easy to perform. Validated tests can be used as reliable diagnostic tools even in nonspecialized centers. Deeb et al. [53] found that a basic smell test is as sensitive as a dopamine transporter scan. According to this study, the sensitivities of the University of Pennsylvania Smell Identification Test [54] and DaTSCAN are high at 86% and 92%, respectively. Although DaTSCAN is superior for "localization," a smell test is considerably "cheaper," and neither is disease specific. Consequently, structured and validated tests of olfactory function should be a mandatory part of the early and differential diagnosis of PD.

Our experience suggests that it only takes little time to follow up patients with a diagnosis of idiopathic smell loss neurologically as an essential part of their regularly scheduled visit to the Smell and Taste Clinic which is a time- and expense-efficient process well warranted. Such a comprehensive multidisciplinary approach might enable the physician to detect slight motor abnormalities in an at-risk population as early as possible. This may also give rise to clinical studies which allow administration of neuroprotective substances in individuals with, for example, unexplained smell loss. Up till now, therapeutic studies with

neuroprotective agents in hyposmic PD patients are currently underway and may help us to evolve preventive strategies for PD in future.

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## Review Article

# Neurobiology of Depression and Anxiety in Parkinson's Disease

**Osamu Kano,<sup>1,2</sup> Ken Ikeda,<sup>1</sup> Derek Cridebring,<sup>3</sup> Takanori Takazawa,<sup>1</sup>  
Yasuhiro Yoshii,<sup>1</sup> and Yasuo Iwasaki<sup>1</sup>**

<sup>1</sup> Department of Neurology, Toho University Omori Medical Center, 6-11-1 Omorinishi, Otaku, Tokyo 143-8541, Japan

<sup>2</sup> Department of Neurology, Methodist Neurological Institute, 6565 Fannin Street, B05-039G, Houston, TX 77030, USA

<sup>3</sup> Department of Bioinformatics and Bioengineering, Methodist Hospital Research Institute, 6565 Fannin Street, R6-212, Houston, TX 77030, USA

Correspondence should be addressed to Osamu Kano, osamukano@aol.com

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Depression and anxiety are common in Parkinson's disease (PD) and have important consequences on quality of life. These have long been recognized as frequent accompanying syndromes of PD, and several reports suggest that these are the causative process or risk factors that are present many years before the appearance of motor symptoms. The neurochemical changes in PD involving dopamine, norepinephrine, and serotonin might be related to the pathophysiology of depression and anxiety, but this is still not clear. Several studies showed that anxiety in PD patients occurs earlier than depression, during premotor phase, suggesting that there may be a link between the mechanisms that cause anxiety and PD. Whereas a recent study reported that PD patients with depression and anxiety were associated with different demographic and clinical features.

## 1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that results in progressive extrapyramidal motor dysfunction primarily related to loss of dopaminergic nigrostriatal function. The loss of dopamine leads to difficulty with movement, including slowness or lack of movement, rigidity, and resting tremor. Though less acknowledged, non-motor symptoms (NMSs) in PD are common and were recognized by Parkinson himself [1]. He referred to urinary incontinence, constipation, sleep disturbance and delirium. PD patients also suffer from a variety of NMSs, including significant changes in emotional well-being that deleteriously impact their quality of life [2]. O'Sullivan S. S. et al. attempted to correlate NMSs in PD by reviewing medical histories of pathologically identified patients. Twenty-one percent of patients presented with NMSs including pain, urinary dysfunction, depression, and anxiety [3]. In addition, premorbid personality traits consisted of cautiousness, inflexibility, introversion, and

lack of novelty seeking, which also persist after the onset of motor illness. It has been suggested in the general population study that these traits, as well as the low premorbid rates of coffee drinking and alcohol consumption, may reflect an underlying damage to the mesolimbic dopaminergic pathways among individuals predisposed to PD [4].

However, the NMSs of PD are not well recognized in clinical practice and one US study reported that existing depression, anxiety, and fatigue are not identified by neurologists in 50% of consultations, and sleep disturbances are not identified in over 40% of consultations [5]. Psychiatric symptoms may be missed if a clinician's interest is mainly focused on motor impairment. Patients' reluctance to report psychological symptoms may also contribute to the limited detection of these disorders.

This paper is a review of current data on psychiatric features in PD, specifically depression and anxiety, which are important determinants of quality of life, and, therefore, requires early detection and intervention.

## 2. When Do Depression and Anxiety Occur in PD?

PD cannot be clinically diagnosed until motor symptoms appear, and it is commonly thought that NMSs occur only in late or advanced PD. However, NMSs can indeed present at any stage of the disease, including the early and pre-motor phase [6–9]. Several case-control or cohort studies suggest that anxiety may be one of the earliest manifestations in PD. In a population-based, case-control study, PD patients historical medical records were examined for depression and anxiety in pre-motor phase of PD (Table 1). This finding held true even when the analysis went as far back as 20 years before the onset of motor symptoms [10]. In addition, the Health Professionals Follow-up study showed that “phobic anxiety” was a significant risk factor for the development of PD [11], and the composite Minnesota Multiphasic Personality Inventory of neuroticism also showed that patients with high anxiety were at an increased risk for PD [12].

While the previously mentioned articles do not look at or show a link between depression and PD, there are several supporting articles. One study found that the initiation of any antidepressant therapy was associated with a higher risk of PD within 2 years after the start of treatment, suggesting that depressive symptoms could be an early manifestation of PD [14]. The second study used a self-report of depression and use of psychotropic medication to identify a link between depression and PD [15]. The third study looked at a database of medical histories in the Netherlands and found a positive association between depression and subsequent incidence of PD [13]. While there are some disparities between depression and PD during the pre-motor phase, all the articles that have looked at anxiety and PD have shown a link, suggesting that there may be an association between the mechanism that causes anxiety and PD. In summary, these reports show that anxiety and depression are associated with PD and suggest that the causative process or risk factors underlying PD may be present many years before the appearance of motor symptoms.

## 3. Depression

According to DSM-IV criteria, a major depressive disorder is defined as a person who must either have a depressed mood or a loss of interest or pleasure in daily activities consistently for at least a two-week period in addition to fatigue, insomnia, weight loss, and so on. It is estimated that between 30–45% of PD patients are depressed, which reduces both subjective and objective quality of life independent of motor deficits [16–19]. By contrast, the average prevalence of clinically relevant depression in an age-matched group of the general population is roughly 13.5% [20].

One potential explanation for this increased prevalence of depression is the damage that PD has on the dopaminergic, serotonergic, and noradrenergic systems [21]. Remy et al. [22] used [<sup>11</sup>C]RTI-32 PET, an *in vivo* marker of both dopamine and noradrenaline transporter binding, to localize differences between depressed and nondepressed PD patients. Depressed PD patients had lower [<sup>11</sup>C]RTI-32

binding than nondepressed PD patients in the limbic system, but also in locus coeruleus, which is the noradrenergic nucleus. They suggested that depression in PD might be associated with a loss of dopamine and noradrenaline innervations in the limbic system. A randomized, controlled trial of paroxetine CR (selective serotonin reuptake inhibitor (SSRI)), nortriptyline (Tricyclic antidepressant (TCA)), and placebo in patients with PD and depression showed that Nortriptyline was efficacious in the treatment of depression and paroxetine CR was not [23]. However, Atomoxetine (selective norepinephrine reuptake inhibitor (SNRI)) was not efficacious for the treatment of depression in PD [24]. TCA is a dual (serotonin and noradrenaline) reuptake inhibitor, SSRI inhibits only serotonin, and SNRI inhibits only noradrenaline; therefore, it is possible that the mechanism of the apparent superiority of nortriptyline is its effect on norepinephrine besides serotonin.

The first randomized study done by Rektorova et al. showed possible antidepressive effects, not dependent on motor improvement of pramipexole (PPX) as compared to pergolide [25]. PPX, a D<sub>2</sub>/D<sub>3</sub> receptor agonist, preferentially acts on D<sub>3</sub> receptors in the brain, while pergolide preferentially acts on D<sub>2</sub> receptors. We found that PPX has benefits for depressive symptoms in PD patients, and antidepressant effects did not depend on motor functional improvement [26]. These results suggest that the original serotonergic and noradrenergic hypotheses of depression do not fully account for the neurobiology of depression or mechanism of action of effective antidepressants. In addition, there is a efficacious difference among dopamine receptor agonist. Roy et al. [27] found lower cerebrospinal fluid levels of homovanillic acid (HVA), which is a dopamine metabolite found at lower levels in depressed subjects. In addition, direct measurement of brain monoamine metabolites from the internal jugular vein of patients resistant to depression treatments revealed low HVA levels that were highly correlated with illness severity [28]. These results support the monoaminergic theories of depression, which hold that dysregulation of PD system, involving dopamine in addition to serotonin and norepinephrine, may also be involved in depression.

Ropinirole, another D<sub>2</sub>/D<sub>3</sub> agonist, acts on D<sub>3</sub> preferentially and showed effects on NMSs in PD patients with motor fluctuations and/or dyskinesias [29]. In addition, Pahwa et al. reported in a double-blind placebo-controlled study, that Ropinirole improved NMSs in PD patients [30]. When comparing other dopamine agonists which act on D<sub>2</sub> preferentially, bromocriptine worsened psychotic symptoms in patients suffering from schizophrenia, other psychotic disorders, or psychotic depression [31]. Pergolide works well to treat PD, but this dopamine agonist has no efficacy on depression in PD [25]. In contrast, PPX, which is a nonergot dopamine agonist showed an antidepressant effect in the double-blind study with Placebo [32]. These effects may relate to PPX's preference for D<sub>3</sub> versus D<sub>2</sub> receptors and neurotrophic properties. In addition, D<sub>3</sub> receptors are more abundant in limbic system than D<sub>2</sub> receptors and play an important role in neuronal circuits implicated in depressive states.

TABLE 1: Depression and anxiety in pre-motor phase of PD.

Syndrome	Reference	Prevalence	Notes
Depression	Schuurman et al. (2002) [13]	Hazard ratio 3.13	The relative risk of depressed individuals developing PD
	Alonso et al. (2009) [14]	Rate ratio 1.85	The ratio of PD who initiates antidepressant therapy compared with noninitiators
	Shiba et al. (2000) [10]	Odds ratio 2.2	The frequency of preceding anxiety in PD compared with control subjects
Anxiety	Weisskopf et al. (2003) [11]	Relative risk 1.6	Risk of PD relative to use of anxiolytic medication
	Bower et al. (2010) [12]	Hazard ratio 1.63	The relative risk of anxious personality developing PD
Depression and anxiety	Jacob et al. (2010) [15]	Odds ratio 1.42	The frequency of receiving a diagnosis of depression or anxiety prior to PD

SSRI and TCA are two major categories of antidepressants commonly used to treat depression. SSRIs appear to be tolerated; however, an Italian multicenter study reported that the proportion of patients who recovered, as defined by a final Hamilton Depression Rating Scale score  $\geq 8$ , was significantly higher in the PPX group as compared to sertraline (an SSRI) group [33]. TCAs have been shown to be effective in treating depression in PD patients, while SSRIs have no effect compared to placebo. However, some problems may arise with TCA due to side effects such as sedation and orthostatic hypotension [23, 34].

#### 4. Anxiety

Anxiety is a common NMS among patients with PD and has a reported prevalence of 25–49% [16, 35], which is much higher than what is seen in non-PD subjects. Panic disorder, generalized anxiety disorder, and social phobia are the most common anxiety disorders reported. Anxiety and depression may be difficult to distinguish; however, unlike depression, a core feature of anxiety is the presence of apprehension, fear, or worry. The severity, but not the duration of PD, was positively related to anxiety. In addition, PD patients with postural instability and gait dysfunction symptom clustering were more likely to experience anxiety than tremor-dominant patients. Levodopa dosage had no relationship to anxiety; however, experience of dyskinesias or on/off fluctuations increased the risk of anxiety. Anxiety in PD contributed to a poor quality of life, and younger patients (<62 years) were more likely to experience anxiety disorder. Nortriptyline was significantly better than Paroxetine CR, and placebo in alleviating anxiety [23]. In addition, Atomoxetine, treated patients showed decreased severity of anxiety compared with Placebo group [24]. There was no association between patients who had functional neurosurgery for PD and anxiety; however, history of psychiatric disorders increased the risk for a diagnosis of current anxiety [35].

Anxiety and PD could share some underlying biological mechanisms that lead to them occurring at any stage of disease including pre-motor phase. Abnormalities in dopaminergic transmission are associated with anxiety. Striatal dopamine receptor binding was found to be reduced in both nonhuman primate models of anxiety and humans with anxiety disorders. Humans with anxiety disorders also appear to have reduced levels of dopamine

uptake in the striatum and reduced level of homovanillic acid in cerebrospinal fluid. Other neurotransmitter systems, including those of norepinephrine, serotonin, acetylcholine, and  $\gamma$ -aminobutyric acid, may also play a role in anxiety as suggested by the results of animal experiments and pharmacological studies in humans [36, 37]. These neurotransmitter systems interact with dopaminergic system and might be affected in PD patients.

#### 5. Coexistence of Depression and Anxiety in PD

Depression and anxiety are frequently associated in the same patients, and this can be seen as an argument to support the hypothesis that these two symptoms may share common pathophysiological mechanisms. Dissanayaka et al. reported that comorbid depression with anxiety was observed in 14% of PD patients [35]. While Negre-Pages et al. found that anxiety and depression in patients with PD were associated with different demographic and clinical factors [38]. They also found that PD patients with anxious symptoms were more frequently female and younger than those without such symptoms, whereas those with depressive symptoms had more severe indices of parkinsonism, more comorbidities, and lower cognitive function. These studies support the hypothesis that anxiety and depression may refer to different mechanisms since they are not correlated to the same features in PD. Anxiety may be more related to nonspecific factors, comparable to those observed in the general population, while depression may be more linked to the dopaminergic denervation that characterizes PD.

#### 6. Conclusions

Depression and anxiety in PD can occur at any stage of disease including pre-motor phase and are more frequent in PD patients than in controls. While the link between depression and PD during the pre-motor phase is not clear, all the articles reviewed in this paper support a link between anxiety and pre-motor phase PD. This suggests there may be an association between the mechanism that causes anxiety and PD. However, a recent study reports that PD patients with depression and anxiety were associated with different demographic and clinical features. Further studies are needed to elucidate these differences.

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## Research Article

# Idiopathic REM Sleep Behavior Disorder: Implications for the Pathogenesis of Lewy Body Diseases

Tomoyuki Miyamoto, Masayuki Miyamoto, Masaoki Iwanami, and Koichi Hirata

Department of Neurology, Center of Sleep Medicine, School of Medicine, Dokkyo Medical University, 880 Kitakobayashi, Mibu, Shimotsuga, Tochigi 321-0293, Japan

Correspondence should be addressed to Tomoyuki Miyamoto, miyatomo@dokkyomed.ac.jp

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**Objectives.** Both results of the odor identification and cardiac  $^{123}\text{I}$ -metaiodobenzylguanidine accumulation have been investigated for their potential to enhance the detection of pathogenesis resembling that of Lewy body-related  $\alpha$ -synucleinopathies in patients clinically diagnosed as having idiopathic REM sleep behavior disorder. **Methods.** We performed both the Odor Stick Identification Test for Japanese and  $^{123}\text{I}$ -metaiodobenzylguanidine scintigraphy in 30 patients with idiopathic REM sleep behavior disorder, 38 patients with Parkinson's disease, and 20 control subjects. **Results.** In idiopathic REM sleep behavior disorder, reduced odor identification score and an early or delayed heart to mediastinum ratio on  $^{123}\text{I}$ -metaiodobenzylguanidine were almost as severe as in Parkinson's disease patients. Delayed cardiac  $^{123}\text{I}$ -metaiodobenzylguanidine uptake was even more severe in the idiopathic REM sleep behavior disorder group than in the Parkinson's disease group. **Conclusions.** Reduced cardiac  $^{123}\text{I}$ -metaiodobenzylguanidine uptake, which is independent of parkinsonism, may be more closely associated with idiopathic REM sleep behavior disorder than olfactory impairment.

## 1. Introduction

REM sleep behavior disorder (RBD) is characterized by dream-enacting behaviors and unpleasant dreams and presents a risk for self-injury and harm to others due to abnormal REM sleep during which control of muscle tonus is lacking (REM sleep without atonia) [1, 2]. RBD is a heterogeneous disease entity consisting of a variety of manifestations [1]. Idiopathic RBD (iRBD), which develops in middle age or later and progresses chronically, in particular is a common clinical manifestation of Lewy body-related syndrome and is regarded as a clinical entity from the pathological aspect. For example, it has been elucidated that iRBD is often accompanied by soft motor signs, olfactory and color identification deficits, decreased cardiovascular and respiratory changes between REM and NREM sleep, reduced cardiac  $^{123}\text{I}$ -metaiodobenzylguanidine ( $^{123}\text{I}$ -MIBG) uptake, impairment of visual memory and visuospatial construction on neuropsychological testing, EEG slowing during wakefulness or sleep, and decreased strial dopaminergic innervations, and

reduced presynaptic strial dopamine transporter binding on SPECT or positron emission topography (PET) scans, which are considered as nonmotor symptoms of Parkinson's disease (PD) [3–5]. Furthermore, despite the limited number of pathological reports on iRBD, the characteristics of iRBD have been supported to have a close relationship with Lewy body pathology [6]. Therefore, additional clinical features that could distinguish iRBD with Lewy body-related  $\alpha$ -synucleinopathies from iRBD from other causes would be helpful in clinical practice. Recently, an association between loss of olfactory function and loss of cardiac noradrenergic innervation in PD has been noted [7]. Moreover, both loss of sense of smell and cardiac sympathetic denervation can precede the onset of motor symptoms, suggesting that the combination might provide a biomarker for the risk of Lewy body disease [8].

In this study, by the combination of tests to detect odor identification [9] and to determine cardiac  $^{123}\text{I}$ -MIBG cardiac uptake [4, 5] that were selected from among various tests to examine nonmotor symptoms of PD, we investigated

TABLE 1: Clinical characteristics of patients in the iRBD, PD, and control groups.

	iRBD	PD	Controls	P value
Number of patients, ( <i>n</i> )	30	38	20	—
Age, years	65.8 ± 9.1	65.4 ± 9.2	62.3 ± 6.8	0.210 <sup>a</sup>
Sex (male, %)	83.3	63.2	90.0	0.102 <sup>c</sup>
Disease duration, years	5.7 ± 8.8	4.8 ± 4.8	N/A	0.599 <sup>b</sup>
MMSE (>24)	27.7 ± 2.3	27.9 ± 1.9	28.8 ± 1.4	0.096 <sup>a</sup>
Hoehn and Yahr stage	N/A	2.4 ± 0.8	N/A	N/A
UPDRS motor subset, score	0.6 ± 1.0	14.4 ± 7.8	N/A	0.000 <sup>b</sup>
LEU, mg/day	N/A	238.6 ± 261.9	N/A	N/A
Smoker, (%)	50.0	39.5	5.0	0.464 <sup>c</sup>
OSIT-J, score	5.2 ± 3.0	4.4 ± 2.4	10.3 ± 1.3	0.000 <sup>a</sup>
<sup>123</sup> I-MIBG				
Early H/M ratio	1.85 ± 0.33	2.14 ± 0.52	2.74 ± 0.33	0.000 <sup>a</sup>
Delayed H/M ratio	1.46 ± 0.29	1.83 ± 0.60	2.82 ± 0.47	0.000 <sup>a</sup>

Data are mean ± SD.

PD: Parkinson's disease, iRBD: idiopathic REM sleep behavior disorder, OSAS: obstructive sleep apnea syndrome, MMSE: Mini-Mental State Examination, UPDRS: Unified Parkinson's Disease Rating Scale, LEU: daily levodopa-equivalent unit, OSIT-J: Odor Stick Identification Test for Japanese, H/M: heart-to-mediastinum, and <sup>123</sup>I-MIBG: <sup>123</sup>I-metaiodobenzylguanidine.

<sup>a</sup>P value was determined by one-way ANOVA.

<sup>b</sup>P value was determined by Mann-Whitney U test.

<sup>c</sup>Chi-square test for categorical: PD versus iRBD.

if there was an association between olfaction and cardiac <sup>123</sup>I-MIBG uptake in patients with iRBD and PD to evaluate the correlation between results of these two tests and to determine which would more enhance the detection of pathogenesis resembling that of Lewy body-related  $\alpha$ -synucleinopathies in patients clinically diagnosed as having iRBD.

## 2. Methods

**2.1. Patient Selection.** This study was performed in accordance with the Declaration of Helsinki. Procedures were approved by the Ethics Review Committee of Dokkyo Medical University, and informed consent was obtained from each subject. Subjects were 82 patients matched according to age group: 30 had iRBD (iRBD group; 66.3 ± 5.7 years; 25 males, 5 females), 38 had PD (PD group; 65.4 ± 9.2 years; 24 males, 14 females), and 20 had obstructive sleep apnea (OSA) without RBD (control group; 62.3 ± 6.8 years; 18 males, 2 females; pretreatment AHI = 38.5 ± 31.3 events/h) (Table 1). RBD and OSAS were defined according to the International Classification of Sleep Disorders, second edition [2]. Exclusion criteria were an abnormal neurologic examination in subjects with iRBD and OSAS. PD patients fulfilled the United Kingdom Parkinson's Disease Society Brain Bank criteria for idiopathic PD [10]. Parkinsonism was assessed and classified according to the Hoehn and Yahr stage [11] and the motor subset of Unified Parkinson's Disease Rating Scale (UPDRS-III), which was administered to the PD and iRBD groups [12]. The mean UPDRS-III score was 14.4 ± 7.8 points for PD patients and 0.6 ± 1.0 points for the iRBD subjects. There were two phenotypes of PD among the PD group: tremor-dominant and postural instability gait difficulty- (PIGD-) dominant based on UPDRS components. The mean

PIGD score was defined as the sum of an individual's baseline falling, freezing, walking, gait, and postural stability scores divided by 5. Patients were categorized as having tremor-dominant PD if the ratio of the mean tremor score to the mean PIGD score was 1.5 or higher and as having PIGD-dominant PD if that ratio was 1.00 or lower [13]. According to that categorization, 13 patients in the PD group were placed in the tremor-dominant subgroup and 21 in PIGD-dominant subgroup. For this particular study, all patients with Mini-Mental State Examination (MMSE) scores <24 were excluded [14].

**2.2. Polysomnographic Evaluation and Definition of iRBD.** Polysomnographic (PSG) monitoring included electroencephalography (C3, C4, O1, and O2), electrooculography, chin muscle electromyography (EMG), electrocardiography, detection of airflow by thermistor, plethysmography for ribcage and abdominal wall motion, oximetry for measurement of arterial oxyhemoglobin saturation, detection of changes in sleeping position, and bilateral EMG of the tibialis anterior muscles. PSG monitoring was performed for at least 8 h. Sleep stages were manually scored according to criteria of Rechtschaffen and Kales [15]. Apnea was defined as the absence of breathing for more than 10 s. Hypopnea was defined as a reduction of more than 50% in breathing; when the reduction in breathing was less than 50%, more than 3% oxygen desaturation or arousal for more than 10 s was defined as hypopnea. The apnea-hypopnea index was calculated as the average of the total number of apnea and hypopnea episodes experienced per hour of sleep. For the iRBD group, the presence of REM sleep without atonia was based on EMG findings of excessive sustained or intermittent elevation of submental EMG tone or excessive phasic submental or lower limb EMG twitching according to the ICSD-2ed [2].

TABLE 2: Multiple regression analysis of OSIT-J related parameters for Parkinson's disease ( $N = 38$ ) and iRBD ( $N = 30$ ).

	PD		iRBD	
	$\beta^a$	$P$ value	$\beta^a$	$P$ value
Age	- <b>0.348</b>	<b>0.037</b>	0.016	0.936
Sex	<b>0.404</b>	<b>0.033</b>	0.080	0.701
Disease duration, month	0.147	0.591	- 0.314	0.377
MMSE (>24)	0.189	0.230	0.184	0.377
Hoehn and Yahr stage	- 0.013	0.940	N/A	N/A
UPDRS motor subset	0.079	0.674	- 0.153	0.517
Motor phenotype	- 0.239	0.177	N/A	N/A
LEU	0.074	0.969	N/A	N/A
Smoking atatus	0.007	0.798	- 0.040	0.834
Delayed H/M ratio ( $^{123}\text{I}$ -MIBG)	<b>0.399</b>	<b>0.015</b>	- 0.274	0.183
$R^2^b$	0.493		0.184	

iRBD: idiopathic REM sleep behavior disorder, PD: Parkinson's disease, OSIT-J: Odor Stick Identification Test for Japanese, MMSE: Mini-Mental State Examination, UPDRS: Unified Parkinson's Disease Rating Scale, LEU: daily levodopa-equivalent unit, H/M: heart-to-mediastinum, and  $^{123}\text{I}$ -MIBG:  $^{123}\text{I}$ -metaiodobenzylguanidine.

<sup>a</sup>Standardized regression coefficients.

<sup>b</sup>Coefficient of determination.

Bold values indicate statistically significant values. N/A: not applicable.

2.3. *Cardiac  $^{123}\text{I}$ -MIBG Scintigraphy.*  $^{123}\text{I}$ -MIBG planar images of the chest were obtained using a triple-headed gamma camera (GCA-9300A-HG, Toshiba Co, Tokyo, Japan).  $^{123}\text{I}$ -MIBG (Fujifilm RI Pharma Co., Tokyo, Japan) accumulations were recorded at the early (15 min) and delayed phases (4 h). The heart-to-mediastinum (H/M) ratio was calculated by dividing the count density of the left ventricular region of interest (ROI) by that of the mediastinal ROI [16–18]. None of the subjects took medications that could influence the  $^{123}\text{I}$ -MIBG examination, and none had a history of cardiac disease.

2.4. *Odor Stick Identification Test for Japanese (OSIT-J).* The Odor Stick Identification Test for Japanese (OSIT-J) (Daiichi Yakuhin, Co., Ltd., Tokyo, Japan) is composed of 12 different odorants familiar to the Japanese population [9]. All subjects were free from other conditions that can affect olfactory function such as usage of certain medications, chronic nasal infection, chronic sinonasal disease, head trauma, and abuse of drugs or alcohol by medical history. Subjects with an infection of the upper airways at the time of the investigation were also not allowed to participate. OSIT-J was performed as previously described. In this study, functional hyposmia was defined by an OSIT-J score  $\leq 8$  [9].

2.5. *Statistical Analysis.* Values are expressed as mean  $\pm$  SD. Age, MMSE, OSIT-J scores and degrees of accumulation based on the H/M ratio (early and delayed phase) in cardiac muscle obtained were compared among the three groups by the one-way analysis of variance (ANOVA) followed by post-hoc Bonferroni correction. The Mann-Whitney U-test was applied for statistical comparisons of disease duration and scores of the motor subsets of the UPDRS between the iRBD and PD groups. Group comparisons of the frequency of genders and smokers were performed by the Chi-square test

for categorical variables. The correlations of OSIT-J and early or delayed  $^{123}\text{I}$ -MIBG uptake were assessed by the Spearman correlation coefficient for iRBD and PD. To explore the most influential factor on the OSIT-J score, we included age, sex, disease duration, MMSE, Hoehn and Yahr stage, UPDRS motor subsets, motor phenotypes, levodopa-equivalent unit (LEU), smoking status, and delayed  $^{123}\text{I}$ -MIBG uptake in a multiple regression analysis for PD. Receiver operating characteristic (ROC) curves were analyzed. The significance level was set at  $P < .05$ . Statistical analyses were performed with the Statistical Package for Social Science Software (Graphpad Prism, San Diego, CA and SPSS II Windows Ver 11.0, Japan).

### 3. Results

A total of 30 iRBD patients (mean symptom duration:  $5.7 \pm 8.8$ ), 38 PD patients, and 20 control subjects with a similar age distribution were evaluated. Demographic information is presented in Table 1. Interval between  $^{123}\text{I}$ -MIBG examinations and OSIT-J was a mean of 72 days.

Cardiac  $^{123}\text{I}$ -MIBG accumulation based on H/M (early phase, delayed phase) was significantly decreased in the iRBD group ( $1.85 \pm 0.33$ ,  $1.46 \pm 0.29$ ) and the PD group ( $2.14 \pm 0.52$ ,  $1.83 \pm 0.60$ ) compared with the control group ( $2.74 \pm 0.33$ ,  $2.82 \pm 0.47$ ) ( $P < .000$ ). OSIT-J scores were significantly lower in the iRBD group ( $5.2 \pm 3.0$ ) and the PD group ( $4.4 \pm 2.4$ ) than in the control group ( $10.3 \pm 1.3$ ) ( $P < .000$ ) (Table 1). As shown in Table 2, results of multiple regression analysis of OSIT-J-related parameters in patients with PD, which included age, sex, disease duration, MMSE, Hoehn and Yahr stage, UPDRS motor subset, motor phenotype, LEU, smoking status, and delayed H/M ratio, showed that age, sex, and delayed H/M ratio were the significant factors in the model for the OSIT-J score. There was a significant positive correlation between the OSIT-J score and delayed H/M ratio

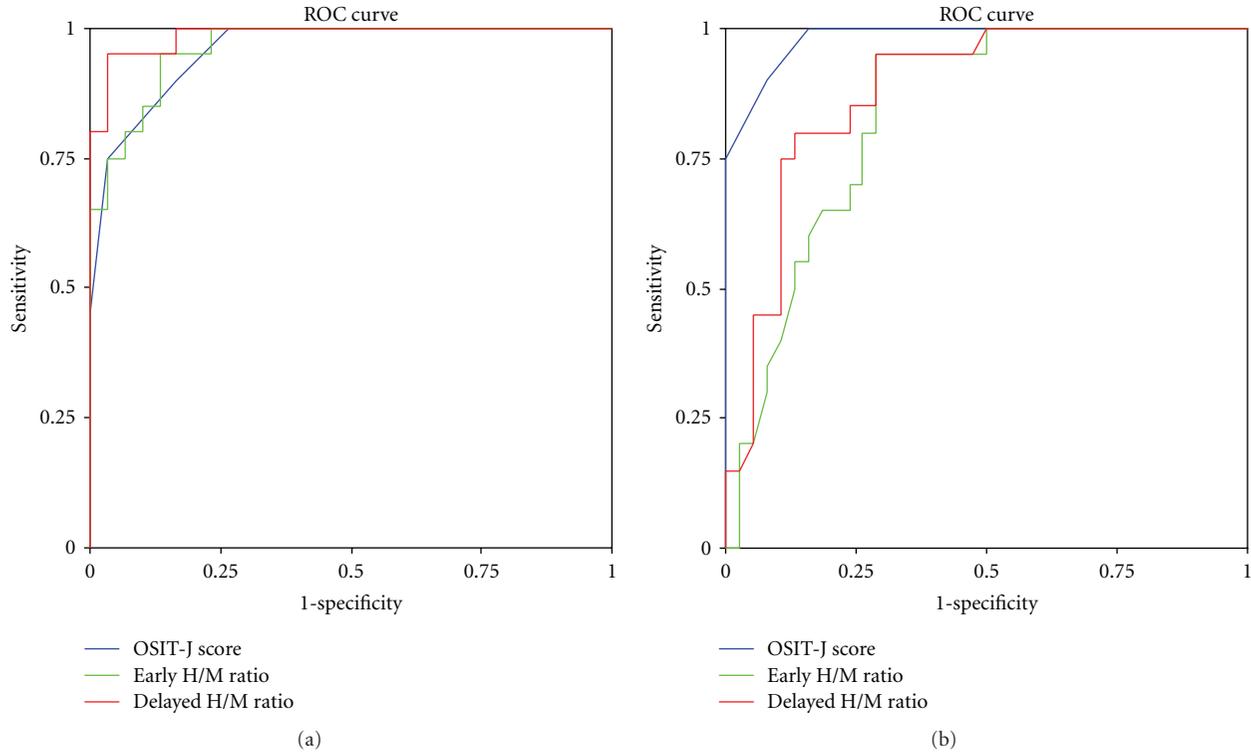


FIGURE 1: (a) ROC analysis of the early or delayed H/M ratio and odor identification showed an area under the curve of 0.96 (95% CI = 0.92–1.00,  $P = .000$ ), 0.99 (95% CI = 0.96–1.00,  $P = .000$ ), and 0.96 (95% CI = 0.91–1.00,  $P = .000$ ) for iRBD. (b) ROC analysis of the early or delayed H/M ratio and odor identification showed an area under the curve of 0.84 (95% CI = 0.74–0.94,  $P = .000$ ), 0.88 (95% CI = 0.79–0.97,  $P = .000$ ), and 0.98 (95% CI = 0.96–1.00,  $P = .000$ ) for PD.

TABLE 3: Sensitivity and specificity of OSIT-J and cardiac  $^{123}\text{I}$ -MIBG scintigraphy.

	OSIT-J score	Early H/M ratio	Delayed H/M ratio
<b>iRBD patients</b>			
<i>(n = 30)</i>			
Cut-off	8.5	2.30	2.03
Sensitivity	90.0%	95.0%	95.0%
Specificity	83.3%	86.7%	96.7%
<b>PD patients</b>			
<i>(n = 38)</i>			
Cut-off	8.5	2.30	2.03
Sensitivity	90.0%	95.0%	95.0%
Specificity	92.1%	71.1%	71.1%

iRBD: idiopathic REM sleep behavior disorder, PD: Parkinson's disease, OSIT-J: Odor Stick Identification Test for Japanese,  $^{123}\text{I}$ -MIBG:  $^{123}\text{I}$ -metaiodobenzylguanidine, H/M: heart-to-mediastinum.

( $r = 0.337$ ,  $P = .039$ , Spearman's correlation). On the other hand, results of multiple regression analysis of OSIT-J-related parameters in patients with iRBD, which included age, sex, disease duration, MMSE, UPDRS motor subset, smoking status, and delayed H/M ratio, showed that there were no significant factors in the model for the OSIT-J score. Among the iRBD group, there was no significant correlation

between the OSIT-J score and delayed H/M ratio ( $r = -0.195$ ,  $P = .302$ , Spearman's correlation) or the duration of RBD ( $r = -0.217$ ,  $P = .249$ , Spearman's correlation).

ROC analysis of the early or delayed H/M ratio and odor identification showed an area under the curve of 0.96 (95% CI = 0.92–1.00,  $P = .000$ ), 0.99 (95% CI = 0.96–1.00,  $P = .000$ ) and 0.96 (95% CI = 0.91–1.00,  $P = .000$ ) for iRBD (Figure 1(a)) and of 0.84 (95% CI = 0.74–0.94,  $P = .000$ ), 0.88 (95% CI = 0.79–0.97,  $P = .000$ ) and 0.98 (95% CI = 0.96–1.00,  $P = .000$ ) for PD (Figure 1(b)).

For differentiating the iRBD patients from control subjects, the sensitivity and specificity of the OSIT-J score with a cut-off value at 8.5 were 90.0% and 83.3%, respectively; those of the early H/M ratio with a cut-off value at 2.30 were 95.0% and 86.7%, respectively, and those of a delayed H/M ratio with a cut-off value at 2.03 were 95.0% and 96.7%, respectively (Table 3). For differentiating PD patients from control subjects, the sensitivity and specificity of the OSIT-J score with a cut-off value at 8.5 were 90.0% and 92.1%, respectively; those of the early H/M ratio with a cut-off value at 2.30 were 95.0% and 71.1%, respectively; and those of the delayed H/M ratio with a cut-off value at 2.03 were 95.0% and 71.1%, respectively (Table 3). With optimal cut-off values set at 2.03 for the delayed H/M ratio and at 8.5 for OSIT-J score for iRBD patients (Table 3, Figure 2), identification of iRBD was confirmed in 23 (76.7%) patients in the iRBD group through abnormal results of both of these

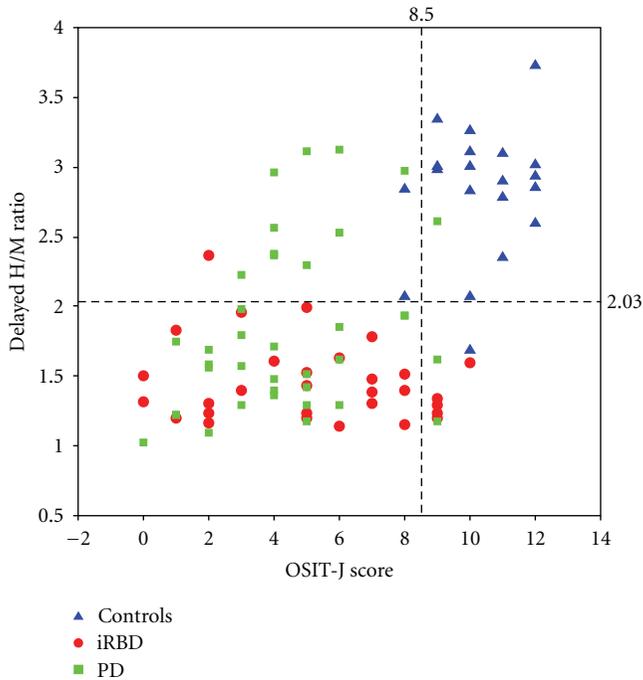


FIGURE 2: The relation between the OSIT-J score and the delayed H/M ratio of  $^{123}\text{I}$ -MIBG uptake in patients with iRBD (the red circle), PD (the green square), and controls (the blue triangle). Broken line (vertical): cut-off value set at 8.5 by OSIT-J to distinguish between iRBD or PD and controls. Broken line (horizontal): cut-off value set at 2.03 by  $^{123}\text{I}$ -MIBG to distinguish between iRBD or PD and controls. OSIT-J: Odor Stick Identification Test for Japanese; H/M: heart-to-mediastinum;  $^{123}\text{I}$ -MIBG:  $^{123}\text{I}$ -metaiodobenzylguanidine; OSAS: obstructive sleep apnea syndrome; iRBD: idiopathic rapid eye movement behavior disorder; PD: Parkinson's disease.

tests. Optimal cut-off values were set at 2.03 for delayed H/M ratio and at 8.5 for OSIT-J score for PD patients (Table 3, Figure 2); as a result, 25 (65.8%) were confirmed through abnormal results of both of these tests to have PD. However, results of both of these tests were normal in the control group.

#### 4. Discussion

In this study, the olfactory dysfunction and reduced cardiac  $^{123}\text{I}$ -MIBG uptake that were found in most iRBD patients share similarities with those described in PD. Moreover, delayed cardiac  $^{123}\text{I}$ -MIBG uptake was more severe in the iRBD group than in the PD group (Figure 1(a)) while reduced odor identification was more severe in those with PD than with iRBD (Figure 1(b)). Also, the degree of olfactory identification impairment correlated significantly with the degree of delayed cardiac  $^{123}\text{I}$ -MIBG uptake only in the PD group. Age, sex, and delayed cardiac  $^{123}\text{I}$ -MIBG uptake were significant factors with regard to PD patients in the model using the OSIT-J score. The degree of reduction of MIBG uptake does not match the degree of reduction in odor identification in iRBD patients but does match in PD

patients. Results of a recent study indicated that the cardiac sympathetic nervous system might degenerate in parallel with the olfactory system in patients with early PD and that these two systems might degenerate at different rates of speed in advanced PD [16].

**4.1. Cardiac Sympathetic Denervation Is Related to Lewy Body Pathology.** There is evidence that  $^{123}\text{I}$ -MIBG cardiac uptake is markedly reduced in patients with Lewy body diseases such as PD, dementia with Lewy bodies (DLB), and pure autonomic failure (PAF) [17–19]. It was reported that cardiac  $^{123}\text{I}$ -MIBG imaging could distinguish between clinically diagnosed DLB and Alzheimer's disease (AD) with high levels of sensitivity and specificity [19]. Interestingly, pathological findings occur even in patients with DLB who have no parkinsonism. Since PAF patients do not have parkinsonism or decreased striatal dopaminergic innervation and since cardiac noradrenergic denervation occurs in both diseases, the pathogenetic mechanisms of cardiac noradrenergic denervation in Lewy body diseases differ from those producing parkinsonism and nigrostriatal dopaminergic denervation [8]. As pathological evidence [20–22], it has been proven that the Lewy body is present in cardiac sympathetic nerve postganglionic fibers and it has been suggested that Lewy body-related pathology potentially causes severe denervation and reduced  $^{123}\text{I}$ -MIBG uptake in the cardiac postganglionic sympathetic nerve. The reduction in  $^{123}\text{I}$ -MIBG uptake in sympathetic terminals was observed in cases with early-phase PD and incidental Lewy body disease (ILBD) irrespective of the presence or absence of remarkable autonomic nerve injury [17].

**4.2. Olfactory Dysfunction Is Related to Lewy Body Pathology.** Olfactory disturbance is present in most PD or PAF cases [8, 23, 24]. The deficit in olfaction in PD contrasts with previous reports of preserved or only mildly reduced olfaction in patients with atypical parkinsonism such as a tauopathy or multiple system atrophy [25, 26]. In dementia patients, neuropathologic studies reported neuronal alterations in several subcortical structures such as the olfactory tract/bulb, anterior olfactory nucleus, orbito-frontal cortex, hippocampus, and amygdala in the olfactory system [27]. Olfactory abnormalities have been reported in AD, but anosmia appears to be common in DLB but not in pure AD [28]. Interestingly, a Lewy body variant of AD had an increased frequency of anosmia compared with "pure" AD [29]. Furthermore, olfactory impairment is more marked in patients with mild dementia with Lewy bodies than in those with mild AD [30]. In addition to reduced odor identification prior to the onset of PD, olfactory dysfunction also has been frequently recognized in patients with ILBD [31]. Also, neuropathological olfactory bulb alpha-synuclein has high specificity and sensitivity for Lewy body formation in confirmed cases of PD and DLB [32]. On the basis of pathological studies of a large number of autopsy cases, Braak et al. proposed a hypothesis as to the onset and advancement pattern of PD in that the disease developed from the medulla and olfactory bulb and extended to

the pons and substantia nigra (SN) [33]. In the Honolulu-Asia Aging Study on Japanese Americans, 2,267 males without PD and dementia at the time of olfaction testing were followed up and significantly more subjects who developed olfactory dysfunction in the first 4-year follow-up period also developed PD [34]. Haehner's study was to clinically follow up patients with idiopathic hyposmia to determine the percentage of patients who developed idiopathic PD after a 4-year interval [35]. In Ponsen's prospective study involving first-degree relatives of PD patients, a low score on three olfactory processing tasks was associated with an increased risk of developing PD within 5 years [36]. The point of view that reduced odor identification is manifested at the very beginning of the development of PD has been supported. These reports indicate that the rhinencephalon may be an area of selective vulnerability for  $\alpha$ -synuclein accumulation [37] and iRBD that develops in middle age or older progresses mostly to Lewy body diseases among synucleinopathies such as PD and DLB, which have some pathological features in common.

**4.3. RBD and Relevance to Lewy Body Pathology.** Men over the age of 50 years who have iRBD are at very high risk for future PD or DLB several years after the onset of RBD [38, 39]. Neuropathologic studies at autopsy of cases that had been diagnosed with RBD while alive showed that every case had Lewy bodies [6]. For example, cognitive abnormalities appeared 15 years after the onset of RBD and probable DLB was diagnosed, and eventually the presence of Lewy bodies was confirmed pathologically [40]. In PD, approximately 60% of the nigrostriatal neurons of the substantia nigra are degenerated before patients fulfill the clinical criteria of PD [41]. In some cases of PD, the patient appears to develop cortical disease before the motor sign of "stage 3" disease, whereas, iRBD patients with ILBD could be diagnosed after long-standing disease with no evidence of motor or cognitive abnormalities [3, 4]. If progression of synucleinopathies is not universal, it is essential to understand the reason. Since a variety of symptoms of PD and disorders resembling PD have been elucidated, Langston [42] proposed a "Parkinson's complex" because parkinsonism would represent only the tip of the iceberg as typically viewed by both clinicians and researchers. However, when the disease process is measured by neuronal degeneration, the presence of Lewy bodies and neuritic pathology are widespread in the central and peripheral nervous systems. From this point of view, iRBD can be positioned as an earlier preclinical stage of PD or DLB, or a variant of Lewy body-related  $\alpha$ -synucleinopathies. To gain such an understanding, it is necessary to extract a group with abnormalities in a combination of markers from among iRBD patients and provide follow up, considering the possibility that some patients in that group may develop neurodegenerative disease. These steps may help elucidate the possibility that iRBD is the spectrum of manifestations or a subtype of Lewy body-related  $\alpha$ -synucleinopathies.

In conclusion, reduced cardiac  $^{123}\text{I}$ -MIBG uptake may be more closely associated with iRBD than olfactory impairment. Moreover, odor identification impairment or cardiac

sympathetic function assessed by cardiac  $^{123}\text{I}$ -MIBG uptake and the nigrostriatal dopaminergic function would occur and progress independently in iRBD patients or PD patients.

Limitations of this study include the small number of OSAS patients that comprise the control group. Untreated sleep apnea syndrome may be associated with physical movements during sleep [1], and, therefore, it is important to first differentiate between those with iRBD and OSAS with abnormal sleep behavior. A second limitation is that more than 80% of patients presenting at sleep centers with iRBD are men [1, 3, 39] so that the male-to-female ratio was not matched in the iRBD, PD, and control groups.

## Conflict of Interests

The authors report no financial conflict of interest. This work is not an industry supported study.

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## Review Article

# Dopamine-Induced Nonmotor Symptoms of Parkinson's Disease

**Ariane Park<sup>1</sup> and Mark Stacy<sup>2</sup>**

<sup>1</sup> *Department of Neurology, The Ohio State University, Columbus, OH 43210, USA*

<sup>2</sup> *Division of Neurology, Duke University Medical Center, Durham, NC 27705, USA*

Correspondence should be addressed to Mark Stacy, mark.stacy@duke.edu

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Nonmotor symptoms of Parkinson's disease (PD) may emerge secondary to the underlying pathogenesis of the disease, while others are recognized side effects of treatment. Inevitably, there is an overlap as the disease advances and patients require higher dosages and more complex medical regimens. The non-motor symptoms that emerge secondary to dopaminergic therapy encompass several domains, including neuropsychiatric, autonomic, and sleep. These are detailed in the paper. Neuropsychiatric complications include hallucinations and psychosis. In addition, compulsive behaviors, such as pathological gambling, hypersexuality, shopping, binge eating, and punting, have been shown to have a clear association with dopaminergic medications. Dopamine dysregulation syndrome (DDS) is a compulsive behavior that is typically viewed through the lens of addiction, with patients needing escalating dosages of dopamine replacement therapy. Treatment side effects on the autonomic system include nausea, orthostatic hypotension, and constipation. Sleep disturbances include fragmented sleep, nighttime sleep problems, daytime sleepiness, and sleep attacks. Recognizing the non-motor symptoms that can arise specifically from dopamine therapy is useful to help optimize treatment regimens for this complex disease.

## 1. Neuropsychiatric

Hallucinations and psychosis have long been known to be associated with dopaminergic therapy. Psychosis in PD refers to the combination of chronic hallucinations and delusions occurring in the setting of otherwise clear senses. Hallucinations can involve various sensory modalities; however, visual hallucinations are the most common. Some may be benign and nonbothersome, while others can be terribly frightening to patients. Risk factors for developing hallucinations include older age, longer duration of PD, history of sleep disorder, depression, and coexisting cognitive impairment [1, 2]. Interestingly, there has been no evidence that increased dose or specific dopaminergic drug class (agonists versus L-dopa) is related to this problem [1, 3], and it is clear that hallucinations and psychosis are not just mere side effects of treatment. The likely pathogenesis is multifactorial involving pharmacologic mechanisms in conjunction with disease-related elements. Treatment for chronic hallucinations includes reduction of dopaminergic medications and discontinuation of anticholinergics or other drugs. If needed,

antipsychotic medications may be used. Clozapine has demonstrated efficacy in a double-blind placebo-controlled trial [4]; however, in clinical practice quetiapine is preferred, despite the fact that, it has not been proven more effective than placebo in clinical trials [5–7].

Dopaminergic medications, particularly dopamine agonists [8], are known to be associated with impulse control disorders, with no differences seen between specific drugs [9, 10]. The prevalence of any ICD in PD patients on dopamine agonists ranges from 13.7 to 17.1% [11]. The formal definition for impulse control disorders in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) is a group of psychiatric disorders characterized five stages of symptomatic behavior. Essential to this is “a failure to resist an impulse, drive or temptation to perform an act that is harmful to the person or to others.” Patients feel an increasing sense of tension or arousal before the act, experience pleasure, gratification, or relief while committing the act, and finally feel a sense of relief from the urge after the act. Individuals may or may not feel regret, self-reproach, or guilt about these activities [12]. Pathological

gambling (PG) is the most extensively studied ICD in PD, first noted in 2003 by Driver-Dunckley et al. [13] in a retrospective study of 1,884 patients. The essential feature of pathological gambling is that it is a “persistent and recurrent maladaptive gambling behavior that disrupts personal, family, or vocational pursuits” [12]. A recent prospective study of 200 PD patients reported a prevalence of PG to be as high as 7% [14]. Compulsive sexual behavior or hypersexuality as well as compulsive buying are not formally defined in the DSM-IV-TR. However, they are easily identified problems once patients cross the threshold of reasonable urge into compulsions leading to personal, familial, and/or occupational suffering and consequences. Hypersexuality can include not only increased libido, but also exhibitionism, excessive masturbation, phone/internet sex, use of prostitutes, and new sexual orientations. More seriously, criminal behaviors such as rape, pedophilia, and incest have been reported [15]. Hypersexuality can be seen in up to 4% of PD patients [16]. Compulsive buying of items that are unnecessary and go unused (i.e., shirts, shoes, jewelry) has been reported in up to 5.7% of PD patients [17] and often leads to financial distress. These patients tend to have traits of both obsessive-compulsive and impulse control disorders [18]. Binge eating is a proposed diagnosis in the DSM-IV-TR as an eating disorder marked by “uncontrolled eating of food that is larger in amount than most people would eat in a similar period of time under similar circumstances, without emesis or laxative abuse” [12]. Patients have a sense of lack of control over eating during the episode, and some report nocturnal awakening with an extreme sweet craving, eating excessive amounts. This has been reported in 4.3% of PD patients [17]. Punding refers to stereotypic, complex, and repetitive behavior involving meaningless activities (i.e., examining, sorting, collecting, arranging, dismantling objects) sometimes to the point of ignoring basic needs such as eating and sleeping. Patient may be irritable when interrupted, and this behavior can lead to social avoidance and isolation. Interestingly, participating in these activities may or may not be enjoyable for patients. One study involved demonstrated a punding prevalence of 1.4% in an ambulatory PD population [19], but it has been reported to be as high as 14% [20].

Dopamine dysregulation syndrome (DDS), also known as hedonistic homeostatic dysregulation (HHD), is a neuropsychiatric disorder characterized by addiction, self-medication, and escalation of antiparkinsonian medication. It is thought to have a prevalence of approximately 3.4% [21]. Not all patients with DDS have an ICD, although the majority of patients with DDS also exhibit punding [22]. Unlike ICD, DDS is typically associated with levodopa or short-acting dopamine agonist medications (i.e., subcutaneous apomorphine) [23], although it has been described with ergot- and nonergot-derived dopamine agonists as well [24]. These patients often do not have insight into the problem and will often take larger- than-recommended total daily doses, far beyond what is necessary for their motor disabilities. Unfortunately, they do not recognize the harm it is causing to themselves and their loved ones and demand increasing quantities of medication despite the development

of complications (i.e., dyskinesia, “off” state dysphoria). Attempts to reduce the dose are met with great resistance, making management quite difficult.

DDS behaviors can be viewed as both a substance dependence disorder and an addiction. In fact, the term hedonic homeostatic dysregulation was coined based on the addiction model that addicts take drugs not only for pleasure but also to avoid unpleasant withdrawal symptoms [25, 26]. Other theories of psychostimulant addiction including pleasure seeking, habit models, and chronic neuroadaptations induced in the ventral striatum and nucleus accumbens may help to explain DDS [24]. Supportive of addiction theories, one study utilizing positron emission tomography (PET) showed that PD patients with DDS had enhanced levodopa-induced ventral striatal dopamine release, perhaps due to sensitization, compared with levodopa-treated patients with PD who did not have DDS [27]. In fact, it has been theorized that the pulsatile stimulation of striatal dopamine receptors inherent in the oral delivery of dopamine may cause changes in the basal ganglia circuitry leading to sensitization [28], leading to motor fluctuations, dyskinesia, and possibly even DDS. Interestingly, patients without PD but treated with dopaminergic therapy for restless legs syndrome have also been reported to have DDS, indicating that drug exposure itself plays a physiologic role, perhaps in triggering these behaviors [13, 29].

Treatment for these impulse control disorders starts with recognizing that they exist. It is important for physicians to be aware of these neuropsychiatric side effects of dopaminergic therapy and to actively screen for them, as patients often do not volunteer the information either because they do not have insight into these issues, they are in denial, or they are embarrassed. This is where family/caregiver input can be particularly helpful. One study found that only 25% of PD patients with an active ICD were identified clinically [9]. The risk factor profile of these patients includes male gender, early-onset PD, novelty-seeking personality, history of substance dependence, history of depression, high alcohol intake, and early emergence of dyskinesia [30–32]. Once identified, a thorough review of the patient's medications is warranted, followed by a systematic reduction or cessation of dopaminergic treatment. For ICDs, this would involve dopamine agonists. If parkinsonism worsens, it may be prudent to concomitantly increase levodopa. In DDS, the strategy is reversed and levodopa is the initial agent to wean, with a subsequent increase in dopamine agonist treatment. However, as previously mentioned, patients with DDS often are not complaint with this, and therefore counseling with both the patients and their families/caregivers is important. As far as additional pharmacologic options, antidepressants for obsessive thoughts and antiandrogens to help decrease hypersexuality may be considered. A recent study found amantadine to be effective in the treatment of pathological gambling in PD [33]. Deep brain stimulation to the subthalamic nucleus may allow dopaminergic drug reduction and therefore improvement in these symptoms [34, 35] although DDS and ICDs may worsen or develop for the first time after DBS surgery [36].

## 2. Autonomic

Nausea is very commonly associated with dopaminergic therapy. It is thought to result from stimulation of the area postrema [37]. Orthostatic hypotension and constipation may be intrinsic to neurodegenerative changes related to PD, but these can clearly worsen with dopaminergic therapy. Higher rates of constipation and nausea have been seen in patients treated with dopamine agonists versus levodopa [38], suggesting that the different pharmacodynamic properties of the various dopamine formulation may contribute to adverse effects. Autonomic symptoms in PD are attributed to the involvement of the central and peripheral postganglionic autonomic nervous system. Constipation in PD may be attributed to Lewy body pathology in the myenteric plexus and colonic sympathetic denervation. These symptoms are exceedingly common. One study found that 60% of patients had orthostatic hypotension early in the course of the disease [39], and 58% of PD patients may experience constipation [40].

In the vast majority of cases, nausea subsides with a slow titration up on dosage, with the addition of carbidopa or domperidone, a peripheral dopamine receptor blocking agent, or taking dopaminergic medications with food.

Conservative measures for the treatment of orthostatic hypotension include increasing salt and fluid intake, elevating the head of the bed (>30 degree incline), and the use of thigh and abdominal compression bands. Patients should be advised to avoid Valsalva maneuvers, warm temperatures, and meals rich in carbohydrates and alcohol, as these may be triggers. Pharmacologic treatments include fludrocortisone, a salt-retaining mineralocorticoid, midodrine, a selective peripherally acting  $\alpha$ -adrenergic agent, and droxidopa, an orally active synthetic precursor of norepinephrine [41]. Pyridostigmine has been found to be effective in neurogenic orthostatic hypotension but has not been formally tested in PD [42]. Reduction in dopaminergic medication may be warranted if these medications are not tolerated or if orthostatic hypotension is severe.

Nonpharmacologic treatments for constipation include regular exercise, adequate water intake, and diet including symbiotic yogurts containing *Bifidobacterium*, fructooligosaccharide, and bulking agents (fibers, psyllium, and polycarbophil). A dietary herb extract, Dai-kenchu-to, has been found to ameliorate PD-related constipation [43]. Osmotic laxatives including magnesium sulfate and polyethylene glycol can be effective. Other laxatives include lubiprostone [44] and macrogol [45]. Serotonergic agents such as cisapride [46], mosapride citrate [47], tegaserod [48], and pyridostigmine [49], an acetylcholinesterase inhibitor, have been shown to be beneficial as well. Constipation in PD may be associated with focal dystonia of the puborectalis muscle, and botulinum toxin A injections to the puborectalis muscle have demonstrated clinical benefit [50]. Sacral nerve stimulation has shown some promise [51]; however, it has not been extensively studied and is not widely used. Reduction of dopaminergic medications, amantadine, and anticholinergics should also be considered. Highlighting the complexity of the pathophysiology involved in PD-related

constipation, some dopaminergic agents such as apomorphine [52] and intrajejunal continuous infusion of levodopa [53] can improve constipation and bowel dysfunction.

## 3. Sleep

Sleep dysfunction is very common in PD, seen in 60–98% of patients [54], and if severe enough can lead to decreased quality of life, impaired function, and caregiver burden. Many sleep problems, are intrinsic to PD, such as fragmented sleep, nighttime sleep problems and daytime sleepiness. Complicating matters, all of these symptoms can be associated with dopaminergic medications [55], and these effects are dose related [56]. Dopaminergic medication is thought to have a desynchronizing effect on sleep architecture that causes disruption of sleep continuity [57]. Low-dose dopamine agonists have been associated with insomnia, whereas higher doses can lead to excessive daytime sleepiness (EDS). EDS has been defined as those patients who are experiencing unusually severe sleepiness during the day, sleeping more than 2 hours in the daytime, or falling asleep three or more times a day [58]. “Sleep attacks,” sudden transitions from wakefulness to sleep without a prodrome, were first described in patients treated with pramipexole or ropinirole [59]. Sleep attacks may be a severe form of excessive daytime sleepiness, and the prevalence in patients treated with dopaminergic medications has been reported to be as high as 43% [60]. While initially associated with dopamine agonists, they can be induced by levodopa as well. One study showed that levodopa monotherapy carries the lowest risk, and combination therapy with levodopa and dopamine agonists has the highest risk [61] of sleep attacks. Drugs that are not associated with excessive daytime sleepiness/sleep attacks include selegiline, amantadine, and entacapone. Selegiline and amantadine have stimulating properties and therefore can induce problems with sleep initiation. Sleep attacks are important to be aware of because these abrupt sleep episodes can have dangerous implications, particularly when driving; thus, it is important to continuously monitor for this side effect.

Management of these sleep issues first begins with education regarding healthy sleep hygiene. Patients should try to maintain regular sleep/wake schedules, exercise regularly, and minimize the use of alcohol and caffeine. Some PD patients have coexisting sleep disorders, including sleep apnea and restless legs syndrome (RLS), and in these cases, a referral to a sleep specialist may be necessary. Physicians should carefully review medication lists and remove those that may be contributing to sleepiness. Medications that may be stimulating should be given earlier in the day. Dopaminergic medication may need to be reduced or discontinued, particularly in cases involving sleep attacks. The use of prolonged release dopamine agonists should be considered, as a recent study using ropinirole prolonged release demonstrated improved subjective quality of sleep, reduced daytime sleepiness, and disappearance of sleep attacks in some PD patients [62]. Possible pharmacologic therapies for daytime sleepiness that have demonstrated benefit in PD patients include methylphenidate [63], modafinil [64], and sodium

TABLE 1: Dopamine-induced nonmotor symptoms of Parkinson's disease.

Neuropsychiatric
Hallucinations
Impulse control disorders
Dopamine dysregulation syndrome
Autonomic
Nausea
Orthostatic hypotension
Constipation
Sleep
Fragmented sleep
Nighttime sleep problems
Daytime sleepiness
Sleep attacks

oxybate [65]. For fragmented sleep and sleep initiation, melatonin, a neurohormone produced in the pineal gland at night, has been shown to improve sleep quality and daytime sleepiness [66]. Patients who have undergone deep brain stimulation (DBS) of the subthalamic nucleus (STN) have reported improvements in nocturnal sleep [67]; however, it is not clear how DBS affects daytime sleepiness.

#### 4. Conclusion

The management of dopamine-induced nonmotor symptoms of PD can be challenging, especially as treatment strategies often involve tapering off of these drugs, and such changes to therapy can worsen motor symptoms (Table 1). However, these effects of dopaminergic therapy are important to recognize given the impact they can have on patients' quality of life. Hallucinations and psychosis can be frightening to both patients and their loved ones. ICD and DDS can lead to serious personal, social, and financial consequences, and autonomic and sleep symptoms can often be more debilitating than PD motor symptoms themselves. Thus, it is important to exercise sound clinical judgment when initiating and titrating medication and closely monitor patients with the involvement of family and caregivers.

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## Review Article

# A Review of Social and Relational Aspects of Deep Brain Stimulation in Parkinson's Disease Informed by Healthcare Provider Experiences

Emily Bell,<sup>1</sup> Bruce Maxwell,<sup>1</sup> Mary Pat McAndrews,<sup>2</sup> Abbas F. Sadikot,<sup>3</sup> and Eric Racine<sup>1,4,5</sup>

<sup>1</sup>Neuroethics Research Unit, Institut de recherches cliniques de Montréal (IRCM), Montréal, QC, Canada H2W 1R7

<sup>2</sup>Division of Brain, Imaging & Behaviour-Systems Neuroscience, Toronto Western Research Institute, Toronto, ON, Canada M5G 2M9

<sup>3</sup>Montreal Neurological Institute and Hospital, McGill University, Montréal, QC, Canada H3A 2B4

<sup>4</sup>Department of Medicine and Department of Social and Preventive Medicine, Université de Montréal, Montréal, QC, Canada H3C 3J7

<sup>5</sup>Departments of Medicine and Neurology and Neurosurgery and Biomedical Ethics Unit, McGill University, Montréal, QC, Canada H3A 2T5

Correspondence should be addressed to Eric Racine, eric.racine@ircm.qc.ca

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*Background.* Although the clinical effectiveness of deep brain stimulation (DBS) in Parkinson's disease is established, there has been less examination of its social aspects. *Methods and Results.* Building on qualitative comments provided by healthcare providers, we present four different social and relational issues (need for social support, changes in relationships (with self and partner) and challenges with regards to occupation and the social system). We review the literature from multiple disciplines on each issue. We comment on their ethical implications and conclude by establishing the future prospects for research with the possible expansion of DBS for psychiatric indications. *Conclusions.* Our review demonstrates that there are varied social issues involved in DBS. These issues may have significant impacts on the perceived outcome of DBS by patients. Moreover, the fact that the social impact of DBS is still not well understood in emerging psychiatric indications presents an important area for future examination.

## 1. Introduction

There is evidence that deep brain stimulation (DBS) can improve both motor function and quality of life in patients suffering from inadequately controlled symptoms of Parkinson's disease (PD), when compared to patients on best medical therapy alone [1, 2]. In addition, DBS is a neurosurgical intervention utilized for the treatment of patients with essential tremor and dystonia [3]. However, aside from the apparent efficacy of DBS, there are also data suggesting psychosocial adjustment difficulties in some patients with DBS which paint a more complex picture of patient outcomes. Powerful questions about whether "the doctor is happy, the patient less so?" [4] and whether there might be a "distressed mind in a repaired body?" [5] suggest

that psychosocial factors after DBS may have a large impact on patients.

The psychosocial challenges that may present after DBS have been explored by Agid and colleagues [4–6]. In their qualitative interview study of PD DBS patients, the authors observed that some patients faced a range of psychosocial challenges including what they interpret to be repercussions and difficulties for the "self" (the patient), with "the other" (the spouse) and with "others" [4]. Additionally, a qualitative interview study of patients and healthcare providers performed by Gisquet demonstrated that some patients who have undergone DBS communicate "a loss of control over managing their illness and over their life," characterized by the fact that patients report being tied to the medical team

to manage their stimulator and their treatment in a way that they were not before [7].

Although, at the core, evaluating the clinical efficacy of an intervention such as DBS relies on measurements of motor improvement, the evaluation of psychosocial factors and challenges is important because these factors will impact overall quality of life, may be integral to the success of the intervention, as well as may impact how successful the intervention is perceived to be by patients and families. These challenges also draw our attention to areas where providers can target psychosocial assistance for patients after DBS (i.e., in their home life and work life). The analysis of the psychosocial aspects of DBS reflects an understanding of the impact of interventions and clinical effectiveness beyond the limits of generic health-related quality of life (HRQoL) measures [8] and motor scales.

In this paper, we discuss and review social and relational aspects of DBS, focusing on issues brought to light in a qualitative interview study examining healthcare provider perspectives on ethical and social issues in DBS (methods published in detail elsewhere, Bell et al., submitted). From these interviews, we have pulled examples provided by healthcare providers describing social contexts and psychosocial challenges for DBS patients. Six examples, provided by healthcare providers in the field, serve as a catalyst for our discussion and allow us to discuss the literature from different disciplines (e.g., neurosurgery, sociology, ethics) to explore social and relational issues of DBS. The examples illustrate the challenges of: (1) social support for patients undergoing the surgical procedure, (2) changes in “self” experienced by patients and families, (3) changes in the relationship with the spouse experienced by patients and spouses, and (4) occupational and social system obstacles for patients. After each case is presented, we explain the challenge communicated by providers in the example, provide any additional qualitative material from the interviews to illustrate this challenge, explore the published literature across disciplines on the topic and conclude by providing considerations of how this challenge may translate for future emerging applications of DBS in psychiatric disorders such as refractory depression [9–11]. Additional qualitative material from the interviews illustrating the challenges is presented as available online supplemental material at doi: 10.4061/2011/871874. Ethics approval and consent were obtained for the qualitative study from which we draw examples.

### 1.1. Social Support for Patients Undergoing the Procedure

*Example 1.* “[ . . . ] I can think of an example where we had somebody who has very low level of education, basically doesn't probably read very . . . not illiterate but very low level and lives on his own and um travelling to and from appointments it's a financial strain because he's not working. We did surgery because there were no other medical options but it makes the management very difficult. [ . . . ] because he lives a distance away, it's a lot more work for us to coordinate and to set up things to make sure that he knows

his appointments and where he's going and how to get to and from. We do it, but it's not ideal, and we, I actually, I guess we set the expectation that there needs to be somebody that I can teach along with that person uh who will be close to them to know how to use the device for turning the stimulator on and off. I don't, we won't do it without somebody who can come with him to learn that sort of thing” (D6).

This example highlights the importance of social support for patients undergoing DBS, and also demonstrates the weight that considerations of social support carry for healthcare providers in selecting patients for DBS and in assuring adequate patient management over the long term. Here, delicate considerations of a patient's social situation, including their level of education, access to a social support system, and access to nearby care impact the patient's suitability for the procedure because in the long run these factors may influence success or failure of the intervention. As the provider in this example strongly states, “we won't do it without somebody who can come with him to learn” (D6). Evidenced in the example, patients who present with one or more obstacles in social function are not ideal candidates for DBS, and providers may struggle with ways to sufficiently accommodate the patient and remain confident of overall outcome. Although, as this example also demonstrates, providers strive to find solutions with which all parties are comfortable, ensuring as much as possible that a patient will not be turned down for DBS based on a lack of social support, or social means to manage the process or device. The critical nature of assuring caregiver support for patients was also alluded to by other healthcare providers (see online Supplemental Material, Table 1).

A second reason why healthcare providers in our study suggested that a patient's social support network is important was because family members can provide useful collateral information about the patient, their symptoms, and their illness (see online Supplemental Material, Table 1). In some cases, this sort of information might contribute to the patient selection process, helping to better identify symptoms that are present, symptoms which may or may not respond to DBS. In other cases, after DBS has been performed this sort of collateral information is important because family members may be in a unique position to identify unwanted side-effects of stimulation such as cognitive deficits or behavioral or psychiatric problems than either the patient or healthcare team.

*1.1.1. Implications.* The importance of caregiver support, the role they play in assisting patients in receiving care, and the interplay of social support and potential barriers to care such as the physical distance between patient and team have been emphasized in many different contexts related to DBS and PD. In a previous review of ethical and social issues in DBS, Bell and colleagues suggested that considerations of caregiver support factor into patient selection decisions, since physicians have a duty to select the best candidates for DBS. Maximizing the best outcomes involves an estimation of whether the patient has sufficient support to attain

appropriate levels of care and management of the device after the procedure [12]. This may be particularly important as self-programmable devices and rechargeable batteries are introduced for patients with movement disorders. Because of differences in the amount of medication management required after DBS [13], there may also be subtle differences in the need for support by patients and caregivers depending on the site of stimulation. Bell et al. have suggested that lack of adequate support should not necessarily prohibit patients from accessing DBS, but rather highlight where provisions should be put in place to manage special circumstances [12]. Perozzo et al. have discussed the importance of evaluating the family's capability to offer moral and physical support post-operatively [14]. Accordingly, Okun et al. have stressed the importance of assessing family support, while additionally emphasizing that teams assess the patient's ease of access (including distance) to specialized care and for follow-up care before providing DBS [15]. The authors even relate such strong meaning to this point that they suggest patients who live in "remote areas or without access to care may want to consider other alternatives to device-based therapy (e.g., ablative therapy)" [15].

In another context (examining a potential fast-track inpatient procedure for device programming), Cohen and colleagues also comment on the issue of distance between patients and their care centre. In fact, decreasing the difficulties associated with large amounts of travel to and from specialized centers for patients who do not live close to the programming team is one of the reasons why they suggest an inpatient stay for programming might be beneficial and improve outcomes and speed of programming [16].

Collectively, these studies support the view that family support and social means to access the care team are influential in the potential successes or failures of DBS. However, Lang and colleagues assert that there are no empirical data examining the impact of social support or burdens of travel on clinical success or outcomes in DBS although they also claim that "if the patient does not have transportation available to travel to a center for surgery or programming, they may have to be excluded" [17]. It is evident that patients with poor social networks or social means may become disadvantaged in accessing such specialized care as DBS, or may be susceptible to poorer outcomes or failures if these issues are not identified and managed sufficiently. Therefore, the issue of social support is tightly tied to proper identification of needs for social support and issues of fair access (justice). We therefore would benefit from a better understanding of the impact of social factors in influencing success or failure of DBS, as well as more clarity regarding whether social disadvantages prevent patients from currently accessing DBS, or receiving adequate follow-up care for their stimulators.

*1.1.2. Future Challenges.* Emerging applications of DBS for psychiatric conditions such as major depression may require new considerations about what are sufficient or acceptable social supports and means. Many severely ill psychiatric

patients may have limited social supports. This may compromise their ability to access potentially innovative care, which if successful may even contribute to a re-establishment of social relationships lost due to chronic mental illness. Although a patient's ability to access specialized centers has been proposed as an important selection factor in clinical trials in DBS and psychiatry [18], the issue of social support in these patients has not, to our knowledge, been discussed extensively to date.

### *1.2. Changes in Personality and Changes to the "Self"*

*Example 2.* "So for example one man who had ... bilateral subthalamic stimulation, his wife described him after the surgery basically as being like a spontaneous, impetuous, difficult, teenager. They would be out driving ... they lived near to a boarder ... with the United States and he would say: Hey let's go see if we can get across the boarder without our passports. You know this a man in his sixties. He would come home with an all-terrain vehicle. You know this is a man who previously hiked and enjoyed sort of peaceful serenity in the outdoors and now wanted to drive an all-terrain vehicle through the woods" (D3).

Describing a patient having undergone DBS who is by his family's account a significantly *changed* person, this provider's example highlights a number of important issues. It provokes reflection about the causes of the observed alterations in behavior and makes us wonder if the behaviors observed are brought on directly by the stimulation (represent an induced change in the patient's personality)? Or does the behavior relate to the fact that the patient once hindered by chronic illness may be adapting to a new role and a new health status, as well as a new device implanted in their body? Other providers in our study emphasized that patients may face adaptation challenges after DBS, coming to terms with a new identity which includes foregoing the obligations and behaviors associated with being sick (foregoing the *sick role*, see online Supplemental Material, Table 2). They often likened these challenges to well-documented consequences reported in some epileptic patients having undergone neurosurgery. Ultimately, this example also raises questions about the expected role of the healthcare team with regards to potential changes in behavior, personality, and adaptation following DBS.

*1.2.1. Implications.* There are essentially two different aspects to be discussed regarding the role of DBS towards changes in the "self." The first issue revolves around what amount of influence stimulation itself has as a cause or contributing factor to behavior changes or personality changes in DBS patients. The second issue, brought up by several healthcare providers in the study, is what, if any, personal adaptation challenges are faced by PD patients after DBS.

*The Influence of DBS on Behavior and Personality.* The influence of DBS on behavior and personality has not clearly been delineated, and there is conflicting evidence

that changes in mood and anxiety occur after DBS [12]. There are data which demonstrate increased impulsivity in some PD patients after DBS. Although, it is accepted that impulse control disorders can present in PD patients treated with dopamine agonists, several researchers have also demonstrated increased impulsivity in PD patients treated with DBS regardless of the influence of dopamine agonists [19–21]. In fact, after having observed that 3 out of 19 DBS patients studied had impulse control disorders (i.e., compulsive shopping, pathologic gambling), compared to 3 out of 37 patients treated with best medical therapy, Halbig and colleagues reported this observation as an “unexpectedly high frequency of impulse control disorders in PD patients with STN DBS” [21]. Moreover, Gisquet has suggested that the experience of mood or behavior changes after DBS may be so far reaching for patients such that they “have the feeling that their identity has been affected” [7].

The larger question remains whether these types of changes, or others observed after DBS, are substantial alterations in the personality of the patient, especially when we consider that there are many possible conceptions of the terms personality and self? According to Synofik and Schlaepfer's assertions about personality and DBS, it is likely that on some level personality is affected by DBS; although the authors propose it is more important whether the patient's personality is altered in a way that is evaluated to be good or bad by them and their family [22].

Importantly, changes in mood or behavior observed after DBS are not related to the procedure specifically but rather to the stimulation and target of stimulation and there is still active discussion regarding the site of choice for stimulation in advanced PD patients and the side-effects or advantages of these targets. It has been suggested that stimulation of the subthalamic nucleus (STN) results in more mood related adverse events, than stimulation of the pallidal target (reviewed in [23]) and recent data suggests that adverse events to mood (depression/anxiety) may be higher over the long term in patients who undergo STN stimulation than globus pallidus interna (GPi) stimulation [24]. On the other hand, Okun and colleagues (2009) have observed that stimulating the ventral contacts of both STN and GPi can produce negative mood effects, which they suggest likely owes to the ventral spread of activity to nonmotor and limbic circuits [25].

#### *Personal Adaptation Challenges Faced by Patients after DBS.*

A landmark qualitative interview study of PD patients after DBS, conducted by Agid and colleagues, has revealed some of the important social adaptation challenges faced by patients, despite improvements that they experience in their motor symptoms. The authors describe that some patients reported a difficulty adapting to a new concept of themselves and the improvement of their illness [4], or felt strangely about their after-DBS self [5]. At the same time, they present evidence that for some patients there may be a sudden loss of goal or direction for life once the disease symptoms, a previously large focus of daily life, are improved [4]. Other authors have proposed that DBS may

create adaptation challenges for patients because of a discord created between the patients narrative identity before and after DBS [26], or because of an abrupt alteration created in the patients' experience of chronic illness [7]. As Seaburn and Erba comment, “a discontinuous change in the patient's condition (sudden health) because of a surgical or medical intervention, may eliminate the patient's disease and the disease label from the patient's identity” [27]. Healthcare providers have commented that patient outcomes with DBS may be more modest, and mixed, and have suggested that they dedicate substantial time to dispelling the notion among patients that it is a “miracle cure” [28].

However, a common parallel regarding adaptation issues for the *self* was drawn by healthcare providers in our study between PD DBS patients and patients having undergone epilepsy surgery. There is an extensive literature on the social function of refractory epileptics after surgery, which emphasize the difficulties associated with rejecting behaviors associated with illness (discarding the *sick role*) [29]. The process by which patients undergo a “forced normalization” (a term used by healthcare provider B2, see Online Supplemental Material, Table 2) requires them to incorporate a change in self-image which is concurrent to the improvement seen in their illness [29]. The features of this “burden of normality,” the authors suggest, are comparable across “life-changing” medical interventions, and may present wide-ranging challenges for patients, including in psychological, behavioral, affective and sociological function [30]. Although it should also be noted, and we discuss this further in the future challenges section, that significant difference exist between these two patient populations (PD and epilepsy) in terms of onset of the illness, chronicity and may exist with regards to the relative success and goals of neurosurgical therapy.

*1.2.2. Future Challenges.* There is a small but concise literature demonstrating adaptation challenges for PD patients after DBS [4–6]. Whether or not these challenges, or concurrent changes in personality or behavior, are related or caused by stimulation, we should remain cognizant that these challenges may highly impact patient quality of life and social function after the intervention. In addition, healthcare providers may benefit from engaging patients, and their families, in a discussion about psychosocial challenges thereby increasing the early detection of difficulties and facilitating psychosocial interventions. Cohen and colleagues have highlighted the importance of psychological adjustments to DBS by integrating psychological care and psychosocial education in their inpatient fast track procedure for programming [16]. It remains important to further evaluate and delineate the impacts of DBS on behavior and mood. In particular, we are lacking a good understanding of the effects of DBS on these in the context of real life consequences for patients and families. For instance, although some studies have shown that PD DBS patients display impulse control difficulties in cognitive testing, the observations of actual impulse control disorders in PD DBS patients [21] (as well as a

consideration of what the impacts of excessive gambling and shopping might mean) emphasizes the potential importance of establishing if these are in fact *de novo* problems brought on in the DBS patient. Besides numerous pharmacological and disease related factors, the impact of placement of DBS leads in more lateral sensorimotor or medial associative limbic sectors of the subthalamic nucleus may also play a role in emergence of potential mood disorders. Finally, a better understanding of challenges related to self-identify, and personality may be especially important in the face of emerging applications for DBS in psychiatry. We lack evidence on what the impacts of DBS might be for these patients in the context of social function, how they might adjust to DBS, or to improvements in their chronic illness and disability. The fact that patients will likely have suffered chronic illness for long periods of time might be more antagonistic to the process of restructuring identity after DBS, than in PD, where the duration of illness may have been shorter and the onset later in life. In this regard, we could hypothesize that the course of the burden of normality may end up being more like that experienced in epileptic patients where the onset of disease is earlier and where younger patients may have faced lost early opportunities for personal exploration and growth. In addition, neuropsychiatric conditions are tightly linked to the concept of self; DBS for psychiatric disorders has the *goal* of altering personality [22].

### 1.3. Relationship with the Other

*Example 3.* “A wife who has had a husband who has really been I would have thought a great care to her in terms of his Parkinsonian needs and she fulfilled that role, it was doing something for her. Um, is it pathological what it was doing to her? I don't know. At any rate, she got satisfaction on the fact that he was dependent. Where he had previously been the dominant party in the pair, he was now dependent. I don't think that there was abuse in the story, in the particular case, I don't think there was abuse involved but she got satisfaction on the fact that he was now dependent and in need of her. That was satisfying a need with her. [ . . . ] There began to be conflict situations between husband and wife because now he was much more independent. He was driving again, so he said look, I am going to go down and see some of my friends. So I must say that I am not sure that if in the past he had gone down with some of his buddies and spent a lot of time away from home etc. etc. that I am not sure about. Anyway, it was a bad situation. So the two of them had a great deal of conflict and we had to deal with that and get some counseling for the two of them because of these new exchanged roles.” (C2).

*Example 4.* “[ . . . ] we had one fellow for example. His wife was, they were really having marital problems—quite frankly she just didn't want to care about him anymore. She was really tired and feeling really burnt out and hoped that the surgery would make him more independent so she wouldn't have to. He was really a lot better but not quite as well as she hoped, right. So you just see how expectations affected all around.” (C4).

These two examples, described by healthcare providers in our study, depict very different problems that emerged for two couples (the patient and their spouse caregiver) after DBS, resulting in marital discord, and difficulties within their relationship. The first example describes a couple where the patient regained enough independence after surgery such that the caregiver/spouse no longer felt needed in the same way as before. While it may seem contradictory to think that a patient regaining independence (one of the goals of the therapy) can raise any sort of a problem, we clearly see in this example that the issues brought on in the relationship were severe enough that the couple was referred for counseling. In the second example, a very different dynamic is described; here, it would seem that the spouse actually desired more independence of the patient than was achieved and that this failure to attain some relief in the role of caretaker also created a struggle in the couple's relationship. References to the former (patient-caregiver conflict based on regained independence of the patient) were quite common in our data (see online Supplemental Material, Table 3).

*1.3.1. Implications.* The data that we have collected demonstrates the existence of psychosocial challenges between the patient and the spouse after DBS. These correlate with issues that have been previously detailed by Schupbach et al. and Agid et al. in their qualitative interview study of PD DBS patients [4, 5]. Patients communicated being faced with two of the same types of problems after DBS with regards to the relationship with their spouse. On one hand, some patients (in their study 6 out of 24 patients) sought to reclaim the independence they previously lost and “rejected their spouse,” advertently or inadvertently causing the spouse give up the caregiver role they were playing over the length of the illness. On the other hand, other patients (in their study 11 out of 24 patients) may be “rejected by (their) spouse”. In this scenario, the authors claim, marital problems arise because the spouse's expectations of outcome are not met by the patient's actual real-life abilities, ultimately reflected in the fact that life does not return to the way it was before surgery [4, 5]. It would seem that the failure of DBS to meet caregiver expectations, not unlike what has been previously observed with failure to meet patient expectations, risks creating disappointment, and conflict [28]. In the epilepsy literature, Bladin has described a similar phenomenon [31]. When assessing cases where a couple had divorced following epilepsy surgery, he describes finding a “hidden agenda” in some of the partners, where one of the expectations for seeking surgery was “if once I can be set free. . .” [31]. The marital conflicts that may be exacerbated by DBS are not insignificant. Although Agid and colleagues reported that most patients who suffered from marital problems after the intervention had also suffered from problems beforehand, patients reported that the problems had worsened after DBS [4]. Agid et al. specify that 65% of patients they interviewed who were married experienced a “conjugal crisis” following DBS [4]. It's interesting to note that while Schupbach et al.

report that a greater percentage of patients in their study were “rejected by their spouse,” these cases were mentioned in the minority by healthcare providers in our study. Perozzo et al. have also described conflicts between spouses that emerged after DBS surgery in a sample of 15 PD patients. The authors reported that caregivers were reluctant to maintain the role of caregiver after surgery, while patients were reluctant to give up the attention and special treatments that they received from others prior to DBS. They also suggested that the conflict between the spouses could even be marked by hostility [14].

*1.3.2. Future Challenges.* Based on our cases and others, it is clear that the reasons for marital conflict following DBS and possible ways to manage or alleviate patient and caregiver distress warrant more investigation. Specifically, a better understanding of how spousal and patient expectations of outcome may influence the marital relationship after DBS may constitute a key area where DBS healthcare teams could intervene to prevent future problems. In emerging indications, researchers need to consider early on the important role of expectation in influencing psychosocial outcome and the changing dynamics of caregiver-patient relationships after DBS. Research outcomes into emerging indications such as treatment refractory depression may not yet be extensive enough to guide patients or their families with regards to realistic expectations, and this may influence psychosocial adaptations for these patients. In addition, unique issues with regards to family dynamics may exist in psychiatric patient groups, which may need to be considered in evaluating the potential impacts of DBS on the family and spouse of psychiatric candidates.

#### *1.4. Employment, Vocational Opportunities and Disability*

*Example 5.* “Most of the time, by the time they are in this state most of them have been off of work for a long time and there is no practical employment. Having said that, we have done some younger patients who are having difficulty with their employment. There is a guy [ . . . ] but this fellow was a journalist. His problem, with his Parkinson’s disease wasn’t all that bad but it was right-sided. He did a lot of writing and keyboarding. That is what he was doing for a living. He was having difficulty using his hand on the keyboard and so he was very slow in producing written material. He wanted something done about his tremors and stiffness and slowness. We thought he was relatively well optimized in terms of medication and he had had some side-effects when they tried to push his drugs higher than that—mental changes and some hallucinatory material. So we felt that normally we wouldn’t have done a guy like this surgically but we did him because he had a specific problem and we felt that this was a reasonable approach—he was a young man. He did very well. His tremors disappeared and his bradykinesia became less. He was able to address the keyboard better and write better and he is a happy camper. He hadn’t stopped work in that sense, but he had slowed down his work and he was able to do less.” (C2).

*Example 6.* “[ . . . ] a very striking example of a young woman who developed a pretty bad movement disorder specifically a generalized dystonia at a young age and as a result was disabled enough that she couldn’t really work and uh and at age forty, having failed medical treatment over the years and the surgery comes along and now is the treatment option, we treated her and it cured her, and so now all of a sudden you’ve got a forty year old who’s for the first time in her life normal, and uh that was a major problem. You wouldn’t think fixing a disorder would be an issue uh in that manner but all of a sudden this person’s normal, the social services people are saying: well look, you’re now well you should go get a job. She had not had any employment experience at all in her life, her peer group who were other people that were living in at kind of that level of society, all of a sudden says: ‘well you kind of don’t belong with our group anymore there’s nothing wrong for you,’ and so there is an issue of when it works really well people not really being prepared for not being disabled anymore, which often is what we talk about.” (E2).

In the first example, the provider describes the unique case of a young, and still actively employed, PD patient given DBS. For this patient, DBS is an intervention that not only improved the motor symptoms of PD, but also restored the motor skills necessary for his career. Ultimately, in this case, DBS allowed the patient to remain gainfully employed. His situation was clearly facilitated by the healthcare provider who considered the possible positive impacts of DBS for his job. This example was unique because in our discussions with providers we largely gathered that most patients referred for DBS are no longer working (had already retired or stopped working because of their disorder). This example highlights how DBS applied in specific cases to good candidates at a younger age might maximize work opportunities, and to some extent reduce the burden of disability.

In the second, and the very different example, the provider described a patient with early life onset of dystonia. The patient had been unable to work during the time when she was disabled by the disorder. Once DBS was applied later in life, this patient was at a severe disadvantage because she suffered from a lack of necessary skills to access employment opportunities. Even worse, the provider described that once the patient’s symptoms improved there was an expectation of employment and an expectation that the patient would not need the same social provisions for her disability. Providing the best therapy for this patient created new social and employment challenges.

*1.4.1. Implications.* The topics of employment and occupational disability, while not well discussed in the context of DBS specifically, have been examined in PD patients more generally. In one UK study, Schrag and Banks found that 52% of patients with PD retire early and that the mean time to loss of employment for patients was only 4.9 years from diagnosis [32]. Moreover, 10 years after the onset of the illness, 82% of PD patients are no longer working [33]. This study highlights the importance of, first, having PD

patients plan for the future early on in their disease and second, of providing accommodations to try to keep patients in the workforce later into the course of their disease [33]. The implication for DBS practitioners and patients who may be good candidates is that it may be important to consider acting sooner than later to prevent loss of employment and the accompanying financial burdens. Alternatively, there may also be a role for providers to assist patients and employers in finding appropriate new roles in the workplace for patients with DBS. In fact, this was something that a provider in our study stated having done in the past. In an earlier study Schrag and colleagues described the impact that a loss of employment might mean for young (onset before age 50) PD patients. These patients may suffer substantial economic consequences as a result of occupational losses, and they have been found to perceive that their disease has a greater impact, when compared to their older counterparts with similar disease duration [32]. Moreover, the authors observed that in their sample, younger PD patients were considered unemployed or had retired early, compared to older PD patients who had either already retired (before their illness onset) or were close to retirement age [32]. The financial burden created by this situation, may also play a role in creating marital conflicts for these patients [32].

On the other hand, for some movement disorder patients it may be the loss of opportunities to gain the skills necessary to be employable that poses the specific problem, rather than the loss of current employment (i.e., the second-case example). This challenge may be revealed after a patient's symptoms improve with DBS. The same sort of problem has been alluded to in the context of epilepsy, where patients who undergo epilepsy surgery may have experienced an early age of onset, creating disadvantages to gain life skills and occupational or educational opportunities. Bladin et al. report that 12% of the epileptic patients they studied after surgery recounted grief or bitterness about the fact that the surgery had not been attempted earlier in their life [31]. We can imagine that a portion of this regret was due to losses in achieving what they considered to be their full potential. For some DBS PD patients, Agid et al. have described that feelings of a "retrospective disaster" can be experienced. Although their motor symptoms have improved, patients have suffered irreparable consequences of the disorder (i.e., loss of friends, loss of employment) [4]. Unfortunately, there is no data, to our knowledge, which captures the challenges directly related to social assistance programs and the abilities of patients to access these services after an intervention such as DBS.

*1.4.2. Future Challenges.* The last comments do not imply that younger patients are all good candidates for DBS or that DBS will have an impact on employment or occupational opportunities for every patient. As our cases suggested, many patients undergoing DBS, particularly for PD, have already left their jobs, but providers may want to discuss with patients and their families what goals they may have with respect to occupation. There are some patients who may make an active choice to not go back to work after

DBS. Agid and colleagues have shown that a number of patients actually decide that work carries less importance after DBS than it did before [4]. It is likely that more occupational challenges will be revealed in emerging uses for DBS, such as refractory depression. As a consequence of a long, severely limiting illness such as refractory depression, we can foresee challenges much like those related in the second example. Patients who have been severely limited in seeking out educational or occupational opportunities may perceive that they have truly "lost" time. Severely impacting patients' abilities to access resources and secure employment opportunities, this also has the potential to influence how patients perceive their long term outcome. Providers may be able to help prepare patients to look ahead and plan for future success.

## 2. Conclusion

Patients undergoing DBS may face a range of psychosocial challenges after the intervention, at home and at work, and psychosocial factors may also impact patients' ability to access and continue successful therapy. A richer understanding of the challenges that patients face is achieved through analyzing cases where patients, and healthcare teams, have been confronted with and/or managed psychosocial challenges. With an increased emphasis being placed on the development and contribution of patient reported outcome measures (PROMs) in neurological trials [34], the perspective of patients on aspects of HRQoL including social functioning and relationships with others is important to capture the actual issues faced by patients [35]. Ideally, these perspectives would be incorporated into PROMs and considered in the demonstration of clinical efficacy of interventions such as DBS. The psychosocial success or failure of DBS may become even more important in emerging psychiatric indications of DBS, and, early on, these factors should be explored systematically among these patients and their families.

## Conflict of Interests

The authors have no conflict of interests to report related to the research in this paper.

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## Review Article

# Differential Effects of Dopaminergic Therapies on Dorsal and Ventral Striatum in Parkinson's Disease: Implications for Cognitive Function

Penny A. MacDonald<sup>1</sup> and Oury Monchi<sup>2</sup>

<sup>1</sup> Department of Neurology & Neurosurgery, McGill University, Montreal, QC, Canada

<sup>2</sup> Unité de neuroimagerie fonctionnelle, Institut Universitaire de Gériatrie de Montréal, QC, Canada H3W 1W5

Correspondence should be addressed to Penny A. MacDonald, penny.macdonald@gmail.com

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Cognitive abnormalities are a feature of Parkinson's disease (PD). Unlike motor symptoms that are clearly improved by dopaminergic therapy, the effect of dopamine replacement on cognition seems paradoxical. Some cognitive functions are improved whereas others are unaltered or even hindered. Our aim was to understand the effect of dopamine replacement therapy on various aspects of cognition. Whereas dorsal striatum receives dopamine input from the substantia nigra (SN), ventral striatum is innervated by dopamine-producing cells in the ventral tegmental area (VTA). In PD, degeneration of SN is substantially greater than cell loss in VTA and hence dopamine-deficiency is significantly greater in dorsal compared to ventral striatum. We suggest that dopamine supplementation improves functions mediated by dorsal striatum and impairs, or heightens to a pathological degree, operations ascribed to ventral striatum. We consider the extant literature in light of this principle. We also survey the effect of dopamine replacement on functional neuroimaging in PD relating the findings to this framework. This paper highlights the fact that currently, titration of therapy in PD is geared to optimizing dorsal striatum-mediated motor symptoms, at the expense of ventral striatum operations. Increased awareness of contrasting effects of dopamine replacement on dorsal versus ventral striatum functions will lead clinicians to survey a broader range of symptoms in determining optimal therapy, taking into account both those aspects of cognition that will be helped versus those that will be hindered by dopaminergic treatment.

## 1. Introduction

Parkinson's disease (PD) is a neurodegenerative illness with prominent motor symptoms of tremor, bradykinesia, and rigidity. These motor symptoms result from degeneration of the dopamine-producing cells of the substantia nigra, leading to dopamine deficiency and dysfunction in the dorsal striatum. Cognitive dysfunction has long been recognized as a feature of Parkinson's disease with 20–50% meeting criteria for dementia [1–5] and a far greater proportion displaying features of milder cognitive dysfunction [6]. Unlike the relatively clear-cut explanation for motor symptoms, debate has surrounded the locus of these cognitive impairments in PD. While initial explanations focused on cortical degeneration, which also occurs in PD, particularly at later

disease stages, studies have repeatedly failed to demonstrate correlation between cortical Lewy body dispersion and severity of cognitive impairment [7–11]. Studies in patients with basal ganglia lesions and investigations of cognition in healthy volunteers using neuroimaging are increasingly attributing cognitive functions to basal ganglia [12–17]. Some pathological studies confirm cognitive impairment in PD patients even in the absence of cortical compromise [18, 19]. Taken together, basal ganglia pathology and biochemical deficit might be an important cause for cognitive impairment in PD. Further complicating our understanding of cognitive function in PD, whereas the motor manifestations are clearly improved by dopamine replacement medications such as L-3,4-dihydroxyphenylalanine (L-dopa) or dopamine receptor agonists, the effect of dopamine replacement therapy on

cognition seems paradoxical. Some cognitive functions are improved by dopaminergic therapy whereas others are unaltered or even hindered. Our main aim, in fact, is to review and understand the effect of dopamine replacement therapy on different aspects of cognition, relating these findings to functions of different segments of basal ganglia.

Previous investigations suggest that individual segments of the basal ganglia mediate different elements of cognition. One approach for subdividing the striatum involves distinguishing the ventral striatum, comprising the nucleus accumbens and the most ventral portions of caudate and putamen, from the dorsal striatum, entailing the bulk of the caudate nuclei and putamen [20–22]. This distinction is important in PD given that the dopamine input to these regions are divergent and degenerate at different times and to varying degrees in disease evolution. Whereas dorsal striatum, responsible for the prominent motor symptoms, receives dopamine input from the substantia nigra (SN), ventral striatum is innervated by dopamine-producing cells in the ventral tegmental area (VTA). In PD, the VTA is significantly less affected than the SN at clinical disease onset and a disparity is maintained throughout the disease course [23–26]. Given these differences, functions performed by dorsal striatum should improve disproportionately with dopamine replacement therapy compared to those subserved by ventral striatum. In fact, there is evidence that ventral striatum functions worsen with provision of dopaminergic therapy [13, 27–32]. An explanation offered for this medication-induced impairment is that these less dopamine-depleted brain regions are effectively overdosed by dopaminergic medications that are titrated to dorsal striatum-mediated motor symptoms [13, 28, 29, 32].

A central objective of this paper is therefore to define the different cognitive processes mediated by the more dopamine-depleted dorsal compared to the relatively spared ventral striatum, with the aim of providing a framework for predicting and understanding those cognitive processes that might be enhanced compared to those that will be hindered by dopaminergic therapy, at least at the early stages of the disease. Albeit somewhat simplified in that it does not address the impact of, nor incorporate findings related to, other VTA-innervated regions, such as prefrontal and limbic cortex, we will show that this approach accommodates and explains an impressive array of cognitive and neuroimaging findings in PD, providing a possible principle to predict and understand the effect of dopamine replacement therapy on cognition in this disease.

We will first present subtle cytoarchitectonic distinctions between dorsal versus ventral striatum, as well as the divergent regions to which they are reciprocally connected, as evidence of how these regions are differentially adapted to separate cognitive functions. We will next review the effect of dorsal versus ventral striatum lesions on cognition, as well as the cognitive functions that implicate dorsal versus ventral striatum in neuroimaging studies. As a test of the framework adopted here, that dorsal striatum functions are improved whereas ventral striatum functions are worsened by dopamine replacement, we will next compare those cognitive functions that are known to be improved versus

those that are impaired by dopamine replacement therapy in PD patients to the pattern predicted by the lesion and neuroimaging studies. Table 1 summarizes these findings. Finally, we will survey the results of neuroimaging studies in PD patients on and off dopamine replacement therapy. These studies provide direct evidence of the effect of dopamine supplementation on brain activity in PD. Further, they provide an additional test of the hypothesis that variable effects of dopamine treatment in PD on distinct cognitive processes relate to their differential reliance on dorsal and ventral striatum.

*1.1. Dorsal Striatum.* In the dorsal striatum there are denser dopamine inputs and more numerous dendrites and spines on medium spiny neurons (MSNs) resulting in rapid and maximal dopamine stimulation through a wide range of input firing frequency and intensity [22, 33]. Due to high concentration of dopamine transporter (DAT), which is responsible for synaptic dopamine reuptake and clearance, synaptic dopamine is rapidly cleared, yielding short dopamine stimulation durations [22]. Taken together, this precisely-timed, brief, and consistently maximal receptor stimulation adapts dorsal striatum for rapid, flexible, and more absolute or binary responding as might be needed in deciding between alternatives. Suggesting an important role in performance, the dorsal striatum is reciprocally connected to a number of effector brain regions such as frontal eye fields, dorsal and rostral premotor cortex, supplementary, and primary motor cortex. Dorsal striatum projections also arise from and lead to dorsolateral prefrontal, somatosensory, and parietal association cortices, regions involved in executive functions [34]. In addition to an extremely high degree of convergence in striatum, MSNs receive very few projections from each cortical neuron [35–38]. Dorsal striatum is consequently ideally positioned to sum diverse influences on responding, with vast numbers of cortical neurons each making only small contributions, requiring a concordance among many inputs to influence the excitation status of a given MSN. In turn, through reciprocal connections, single MSNs affect numerous cortical neurons. In this way, dorsal striatum coordinates activity in disparate cortical regions. These characteristics would suggest that dorsal striatum is ideally suited for selecting some stimuli or responses and suppressing others.

*1.2. Ventral Striatum.* Subtle cytoarchitectonic and neurochemical differences for ventral relative to dorsal striatum, such as smaller neuron size with fewer and more widely-spaced dendrites and spines, along with less significant dopaminergic input, have as a functional consequence that receptor stimulation with a single dopamine pulse is slower, and of lower and more variable intensity than in dorsal striatum [22]. This translates to greater differences comparing tonic versus phasic dopamine stimulation in ventral striatum, a fact demonstrated experimentally by Zhang et al. [33] who found nearly maximal dorsal striatum stimulation at even the lowest intensity and frequency dopamine impulses compared to much more graded, incremental responses in the ventral striatum. Owing to lower DAT concentration,

TABLE 1: Cognitive functions that are enhanced, unchanged, or impaired by dopaminergic therapy, grouped according to their association with dorsal striatum, ventral striatum, or other brain regions.

	Enhanced by dopaminergic therapy	Unchanged by dopaminergic therapy	Impaired by dopaminergic therapy
Ventral striatum	Motivation Impulsivity		Implicit and explicit learning Reversal learning Orienting to stimuli
Dorsal striatum	Selective attention Selective responding Complex planning Category judgements Time estimation Visuospatial processing Explicit and implicit retrieval Set shifting Task switching	Complex planning Set shifting Task switching	Time estimation
Other brain regions	Spatial working memory Manipulating contents of working memory	Nonspatial working memory Set shifting Task switching	Simple reaction time Production of self-generated sequences Generation of alternate uses of common objects

Are enhanced to a pathological degree.

dopamine stimulation is also of longer duration in ventral compared to dorsal striatum [22]. Together, these characteristics make the ventral striatum well suited for associating stimuli or events, even across time, in a graded fashion as would be essential for probabilistic or associative learning and for binding events that are temporally coincident into episodes. The regions to which ventral striatum are reciprocally connected also suggest its involvement in encoding and associating salient features of the environment. The ventral striatum receives inputs from and projects to anterior cingulate, orbitofrontal, and anterior temporal cortices, as well as to hippocampus, insula, amygdala, and hypothalamus. Due to a high degree of convergence, with 10–20 000 cortical or limbic neurons projecting to a single medium spiny neuron in the striatum, representations in basal ganglia are highly sparse relative to corresponding representations in cortex and limbic regions [35–38]. This degree of abstraction precludes storing of memory engrams within ventral striatum but given its significant reciprocal interconnectedness to multiple regions simultaneously, ventral striatum receives information about (a) top-down, goal-directed attentional biases, (b) bottom-up object and event salience, (c) multimodal representations of objects and events, and (d) the current motivational state of the organism [20]. Given persistence of stimulation, ventral striatum can further incorporate response outcome and reward information. Because connections to these diverse cortical and limbic regions are reciprocal, ventral striatum is in a position to harmonize activity in these distant brain regions as is needed for associating disparate, temporally coincident features into episodes. These anatomical characteristics suggest that ventral striatum could play an important role in learning and encoding.

## 2. Cognitive Testing (a) in Patients with Basal Ganglia Lesions and (b) Using Neuroimaging in Healthy Volunteers

**2.1. Dorsal Striatum.** Lesions in the dorsal striatum have been shown to impair set shifting and task switching (e.g., [39–42] but see [43–46]), category judgements [41], and suppression of irrelevant information and responses, particularly when the ignored stimulus is highly salient and the to-be-avoided response is over-learned (e.g., [39, 40, 44, 45] but see [46, 47]). Patients with dorsal striatum lesions have been shown in one study to have deficits in reversal of previously acquired stimulus-reward relations [48]. Tests of planning (e.g., tower of Hanoi and porteus mazes [49]) and visuospatial processing [50–52] uncover deficits in patients with dorsal striatum lesions. A number of lesion studies have also revealed deficits in explicit (e.g., [39, 44, 49, 52, 53] but see [46]) and implicit memory [53, 54] but see [55]. Working memory [39, 41, 44, 48], language (e.g., [39, 56] but see [43, 57]), word and face recognition (e.g., [39, 43] but see [58]), as well as explicit [53] and implicit learning (e.g., [41, 51, 53, 59–61] but see [49, 62]), in contrast, tend to be spared.

Consistent with these lesions studies, shifting set and changing stimulus-reward or stimulus-response mappings (e.g., [63–66] but see [15]) are associated with increased activity in dorsal striatum. Responding to less well learned dimensions such as colour versus word in the Stroop task [12] or with less-practiced responses, as when pictures are named in a second language relative to a first language [67], also preferentially activate dorsal striatum. In a similar vein, dorsal striatum is more engaged when responding to a target

location that was inaccurately predicted by a cue when cues had previously been predictive of the correct target location [68]. That is, dorsal striatum is engaged when previously informative stimuli must now be disregarded.

Dorsal striatum is preferentially activated for learned relative to random motor sequences [69], for familiar items in an episodic recognition test [70], during category judgements [17, 71], especially when there is significant category uncertainty [72], for rewarded relative to unrewarded stimuli [17, 73] and responses [74, 75], and in distinguishing and estimating different time durations [76–85]. Dorsal striatum activity remains significantly increased above baseline throughout these experiments, well after sequences, categorization rules, or stimulus-reward and response-reward relations have been acquired, suggesting that dorsal striatum is involved in performance rather than learning. Tests of visuospatial processing, such as mental rotation, further implicate dorsal striatum in fMRI, although significant increases in activity were noted for male subjects only [86].

Dorsal striatum has been associated with risk aversion during decision making [87] although preferential activation has been noted when speed is emphasized over accuracy in a motion judgement task [88]. Recent findings implicated dorsal striatum in encoding the joint dimensions of reward magnitude and subjective value (i.e., marginal utility) as well as temporal discounting, supporting a role for the dorsal striatum in integrating divergent influences on decision making [89, 90].

*2.2. Ventral Striatum.* There have been very few examinations of cognition following lesions circumscribed to the ventral striatum, mostly owing to the rarity of such small and strategically placed lesions. In human participants, Goldenberg and colleagues [91] reported a case of anterograde amnesia for verbal material following a left nucleus accumbens bleed. Despite an inability to learn new verbal material whether testing memory with recall or recognition, this patient performed normally on tests of retrospective verbal memory, divided and shifting attention, Wisconsin card sorting (WCST), tower of London (TOL), working memory, language, encoding and retrieval of nonverbal information. Taken together, this pattern of deficits and spared functions suggests a critical role for the ventral striatum in encoding associations, with left ventral striatum lateralized for language. Calder and colleagues [92] revealed anger recognition deficits in 3 patients with left and 1 patient with right ventral striatum lesions despite otherwise normal visual processing. Martinaud and colleagues [93] found that left ventral striatum lesions, following anterior communicating artery aneurysm, were associated with behavioural deficits, reduced daily activities, and hyperactivity. Finally, Bellebaum and colleagues [48] looked at acquisition and reversal of stimulus-reward associations in 3 patients with isolated ventral basal ganglia lesions compared to patients with dorsal or dorsal plus ventral basal ganglia lesions as well as to control participants. All patients, irrespective of group, displayed deficits in reversing previously acquired stimulus-reward contingencies. There were no specific or consistent

patterns noted for patients with ventral basal ganglia lesions in their experiment, consequently.

Functional magnetic resonance imaging (fMRI) experiments have shown that the degree to which a motor sequence is implicitly learned correlates with ventral striatum activity [69] and that ventral striatum activity is greatest early in learning, and is preferential for positive feedback relative to negative feedback during initial learning [17, 74, 94, 95]. This ventral striatum-mediated, stimulus-reward learning occurs even without intention or consciousness [96]. Ventral striatum activity drops off as performance asymptotes [69]. Once learning is established, ventral striatum activity increases over baseline tasks only (a) for unexpected rewards delivered for previously unrewarded stimuli or when reward is omitted for previously rewarded items (i.e., prediction errors; [97–102]), (b) for punishment after errors [103], or (c) in reversal learning experiments when criterion is reversed and selection of previously rewarded stimuli now elicits negative feedback [17, 65, 104–106]. Ventral striatum is differentially activated by salient [107–109], valued [107, 108, 110, 111], or novel stimuli [17, 112], and even for passively received monetary or social rewards [113]. Differential ventral striatum activity reflects both magnitude and probability of reward [114], as well as probability of a given outcome (e.g., [115–117] but see [114]). Taken together, the ventral striatum seems to be engaged when a stimulus or event in the environment signals the possibility of new learning.

Heightened ventral striatum activity has been shown in a number of studies to be associated with more impulsive choices [118, 119] and ventral striatum has not been implicated in response inhibition or response stopping [120, 121]. Ventral striatum activity is greater for riskier choices [118, 119, 122, 123] and for more immediate rewards (i.e., temporal discounting; [124–126]). Further, negative functional interaction between nucleus accumbens and anteroventral prefrontal cortex was associated with decisions favouring long-term goals relative to an immediate reward [127]. That is, high levels of activity in nucleus accumbens correspond to lower anteroventral prefrontal cortex activity, which in turn was associated with decisions favouring immediate rewards over long-term objectives.

Consistent with findings in patients with ventral striatum lesions, neuroimaging studies have found that nucleus accumbens activity associates with encoding of facial emotional expressions [128]. Mühlberger and colleagues [129] further showed that ventral striatum activity was greater when control participants observed changes from angry to happy or neutral facial expressions. Finally, Liang and colleagues [130] found that ventral striatum activity correlated with extremes of facial attractiveness.

*2.3. Summary: Cognitive Testing (a) in Patients with Basal Ganglia Lesions and (b) Using Neuroimaging in Healthy Volunteers.* The dorsal striatum is implicated in selecting among various stimuli and competing responses, when divergent influences impinge on decision making and particularly when selection requires discounting more salient stimuli or overriding prepotent responses. Dorsal striatum is involved in complex planning tasks and in distinguishing among

groups of stimuli and responses, tracking whether an item belongs to one category over another, is rewarded versus unrewarded, or is familiar versus novel. The dorsal striatum is implicated in time discrimination and estimation, as well as in visuospatial processing. From this review, we surmise that, whereas individual cortical regions might be specifically sensitive to separate aspects of a stimulus, situation, or event, such as salience, preference, motivational value, reward, speed, or accuracy, the dorsal striatum integrates all of these influences to yield an optimal, considered criterion, that maximizes and regulates accurate decision making, selective responding, and planning. Conversely, the dorsal striatum's necessity is significantly lessened for decisions that can be accomplished relying on a single dimension to guide behaviour—particularly if this dimension is most salient [15]. This could account for the inconsistent findings with respect to task- or set shifting deficits in patients with dorsal striatum lesions and for the occasional finding that these tasks do not preferentially activate dorsal striatum in neuroimaging investigations. An aim of future studies should be to better understand these inconsistencies.

In contrast, both lesion and neuroimaging studies suggest that the ventral striatum is extensively implicated in multiple aspects and forms of learning. Ventral striatum is involved in orienting attention to salient, novel, or valued stimuli and seems to mediate motivation, facilitating approach behaviours. Finally, some evidence suggests that ventral striatum might have a role in facial emotional processing. Both implicit and explicit learning and tests of implicit and explicit memory implicate ventral striatum. Unlike hippocampus and associated temporal cortex that seem specialized for encoding information when memory is subsequently explicitly probed, ventral striatum is implicated in more generalized encoding function. To our knowledge, no studies have examined this issue as a central aim and we are currently investigating this question.

### 3. Effect of Dopamine Replacement Therapy on Cognition

A number of studies have investigated the effects of dopamine replacement therapy on cognition in PD. At first blush, these results seem paradoxical. Whereas inconsistencies in this literature surely owe, at least in part, to differences in sample size, diverse methodologies, discrepancies in patient characteristics, such as age, disease duration and severity, PD-dominant side, and even genetic profile, we postulate that the differential reliance on the dorsal and ventral striatum of the cognitive function under investigation, accounts for most of this variability.

The dorsal striatum is significantly depleted of dopamine at all stages of clinical PD. The ventral striatum, in contrast, is substantially less dopamine deprived, especially early in the disease course. Because dopaminergic supplementation is titrated to dorsal striatum-mediated striatum motor functions, it is suggested that ventral striatum is overdosed and its functions are impaired whereas dorsal striatum becomes dopamine replete and operations that it mediates are improved. We test this explanation for the effect of

dopaminergic therapy on cognitive functions in PD, by relating (a) the pattern of cognitive improvements and impairments subsequent to dopamine replacement in PD, to (b) the cognitive functions that seem attributed to the dorsal and ventral striatum outlined above.

*3.1. Cognitive Functions Improved by Dopamine Replacement Therapy in PD.* A number of studies have shown that administration of dopamine replacement therapy improves cognitive function in patients with PD. Impairments for PD patients in switching attention from one stimulus dimension [131–135] but see [29], or one response to another [134, 136], as well as in selecting between alternatives with high response conflict [137] are redressed by dopamine replacement. Similarly, although maintenance and retrieval of nonspatial information in working memory per se seems to be unaffected by dopaminergic therapy ([138–140] but see [141, 142]), medication improves manipulation of the contents of working memory [138, 139]. Patients were impaired on a measure of verbal fluency compared with normal controls when tested off medication but there were no group differences on medication [29]. Remembering to perform an action at a specified time, so-called prospective remembering, was impaired in PD patients tested off but not on medication [143, 144]. Impairment in generating lines of varying lengths—an action planning deficit—in PD patients was improved with dopamine replacement whereas a deficit in repeatedly producing lines of only two lengths in the simple figure replication condition was not [145]. Also suggesting motor planning improvement with dopaminergic medication, PD patients on dopamine medication demonstrated better and normalized chunking of motor movements [146], despite normal sequence learning both off and on medication. In a similar vein, although learning simple stimulus-response relations was unaltered by dopamine replacement, chaining these learned associations to achieve a long-term goal was impaired in PD patients tested off medication. Chaining these events to achieve the end goal was improved when patients were tested on dopaminergic therapy [147]. Whether these results owe to a medication-remediable deficit in planning, learning, or retrieval, is unclear, however. Together, the findings surveyed above dopamine repletion improves cognitive flexibility, planning, and possibly long-term retrieval.

In contrast to nonspatial working memory, spatial working memory deficits have been shown to improve with dopaminergic treatments [148–151], perhaps related to improvement in visuospatial processing. Consistent with the latter interpretation, category-specific (i.e., animals) object recognition using degraded images has been shown to be compromised in de-novo PD patients relative to PD patients receiving dopaminergic therapy and healthy controls. This deficit was remediated with introduction of dopamine replacement medications [152].

Finally, a number of studies have demonstrated impaired behavioural performance on time estimation and motor timing tasks in PD patients relative to controls. These deficits improve with dopaminergic medication ([153–156] but see [157, 158]).

*3.2. Cognitive Functions Unaffected by Dopamine Replacement Therapy in PD.* Some studies have revealed no effect of dopamine replacement therapy on cognitive function. Shifting to a previously irrelevant dimension was impaired in PD patients relative to controls but was not improved by administration of L-dopa [27, 138, 139]. PD patients were impaired compared to controls in generating proper names but this impairment was not improved with dopamine replacement [159]. Nagano-Saito and colleagues [160] found no improvement on performance of the TOL on dopamine agonist relative to off medication.

*3.3. Cognitive Functions Impaired by Dopamine Replacement Therapy in PD.* Learning was most commonly impaired in PD patients tested on dopamine replacement therapy. A number of studies have revealed deficits after dopamine replacement in probabilistic associative learning, although PD patients off medication performed equivalently to controls [29, 140, 158]. Shohamy and colleagues [161] found that dopaminergic medication impaired learning of an incrementally acquired, concurrent discrimination task, whereas off medication PD patients performed as well as controls. Sequence learning was reduced for PD patients on medication [146, 162–164]. Dopamine supplementation in PD patients yielded reduced facilitation for consecutive, consistent stimulus-stimulus pairings in a selection task compared to normal implicit learning and hence facilitated responding when tested off medication [137]. Once stimulus-reward associations have been learned, reversing probabilities of stimulus-reward associations is also impaired for PD patients on dopamine replacement therapy [27, 32, 40, 104, 165–167]. Finally, dopamine therapy impaired learning from negative feedback [168].

Another frequent deficit in PD patients on dopamine replacement therapy is in impulse control [27, 169]. As an example, impulsive betting despite appropriate and deliberate decision making was noted following L-dopa administration in PD patients [132, 140]. L-dopa therapy in PD patients has been shown to increase the tendency to choose earlier relative to later rewards, regardless of reward magnitude (i.e., temporal discounting) compared to decision making on placebo. Dopaminergic therapy, particularly dopamine agonist use, in PD has clearly been shown to increase a number of impulse control disorders such as pathological gambling, compulsive sexual behaviour, compulsive buying, and binge eating [170, 171]. The dopamine dysregulation syndrome in which PD patients overuse their dopamine replacement medications is a further example of enhanced motivation toward rewarding behaviours with therapy [172].

Simple reaction time was increased with administration of L-dopa [173] and apomorphine [174]. Time estimation in the seconds but not millisecond range was impaired in patients on relative to off medication and healthy controls [155, 175]. Finally, impairment in generation tasks such as subject-ordered pointing [29] or production of alternate uses for common objects [167] have also been noted in PD patients on medication.

*3.4. Effect of Dopamine Therapy in Healthy Controls.* A number of studies have investigated the effect of dopaminergic modulation on cognitive function in healthy volunteers. Breitenstein and colleagues [176] found that administering a dopamine agonist significantly impaired novel word learning in healthy volunteers compared to placebo. Similarly, Pizzagalli and colleagues [177] and Santesso and colleagues [178] found that reward learning was impaired in healthy human volunteers after administering a single dose of pramipexole. Probabilistic reward learning relies on the ventral striatum [74, 94, 96] and consequently these findings strengthen the contention that impaired learning in PD patients on medication results from overdose of VTA-innervated ventral striatum. Pine and colleagues [90] showed that in healthy controls administration of L-dopa increased temporal discounting in a decision making task, with more numerous smaller but sooner reward choices relative to larger but later reward options, compared to performance after receiving placebo or haloperidol. Schneider and colleagues [179] found that L-dopa, but not risperidone or placebo, increased false positive responses, without altering overall memory performance, in healthy volunteers tested in a memory paradigm that had previously been shown to be sensitive in confabulating patients. These findings suggest a less conservative response criterion compatible with increased impulsivity seen with dopamine replacement in healthy volunteers, paralleling findings in PD. Finally, Luciana and colleagues [180] found that bromocriptine, a dopamine agonist, facilitated spatial delayed but not immediate memory performance in healthy volunteers.

Conversely, others have investigated the effect of dopamine receptor antagonists on cognition in healthy volunteers with the aim of simulating the dopamine deficiency in PD. Set shifting impairments have been induced by this manipulation, consistent with performance of PD patients off medication [30]. Similarly, Nagano-Saito and colleagues [181] showed that after consuming a drink deficient in the dopamine precursors tyrosine and phenylalanine, post-set shift response times were increased in the WCST compared to when they performed the task, after consuming a drink balanced in amino acids. Finally, the effect of dopamine receptor antagonism on working memory in healthy controls has been inconsistent [30, 182, 183].

*3.5. Summary: Effect of Dopamine Replacement Therapy on Cognition.* Based on our review, the pattern of improvements and impairments in PD patients following dopamine supplementation are well accounted for by differential baseline dopamine innervation of the dorsal and ventral striatum, with very few exceptions. Consistent with conclusions about cognitive functions ascribed to dorsal striatum arising from lesion and neuroimaging studies, selecting among alternative stimuli and responses, particularly when there is high conflict or when enacting a decision requires disregarding previously relevant stimulus dimensions or responses, is improved by dopamine replacement in PD. Also consistent with lesion and neuroimaging studies, dopaminergic therapy remediates long-term memory retrieval, planning, visuo spatial processing, as well as time estimation and

motor-timing deficits. Providing convergent evidence for dopamine's modulatory role in these executive functions, dopamine antagonists in healthy volunteers have been shown to impair set shifting.

Numerous studies reveal impaired learning in PD patients on relative to off dopamine replacement therapy as would be expected in reviewing lesion and neuroimaging studies of ventral striatum function. Impaired simple reaction time in PD patients on medication, which could owe to impaired orienting, also would not be inconsistent with functions ascribed to ventral striatum from our survey of lesion and neuroimaging studies. Further bolstering the dopamine overdose hypothesis to account for deterioration of some cognitive functions in medicated PD patients, dopaminergic therapy in healthy volunteers actually impairs learning, exactly paralleling the pattern observed in PD patients. To reiterate, the central contention of the dopamine overdose hypothesis is that because the VTA is relatively spared and hence ventral striatum dopamine is adequate, especially early in PD, dopamine replacement, dosed to remediate the dorsal striatum-mediated motor symptoms, effectively causes an over-supply of dopamine to the ventral striatum, interfering with its function.

Not consistent with the view that dopamine overdose disrupts ventral striatum-mediated processes, increased impulsivity in PD patients on dopamine replacement actually suggests an *enhancement* of ventral striatum function. Lesion and imaging studies have shown that ventral striatum mediates motivation, approach behaviour, and impulsive choices. Also paralleling findings in PD, dopamine replacement in healthy volunteers increases impulsive choices and enhances false positive responses in a memory paradigm, consistent with greater impulsivity. While still in line with an account of ventral striatum dopamine over-supply, these findings cannot be explained by the claim that dopamine excess *interferes* with functions of ventral striatum. We submit that a possible explanation for opposing effects of dopamine replacement on these ventral striatum-mediated functions could owe to their differential reliance on phasic or relative, versus tonic or absolute dopamine receptor stimulation. In reviewing biological features of the ventral striatum, low tonic, with graded phasic dopamine responses, sensitive to frequency and degree of stimulation, are characteristics that render the ventral striatum particularly suited for encoding associations between stimuli, responses, outcomes, or events. If these graded dopamine signals convey strength of association then administration of bolus dopamine therapy could conceivably interfere with this encoding. Further, decreased DAT for clearing synaptic dopamine makes the ventral striatum even more vulnerable to disruption by bolus dopamine administration. In contrast, those functions of ventral striatum that depend on absolute dopaminergic tone and not upon extracting information from degree of dopamine receptor stimulation or from relative signal-to-noise ratio might be *increased*, albeit to a pathological level, by dopaminergic therapy. Impulsivity, an inclination to act prematurely without adequate consideration of relevant determinants of behaviour, might depend on absolute dopaminergic tone in the ventral striatum. Administration of dopaminergic

therapy and consequent ventral striatum dopamine overdose might enhance this tendency to a detrimental degree.

Some studies have revealed no effect of dopamine replacement therapy on cognitive function. Possibly reflecting bias against publishing null results, there are far fewer examples of functions that are neither helped nor hindered by dopaminergic therapy in PD and hence a clear trend does not emerge. Given a variety of reasons for statistical equivalence, such as true equality between conditions and populations, inadequate power to detect differences, as well as a 20% Type 2 error rate compared to a more acceptable 5% Type 1 error rate, interpretation of null results can be problematic and should be done cautiously.

Remediable deficits in verbal fluency and in manipulating the contents of working memory with administration of dopaminergic therapy are not clearly predicted by the dorsal striatum lesion and neuroimaging studies. Further, time estimation has been attributed to dorsal striatum [14, 15, 39–42] and therefore impairment in this process with dopamine replacement would not be explained by the simple framework applied here. Finally, decreased response generation with medication is not predicted by the lesion and neuroimaging literature reviewed here. These few inconsistencies might relate to effects of dopamine replacement on other brain regions, particularly those that also receive input from the relatively-spared VTA, such as prefrontal and limbic cortices, that we have not discussed in this review. Alternatively, a more complete understanding of the functions of the dorsal and ventral striatum might resolve these discrepancies. Overall, however, the framework adopted in this review accommodates a significant number of findings, despite the few inconsistencies encountered. Next, we review neuroimaging studies in PD patients on and off medication.

## 4. Functional Neuroimaging in PD

*4.1. Neuroimaging in PD Patients off Dopaminergic Medication.* Neuroimaging studies of patients with PD have revealed differences in regions of activation and de-activation at rest. A number of investigations have shown increased activity in the thalamus, globus pallidus, pons, and primary motor cortex compared to reductions in lateral premotor and posterior parietal areas [184]. Those patients who were not demented but performed abnormally on neuropsychological tests relative to controls additionally revealed reductions in medial prefrontal regions, dorsolateral prefrontal cortex, premotor cortex, rostral supplementary motor area, precuneus, and posterior parietal regions along with relative increases in cerebellar cortex and dentate nuclei [184].

Changes in patterns of activation are also described in PD patients off medication performing cognitive tasks. Investigating the effect of retrieval and manipulation of working memory contents on default mode network in PD patients off medication, van Eimeren and colleagues [185] found that PD patients only appropriately deactivated medial prefrontal cortex and in fact increased activation of precuneus and posterior cingulate cortex. The default network involves precuneus, medial prefrontal, posterior cingulate, lateral

parietal, and medial temporal cortices and is characterized by deactivation during the performance of executive tasks in healthy volunteers [186, 187]. Connectivity analysis also revealed that medial prefrontal cortex and the rostral ventromedial caudate nucleus were functionally disconnected in PD, further supporting disturbance of the default network in PD. Others have found that hypometabolism and decreased endogenous dopamine in dorsal striatum, as measured by [<sup>18</sup>F]DOPA PET, [<sup>11</sup>C]-raclopride (RAC) PET, or fMRI, are directly correlated with poorer performance on the WCST and on tests of working, verbal, and visual memory in PD patients [188–190]. Schonberg and colleagues [191] further showed decreased prediction error signals in dorsal striatum in a reinforcement learning study using fMRI in PD relative to controls. Finally, dorsal-striatum-involving tasks (e.g., set-shifting under uncertainty in card sorting tasks) also reveal decreased activations in striatum-associated cortical regions such as posterior parietal regions, ventrolateral and dorsolateral prefrontal cortex when planning a set shift, as well as in premotor cortex during set-shift execution [14, 192].

In contrast, activity in the ventral striatum and cortical regions to which it is reciprocally connected, is comparable or, rarely, is enhanced in PD patients off medication compared to controls in neuroimaging studies. As previously noted, medial prefrontal cortical regions—reciprocally connected to ventral striatum and innervated by VTA—appropriately deactivate during an executive task in PD patients off medication [185]. Prediction error signals in a reinforcement learning study using fMRI, were normal in the ventral striatum in PD patients tested off medication, despite impairments in the dorsal striatum. Sawamoto and colleagues [190] found that the same contrast of spatial working memory versus visuomotor processing that yielded hypometabolism in dorsal caudate for PD patients relative to controls, showed comparable between-group activity in anterior cingulate, a region reciprocally connected to the ventral striatum and receiving dopamine input from VTA. Finally, PD patients revealed increased activations relative to controls in prefrontal and posterior parietal cortex for cognitive processes that did not implicate caudate nucleus, such as in conditions that required neither planning nor executing a set shift in a card sorting task [14, 192]. This enhanced cortical activity was associated with poorer cognitive performance, however.

*4.2. Summary: Neuroimaging Results in PD Patients off Dopaminergic Medication.* Overall, these imaging studies are consistent with the notion that decreased cognitive performance in PD relates primarily to dopaminergic deficit and dysfunction of the dorsal striatum. Functional impairments owe to dorsal striatum dysfunction per se as well as to consequent deregulation of cortical networks involving dorsal striatum. These investigations further support that in undemented PD patients, ventral striatum and its cortical networks are unperturbed in the off state, which we attribute to preserved VTA dopaminergic function. On occasion, increased cortical activity is noted for PD patients off dopaminergic medications relative to controls, although

this does not necessarily translate to improved cognitive performance [14, 149, 192]. Increased number and extent of some cortical regions recruited by PD patients while performing cognitive tasks off medication, could owe to aberrant up-regulation of regions that are normally opposed or inhibited by dorsal striatum and its cortical networks. Studies aimed specifically at contrasting dorsal versus ventral striatum-mediated cognitive functions in PD patients off medication relative to controls using neuroimaging are lacking. These studies are needed not only to directly assess the differential metabolic impairments of the dorsal and ventral striatum in PD but also to understand the impact, if any, of dorsal-striatum dysfunction on baseline ventral striatum metabolic function, independent of medication. The section that follows summarizes the effects of dopamine replacement in PD patients and dopamine modulation in healthy controls on patterns of brain activity assessed by functional neuroimaging.

## 5. Effect of Dopamine Modulation on Brain Activity

*5.1. Normalization of Neuroimaging Patterns with Dopaminergic Therapy in PD Patients.* In the resting state, Wu and colleagues [193] found that PD patients in the off state had significantly decreased functional connectivity between the supplementary motor area, left dorsolateral prefrontal cortex, and left putamen, along with increased functional connectivity among the left cerebellum, left primary motor cortex, and left parietal cortex compared to normal subjects. Administration of L-dopa normalized the pattern of functional connectivity in PD patients with degree of restoration correlating with motor improvements as assessed by the Unified Parkinson's Disease Rating Scale (UPDRS) motor score. Similarly, Feigin and colleagues [194] and Asanuma and colleagues [195] revealed at rest, a decrease in activation of the globus pallidus and subthalamic nuclei and an increase in cortical motor and premotor activity with administration of L-dopa, constituting a correction in the Parkinson's disease related motor pattern.

Investigating the effect of dopamine replacement on neuroimaging patterns in PD patients performing cognitive tasks, Cools and colleagues [196] found that L-dopa effectively normalized cerebral blood flow in PD patients compared to controls, decreasing activity in the right dorsolateral prefrontal cortex during performance of both planning and spatial working memory tasks compared with a visuomotor control task, and increasing cerebral blood flow in the right occipital lobe during a memory task relative to a control task. Mattay and colleagues [149] found that dopamine replacement increased activity in motor brain regions and decreased activity in the prefrontal cortical regions, constituting a correction of the PD pattern and correlating with decreased error rates on a working memory test. Fera and colleagues [197] showed that PD patients off medication had increased Stroop interference-related activity in anterior cingulate and presupplementary motor cortex compared to controls. L-dopa administration attenuated responses in these regions and increased activity

in prefrontal cortex, which correlated with more accurate Stroop performance. Jahanshahi and colleagues [158] found that in PD patients off medication, motor timing tasks activated bilateral cerebellum, right thalamus, and left midbrain relative to a control, reaction time task whereas for healthy volunteers this contrast revealed significantly increased activity in left medial prefrontal cortex, right hippocampus, bilateral angular gyrus, left posterior cingulate, and left nucleus accumbens and caudate. Administration of a dopamine agonist increased activity in prefrontal regions in PD patients and was associated with improved performance. In PD patients, administration of apomorphine during performance of the TOL revealed greater deactivation of ventro-medial prefrontal cortex, a region belonging to the default network, as a function of task complexity [160]. Finally, Jubault and colleagues [198] found that treatment with dopaminergic therapy had no effect on brain activity in regions implicated in planning a set shift (i.e., caudate nucleus, ventrolateral, posterior, and dorsolateral prefrontal cortex) in PD patients but increased activity in the premotor cortex, essentially normalizing the pattern observed for set-shift execution.

*5.2. Impairment of Neuroimaging Patterns with Dopaminergic Therapy in PD Patients.* In some cases, administration of L-dopa is associated with abnormal patterns of brain activity in PD. Feigin and colleagues [162] found that administration of L-dopa reduced sequence learning and was associated with enhanced activation in the right premotor and decreased activity in the ipsilateral occipital association area compared to controls. Argyelan and colleagues [199] showed that L-dopa diminished learning-related ventromedial prefrontal cortex suppression in a sequence learning task compared to unmedicated PD patients and healthy controls. In PD patients, administration of L-dopa correlated with greater attenuation of the dorsal striatum, insula, subgenual cingulate, and lateral orbitofrontal cortices for delayed relative to more immediate rewards, paralleling the behavioural result of increased impulsivity and temporal discounting relative to placebo [90]. Steeves and colleagues [200] found decreased binding of the D2 receptor ligand RAC in the ventral striatum in PD patients with pathological gambling relative to PD patients not known for pathological gambling, following administration of a dopamine agonist during gambling and control tasks. Along similar lines, using  $H_2[^{15}O]$  PET to measure regional cerebral blood flow as an index of regional brain activity during decision making with probabilistic feedback, van Eimeren and colleagues [201] compared PD patients with and without DA-induced pathological gambling before and after apomorphine administration. Pathological gamblers evidenced a dopamine agonist-induced attenuation of impulse control and response inhibition brain regions such as lateral orbitofrontal cortex, rostral cingulate, amygdala, and external pallidum whereas nongamblers revealed increased activity in these brain regions with administration of a dopaminergic agonist. These results suggest good correlation between the general behavioural effects and changes in neural activity precipitated by dopamine replacement, but

highlight that individual differences can also augment or mitigate these correlations. Finally, Delaveau and colleagues [202] investigated the effect of L-dopa on brain regions associated with facial emotion recognition. They found that L-dopa decreased task-associated amygdala activation in PD patients.

*5.3. Effect of Dopamine Modulation in Healthy Controls.* In healthy elderly volunteers, administration of apomorphine, a dopamine agonist, resulted in improved performance on the TOL task [160]. Performance on TOL produced deactivation in ventro-medial prefrontal cortex and posterior cingulate cortex, regions belonging to the default mode network, both on and off medication. On apomorphine, there was an inverse correlation between task complexity and ventro-medial prefrontal cortex [160]. In this example, a dopamine agonist improved performance and enhanced connectivity of underlying brain networks. Given that these patients were elderly, the authors speculated that as aging is related to dopamine cell loss, apomorphine could have corrected a clinically nonmanifest dopaminergic deficit in their controls.

In most cases, however, dopamine modulation in healthy controls produces impairments in patterns of brain activity. L-dopa administration increased functional connectivity among the putamen, cerebellum, and brainstem, and between the ventral striatum and ventrolateral prefrontal cortex activity. It disrupted ventral striatum and dorsal caudate functional connectivity with the default mode network, however [203]. Delaveau and colleagues [204, 205] showed that L-dopa administration reduced bilateral amygdala activity, a region reciprocally connected to ventral striatum, in healthy elderly volunteers performing a facial emotional recognition task. Finally, Nagano-Saito and colleagues [181] found changes in brain activity, which correlated with performance of the WCST, in healthy controls after consuming a drink deficient in the dopamine precursors tyrosine and phenylalanine compared to after they consumed a drink balanced in amino acids. Following the balanced drink, greater connectivity occurred between the frontal lobes and striatum, correlating with faster set-shift response times, and deactivation was noted in areas normally suppressed during attention-demanding tasks, including the medial prefrontal cortex, posterior cingulate cortex, and hippocampus. Following the dopamine precursor-depleted drink, fronto-striatal connectivity was abolished and deactivations in medial prefrontal cortex, posterior cingulate, and hippocampus were no longer observed, associated with longer set shifting response times.

*5.4. Summary: Effect of L-Dopa Administration on Neuroimaging Results.* Overall, these results are consistent with the notion that dopamine replacement normalizes activity in the dorsal striatum and cortico-striatal networks that implicate dorsal striatum, both at rest and during performance of cognitive tasks. These changes consist of increases in some cortical regions and decreases in others, correlating with improved performance on a variety of cognitive tasks such as spatial working memory, selective attention, planning, and set shifting.

Dysfunctional patterns of brain activity precipitated by dopamine replacement in PD are noted exclusively for ventral striatum-mediated processes. Although only Steeves and colleagues [200] observed direct dopamine enhancement in the ventral striatum with dopamine agonist administration, abnormal patterns of activity produced by dopaminergic medication in PD patients solely implicated brain regions that are reciprocally connected to the ventral striatum. That is, reduced learning-related suppression in ventromedial prefrontal cortex occurred during sequence learning, increased activation of amygdala was noted on tests of facial emotional recognition, and greater attenuation of impulse control and response inhibition regions such as the dorsal striatum, insula, cingulate, and orbitofrontal cortex, were observed during more impulsive decisions in PD patients treated with dopaminergic medications. The studies reviewed here replicate the behavioural studies of dopamine replacement in cognition and confirm that those cognitive functions impaired by dopaminergic therapy in PD are related to changes in the ventral striatum and cortical networks that implicate the ventral striatum. The effect of dopamine supplementation in healthy controls on neural activity in the ventral striatum-associated cortical networks exactly mirrors the changes noted in PD, in line with the ventral striatum dopamine over-supply account of cognitive functions that worsen with treatment in PD.

We found rare direct but significant indirect evidence that dopamine replacement improves some aspects of cognition by remediating dorsal striatum function and worsens others by inducing pathological activity in ventral striatum. Studies are needed that directly contrast dorsal versus ventral striatum-mediated cognitive functions and associated neural activity in the same PD patients, on and off medication. Contrasting changes in brain activity noted for patients early in the disease course relative to those observed with more advanced disease will also enhance our understanding of how the relation between dopamine replacement and these divergent cognitive functions evolve in PD.

## 6. General Discussion

Cognitive dysfunction has long been recognized as a feature of PD. Cognitive functions are increasingly attributed to the basal ganglia [12–17, 19]. Dopamine replacement therapy has contrasting effects on different cognitive functions. In the current review, we present evidence that improvements with dopamine replacement arise for cognitive processes that are mediated by the dopamine-depleted dorsal striatum. In contrast, cognitive operations that are impaired by dopaminergic therapy are supported by the relatively spared ventral striatum.

Selecting among alternative stimuli and responses, particularly when there is high conflict or when enacting a decision requires disregarding previously relevant stimulus dimensions or responses, is improved by dopamine replacement. Dopaminergic therapy also remediates long-term memory retrieval, planning, visuo-spatial processing, as well as time estimation and motor-timing deficits. These cognitive functions are ascribed to the dorsal striatum in

studies of patients with dorsal striatum lesions and in investigations of healthy controls using functional neuroimaging. Neuroimaging studies in PD confirm the notion that dopamine replacement improves cognitive functions mediated by dorsal striatum. Dopamine replacement normalizes activity in the dorsal striatum as well as in cortical networks involving dorsal striatum both at rest and during performance of cognitive tasks. These changes in neural activity are associated with improvements in cognitive performance.

In contrast, numerous studies reveal impaired probabilistic, associative, and sequence learning, decreased attentional orienting, as well as poorer facial emotional recognition in PD patients on relative to off dopamine replacement therapy. Impulsivity is enhanced to a pathological degree in PD patients on dopaminergic therapy. Studies of patients with ventral striatum lesions and neuroimaging investigations in healthy volunteers demonstrate that these behavioural phenomena are mediated by the ventral striatum. Imaging studies in PD on and off medication are therefore also consistent with the framework presented here for understanding medication effects on cognition in PD. Neuroimaging studies in PD patients in the off state confirm that ventral striatum and its cortical networks are unperturbed. Administration of dopaminergic therapy produces abnormal patterns of brain activity, with an increase in ventral striatal dopamine having been noted and alterations in levels of activation of cortical regions that are reciprocally connected to the ventral striatum being frequently observed. These neuroimaging changes are associated with behavioural impairments in ventral striatum-mediated cognitive processes. In line with claims that the ventral striatum receives adequate dopamine innervation early in PD and that dopamine supplementation over-supplies this region resulting in abnormal ventral-striatum mediated behaviour, the neuroimaging and behavioural consequences of dopamine supplementation in healthy controls with respect to learning, facial emotion recognition, and impulse control, exactly mirror those obtained with PD patients.

Although ventral-striatum mediated cognitive processes and their neural correlates are consistently adversely affected by dopamine supplementation in PD, medication-induced effects in learning, orienting, and facial emotional recognition suggest *reduced*, whereas increased impulsivity reflects *enhanced* ventral striatum function. We speculate that these contrasting effects of dopamine replacement on ventral striatum-mediated cognitive functions relate to their differential reliance on graded versus absolute ventral striatum dopamine levels. Whereas dopamine replacement resulting in excessive dopamine concentration in ventral striatum conceivably disrupts processes that are informed by subtle relative or phasic changes in dopamine level—perhaps learning, orienting, and emotion discrimination, it might pathologically enhance processes that are governed by absolute or tonic dopamine signals. We submit that rapid decision making, guided by heuristics rather than complete consideration of all determinants and consequences of behaviour (i.e., impulsivity) is enhanced to a detrimental extent by dopamine replacement in PD.

The cognitive profile in PD has many determinants. The importance of each of these factors evolves over the disease course. Some cognitive deficits owe to dopamine deficiency in the dorsal striatum, which are at least partially remediated by optimal dopaminergic therapy. In addition, dopamine overdose of the ventral striatum reduces some functions and heightens others to a pathological degree in PD patients receiving dopamine replacement. As functional neuroimaging studies demonstrate, dopamine deficiencies and excesses in the dorsal and ventral striatum, as a function of medication status, correlate with aberrant patterns of neural activity in cortical networks that are directly or even indirectly regulated by these respective brain regions. Although not addressed in this paper, cognitive dysfunction in PD also results from degeneration of cortex and other neurotransmitter systems, especially with advancing disease. Further, cortical regions receiving dopamine input from VTA, such as prefrontal and limbic regions, are also likely overdosed to varying extents by dopamine replacement in PD, impacting cognitive functions that they mediate. Finally, dopamine agonists and L-dopa have distinct mechanisms of action with somewhat different consequences on cognition [206], an issue glossed over in this paper. In light of numerous variables interacting to produce patterns of cognitive dysfunction and sparing in PD, given that these variables are differentially affected by dopaminergic therapy in general and by type of therapy specifically, and finally, because these interactions evolve over disease course, the framework adopted in this paper is clearly an over-simplification. That notwithstanding, it accommodates and explains an impressive array of cognitive and neuroimaging findings, providing a basic tenet for predicting and understanding the effect of dopamine replacement therapy on cognition in PD.

#### 6.1. Controversies and Areas Warranting Further Investigation.

Our review brings to light a number of inconsistencies as well as areas that warrant further consideration. Although dorsal striatum is implicated in selective attention and decision making, the specific aspect of these situations that depends upon the dorsal striatum remains somewhat unclear. Occasionally these executive functions are unimpaired in patients with dorsal striatum lesion or PD, and are not associated with preferential activation of the dorsal striatum using neuroimaging. We submit that decisions requiring integration of multiple dimensions, particularly those that require resolving conflicting influences on responding, depend to the greatest extent on the dorsal striatum. We predict that these instances will be most improved by dopamine replacement. Further investigation, however, is required.

With respect to the ventral striatum, whether this region mediates encoding for implicit or explicit uses of memory differentially has not yet been directly investigated although our survey of the literature does not suggest such specificity. Further, although the effects of dopamine replacement are consistently adverse with respect to ventral-striatum mediated behavior, some functions are reduced whereas others are pathologically enhanced. We argue that this relates to whether a function derives from graded, phasic dopamine responses, which bolus dopamine treatment will interrupt,

versus absolute dopaminergic tone that will be heightened by dopamine replacement. Direct empirical investigations of this hypothesis are needed.

Finally, studies aimed specifically at contrasting dorsal versus ventral striatum-mediated cognitive functions in PD patients on and off medication relative to controls using neuroimaging are lacking. These studies will provide a greater understanding of the changes within the dorsal and ventral striato-cortical networks that occur in PD and how these are modulated by dopamine therapy. Investigations of how these interactions evolve over the disease course will also improve our understanding of the effect of dopamine replacement on cognition in PD.

## 7. Conclusion

This review highlights the fact that currently, titration of therapy in PD is geared to optimizing dorsal striatum-mediated motor symptoms, at the expense of ventral striatum-mediated operations. This consequence is only beginning to be recognized and the impact fully appreciated. Enhanced awareness of the differential effects of dopamine replacement on disparate cognitive functions will translate to medication strategies that take into account both those symptoms that dopamine replacement might improve versus hinder. Ultimately, this knowledge will lead clinicians to survey a broader range of symptoms and signs in determining optimal therapy based on individual patient priorities.

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## Review Article

# New Thoughts on Thought Disorders in Parkinson's Disease: Review of Current Research Strategies and Challenges

**Jennifer G. Goldman**

*Section of Parkinson Disease and Movement Disorders, Department of Neurological Sciences, Rush University Medical Center, 1725 W. Harrison Street, Suite 755, Chicago, IL 60612, USA*

Correspondence should be addressed to Jennifer G. Goldman, jennifer.g.goldman@rush.edu

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Psychosis is a frequent nonmotor complication in Parkinson's disease (PD), characterized by a broad phenomenology and likely due to a variety of intrinsic (i.e., PD-related) and extrinsic factors. Safe and effective therapies are greatly needed as PD psychosis contributes significantly to morbidity, mortality, nursing home placement, and quality of life. Novel research strategies focused on understanding the pharmacology and pathophysiology of PD psychosis, utilizing translational research including animal models, genetics, and neuroimaging, and even looking beyond the dopamine system may further therapeutic advances. This review discusses new research strategies regarding the neurobiology and treatment of PD psychosis and several associated challenges.

## 1. Introduction

Psychosis is a frequent nonmotor complication of Parkinson's disease (PD) [1–3]. Psychotic symptoms in PD manifest predominantly as hallucinations and delusions, although recently revised criteria for PD psychosis extend the spectrum to include illusions, a false sense of presence, hallucinations, and delusions [4]. These neuropsychiatric phenomena likely stem from a combination of drug-related (i.e., exogenous or extrinsic) factors and PD-related (i.e., endogenous or intrinsic) complications, although the exact pathophysiology of PD psychosis is unknown. Improved treatments for PD psychosis are greatly needed since hallucinations and delusions are important contributors to morbidity, mortality, nursing home placement, and quality of life [5–7]. To date, many clinical research trials for antipsychotic medications in PD have been affected by issues of trial design, medication side effects, and negative outcomes. As such, the goal of optimally designed clinical trials with effective and safe medications presents a challenge. Use of animal models or biomarkers (e.g., genetic or neuroimaging) may provide additional and complementary ways to advance treatments for PD psychosis. Thus, the aim of this review is to discuss new research strategies regarding PD psychosis and their

associated challenges. This review will highlight research on nondopaminergic substrates, comorbid neuropsychiatric features often associated with PD psychosis and the potential roles for integrating *in vivo* neuroimaging, genetic risk factors, and animal models in studying PD psychosis, and lastly discuss challenges of medication trials.

Dopaminergic medications have been well recognized to induce psychosis in PD by stimulating or inducing hypersensitivity of mesocorticolimbic dopamine receptors [8–10]. Virtually all classes of anti-parkinsonian medications may produce psychosis in PD. Some studies suggest particular susceptibility with dopamine agonists compared to levodopa [11–15] and with anticholinergics especially in elderly PD patients [16]. While dopaminergic medications contribute to PD psychosis, exploration of other extrinsic and intrinsic factors is needed to advance our understanding of and our treatments for PD psychosis. Intrinsic or PD-related factors that may contribute to PD psychosis include abnormalities in the visual system; levels of visual dysfunction range from ocular pathology and retinal dopamine loss, impaired visual acuity and color or contrast discrimination, to disturbed attentional and visuospatial processing and abnormal cortical activation patterns [17–22]. Other factors, often noted in epidemiological studies, encompass clinical

risk factors such as age, PD duration and severity, depression, cognitive impairment and dementia, and sleep disturbances [2, 3]. PD hallucinators exhibit worse cognitive function overall including executive, attentional, and visuospatial abilities [23–26] and also have been observed to have greater sleep disturbances and REM behavior disorder [27–33]. Neuroimaging studies also suggest that there are distinct structural, functional, and metabolic abnormalities in PD hallucinators [20, 22, 34–40]. This review highlights several of these risk factors or comorbid neuropsychiatric features associated with PD psychosis as potential avenues for selective therapeutic strategies.

## 2. Beyond Dopamine: Other Neurochemical Substrates and Neuropsychiatric Features Associated with PD Psychosis

While nondopaminergic substrates have long been thought to play a role in PD psychosis, they form the basis for several current therapeutic strategies of PD psychosis and merit continued attention. This section will review the importance of the cholinergic and serotonergic systems and other neuropsychiatric features commonly associated with PD psychosis.

**2.1. Cholinergic System.** The role of the central cholinergic system in PD psychosis is underscored by its involvement in cognition and sleep, two neuropsychiatric areas that are intricately linked to hallucinations and delusions in PD. PD dementia and dementia with Lewy bodies exhibit pronounced frontal cortical denervation due to disruption of the ascending cholinergic transmitter system and degeneration of central cholinergic structures involved in attention, cognition, and REM sleep such as the nucleus basalis of Meynert and pedunculopontine nucleus [41, 42]. In addition, pharmacological interventions with anticholinergic medications such as scopolamine or trihexyphenidyl are recognized to cause confusion in PD [16, 43].

Cognitive impairment and dementia have been associated with PD psychosis in many studies [2, 23, 44]. Presence of hallucinations is a significant predictor of dementia in PD, and cognitive decline is faster in those PD patients with hallucinations [45, 46]. More recently, clinical trials in PD dementia, Alzheimer's disease, and dementia with Lewy bodies have demonstrated a positive effect of cholinesterase inhibitors on hallucinations and psychosis [47]. A subanalysis of 188 PD hallucinators from a large, multicenter, double-blind, placebo-controlled trial of rivastigmine in mild to moderate PD dementia was conducted [47], and rivastigmine-placebo differences for several measures (i.e., ADAS-cog, ADCS-CGIC, and NPI-10) were found to be significantly larger in the hallucinators than in the nonhallucinators. Greater therapeutic benefit could be potentially derived from the use of cholinesterase inhibitors in select PD patients with dementia and hallucinations [48].

Sleep disturbances are frequent in PD patients, including those with hallucinations. Several studies suggest that PD

hallucinations are related to sleep fragmentation and altered dream phenomena, but whether this represents a stepwise pattern or “continuum” [27], distinct but related factors [49], or predictors of future hallucinations [49, 50] is uncertain. Compared to PD patients without hallucinations, the hallucinators have decreased sleep efficiency, total REM sleep time, and REM sleep percentage on polysomnography [51–53] and altered circadian rest-activity rhythms on actigraphy [33]. These disturbances in sleep architecture, REM sleep, and circadian patterns suggest involvement of brainstem and hypothalamic sleep centers with complex interactions among neurotransmitters such as acetylcholine, serotonin, noradrenaline, histamine, GABA, hypocretin as well as dopamine [54]. Few PD studies, to date, have assessed the effect of antipsychotics on sleep and hallucinations. In a small, pilot study, Fernandez et al. assessed quetiapine's efficacy in improving visual hallucinations and its effect on sleep using polysomnography [55]. No significant differences in REM duration were found in either the quetiapine or placebo groups, although the sample size was small and study completion rate was low. The control of sleep-wake patterns integrates many neurotransmitters involved in PD, and sleep and circadian disturbances may represent important targets not only for PD sleep but also for hallucinations.

**2.2. Serotonergic System.** The serotonin (5HT) system has been implicated in PD psychosis as well as in mood disturbances such as depression and anxiety. While an imbalance in serotonin and dopamine contributing to PD psychosis was suggested as early as 1975 by Birkmayer and Riederer [56], the development of antipsychotics with greater serotonergic affinity including 5HT-2a receptors, such as second-generation antipsychotics, clozapine, or quetiapine, has brought renewed attention to the serotonin system. In PD, there is an extensive loss of serotonergic raphe neurons and a reduction of serotonergic projections to the frontal cortex, temporal cortex, and putamen. Complex interactions among dopamine, serotonin, acetylcholine, and norepinephrine, among others occur. Dopamine administration may lead to hyperstimulation of 5HT-2a receptors that affects glutamatergic-modulated activity of dopamine neurons in the ventral tegmental area; this may lead to excitation of the limbic system and inhibition of the prefrontal cortex [9], areas important to cognitive and behavioral processes. Additional evidence for serotonin's contribution to PD psychosis stems from a recent positron emission tomography study using a selective 5HT-2a receptor ligand, [<sup>18</sup>F]-setoperone, in 7 nondemented PD patients with visual hallucinations compared to 7 age-matched PD without visual hallucinations [57]. In this pilot study, the PD hallucinators had increased 5HT-2a receptor binding in multiple brain regions including the ventral visual pathway, bilateral dorsolateral prefrontal cortex, medial orbitofrontal cortex, and insula, suggesting alterations in pathways mediating visual and cognitive processing and a role for 5HT-2a in PD hallucinations. Furthermore, abnormalities in brain 5HT2a receptors were found in a recent postmortem tissue study [58]; increased [<sup>3</sup>H]-ketanserin binding in the inferolateral temporal cortex was found in PD patients who had visual

hallucinations, compared to those who did not, though potential confounders such as dementia, mood disorders, medications, and disease duration await further study.

PD psychosis and mood disorders both involve the serotonin system, and this relationship has been explored in some studies. Several reports demonstrate positive effects of antidepressants on PD psychosis [59–61]. However, the use of antidepressants in PD psychosis has been historically controversial as there also have been a few case reports of antidepressants (e.g., bupropion, fluoxetine, and mirtazapine) exacerbating PD psychosis [62–64]. The worsening of psychosis has been attributed to enhanced dopamine release by stimulation of serotonin receptors by the antidepressants. Despite this, antidepressants, particularly serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs), have been widely used in mood disturbances in PD without clear evidence of triggering or aggravating psychosis. In a review of depressed PD patients from our movement disorders clinic, the addition of SSRIs did not exacerbate hallucination risk, as measured by changes in thought disorder scores from the Unified Parkinson's disease Rating Scale, in depressed PD patients on stable dopaminergic medication regimens [65].

Several case reports and a small case series have suggested a beneficial effect of antidepressants in PD psychosis, particularly those patients with coexisting mood disorders [59–61]. Voon et al. reported a series of 10 PD patients with psychotic symptoms and comorbid depression or anxiety who were treated with antidepressants (citalopram or venlafaxine) and had pre- and posttreatment evaluations of their psychosis and mood disorders, in a prospective but unblinded fashion. Psychotic symptoms improved in 8/10 patients when antidepressants were used either as monotherapy or as adjuncts to baseline antipsychotics (in 2/10). Proposed mechanisms for the positive effects of antidepressants on PD psychosis included the following: (1) improvement in underlying depression which could have exacerbated psychotic symptoms; (2) increased serotonergic tone since low serotonin levels can be associated with depression, aggression, and impulsivity; (3) restoration of serotonin-dopamine imbalance; (4) decrease in the upregulation of postsynaptic serotonin receptors due to raphe nuclei degeneration; or (5) REM suppression by the antidepressants [60, 61, 66]. Limitations, however, included a small, open-label design, disease-related, and treatment-related differences among patients and heterogeneity of hallucinations, psychosis, and psychiatric diagnoses.

Despite the limitations and lack of controlled studies of antidepressants and PD psychosis, these reports raise questions regarding interactions between serotonin-dopamine systems, the relationship between hallucinations, psychosis and mood disorders in PD, and the occurrence of psychotic depression in PD and how this differs from psychotic depression in other populations. Well-designed, controlled studies of select SSRIs or other antidepressants will be needed to determine if they may be an appropriate pharmacological strategy for treating psychosis in PD with or without comorbid mood disorders. Treatment rationales that incorporate comorbid neuropsychiatric phenomena

such as cognition, sleep, and mood may provide alternative treatment strategies for PD psychosis.

### 3. Neuroimaging: A Window into PD Psychosis

Neuroimaging studies permit *in vivo* investigations of brain alterations in PD patients with hallucinations. Techniques utilized include structural magnetic resonance imaging (MRI) to assess gray matter atrophy, functional MRI to examine activation patterns, and perfusion scans to investigate changes in regional cerebral blood flow or glucose metabolism. The neuroimaging studies of PD and visual hallucinations provide clues as to underlying neuroanatomical substrates and pathophysiology of PD hallucinations.

**3.1. Structural MRI.** Structural MRI studies of visual hallucinations in PD have examined regional and global brain atrophy patterns. Using whole-brain voxel-based morphometry (VBM) to study cerebral atrophy, Ramírez-Ruiz et al. found significantly reduced gray matter volume in the lingual gyrus and superior parietal lobe, regions involved in higher-order visual processing, in the PD hallucinators, compared to nonhallucinating PD and healthy controls [40]. In another study, hippocampal atrophy was detected in 3 groups of PD patients (i.e., PD with dementia, nondemented PD with hallucinations, and nondemented PD without hallucinations), compared to healthy controls, at rates of 78%, 31%, and 26%, respectively, [35]. The nondemented, hallucinating PD group exhibited greater gray matter reduction in the hippocampal head, an area associated with specific memory functions. Of note, although the hallucinating PD patients were not demented, they performed worse on neuropsychological tests. The same authors studied 12 nondemented, hallucinating PD patients, compared to 14 PD patients without hallucinations, and 12 healthy controls for a mean 29.91 (5.74) months with MRI (VBM analyses) and neuropsychological tests [67]. At follow-up, 75% of the hallucinating PD had developed dementia. The PD hallucinators demonstrated widespread limbic, paralimbic and neocortical gray matter loss, regions also abnormal in PD dementia. These studies support regional neuroanatomical changes and clinical links between hallucinations and cognitive impairment in PD.

**3.2. Functional MRI.** Functional MRI (fMRI) studies in PD patients with hallucinations demonstrate altered cortical activation patterns compared to PD nonhallucinators. Stebbins et al. studied 12 PD patients with chronic visual hallucinations, matched for age, disease duration, and dopaminergic drug exposure to PD patients who had never hallucinated using two visual stimulation fMRI paradigms (i.e., stroboscopic and kinematic). The PD hallucinators had significantly greater frontal and subcortical activation to both visual stimulation paradigms and decreased cerebral activation in occipital, parietal, and temporal-parietal regions, compared to the nonhallucinators [22], thereby suggesting a disruption in normal visual processing mechanisms in the hallucinators. Another study using complex visual stimuli

(e.g., face recognition task) revealed significant reductions in right prefrontal areas including the inferior, superior, and middle frontal gyrus and anterior cingulate gyrus in PD hallucinators to the face stimulus, compared to non-hallucinating PD and healthy controls [68]. These findings suggest disruptions between anterior (e.g., frontal) and posterior (e.g., parietal, temporal, occipital) regions that are important in processing visual stimuli and impaired abilities to distinguish relevant from irrelevant visual information in PD hallucinators. Further evidence for impaired “bottom-up” visual processing in hallucinating PD comes from a fMRI study by Meppelink et al. in which several seconds prior to image recognition task, the nondemented, hallucinating PD patients showed reduced activation of the lateral occipital cortex and extrastriate temporal visual cortices, compared to nonhallucinating PD and healthy controls [69]. In contrast to other studies, however, the authors did not find increased “top-down” frontal activation in their sample.

**3.3. Metabolic Studies.** Decreased perfusion or glucose metabolism in predominantly posterior brain regions has been reported in PD hallucinators using single photon emission computed tomography (SPECT) or positron emission tomography (PET) modalities. Using  $^{99m}\text{Tc}$ -HMPAO SPECT, Okada et al. found decreased cerebral blood flow to the left temporal lobe and temporal-occipital lobe regions in hallucinating PD patients [70]. In one  $^{123}\text{I}$  IMP SPECT study, hypoperfusion in the right fusiform gyrus but hyperperfusion in the right superior and middle temporal gyri was found in PD hallucinators, when covarying for MMSE score and PD duration [71], suggesting importance of the visual ventral stream. Also using  $^{123}\text{I}$  IMP SPECT scans, Matsui et al. found reduced perfusion in bilateral inferior parietal lobules, inferior temporal gyrus, precuneus gyrus, and occipital cortex in 31 PD patients with visual hallucinations, compared to 39 without hallucinations [38]. Decreased metabolism in temporal-occipital-parietal regions was found in 8 PD hallucinators compared to 11 nonhallucinators with  $^{18}\text{F}$  FDG-PET [34]. Similar to some fMRI results which indicate disruptions in frontal and posterior activation patterns, Nagano-Saito et al. found greater regional cerebral glucose metabolic rates in frontal regions, especially the left superior frontal gyrus, in 8 nondemented, PD patients with visual hallucinations, compared to nonhallucinating PD and healthy controls, using  $^{18}\text{F}$  FDG-PET [72]. Overall, neuroimaging studies using different modalities emphasize the relationship between frontal and posterior brain regions, visual and cognitive processing, and pathogenesis of PD hallucinations.

**3.4. Challenges.** While the neuroimaging studies allow for an *in vivo* assessment of the brain in PD hallucinators, there are several limitations, confounders, and challenges. Acquiring neuroimaging studies in PD patients can be difficult due to issues of motor fluctuations, tremor or dyskinesias, impaired attention, dementia, and active psychosis. Moreover, fMRI studies in particular can be affected by factors such as impaired attention, motivation, and cognition; medication

effects including antipsychotics; and visual acuity deficits. Although interesting, imaging PD patients while they are actively hallucinating or delusional could pose certain challenges. The majority of the neuroimaging studies, to date, have focused on chronic visual hallucinations, and thus, whether the findings reflect the pathogenesis of delusions or hallucinations in other sensory modalities is not known. Additionally, comorbid neuropsychiatric issues such as cognitive impairment, even mild, and depression may share neuroanatomical substrates (e.g., temporal lobe) and could influence interpretations of studies. Despite these challenges, studies using different neuroimaging modalities, applied individually or in combination, have the potential to enhance our understanding of the pathogenesis of PD psychosis.

#### 4. Genetic Risk Factors for PD Psychosis

Besides clinical risk factors such as age, PD duration and severity, depression, cognitive impairment and dementia, and sleep disturbances [2, 3], genetic factors may be involved in the development of PD psychosis. Genetic polymorphisms that affect levodopa or dopamine-agonist metabolism have been shown to play a role in other medication-related complications such as dyskinesias or motor fluctuations [73, 74]. With the growing field of pharmacogenetics, interindividual differences in medication responses due to underlying genetic polymorphisms may become increasingly important in drug development, evaluation of drug efficacy and toxicity, and ultimately, individualized patient care.

Various genetic polymorphisms have been considered regarding increased risk of psychosis in PD. This section will discuss several studies of genetic polymorphisms in the dopamine, serotonin, and cholecystokinin systems as well as apolipoprotein E (APOE) 4 allele status in PD hallucinators. In general, many of the studies have yielded conflicting results, and thus, the relationship between genetic interindividual variability and disease-related complications of PD awaits further exploration. Differences in methodologies and ethnic backgrounds of subjects may be critical contributions to the negative or conflicting study results.

**4.1. Dopaminergic System.** Investigations of the dopaminergic system have included D1 class receptors (DRD1 and DRD5), D2 class receptors (DRD2, DRD3, DRD4), as well as the dopamine transporter gene (DAT). Makoff et al. studied polymorphisms of DRD2 (-141C/del in the promoter region and TaqIA restriction fragment length polymorphism C > T) and DRD3 (Ser9Gly) in hallucinating and nonhallucinating white PD patients [75]. No association of these DRD2 or DRD3 polymorphisms was found when comparing the 84 hallucinators to the 71 nonhallucinators as a group. However, an association was found with the C allele of the TaqIA polymorphism to DRD2 and late-onset hallucinators (i.e., those PD patients who developed hallucinations after 5 years of disease). The nonhallucinating controls for the whole group were matched for disease duration, age at disease onset, duration of dopaminergic therapy, and gender, but not medication doses or classes of dopaminergic agents.

In a case-control study of 44 matched pairs of white PD patients with and without chronic hallucinations, Goetz et al. assayed dopamine receptor genes, including DRD1, DRD2, and DRD3 [76]. They found no significant difference in allele frequencies or distribution of genotypes between hallucinating and nonhallucinating PD patients for DRD1 and DRD3, although the DRD3 2 allele had a borderline increased frequency in hallucinators ( $P = .047$ ). Similarly, a case-control study of Chinese PD patients with and without hallucinations did not find an association at DRD2 (TaqIA, 32806 C > T), DRD3 (Ser9Gly and Msp1), or DRD5 (978 T > C) [77]. Of note, the DRD2 polymorphism has been associated with dyskinesias and wearing off in PD [78, 79]. The positive association of the DRD2 polymorphism with dyskinesias and wearing off but not with hallucinations suggests that the underlying pathogenesis of neuropsychiatric and motor complications in PD differs. Alternatively, polymorphisms in the dopamine receptor genes may be minimally involved in PD psychosis, given the negative results from the three studies described.

Other studies have focused on the dopamine transporter gene (DAT) since the dopamine transporter controls the presynaptic reuptake of dopamine. In some reports, a 40 bp variable number of tandem repeat (VNTR) polymorphism in the 3'-untranslated region of the DAT gene has been associated with psychiatric conditions such as attention-deficit hyperactivity disorder, alcoholism, and schizophrenia. In a study of white PD patients, Kaiser et al. examined the VNTR polymorphism of the DAT gene, along with DRD2, DRD3, and DRD4 polymorphisms, and found that the  $9 \times 40$  bp VNTR allele of the DAT gene was more frequently present in those levodopa-treated PD patients with psychosis or dyskinesias, compared to nonaffected patients (odds ratio 2.6; 95% CI: 1.3–5.3;  $P = .008$  and odds ratio 2.5; 95% CI: 1.3–4.7;  $P = .007$ , respectively, for psychosis and dyskinesia) [80]. The finding of differences in the 9-copy allele of the DAT VNTR, however, was not confirmed in either a case-control study of Chinese PD patients with and without hallucinations [77] or in our case-control study of white PD patients with and without hallucinations [81]. Larger studies of different ethnic populations are needed to further study the role of the DAT gene and dopaminergic system in PD psychosis.

**4.2. Serotonergic System.** Polymorphisms in the serotonin (5HT) transporter gene have been thought to influence anxiety and depression by altering serotonergic tone [82, 83]. The serotonin transporter gene, similar to the dopamine transporter gene, plays a critical role in the termination of 5HT transmission by controlling presynaptic reuptake [84]. Two functional polymorphisms in the serotonin transporter gene have been identified and contribute to protein expression. These include a promoter VNTR (short, long alleles) and intron 2 VNTR (9, 10, 11, 12 alleles). Less efficient transcription and decreased reuptake results from a deletion (short [s] allele compared to long [l] allele) or presence of 10-copy allele in intron 2 VNTR in the transporter gene. Some studies have reported a significant association of the s/s and l/s genotypes and anxiety-related

traits in the general population as well as in depressed or anxious PD patients [82]. In a study of 32 genotyped PD patients who were administered the Hamilton Depression and Anxiety scales, those PD patients who had the short allele had significantly higher scores on the depression and anxiety measures [85]. For the VNTR element in intron 2 of the serotonin transporter gene in which four variants may occur, increased frequency of the 9-copy allele has been reported in affective disorders [83]. However, this finding was not confirmed in PD patients with depression [86]. In our case-control study, we examined these two serotonin transporter gene polymorphisms in white PD patients with and without hallucinations but did not find any differences in allelic or genotypic frequencies of short or long alleles or intron sequences of the VNTR element [87]. Thus, the serotonin transporter gene polymorphisms may have greater association with anxiety and other affective disorders rather than psychosis, although further study is needed. Alternatively, since the serotonin system encompasses many receptor subtypes, individual receptors rather than the transporter itself may be associated with psychosis, as suggested by atypical antipsychotic pharmacology. Kiferle et al. examined polymorphisms in the 5HT-2a gene (T102C) as well as the serotonin transporter gene (short, long alleles) [88]. However, in their nondemented, white PD group, no significant differences in either polymorphism between PD patients with and without hallucinations were found.

**4.3. Cholecystokinin.** Cholecystokinin (CCK), a neuropeptide found in both the gut and central nervous system, is involved in dopaminergic regulation and colocalizes with dopaminergic neurons. The CCK receptor genes, CCKAR and CCKBR, have been cloned and sequenced in humans [89]. Centrally, CCKAR mediates the behavioral actions of CCK and CCK-stimulated dopamine release in the posterior nucleus accumbens. In contrast, CCKBR mediates CCK inhibition of dopamine release in the anterior nucleus accumbens [90]. The nucleus accumbens, part of the cortico-striato-thalamo-cortical loop, is associated with the mesolimbic pathway and behaviors such as reward, pleasure, and addiction. Due to their role in mesocorticolimbic circuitry, CCK and its receptors were initially studied in alcoholism and schizophrenia with auditory hallucinations and later in PD psychosis.

Studies in Asian PD patients suggest that CCK polymorphisms may differ in hallucinating PD patients. Fujii et al. reported that Japanese PD patients with hallucinations differed at the CCK – 45 C/T locus, with overrepresentation of CT and TT genotypes in the hallucinators, though this did not remain significant when correcting for multiple comparisons [91]. Since the C to T transition occurs in the Sp1-binding cis element of the CCK gene promoter, mutations at this site might affect promoter activity and gene transcription [92]. In a study of Chinese hallucinating and nonhallucinating PD patients treated with levodopa, the hallucinators significantly differed at the CCK – 45 C/T locus, with overrepresentation of the T allele in the hallucinators [93]. Moreover, there was an almost 6-fold increased risk for

developing hallucinations if the CCK T allele and CCKAR C allele were present in combination. In our investigation of the CCK system in a matched sample of white PD hallucinating cases and nonhallucinating controls, we did not find any difference in allele frequencies or genotype distribution for CCK but detected a trend for an over-representation of the CCK T allele in hallucinating PD patients ( $P = .06$ ) [94].

**4.4. APOE4.** The APOE4 allele is recognized as an important genetic risk factor in Alzheimer's disease but has been variably reported in PD dementia. Because dementia and psychosis may coexist, polymorphisms in APOE4 have been investigated as genetic risk factors for PD hallucinations. In a study of nondemented PD patients, the APOE4 allele was present in 13/17 (76%) hallucinators compared to 20/88 (23%) nonhallucinators, remaining significant after adjustment for age, PD severity, treatment duration, levodopa dose, and agonist treatment [95]. Other studies, however, have failed to replicate these findings. Whether or not the APOE4-positive, hallucinating patients subsequently developed dementia or had coexisting Alzheimer's disease pathology is not known. Goetz et al. did not find any difference in APOE4 alleles in their case-control study, despite the PD hallucinators having lower Mini-mental State examination scores (mean [SD] for hallucinators 23.7 [5.3] and nonhallucinators 28.8 [2.4]) [76]. No association between APOE4 and PD hallucinations was found in a study of 47 autopsy-proven PD patients [96]; in this study, Camicioli et al. included patients as "hallucinators" if hallucinations were ever recorded in the charts regardless of persistence or etiology. While even transient hallucinations may not be "benign" in their course, it remains to be seen whether genetic susceptibilities differ in PD patients with illusions, intermittent hallucinations, chronic hallucinations, or delusions.

**4.5. Challenges.** Conflicting results and methodological issues have complicated the studies of genetic polymorphisms and PD hallucinations. Confounding variables that may influence these genetic association studies include but are not limited to small sample sizes, methodological differences (case-control studies versus larger population-wide studies), and differences in demographic or PD-related issues such as age, gender, disease duration, medications, cognitive, and mood disorders. Moreover, an important consideration is that genetic polymorphisms vary greatly among different ethnic groups. In addition, it remains possible that some nonhallucinating patients examined in cross-sectional studies might convert to hallucinators over time. Longitudinal follow-up would be necessary to assess conversion risk and genetic status as a predictor of hallucinations. Nevertheless, the genetic association studies may prove to be informative and useful regarding genetic susceptibility, drug development, and potentially individualized treatment regimens.

## 5. Animal Models of Psychosis

Animal models provide important translational tools by which to study the neurobiological substrates of disease

and to investigate treatments for specific disease-related symptoms. Animal models such as the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine- (MPTP-) lesioned primates and 6-hydroxydopamine- (6-OHDA-) lesioned rodents have been influential in studying parkinsonism and levodopa-induced dyskinesias. However, hallucinations and other psychotic behavior have been more difficult to study in animals given the subjective nature of the hallucinatory experience and the challenge of inferring meaning from an animal's behavior. In rodents and primates, amphetamine and other stimulants (e.g., the glutamate NMDA receptor antagonists ketamine and phencyclidine) have been long used as potential models of psychosis or positive symptoms of schizophrenia due to their ability to stimulate locomotor activity, produce stereotypies, and enhance striatal dopamine release [97]. In primates treated with chronic amphetamine, induced movements such as stereotypies and hyperactivity and behaviors such as hypervigilance, checking, grasping, and staring may occur [98, 99].

**5.1. Studies of Psychosis-Like Behaviors in MPTP-Lesioned Primates.** MPTP-lesioned primates have been noted to experience abnormal psychomimetic behaviors that are reminiscent of the "psychosis-like" behaviors in the amphetamine-sensitized animals, and these behaviors may have utility in studying PD psychosis [100, 101]. Fox et al. examined these phenomena in primates; marmosets treated with MPTP and housed under controlled conditions were subsequently exposed, after a stable parkinsonian period, to several different dopaminergic and antipsychotic medications. In order to quantify the psychosis-like behaviors, the authors proposed a rating scale with behavioral categories including: (1) agitation, hyperkinesias; vocalizations; (2) hallucinatory-like response to apparent nonstimuli, tracking, staring; (3) obsessive grooming, scratching or grooming repetitively; and (4) stereotypes, repetitive side-to-side jumping, head checking movements, purposeless running, and grasping at the bars [101]. These behaviors, deemed distinct from dyskinesias, were rated by a blinded observer, in addition to parkinsonism and dyskinesias, and summed for a total psychosis-like behavior score.

In a series of experiments, the authors examined responses to various dopaminergic medications and antipsychotics. Both levodopa and dopaminergic receptor agonists (pergolide, pramipexole, and ropinirole) induced peak-dose psychosis-like behavior in the MPTP-lesioned primates as well as reversed parkinsonian disability, compared to the vehicle [100]. No difference in psychosis-like behavior was observed among the dopaminergic agents. In a companion study using a similar protocol [101], the authors found that levodopa produced psychosis-like behavior in the 7 marmosets studied. Of the psychosis-like behaviors exhibited, stereotypies were the most common, and all animals exhibited staring and tracking behavior (hallucinatory-like). There was no correlation between severity of dyskinesias and psychosis-like behavior in individual animals with levodopa. Amantadine coadministered with levodopa significantly increased total peak-dose psychosis-like behavior but reduced peak-dose dyskinesias. Psychosis-like

behaviors, particularly stereotypies, were decreased when haloperidol was coadministered with levodopa. Not surprisingly, haloperidol, compared to vehicle, worsened parkinsonism and reduced dyskinesias. Although quetiapine was coadministered with levodopa in only 6 animals, results differed based on dose; significant reduction in the total psychosis-like score was seen in the 1.5 mg/kg group but not the 0.5 mg/kg or 4.5 mg/kg doses, compared to vehicle. Clozapine reduced psychosis-like behaviors, compared to vehicle, with a decrease in hallucinatory-like behavior. Neither quetiapine nor clozapine worsened parkinsonism or produced somnolence.

**5.2. Challenges.** One of the greatest challenges of the animal models is whether one can infer that the primates' behaviors recapitulate the human experiences of hallucinations and psychosis. However, these dopaminergic-stimulated abnormal behaviors, as distinguished from dyskinesias, may represent a close approximation of PD neuropsychiatric disturbances and an opportunity to evaluate pathophysiology and therapeutics for psychosis and heightened dopaminergic states.

## 6. Recent Pharmacological Trials and Challenges of PD Psychosis Trials

Atypical antipsychotics, such as clozapine and quetiapine, which have greater serotonergic antagonism than dopamine receptor blockade have been generally favored in the management of PD psychosis due to the decreased risk of worsened parkinsonism and other extrapyramidal syndromes. Much of the serotonin effect of these atypical antipsychotics relates to drug interactions with the 5HT-2a receptors, which in the central nervous system can be found in the cortex, basal ganglia (caudate and putamen), and hippocampus [102]. Interestingly, 5HT-2a antagonists or inverse agonists including clozapine also have demonstrated improvement in parkinsonian motor function in primates and humans [103, 104]. Based on these pharmacological profiles, several atypical antipsychotics acting on the 5HT-2a system, such as melperone and pimavanserin (ACP-103), have been recently studied in PD psychosis. The following section will briefly discuss findings related to these newer agents and challenges of PD psychosis trials. Other medications studied in PD psychosis, including quetiapine, clozapine, among other atypical antipsychotics, have been the subject of other recent reviews and are not discussed here [105].

**6.1. Melperone.** Melperone has been available in some European countries and in use as an antipsychotic for schizophrenia for over 10 years. Although a butyrophenone, melperone has been considered an atypical antipsychotic due to its low extrapyramidal symptoms and lack of increase in plasma prolactin [106, 107]. It is similar to clozapine in that it also has high 5HT-2a affinity relative to dopamine (D2) receptor binding affinities. In an open-label trial for PD psychosis, Barbato et al. assessed the clinical efficacy and safety of melperone in 30 PD patients with psychosis over

a 24-month period [108]. In 28/30 PD patients, psychotic symptoms, as measured by the Brief Psychiatric Rating Scale (BPRS), improved with a mean daily dose of 37.5 mg (range 12.5–75 mg daily) without worsening motor scores. Doses were much smaller than those utilized in schizophrenia, similar to the low clozapine and quetiapine doses used in PD psychosis. Side effects included hypotension, dizziness, and sedation (leading to discontinuation by 2 patients). Based on this study, a multicenter, randomized, double-blind, placebo-controlled, 10-week, Phase II trial evaluating the safety and efficacy of melperone in PD psychosis was conducted in the US and recently finished. However, to date, no results have been published in scientific journals.

**6.2. Pimavanserin (ACP-103).** Pimavanserin (ACP-103) is a 5HT-2a receptor inverse agonist, which has been recently investigated in PD psychosis [109, 110]. Although pimavanserin (ACP-103) also has some 5HT-2c receptor affinity, it exhibits about 30-fold greater selectivity for the 5HT-2a receptor compared to the 5HT-2c receptor [103]. Results from a multicenter, randomized, double-blind, placebo-controlled, 28-day, Phase II study to evaluate the tolerability, safety, and efficacy of pimavanserin in 60 PD patients were recently published [111]. The study, powered for differences in the UPDRS Parts II and III scores, had favorable results regarding motor function, with no significant differences observed between drug and placebo groups. In addition, there were no significant differences in adverse events between treatment groups. Regarding psychosis outcomes, the Scale for the Assessment of Positive Symptoms (SAPS) total domain score was chosen as the primary outcome measure for efficacy based on its use in the Parkinson's Study Group clozapine trial, and a trend for greater improvement in pimavanserin-treated patients was detected ( $P = .09$ , effect size = 0.52). Analyses of many individual items from the SAPS and UPDRS psychosis question failed to reveal significant differences between treatment groups; however, the global ratings for hallucinations and delusions significantly favored the pimavanserin arm. Subsequently, a multicenter, randomized, double-blind, placebo-controlled, Phase III trial with a larger sample of PD patients was completed; reports reveal that although the drug was tolerated in terms of motor function and side effects, a statistically significant benefit for psychosis measures was not achieved [112]. Of note, this same compound has been under evaluation in primate models of levodopa-induced dyskinesias [103] and schizophrenia-related psychosis and insomnia. Since serotonin may influence sleep architecture, pimavanserin and similar compounds could also improve sleep maintenance and quality in those with insomnia [109, 113].

**6.3. Challenges.** In addition to the pharmacological challenges of finding antipsychotics that safely treat PD psychosis without worsening parkinsonism or causing other adverse effects, there are challenges related conducting the trials and many issues pertaining to optimal trial design, inclusion/exclusion criteria, subject recruitment, and study completion. In 2006, the Quality Standards Subcommittee

of the American Academy of Neurology published a Practice Parameter report on the evaluation and treatment of depression, psychosis, and dementia in PD. Of 23 articles on psychosis treatment in PD patients identified by the authors, only four Class I and II articles were accepted for review. Based on a review of these PD psychosis studies on clozapine, quetiapine, and olanzapine, the authors concluded that, as demonstrated by one Class I study [114] (PSG) and one Class II study [115], clozapine was probably an effective treatment for PD psychosis without motor worsening. Clozapine use, despite its efficacy, is often limited in clinical practice due to the risk of fatal agranulocytosis and requirement for neutrophil count monitoring. Only one Class II study [115] demonstrated that quetiapine possibly improved PD psychosis. Olanzapine failed to improve psychosis and worsened parkinsonism [116, 117]. As such, the Practice Parameter authors recommended that clozapine could be considered as Level B and quetiapine, as Level C treatments, for PD psychosis [118]. The conclusions from the AAN Practice Parameter underscore the need to identify novel compounds that are safe and effective in reducing psychosis without compromising motor function. Furthermore, these agents will require evaluation in well-designed, randomized, controlled trials in order to withstand rigorous methodological review and meet criteria for evidence-based medicine. Two double-blind, placebo-controlled studies, subsequently published and thus not included in the AAN review, have failed to demonstrate significant improvement with quetiapine in ratings of psychosis although parkinsonism did not worsen [119, 120]. The quetiapine studies, however, have been criticized for methodological issues, such as poor recruitment, patient populations with mixed diagnoses (some with PD, PD and dementia, dementia with Lewy bodies, or Alzheimer disease with parkinsonism), low doses of medications, selection of psychosis rating scales or primary outcomes, and small sample sizes. Recruitment for PD psychosis clinical trials remains a challenging issue; influential factors include the widespread clinical use of quetiapine despite negative double-blind, placebo-controlled trial results; patient and caregiver concerns about placebo assignment especially when hallucinations are frightening and delusions are present; risk of worsened motor function; and recent “black box” warnings by the FDA regarding increased risk of death in elderly patients with dementia who received treatment with antipsychotics. These important issues also must be addressed in trials for PD psychosis.

## 7. Conclusions and Future Directions

Although the dopaminergic system remains important in the pathogenesis of psychosis in PD, new research strategies should consider the complex relationships among other neurochemical and neuroanatomical substrates and potentially integrate these elements into targets for drug development. Similarly, investigations of PD psychosis should examine the influences of other neuropsychiatric features of PD such as attention, cognition, sleep, and mood. Alterations in visual and cognitive processing may provide useful targets, as deficits span from the retina to brainstem to cortical regions.

While the optimal treatment of PD psychosis remains a challenge, integrating studies of neuroimaging and genetic susceptibility, and perhaps, animal models may permit advances in drug development. Examination of clinical and genetic factors of those PD patients who never hallucinate despite high dopaminergic medication doses may also provide useful information on protective mechanisms and strategies.

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## Review Article

# Impulse Control Disorders Following Deep Brain Stimulation of the Subthalamic Nucleus in Parkinson's Disease: Clinical Aspects

**Polyvios Demetriades,<sup>1</sup> Hugh Rickards,<sup>1</sup> and Andrea Eugenio Cavanna<sup>1,2,3</sup>**

<sup>1</sup> University of Birmingham Medical School, Birmingham B152TT, UK

<sup>2</sup> Department of Neuropsychiatry, University of Birmingham and BSMHFT, Barberry Building, 25 Vincent Drive, Birmingham B152FG, UK

<sup>3</sup> Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, UCL, London WC1N 3BG, UK

Correspondence should be addressed to Andrea Eugenio Cavanna, a.cavanna@ion.ucl.ac.uk

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Parkinson's disease (PD) has been associated with the development of impulse control disorders (ICDs), possibly due to overstimulation of the mesolimbic system by dopaminergic medication. Preliminary reports have suggested that deep brain stimulation (DBS), a neurosurgical procedure offered to patients with treatment-resistant PD, affects ICD in a twofold way. Firstly, DBS allows a decrease in dopaminergic medication and hence causes an improvement in ICDs. Secondly, some studies have proposed that specific ICDs may develop after DBS. This paper addresses the effects of DBS on ICDs in patients with PD. A literature search identified four original studies examining a total of 182 patients for ICDs and nine case reports of 39 patients that underwent DBS and developed ICDs at some point. Data analysis from the original studies did not identify a significant difference in ICDs between patients receiving dopaminergic medication and patients on DBS, whilst the case reports showed that 56% of patients undergoing DBS had poor outcome with regards to ICDs. We discuss these ambivalent findings in the light of proposed pathogenetic mechanisms. Longitudinal, prospective studies with larger number of patients are required in order to fully understand the role of DBS on ICDs in patients with PD.

## 1. Introduction

Parkinson's disease (PD) is increasingly recognized as a neurodegenerative condition characterized by motor dysfunction and both physiological and psychological disturbances [1]. Although PD has been classically associated with psychiatric comorbidities such as dementia [2] and psychosis [3], recent studies have shown that patients with PD can develop a variety of behavioral problems associated with impulse dyscontrol, including pathological gambling, hypersexuality, punding (repetitive purposeless motor acts not distressing to the patient), and compulsive shopping and eating [4]. These pathological behaviors are currently classified as impulse control disorders (ICDs) and exert negative consequences in terms of the patients' health-related quality of life, mainly because of the interference with their social functioning [5]. The aetiopathogenesis of ICDs in patients with PD is not completely understood, but previous

studies showed that dopamine replacement therapy can lead to the development of ICDs due to overstimulation of the mesolimbic dopaminergic system [6] which modulates behavioral responses to reward, motivation, and reinforcement. A recent large cross-sectional study has shown that up to 13.6% of patients with treated idiopathic PD may suffer from ICDs [7], with hypersexuality, pathological gambling, and compulsive shopping being the most common ones. Levodopa use, younger age of onset of PD, and unmarried status were associated with the development of ICDs. Other predictive factors included being male, history of alcohol abuse, and novelty seeking or impulsive personality traits [8]. Finally, it has been consistently found that patients using dopamine agonists are more likely to develop ICDs (6.3%) than those using L-dopa (0.6%) [9].

In some patients, dopaminergic medication becomes less effective in treating motor symptoms. Deep brain stimulation (DBS) is an effective neurosurgical procedure

that can reduce motor symptoms in patients with treatment-refractory PD (especially patients who developed levodopa-induced dyskinesia), thus allowing decrease in their medication [10]. Consequently, DBS might have an indirect beneficial role in patients suffering from ICDs. However, DBS may also have detrimental effect on patients' behaviours. The most effective target of DBS in PD is arguably the subthalamic nucleus (STN), which plays a part in the fronto-striato-thalamic-cortical loops mediating motor, cognitive, and emotional functions [11], thus suggesting that DBS may affect patients' behavior, in addition to motor performance. Both case reports and clinical studies associating DBS with the postoperative development of ICDs have provided support to this hypothesis.

As the popularity of DBS increases and this neuro-surgical procedure is offered to patients suffering from other treatment-resistant movement disorders commonly associated with ICDs, such as Tourette syndrome [12], there is a need of more conclusive results on its role in the development of ICDs. This literature review assesses the current evidence on the clinical implications of ICDs in patients with PD who underwent DBS of the subthalamic nucleus.

## 2. Literature Search Methodology

We performed a literature search across the databases Medline, EMBASE, and PsycInfo to identify original studies and case reports which examined the behavioral effects of DBS in patients with PD, with focus on ICDs, as defined in Chapter 5 of the ICD-10 classification system [5]. We used the search terms "Parkinson," "deep brain stimulation," "impulse control disorder," "impulsivity," "hypersexuality," "pathological gambling," "punding," "compulsive shopping," "compulsive eating," and "addiction", and we limited our search to papers published in English language.

## 3. Original Studies

Four original studies met our search criteria, examining a total of 182 patients for ICDs. We selectively reviewed studies reporting patients with ICDs. As a result, due to publication bias, the prevalence of ICDs after DBS cannot be extrapolated from the reviewed data.

Two studies (Funkiewiez et al. [13] and Contarino et al. [14]) followed up patients with PD after DBS surgery, in order to identify any changes in their behavioral profile, including impulse dyscontrol. The other two studies (Hälbig et al. [15] and Czernecki et al. [16]) performed a cross-sectional evaluation comparing patients with PD-treated DBS (PD + DBS) with those treated with dopaminergic medication (levodopa and/or dopamine agonists) (PD + DA). A proportion of patients from the latter group remained on medication postoperatively.

Table 1 summarizes the demographic and clinical characteristics of the two groups of patients (PD + DBS and PD + DA) across the four studies. The PD + DBS group was larger than the PD + DA group since only two of the four studies included controls (PD + DA). The mean age of the

TABLE 1: Summary of demographic and clinical characteristics of patients with Parkinson's disease from four original studies evaluating the effects of deep brain stimulation on impulse control disorders.

	PD + DBS	PD + DA
No. of patients	122	60
Gender: M/F/unknown	62/42/18	26/11/23
Mean age (years)	55	57
Mean disease duration (years)	14	10

Abbreviations. PD: Parkinson's disease; PD + DBS: patients with Parkinson's disease who underwent deep brain stimulation surgery (some remained on medication postoperatively); PD + DA: patients with Parkinson's disease treated with dopaminergic medication.

patients was similar in both groups whereas disease duration was higher in PD + DBS than in PD + DA, consistent with the clinical practice of referring to neurosurgery patients with longer disease duration who failed to respond to medication. Motor evaluation of the patients in all studies was performed using the Unified Parkinson's Disease Rating Scale III (UPDRS III). In the PD + DBS group, the UPDRS III ranged from 10.1 (SD  $\pm$  2.4) (Czernecki et al.) to 20.8 (SD  $\pm$  12.1) (Contarino et al.), whereas in the PD + DA group, the UPDRS III scores ranged from 16.3 (SD  $\pm$  10.6) (Hälbig et al.) to 38.7 (SD  $\pm$  2.8) (Czernecki et al.). Exclusion criteria included severe psychiatric conditions and cognitive impairment measured by Minimal State Examination (MMSE), possibly masking severe cases of ICDs.

Unfortunately, the methodology of each study differed, and hence no conclusive results can be drawn from the patients as a group. Table 2 outlines the total number of patients in each group (PD + DBS and PD + DA) and the percentage of each group who developed ICDs.

Hälbig et al. [15] identified a higher percentage of patients with newly developed ICDs in the PD + DBS group (19%) than in the PD + DA group (8%), but this was not statistically significant with  $P = .26$  (Table 2). However, this study identified a statistically significant difference in overall impulsivity ( $P = .04$ ) between the two groups, with PD + DBS reporting higher impulsivity scores (Table 3). Notably, preoperative assessment of ICDs was not performed, so the two groups may have been different from the start. All of the patients in the PD + DBS group were with stimulation "on" at the time of the assessment and remained on dopaminergic medication after surgery (56% on levodopa monotherapy, 44% on combined levodopa and dopamine agonist therapy) with mean LEDD 682mg (SD  $\pm$  427 mg). The PD + DA group's mean LEDD was 582 mg (SD  $\pm$  480 mg), with 38% of the patients on levodopa monotherapy, 16% on dopamine agonist monotherapy, and 46% on combined therapy.

Contarino et al. [14] and Funkiewiez et al. [13] reported the development of ICDs in 18% (hypersexuality) and 2.5% (aggressive impulsive behaviour) of their patients (Table 2). Czernecki et al. [16] used methods described in Rolls et al. [17] and Bechara et al. [18] to compare the reward sensitivity (an indirect measure of impulsivity) of patients receiving DBS (in both "on" and "off" conditions) with patients

TABLE 2: Development of impulse control disorders after deep brain stimulation or dopaminergic pharmacotherapy in patients with Parkinson's disease.

Study	Type of study	Number of patients in each study; n		Number of patients developing ICDs; n (%)	
		PD + DBS	PD + DA	PD + DBS	PD + DA
Halbig et al.	Cross-sectional	16	37	3 (19%)	3 (8%)
Contarino et al.	Longitudinal	11	0	2 (18%)	n/a
Funkiewiez et al.	Longitudinal	77	0	2 (2.5%)	n/a
Czernecki et al.	Cross-sectional	18	23	n/a	n/a

Abbreviations. ICDs: impulse control disorders; PD: Parkinson's disease; PD + DBS: patients with Parkinson's disease who underwent deep brain stimulation surgery; PD + DA: patients with Parkinson's disease treated with dopaminergic medication (levodopa and dopamine agonists).

TABLE 3: Measures of impulsivity after deep brain stimulation or dopaminergic pharmacotherapy in patients with Parkinson's disease.

Study	Outcome measures		PD + DBS	PD + DA	<i>P</i> value
Halbig et al.	Barratt impulsiveness Scale; mean (SD)	"on" treatment	44.97 (17.29)	36.11 (17.29)	0.04
		"off" treatment	19.2 (3.9)	22.6 (5.6)	0.37 (group)
Czernecki et al.	Stimulus reward association learning (number of trials) ; mean (SEM)	"on" treatment	23.1 (4.6)	28.8 (4.8)	
		"off" treatment	1.6 (0.2)	1.3 (0.2)	
	Reversal (number in 30 trials); mean (SEM)	"on" treatment	1.3 (0.2)	1.3 (0.2)	0.13 (group)
		"off" treatment	8.1 (1.1)	14.2 (2.5)	
	Extinction (last error); mean (SEM)	"on" treatment	10.5 (1.6)	11.8 (1.9)	0.39 (group)
		"off" treatment	25.4 (10.2)	13.4 (6.9)	
Gambling task; mean (SEM)	"on" treatment	19.4 (9.6)	14.2 (6.4)		
	"off" treatment				

In all measures (except the Barratt impulsiveness scale and the extinction test), lower scores indicate higher impulsivity.

Tasks described in Rolls et al. [17] ANOVA results of *P*-value of group effect (patients on stimulation *versus* patients on medication)

Abbreviations. PD + DBS: patients with Parkinson's disease who underwent deep brain stimulation surgery; PD + DA: patients with Parkinson's disease treated with dopaminergic medications (levodopa and/or dopamine agonists); "on" treatment: on medication and stimulation (if applicable) on the time of assessment; "off" treatment: off medication and stimulation.

receiving dopaminergic medication. The methods included stimulus reward learning with either reversal or extinction and the gambling task (Table 3). In the stimulus reward learning procedure, the subjects were faced with a screen challenging them to learn how to choose the correct pattern in order to gain maximum points and to progress to further trials. The task continued to either the reversal phase (testing sensitivity to reward flexibility) or the extinction phase (testing the ability to control impulsivity). The gambling task included making a choice between advantageous (small gains but smaller losses) and disadvantageous (big gains but bigger losses) decks. Previous reports by the same authors using the same tasks identified that patients with PD had impaired explicit and implicit reinforcement-associated learning and "sensitivity to reward" flexibility, compared to healthy controls [19]. In this study, there was no difference between the PD + DBS and PD + DA groups, implying

that although patients with PD may have higher impulsivity than controls, DBS does not seem to increase it further. In this study, the preoperative LEDD of the PD + DBS group did not differ significantly from the PD + DA group, whilst the postoperative mean LEDD of the PD + DBS group was 133.3 mg (SEM  $\pm$  58.7), compared to 982.3 mg (SEM  $\pm$  53.9) in the PD + DA group.

#### 4. Case Reports

We found 9 case reports of 39 patients with PD (33 men and 6 women) who underwent DBS and developed ICDs or whose ICDs worsened ( $n = 22$ ). In other cases ( $n = 17$ ), patients presented with ICDs that resolved or improved postoperatively. Although our study selection again involves publication bias, the case reports will provide detailed information about the phenomenology of ICDs and the

clinical characteristics of the patients who develop ICDs. The demographic and clinical characteristics for each patient are described in Table 4.

Romito et al. [20], Doshi and Bhargava [21], Smeding et al. [22], Sensi et al. [23], and Lim et al. [24] reported patients with no preoperative ICDs who developed ICDs after surgery (patients 1–7, 19, 38) (Table 5). The time period between surgery and the development of ICD varied in each case from immediately after surgery to months later. Most of the ICDs were transient and resolved within a year of their development. Lim et al. [24] described a series of patients with preoperative ICDs that worsened after surgery (patients 20–32); some of these patients developed a wider spectrum of ICDs after the operation compared to what they had preoperatively (patients 20–22, 31–32).

Witjas et al. [25], Bandini et al. [26], Ardouin et al. [27], and Lim et al. [24] described patients with preoperative ICDs that resolved completely (patients 8–18, 33–35, 39) or improved significantly (patients 36–37) postoperatively. In all cases, there was a significant reduction (reduction to less than 50% of preoperative dose) in levodopa equivalent daily dose (LEDD), most commonly in the first 3 months after DBS. Most of the studies provided the LEDD for the patients; where not explicitly stated, it was calculated as described in Wenzelburger et al. [28].

Analysis of the findings of the case reports revealed that 22 patients (1–7, 19–32, 38) had a “poor outcome” after DBS, defined as worsening of existing ICDs, new development of ICDs, or no postoperative improvement of existing ICDs, and 17 patients (8–18, 33–37, 39) had a “good outcome” after DBS, defined as improvement of existing ICDs or resolution of existing ICDs postoperatively (Table 5). Of the patients with “poor outcome”, 91.1% were males and 72.7% were older than 55 years, whereas in the “good outcome” group, only 76.5% were males and 70% of them were older than 55 years. Age information is not available for all patients in the “good outcome” group. Previous psychiatric history and postoperative psychiatric conditions were not available for all the patients. However, it was noted that only 36.4% of patients in the “good outcome” group had previous behavioral problems, compared to 42.9% in the “poor outcome” group. The patients who developed ICDs or whose ICDs worsened after DBS had a 36.4% chance of developing other psychiatric conditions. These included depression, manic syndrome, agitation, anxiety, and psychosis. On the other hand, only 17.7% of the patients in the “good outcome” group developed other psychiatric conditions postoperatively (depression).

## 5. Comments and Clinical Implications

This review paper specifically examined the literature on the role of DBS of the subthalamic nucleus on ICDs in patients with PD. In general, the existing evidence on this topic is poor, not allowing definitive conclusions whether DBS benefits patients with ICDs or whether it actually causes the development of ICDs.

*5.1. Development of ICDs after DBS.* Three out of the four studies described in Tables 1–3 reported the development of ICDs after DBS surgery. These findings are in agreement with 22 case reports of patients who had a poor postoperative outcome in terms of ICDs. In most cases, the ICDs developed despite a postsurgical reduction of dopaminergic medication. The reasons for the development of ICDs after DBS are still unknown, and hence a lot of different hypothesis have been proposed.

The first hypothesis suggests that STN-DBS increases impulsivity by stimulating the STN or neighboring fiber tracts, since the STN is interconnected with structures linked to both associative and limbic circuits within the basal ganglia. It is proposed that the STN can regulate the processing of associative and limbic information towards cortical and subcortical regions, thus influencing changes in behavior [29]. This is compatible with studies suggesting that the STN mediates not only motor but also cognitive and emotional functions [30]. Even the surgical procedure itself may have an adverse result on impulsivity, since the STN is a very compact structure, and it may be difficult to selectively influence the motor part of it without damaging it or its neighboring structures which are associated with motivational behaviors. This hypothesis was proposed by Sensi et al., who suggested that a microtraumatic effect of surgery or a misplacement of the electrodes may be the reason behind the development of ICDs after DBS [23]. Moreover, minimal changes in the stimulation site can cause different effects; Smeding et al. [22] showed that with the stimulation of the most dorsal contact of the STN nucleus, the performance on decision making tasks is worse than with stimulation of the ventral contact.

Previous reports have shown that in medically treated patients, higher levodopa dosages are associated with the development of ICDs [7]. Hence, a possible explanation for the development of ICDs after DBS is the higher cumulative exposure to dopaminergic medication due to longer disease duration and greater disease severity of the patients who underwent DBS. However, this hypothesis would not explain why some patients developed ICDs *ex novo* after surgery. Further complicating the picture, postoperative dopaminergic therapy reduction is also likely to play an important role. As seen in the case reports, unlike 100% of patients in the “good outcome” group, only 57.1% of patients in the “poor outcome” group had a significant reduction in their medication. This means that if preoperative ICDs exist, only a significant reduction in the patient’s medication would improve the patient’s impulsivity [26]. Moreover, the reduction would presumably be allowed only if the patient’s motor symptoms improve after surgery [25]. This explanation may also be supported by the findings of the study by Halbig et al., where surgery did not allow a major reduction in medication postoperatively (with PD + DBS and PD + DA having similar LEDD). Hence, in the probable background of preoperative ICDs and with a high dose of postoperative dopaminergic medication, the authors identified higher impulsivity in the PD + DBS group. Patients who remained on dopaminergic medication postoperatively had a poor outcome in terms of ICDs possibly because DBS

TABLE 4: Demographic and clinical characteristics of the patients with Parkinson's disease with development/ resolution of impulse control disorders after deep brain stimulation.

Study	Pt no	Age/Gender	Time to DBS after PD diagnosis	ICD pre-op	ICD post-op	Other psychiatric condition post-op	Psychiatric history	LEDD pre-op	LEDD post-op
Romito et al.	1	52/m	11 years	None	HS CS	MS	DE	900 mg	0
Romito et al.	2	42/m	15 years	None	HS	MS	None	1800 mg	0
Doshi Bhargava	3	70/m	n/a	None	HS	None	DE, PS	1100 mg	450 mg
Doshi Bhargava	4	58/f	n/a	None	HS	None	None	1200 mg	700 mg
Smeding et al.	5	63/m	10 years	None	PG	DE	AA	880 mg	560 mg
Roane et al. <sup>x</sup>	6	57/m	20 years	None	HS	AX, DDS	None	825 mg	1000 mg
Sensi et al.	7	64/m	8 years	None	KM	AG	None	1000 mg	300 mg
Witjas et al.	8	38/m	8 years	HS & DDS	None	None	AA, AG, HM	2500 mg	0
Witjas et al.	9	52/m	5 years	HS & DDS	None	None	PS, AG	1450 mg	300 mg
Bandini et al.	10	43/m	4 years	PG	None	None	None	1220 mg	0
Bandini et al.	11	51/m	5 years	PG & DDS	None	None	None	1500 mg	200 mg
Ardouin et al.	12-18	Age: n/a m (n = 6), f (n = 1)	n/a	PG (n = 7), DDS (n = 4)	None	DE (n = 3)	AA (n = 1), OCD (n = 1)	1395 ± 342 mg	368 ± 204 mg
Lim et al.	19	65/m	5 years	None	DDS, PG	PS	None	n/a	n/a
Lim et al. <sup>+</sup>	20	47/m	4 years	HS	DDS, PU, HS, CS, BE	None	None	n/a	n/a
Lim et al.	21	57/m	14 years	DDS, PG	DDS, PU, HS, PG	None	None	n/a	n/a
Lim et al.	22	55/m	10	DDS	DDS, PU, HS, BE	None	None	n/a	n/a
Lim et al.	23	56/f	13 years	DDS, PU, PG	DDS, PU, PG	None	None	n/a	n/a
Lim et al.	24	45/m	8 years	DDS, PU	DDS, PU	None	48% of patients: depression; 24 % of patients: alcohol abuse; 14% illicit drug abuse, 5% psychosis	n/a	n/a
Lim et al.	25	46/m	9 years	DDS, PU, HS, CS	DDS, PU, HS, CS	None	None	n/a	n/a
Lim et al.	26	66/m	12 years	DDS, PU	DDS, PU	None	None	n/a	n/a
Lim et al.	27	55/m	9 years	DDS, PG, HS	DDS, HS	None	None	n/a	n/a

TABLE 4: Continued.

Study	Pt no	Age/Gender	Time to DBS after PD diagnosis	ICD pre-op	ICD post-op	Other psychiatric condition post-op	Psychiatric history	LEDD pre-op	LEDD post-op
Lim et al.	28	68/m	10 years	DDS, PU	DDS, PU	None		n/a	n/a
Lim et al.	29	56/m	6 years	DDS, PU	DDS, PU	None		n/a	n/a
Lim et al.	30	60/m	12 years	DDS, PU	DDS, PU	None		n/a	n/a
Lim et al.	31	52/m	9 years	DDS, HS	DDS, PU, HS	PS		n/a	n/a
Lim et al.	32	64/m	9 years	DDS, HS	DDS, PU, HS	PS		n/a	n/a
Lim et al.	33	52/f	13 years	DDS, PU, HS, CS	None	None		n/a	n/a
Lim et al.	34	29/m	10 years	DDS, HS	None	None		n/a	n/a
Lim et al.	35	63/f	9 years	DDS, PU, PG, CS	None	None		n/a	n/a
Lim et al.	36	61/f	24 years	DDS, PU	PU (i)	None		n/a	n/a
Lim et al.	37	52/m	24 years	DDS, PU, HS, CS	PU (i)	None		n/a	n/a
Lim et al.	38	56/m	14 years	None	PG	None		n/a	n/a
Lim et al.	39	64/m	10 years	PG	None	None		n/a	n/a

Study did not provide information for individual patients; ( ) = number of patients.

+Study did not provide information regarding patient's medications, or psychiatric history.

<sup>x</sup>Patient no. 6 underwent DBS targeting the Globus Pallidus – Pars Interna.

Abbreviations. Pt no: patient number; LEDD: levodopa equivalent daily dose; HS: hypersexuality; PG: pathological gambling; KM: kleptomania; DDS: dopamine dysregulation syndrome; CS: compulsive shopping; BE: binge eating; PU: punding; AX: anxiety; PS: psychosis; AG: agitation; MS: manic syndrome; HM: hypomania; AA: alcohol abuse; OCD: obsessive compulsive disorder; (i): improved.

TABLE 5: Analysis of the outcomes in the case reports presented in Table 4.

	Poor outcome	Good outcome
Total Number	22	17
Male gender (%)	20/22 (91.1)	13/17 (76.5)
Age 55 years	16/22 (72.7)	7/10 (70)
Post-op medication reduction to less than 50% of pre-op dose	4/7 (57.1)	11/11 (100)
Psychiatric history	3/7 (42.9)	4/11 (36.4)
Other psychiatric condition post-op	8/22 (36.4)	3/17 (17.7)

“Poor outcome” is defined as worsening of existing ICDs, development of more ICDs, or no improvement of existing ICDs postoperatively; “good outcome” is defined as improvement of existing ICDs, disappearance of existing ICDs postoperatively.

Information not available for the rest of the patients.

can sensitize the brain to the behavioral effects of dopamine replacement therapy, especially on the background of high impulsivity [22].

Finally, a less likely explanation for the appearance of ICDs after DBS surgery is that the improvement of motor function in some patients may have facilitated the full expression of behavioral abnormalities that had been developed by the use of dopamine replacement therapy before the operation, as suggested by Houeto et al. [31].

**5.2. Improvement of ICDs after DBS.** A number of case reports in this paper described patients whose ICDs either resolved or markedly improved after surgery. However, the potential role of DBS in the resolution of ICDs is far from being clear.

Different mechanisms have been proposed to explain the resolution of ICDs after DBS. First of all, it is well known that dopaminergic stimulation is implicated in impulsive behaviors. Moreover, it has been consistently shown that dopaminergic medications, and in particular dopamine agonists, may predispose patients with PD to the development of ICDs [32]. The significant motor improvement after DBS allows an important reduction in dopamine replacement therapy and thus a less pulsatile and nonsuprathreshold stimulation of the mesolimbic dopamine receptors [27]. Table 4 reveals that all the patients in the “good outcome” group had a significant reduction in their medication. Additionally, Czernecki et al. did not identify higher reward sensitivity in the PD + DBS group compared to controls, probably because the postoperative mean LEDD in the former group was much lower than in the latter. Moreover, Lim et al. [24] stated that the ICDs persisted or even worsened in patients who had to remain on high dopamine replacement therapy due to poor or moderate motor benefit after DBS. Consistent to this hypothesis, Ardouin et al. [27] observed that the progressive improvement of the symptoms of their patient closely matched the reduction in his medication.

Another possible explanation is that the improvement of ICDs was due to a direct effect of DBS on the reward seeking brain circuitry [33]. The inhibition of neuronal circuits resulting from STN-DBS may affect the direct ascending dopaminergic and serotonergic pathways towards the limbic area which are known to have a role in positive reinforcing behaviors [25]. Further studies with long-term

followup of patients after DBS using impulsivity measures and neuroimaging techniques may provide useful information on the role of DBS in resolution of ICDs.

**5.3. Outcome Predictors.** Our results agree with previous studies suggesting that male sex, younger age of PD onset, and previous psychiatric history are predisposing factors to the development of ICDs during the disease course [7, 8].

Most of the patients in the reviewed studies were of male gender, in agreement with the existing literature that females are less likely to develop ICDs. However, other reasons may also explain this; patients with ICDs rarely volunteer and often deny having these behaviors. Being a female may exacerbate this effect since most of these conditions (hypersexuality, compulsive eating, and pathological gambling) are perceived as socially inappropriate and stigmatizing. It was also noted that being female resulted in better outcome after surgery; however, the role of confounding factors like age of disease onset and medication dose should be taken into account.

Although studies suggested that younger patients may be more compliant to medication changes and therefore are less likely to develop ICDs postoperatively [25], the analysis of the case reports revealed that the number of patients over 55 in the “good outcome” and “poor outcome” groups were similar.

A number of patients in the “poor outcome” group were diagnosed with PD early in their life. This is consistent with previous studies showing that patients with young onset PD are more likely to present with ICDs [34], findings which may reflect a confounding effect of prescribing of dopamine agonists to younger PD patients [35].

Only a few types of ICDs were reported in this paper. Hypersexuality and pathological gambling are the most commonly reported and are clearly disabling not only to the patient but also to his/her relatives. Sometimes, the family of the patient is more likely to volunteer this information to the psychiatrist. This is probably the reason why less distressing ICDs (e.g., compulsive shopping) were reported less commonly. It is important for the doctor to be aware of the possibility of development of ICDs in PD patients in order to provide support to the patient as quickly as possible.

Although information regarding the presence of previous psychiatric disorders was not always available, more patients

in the “poor outcome” group had history of psychiatric disorders compared to those in the “good outcome.” This suggests a possible association between previous psychiatric disorders/ history of abuse and ICDs.

Finally, fewer patients in the “good outcome” group suffered from psychiatric comorbidities after surgery compared to those in the “poor outcome” group. This was expected as the most common psychiatric disorder was depression, which would most likely be related to the poor outcome of the patient as the disease progresses. This stresses the importance of postoperative followup of these patients in order to treat any other developing conditions.

**5.4. Limitations.** At present, there is a clear need for more conclusive results on the effects of DBS on impulsivity in patients with PD. The small number of patients in the original studies did not allow to reach statistical significance and two studies lacked a control group (PD + DA). Additionally, the studies had different follow-up periods in which ICDs may have been missed. Although similar eligibility criteria may have made the patients comparable, some of the exclusion criteria, including cognitive impairment, may have introduced a bias, since patients with ICDs are more likely to develop psychiatric comorbidities. Moreover, patients were lost to follow-up and most likely these patients had worse outcomes than the rest, further biasing the sample. The authors adopted different methodologies for the analysis of their results, thus making direct comparison impossible. Some studies had poor information regarding the patients' condition before DBS surgery, suggesting that some groups may have been different from the start. Finally, the patients who had ICDs at the baseline which was not recorded could have been more likely to choose to undergo DBS, thus introducing selection bias. To draw more accurate results, controlled longitudinal studies with baseline impulsivity measures and long-term follow-up should be conducted on large numbers of subjects undergoing DBS.

## 6. Conclusion

The results of this literature review show that existing data are ambivalent about the role of DBS on impulsivity in patients with PD. Several studies support the idea that DBS is an effective indirect treatment of ICDs, whilst other studies report the worsening or *ex novo* development of ICDs after surgery. Various pathophysiological mechanisms, including altered dopaminergic stimulation, have been proposed to explain both situations. The selection of patients for DBS should be extremely careful in order to avoid surgery on patients who are already predisposed to develop ICDs. Finally, since the patients are not likely to volunteer their symptoms, it is important to recognize ICDs both preoperatively and postoperatively, and to adopt a multidisciplinary team approach to diagnose and manage the patients accordingly.

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## Review Article

# Neuropathology and Neurochemistry of Nonmotor Symptoms in Parkinson's Disease

**Isidro Ferrer**

*Institut de Neuropatologia, Servei Anatomia Patològica, IDIBELL-Hospital Universitari de Bellvitge, Universitat de Barcelona, carrer Feixa L'Larga s/n, CIBERNED, 08907 Hospitalet de L'Lobregat, Spain*

Correspondence should be addressed to Isidro Ferrer, 8082ifa@gmail.com

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Parkinson disease (PD) is no longer considered a complex motor disorder characterized by Parkinsonism but rather a systemic disease with variegated non-motor deficits and neurological symptoms, including impaired olfaction, autonomic failure, cognitive impairment, and psychiatric symptoms. Many of these alterations appear before or in parallel with motor deficits and then worsen with disease progression. Although there is a close relation between motor symptoms and the presence of Lewy bodies (LBs) and neurites filled with abnormal  $\alpha$ -synuclein, other neurological alterations are independent of the amount of  $\alpha$ -synuclein inclusions in neurons and neurites, thereby indicating that different mechanisms probably converge in the degenerative process. Involvement of the cerebral cortex that may lead to altered behaviour and cognition are related to several convergent factors such as (a) abnormal  $\alpha$ -synuclein and other proteins at the synapses, rather than LBs and neurites, (b) impaired dopaminergic, noradrenergic, cholinergic and serotonergic cortical innervation, and (c) altered neuronal function resulting from reduced energy production and increased energy demands. These alterations appear at early stages of the disease and may precede by years the appearance of cell loss and cortical atrophy.

## 1. Introduction

Parkinson disease (PD) is clinically characterized by a complex motor disorder known as parkinsonism and is manifested principally by resting tremor, slowness of initial movement, rigidity, and general postural instability. These symptoms are mainly due to the loss of dopaminergic neurons in the substantia nigra pars compacta, leading to reduced dopaminergic input to the striatum and accompanied by adaptive responses in the internal and external globus pallidus, subthalamus, thalamus and substantia nigra pars reticularis. Round, hyaline neuronal cytoplasmic inclusions called Lewy bodies (LBs) and enlarged aberrant neurites and threads are found in the Parkinsonian substantia nigra [1, 2]. In addition to the substantia nigra, other nuclei are involved such as the locus ceruleus, reticular nuclei of the brain stem, and dorsal motor nucleus of the vagus, as well as the basal nucleus of Meynert, the amygdala and the CA2 area of the hippocampus. LBs and aberrant neurites are also found in these locations [1–7]. Similar lesions but extended

to the cerebral neocortex are characteristic of a closely-related disease named Dementia with Lewy bodies (DLB) [8]. PD and DLB are therefore considered Lewy body diseases (LBDs). Neuropathology and clinical aspects of DLB have been revised in detail elsewhere [9, 10].

LBs and neurites are composed of aggregates of normal, misfolded and truncated proteins, and ubiquitin, all of which are stored in the cytoplasm as nondegraded by-products of the degenerative process [11–14]. The main component of LBs and aberrant neurites is  $\alpha$ -synuclein which is abnormally phosphorylated, nitrated and oxidized, has an abnormal crystallographic structure and abnormal solubility, and is prone to the formation of aggregates and insoluble fibrils [15–23]. For this reason, LBDs are categorized as  $\alpha$ -synucleinopathies.

Mutations (A53T, A30P, E46K) in the  $\alpha$ -synuclein gene (*SNCA*; *PARK1*) are causative of autosomal dominant PD [24–26]. In addition, triplication or duplication of the  $\alpha$ -synuclein locus is associated with PD [27–30]. Together, these observations lay bare the crucial role of  $\alpha$ -synuclein

in the pathogenesis of a percentage of familial cases of PD. Recent studies have shown that methylation of the human *SNCA* intron 1 reduces gene expression, and inhibition of DNA methylation activates *SNCA* expression. Methylation of *SNCA* intron 1 is reduced in substantia nigra, putamen and cerebral cortex in PD, suggesting activation of *SNCA* in PD [31].  $\alpha$ -synuclein also appears to be regulated posttranscriptionally as two microRNAs, mir-7 and mir-153, which bind specifically to the 3'-untranslated region of  $\alpha$ -synuclein and downregulate its mRNA and protein levels [32]. The two microRNAs reduce endogenous expression of  $\alpha$ -synuclein [32, 33]. Whether variation in the miRNA-433 binding site of fibroblast growth factor 20 confers risk for PD by overexpression of  $\alpha$ -synuclein [34] requires further validation.

Mutations in other genes are also the origin of familial and, in some cases, sporadic PD. These include *parkin* (*PARK2*) [35], *DJ1* (*PARK7*) coding for Parkinson disease protein 7 [36], *PINK1* (*PARK6*) coding for PTEN-induced putative kinase 1 [37], *LRRK2* (*PARK8*) coding for leucine-rich repeat kinase 2 [38, 39] and *HTRA2* (*PARK13*) coding for HtrA serine peptidase 2: HtrA2 [40]. Another gene involved in familial PD is *UCHL1* (*PARK5*) coding for ubiquitin carboxyl-terminal hydrolase L1 [41]. A strong association between galactocerebrosidase mutations and PD has recently been reported [42]. Additional loci associated with autosomal or recessive PD have been described (see [43–45]). An important point is that not all familial cases with PD due to *parkin* and *LRRK2* mutations have LBs, although all of them have predominant degeneration of the substantia nigra pars compacta (see [46], for review). Therefore, PD cases due to *parkin* and *LRRK2* mutations without LBs cannot be considered as instances of LBD. Yet mutations in *PINK1* are associated with LB pathology similar to that seen in sporadic PD [47].

## 2. Stages of PD-Related Pathology

Systematic study of cases with LB pathology has prompted a staging classification of PD based on the putative progression of LB pathology from the medulla oblongata (and olfactory bulb) to the midbrain, diencephalic nuclei, and neocortex [48–50]). Stage 1 is characterized by LBs and neurites in the dorsal IX/X motor nuclei and/or intermediate reticular zone; there is also myenteric plexus involvement. Stage 2 affects the medulla oblongata and pontine tegmentum and covers pathology of stage 1 plus lesions in the caudal raphe nuclei, gigantocellular reticular nucleus, and ceruleus-subceruleus complex; the olfactory bulb is also involved. Stage 3 refers to pathology of stage 2 plus midbrain lesions, particularly in the pars compacta of the substantia nigra. Stage 4 includes basal prosencephalon and mesocortex pathology (cortical involvement confined to the transentorhinal region and allocortex, and CA2 plexus) in addition to lesions in the midbrain, pons and medulla oblongata. Stage 5 extends to sensory association areas of the neocortex and prefrontal neocortex. Stage 6 includes, in addition, lesions in first order sensory association areas of the neocortex and premotor areas; occasionally there are also mild

changes in primary sensory areas and the primary motor field.

Cases with Lewy pathology in the brain stem without clinical evidence of parkinsonism are considered premotor PD or incidental LBD [1, 2]. Risk factor profiles in incidental LBD and PD are similar thus further supporting the idea that iLBD represents preclinical PD, arrested PD or a partial syndrome [51].

Furthermore, several atypical cases have been reported, the majority of them not following a clear gradient of Lewy body pathology from the medulla oblongata to the neocortex. LBs in the amygdala are predominant or even unique in some cases, most of them related with Alzheimer's disease and Down syndrome. For this reason, amygdala-predominant LB disease has been categorized as a distinct entity [52]. Finally, a few cases have been reported with predominant cortical LB pathology and discrete numbers of LBs in the brain stem [53, 54]. Atypical cases constitute from five to ten percent of total LBD victims [55–58].

Cumulative clinical evidence reveals that olfactory dysfunction, dysautonomia, sleep fragmentation, rapid eye movement behaviour disorder, mood and anxiety disorders, and depression may precede parkinsonian symptoms in a number of patients with PD clinically characterized by parkinsonism [59–70]. Whether these clinical symptoms are associated with LBs in selected regions of the central, autonomous and peripheral nervous systems is a matter of study.

The neuropathological substrates of selected nonmotor symptoms in PD have been examined in previous reports [7] and will be reviewed in the following paragraphs.

## 3. Loss of Olfaction and the Olfactory Bulb and Tract in PD

$\alpha$ -synuclein pathology affecting neurons and neurites occurs in the olfactory bulb and related olfactory nuclei at very early stages of cases with PD-related pathology [50, 71–75]. It also occurs in cases of AD with amygdala-predominant LB pathology [76]. Double-labelling immunohistochemical studies have shown that dopamine- and somatostatin-positive cells are rarely affected, whereas mitral cells, calcium-binding protein- and substance-P-positive cells are vulnerable [77]. Olfactory bulb synucleinopathy has high specificity and sensitivity for Lewy body diseases, and it has been suggested that olfactory bulb biopsy might be considered to confirm diagnosis in PD [78], an indication not approved by others [79].

The number of intracytoplasmic and neuritic  $\alpha$ -synuclein inclusions in the olfactory bulb and tract is low in the majority of cases, thus suggesting that  $\alpha$ -synuclein aggregates as visualized in current histological preparations barely begin to explain the severity of olfactory decline. It may be hypothesized that as in other regions, olfactory alterations in PD are the result of more complicated settings resulting from several molecular deficits. Although no direct information is as yet available in PD, recent studies have yielded substantial data about the molecular pathology of the olfactory bulb.

Despite the relatively high content of glucose-6-phosphate dehydrogenase (G6PD), NADPH-cytochrome P450 oxidoreductase, glutathione reductase (GR) and NADPH-diphosphorase (NADPH-d) in the olfactory bulb of rodents [80], significant changes in carbonylation and nitration have been found in the olfactory bulbs of old mice [81]. Targets of oxidation in aged olfactory bulbs, as revealed by redox proteomics, are aldolase 1 and ferritin heavy chain [81]. The effects of aging on oxidative stress damage in the olfactory bulb have been further demonstrated in accelerated senescence-prone, short-lived (SAMP) mice when compared with accelerated senescence-resistant, longer lived (SAMR) strains [82]. Therefore, aging in the olfactory bulb is associated with increased oxidative stress and oxidative damage. Whether these modifications are augmented in PD is not known, but, needless to say, future work will help to increase our understanding of molecular alterations, other than those related to  $\alpha$ -synuclein, in the olfactory bulb and tract in PD.

A different approach has brought about interesting results. A series of PD patients underwent [(11C)methyl-4-piperidinyl propionate acetylcholinesterase brain PET emission tomography and olfactory testing with the University of Pennsylvania Smell Identification Test. The diagnosis of PD was confirmed by [(11C)dihydrotrabenazine vesicular monoamine transporter type 2 PET. Cholinergic denervation of the limbic archicortex was a more robust determinant of hyposmia than nigrostriatal dopaminergic denervation in subjects with moderately severe PD [83]. However, it is worth stressing that no apparent abnormalities in the cholinergic system appear to be present at stages 1 and 2 of Braak, and, therefore, cholinergic denervation of the limbic cortex is probably not the only factor accounting for olfactory disorder in early premotor stages of PD.

Disorders of olfaction also occur in familial PD but they appear to be more benign in certain familial cases, linked with LRRK2 or parkin mutations, than in sporadic PD [84, 85].

#### 4. Dysautonomia and Autonomic Nervous System in PD

Early studies demonstrated the presence of LBs in the parasympathetic ganglia, sympathetic ganglia, and enteric nervous system in PD [86, 87]. LBs are consistently found in the hypothalamus, sympathetic (intermediodorsal nucleus of the thoracic cord and sympathetic ganglia) and parasympathetic system (dorsal vagal and sacral parasympathetic nuclei, and peripheral parasympathetic ganglia), and enteric plexus [88–90]. Regarding central medullary autonomic areas, the number of catecholaminergic and serotonergic neurons is not significantly reduced in PD, although raphe neurons decline in number with disease progression [91]. Neuropathological studies in large cohorts of neurologically unimpaired aged individuals have shown that the autonomic nuclei of the spinal cord and the peripheral autonomic nervous system are affected early on by LB pathology [74, 92–94]. Finally,  $\alpha$ -synuclein-immunoreactive inclusions are seen in neurons of the Meissner's and Auerbach's plexuses

and in the corresponding axons projecting into the mucosa [56, 95].

Sensitive immunohistochemical methods to detect phosphorylated  $\alpha$ -synuclein have revealed multiorgan localization and gradient distribution of aberrant  $\alpha$ -synuclein deposits. The highest densities occurred in the spinal cord, paraspinal sympathetic ganglia, vagus nerve, gastrointestinal tract and endocrine organs. Within the gastrointestinal tract, the lower esophagus and the submandibular gland had higher numbers of inclusions than the colon and rectum [96].

The cardiovascular autonomic system is also affected in PD, and alterations implicate both tyrosine hydroxylase-positive (extrinsic) and negative (intrinsic) nerves of the cardiac plexus [76, 97]. Functional studies have also demonstrated cardiac involvement in PD. [123I] metaiodobenzylguanidine (MIBG) myocardial scintigraphy has shown reduced MIBG uptake in PD [98–102]. Importantly, decreased MIBG uptake precedes neuronal loss in the sympathetic ganglia [103–105]. Interestingly, accumulation of  $\alpha$ -synuclein aggregates occurs in the distal axons of the cardiac sympathetic nervous system preceding that of neuronal somata or neurites in the paravertebral sympathetic ganglia, thus indicating a centripetal degeneration of the cardiac sympathetic nerve in PD [105]. Olfactory tests, polysomnographic studies and MIBG myocardial scintigraphy in combination may be used to discover early signatures of the disease [106]. Interestingly, cardiac sympathetic denervation precedes nigrostriatal loss in individuals bearing the E46K mutation in SNCA [107].

These observations point to an association between synuclein deposits and impaired function in the autonomic nervous system. But this does not imply a causal relationship between these events. Several aspects are still elusive and require further study. (i) Autonomic symptoms are not always present in PD. (ii) LB pathology in autonomic peripheral ganglia and plexus is not always associated with clinical symptoms. (iii) Little is known about the nature and composition of LBs in peripheral autonomic nervous system. (iv) No data are available about molecular changes preceding, or associated with, early and late stages of LB pathology in the autonomic peripheral nervous system. (v) Little is known about the alterations other than the accumulation of abnormal  $\alpha$ -synuclein that might cause altered autonomic functions in DLBs.

#### 5. Sleep Disorders

Sleep disorders including sleep fragmentation, REM sleep behaviour disorders, and complex paroxysmal nocturnal motor behavioral disorders are common in PD [108–110], and they may precede by decades motor symptoms [111]. The neuropathological substrates are poorly understood although affected nuclei in the brain stem including the pedunculopontine nucleus probably play key roles [112]. The ventral visual stream appears involved in visuoperceptive alterations associated with REM disorders [113]. Finally, hypocretin (orexin) cell loss following an anterior to posterior gradient has been found in the hypothalamus of PD

cases with disease progression [114, 115]. This is not clearly accompanied by constant decrease in the expression levels of CSF orexin [116]. Whether orexin correlates with sleep attacks and its action is mediated by dopamine receptors 3 needs validation [117].

## 6. Cognitive Impairment and the Cerebral Cortex in PD

Changes in personality and moderate or mild cognitive debilitation are found in PD. Neuropsychiatric alterations and cognitive decline may occur at early stages of parkinsonism suggesting that they are an integral part of PD from the beginning of the disease in some patients. Characteristically, symptoms are often subtle at the beginning and difficult to detect without neuropsychological tests, although they become aggravated with progression of the disease. Deficits mainly affect executive function including working memory and visuospatial capacity. These are often accompanied by anxiety and depression, and excessive daytime sleepiness probably related with sleep disturbances (see [118, 119], for review).

Certain studies have shown an association between cortical LBs and cognitive impairment [120–123]. Yet other studies have not confirmed this assumption [57, 58, 124–127]. Moreover, associated AD pathology has been suggested as an important cofactor in the progression of cognitive impairment in PD [58]. Additional studies have not clarified a predictive role of LBs in the occurrence of cognitive deficits [128, 129] although LB pathology correlates with visual hallucinations when present in the medial temporal lobe and visual areas [130, 131]. Statistical analysis reveals that  $\alpha$ -synuclein aggregates in limbic regions are related to dementia in PD as well as to visual hallucinations when there is an underlying dementia [132].

Neuropathological studies in a large series have confirmed that staging of LB pathology is barely applicable to cognitive impairment and dementia. Only a percentage of cases showed a relationship between cortical LBs and cognitive impairment and dementia [127]. Taken together, these observations strongly indicate that cortical Lewy bodies are not *per se* causative of dementia, but rather indicators of aggregates of pathological synuclein. Other factors are probably more responsible of altered cognitive function in PD.

It must be stressed that tau phosphorylation and  $\alpha$ -synuclein phosphorylation are increased in synaptic-enriched fractions of frontal cortex homogenates in PD in the absence of LBs in the same tissue samples [133]. This indicates early  $\alpha$ -synuclein alterations at the synapse even in cases with no cognitive impairment [133]. Recent observations have further demonstrated the presence of small abnormal aggregates of  $\alpha$ -synuclein at the synapses [134, 135]. Therefore, abnormal aggregates at the synapses in greater numbers than large cytoplasmic and neuritic aggregates (LBs and aberrant neurites, resp.) may account for impaired function in PD. These are important independent observations showing that synaptic pathology occurs in the absence of LBs and that the most common alteration in the

cerebral cortex in PD is pathology at the synapses rather than the presence of LBs.

It is worth stressing that altered  $\alpha$ -synuclein may result in altered protein-protein interactions leading to altered synaptic function. Although these modifications are barely understood as yet, it is worth stressing that abnormal interactions have been reported between  $\alpha$ -synuclein and Rab3a, a protein involved in synaptic vesicle trafficking, Rab5, a protein involved in dopamine endocytosis, and Rab8, a protein engaged in transport [136]. Altered interactions have also been suggested between altered  $\alpha$ -synuclein and phospholipase C ( $PLC\beta 1$ ), a signalling downstream step of metabotropic glutamate receptors [137].

In other words, LBs *per se* have no direct impact on clinical symptoms but other more subtle abnormalities are causative of impaired cortical function. In addition to abnormal accumulation of altered proteins at the cortical synapses, a series of convergent approaches may help to increase understanding of the different factors leading to impaired cerebral function in PD. Some of them relate to impaired dopaminergic, noradrenergic, cholinergic and serotonergic innervation of the cerebral cortex; others, to intrinsic metabolic deficits.

Cognitive and executive deficits have been related, in part, to reduced dopaminergic innervation in the nigrostriatal and mesocortical dopaminergic systems compromising directly and indirectly, via alteration of the basal ganglia, prefrontal cortical function [138–142]. [18F] FDOPA uptake is reduced in frontal association areas in later stages of PD [143]. However, altered cognitive performance is not clearly related with impaired dopaminergic innervations of the cerebral cortex at early stages of the disease. PET studies with [11C] NNC112 and [18F] FDOPA have not shown significant associations between D(1) receptor density in the frontal cortex and performance at early stages of PD, in spite of a significant association between reduced [18F] FDOPA uptake in the putamen and poor performance in cognitive tests [144]. Along the same lines, attenuated dopamine release has been observed in the dorsal caudate but not in the medial prefrontal cortex in early PD patients [145].

Yet nondopaminergic systems are known to be damaged in PD, including the monoaminergic cells of the locus ceruleus, serotonergic neurons of the raphe and cholinergic neurons of the nucleus basalis of Meynert [146–149].

Cholinergic deficits have been postulated as causative of frontal dysfunction in PD [150, 151]. Recent studies have shown early alteration of the cholinergic innervation of the cerebral cortex in PD which increases in cases with dementia, thus correlating impaired cholinergic innervation and cognitive impairment [152–154].

In the same line, alteration of the serotonin transporter, as revealed by 123I-FP-CIT SPECT, has been observed in PD and with much more severe involvement in DLB, despite the comparable loss of striatal dopamine transporter [155].

Besides the loss of afferencies, primary impaired metabolism of the cerebral cortex may be causative of intrinsic cortical decay.

Cerebral glucose metabolism is reduced in the cerebral cortex in PD patients suffering from cognitive impairment

[156]. Limited, mainly posterior, blood flow reductions have been reported in PD cases with mild cognitive deficits assessed by rCB scintigraphic study using TC-HMPAO-SPECT [157]. Metabolic and neuroimaging observations have recently documented decreased prefrontal and parietal 18F-fluorodeoxyglucose uptake in PD cases with mild cognitive deficits [158, 159]. Parallel conclusions have been obtained using magnetic resonance; T1-weighted images and mean diffusivity and fractional anisotropy values are increased in the frontal cortex in PD [160, 161]. White matter hyperintensities are more frequent in PD cases with altered cognition than in cases with preserved cognitive functions [162]. Yet vascular abnormalities are very common in aged patients with PD [163], and we cannot rule out the possibility that white matter alterations are related to associate vascular/circulatory lesions rather than to primary lesions of PD.

A detailed discussion of molecular events leading to intrinsic cortical deficiencies is provided in the following paragraph.

## 7. Mitochondria and Energy Machinery Failure in the Cerebral Cortex in PD

Classical studies revealed abnormalities in complex I of the respiratory chain in the substantia nigra in sporadic PD (see [164], for review). More recently, several genes encoding proteins relevant to maintaining mitochondrial integrity have been shown to be causative of familial PD [165, 166]. These data further reinforce the role of mitochondria in the pathogenesis of PD. Interestingly, several mutant proteins associated with familial PD are linked to mitochondria [167]. DJ1 is localized in the mitochondria and modulates responses to oxidative stress [168, 169]. PINK1 is a protein kinase localized in the mitochondria in which mutations in the kinase domain are associated with mitochondrial deficits [170]. Furthermore, PINK1 is required for mitochondrial function as it interacts with and complements parkin [171–173]. LRRK2 is a kinase localized in the outer mitochondrial membrane [174]. Finally, HtrA2 is localized in the mitochondria and is involved in apoptosis [175]. Deficits in mitochondrial function have also been identified in patients with DJ1, parkin and PINK1 mutations [176]. Interaction of these different gene products seems necessary to maintain mitochondrial homeostasis [177–179]. Moreover, mutations in mitochondrial DNA have also been noted in familial parkinsonism due to PINK1 mutations [180].

These observations point to the possibility that mitochondrial dysfunction plays a crucial role not only in dopaminergic neurons of the substantia nigra but also in the whole brain. In this line, brain cortex and mitochondrial O<sub>2</sub> uptake and complex I activity are significantly lower in PD, whereas mitochondrial nitric oxide synthase activity, cytochrome content, expression of Mn-superoxide dismutase (SOD2), mitochondrial mass, and oxidative damage are significantly higher in the frontal cortex in PD. The decreases in tissue and mitochondrial O<sub>2</sub> uptake and in complex I activity are considered the consequences of mitochondrial oxidative damage in the cerebral cortex in PD [181, 182].

Moreover, subunits of mitochondrial complex I are oxidatively damaged, functionally impaired and misassembled in PD [183]. Finally, phosphorus and proton magnetic resonance spectroscopy confirm generalized mitochondrial dysfunction in PD [184]. It is not reckless to assume that loss of mitochondrial function is a primary cause of energy production decay.

Increased oxidative damage has also been detected in the frontal cortex, in addition to that reported several years ago in the substantia nigra, in PD [185]. Several key proteins are targets of oxidative damage in the frontal cortex even at very early stages of PD-related pathology, including  $\alpha$ -synuclein,  $\beta$ -synuclein and SOD2 [186, 187]. Other relevant proteins are also oxidatively damaged in PD: UCHL1, Cu, Zn-superoxide dismutase and DJ-1 [188–190]. In addition, increased oxidative damage of aldolase A, enolase 1 and glyceraldehyde dehydrogenase (GAPDH), all of them involved in glycolysis and energy metabolism, is found in the frontal cortex in premotor stages of PD and in established parkinsonian PD disease as well [191]. In the same line of generalized oxidative stress and stress responses is the observation of increased glutathione peroxidase, one of the main antioxidant enzymes inactivating hydrogen peroxide, in microglial cells of the gray matter and white matter in PD and DLB [192].

Recent observations have shown abnormal lipid composition in the frontal cortex at very early stages of PD-related pathology with significantly increased expression levels of the highly peroxidizable docosahexanoic acid (DHA) and increased peroxidability index [186]. Together, these features indicate that mitochondrial abnormalities, altered lipid composition and increased oxidative damage of proteins involved in the cytoskeleton, neurotransmission, mitochondrial function and energy metabolism occur at early, premotor stages of PD and persist with disease progression [193]. In the same line, recent observations have shown impaired lipid composition of lipid rafts with dramatic reductions in their contents of n-3 and n-6 LCPUFA, especially docosahexanoic acid (22:6-n3) and arachidonic acid (20:4n-6), and increased saturated fatty acids (16:0 and 18:0) when compared with control brains, thus leading to increased membrane viscosity and, probably, to increased energy demands [194].

The term “exhausted neuron” was employed in Alzheimer's disease to designate a combination of metabolic events leading to impaired and persistent energy production accompanied by increased energy demands that may be detected at very early stages of disease even in cases without overt clinical symptoms of cognitive impairment and dementia [195]. A similar scenario also occurs, albeit with different targets (different primary involvement of respiratory chain complexes, different lipoxidative and glycoxidative damage, different alteration of membrane lipid composition), in PD. It may be postulated that intrinsic exhaustion of neurons plays an important role in the subtle but inexorable progression of clinical symptoms once thresholds of neuronal tolerance cannot longer support energy demands.

Oxidative damage in cerebral cortex has also been reported in familial cases bearing the LRRK2 mutation in

TABLE 1: Convergence of altered metabolic events in the cerebral cortex in Parkinson disease.

<i>Altered cortical innervation</i>
(i) Dopamine (nigrostriatal and mesocortical pathways): indirect and direct pathways
(ii) Noradrenaline (locus ceruleus)
(iii) Serotonine (raphe nuclei)
(iv) Acetylcholine (nuclei of the basal forebrain)
<i>Synaptic pathology</i>
(i) Tau phosphorylation in synaptic fractions
(ii) $\alpha$ -synuclein phosphorylation in synaptic fractions
(iii) Small $\alpha$ -synuclein aggregates at the synapses
<i>Altered <math>\alpha</math>-synuclein and <math>\alpha</math>-synuclein interactions</i>
(i) Oxidation and phosphorylation of $\alpha$ -synuclein
(ii) Abnormal synuclein interactions with
(a) rab3a: possible altered synaptic traffic
(b) rab5: possible altered endocytosis
(c) rab8: possible altered transport
(d) PLC $\beta$ : altered mGluR1 signalling
<i>Altered mitochondria</i>
(i) Mitochondrial mass
(ii) Complex I of the respiratory chain
(iii) Mitochondrial O <sub>2</sub> uptake
(iv) Oxidative damage of subunits of mitochondrial complex I and DJ1
(v) (altered DJ1, PINK1, LRRK2, and Htr2 in familial PD)
<i>Increased oxidative damage</i>
(i) Lipoxidative and glycoxidative damage of proteins and oxidative damage of DNA
(ii) Oxidative damage of proteins linked with glycolysis and energy metabolism
(iii) Oxidative damage of superoxide dismutase 2
(iv) Oxidative damage of $\beta$ -synuclein, $\alpha$ -synuclein, cytoskeletal proteins and UCHL1
<i>Altered composition of membrane lipids in the grey matter</i>
(i) Total homogenates
(ii) Lipid rafts: viscosity
<i>Late, secondary events</i>
(i) Synaptic loss
(ii) Lewy bodies and neurites
(iii) Neuronal death

the absence of apparent cognitive impairment and in the absence of LBs in cerebral cortex [196]. This further supports the concept that the cerebral cortex is affected in PD independently of its being associated (or not) with the presence of LBs.

Altered metabolic events in the cerebral cortex in Parkinson disease are summarized in Table 1.

## 8. Psychiatric Symptoms and Neuropathological Correlates

Anhedonia, apathy, anxiety, panic attacks, social phobias and depression also occur in patients with PD even at early premotor stages and not related to medication [68, 197, 198]. Psychotic symptoms are frequent such as visual and auditory hallucinations, agitated confusion, vivid dreaming, delirium and delusions [199–203]. The molecular substrates of such alterations are scarcely known but several hypothesis have been proposed including imbalance between serotonergic and dopaminergic systems, cortical cholinergic deficiency and overstimulation of mesocorticolimbic dopamine receptors [201, 203–207]. Neuropathological studies have helped little to increase understanding of depression and psychoses although recent observations have suggested that depression is related more to catecholaminergic than serotonergic dysfunction [208], and that hallucinations correlate with the number of Lewy bodies in the temporal lobe, claustrum and visual cortex [130, 131].

Finally, an interesting and not fully understood paradigm is the consequence of alterations in amygdala in PD in spite of its constant involvement in classical PD and its almost unique alteration in amygdala-predominant LBD. The amygdala is activated in appetitive and emotional learning [209, 210]. Yet decreased responsiveness is found in the amygdala in PD in the face of fearful facial expressions, facial, prosodic and written verbal stimuli, and decision-making and facial emotion recognition [211–213]. Whether these modifications are the result of impaired dopaminergic regulation [214] or the consequence of primary pathology in the amygdala is not known.

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## Clinical Study

# Nonmotor Symptoms in Patients with *PARK2* Mutations

Asako Yoritaka,<sup>1</sup> Yumi Shimo,<sup>1</sup> Yasushi Shimo,<sup>1</sup> Yuichi Inoue,<sup>2</sup> Hiroyo Yoshino,<sup>1</sup>  
and Nobutaka Hattori<sup>1</sup>

<sup>1</sup> Department of Neurology, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan

<sup>2</sup> Japan Somnology Center, Neuropsychiatric Research Institute, 1-24-10 Yoyogi, Shibuya-ku, Tokyo 151-0053, Japan

Correspondence should be addressed to Asako Yoritaka, ayori@juntendo.ac.jp

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Decreased <sup>123</sup>I-meta-iodobenzylguanidine (MIBG) uptake in MIBG myocardial scintigraphy, olfactory dysfunction, and rapid eye movement (REM) sleep behavior disorder (RBD) are considered useful early indicators of Parkinson disease. We investigated whether patients with *PARK2* mutations exhibited myocardial sympathetic abnormalities using MIBG scintigraphy, olfactory dysfunction using the Sniffin' Sticks olfactory test, and RBD using polysomnography. None of the examined patients had RBD, and all except 1 patient exhibited an increase in the olfactory threshold. Moreover, one of the oldest patients exhibited impairment in identification and discrimination. Of 12 patients with *PARK2* mutations, 4 patients, who were older than patients without abnormal uptake, exhibited decreased MIBG uptake. The results obtained in this study suggest that some patients with *PARK2* mutations have increased thresholds of olfactory function and myocardial sympathetic dysfunction as nonmotor symptoms.

## 1. Introduction

Mutations in the *parkin* gene (*PARK2*) are considered to be the predominant cause of early-onset Parkinson disease particularly when the family history is compatible with autosomal recessive inheritance [1]. This condition is characterized by early onset of disease, usually before the age of 40 years, dystonia, sleep benefit, early complications from levodopa treatment, and slow progression. *Parkin*-associated tremor-dominant parkinsonism includes a spectrum of late-onset disorders without manifestations of foot dystonia, hyperreflexia, diurnal fluctuations, sleep benefit, or early susceptibility to levodopa-induced dyskinesia [2]. Therefore, patients with *PARK2* mutations are often clinically indistinguishable from those with sporadic Parkinson's disease (PD).

PD patients exhibit decreased myocardial uptake of meta-iodobenzylguanidine (MIBG) during <sup>123</sup>I-MIBG myocardial scintigraphy—a finding indicative of cardiac sympathetic denervation [3]. Olfactory impairment, an early symptom of PD, occurs in more than 70% of patients with PD [4]. Rapid eye movement (REM) sleep behavior disorder (RBD) is characterized by a loss of normal skeletal muscle atonia and complex motor activity, specifically during REM sleep associated with dream mentation. Thirty-eight percent

of RBD patients aged > 50 years were eventually diagnosed with PD [5]; therefore, RBD may serve as an early indicator of PD.

Here, we examined nonmotor symptoms in patients with *PARK2* mutations.

## 2. Methods

Mutation of the *parkin* gene was confirmed by gene analysis [1]. Eight women and 7 men possessed mutations in the *PARK2* gene: cases 1, 2, 3, 8, and 13 carried homozygous deletions, and the remaining carried heterozygous mutations or deletions (Table 1). Clinical findings and medications are shown in Table 1.

The MIBG study involved 6 women and 7 men (mean (SD) age, 58.5 (11.4) years) with *PARK2* mutations: 5 subjects had homozygous deletions, and 8 had heterozygous mutations or deletions. Patients had parkinsonism for a mean (SD) period of 22.0 (11.59) years (range, 10–44 years). When MIBG scintigraphy was performed, the patients were not medicated with monoamine oxidase B (MAOB) inhibitors, selective serotonin reuptake inhibitors, or antidepressant drugs. Data was collected by E CAM at 30 minutes and 3 hours after injection of <sup>123</sup>I-MIBG



(MyoMIBG-I 123 injection, 111 MBq; FUJIFILM RI Pharma Co. Ltd.). The cut-off ratio of the heart to mediastinum (H/M) uptake ratio of  $^{123}\text{I}$ -MIBG in our hospital was set at 1.45.

The olfactory function and polysomnography (PSG) study involved 3 women and 3 men (mean (SD) age, 47.8 (13.2) years) with *PARK2* mutations (Table 1).

The mean olfactory function scores of the PD patients and 10 age-matched Japanese controls, who were evaluated for comparison with patients with *PARK2* mutations, were determined by the Sniffin' Sticks test. Mean age of the controls without neurological disease or dementia was 46.0 (15.3) years (range, 39–79 years). The PD patients (mean age, 69.6 (6.6) years; range, 60–89 years; not age matched to patients with *PARK2* mutations) fulfilled the UK Brain Bank criteria for possible or probable clinical PD, with Hoehn-Yahr stages II and III without dementia.

Olfactory testing was examined by following 3 components. Olfactory threshold and odor discrimination and identification were investigated in 3 separate substrates using standardized Sniffin' Sticks [6]. Sniffin' Sticks are commercially available felt-tip pens.

**Odor Thresholds.** The olfactory threshold subset consisted of 16 Sniffin' Stick triplets with different concentrations of *n*-butanol. Three sticks were presented to the subject in randomized order. Two contained only the solvent and the third the odorant at a particular dilution. The subjects were tasked to identify the stick with the odorant.

**Odor Discrimination.** In the odor discrimination subset, 16 Sniffin' Stick triplets were presented in randomized order. Two pens contained the same odorant and the third a different odorant. The task was to identify the stick that had the different smell.

**Odor Identification.** The third subtest consisted of 16 single sticks and assessed the ability to identify an odor. Using a multiple-choice task, identification of individual odorants was performed from a list of 4 descriptors.

RBD was confirmed by studying the patients' clinical history and video-PSG findings (International Classification of Sleep Disorders, 2nd edition) [7].

Informed consent was obtained from patients with *PARK2* mutations, and patients with PD, and normal volunteers.

The data was statistically analyzed using SPSS ver.11 for Windows.

### 3. Results

The mean H/M uptake ratio of  $^{123}\text{I}$ -MIBG scintigraphy in *PARK2* patients was 1.79 (0.31) in the early phase and 1.75 (0.51) in the delayed phase (Table 2). However, a 58-year-old woman, with a 10-year disease duration and orthostatic hypotension and constipation without myocardial damage, exhibited accelerated MIBG elimination (H/M ratio: early,

1.23; delayed, 1.15). Three patients (cases 2, 7, and 12) had exhibited slightly decreased uptake in the delayed phase.

The Sniffin' Sticks test revealed a slight olfactory dysfunction with the following mean scores in examined *PARK2* patients (Table 3): threshold score, 6.1 (1.6) ( $P < .05$  when compared with controls); odor discrimination score, 10.0 (2.4); odor identification score, 10.1 (4.8) (no significant differences when compared to controls). Odor discrimination and identification functions were not impaired in any of the patients with *PARK2* mutations, except in patient 1. In the Japanese examined normative controls, the mean olfactory function scores were as follows: threshold score, 8.0 (1.3); discrimination score, 11.9 (2.4); identification score, 10.9 (2.0); in PD patients, these mean scores were 2.2 (6.6), 6.1 (2.5), and 5.1 (1.8), respectively.

PSG did not reveal tonic responses in the mentalis and tibialis muscles during REM (Table 3). Twitching of the tibialis muscle was observed in 2 patients. None of the patients with *PARK2* mutations met the ICSD-II criteria for RBD.

### 4. Discussion

Decreased  $^{123}\text{I}$ -MIBG uptake was observed clearly in 1 patient with *PARK2* mutations who had autonomic dysfunction. Early phase myocardial uptake of MIBG in all of the other patients showed no decrease, and patients had no autonomic dysfunction. Similar to our study, in a previous study [8], 1 of 4 patients with *PARK2* mutations with a 12-year disease duration and unclear autonomic dysfunction exhibited decreased uptake of  $^{123}\text{I}$ -MIBG. Additionally, 3 patients in our study who showed decreased  $^{123}\text{I}$ -MIBG uptake were slightly older than the other patients, although a significance in mean age (63.0 (9.1) versus 55.9 (10.8);  $P > .05$ ) did not exist. Estorch et al. and Tsuchimochi et al. reported that the uptake of  $^{123}\text{I}$ -MIBG decreased with age, suggesting that aging could affect patients with *PARK2* mutations [9, 10]. Decreased myocardial uptake of MIBG is considered to indicate the presence of alpha-synuclein aggregates in the axons in PD [11]. In MIBG-myocardial scintigraphy, the H/M ratio of patients with *PARK2* mutations was reported to be within the range of the normal controls [12]. Moreover, postmortem examination of patients with *PARK2* mutations revealed that tyrosine hydroxylase immunoreactive nerve fibers in the epicardium were well preserved [13]. These findings might reflect normal functioning myocardial sympathetic nerve terminals in patients with *PARK2* mutations. MIBG scintigraphy might be a marker for alpha-synuclein in patients with *PARK2* mutations; however, there are no pathological reports on the presence of Lewy bodies in patients with *PARK2* mutations exhibiting decreased MIBG uptake.

Olfactory impairment is a nonmotor symptom of PD. We found that the olfactory threshold was slightly higher in patients with *PARK2* mutations than in controls. The oldest woman in our study, who did not have dementia, exhibited the highest degree of olfactory impairment. Although in self-completed questionnaire study, 3 of 16 patients with *PARK2* mutation had loss of taste/smell [14]. However, in previous

TABLE 2: The findings of  $^{123}\text{I}$ MBG myocardial scintigraphy in PARK2 patients.

Case	1	2	3	5	7	8	9	10	11	12	13	14	Average $\pm$ SD
Examined age	65	55	46	41	76	70	63	61	61	60	57	44	58.3 $\pm$ 10.5
Early H/M	2.27	1.64	1.91	1.75	1.52	2.05	1.75	1.66	1.23	1.75	1.62	2.35	1.79 $\pm$ 0.31
Delay H/M	2.14	1.33	1.67	1.93	1.34	2.93	1.65	1.54	1.15	1.40	1.60	2.35	1.75 $\pm$ 0.51

H/M: the heart to mediastinum uptake ratio of  $^{123}\text{I}$ MBG.

TABLE 3: Olfactory function by Sniffin' sticks and PSG study in patients with PARK2 mutation, controls, and Parkinson's disease.

Case	1	2	3	4	5	6	PARK2 total (n = 6)	Control (n = 10)	Parkinson's disease (n = 15)
Age	71	55	46	41	38	36	47.8 $\pm$ 13.2	46.0 $\pm$ 15.3	69.6 $\pm$ 6.6
Sniffin' sticks Test									
Threshold test	4.5	6.3	6.3	5.8	5.0	9.0	6.1 $\pm$ 1.6	8.0 $\pm$ 1.3	2.2 $\pm$ 2.3
Discrimination test	8.0	9.0	12.0	14.0	9.0	8.0	10.0 $\pm$ 2.4	11.9 $\pm$ 2.4	6.1 $\pm$ 2.5
Identification test	1.0	13.0	10.0	14.0	13.0	10.0	10.1 $\pm$ 4.8	10.9 $\pm$ 2.0	5.1 $\pm$ 1.8
PSG findings									
Apnea index (times/H)	10.1	22.5	1.2	0.4	1.0	2.1			
Hypopnea index (times/H)	2.2	14.0	4.7	0.3	1.9	9.4			
Apnea Hypopnea index (times/H)	12.3	36.5	5.9	0.8	3.0	11.4			
Arousal index (times/H)	16.0	39.8	37.7	13.4	14.3	11.1			
Respiratory arousal index (times/H)	5.5	27.3	4.6	0.2	1.6	3.3			
PLM index(times/H)	7.8	0.0	7.7	0.0	29.5	0.0			
PLM arousal index(times/H)	0.0	0.0	5.3	0.0	2.8	0.0			
REM sleep twitching on TA muscle	-	+	-	+	-	-			

H/M: the heart to mediastinum uptake ratio, NE: not examined.

PLM: periodic limb movements, TA: tibialis anterior.

*t*-test: compared with PARK2 patients  $P < .05$ .

*t*-test: compared with PARK2 patients and control  $P < .01$ .

studies, individuals with PARK2 mutations were found to have normal olfactory function [15, 16]. The discrepancy between our results and previous ones may be because previous studies used the Pennsylvania Smell Identification Test, which does not include the threshold test. In Kahn's study [15], the odor identification score did not significantly differ between patients with PARK2 mutations and controls, although this did not necessarily imply that the threshold score was normal in the patients.

PSG did not reveal RBD in any of our patients. However, in a study by Kumru et al., 6 of 10 patients had RBD [17]. We cannot explain this discrepancy, but we hypothesize that it may be due to the differences in patient mean age between the 2 studies. Some of our patients with PARK2 mutations have twitching in the tibialis muscle; therefore, the possibility that they will eventually develop RBD cannot be ruled out. Neuropathological studies on patients with PARK2 mutations have revealed neuronal loss and gliosis in the pars compacta of the substantia nigra and in the locus coeruleus [18]. However, these studies have not described the state of the subcoeruleus nucleus, which is considered the primary site affected in RBD.

The results obtained in this study suggest that some patients with PARK2 mutations have increased thresholds of olfactory function and myocardial sympathetic dysfunction as nonmotor symptoms. We might show that the nonmotor symptoms of PARK2 were impaired heterogeneously.

### Author Contributions'

A. Yoritaka was responsible for conception, execution of research projects, statistical analysis, writing of first draft and review and critique; Yasushi Shimo was responsible for execution of research project; Yumi Shimo and Y. Inoue were responsible for execution of research project (PSG study); H. Yoshino was responsible for gene analysis; N. Hattori was responsible for conception and organization of research project.

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## Research Article

# Paired-Pulse Inhibition in the Auditory Cortex in Parkinson's Disease and Its Dependence on Clinical Characteristics of the Patients

Elena Lukhanina,<sup>1</sup> Natalia Berezetskaya,<sup>2</sup> and Irina Karaban<sup>2</sup>

<sup>1</sup> Department of Brain Physiology, Bogomoletz Institute of Physiology, 01024 Kiev, Ukraine

<sup>2</sup> Parkinson's Disease Treatment Centre, Institute of Gerontology, 04114 Kiev, Ukraine

Correspondence should be addressed to Elena Lukhanina, luh@biph.kiev.ua

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We aimed to determine the value of the paired-pulse inhibition (PPI) in the auditory cortex in patients with Parkinson's disease (PD) and analyze its dependence on clinical characteristics of the patients. The central (Cz) auditory evoked potentials were recorded in 58 patients with PD and 22 age-matched healthy subjects. PPI of the N1/P2 component was significantly ( $P < .001$ ) reduced for interstimulus intervals 500, 700, and 900 ms in patients with PD compared to control subjects. The value of PPI correlated negatively with the age of the PD patients ( $P < .05$ ), age of disease onset ( $P < .05$ ), body bradykinesia score ( $P < .01$ ), and positively with the Mini Mental State Examination (MMSE) cognitive score ( $P < .01$ ). Negative correlation between value of PPI and the age of the healthy subjects ( $P < .05$ ) was also observed. Thus, results show that cortical inhibitory processes are deficient in PD patients and that the brain's ability to carry out the postexcitatory inhibition is age-dependent.

## 1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder primarily related to pathology in the substantia nigra pars compacta dopaminergic neurons that results in the development of the brain dopamine deficit. The mechanisms and pathophysiology of this disease are not completely understood [1]. Although the cardinal features of the disease are movement disorders (rigidity, tremor, bradykinesia), the manifestations of PD also comprise a variety of diverse abnormalities including disturbance of sensory gating and cognitive decline [2–4].

It has been previously reported that disorders in PD largely occur due to the imbalance of inhibitory and excitatory processes in cortical and subcortical neuronal circuits [5–10]. A paired-pulse paradigm is usually used to study postexcitatory inhibition effect related to sensory gating mechanisms and synaptic processes in neurotransmitters release [11, 12]. There are two mechanisms that might explain paired-pulse inhibition (PPI) phenomena. The first

mechanism is the decrease in release probability of excitatory neurotransmitters from terminals of afferent axons [13–15]. This effect is likely the result of an inhibition of calcium influx through presynaptic receptors which play a causal role in the release of glutamate from synaptic vesicles on afferent stimulation [16]. Another possible mechanism of the decrement of the second response on paired stimulation is connected with synaptically released GABA from terminals of inhibitory interneurons [17–19]. As the paired-pulse facilitation, PPI is considered to be a form of a short-term synaptic plasticity [20, 21].

Several studies demonstrated a decreased postexcitatory inhibition of the midlatency (P 49) auditory evoked responses and median nerve somatosensory evoked potentials (P13–N18, P24–N31, P44–N75) on paired stimulation in patients with PD compared to healthy age-matched people [22, 23]. In the work of Perriol et al., the authors revealed a pronounced reduction of the prepulse inhibition of the N1/P2 component of auditory evoked potentials in PD and dementia with Lewy bodies [24]. In our previous study,

we showed reduction of the postexcitatory inhibition of the N1/P2 complex in the auditory cortex in patients with PD and positive effect of Levodopa administration on its value [25].

The aim of this study was to analyze the dependence of the PPI value of the N1/P2 component of auditory cortical evoked potentials on the clinical parameters of the PD patients: age, sex, disease duration, age at disease onset, Hoehn and Yahr stage, duration of the Levodopa intake, Levodopa dosage, and indices of motor and cognitive functions determined by using Unified Parkinson's Disease Rating Scale (UPDRS) and Mini Mental State Examination (MMSE).

## 2. Subjects and Methods

**2.1. Subjects and Study Conditions.** Studies were performed in two groups. The first group included 58 PD patients, with the severity of the disease corresponding to 1.5–3.0 of Hoehn and Yahr [26] scale (28 men and 30 women, mean  $\pm$  SE age  $61.5 \pm 1.1$ , range 45–74 years). The second group was control and had 22 age-matched healthy subjects (10 men and 12 women, mean  $\pm$  SE age  $61.4 \pm 1.2$ , range 48–73 years).

The study was approved in advance by the Ethical Committee of the Institute of Gerontology and was in accordance with the Helsinki declaration. The patients regularly underwent treatment at the Parkinson's Disease Centre of the Institute of Gerontology and gave written informed consent to participate in this study. The diagnosis of Parkinson's disease was determined according to the UK Bank Criteria [27]. The patients had from 2 to 22 year individual histories of idiopathic PD and were taking antiparkinsonian therapy at individual doses of 187.5–700 mg of Levodopa/Carbidopa daily. Besides Levodopa/Carbidopa, the patients were using other antiparkinsonian medication: Selegiline, Pramipexol, and Amantadine. The neurological status of PD patients was evaluated with UPDRS [28, 29] in the ON state one hour after Levodopa/Carbidopa intake. MMSE was used to study general cognitive status of the PD patients. The 53 (91%) individuals with PD did not show substantial dysfunctions in memory, attention, or orientation and the averaged value of the MMSE scores for whole group was relatively high ( $27.9 \pm 0.3$ ). Only 5 (9%) subjects had scores of 24 (i.e., a boundary index testifying to the doubtful signs of cognitive dysfunction). Table 1 represents the details of the PD patients' evaluation.

Auditory evoked potentials were recorded in the PD patients in their "OFF" state in the morning, after they were free from Levodopa treatment and other antiparkinsonian medications for at least 12 hours.

**2.2. Recordings.** The subjects were sitting comfortably in a semireclined armchair in a quiet room with closed eyes. Auditory evoked potentials were recorded at the vertex (Cz) referenced to a linked-ear electrode. The ground electrode was placed at the left wrist. The impedance of the electrodes was less than 10 k $\Omega$ . The electrode signal was amplified using a band pass filter (0.53–30 Hz), digitized with 200 Hz sampling rate, and stored for further analysis.

TABLE 1: Backgrounds of patients with Parkinson's disease.

Total No of patients	58
Men	28
Women	30
Age, years (Mean $\pm$ SE)	$61.5 \pm 1.1$ (45–74)
Duration of illness, years (Mean $\pm$ SE)	$7.6 \pm 0.7$ (2–22)
Hoehn and Yahr stage (No of cases)	
Stage 1.5	4
Stage 2.0	25
Stage 2.5	14
Stage 3.0	15
UPDRS scores (Mean $\pm$ SE)	$58.6 \pm 2.2$ (29–94)
MMSE scores (Mean $\pm$ SE)	$27.9 \pm 0.3$ (24–30)
Levodopa dosage, mg/day (Mean $\pm$ SE); 46 cases	$359.2 \pm 23.3$ (187.5–700)

Numerals in the parentheses represent data range. The Levodopa dosage in the table represents the dosage of Levodopa in Nacom (250 mg L-Dopa and 25 mg L-Carbidopa).

The pattern for double stimulation consisted of paired auditory clicks with 500, 700, and 900 ms interstimulus intervals (ISIs). The identical parameters (duration of 0.15 ms and intensity of 80 dB HL-hearing level) were used for the preceding conditioning click and following test click. Pairs of clicks were delivered once every 7 s for each ISI. Previous studies have shown that stimulation at faster frequencies can lead to a decrement in the cortical evoked potentials [30, 31]. A 2000–3000 ms electroencephalography (EEG) epoch was recorded for each trial, including a 300 ms prestimulus baseline. The recording time depended on ISIs. The epochs contaminated with blinks or other artifacts were excluded from the data and twenty acceptable artifact-free trials were averaged for each ISI and used for further analysis.

**2.3. Data Analysis.** In EEG recordings to paired stimulation, amplitudes of N1-P2 complex (peak to peak) in the first (A1) and the second (A2) responses were measured. The amplitudes of the components N1 and P2 were estimated in the 60–150 ms and 120–220 ms ranges of time, respectively. The percent PPI of the N1-P2 complex was calculated using the following formula:  $(A1 - A2)/A1 \cdot 100$ .

The results were analyzed statistically. Comparisons between PD patients and control groups were made using the nonparametric two-tailed Mann-Whitney criterion and ANOVA statistics. The nonparametric Spearman test was used to evaluate possible correlation between the value of PPI and characteristics of the investigated cohorts.

## 3. Results

**3.1. Exploration of the Postexcitatory Inhibition upon Paired Stimulation.** Results showed a significant difference in PPI of the N1/P2 component of auditory cortical evoked potentials in two investigated groups. In PD patients, the postexcitatory

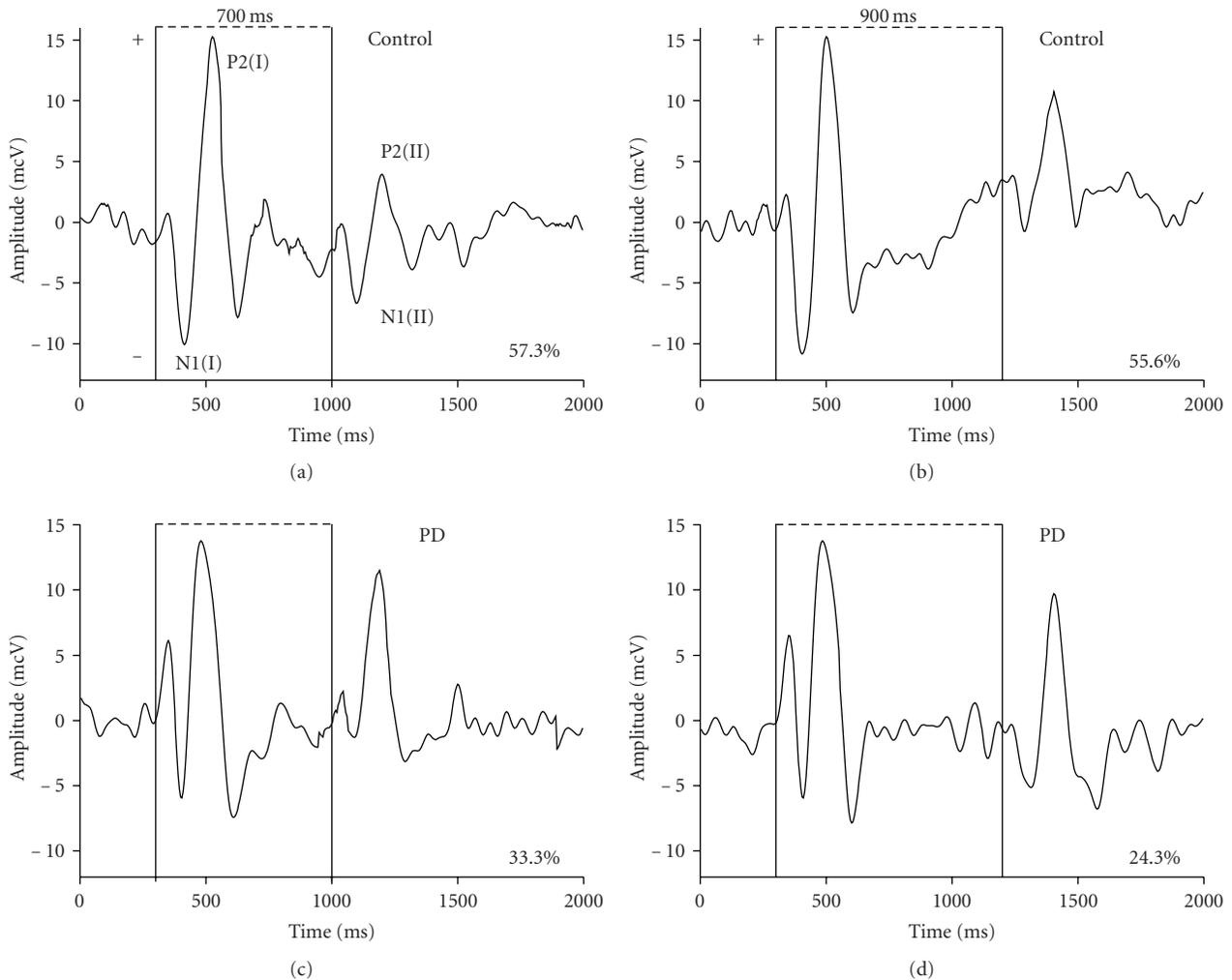


FIGURE 1: Cortical auditory evoked potentials at paired-pulse stimulation with interstimulus intervals 700 and 900 ms in the age-matched healthy subject and in the patient with Parkinson's disease (PD). N1 (I), P2 (I)—the components of evoked potentials on the first conditional and N1 (II), P2 (II)—on the second test stimuli. In the PD patient, the N1-P2 complexes appearing on second stimuli have greater amplitudes, hence the postexcitatory inhibition is reduced compared to control subject. Vertical solid bars correspond to the onset of auditory signals. Numerals in % represent value of paired-pulse inhibition calculated using the following formula:  $(A1 - A2)/A1 \times 100$  where A1 and A2 are amplitudes of the N1 (I)/ P2 (I) and N1 (II)/ P2 (II) components, respectively.

cortical inhibition was substantially reduced compared to control subjects for ISIs 500, 700, and 900 ms. Figure 1 demonstrates the native EEG recordings of the healthy age-matched control and of the patient with Parkinson's disease. The recordings clearly illustrate greater amplitudes of N1-P2 complexes following the second stimulus of a pair in the PD patient than in the control subject at ISIs of 700 and 900 ms. The mean values of PPI in the group of PD patients were decreased to  $29.8 \pm 4.8\%$  ( $P < .01$ ),  $25.4 \pm 3.2\%$  ( $P < .001$ ), and  $15.1 \pm 2.6\%$  ( $P < .001$ ) for intervals 500, 700, and 900 ms, respectively, as compared to these values ( $54.1 \pm 4.2\%$ ;  $49.8 \pm 2.3\%$  and  $42.9 \pm 2.7\%$ ) in the group of age-matched controls. It was observed that the postexcitatory cortical inhibition became statistically significantly affected on the stages of PD corresponding to 1.5–2.0 of Hoehn and Yahr [26] scale. Where PD was advanced, the reduction of inhibition was expressed even stronger (Table 2). The mean amplitude of

N1-P2 complex elicited by a single (first) auditory stimulus in the group of PD patients was  $16.2 \pm 0.8$  mcV which was less than in age-matched subjects ( $18.5 \pm 1.6$  mcV) but this difference was not statistically significant ( $P > .05$ ).

**3.2. Correlation Study.** Correlation analysis revealed negative connection ( $P < .05$ ) between the averaged value of the PPI (evaluated for ISIs of 500, 700 and 900 ms) and age of both healthy subjects (Figure 2) and PD patients (Table 3). In the group of PD patients, the negative correlation ( $P < .05$ ) between the PPI value and the age at the onset of the disease was also observed. It was further revealed that the reduction of cortical inhibition negatively affected the cognitive functions: lower values of PPI corresponded to decreased MMSE scores and vice versa. The degree of PPI correlated positively with the summary MMSE score ( $P < .01$ ) and with the score of attention plus memory

TABLE 2: Inhibition of the second N1-P2 complex of cortical auditory evoked potentials at paired-click stimulation in age-matched control group and patients with Parkinson's disease (Mean  $\pm$  SE).

Study groups	Inhibition in % of the second N1-P2 complex at interstimulus intervals			Averaged
	500 ms	700 ms	900 ms	
Age-matched control; $N = 22$	54.1 $\pm$ 4.2	49.8 $\pm$ 2.3	42.9 $\pm$ 2.7	48.0 $\pm$ 2, 1
PD patients with stage 1.5–2.0; $N = 29$	31.1 $\pm$ 6.6	27.2 $\pm$ 3.0	18.0 $\pm$ 3.3	24.1 $\pm$ 2, 3
PD patients with stage 2.5–3.0; $N = 29$	28.0 $\pm$ 5.7	23.9 $\pm$ 5.4	12.6 $\pm$ 4.0	19.3 $\pm$ 3, 1
All PD patients; $N = 58$	29.8 $\pm$ 4.8	25.4 $\pm$ 3.2	15.1 $\pm$ 2.6	21, 4 $\pm$ 2, 4

The inhibition was defined:  $(A1 - A2)/A1 \cdot 100$ , where A1 is amplitude of the first and A2 is amplitude of the second evoked potential upon paired-click auditory stimulation.  $P < .01$ ;  $P < .001$  compared to control subjects (ANOVA, Mann-Whitney U test).  $N$ :-number of subjects in the investigated groups.

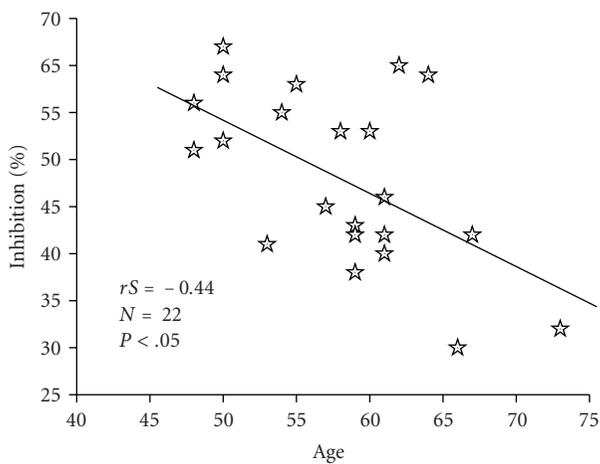


FIGURE 2: Correlation of the averaged value of the paired-pulse inhibition (evaluated for ISIs of 500, 700, and 900 ms) and age of the healthy age-matched subjects.  $rS$  is a coefficient of nonparametric Spearman rank-order correlation.  $N$ :-number of control subjects.

( $P < .001$ ). No significant relationship was observed between the PPI value and the summary UPDRS score. Only negative association ( $P < .01$ ) of the body bradykinesia score (point 31 of UPDRS) with the PPI value was observed. The scores of the other UPDRS subitems had no significant correlation with the PPI value. Levodopa dosage and duration of the Levodopa intake did not significantly influence the brain capacity for inhibition. We did not observe any significant correlation between the PPI value and sex, disease duration, or Hoehn and Yahr stage (Table 3).

#### 4. Discussion

The main result of this study showed that PD patients had significantly reduced PPI of the N1/P2 component of evoked potentials in the auditory cortex for ISIs 500, 700, and 900 ms compared to the healthy age-matched subjects. The degree of PPI correlated negatively with age of both control individuals

TABLE 3: Correlation coefficients between the averaged value of the paired-pulse inhibition (PPI) and the characteristics of the PD patients.

Characteristics of the PD patients	Averaged value of PPI (%) in patients ( $N = 58$ )
Age	- 0.29
Sex	0.13
Disease duration	- 0.04
Age of the onset of the disease	- 0.28
Hoehn and Yahr stage	- 0.15
Summary UPDRS score	- 0.14
Body bradykinesia score (point 31 of UPDRS)	- 0.35
Duration of the levodopa intake	0.10 ( $N = 46$ )
Levodopa dosage	0.28 ( $N = 46$ )
Summary MMSE score	0.40
Attention and memory score (points 3 plus 4 of MMSE)	0.43

Averaged value of PPI was evaluated for 500, 700, and 900 ms interstimulus intervals.  $N$ :-number of patients. Level of significance: is  $P < .05$ ; is  $P < .01$ ; is  $P < .001$  (nonparametric Spearman rank-order correlation).

and PD patients. In the group of PD patients, a positive correlation of the PPI value with the MMSE cognitive scores and a negative correlation with age of disease onset and body bradykinesia scores of the patients were observed.

Our results of decreased inhibition in the auditory cortex are consistent with the data on a reduced postexcitatory inhibition in the motor cortex in the patients with PD [6, 8–10, 12, 32, 33]. Decreased cortical inhibition is also in agreement with the data on a reduced postexcitatory inhibition of the midlatency auditory (P49) and somatosensory (P13–N18, P24–N31, P44–N75) evoked responses to paired stimulation in PD patients [22, 23]. These facts give us evidence that deficient inhibitory mechanisms may be specific not only for cortical but also for subcortical structures in PD.

PPI is usually considered to reflect presynaptic changes in transmitters release [13–15]. Inhibitory GABA-dependent properties are great contributor to PPI. As already established [34], afferent volleys after initial excitatory postsynaptic potentials (EPSPs) result in inhibitory postsynaptic potentials (IPSPs). A system of GABAergic interneurons, which can be activated by direct and indirect stimulations, may play the major role in the genesis of these IPSPs [34, 35]. The synaptic release of GABA is suggested to be mediated by presynaptic GABA receptors of the B-type [18, 36, 37]. There is also strong evidence that DA may regulate inhibitory transmission at the synapses between pyramidal cells and interneurons by activating D1-like receptors located on the presynaptic terminals of GABAergic axons [38, 39]. Calcium and sodium channels are potential DA targets [40, 41]. It is noteworthy that DA reveals regulation of both spontaneous and evoked GABA release in cortical neurons [39, 42].

Another possible explanation of the reduced inhibition in the auditory cortex in patients with PD may be the loss of dopaminergic transmission in the basal ganglia and the dysfunction of the caudal pallidum that sends its direct projections to the inferior colliculus, medial geniculate nucleus, and temporal cerebral cortex [43]. The basal ganglia appear to “gate” sensory inputs at various levels [44] and activation of basal ganglia outputs (entopeduncular nucleus and substantia nigra pars reticulata) is able to inhibit sensory responses [45].

The decreased inhibition of the second cerebral evoked response on paired or repetitive auditory and somatosensory stimulations also was shown in some other neurological and psychiatric diseases: in patients with Huntington's disease [46], with myoclonus [47], in schizophrenic subjects [48], and in Down's syndrome individuals [49]. Several researches presented convincing data demonstrating association between the deficit in inhibitory capacity and cognitive impairment [24, 50]. For example, in schizophrenics, decreased level of attention correlated with the increased ratio of the second to the first amplitude of the P50 auditory evoked response in a paired stimulus [50]. Recent studies that used a prepulse inhibition paradigm revealed a significant reduction of inhibitory processes in the auditory cortex in individuals suffering from PD dementia and dementia with Lewy bodies [24]. A prepulse inhibition paradigm is considered to reflect the state of attention control or ability to filter out repeated irrelevant sensory information [51, 52]. In line with the above-mentioned studies, our data about significant positive correlation of the PPI value in auditory cortex with summary MMSE score ( $rS = 0.40$ ,  $P < .01$ ) and attention plus memory score of MMSE ( $rS = 0.43$ ,  $P < .001$ ) provide additional evidence that a deficit of inhibition might contribute to cognitive disturbances in PD patients.

In the present study, along with a correlation between the degree of PPI and cognitive indices, we found a negative association of the body bradykinesia scores of the PD patients with PPI value ( $rS = -0.35$ ,  $P < .01$ ). This fact may be interpreted as evidence of the essential participation of the brain inhibitory processes in motor realizations that need sensory guidance, such as rapidity, amplitude of movements, and arm swings while walking (cheirokinesia).

Interestingly, a recent study which investigated possible associations between cognitive status and six different motor activities (facial expression, tremor, rigidity, bradykinesia, axial impairment, speech) found that only bradykinesia and speech significantly correlated with incident dementia in PD patients [53].

Our investigation showed that the degree of PPI in the auditory cortex correlated negatively with the age of both control individuals and PD patients. Age-related decrease in PPI was described earlier in motor cortex of healthy subjects during paired-pulse transcranial magnetic stimulation [54, 55]. Inhibitory processing deficit related with age was observed also in study of the cortical auditory evoked potential N2 in two groups of young and elderly participants [56]. Based on experimental researches, it is possible to suppose that this age-dependent decline of inhibition is due to a decrease of the density of GABAergic neurons and alteration of the GABA-receptors composition in the neocortex in aged subjects [57, 58]. Some researchers suggest that the age-related deficit of inhibitory function results in inability to suppress effectively the irrelevant information that causes cognitive impairment and deterioration in motor performance with advancing age [59, 60].

Our data showed negative connection ( $rS = -0.28$ ,  $P < .05$ ) between the PPI value and the age of PD onset. Perhaps, an important determinant of inhibitory dysfunction in PD is the combined effect of the natural aging process (senescence of cerebrum) and neurodegenerative changes, characteristic for this disease. Notably, several studies reported the relationship between the age of the disease onset and cognition, namely, older age at disease onset was associated with more marked cognitive decline in PD patients [61–63].

Recently, there have been a lot of discussions regarding the influence of Levodopa-containing preparations on cerebral functions. While one study proved the absence of negative influence of Levodopa-therapy [63], another revealed that Levodopa can worsen cerebral activity [64]. In this study, we did not find any significant dependence of PPI value on duration of the Levodopa intake and Levodopa dosage.

Overall, this study demonstrated that: (i) the PPI in response to paired auditory stimulation was significantly reduced in patients with PD compared to control subjects; (ii) the value of PPI in the auditory cortex correlated negatively with the age of both control individuals and PD patients; (iii) the value of the brain inhibitory function correlated positively with cognitive functions and negatively with age of the disease onset and body bradykinesia scores of the PD patients. We propose two possible mechanisms for the reduced postexcitatory cortical inhibition in PD: dopaminergic transmission deficiency in the basal ganglia and functional impairment of GABAergic cortical interneurons caused by lack of dopamine regulating influences through the depletion of dopaminergic innervation in the cerebral cortex. Our findings may suggest that preparations, being the derivatives of GABA, can be useful in medication of PD. Phenibut (Noofen) belongs to such preparations and it is able to activate cerebral inhibitory GABAergic system [65, 66]. Application of Noofen in complex therapy

of PD appeared effective for the improvement of cognitive functions, enhancement of emotional state, and increase of social adaptation of the PD patients [67].

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