

Neurobehavioral Disorders associated with Parkinson's Disease

Guest Editors: Gregory P. Crucian, Kenneth M. Heilman, Paul S. Foster,
and Daniel H. Jacobs





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Clinical Study

Neuropsychiatric Symptoms in Parkinson's Disease with Mild Cognitive Impairment and Dementia

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Neuropsychiatric symptoms commonly complicate Parkinson's disease (PD), however the presence of such symptoms in mild cognitive impairment (PD-MCI) specifically has not yet been well described. The objective of this study was to examine and compare the prevalence and profile of neuropsychiatric symptoms in patients with PD-MCI ($n = 48$) to those with PD and no cognitive impairment (PD-NC, $n = 54$) and to those with dementia in PD (PDD, $n = 25$). PD-MCI and PDD were defined using specific consensus criteria, and neuropsychiatric symptoms were assessed with the 12-item Neuropsychiatric Inventory (NPI). Self-rated apathy, depression, and anxiety rating scales were also administered. Over 79% of all participants reported at least one neuropsychiatric symptom in the past month. The proportion in each group who had total NPI scores of ≥ 4 ("clinically significant") was as follows: PD-NC, 64.8%; PD-MCI, 62%; PDD 76%. Apathy was reported in almost 50% of those with PD-MCI and PDD, and it was an important neuropsychiatric symptom differentiating PD-MCI from PD-NC. Psychosis (hallucinations and delusions) increased from 12.9% in PD-NC group; 16.7% in PD-MCI group; and 48% in PDD group. Identifying neuropsychiatric symptoms in PD-MCI may have implications for ascertaining conversion to dementia in PD.

1. Introduction

In Parkinson's disease (PD), cognitive impairment and the development of dementia (PDD) are increasingly being considered part of the disease course. Mild cognitive impairment in PD (PD-MCI) occurs in about 25% of patients and may predict conversion to PDD [1, 2]. Formal diagnostic criteria for PD-MCI have recently been proposed by the Movement Disorder Society (MDS) Task Force [3]. Risk factors for the development of PD-MCI include older age at disease onset, male gender, depression, severity of motor symptoms, and advanced disease stage [4].

According to the MDS Task Force proposal, PD-MCI is a syndrome defined by three sets of criteria: clinical, cognitive and functional. The proposed cognitive criteria comprise

two levels of assessment. Level I involves an abbreviated assessment using a global scale of cognition or limited neuropsychological test batteries for a diagnosis of "possible PD-MCI." Level II involves more extensive neuropsychological testing using tests in five domains, with impairment on at least two tests in one or more domains for a diagnosis of PD-MCI subtypes. The domains are attention and working memory, executive dysfunction, language, memory, and visuospatial function. PD-MCI predominantly affects the memory, visual-spatial, and attention/executive domains, with the most common subtype being "non-amnesic single domain" MCI [3].

Since PD-MCI is a newly defined entity, extensive studies examining the clinical features, associated factors, prognosis, and response to interventions have not yet been undertaken.

In particular, the psychiatric and behavioural symptoms of PD-MCI defined in this way are not yet well understood. The MDS Task Force report specifically points out that although psychiatric complications such as psychosis or apathy have been associated with PDD, “there is insufficient evidence to recommend that the presence of these symptoms strongly supports a diagnosis of PD-MCI.” Greater understanding of PD-MCI is critical in order to determine the impact of this entity on patients and caregivers and whether or not these non-cognitive aspects of PD-MCI are risk factors for conversion to PDD.

Neuropsychiatric symptoms form part of the constellation of non-motor symptoms in PD which has a significant impact on the quality of life of PD patients, as well as caregiver burden and distress [5–8]. The most common neuropsychiatric symptoms in PD, regardless of cognitive status, are depression and hallucinations [5]. However, the frequency of these and other neuropsychiatric symptoms in PD patients with MCI is not known. A population-based study of 824 people *without* PD revealed that the prevalence of these symptoms in those with MCI is as high as 43%, with 29% having “clinically significant” symptoms [9]. Neuropsychiatric symptoms are more prevalent in older people who meet criteria for MCI compared to those who have cognitive impairment that have not yet met MCI criteria [10].

Compared with PD patients without dementia, those with PDD have a much greater prevalence (up to 89%) of at least one neuropsychiatric symptom, and 77% have two or more neuropsychiatric symptoms [11]. In a study that examined clusters of neuropsychiatric symptoms and cognitive status in PD, it was found that PDD was most commonly represented in the cluster characterised by hallucinations (79.3% had PDD), mixed neuropsychiatric symptoms (57.1% had PDD), and mild depression (31% had PDD) [12]. The lowest PDD representation within a cluster was in the sleep disturbances group (7.1% had PDD). Patients in the hallucination cluster also tended to have longer disease duration, more severe motor symptoms, and older age. Another cluster analysis, this time in PD patients without dementia, revealed clustering into five sub-groups: apathy, psychosis, depression, anxiety, and “low total neuropsychiatric symptoms.” Patients with “low total neuropsychiatric symptoms” had more preserved cognitive function [11].

It is important to assess the prevalence, profile, and magnitude of neuropsychiatric symptoms in PD-MCI since it is likely that the majority of PD-MCI sufferers are still functionally unimpaired, in active employment and may be suffering under an added burden of behavioural symptoms. Furthermore, neuropsychiatric symptoms may have prognostic implications and may be a risk factor for conversion to PDD amongst those who fall within the PD-MCI group. The aim of this present study was to (1) compare the frequency, magnitude and profile of neuropsychiatric symptoms in PD with intact cognition, PD-MCI, and PDD and (2) to explore the relationship of neuropsychiatric symptoms in these groups with their motor and cognitive profiles. We hypothesised that there would be an increase in

the frequency and magnitude of neuropsychiatric symptoms as cognition declined across the groups in a pattern of PD without cognitive impairment (PD-NC) < PD-MCI < PDD. Furthermore, we hypothesised that the core psychiatric syndromes of apathy and psychosis would be more frequent and of greater magnitude as cognitive impairment developed.

2. Methods

This study was approved by a regional ethics committee, and all participants and their informants gave informed consent. For participants with cognitive impairment in whom the capacity to consent may have been in doubt, caregivers were asked to sign an additional “assent” form.

2.1. Participants and Classification of Cognitive Groups. Participants ($n = 127$) with idiopathic PD, diagnosed according to UK Brain Bank criteria, were consecutively recruited from community-based PD clinics in the North West of England as part of two clinical research protocols [13]. Of these, the data for the participants with a diagnosis of PDD ($n = 25$) were part of a randomised-controlled clinical trial of memantine, and data for the current study were taken from the baseline assessments [14]. The participants without dementia (PD-NC, $n = 54$; PD-MCI, $n = 48$) were recruited as part of the current descriptive study. In all cases, the screening evaluation, involving a neurologic and mental state exam, cognitive screen, and informant interview for collateral information, was undertaken to determine whether criteria for probable PDD were met [15]. All assessments were done during the “on” motor state. Participants’ medication for the motor aspects of PD remained unchanged for at least four weeks prior to and during the study, and no participants were taking anticholinergic medications at the time of the assessment.

The criteria for PDD were according to the MDS Task Force criteria for PDD and operationalised according to the diagnostic algorithm outlined by Dubois et al. (2007) [15, 16]. Briefly, this involved the following: (1) onset of cognitive impairment after the onset of motor symptoms; (2) decreased global cognitive efficiency as evidenced by a Mini-Mental State Exam [17] (MMSE; score of <26); (3) functional impairment due to cognitive deficits, determined by caregiver reports; (4) deficits in more than one cognitive domain (attention, executive function, visuospatial functioning, memory, and language).

The syndrome of PD-MCI ($n = 48$) was identified in those who did not meet PDD criteria, had a MMSE score of ≥ 26 , and who met the proposed inclusion and exclusion criteria for this category according to the MDS Task Force [3]. Briefly, this involved (1) gradual cognitive decline reported by the patient, clinician, or caregiver; (2) cognitive deficits on at least two tests of a formal neuropsychological battery with deficits defined as at least 1.5 SD more impaired than the mean scores for an age- and gender-matched healthy control group; (3) cognitive deficits not severe enough to significantly interfere with functional ability or activities of daily living as determined by caregiver or patient report.

TABLE 1: Pragmatic neuropsychological test battery and cognitive domains administered to the PD participants without dementia.

Cognitive domain	Neuropsychological test
Attention and working memory	Trail Making Test A and B [18] Serial 7's; Digit n -back [19] ⁱ "FAS" verbal fluency task [20]
Executive dysfunction	WCST ⁱⁱ [21] Digit n -back
Memory	5-minute recall of 3 words
Visuospatial function	Intersecting pentagons

ⁱThe digit n -back evaluates working memory, which comprises both attentional and executive components of short-term memory. This task has been used in PD (e.g., [22]). ⁱⁱComputerised version of the Wisconsin Card Sorting Test.

The specific neuropsychological battery chosen was a short, pragmatic battery that was tolerated by the participant group in the context of a wider study involving further assessments. The test battery comprised four of the five MDS Task Force recommended domains (Table 1), including three tests of attention and working memory, three tests of executive dysfunction, one test of memory, and one test of visuospatial function. This is consistent with Level 1 of the PD-MCI criteria which precluded the definition of specific PD-MCI subtypes.

The remaining participants were classified as PD-NC ($n = 54$). Premorbid intellect was assessed using the National Adult Reading Test (NART) and no significant differences were found between groups [23]. Each participant had a caregiver or informant who knew them well, had contact at least once a week, and could provide information on the participant's behaviour. Finally, in order to establish the norms on the cognitive battery, from which to derive the PD-MCI criteria, a healthy control group ($n = 33$) was recruited from non-caregiver acquaintances of the PD participants. This group was age-, culture-, education- and gender-matched to those with PD. All participants in this group were free of significant medical problems. They were assessed using the same battery as outlined in Table 1.

2.2. Assessment. The Unified Parkinson's Disease Rating Scale part III was used to assess motor severity, and stage of disease was categorised according to the Hoehn-Yahr scale [24, 25]. In the two groups without dementia, levodopa daily equivalent dose (LEDD) was calculated according to a recommended formula for total dopaminergic replacement as well as for dopamine agonists only [26].

Neuropsychiatric symptoms were assessed using the 12-item Neuropsychiatric Inventory (NPI) according to published procedures [27]. The NPI is a validated informant-rated scale which assesses 12 domains of behavioural disturbance including delusions, hallucinations, agitation/aggression, dysphoria/depression, anxiety, apathy, euphoria, disinhibition, irritability/lability, aberrant motor behaviour, appetite, and sleep disturbances. Each domain is rated on presence and magnitude of symptoms (frequency \times

severity). The maximum score per domain is 12, with clinically significant symptoms for a given domain occurring at (frequency \times severity) scores ≥ 4 . Total NPI scores range from 0 to 144, with higher scores indicating greater behavioural disturbance. The NPI has been extensively used in PD and has been shown to be valid in PD populations both with and without dementia [5, 11].

Since caregiver ratings may be influenced by such factors as stress, depression, and burden in the caregiver, we included two self-rated scales for the assessment of psychopathology in the PD-NC and PD-MCI groups. These scales were the Hospital Anxiety and Depression Rating Scale (HADS) and the Apathy Scale [28, 29]. They were not administered to the PDD group because both scales depend upon the ability of the participant to be able to report on their own symptoms and are therefore less valid once dementia emerges [30, 31]. Since apathy was hypothesised as being a core psychiatric syndrome that might differentiate PD-NC from PD-MCI, it was further assessed in the two groups without dementia using the Apathy Inventory (AI). The AI, which is an informant-rated scale, is scored in a similar manner to the NPI (i.e., frequency \times severity) and assesses three dissociable dimensions of apathy: emotional blunting, lack of initiative, and lack of interest [32]. Data for the AI were not available for the PDD group.

2.3. Statistical Analysis. Analysis was performed using SPSS version 16 [33]. Initial univariate analysis comparing proportions among the three groups was undertaken using the chi-square (χ^2) test, and comparison of group differences was undertaken using either ANOVA (with *post hoc* Bonferroni two-group comparisons) or the Kruskal-Wallis (with *post hoc* Mann-Whitney U comparison) tests, depending on the distribution of the data. ANCOVA was used to control for confounding variables, where appropriate. Bivariate correlations (Pearson or Spearman) were also performed to explore associations of neuropsychiatric symptoms with demographic, motor, and cognitive variables.

3. Results

3.1. Sample Characteristics. The majority of participants in each group was male, and the mean (SD) age across the entire group was 65.40 (11.16) years. The mean (SD) education level was 12.81 (2.80) years of formal education. The mean (SD) duration of PD was 93.77 (64.10) months, and mean MMSE was 26.72 (4.71), range (10–30). The median Hoehn and Yahr stage was 2.50 (interquartile range 2-3).

Demographic and clinical characteristics of the three groups are outlined in Table 2. The mean age at time of assessment and at onset of motor symptoms differed significantly across the three groups in the order of PD-NC < PD-MCI < PDD. However, duration of disease did not differ among the groups and all participants were between Hoehn-Yahr stages 2-3. Motor severity, as measured by the UPDRS part III, was worse in the PD-MCI group compared to the other two groups, which did not differ from each other. The PDD group had significantly fewer complications of therapy,

TABLE 2: Demographics and clinical characteristics of PD participants by group: without cognitive impairment, mild cognitive impairment, and dementia.

	PD No cognitive impairment (PD-NC; <i>n</i> = 54)	PD Mild cognitive impairment (PD-MCI; <i>n</i> = 48)	PD dementia (PDD; <i>n</i> = 25)	Statistic (<i>F</i> or χ^2); <i>P</i> value
	Mean (SD) or <i>n</i> (%)			
Demographics				
Age (years)	58.11 (9.87)	68.63 (8.39)	75.58 (7.47)	23.30; <0.001 ^{a,b,c}
Male gender <i>n</i> (%)	38 (71.7)	34 (70.83)	13 (52.0)	3.05; 0.22
Married <i>n</i> (%)	40 (75.5)	40 (83.3)	14 (56.0)	0.65; 0.42
In active employment <i>n</i> (%)	14 (25.9)	3 (6.2)	0 (0)	136.38; <0.001
Disease characteristics				
Age of PD onset (years)	50.62 (9.81)	60.02 (11.56)	66.68 (10.95)	21.35; <0.001 ^{a,b,c}
Duration of PD (months)	87.74 (47.57)	103.66 (79.84)	86.85 (60.94)	0.92; 0.40
UPDRS ⁱ motor score	25.33 (12.36)	31.26 (10.61)	24.12 (9.89)	4.69; 0.01 ^{a,b}
UPDRS complications of therapy	3.70 (3.25)	3.66 (3.37)	0.42 (1.25)	11.26; <0.001 ^{b,c}
LEDD ⁱⁱ	759.90 (537.85)	852.48 (625.56)	Not obtained	0.63; 0.43
LEDD-DA ⁱⁱⁱ	208.81 (174.85)	67.95 (110.99)	Not obtained	22.11; <0.001
Hoehn-Yahr staging	2.04 (0.65)	2.28 (0.65)	3.40 (0.80)	23.39; <0.001 ^{b,c}
MMSE ^{iv}	29.30 (0.82)	27.64 (1.90)	19.36 (5.96)	102.74; <0.001 ^{a,b,c}
Pre-morid IQ (NART ^v)	113.48 (9.84)	112.1 (11.77)	110.45 (7.98)	0.18; 0.84

ⁱUnified Parkinson's Disease Rating Scale; ⁱⁱtotal daily dopaminergic load based on levodopa equivalents or "levodopa equivalent daily dose" (LEDD); ⁱⁱⁱLEDD-DA: levodopa equivalent daily dose-dopamine agonist only; ^{iv}Mini-Mental State Exam; ^vNational Adult Reading Test [28].

Post hoc bonferroni for two group comparison, *P* < 0.05: ^aPD-NC versus PD-MCI; ^bPD-MCI versus PDD; ^cPD-NC versus PDD.

as measured by the UPDRS part IV, compared to both groups without dementia. None of the PDD group participants was in active employment at the time of the study. Dopaminergic replacement load (calculated as levodopa equivalent daily dose, LEDD) did not significantly differ between the two groups without dementia. However, LEDD for dopamine agonists only was significantly lower in the PD-MCI group compared to the PD-NC group.

Cognitive measures for the two PD groups without dementia as well as the healthy control group are shown in Table 3. For all cognitive tests across the four domains, the PD-MCI scores were significantly worse than both the PD-NC group and the healthy control group, which did not significantly differ from each other. The proportion of those in the PD-MCI group who were impaired in each of the specific domains was as follows (in ascending order): memory, 29%; attention and working memory, 37%; visuospatial function, 58%; executive function ("FAS" test and computerised Wisconsin Card Sorting Test), 60.4%.

3.2. Comparison of Neuropsychiatric Symptoms in the Three PD Groups

3.2.1. Informant-Rated. At least one neuropsychiatric symptom on the NPI was reported by 97 (77.9%) of the 127 participants. The most common neuropsychiatric symptoms were sleep disturbances (53.1%), anxiety (40.6%), dysphoria/depression (38.3%), apathy (35.2%), irritability/labidity

(25%), hallucinations (16.4%), and agitation/aggression (12.5%). The remaining NPI domains were present in less than 10% of the sample. The most commonly reported "clinically significant" neuropsychiatric symptoms (NPI domain score ≥ 4) were sleep disturbances (37.5%), apathy (25.8%), anxiety (10.9%), and dysphoria/depression (9.4%). The remaining NPI domains were "clinically significant" in less than 10% of the sample. The mean (SD) total NPI score across the entire sample was 11.61 (12.44).

Table 4 outlines the mean neuropsychiatric symptom scores (frequency \times severity) in each NPI domain for the three groups, which were not significantly different. For the individual NPI behavioural domains, the key differences between groups were driven by the PDD group having significantly worse mean scores compared to both the PD-NC and PD-MCI groups in the domains of delusions, aberrant motor behavior, and disorders of appetite. Hallucinations were significantly worse in the PDD group compared to the PD-NC group only. The only significant difference in any of the NPI behavioural domains between the PD-NC and PD-MCI groups was apathy. This difference was also reflected in the differences in the more detailed caregiver-rated Apathy Inventory (AI). On the AI, two of the three subdomains ("lack of interest" and "lack of initiative") were significantly greater in the PD-MCI group compared to the PD-NC group and the subdomain of "emotional blunting" reached a trend towards significance.

In both the PD-NC and the PD-MCI groups, the domains with the greatest magnitude (frequency \times severity)

TABLE 3: Neuropsychological test scores for the PD groups without cognitive impairment and with mild cognitive impairment, and the healthy control group.

	PD No cognitive impairment (PD-NC; $n = 54$)	PD Mild cognitive impairment (PD-MC; $n = 48$)	Healthy control (HC; $n = 33$)	Statistic (F or χ^2); P value
	Mean (SD)			
Attention and working memory				
Trails B-Trails A (reaction time in seconds)	41.55 (17.41)	136.68 (71.30)	41.27 (26.23)	85.32; <0.001
Serial 7's	4.65 (0.59)	3.78 (1.40)	5.09 (0.52)	20.65; <0.001
Digit n -back	17.76 (3.24)	13.48 (2.76)	19.68 (3.09)	43.89; <0.001
Executive function				
cWCST total ⁱⁱ	39.04 (7.41)	32.32 (9.47)	40.82 (8.63)	11.55; <0.001
FAS total	47.89 (12.41)	34.06 (10.40)	52.71 (12.09)	26.84; <0.001
Memory				
5-minute recall of three words	2.72 (0.49)	2.20 (1.03)	2.78 (0.78)	7.62; 0.001
Visuospatial function				
Intersecting pentagons	0.98 (0.14)	0.40 (0.49)	1.00 (0)	71.95; <0.001

ⁱⁱ cWCST: Computerised version of the Wisconsin Card Sorting Test.

were sleep, apathy, and anxiety. In the PDD group, the highest magnitude NPI domains were apathy followed by sleep, then irritability, depression, and anxiety. In the two groups without dementia, the majority of domains had mean magnitude scores <1.0 (not clinically significant), whereas in the PDD group, only three of the 12 domains (disinhibition, elation, agitation/aggression) had mean scores <1.0.

In the PD-NC group, 39 (72.2%) participants reported at least one neuropsychiatric symptom compared to 38 (79.2%) in the PD-MCI and 24 (96%) in the PDD groups ($\chi^2 = 6.32$; $P = 0.04$; PD-NC *versus* PDD, $P = 0.01$). Those with total NPI scores of ≥ 4 ("clinically significant") were as follows: PD-NC, 64.8%; PD-MCI, 62%; PDD, 76% ($\chi^2=4.48$; $P = 0.10$). Table 5 shows the proportion of patients in each of the three groups who endorsed "any" or "clinically significant" (NPI ≥ 4) symptoms in each of the NPI domains. The most commonly reported psychiatric symptoms (reported in over 20% of participants and excluding sleep and appetite) in each of the three groups was as follows: (1) PD-NC, anxiety, dysphoria/depression and irritability/lability; (2) PD-MCI, apathy, anxiety and dysphoria/depression; (3) PDD, dysphoria/depression, apathy, irritability/lability, anxiety, agitation/aggression, hallucinations, delusions and aberrant motor behaviour. The only neuropsychiatric symptom which differed significantly in frequency between PD-MCI and PD-NC was apathy, which was reported almost as frequently in PDD as in PD-MCI (52% and 48% resp.). Of all those reporting "any" apathy (entire PD sample), 60% also reported any "any" depression. However, once clinically significant apathy only was considered (NPI apathy ≤ 4), the proportion of those also reporting clinically significant depression (NPI dysphoria/depression ≤ 4) as well decreased to 11.8%. Sleep problems were reported in >40% in all three groups with the two groups without dementia endorsing this

domain most frequently (55% in PD-NC and 58% in PD-MCI). In contrast, appetite problems were reported in <10% in the two groups without dementia but were endorsed by 20% (16% were "clinically significant") of the PDD group.

In contrast to the PD-MCI group, those with PDD endorsed neuropsychiatric symptoms in several domains significantly more frequently compared to the two groups without dementia. These domains were delusions, agitation/aggression, dysphoria/depression, irritability/lability, and aberrant motor behaviour. The proportions reporting apathy and hallucinations were significantly different between the PDD and PD-NC groups only. It was notable that psychosis (the presence of any hallucinations, delusions, or both) increased markedly with the extent of cognitive impairment: 12.9% in the PD-NC group, 16.7% in the PD-MCI group, and 48% in the PDD group ($\chi^2 = 14.26$; $P = 0.001$). Finally, over 30% of each of the two groups without dementia endorsed the domains of anxiety and depression. For the PDD group, these figures increased to 48% and 56% for the two domains, respectively.

3.2.2. Self-Rated. As shown in Table 4, self-rated anxiety (HADS-A) did not differ significantly among the two PD groups without dementia and the healthy control group. However, in the PD-MCI group, both self-rated depression (HADS-D) and self-rated apathy (AS) were significantly worse compared to both the PD-NC and the healthy control groups. Furthermore, the PD-NC group was also significantly more depressed than the healthy control group. Since the PD-MCI group was significantly older, had worse motor function and had a lower dopamine agonist load compared to the PD-NC group, ANCOVA was performed for the self-rated depression and apathy scores with these variables as

TABLE 4: Mean domain scores (*frequency* × *severity*) of the neuropsychiatric inventory items, apathy ratings, and self-rated depression and anxiety.

Psychiatric measure	PD	PD	PD dementia (PDD; <i>n</i> = 25)	Statistic (<i>F</i> or <i>t</i>); <i>P</i> value
	No cognitive impairment (PD-NC; <i>n</i> = 54)	Mild cognitive impairment (PD-MCI; <i>n</i> = 48)		
Informant-rated scales:		Mean (SD)		
Neuropsychiatric Inventory (NPI) total and domain subscores				
NPI total score	9.53 (13.03)	12.38 (12.55)	14.56 (10.50)	1.55; 0.22
Delusions	0.19 (0.99)	0.15 (0.88)	1.08 (1.93)	5.68; 0.004 ^{b,c}
Hallucinations	0.21 (0.70)	0.40 (1.35)	1.00 (1.97)	3.17; 0.045 ^c
Agitation/aggression	0.33 (1.25)	0.34 (1.78)	0.84 (1.67)	1.06; 0.35
Dysphoria/depression	0.92 (1.67)	1.02 (1.91)	1.52 (1.80)	0.99; 0.37
Anxiety	1.04 (1.41)	1.21 (2.07)	1.36 (2.81)	0.23; 0.79
Elation	0.25 (0.96)	0.26 (1.75)	0.12 (0.60)	0.11; 0.89
Apathy	1.01 (2.62)	3.79 (4.91)	2.8 (3.87)	6.43; 0.002 ^a
Disinhibition	0.15 (0.87)	0.13 (0.88)	0.24 (0.72)	0.15; 0.86
Irritability/lability	0.71 (2.00)	0.70 (2.19)	1.52 (2.33)	1.44; 0.24
Aberrant motor behaviour	0.25 (1.67)	0.13 (0.88)	1.20 (2.53)	3.77; 0.03 ^{b,c}
Sleep	3.29 (3.75)	3.91 (4.08)	2.16 (3.39)	1.73; 0.18
Appetite	0.27 (1.03)	0.06 (0.44)	1.28 (3.05)	5.40; 0.006 ^{b,c}
Apathy Inventory (AI)				
AI ^{vi} total score	3.57 (7.61)	8.67 (11.77)	NA	6.05; 0.02
AI, emotional blunting	0.91 (2.11)	2.18 (4.03)	NA	3.54; 0.06
AI, lack of initiative	1.24 (3.01)	3.24 (4.50)	NA	6.28; 0.02
AI, lack of interest	1.41 (3.07)	3.24 (4.31)	NA	5.48; 0.02
Psychiatric measure	PD	PD	Healthy controls (HC; <i>n</i> = 33)	Statistic (<i>F</i> ; <i>P</i> value)
	No cognitive impairment (PD-NC; <i>n</i> = 54)	Mild cognitive impairment (PD-MCI; <i>n</i> = 48)		
Self-rated scales:		Mean (SD)		
HADS ^{vii} -anxiety subscore	6.15 (4.61)	6.24 (4.10)	4.50 (2.74)	2.10; 0.27
HADS-depression subscore	4.92 (3.67)	7.12 (3.50)	2.78 (2.59)	12.56; <0.001 ^{a,d,e}
Apathy Scale	7.94 (8.54)	17.62 (11.92)	9.87 (5.09)	10.17; <0.001 ^{a,e}

^{vi}Apathy Inventory (AI); ^{vii}Hospital Anxiety and Depression Scale.

Post hoc bonferroni for two group comparison, $P < 0.05$: ^aPD-NC versus PD-MCI; ^bPD-MCI versus PDD; ^cPD-NC versus PDD; ^dPD-NC versus HC; ^ePD-MCI versus HC.

covariates. This revealed that the initial differences seen between the two groups remained significant for both depression ($F = 4.81$; $P = 0.001$) and apathy ($F = 9.33$; $P < 0.001$).

3.3. Correlation of Neuropsychiatric Symptoms with Other Key Variables. In the entire study group, significant correlations were seen between neuropsychiatric symptoms (represented by NPI total) and the following variables: duration of disease ($\rho = 0.20$; $P = 0.03$), Hoehn-Yahr stage ($\rho = 0.23$; $P = 0.01$) and MMSE score ($\rho = -0.20$; $P = 0.02$). Significant

correlations were not seen between this variable and age, LEDD, age of disease onset, and motor severity (UPDRS motor and complications of therapy subscores). As shown in Table 6, psychosis (NPI delusions or hallucinations) also correlated with disease staging, MMSE, duration of disease, and age. Both self-rated apathy (in those without dementia) and informant-rated apathy (in the entire study sample) had several significant correlations, including markers of advanced disease (disease stage, MMSE, and motor severity), as well as dopamine agonist load (LEDD-dopamine agonist only), age, and age of disease onset (see Table 6). Finally, as is

TABLE 5: Proportion of Neuropsychiatric Inventory (NPI) domains endorsed by the three PD groups.

NPI sub-scores	PD No cognitive impairment (PD-NC; <i>n</i> = 54)		PD Mild cognitive impairment (PD-MCI; <i>n</i> = 48)		PD dementia (PDD; <i>n</i> = 25)		Statistic (χ^2 ; <i>P</i> -value)	
	% Any* $\geq 4^{**}$ Any ≥ 4 Any ≥ 4						Any ≥ 4	
	Any*	$\geq 4^{**}$	Any	≥ 4	Any	≥ 4	Any	≥ 4
Delusions	3.7	3.7	4	2	28.0	12.0	28.40; <0.001 ^{b,c}	10.08; 0.07
Hallucinations	11.1	1.9	14.0	4.0	32.0	12.0	37.21; <0.001 ^c	18.2; 0.003 ^c
Agitation/aggression	7.4	3.7	6.0	2	36.0	8.0	32.47; <0.001 ^{b,c}	6.38; 0.23
Dysphoria/depression	33.3	9.3	36.0	6.0	56.0	20.0	48.92; <0.001 ^{b,c}	15.07; 0.01 ^a
Anxiety	42.6	11.1	36.0	12.0	48.0	12.0	43.62; <0.001 ^{b,c}	9.19; 0.10
Euphoria	7.4	3.7	2.0	2.0	4.0	0.0	8.84; 0.12	8.53; 0.13
Apathy	16.7	11.1	48	38	52.0	36.0	50.99; <0.001 ^{a,c}	37.43; <0.001 ^{a,c}
Disinhibition	3.7	1.9	2	2	12.0	0.0	9.10; 0.11	4.79; 0.44
Irritability/lability	22.2	9.3	14.0	4.0	52.0	16.0	44.65; <0.001 ^{b,c}	11.75; 0.04 ^c
Aberrant motor behaviours	5.6	3.7	0	0	24.0	16.0	23.18; <0.001 ^{b,c}	15.49; 0.01 ^c
Sleep	55.6	37.0	58.0	42.0	40.0	32.0	44.04; <0.001	52.93; <0.001 ^b
Appetite	7.4	1.9	2.0	0	20.0	16.0	15.85; 0.003 ^c	12.9; 0.01 ^c

* Indicates any Neuropsychiatric Inventory (NPI) symptoms >0; ** indicates NPI score of ≥ 4 .

Post hoc bonferroni for two group comparison, $P < 0.05$: ^aPD-NC versus PD-MCI; ^bPD-MCI versus PDD; ^cPD-NC versus PDD.

TABLE 6: Correlations between behavioural scores and key demographic, disease, and cognitive variables.

Demographic and disease variables	Self-rated (participants without dementia; <i>n</i> = 102)	Informant-rated (all participants; <i>n</i> = 127)	
	Apathy Scale	NPI ^{viii} -apathy	NPI-psycho- sis (hallucinations or delusions)
	ρ ; <i>P</i> value		
Age	0.39; 0.001	0.31; 0.001	0.19; 0.04
LEDD ⁱⁱ	0.01; 0.92	0.07; 0.52	0.07; 0.49
LEDD-DA ⁱⁱⁱ	-0.38; <0.001	-0.33; 0.001	0.07; 0.47
Age of onset	0.30; 0.003	-0.21; 0.02	0.05; 0.61
Duration of illness	0.01; 0.89	0.13; 0.15	0.25; 0.006
Hoehn-Yahr	0.33; 0.001	0.25; 0.006	0.21; 0.02
UPDRS ⁱ motor	0.33; 0.001	0.22; 0.02	0.02; 0.83
UPDRS complication	0.28; 0.93	-0.12; 0.19	-0.08; 0.39
MMSE ^{iv}	-0.41; <0.001	-0.21; 0.02	0.27; 0.003
Self-rated scales in the participants without dementia (<i>n</i> = 102)			
	Apathy Scale	HADS ^{vi} -depression	HADS -anxiety
	ρ ; <i>P</i> value		
Trails B-Trails A (reaction time in seconds)	0.23; 0.03	-0.19; 0.07	-0.12; 0.30
Serial 7's	-0.27; 0.007	-0.08; 0.40	0.01; 0.88
Digit <i>n</i> -back	-0.29; 0.007	-0.23; 0.03	0.08; 0.45
cWCST ^x	-0.27; 0.01	-0.16; 0.12	0.08; 0.42
FAS ^{ix} total	-0.23; 0.03	-0.20; 0.04	0.18; 0.08
5-min recall of three words	-0.21; 0.04	-0.14; 0.18	0.00; 1.00
Intersecting pentagons	-0.25; 0.02	-0.12; 0.20	0.07; 0.37

ⁱUnified Parkinson's Disease Rating Scale; ^xcomputerised version of the Wisconsin Card Sorting Test; ⁱⁱtotal daily dopaminergic load based on levodopa equivalents or "levodopa equivalent daily dose"; ⁱⁱⁱlevodopa equivalent daily dose-dopamine agonist only; ^{iv}Mini-Mental State Exam; ^{vi}HADS: Hospital Anxiety and Depression Rating Scale; ^{viii}Neuropsychiatric Inventory; ^{ix}verbal fluency FAS test.

also shown in Table 6, in the participants without dementia, self-rated apathy was shown to have significant correlations with all the cognitive measures, whereas self-rated depression correlated with working memory (digit n -back) and verbal fluency (FAS) only. In contrast, self-rated anxiety did not correlate significantly with any of the cognitive measures.

4. Discussion

To our knowledge this is the first study to specifically examine neuropsychiatric symptoms in MCI related to PD identified using the new specific MDS Task Force criteria. This is a group of PD patients who have cognitive impairment but functional impairment not severe enough to warrant a diagnosis of dementia. They may, nonetheless, have non-motor symptoms that impact significantly on quality of life and other aspects of functioning. An understanding of the clinical correlates, particularly the neuropsychiatric correlates, of PD-MCI is crucial because this clinical entity has prognostic implications and may predict conversion to dementia. In addition, by examining non-motor manifestations such as neuropsychiatric symptoms, it may be possible to intervene and delay the conversion to dementia. In this study, we hypothesised that there would be an increase in the frequency and magnitude of neuropsychiatric symptoms as cognition declined across the groups from PD without cognitive impairment to PDD. Our findings only partially supported this presentation. Rather, aside from apathy and self-rated depression, the two groups without dementia appeared quite similar with regards to neuropsychiatric symptoms. In contrast, the PDD group was distinguished from both comparator groups by a greater proportion of neuropsychiatric symptoms (both presence of “any” symptom and “clinically significant” symptoms) across several domains as well as a higher magnitude and frequency of psychosis (delusions and hallucinations) and aberrant motor behaviour. Only apathy was as frequent in the PD-MCI as in the psychiatrically more vulnerable PDD group.

The finding that the frequency and magnitude of neuropsychiatric symptoms were similar in the PD-NC and PD-MCI groups diverges from the pattern that has been described for neuropsychiatric symptoms in MCI in the general population. In this case, the prevalence of neuropsychiatric symptoms was midway between the prevalence in healthy control participants and in those with dementia [9]. These findings were felt to support the notion that MCI was a precursor to dementia, as may be the case in PD. According to evidence building from longitudinal studies in PD, MCI is likely to be a precursor to dementia. Based on the findings in our study, it may be possible to identify conversion from PD-MCI to PDD with the emergence of significant neuropsychiatric symptoms. The profile of symptoms in our PDD sample was similar to previously reported PDD samples however we did not examine “clusters” of symptoms but instead examined individual NPI domains.

It is noteworthy that apathy was the key neuropsychiatric feature distinguishing the two groups without dementia, and

it was evident on both informant- and self-rated scales. This suggests that the apathy syndrome is closely linked to cognitive impairment and may even be a harbinger of conversion to dementia, a finding that has previously been observed. For example, a recent longitudinal study of a PD cohort without dementia found that after a median period of 18 months, the proportion of those who converted to dementia was significantly higher in those with apathy [34]. Moreover, in those who did not develop dementia, cognitive decline was still greater in the apathy sufferers. In our study, the correlation between apathy and all the cognitive measures tested supports the notion of a very tight link between these factors.

In PD populations without dementia, apathy has been associated with older age, older age of disease onset, psychiatric complications, greater global cognitive impairment, and lower dopamine agonist load as well as depression [35]. In our sample, apathy was also associated with all these factors as well as dopamine agonist load and motor severity, even though the UPDRS motor score in the PDD group was lower than in the PD-MCI group. The lower severity score may reflect the loss of tremor that has been associated with the onset of dementia in PDD [36]. Since age, age of onset and cognitive impairment all increased across the groups from PD-NC to PDD, the emergence of apathy might be accounted for by these factors rather than the presence of the “MCI” status *per se*. Nonetheless, the differences in apathy between the PD-NC and the PD-MCI group remained significant even after controlling for possible confounding factors such as age and motor severity. Finally, the difference in dopamine agonist load between the PD-NC and PD-MCI groups needs to be considered as a possible factor in the appearance of apathy in those with MCI. Dopamine and dopamine agonists may have a role in reward and motivation processing, and it is possible that with the emergence of cognitive impairment and more advanced disease in the PD-MCI group, dopamine agonists were prescribed more sparingly, which may have contributed to the emergence of apathy [37, 38]. In addition, identifying apathy in those with PD without dementia is important, due to the impact apathy has on level of disability and caregiver burden [5, 6, 8].

The increased level of self-rated depression in the PD-MCI group was also of considerable interest. It is possible that as cognitive changes start to appear, particularly the point of PD-MCI, symptoms of depression are seen as well. This was supported by the positive correlations between depression ratings and measures of executive dysfunction (working memory and verbal fluency). An overlap between depression and apathy was also seen; however, as apathy severity increased, the proportion who also reported comorbid depression decreased. This suggested the emergence of a “purer” form of apathy. The association of apathy with depression in PD is complex and there are studies which have shown a significant level of discrepancy between apathy and depression. For example, a longitudinal study of 65 patients with Alzheimer disease found that apathy and depression had different natural histories which are possible to discriminate [39]. On another note, the high rates of both anxiety and

depression in the two groups without dementia should also be considered. This finding corroborates evidence from an Australian survey of patients with PD without dementia, where the occurrence of anxiety disorders was found to be 25% [40].

Our study demonstrates that the profile of neuropsychiatric symptoms differed in those with PDD compared to those without dementia. In particular, a greater number of specific neuropsychiatric symptoms were reported by over a quarter of those with PDD compared to the other two groups. Moreover, the symptoms of psychosis (hallucinations and delusions) emerged as clinically significant and frequent. Psychosis was associated with markers of advanced disease (longer disease duration, later disease stage, lower MMSE) as well as increasing age. This pattern supports previous findings in which psychotic symptoms increased linearly with degree of cognitive impairment when comparing PD without cognitive impairment to PDD [41]. Both psychosis and significant cognitive impairment in PD have been associated with cholinergic deficits and may be improved with the use of cholinesterase inhibitors [42, 43].

Limitations to the current study were that the sample size was relatively small and that the participants were consecutively drawn from a convenience sample in community clinics, rather than using strict epidemiologic methods. Furthermore, we examined neuropsychiatric symptoms as single domains whereas studies using cluster analysis have demonstrated that groups of neuropsychiatric symptoms are linked. Further investigation of such clusters in PD-MCI might prove fruitful [12]. Another limitation was that the neuropsychiatric tool used in this study (the NPI) is informant-rated and may therefore be subject to bias due to caregiver factors such as distress, fatigue, and depression. In addition, the current methods did not enable us to specifically determine whether or not our findings in relation to the neuropsychiatric symptoms were due to cognitive state, rather than other factors such as stage of disease or differences in age. However, this is less likely since disease duration did not differ among groups. Finally, our neuropsychological battery was designed to be short and pragmatic, and the tests chosen in each domain, particularly the memory domain, were restricted and did not enable us to subtype the PD-MCI group. Nonetheless, the battery was still able to fulfil the MDS Task Force Level I criteria for PD-MCI and may reflect findings in a clinical setting where more extensive and time-consuming test batteries are not practicable or tolerated.

In conclusion, this study found that neuropsychiatric symptoms are increasingly prevalent with increasing levels of cognitive impairment in PD, particularly as dementia emerges. Identifying PD-MCI as a clinical entity and estimating neuropsychiatric symptoms, particularly apathy, in this group can aid in understanding the risk for conversion to dementia. To our knowledge, this is the first study to specifically examine the prevalence and magnitude of such symptoms in a group of PD participants identified as PD-MCI. A deeper understanding of these symptoms may guard against a "hypercognitive" definition of PD-MCI.

Conflict of Interest

The authors have no conflict of interest to declare.

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Research Article

The Anticholinesterase Phenserine and Its Enantiomer Posiphen as 5' Untranslated-Region-Directed Translation Blockers of the Parkinson's Alpha Synuclein Expression

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There is compelling support for limiting expression of alpha-synuclein (α -syn) in the brains of Parkinson's disease (PD) patients. An increase of SNCA gene copy number can genetically cause familial PD where increased dose of this pathogenic protein correlates with severity of symptoms (triplication of the SNCA gene causes dementia in PD patients). Gene promoter polymorphisms were shown to increase α -synuclein expression as a risk for PD. Cholinesterase inhibitors can clinically slow cognitive decline in the later stages of PD etiology similar to their widespread use in Alzheimer's disease (AD). Pertinent to this, we identified that the well-tolerated anticholinesterase, phenserine, blocked neural SNCA mRNA translation and tested for targeting via its 5' untranslated region (5' UTR) in a manner similar to its action to limit the expression of the AD-specific amyloid precursor protein (APP). Posiphen, its better-tolerated (+) enantiomer (devoid of anticholinesterase action), repressed neural α -synuclein translation. Primary metabolic analogs of posiphen were, likewise, characterized using primary fetal neurons grown *ex vivo* from the brains of Parkinson's transgenic mice expressing the human SNCA gene.

1. Introduction

Parkinson disease (PD) is a slowly progressive neurodegenerative disease affecting up to 3% of the population over the age of 65 years. Clinically, it is characterized by a set of motor symptoms and nonmotor symptoms that can include dementia. Motor symptoms include rigidity, postural instability, bradykinesia, and resting tremor [1, 2]. The core pathological feature correlating with most of these motor symptoms is a loss of dopaminergic neurons from the substantia nigra pars compacta (SNc). Pathological inclusions, known as Lewy bodies, are found within some of the remaining dopaminergic neurons [3]. The destruction of the dopaminergic neurons at onset is at least 70% and, at the end

stage of the disease the loss of dopamine (DA) neurons, can exceed 95% [3]. Therapy for the symptoms of PD is based primarily on replacement of dopaminergic function and can be remarkably effective in alleviating motor symptoms for a number of years [1, 4]. Additional nonmotor symptoms can be present and include depression, anxiety, sensory abnormalities, anosmia, sleep, and autonomic disorders, in addition to dementia [1, 5–8].

Particular nonmotor symptoms, like sleep disturbances [9], loss of smell [6, 10], and depression, can occur well before the presence of detectable motor symptoms [5]. The presence of psychotic symptoms, which can affect up to 40% of the patients, is often associated with anti-parkinsonian

treatment and is dose dependent [2, 7]. By contrast, the neuropsychiatric symptoms of PD, like depression and dementia, are more common at the later stages of the disease [6, 8, 11, 12]. These neuropsychiatric symptoms may be correlated directly to the progression of PD itself as in PD dementia or PDD, to the presence of Dementia with Lewy Bodies (DLB) or to the presence of comorbidities like Alzheimer's Disease (PD/AD) [2]. The incidence of dementia in PD is six times higher than in age-matched controls; in all forms of dementia associated with PD, the use of cholinesterase inhibitors may be beneficial [2, 13–17].

The etiology of PD is still elusive [18]. A variety of genetic factors have been linked to the etiology of familial PD [19]. The first was the protein alpha-synuclein (α -syn), an abundant brain protein that appears to be involved in vesicle trafficking and participates in the regulation of DA release [20]. The first reports to implicate α -syn in PD described mutations in the protein, which cause autosomal dominant forms of the disease [21, 22]. Subsequent studies revealed that such mutations were exceedingly rare but also that aggregates of α -syn could be found in all cases of familial and sporadic PD [23]. It is important to recognize that the genetic mechanisms identified to date are individually rare and, collectively, represent only a small fraction of the cases of PD observed by practitioners. This hence leaves the vast majority of PD unexplained at present.

Events associated with the inflammatory cascade [24] as well as with iron metabolism [25, 26] and translational control of gene expression have been modeled to be associated with PD and LBD [27]. There are also reported examples of disrupted signaling events such as occurring in response to inflammation cytokines: for example, mutations to the signaling kinase LRRK-2 may activate inflammatory events in this neurodegenerative disease [24, 28], perhaps affecting novel signalling pathways [24]. Certainly, increased iron in the individual dopaminergic neurons of the substantia nigra (SN) has been reported to be closely associated with the pathogenesis of PD [29], and antioxidants have been tested as a means to alleviate the severity of PD [30]. DLB brains exhibit lowered *SNCA* mRNA but higher insoluble protein, suggesting misregulation of *SNCA* mRNA translation additional to its clearance by chaperones [31], although reduced autophagy may provide the explanation. Translational control of α -syn may be governed, at least in part, by a uniquely configured 5' untranslated region (5'UTR) of its transcript, which encodes a homology with the known APP and ferritin iron-responsive elements [32–35].

α -Synuclein is, in fact, the central ~15 kDa protein implicated in the pathogenesis of neurodegenerative α -synucleinopathies [36], including PD—the most prevalent movement disorder in humans. Other alpha synucleinopathies include DLB, Lewy body variant of Alzheimer's disease (AD), and multiple system atrophy. In these disorders, α -syn undergoes a conformational change and oligomerization, causing a toxic gain of function. Neurodegenerative deposition of α -syn aggregates occurs, most commonly in Lewy bodies. Lewy bodies are rare in PD patients, present only in the surviving neurons. α -syn aggregates are in dystrophic neurites. Glial cytoplasmic inclusions are in multiple

systems atrophy [37]. Pathogenic pathways of α -synuclein and amyloid- β (A β) converge via interaction of these two amyloidogenic proteins, which coprecipitate into β -pleated oligomers and insoluble fibrils [38–40], although A β and α -syn rarely colocalize in brain amyloid deposits [41]. There is certainly also overlap between the 5'UTRs of the *SNCA* and amyloid precursor protein (APP) transcripts, another similarity that provides a further link between PD and AD [27, 33–35].

Such overlap in the 5'UTRs of *SNCA* and APP mRNAs is consistent with our and other groups' recent demonstrations that both are key players in iron metabolism and α -syn may be translationally controlled by cellular iron levels as was demonstrated for APP expression [35, 42]. In this regard, APP is a copper-dependent iron export ferroxidase [43], and α -syn a Cu-binding ferrireductase [44, 45]. These similarities, together with the utility of anticholinesterases in AD and PD, provided our rationale to test whether known anticholinesterases that are beneficial and A β lowering [46] would, likewise, provide anti- α -syn activity in neural cells.

The most common therapy for PD is L-dopa that is routinely used to overcome the archetypical problems of tremor. As disease progresses, however, clinically available anticholinesterases have been increasingly empirically used, based in part on an putative impairment of the cholinergic system in developing PD [47].

Therefore, our study investigated the effectiveness of the cholinesterase inhibitor phenserine and its noncholinergic (+) chiral enantiomer, posiphen in lowering α -synuclein expression in neural cell lines. Both agents have been shown to effectively lower APP synthesis rate both in neuronal cultures and animals via translational regulation mediated at the level of the APP mRNA 5'UTR. As both agents have been developed through to clinical studies and appear well tolerated in AD, if effective in reducing α -syn levels, they hold translational promise as potential therapeutics for PD.

Furthermore, as posiphen can be effectively dosed in rodents and humans in far greater amounts than phenserine, thereby generating high levels of its primary metabolites, the three most prominent primary metabolic products of posiphen were also characterized. As a model to examine the α -syn-lowering efficacy of these agents, we assessed the cellular therapeutic impact of these screened *SNCA* 5'UTR-directed translation blockers to reduce α -synuclein expression in neural cells lines and subsequently also in the primary neurons from the PAC/Tg(*SNCA*) genomic human *SNCA* mouse model of PD (Figures 2 and 6) [48].

1.1. Hypothesis/Model. Our model to be tested is shown in Figure 7. The overarching hypothesis is that the drug phenserine (anticholinesterase) and its enantiomer are known translation blockers of the amyloid precursor protein of Alzheimer's disease (AD) and, as such, have been tested in clinical trials for their anti-amyloid efficacy and potential to improve cognition. We noted that the RNA target in the 5'UTR of APP mRNA was similar to that found in the alpha-synuclein transcript. Therefore, we decided to see if posiphen and phenserine might block α -synuclein,

the central culprit protein in PD. To achieve this end, we conducted Western Blot experiments firstly with SH-SY5Y dopaminergic neuroblastoma cells and then with primary E18 neurons from a genomic mouse model of PD. Our rationale for conducting this study was to determine if posiphen and phenserine are two 5'UTR-directed drugs that would reduce alpha-synuclein expression to provide therapeutic benefit to Parkinson's disease patients.

2. Materials and Methods

2.1. Materials. Dulbecco's modified essential medium (DMEM, catalog no. 12-614Q); FBS (catalog no. 14-503E), L-glutamine (catalog no. 17-605E), penicillin/streptomycin (catalog no. 17-602E); phenol red free media (phenol red-free DMEM with 4.5 g/L D-glucose (catalog no. 12-917F)) were purchased from Lonza (Portsmouth, NH). Trypsin/EDTA (catalog no. 25-053-Cl) was purchased from Cellgro. Steady-Glo (catalog no. E2250) was purchased from Promega (Madison, WI). For the Western Blot secondary screen, penicillin/streptomycin was acquired from Bio-Whittaker (Walkersville, MD), mouse monoclonal anti-alpha-synuclein was purchased from BD Transduction Laboratories, and anti-beta-actin was acquired from Chemicon, Inc. We routinely use 384-well plates (catalog no. 3570), which were purchased from Corning and Falcon TC flasks (catalog no. 353112) were purchased from Becton Dickinson (Waltham, MA). SH-SY5Y cells were purchased from the ATCC, Manassas, VA.

2.2. Cell Culture. Transfected SH-SY5Y neuroblastoma cells were grown to confluency in 35 mL complete DMEM with 4.5 g/L D-glucose supplemented with 10% FBS, 200 μ M L-glutamine, 100 μ M penicillin/streptomycin, and 200 μ g/mL geneticin in a T175 TC flask in a TC incubator (37°C, 95% humidity, 5% CO₂) (doubling time = 24 h). Untransfected SH-SY5Y counterparts were grown in the absence of geneticin. Cells were harvested by washing the monolayer quickly with 5 mL trypsin/EDTA (1X), aspirating, then adding 5 mL trypsin/EDTA and incubating for 5 min at 37°C, 95% humidity, 5% CO₂, after which cells were collected into phosphate-buffered saline and centrifuged into a pellet for storage at -70°C.

Primary cortical neurons from wild-type mice and from the PAC-Tg(SNCA(wt)) human SNCA genomic mice [48] were cultured as outlined by the method of Ray et al., 2009 [49]. Briefly, we recovered the embryonic day 15–18 pups after sacrificing pregnant females, separated out the brain, and removed the meninges and blood vessels. We then dissected out the cortices and placed them in separate eppendorf tubes containing 500 μ L of HBSS without Ca⁺²/Mg⁺² salts supplemented with 1 mM sodium pyruvate and 10 mM HEPES, pH 7.4. On ice, individual cells were isolated by titrating 10 times using a glass pasture pipette with the tip barely fire polished. We adjusted the volume to 1.5 mL, by adding 1 mL of HBSS with Ca⁺²/Mg⁺² salts + Na pyruvate + HEPES, restoring the divalent cations by adding HBSS so that the nondispersed tissue could settle for 5 min,

on ice. In the tissue culture laminar hood, we transferred the supernatant into a new 15 mL tube and centrifuged for 1 min at 900 rpm, 4°C. We gently resuspended the pellet in 2 mL of HBSS with Ca⁺²/Mg⁺² salts + Na pyruvate + HEPES and took an aliquot for counting (2 mL for approx. 5 embryos). We then plated $\sim 1 \times 10^5$ cells/well of a 24-well or 2×10^5 /in 12-well plates. Each set of plates were coated with poly D-lysine containing poly L-lysine coverslips for micro immunocytochemical confirmation of neuronal integrity.

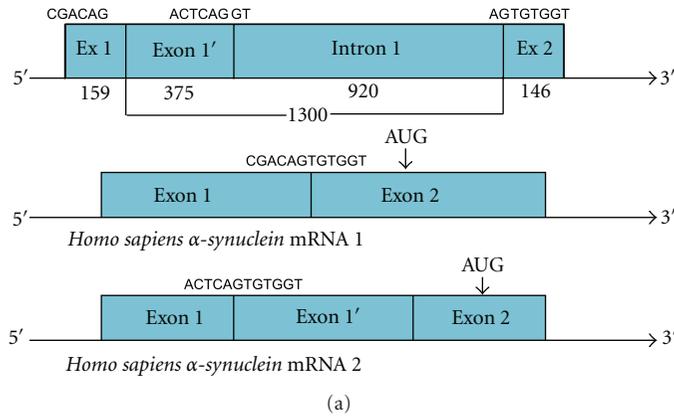
2.3. Bioinformatics Methods. The α -synuclein RNA sequences were selected using the NCBI Gene search and the Ensembl database (see [34]). Since the 5' UTRs were of primary interest, the coding sequences (CDS) were mostly disregarded, apart from the initiating AUG. As we reported [34], the splice junction between two exons occurred at a CAGUGU site 25 = nucleotides from the AUG and that this pattern was conserved among the other species investigated. Thus, in order to study a balanced sequence, 25 nucleotides before the splice junction from the first exon were used to create 50 nucleotide RNA sequences (mouse and rat had 52 nt sequences due to insertions).

The ClustalX2 graphical program was used to align the RNA sequences to identify any evolutionary conservation between species. For alpha synuclein, the AUG start region of the CDS was a reference point for sequence alignments, allowing a comparison of the sequences in both exons around the splice junction, due to high local conservation fidelity. Secondary sequences were then generated by the University of Vienna's RNAfold webserver (with standard settings) and were annotated using the RNAfold command-line software. The RNAfold server provided the most probable secondary structure based on minimum-free energy calculation.

We calculated the alignment homology by comparing any species' RNA sequence (as listed) against the *Homo sapiens* sequence on each side of the splice junction. We also calculated the homology between the core L- and H-ferritin IREs with that of alpha synuclein and APP mRNAs. Only nucleotides that matched respective to the *Homo sapiens* sequence were scored a point; we determined the percent homology on each side by totaling the points scored and dividing by the total number of nucleotides on that side. The results from each side were then compared to illuminate the difference in conservation across the splice junction.

2.4. Constructs. The SNCA-5'UTR-pGL3 construct was generated from the pGL3 expression vector (Promega). In this case, a PCR fragment encoding 48 base α -synuclein 5'UTR was cloned between the Hind-III and NcoI sites in front of start codon of the luciferase gene in PGL3. Transiently transfected cells expressed either pGL3 or the SNCA-5'UTR-pGL3 construct. Stably transfected neural cell lines were generated via neomycin selection after cotransfection with the RSV2-neomycin plasmid to express the SNCA-5'UTR-pGL3 construct (H2A cells) or pGL3 (control cells).

2.5. Stable-Transfection-Based Screen of a Library of Natural Product Inhibitors of α -Synuclein Translation. A 720 compound natural products, including added phenserine and



(a)

Legend
Homology: Less (light blue) to More (dark blue)

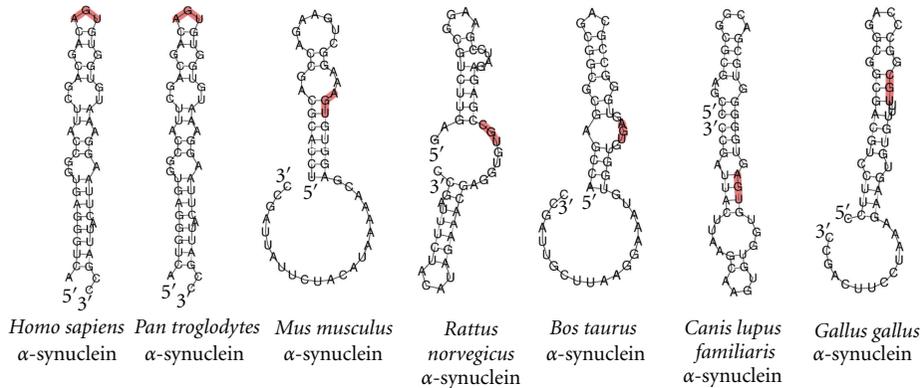
Splice junction 5' UTR end/CDS start

<i>Homo sapiens</i>	ACUGGGAGUGGCCAUUCGACG - ACAGUGGUGUGUAAAGGAUUCAUU - - AGCC AUG
<i>Pan troglodytes</i>	ACUGGGAGUGGCCAUUCGACG - ACAGUGGUGUGUAAAGGAUUCAUU - - AGCC AUG
<i>Mus musculus</i>	- - UCCACGCAGCCAGAAGUCGGAAGAGUGGGAGCAAAAUAUCAUCUUAUAGCC AUG
<i>Rattus norvegicus</i>	GAGUUCUGCGGAAGCCUAGAGAGCCGUGGGAGCAAAAGUAUCAUCUU - - UAGCC AUG
<i>Bos taurus</i>	ACCAGCGCGGCAGCCGCGG - UGAGUGGUGUGUAAAGGAUUUCGUU - - AGCC AUG
<i>Canis lupus familiaris</i>	- CCGAGCGCGGCAGCGUGGGUGAGUGGUGUGAAGCAAAUUCAUU - - AGCC AUG
<i>Gallus gallus</i>	CCUCCUGCAGCGGC - GACC CGGUUUGUGUGAAGAAUCCUUC - - AGCC AUG

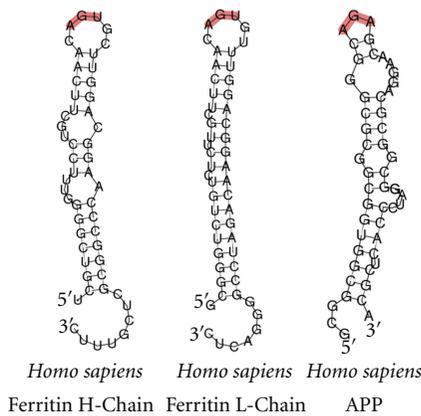
Known 5' UTR IRE regions in human genes

Ferritin H-chain	- UCGUCGGGGUUUCCUGCUUCAACAGUGCUUGGAC - - GGAACCCGGCGCUCGUUUC -
Ferritin L-chain	- GCGGUCUGUCUCUUGCUUCAACAGUGUUGGAC - - GGAACAGAUCCGGGACUC -
APP	- - CGGCGCGGUGGCGCGCGGGAGAGCAAGGACGCGCGGAUCCACUCGCACUC

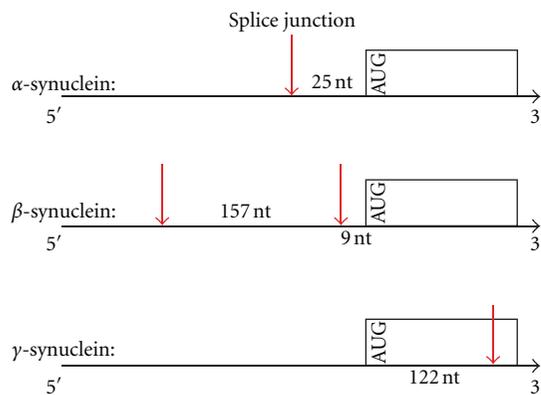
Evolutionary α -synuclein RNA IRE structures



Known IREs in human genes



Comparison of human synuclein homologs



(b)

FIGURE 1: Continued.

Quantified homologies across the splice junction

Quantified homology against <i>Homo sapiens</i>		
Species	Exon 1 (%)	Exon 2 (%)
<i>Pan troglodytes</i>	100	100
<i>Mus musculus</i>	42.3	61.5
<i>Rattus norvegicus</i>	23.1	65.4
<i>Bos taurus</i>	46.2	96.2
<i>Canis lupus familiaris</i>	42.3	92.3
<i>Gallus gallus</i>	34.6	69.2

Quantified IRE control homology against <i>Homo sapiens</i>	
Controls	Homology (%)
L-Ferritin	31.5
H-Ferritin	38.9
APP	31.5

(c)

FIGURE 1: The 5' untranslated region (5'UTR) of the Parkinson's disease alpha-synuclein (*SNCA*) transcript is homologous to the iron-responsive element (IRE) in H-ferritin mRNA. (a) *Top panel*: The *SNCA* 5'UTR is encoded by exon-1 and exon-2 of the *SNCA* gene, which can be alternatively spliced to generate either a shorter exon-1/-2 transcript or a longer exon-1'-2 transcript [58]. *Bottom panel*: evolutionary alignment of the *SNCA* 5'UTR relative to the human sequence and the CAGUGN loop/splice site sequences [33]. We quantified the homology across the *SNCA* splice junction in the 5' untranslated region. (b) RNA/FOLD computer program predictions of RNA stem loops from *SNCA* 5'UTR sequences ($\Delta G = 53$ kcal/mol). The human *SNCA* stem loop resembles the classical IRE RNA stem loop (5' CAGUGN3' loop motif) that controls iron-dependent L- and H-ferritin translation and transferrin receptor (TfR) mRNA stability. Stem loops from the 5'UTRs of several species were predicted to be folded, as described in the Materials and Methods section, and the pseudotri-loop AGU is depicted in red lettering at the apex of the H-ferritin IRE [59] where the analogous AGA from the APP IRE is depicted [50]. The human *SNCA* mRNA exhibited an AGU tri-loop, whereas, in lower vertebrates, this AGU motif was located in the stem regions of these transcripts. Shown are the arrangement of splice sites and 5'UTR structures in the *SNCA*, *SNCB*, *SNCG* mRNAs. *Tabulated*: the first table shows the homology between the IRE-like domains in each exon of the human alpha-synuclein compared to its counterparts in different mammalian species. The second table shows the homology between the 5' untranslated regions of *SNCA* with the APP and ferritin L- and H-chains. This data underscored our identification of cotranslational repression of APP and alpha-synuclein by small molecules, such as phenserine and posiphen.

posiphen, from Microsource Discovery Systems, Inc, was screened at a concentration of 2 μ M in triplicate for inhibition of luciferase expression using (APP cells) and (*SNCA* cells). A compound was scored as a hit if all replicates gave >65% inhibition in this assay, and as contradictory if at least one, but not all replicates gave >65% inhibition. In order to rule out compounds that reduced luciferase expression due to toxicity, the entire library was also screened in both cell lines for cytotoxicity, using alamar blue (Biosource, Inc.) as the readout. Percent inhibition in the alamar Blue assay was calculated and compared with percent inhibition of luciferase activity. Posiphen and phenserine were among the compounds for which the difference was greater than 40 and which scored as a hit or contradictory in the luciferase assay.

2.6. Transient Transfection Assays. After 24 hr transfection of SH-SY5Y cells in a 100 mm dish with either (i) *SNCA*-5'UTR-pGL3 or (ii) pGL3 parental vector, cells were then passaged into 6 wells and tested with posiphen and phenserine (15 μ M = for 48 hr) as shown in Figures 3 and 4 for which dose-response assays were also conducted (not shown) [34, 50].

2.7. Luciferase Assay. Cells were plated at 2000 cells/well (APP) or 4000 cells/well (*SNCA*) in a 384-well white flat-bottom plate (Greiner) in a volume of 50 μ L of media. Following overnight incubation, 50 μ L of 5 μ M in DMSO were added using a VPN Pintool. Cells were returned to the incubator of 48 h, then assayed for luciferase activity. Plates were allowed to equilibrate to room temperature. After addition of 25 μ L Steady-Glo reagent (Promega), plates were

vortexed for 30 sec and 35 minutes later luminescence read on an Infinite F2000 plate reader (Tecan) [34, 50].

2.8. Western Blot Assay. Human SH-SY5Y cells and primary cortical neurons (E18 fetal cells) were exposed to increasing concentrations of phenserine and posiphen for 48 hours. Cytoplasmic protein lysates were prepared by homogenizing the cells in midRIPA buffer (25 mM Tris pH 7.4, 1% NP40, 0.5% sodium deoxycholate, 15 mM NaCl, protease inhibitors, RNase inhibitor, and 10 μ M DTT). Western Blotting for alpha-synuclein was performed using mouse monoclonal anti-alpha-synuclein (BD Transduction Laboratories) and anti-beta-actin (Chemicon). The blots were developed using chemiluminescence (PIERCE) and visualized with a PhosphoImager (BioRad, Hercules, CA), and bands were quantified using QuantityOne software (BioRad).

3. Results and Discussion

In Figure 1, we performed a full bioinformatic analysis of the *SNCA* 5'UTR demonstrating by computer-mediated predictions [50] that the 5'UTR of the *SNCA* transcript folds into a unique RNA stem loop resembling an iron-responsive element (IRE) RNA structure that is related to, but distinct from, the H-ferritin and APP 5'UTR-specific IREs [33]. We are currently testing the capacity of intracellular iron chelation with desferrioxamine to repress neural α -synuclein translation acting via the IRE in the 5'UTR of its transcript, as we reported for the APP and ferritin mRNAs [42, 51].

Previously, the RNA-directed anticholinesterase drug phenserine, together with its cholinergically inert chiral (+)

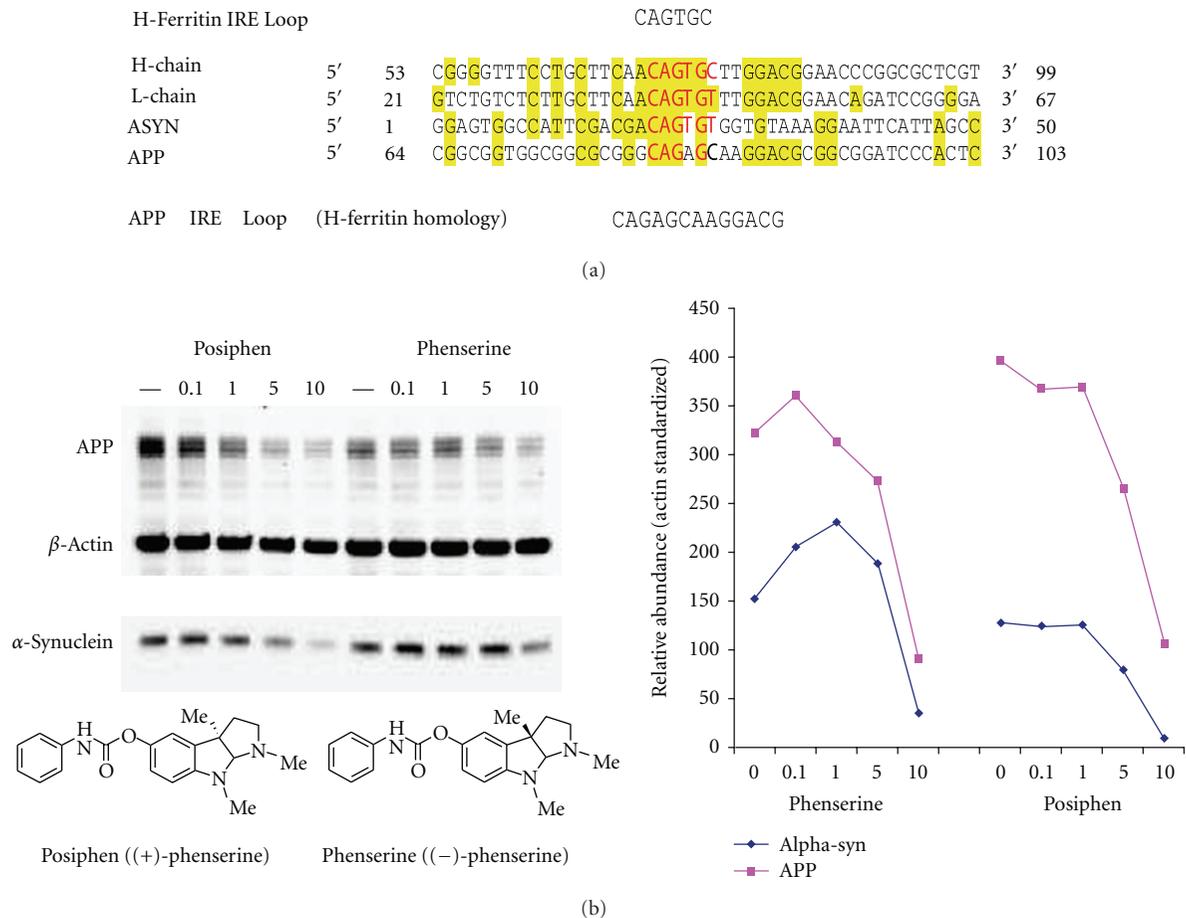


FIGURE 2: Posiphen and phenserine decrease both APP and α -synuclein levels dose-dependently in dopaminergic SH-SY5Y cells. Panel A: the 5'UTRs of both the *APP* and *SNCA* genes are 50% homologous with the IRE H-ferritin mRNA. Panel B: SH-SY5Y cells were treated with concentrations ranging from 0 to 10 μ M phenserine and posiphen for 48 h. Harvested cell lysates were prepared. Quantitative Western Blotting established the anti- α -syn efficacy of posiphen and phenserine ($IC_{50} < 5 \mu$ M); after standardization for β -actin (Densitometry of multiple lanes ($n = 8$) by ImageQuant). Cell viability was unaffected (measured by standardized ATP levels/cell (Tm (Cell-Titer-glo, Promega, Inc.))).

enantiomer, posiphen, which are both in clinical development for AD, was shown to therapeutically limit brain $A\beta$ levels in wild-type and AD mouse models [46]. This action was mediated, in whole or in part, by lowering the rate of synthesis of APP, from which $A\beta$ is proteolytically cleaved. Here, we sought to demonstrate that phenserine and posiphen, likewise, blocked α -synuclein expression via their related 5'UTRs, encoding variant versions of the iron-responsive element RNA elements that potentially bind iron-regulatory proteins.

To elucidate whether our defined target would translate across species, we provide the results of an evolutionary evaluation of the conservation of IRE RNA stem loops in *SNCA* mRNA as shown in Figure 1. This is the RNA secondary structure sequence, together with the APP 5'UTR, that is targeted by phenserine and posiphen, as shown in Figures 2–4. The alpha-synuclein-specific IRE stem loop was formed

at the splice junction of the first two exons in *SNCA* gene [35]. We also compared the predicted structure of the *SNCA* mRNA IRE with the canonical IREs in the H-ferritin and APP transcripts, which are transcribed from the single first exon of their genes confirming the uniqueness of translational repression of *SNCA* mRNA via its 5'UTR.

The anticholinesterase phenserine and its (+) enantiomer, posiphen, are proven APP 5'UTR mediated drugs with known pharmacokinetics in rodents and humans and identified target concentrations [46, 52]. Since we anticipated that both agents would be active in limiting α -synuclein translation via its 5'UTR, we had spiked an FDA library with posiphen and phenserine when we formerly screened against the *SNCA* 5'UTR RNA target [34]. Here, we confirm that both posiphen and phenserine repressed the *SNCA* 5'UTR-driven translation of a luciferase reporter in stable cells lines. Their capacity to inhibit *SNCA* mRNA translation is similar

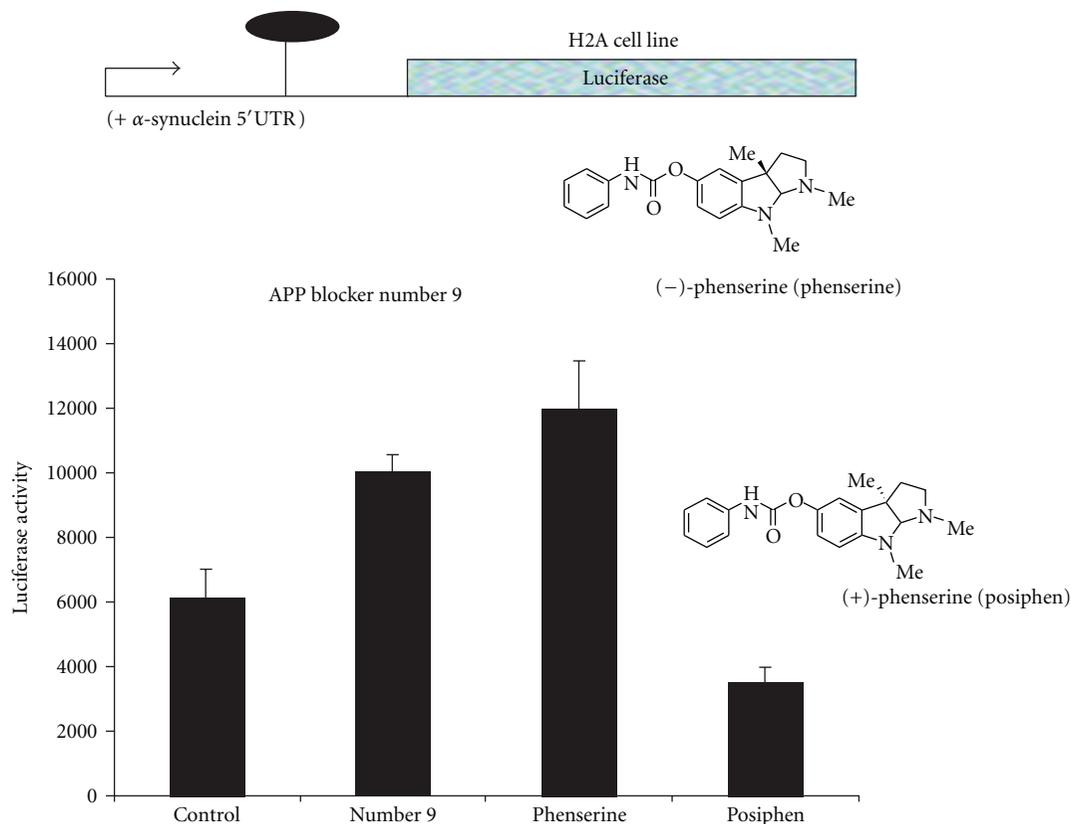


FIGURE 3: Posiphen is a stereospecific inhibitor of alpha synuclein 5'UTR-directed translation. Transient transfection assays with the SNCA-5'UTR-pGL3 construct (H2A cell line). Posiphen was a highly selective inhibitor (10 μ M) of α -synuclein 5'UTR-driven expression of a luciferase reporter gene. This stereoisomer of phenserine inhibited α -synuclein 5'UTR-driven luciferase expression in neural cells (SNCA 5'UTR-positive transfected neural cells ($N = 7$)). By contrast, phenserine and the known APP-specific translation number 9 blocker did not suppress alpha synuclein 5'UTR-conferred translation in H2A cells. Phenserine and APP blocker number 9 increased SNCA 5'UTR-conferred translation. These data support the mechanism-of-action of posiphen as a highly selective blocker of alpha synuclein 5'UTR activity, whereas phenserine (same chemical structure but stereoisomer of posiphen) was previously shown selectively inhibiting translation driven by the APP 5'UTR.

to that of certain other defined FDA drug leads, including three glycosides and an immunosuppressant, mycophenolic acid (secondary Fe chelator), as we previously reported [34].

In Figure 2(a), the 5'UTRs of both APP and SNCA showed 40% homology to each other and also 50% homology to the IRE in H-ferritin mRNA. Multiple Western blot experiments were hence conducted to determine the impact of phenserine compared to posiphen to limit α -syn compared to APP expression. In this regard, SH-SY5Y cells were treated with both compounds for 48 hours with concentrations ranging from 0 to 10 μ M. Viability studies determined that this range was well tolerated, in accordance with prior studies. In general and as shown in Figure 2(b), posiphen (in addition to but potentially slightly more potently than phenserine) decreased levels of α -syn in a dose-dependent manner in cultured neural cells (SH-SY5Y) as previously reported for APP. Whether this higher potency

would translate to primary neurons and *in vivo* is a focus of future studies. In this paper, this was achieved with a preliminary determined IC_{50} in the order of 5 μ M, in the absence of toxicity.

Multiple transient transfections of SH-SY5Y cells were performed with the constructs that either translated luciferase driven by the 48 base SNCA 5'UTR (SNCA-5'UTR-pGL3) or the empty pGL3 expression vector (Figures 3 and 4). As shown (Figures 3 and 4), posiphen 50% repressed SNCA 5'UTR-conferred translation of a luciferase reporter transcript. In this regard, posiphen proved a highly selective inhibitor of SNCA 5'UTR driven activity since this chirally pure compound inhibited SNCA 5'UTR-driven luciferase expression in H2A neural cells (i.e., SNCA 5'UTR-positive stably transfected neural cells). By contrast, phenserine and the known APP translation blocker, compound number 9 (included as a comparator), did not suppress

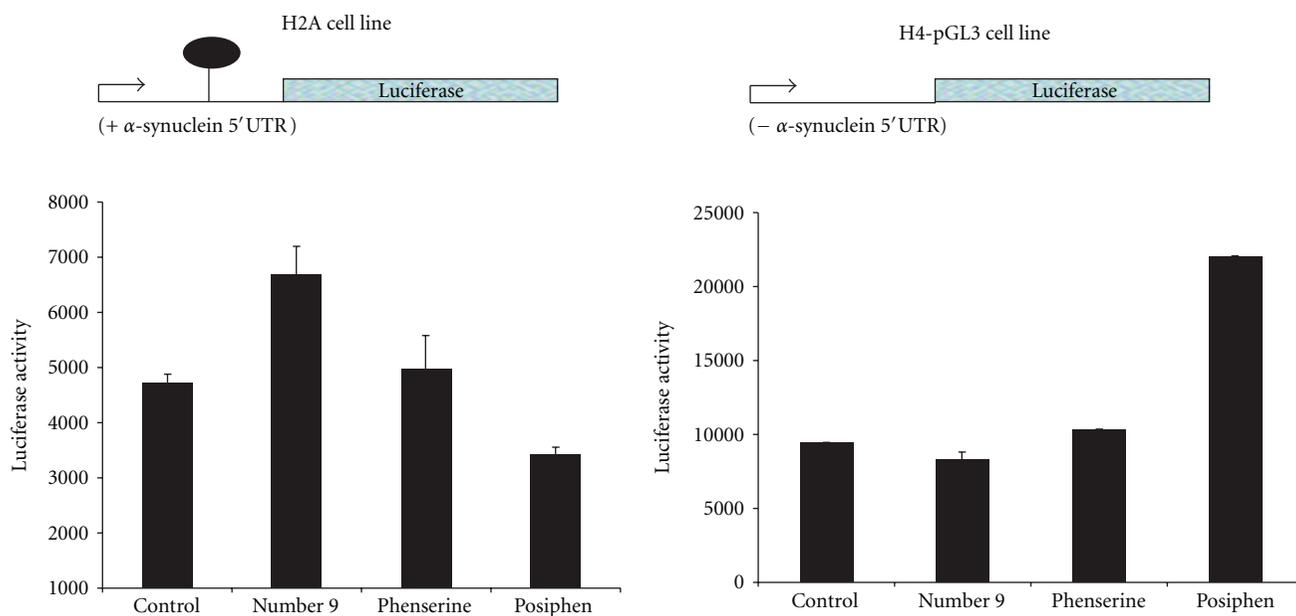


FIGURE 4: Selectivity of posiphen to inhibit translation driven by alpha-synuclein 5'UTR sequences: a second set of transient transfection experiments in which posiphen ($10\ \mu\text{M}$) selectively inhibited alpha-synuclein 5'UTR-conferred luciferase expression in SH-SY5Y neural cells (SNCA 5'UTR-positive transfectants, $N = 6$). Confirming selectivity, posiphen increased luciferase expression in pGL3-transfected SH-SY5Y cells (**pGL3-SH-SY5Y serves as an experimental control since these cells were transfected with pGL3, which is the same as the H2A construct but lacks the α -synuclein 5'UTR).

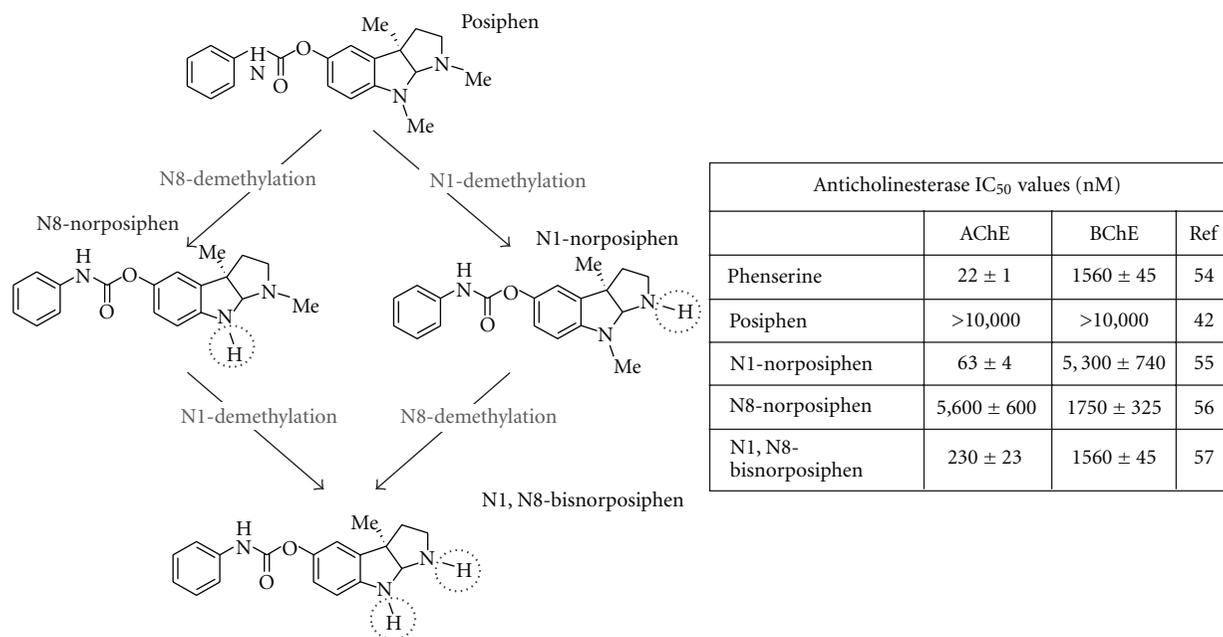


FIGURE 5: Metabolic analogs of posiphen and their respective anticholinesterase activities [60]. Posiphen is devoid of anticholinesterase activity. However, its phase I metabolites, N8 demethylated, N1 demethylated, and di-demethylated N1, N8-bisnorposiphen showed *ex vivo* AChE and BChE inhibitory activity of clinical relevance [61, 62]. The compound N8-bisnorposiphen demonstrated no AChE activity. This activity has proven to be dose limiting in human safety studies.

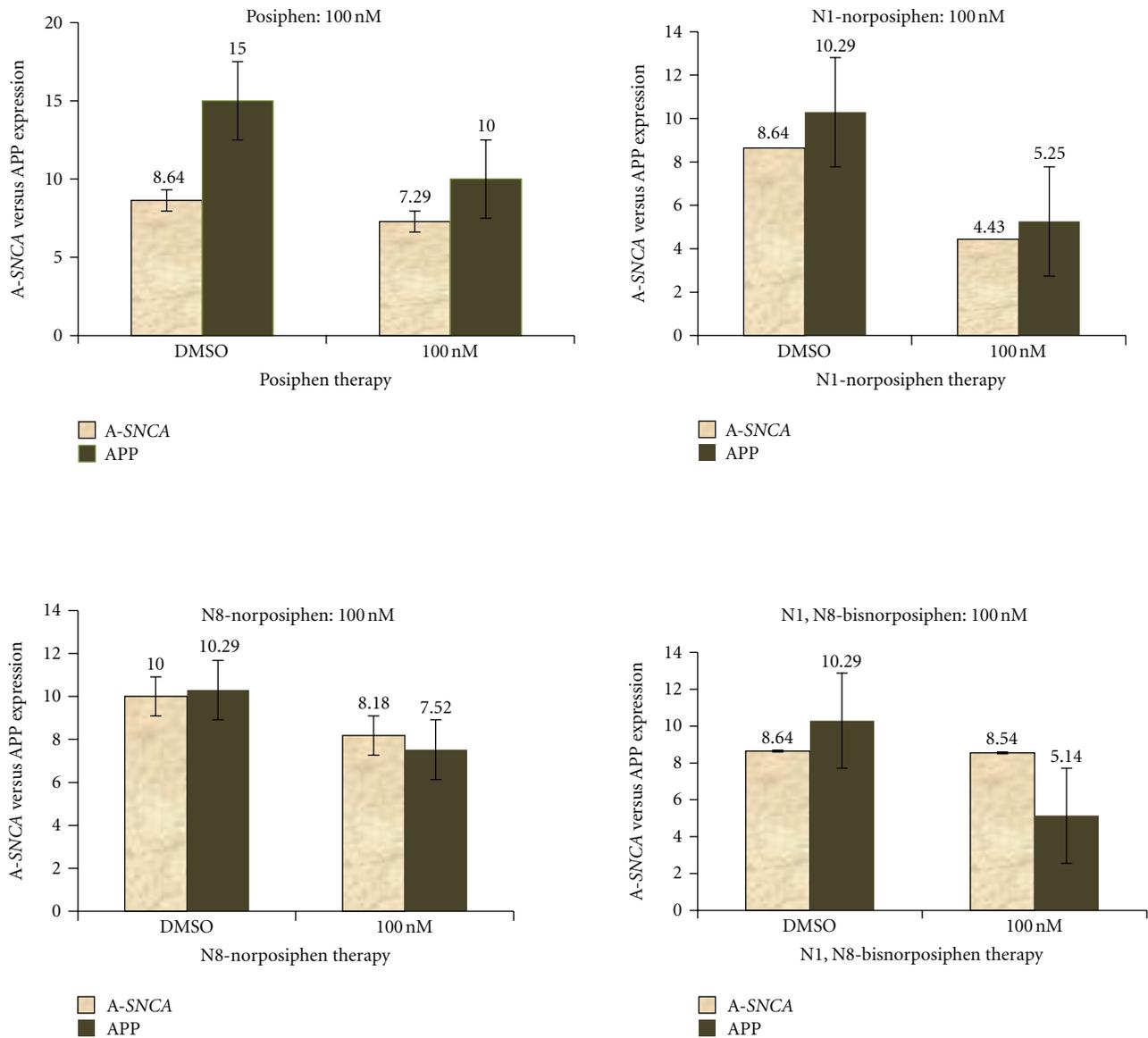


FIGURE 6: Percent inhibition of α -synuclein/APP by posiphen compared with its metabolic analogs in primary E18 neurons (from PAC-Tg(SNCA) mice). Densitometry and quantitation of the relative levels α -synuclein/APP from western blots (β -actin standardized) after treating primary neurons with posiphen and each of its three metabolic analogs at 100 nM concentration for 48 hours.

SNCA 5'UTR conferred translation in H2A cells. Indeed, phenserine and compound number 9 elevated SNCA 5'UTR-conferred translation.

These data support the mechanism-of-action of posiphen as a highly selective blocker of SNCA 5'UTR activity. However, phenserine—with the identical chemical structure but in a different three-dimensional (chiral) configuration—that has previously been shown to effectively inhibit translation driven by the APP 5'UTR clearly has different actions to posiphen at the SNCA 5'UTR. From this, we can deduce that the element of the SNCA 5'UTR targeted by posiphen has a stereospecific component. Additionally, since phenserine lowers α -syn levels (Figure 2(b)), further SNCA

RNA sequences are likely involved in controlling this pathway of α -syn translational regulation.

Extending beyond transformed neuronal cell lines, primary neurons from *wild-type mice* and PAC SNCA transgenic mice (PAC-Tg SNCA) were evaluated for the capacity of posiphen to repress α -syn expression, as shown in Figure 6 (tested at 100 nM drug concentration). Posiphen proved not only active and well tolerated in SH-SY5Y cells but consistently reduced human α -synuclein expression in primary neurons (E18) at doses as low as 1 μ M (75% reduction, not shown) without toxicity. This margin appeared to be greater than its capacity to lower APP production (20%) (utilized as a positive control) in these same cells (data not shown).

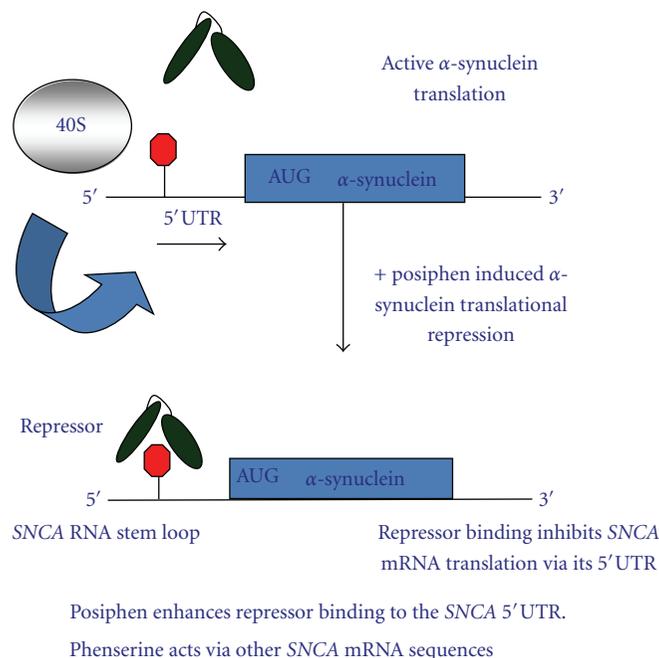


FIGURE 7: A model for translation repression of alpha-synuclein in which its transcript interacts with an RNA repressor protein. In the classical translation repression model, Iron-regulatory protein-1 (IRP1) controls iron dependent expression of the ferritin L- and H-chains. By analogy, phenserine, posiphen and its metabolic analogs would be predicted to increase the repressor as an RNA binding protein to interact with the SNCA 5'UTR after drug treatment. This should prohibit 40S ribosome access to the 5'UTR of SNCA mRNA to lower translation.

Following oral administration of posiphen to rodents, dogs, and human, the compound is subjected to metabolic processes and generates the same metabolic profile across these species. Specifically, via a phase 1 metabolism, posiphen undergoes N-demethylation in both the N1 and N8 positions to generate the respective primary metabolites, N1-norposiphen and N8-norposiphen (Figure 5). Each then undergoes further N-demethylation to generate the common metabolite, N1, N8-bisnorposiphen. Unlike phenserine, posiphen is devoid of cholinesterase inhibitory activity and, therefore, can be advantageously administered at higher clinical doses (in the order of 5, to 8-fold greater).

As shown in Figure 5, specific N-demethylated metabolites (in particular the N1-nor and N1,N8-bisnorposiphen) possess potentially clinically relevant IC_{50} values to inhibit acetylcholinesterase (AChE). Such activity is less than phenserine and would be expected to have a slow onset in line with the time-dependent metabolism of posiphen to generate its metabolites. However, with regard to actions on α -synuclein expression, activity of the metabolites at this target, where posiphen is potent, could usefully increase and extend the drug's *in vivo* efficacy. To elucidate this and aid planning for future animal studies, we characterized the relative capacities of posiphen's metabolic analogs to impact α -syn expression (Figure 6).

Figure 6 shows a Western Blot analysis representative of three experiments that compared the efficacy of posiphen

with that of its three primary metabolites to limit α -synuclein expression *ex vivo* using E18 primary cortical neurons from human SNCA PAC mice. We consistently measured that N1-norposiphen (possessing AChE activity) proved most potent to limit α -synuclein expression (by 50%), and, likewise, APP expression was also reduced. As assessed at 100 nM in Figure 6, the other metabolites proved to be less active at these targets, indicating that relatively small structural changes (i.e., the loss of a methyl moiety) have significant impact. An assessment of dose-response for each metabolite is a focus of future studies, particularly within the achievable clinical range of the agents in human and *in vivo* range in animal models (Dr. Maria Maccacchini and Dr. Robert Nussbaum, personal communications).

4. Conclusions

We previously reported that phenserine, a (-)-physostigmine analogue and anticholinesterase that reached phase III clinical assessment for AD [53–55], inhibited APP translation through its 5'UTR [56, 57]. Phenserine was found to be dose limiting consequent to its AChE inhibitory action, causing the classical cholinergic action of tremors in animal models and nausea in humans. Posiphen, the chirally pure (+) enantiomer of phenserine, by contrast possesses no direct anticholinesterase activity and, likewise, repressed neural

AD-specific APP translation via its 5'UTR in mice. It has recently been developed (QR Pharma, Berwyn, PA) to the clinic as an APP synthesis inhibitor in AD to lower both brain A β generation as well as the levels of other toxic proteolytic products of APP. With a very different pharmacological and pharmacokinetic profile to phenserine, it has recently completed single- and multiple-dose escalating phase I clinical assessment in humans, appearing well-tolerated, and a proof of mechanism study, indicating target engagement.

In this paper, we demonstrated in human immortal neuronal cultures, and then *ex vivo* in primary cortical neurons from a human SNCA genomic mouse model, that *posiphen* acts as a safe 5'UTR-directed inhibitor of toxic α -synuclein buildup. A final validation of the SNCA 5'UTR target is to be achieved by unchanged β -synuclein (β -syn) and γ -synuclein (γ -syn) expression and is a focus of current studies. Importantly, we determined that key primary metabolites of *posiphen*, likewise, lower α -syn expression and may hence add to *posiphen*'s actions on this target in animal and human studies.

Of further interest, we established that phenserine similarly effectively reduced α -syn levels but achieves this via a different mechanism, compared to *posiphen*, potentially by interacting through other elements in the 5'UTR or even 3'UTR, and thereby highlighting the sensitivity of the target to small structure-activity changes. These studies additionally demonstrate how α -synuclein and A β pathomechanisms can converge via interaction of the two amyloidogenic proteins [38–40], although A β and α -syn rarely co-localize in amyloid deposits [41], but provide evidence that a drug targeting one disease may have therapeutic potential in another.

In this regard, we noted that there is 50% sequence similarity between the 5' UTRs of the APP and SNCA genes. We therefore predicted overlap in the spectrum of drugs that would suppress APP mRNA translation through its 5'UTR with those that suppress α -synuclein, highlighting in particular phenserine and *posiphen* (with preliminary IC₅₀ values in the order of 5 μ M and less). In future studies, we aim to characterize the anti- α -synuclein efficacy of *posiphen* analogs in addition to metabolic analogs and other compounds in primary neurons and establish the *in vivo* efficacy of the most effective SNCA 5'UTR translation blockers.

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Clinical Study

Psychosis Assessment in Early-Stage Parkinson's Disease: Comparing Parkinson's Psychosis Questionnaire with the Brief Psychiatric Rating Scale in a Portuguese Sample

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Psychotic symptoms in Parkinson's disease (PD) are frequent, disabling, and an important prognostic factor. Thus, screening instruments for detecting psychosis in PD are needed. For this purpose, we applied the Parkinson's Psychosis Questionnaire (PPQ), a short structured questionnaire, which requires no specific training, along with the Brief Psychiatric Rating Scale, expanded version (BPRS-E), for rating general psychopathology, including psychotic symptoms. We evaluated, in a cross-sectional study, a Portuguese sample of 36 early-stage PD patients (mean age of 73 years; mean duration of illness of 3.2 years). The PPQ total score correlated with the BPRS-E total score (0.359; $P = 0.032$) and with the BPRS-E-positive symptoms score (0.469; $P = 0.004$). The prevalence of psychosis (41.7%) was higher than expected. Sampling bias and detection of minor psychotic phenomena may have contributed to this result. These findings suggest that the PPQ should be further evaluated as a feasible assessment for psychotic symptoms in PD.

1. Introduction

In the context of Parkinson's disease (PD), the term psychosis usually referred to a mental state characterized by hallucinations and/or delusions, occurring with a clear sensorium and a chronic course. In the past years, definitions have changed and the typical hallucinatory syndrome in PD now encompasses other related phenomena, such as minor phenomena, like illusions, sense of presence, and passage hallucinations [1].

Among the nonmotor features of Parkinson's disease (PD), psychotic symptoms are frequent, ranging from 20 to 30% of patients [2]. Over the course of PD, psychotic symptoms, once present, tend to be persistent and progressive [3].

The impact of psychosis is substantial in that it is associated with dementia, depression, earlier mortality, greater caregiver strain, and nursing home placement. Psychosis also has important treatment implications, as it limits the therapy of motor symptoms [4].

Recently, the Task Force of the Movement Disorder Society comprehensively reviewed the scales used to assess psychosis in PD [5]. Albeit none of the current scales has been shown to possess the necessary basic mechanistic and psychometric properties, it was suggested that, in the meantime, the selection of the current scales should be based on the goals of the assessment [5]. Therefore and aiming for a precocious detection of psychotic symptoms in PD, especially in early stage patients, we were interested in exploring

easy-to-use instruments and we selected the Parkinson's Psychosis Questionnaire (PPQ) [2, 5]. It is a brief, structured instrument that was designed for screening psychotic symptoms in PD patients.

We set out to compare the use of a brief and structured screening tool for psychosis in PD, the PPQ, and of the Brief Psychiatric Rating Scale, expanded version (BPRS-E), as a gold standard [6].

2. Material and Methods

2.1. Study Type, Sample, and Location. The study had a cross-sectional design. The sample consisted of 36 consecutive patients (19 females and 17 males) with early stage PD, recruited from Hospital Egas Moniz Neurology Department's outpatient clinic (Lisbon, Portugal). None of the patients refused to enter the study.

To be included, patients were required to have less than 5 years of disease duration since the first motor symptoms were reported and a Hoehn and Yahr stage [7] from 1 to 2.5. Informed consent was obtained from all patients. Patients with diseases of the central nervous system other than PD were excluded from the study.

2.2. PD Diagnosis. PD was diagnosed by P.B., an experienced movement disorder specialist, according to validated clinical criteria [8].

2.3. Demographics and Clinical Variables. Patients' demographic data (gender, age, and education level) and clinical data (duration of illness, levodopa equivalent dose, Hoehn and Yahr stage) were collected. The method for converting the total daily dopaminergic therapeutic dose in levodopa equivalent dose was obtained from published formulas [9].

The evaluation of the patients' cognition was made using the Portuguese version of the Mini-Mental State Examination (MMSE) from Guerreiro et al. [10]. MMSE is a simple, widely used scale to detect cognitive impairment. Although there is a debate on its usefulness as a screening tool for cognitive impairment in PD [11], it may still be considered appropriate for this purpose [5, 12]. In addition, the Frontal Assessment Battery (FAB) was applied for the same purpose [10]. FAB is a rapid screening battery that has been validated for PD [13–15].

2.4. Evaluation of Psychosis/Psychotic Symptoms. Psychiatry trainees (I.C., M.S., J.A.S., and B.N.) assessed the patients for psychotic symptoms, using two different instruments: a structured and easy-to-administer questionnaire that specifically addresses psychotic and related symptoms in PD—the PPQ [2]—and a widely used general psychopathology semistructured instrument—the BPRS-E [6].

The PPQ was developed as a 14-item screening instrument for early recognition of psychosis in PD. The specificity and sensitivity reported by the developers of PPQ were 92.1% and 100%, respectively, using Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID) as the gold standard [2]. This scale includes probe questions followed by detailed questions regarding four domains. The first domain

includes three questions about the presence or absence of sleep disturbance. The following domain assesses, in four questions, the occurrence of hallucinations and/or illusions, including visual, auditory, and tactile hallucinations. The third domain includes five questions to detect different types of delusions: persecutory, jealousy, poisoning, abandonment, and control. The fourth domain assesses place and time orientation. Within a domain, any positive answer triggers inquiries about frequency (1–3 points) and severity (1–3 points). Each subscore is the product of the frequency multiplied by the severity score for that symptom domain. The total score is obtained by summing all subscores. PPQ case-ness is defined by at least a positive score on the domains of hallucinations/illusions and/or delusions. We used our Portuguese translation of the PPQ. Two English-fluent medical doctors among the authors (BN, JAS) were responsible for this translation. Given the simple straightforward nature of the translation process, backtranslation procedures were skipped. Moreover, face and content validity of the original version are assumed to be preserved.

The BPRS-E [6, 16] was designed for measuring overall psychopathological change in patients with schizophrenia. Validity and reliability have been widely documented [6, 16, 17]. It is administered in a semistructured manner, and it takes about 30 minutes to complete. It comprehends 24 items that can be scored from 1 (not present) to 7 (very severe). The total BPRS-E score is the sum of the scores for each of the 24 items. A Portuguese translation (Caldas de Almeida, Gusmão, Talina, and Xavier—Universidade Nova de Lisboa, 1996; unpublished document) of the BPRS-E was used. Since there is no study describing the factor structure of BPRS-E for PD, we used a BPRS-E factor solution that was described in a sample of European patients with schizophrenia [17] and recently used in Portuguese research [18]. This factor solution includes four subscales: positive symptoms (grandiosity, suspiciousness, hallucinations, unusual thought content, and conceptual disorganisation), negative symptoms (disorientation, blunted affect, emotional withdrawal, motor retardation, self-neglect, uncooperativeness, mannerism, and posturing), manic excitement/disorganization items (hostility, elevated mood, bizarre behaviour, self-neglect, uncooperativeness, excitement, distractibility, motor hyperactivity, mannerism and posturing), and depression/anxiety components (anxiety, depression, suicidality, guilt content, somatic concern, and tension). The subscales score is the sum of the scores for each item within a subscale. In this paper, mean scores (1 to 7) are presented for total BPRS-E and subscale scores.

Assessments with the BPRS-E and PPQ were conducted by the same interviewer for each patient. However, to minimize the bias related to the lack of occultation, the semistructured instrument (BPRS) was applied first. Each psychiatric trainee evaluated approximately 25% of the sample.

2.5. Statistical Analysis. Due to small sample size and the lack of a normal distribution in most continuous variables, we chose to use a nonparametric statistical analysis. Mann-Whitney test was used to compare the mean values of the BPRS-E factors and levodopa equivalent dosages (LED)

TABLE 1: Sociodemographic and clinical data ($n = 36$).

Gender (male/female)	17/19
Age (years)	73.17 (6.54)*
Education	4 (4)*
Duration of illness (years)	3.17 (1.30)*
Levodopa equivalent dose (mg)	300** (range 0–1500)
Hoehn and Yahr stage (on)	2** (range 1–3)
MMSE	27.22 (2.53)*
FAB	13.31 (3.13)*
PPQ (total score)	3.69 (3.42)* (range 0–12)
PPQ (% cases)	41.7
BPRS (total score) ⁺	1.26 (0.16)*
BPRS (positive symptoms score) ⁺	1.24 (0.31)*
BPRS (negative symptoms score) ⁺	1.19 (0.24)*
BPRS (depression/anxiety score) ⁺	1.60 (0.54)*
BPRS (mania/hostility score) ⁺	1.04 (0.05)*

*mean (standard deviation).

**median.

⁺weighted scores; range 1 (not present) through 7 (extremely severe).

between PPQ cases and noncases. The Spearman's rank correlation coefficient was used to evaluate the association strength between LED and psychotic symptoms severity and also between PPQ scores and BPRS-E scores. The level of statistical significance was set at $P \leq 0.05$.

All statistical analyses were performed using SPSS 18.0. (SPSS, Inc., Chicago, IL).

3. Results and Discussion

3.1. Results. The clinical and demographical characteristics of the 36 patients in the sample are summarized in Table 1.

Thirty-two patients were on dopaminergic treatment: 17 on levodopa only, 6 exclusively on dopaminergic agonists, and 9 on both types of drugs. Amantadine was not used and neither neuroleptic nor cholinesterase inhibitors.

Considering the whole sample, LED showed a correlation trend, although with a low level of evidence, with PPQ total score ($r_s = 0.311$; $P = 0.065$), and BPRS-E positive symptoms ($r_s = 0.322$; $P = 0.056$). There was no evidence of correlation between LED and the other BPRS-E factor scores, or between LED and the Total BPRS-E score.

Fifteen patients were defined as cases by the PPQ. Of these, 4 reported the presence of illusions but not of major psychotic phenomena. In fact, as these psychotic symptoms were not disturbing to the patients, they did not lead to any specific changes in the management of the patients.

Although the mean LED was higher in PPQ cases than in noncases, this difference was not statistically significant after correcting for multiple comparisons (Table 2). MMSE and FAB scores were similar between cases and noncases.

Mean scores of the BPRS subscales did not differ in PPQ cases and noncases, except for the positive symptom subscale scores, which were higher in the cases' group (Table 2).

The PPQ total score was significantly correlated with total BPRS-E and positive symptoms BPRS-E scores (Table 3).

3.2. Discussion. Prevalence of psychotic symptoms in PD is variable among different studies. Cross-sectional studies of clinical populations have reported prevalences as disparate as 25% [19] and 75% [20]. This may be due to differences regarding the type of psychotic phenomena assessed, different diagnostic criteria, and other methodological issues. Williams et al. [20], for instance, encompassed minor psychotic phenomena in their definition of psychosis and identified them in a large majority (72%) of their PD patients. However, this study was not limited to early stage patients.

In our study, minor psychotic phenomena were responsible for the definition of approximately one quarter of cases. This could help to explain the high prevalence of psychotic symptoms found in our sample of patients with early stage PD. Furthermore, Graham et al. [19] described that the proportion of hallucinations did not increase in a linear fashion with PD progression. They found that there was a peak of onset of perceptual disturbances during the first five years of disease. However, subsequent longitudinal studies did not confirm this finding [21].

A number of studies have also suggested that demographic factors, like age, could be related to a high prevalence of hallucinations in an early stage population, independent of disease duration [22, 23]. Actually, the majority of our patients were aged and that may have contributed to a higher prevalence of psychotic symptoms in our sample.

Sampling bias could have also contributed to these results: first, our sample was not randomized; second, one may argue that early PD patients with manifest psychotic symptoms are more easily referred to a neurology outpatient clinic.

LED was not significantly associated with psychotic symptoms in this sample. The relation of dopaminergic treatment with psychotic symptoms in PD is still a matter of debate. Data on untreated patients with early PD is scarce and conflicting [4]. Furthermore, several cross-sectional studies could not identify differences in LED between patients with and without hallucinations [4]. However, a recent meta-analysis [24] reported that dopamine agonists were associated with higher odds of experiencing hallucinations, when compared with both placebo and levodopa. Dopaminergic treatment may be an important risk factor for psychotic symptoms in PD, as hallucinations in drug-free PD patients are very rare. In fact, none of our drug free patients presented with hallucinations. We were not able, though, to evaluate the association of different treatment profiles with psychosis because of the small number of patients in each group (levodopa, dopaminergic agonists, or both).

A longitudinal study found that cognitive impairment in early PD predicted the development of psychotic symptoms with treatment [25]. In this cross-sectional scenario, we were not able to reproduce an association between cognitive scores and the presence of psychosis according to the PPQ case definition.

TABLE 2: Comparison of levodopa equivalent dose and BPRS scores between PPQ cases and noncases.

	PPQ non-cases mean (standard deviation)	PPQ cases mean (standard deviation)	Adjusted [†] <i>P</i> value (Mann-Whitney test)
Levodopa equivalent dose	302.38 (377.07)	527.00 (363.73)	0.336
MMSE	27.33 (2.9)	27.07 (1.9)	>1
FAB	11.67 (3.12)	10.80 (3.19)	>1
BPRS—total score	1.23 (0.16)	1.31 (0.16)	>1
BPRS—positive symptoms	1.10 (0.16)	1.43 (0.37)	0.016
BPRS—negative symptoms	1.15 (0.24)	1.24 (0.23)	0.936
BPRS—mania/disorganization	1.04 (0.06)	1.03 (0.051)	>1
BPRS—depression/anxiety	1.62 (0.57)	1.57 (0.51)	>1

[†] Bonferroni correction was used to correct for multiple comparisons.

TABLE 3: Correlations between PPQ total score and BPRS scores (total and subscale scores). Spearman's rank correlation coefficient was used ($n = 36$).

	PPQ total score
BPRS (total score)	0.359; <i>P</i> = 0.032
BPRS (positive symptoms score)	0.469; <i>P</i> = 0.004
BPRS (negative symptoms score)	0.124; <i>P</i> = 0.472
BPRS (depression/anxiety score)	0.205; <i>P</i> = 0.231
BPRS (mania/hostility score)	-0.109; <i>P</i> = 0.528

Albeit not above moderate levels, an association was found between the PPQ scores and the BPRS-E scores. Interestingly, this association was only evident concerning the BPRS-E total score and the positive symptoms subscale score, which includes the psychotic symptoms most often reported in PD. In fact, BPRS-E-positive symptoms would be expected to correspond *grosso modo* to the hallucination/illusion and delusional categories of the PPQ. Moreover, PPQ cases presented significantly higher scores of BPRS-E positive symptoms when compared to noncases. Therefore, there is an argument to further explore the use of the PPQ for PD psychosis both in research and clinical settings.

Along with selection bias, the main limitations of this study are the small sample size and the lack of a control group. Furthermore, our evaluation did not include follow-up data. Regarding assessments, we had no previous knowledge of the detailed psychometric properties of the PPQ in Portugal, and we postulated a BPRS-E factor structure, which in fact was not originated in PD populations. Also, since the BPRS-E is an instrument that provides a continuous measure of psychopathology and is not a diagnostic tool, we could not calculate PPQ sensitivity and specificity in this population. The fact that evaluations were not conducted blindly by the interviewers, who used the PPQ and the BPRS in the same patient, may have contributed to some bias. Nevertheless, by applying the PPQ systematically after the BPRS, we tried to reduce this bias. The structured nature of the PPQ would not allow for any probing that could have been prompted by the answers to the BPRS-E.

4. Conclusions

In this paper, we described a small nonrandomized sample of early stage PD Portuguese outpatients, exploring PPQ validity as related to BPRS-E results in the detection of PD psychosis.

We found an acceptable agreement between PPQ and BPRS-E assessments, and this supports, to some extent, the PPQ as a feasible and valid screening instrument for psychosis in PD, namely, in early stages of the disease. While the PPQ is easily used and allows for quick administration procedures, the BPRS-E remains a more demanding, semi-structured instrument that requires specific training.

Easy and quick-to-use tools like PPQ, if valid in early PD, may contribute to a precocious identification of psychotic symptoms and hopefully to a better clinical management of patients with PD.

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Clinical Study

The Prevalence of Fatigue Following Deep Brain Stimulation Surgery in Parkinson's Disease and Association with Quality of Life

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Fatigue is a common and disabling nonmotor symptom seen in Parkinson's disease (PD). While deep brain stimulation surgery (DBS) improves motor symptoms, it has also been associated with non-motor side effects. To date no study has utilized standardized instruments to evaluate fatigue following DBS surgery. Our objective was to determine the prevalence of fatigue following DBS surgery in PD its impact on quality of life and explore predictive factors. We recruited 44 PD subjects. At least one year following DBS placement, we administered the Fatigue Severity Scale (FSS), the Parkinson's Disease Questionnaire (PDQ-39), the Beck Depression Inventory, the Beck Anxiety Inventory, the UPDRS, and a neuropsychological battery. Fifty-eight percent of subjects had moderate to severe fatigue. Fatigue was significantly associated with quality of life, depression, and anxiety. Depression preoperatively was the only predictive factor of fatigue. Fatigue is common following DBS surgery and significantly impacts quality of life.

1. Introduction

Fatigue is one of the most common and disabling non-motor symptoms seen in Parkinson's disease (PD) with studies showing a prevalence of moderate to severe fatigue in 33–58% of PD patients [1]. Fatigue is reported by one-third of patients as their most disabling symptom and is associated with a worse quality of life [2, 3]. The cause of fatigue in PD remains unclear. Fatigue is seen even in newly diagnosed PD patients and does not correlate with motor symptoms, other measures of disease severity, sleep dysfunction, or medication use [1–4]. While studies have shown depression to be the variable most strongly and consistently associated with fatigue in PD they also demonstrate that these symptoms are frequently independent [5, 6]. Cognitive dysfunction is also

associated with fatigue in PD in some studies but is clearly independent from fatigue in many patients [4, 7].

While deep brain stimulation surgery (DBS) has proven to be an effective treatment to address the motor symptoms/fluctuations in PD, more recent literature has demonstrated that DBS may also be associated with significant non-motor side effects, including changes in speech, worsening cognition, and negative mood states [8–11]. These non-motor side effects may limit the benefit of DBS for some patients, particularly in terms of overall quality of life (QOL). Fatigue has been largely unexamined in this population, but given the prevalence of other non-motor issues in this population, the potential for adverse effects on QOL is worthy of further study. Funkiewiez and colleagues utilized the Addiction Research Center Inventory (ARCI) questionnaire

Parkinson's Disease to evaluate fatigue on and off of DBS patients three months following surgery [12]. They observed some improvement in momentary "fatigue" when subjects were in their on-DBS state. However, it is unclear how their measure of fatigue, designed to test the affect of psychoactive substances, relates to fatigue in PD, and whether the acute on/off effects are representative of the chronic effects of long-term DBS stimulation.

To date, no study has utilized standardized fatigue instruments to evaluate the prevalence of fatigue or its impact on HR QOL following DBS surgery. Our primary objectives were to (1) determine the prevalence of clinically significant fatigue in PD patients who have undergone DBS surgery; (2) determine the association of fatigue with health related quality of Life (HR-QOL). We hypothesized that fatigue is common following DBS and inversely associated with HR-QOL. Exploratory aims were to (1) identify disease characteristics, mood, or neuropsychological variables associated with fatigue in this cohort; (2) identify whether any aspects or preoperative testing predicted fatigue following DBS. We hypothesized that depression and cognitive dysfunction would be associated with fatigue in this population and also predict fatigue following DBS when detected preoperatively.

2. Methods

The investigational protocol was approved by the University of Florida Institutional Review Board. All participants gave written informed consent.

2.1. Participants. Forty-four consecutive patients with PD who were at least one year after DBS surgery, able to give consent, and interested in participating in research were recruited from the University of Florida Movement Disorder Clinics and clinical research database from May 2006 to July 2007.

2.2. Procedure. All subjects completed the following questionnaires at the time of recruitment: the Fatigue Severity Scale (FSS) [13], the Parkinson's Disease Questionnaire Quality of Life-39 (PDQ-39) [14], the Apathy Scale [15], the Beck Anxiety Inventory (BAI) [16], and the Beck Depression Inventory (BDI-II) [17]. These scales have all been validated within the PD population [14, 18–21]. Moderate to severe fatigue was defined as a score of 4 or greater on the FSS. Disease severity was assessed using the Hoehn and Yahr scale [22] and motor section of the Unified Parkinson's Disease Rating Scale (UPDRS) [23] in the on-DBS and On medication state.

For our exploratory objectives, a substantial subset of patients ($N = 28$) had additional data available through our clinical research database collected within six months of recruitment for the current study and also pre-operatively. This data included the State Trait Anxiety Inventory [24], and a standard battery of neuropsychological function: Mini Mental Status Exam [25], Dementia Rating Scale-2 [26], Wechsler Abbreviated Scale of Intelligence [27], Wechsler

Adult Intelligence Scale III (test the digit span, and digit symbol) [28], Stroop Color and Word Test [29], Trail A and B [30], Boston Naming test [31], Controlled Oral Word Association Test [32], Category Fluency Test [33], Hopkins Verbal Learning Test-Revised [34], Wechsler Memory Scale III [28], Judgment of Line Orientation Test [35], Face Recognition Test [36], and Benton Visual Retention Test [37]. Disease severity was assessed preoperatively (on medications) using the Hoehn and Yahr scale [22] and the motor section of the UPDRS [23].

2.3. Statistical Analysis. Statistical analysis was performed using SAS version 9.2 (SAS Inc., Cary, NC). Wilcoxon rank-sum test was used to determine differences between groups. Spearman's correlation was performed to determine relationships between continuous variables. Chi-square test, or Fisher exact test, was when appropriate used to assess the relationship between categorical variables. Linear regression models were used to assess the association of multiple variables, including controlling for confounding variables. P values $< .05$ were considered significant.

3. Results

3.1. Prevalence of Fatigue and Characteristics of the High and Low Fatigue Patients. Fifty-eight percent of subjects (95% confidence interval: 43–73%) had a score of 4 or greater on the FSS. The mean FSS score for this cohort was 4.2 (SD 1.3). When subjects were divided into low (FSS < 4 ; mean FSS 3.0, SD 0.6) and high (FSS ≥ 4 ; mean FSS 5.2, SD 0.8) fatigue groups, significant differences were found only in anxiety (BAI 8.0 versus 15.9, $P = 0.001$) and quality of life (PDQ 39 23.8 versus 33.0, $P = 0.02$) in low versus high fatigue groups, respectively. Trends for differences were also noted in depression (BDI 7.4 versus 12.0, $P = 0.07$) and disease duration (17.1 versus 14.1 yrs, $P = 0.10$). Table 1 outlines these comparisons and summarizes group demographic data.

3.2. Correlation of Fatigue with Quality of Life. FSS scores were significantly associated with the total score of the PDQ 39 ($r = 0.37$, $P = 0.01$) as well as the majority of PDQ subscales including mobility, emotional well-being, social support, cognition, and bodily discomfort. See Table 2 for the correlation of fatigue with PDQ 39 subscores. Linear regression models demonstrated that the association between the FSS and PDQ 39 remained significant even after controlling for age, disease duration, and motor severity (FSS F-value in model 9.83, $P < 0.01$).

3.3. Correlation of Fatigue with Disease Severity, Mood, and Neuropsychological Test Results. Fatigue was associated with depression as measured by the BDI ($r = 0.47$, $P = 0.01$) and anxiety as measured by the BAI ($r = 0.49$, $P < 0.01$) but not with apathy, age, disease duration, time since DBS, the UPDRS (on or off), Hoehn and Yahr (on or off), anxiety measured with State and Trait Anxiety Inventory (STAI), or any neuropsychological test scores.

TABLE 1: Comparison of clinical characteristics in high and low fatigue patients. Data reported as mean (standard deviation).

	Total ($n = 44$)	Low fatigue (FSS < 4) ($n = 19$)	High fatigue (FSS ≥ 4) ($n = 25$)	P value
Age (years)	63.3 (10.0)	61.5 (11.4)	64.7 (8.8)	0.32
Gender (% male)	86%	84%	88%	0.71*
DBS target	STN (30)	STN (14)	STN (16)	0.59**
	GPI (10)	GPI (3)	GPI (7)	
	VIM (4)	VIM (2)	VIM (2)	
Disease duration (years)	15.5 (5.5)	17.1 (6.0)	14.1 (11.8)	0.10
Months after DBS	26.1 (20.9)	27.3 (25.8)	25.3 (12.4)	0.81
Hoehn and Yahr (on)	2.5 (0.7)	2.5 (0.5)	2.5 (0.7)	0.92
UPDRS motor (on)	28.1 (12.6)	26.9 (12.7)	28.9 (12.7)	0.64
FSS	4.2 (0.8)	3.1 (0.6)	5.1 (0.8)	<0.0001
MMSE	27.8 (2.4)	28.2 (1.9)	27.2 (3.0)	0.25
BDI	9.2 (7.2)	7.4 (6.6)	12.0 (7.4)	0.07
BAI	12.2 (8.2)	8.0 (5.2)	15.9 (8.6)	0.001
Apathy Scale	13.2 (6.6)	11.7 (7.1)	14.4 (6.1)	0.20
PDQ 39	28.7 (13.9)	23.8 (12.0)	33.0 (14.2)	0.02

Wilcoxon test was used except for: *Chi Square test was used and **Fisher's Exact Test was used.

BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; DBS: deep brain stimulation; FSS: Fatigue Severity Scale; GPI: globus pallidus interna; MMSE: Mini Mental State Examination; PDQ: Parkinson's Disease Questionnaire; STN: subthalamic nucleus; UPDRS: Unified Parkinson's Disease Rating Scale; VIM: ventral intermediate nucleus of thalamus.

TABLE 2: Correlation of Fatigue Severity Scale with Parkinson Disease Questionnaire (PDQ) 39 subscores.

PDQ 39 subscore	Spearman's correlation (P value)
Total	0.37 (0.02)*
Mobility	0.33 (0.04)*
Activities of daily living	0.27 (0.08)
Emotional well-being	0.38 (0.01)*
Stigma	0.16 (0.32)
Social support	0.20 (0.20)
Cognition	0.42 (0.006)**
Communication	0.11 (0.50)
Bodily discomfort	0.49 (0.001)**

* P value significant <0.05; ** P value < 0.01.

3.4. Factors Predictive of Fatigue in PD Patients Who Have Undergone DBS Surgery. Depression as measured by BDI was the only preoperative measure associated with fatigue (Spearman's $r = 0.48$, $P = 0.03$). While there was a strong correlation between pre and postoperative BDI scores ($r = 0.68$, $P < 0.01$), preoperative BDI scores remained associated with the FSS even when controlled for postoperative BDI in a linear regression model (BDI F-value in model 4.64, $P = 0.05$). There was no association between DBS target and fatigue (see Table 1; Fisher exact test $P > 0.05$), anxiety (as measured by STAI only), apathy, or any neuropsychological test scores.

4. Discussion

Fatigue is a common non-motor symptom following DBS surgery and seems to significantly impact HR-QOL. Our

finding of 58% prevalence among DBS subjects is on the higher end of the range of previously reported fatigue prevalence in PD subjects without DBS which have ranged from 33–58% [1]. Our data suggest that fatigue may be related to mood disturbances, and this finding may have implications for future research into the causes of fatigue in DBS subjects.

The association of depression and fatigue has been well documented in PD patients [1, 38]. The correlation with anxiety as measured by the BAI, however, has not been reported. Given the high prevalence of both symptoms, it is not surprising that there would be some comorbidity between these two symptoms [39]. It should be noted, however, that the State and Trait Anxiety Inventory failed to show a significant correlation with fatigue. This finding suggested that part of this association may be related to test factors, for instance the weight of somatic questions on the BAI. It is also possible that certain types of anxiety disorders (e.g., panic disorders which is better screened by the BAI) may be more associated with fatigue and better measured by certain scales [40]. Whether this association has relevance to PD patients without DBS is unknown but worthy of further study given the prevalence of both fatigue and anxiety in PD.

The lack of correlation between fatigue and apathy or neuropsychological performance is notable. One prior investigation demonstrated a trend toward correlation between fatigue and the Wisconsin Card Sorting task as well as a significant association with frontal hypometabolism on PET [41]. A second study suggested that MMSE scores were higher in subjects with greater fatigue, but this result may have been confounded by other differences between high and low MMSE groups [7]. Our findings may suggest that fatigue arises independently of other neuropsychological symptoms in patients following DBS. However, objective testing specifically for mental fatigue may prove to be more

sensitive in investigating this possible association [42]. It should also be noted that DBS patients are a highly selected population to begin with and may not have sufficient variability in cognitive measures to fully explore a potential association with fatigue. Moreover, our sample size of subjects with adequate neuropsychological results ($N = 28$) is not sufficient to detect subtle associations, and testing was often not performed at the time of other subjective measurements but included if performed within a six month window.

This study has several notable limitations, including its relatively small size, lack of longitudinal data, capture of several variables at disparate time points (e.g., neuropsychological test results), and lack of a control group. Regarding our definition of fatigue, while the FSS has been widely used to define clinically significant fatigue in many diseases, including in PD, there are clear differences between the various subjective scales and even more so with objective measures of fatigability [19, 42]. Importantly, as fatigue was not assessed prior to DBS surgery, we cannot determine whether DBS impacts fatigue in this population. Future investigations should consider using a larger sample size, assessing fatigue and other explanatory variables longitudinally (particularly prior to DBS), assessing sleep, and having a control group of PD patients on medical treatment.

4.1. Conclusions. Fatigue is common following DBS surgery in PD and has a negative impact on HR QOL of the patients. Fatigue in this population appears associated with depression and possibly anxiety but did not correlate with other neuropsychological tests or disease characteristics. Future research should investigate fatigue before and after DBS to determine whether DBS impacts this important symptom.

Conflicts of Interests

The authors report no conflict of interest.

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Clinical Study

Metacognitive Performance, the Tip-of-Tongue Experience, Is Not Disrupted in Parkinsonian Patients

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The present study investigated whether a form of metamemory, the tip-of-tongue phenomenon (TOT), was affected in patients with Parkinson's disease (PD). The PD patient ($n = 22$), age-matched elderly control ($n = 22$), and college student control ($n = 46$) groups were compared on a motor timing task and TOT measures. Motor timing was assessed using a cued hand-clapping task, whereas TOT was assessed using general knowledge questions. The results indicated that motor timing was significantly impaired in the PD group relative to both control groups. However, all of the TOT metacognitive measures: frequency, strength, and accuracy were statistically equivalent between the PD patients and elderly control groups, both of whom showed significantly better memory performance than college controls. These findings demonstrate that TOT metamemory is not compromised in PD patients, and that further insight into TOT mechanisms in PD may prove helpful in developing novel intervention strategies to enhance memory and general cognitive functions in these patients.

1. Introduction

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder characterized by the selective degeneration of dopamine-producing neurons extending from the substantia nigra pars compacta (SNc) to the striatum [1]. Whereas motor symptoms are perhaps the most obvious and well-known clinical features of PD [2], there is also a constellation of nonmotor symptoms that precede motor symptoms, which are both debilitating and problematic [3]. Cognitive deficits are perhaps the broadest group of nonmotor symptoms, and these symptoms can be generally grouped into categories of impairments in visuospatial function [4], learning and memory [5], and executive function [6, 7]. These early cognitive symptoms are thought to be, at least partly, the result of a denervation of dopaminergic neurotransmission from the SNc [8] and may share common

underlying pathogenic factors to motor symptoms manifested at later stages of the disease [9].

Dopamine dysfunction in PD has also been associated with a range of memory difficulties [10], including working memory [11–13], prospective memory [14, 15], emotional memory [16], and category memory [17]. Moreover, memory deficits are often observed before any clinically significant motor symptoms are detected [18], giving them both diagnostic and therapeutic relevance [19]. Unfortunately, the treatment of memory impairments is often difficult, particularly when multiple symptoms are present [3]. One potentially useful strategy for improving memory in PD is to promote one's ability to monitor and control one's own cognitive functions, also known as metacognition [20–22]. The rationale behind these investigations is that poor memory performance in PD may stem from poor monitoring and control of one's memory functions [23, 24]. Monitoring

and control can occur at every stage of memory operation (i.e., encoding, storage, and retrieval), and the assumption is that one's awareness of the current state of memory at each stage or metacognitive knowledge is causally related to the control processes one would adopt (e.g., spending more time searching for the answer). Among PD patients, many of the studies have focused on metamemory processes referred to as feelings-of-knowing (FOK) judgments [25–27]. In the present investigation, another, albeit similar, type of metacognitive judgments, referred to as a tip-of-the-tongue (TOT) metamemory judgments, was investigated because there is some evidence to indicate that these two types of judgments are based on different processes, which may be supported by distinct neural basis. In the present study, we focused on TOT during retrieval, because for elderly population including PD patients, TOT judgments associated with retrieving the knowledge they already have are not only central in decision making and in day-to-day activities, but also has an important clinical and prognostic implications.

FOK judgments are one's judgment that a piece of information that cannot currently be recalled is still in memory and can be recognized correctly if shown it at a later point in time [28–30]. Several studies demonstrated that the integrity of the frontal lobe function associated with executive cognitive function appears to be closely related to FOK [28, 29, 31]. Patients with frontal lobe injuries have also shown deficits in FOK accuracy [32]. Further support for the link between FOK and PFC comes from studies which have demonstrated that FOK metacognitive abilities are severely impaired in PD patients [25–27], who exhibit PFC dysfunction that is associated with degeneration of the basal ganglia motor circuitry [33, 34]. Also consistent are results from prospective memory studies indicating that patients with PD were preferentially impaired on event-based or time-based prospective memory tasks with higher levels of executive control, possibly associated with prefrontal lobe dysfunction in PD [14, 15, 35].

The first behavioral investigation of FOK was conducted by Hart [30] using the RJR (recall-judgment-recognition) paradigm. In this paradigm, participants are asked to answer general knowledge questions. If they are unable to retrieve the answer, they are asked to judge whether they have the answer (even though they are unable to retrieve it at the moment) and would be able to recognize the answer if it is presented among distractors at a later point in time. The RJR paradigm has been used to assess FOK in both episodic (e.g., paired-associate lists) and semantic memory (e.g., general knowledge questions) [31, 36, 37]. In the present study, general knowledge questions were used because answering these questions represents semantic modality that involves judgments about already existing information that is well integrated in the semantic network [38–40].

A TOT experience reflects a state of mind in which people are temporarily unable to think of target words or sought after information but feel that retrieval is imminent. A TOT is a frustrating emotional experience of not being able to retrieve the information on demand, but having an intense feeling that the sought-after information will pop into one's mind at any moment [41–43]. This intense feeling of

imminence that the sought-after information will come to consciousness [36] is what differentiates TOTs from FOKs [44]. It has been suggested that TOTs are qualitatively different from FOK experiences [31, 43, 45] and that TOT and FOK are disparate neuropsychological states, perhaps regulated by different neural substrates [29, 46].

Studies in the area of neuroimaging have indicated that brain activity differs during TOT and FOK experiences. TOT appears to be localized within specific frontal lobe areas, but FOK activity is more generalized throughout the frontal and limbic areas. Activity in the anterior cingulate cortex (ACC), right dorsolateral prefrontal cortex, and right inferior cortex is uniquely associated with TOT judgments and resolution during the retrieval process [46–48]. On the other hand, the same ACC-prefrontal regions together with left prefrontal regions along the inferior frontal gyrus and several parietal regions were associated with FOK judgments [46, 47]. These differences in the neural correlates are reflected, in part, by the overall selective effect of PFC functioning on FOK, but not on TOT experiences. This research together with multiple independent observations [31, 45, 48–50] indicates that different areas of the brain may be activated during TOT as opposed to FOK and further lends support for the notion that TOT and FOK are disparate cognitive states, perhaps regulated by different neural substrates. It is, therefore, possible that TOT, but not FOK, is localized within specific areas including the right prefrontal and ACC regions, and the damages to within these brain regions summate to produce impairments on tasks sensitive to TOT metacognitive processes. On the other hand, if these brain regions remain intact, TOT should not be impaired in these individuals. Based on these studies and current findings pointing to the dissociation between FOK and TOT judgments, with FOK, but not TOT, being closely linked to generalized PFC function, it could be predicted that TOT metacognitive function, subserved by localized and specific frontal areas, may remain unaltered in PD patients [29, 31, 46].

In regards to TOTs in PD, one study revealed that PD patients experience TOT-like states when given a variety of verbal and naming tasks, such that participants experienced word-finding difficulties in the absence of memory loss [51]. In this study, PD patients showed impaired semantic performances during confrontation naming and category naming tasks, suggesting a problem in cognitive strategies necessary for appropriate word production and naming [51]. Although these behavioral deficiencies share some characteristics of TOT phenomenon, TOT metamemory was not directly measured in their study. The present study utilizes aforementioned RJR paradigm with general knowledge questions to evaluate comprehensive measures of TOT metamemory: its frequency, strength, and accuracy, during semantic knowledge retrieval process.

The goal of this study was to examine whether there is a deficit in TOT in nondemented patients with PD. In the present study, groups of PD patients, elderly control participants, and college control participants were compared on a motor timing task and a TOT metamemory task. First, PD patients and control participants were compared on their ability to clap in time to a cued metronome beat to show

TABLE 1: Characteristics of participants (means and standard deviations).

	College control ($n = 46$)	Elderly control ($n = 22$)	PD ($n = 22$)
Age	20.65 (3.54)	68.41(9.70)*	71.50 (8.04)*
Education (in years)	13.26 (1.60)	13.36 (2.11)	14.36 (3.13)
MMSE	27.87 (2.00)	26.55 (2.37)*	25.36 (2.80)*
Age at diagnosis (PD)	—	—	62.91 (10.47)
Duration of disease	—	—	8.52 (5.80)

* $P < .05$ compared to college students. PD = patients with Parkinson's disease.

that PD patients exhibit typical motor impairment [52]. Second, PD patients and control participants were compared on a TOT task based on general knowledge questions. Because motor timing impairment in PD is closely linked to dysfunction in PFC [52–56], and because TOT does not appear closely linked to PFC function, it was predicted that individuals with PD would not show compromised TOT metacognition. The absence of TOT deficit would provide evidence that cortical and subcortical networks mediating this function are most likely still intact in patients with PD. Having intact metamemory functions, such as TOT, is believed to be important for normal functioning of one's memory, such as selecting effective retrieval strategies [57], and consequently would lead to improvement in the quality of life for these patients [58, 59]. The present study was, therefore, designed to test the hypothesis that TOT metamemory is unimpaired in PD patients who demonstrate motor response timing deficits.

2. Method

2.1. Participants. Twenty two PD patients (13 men and 9 women) were recruited from various mid-Michigan Parkinson's disease support groups. These patients received \$25 for their participation and were tested in their home or at a local community center. They ranged in age from 55 to 83 years (Table 1). PD diagnosis was made by the patient's primary neurologist prior to this study. Patients were asked to report the time elapsed since their first diagnosis of PD and asked to indicate their perceived symptom severity [60]. At the time of testing, the average disease duration of the PD patients was 8.52 years ($SD = 5.80$). Patients were assessed on their regular medication (levodopa = 14, dopamine agonists = 11, COMT inhibitor = 5, MAO-B inhibitor = 4, anticholinergic = 1, and NMDA receptor antagonist = 1, SSRI = 2, with the exception of one individual who was taking no medication). Twenty two normal elderly control participants (9 men and 13 women) were either spouses or family members of those PD patients. Elderly control participants received \$15 for participation and were tested in their home or at a local community center. Elderly participants ranged in age from 49 to 86 years (Table 1). Forty six normal college control participants (23 men and 23 women) were recruited from the subject pool at Central Michigan University. They received extra course credit. Participants ranged in age from 18 to 34 years (Table 1). The guidelines for ethical treatment of human participants were followed with approval given by the IRB at Central Michigan University.

Participant's age, educational background, and Mini-Mental State Examination (MMSE) scores are summarized in Table 1. The elderly control group did not differ from the PD with regard to age, education level, or MMSE scores.

2.2. Materials and Procedure. Participants, tested individually, were given verbal instructions as well as a written copy of the instructions. They were informed that they would be participating in a motor timing task, where they would be asked to clap in time to a cued metronome beat. The Groove metronome device and software were used (New York, NY) [61]. Participants were asked to put on a headphone and a touch-sensitive hand device. They then clapped their hands in time to a cued metronome beat, which provided an auditory feedback. Visual feedback was provided via the computer monitor, such that participants could see how many milliseconds they were off from the cued beat with each clap. Their average timing responses were recorded by the computer program in an average of milliseconds they were off from the cued sound. It also provided the percentage of times the participants responded early and late (% early/late) during each session. Timing scores ranged from 0 to 500 milliseconds, with zero indicating that the participant was clapping directly on time with the cued metronome beat. Participants performed three different sessions (1 minute, 2 minute, and 1 minute) with a short break (30–40 seconds) between each session. In addition, motor impairment was assessed by asking the PD patients the extent to which they felt physically impaired by PD, as well as to indicate the extent to which they felt mentally impaired by PD. Scores on this index range from 1 to 7, with 1 indicating no impairment and 7 indicating severe impairment.

TOT performance was assessed by 30 general knowledge questions from the Nelson and Narens [58] norms that were presented on a computer screen, one at a time. These questions were the same as those used by Widner et al. [31] and were selected from the questions that had a normative recall probability between .41 and .58. For each question, participants were asked to orally respond with (1) the answer they thought fit, (2) say "do not know" if they did not know the answer, or (3) indicate that they were having a TOT experience, where they believed that they knew the answer but they could not currently recall it and that the answer would pop into their mind at any moment. When participants indicated a TOT state, they were asked to provide the strength of TOT experience by indicating how strong this feeling was on a scale of 1–20 (1—extremely weak; 20—extremely strong). They were given 20 seconds for each question, and

the experimenter wrote down the response given for each question. No feedback was provided. Next, participants were given a 4-alternative forced-choice recognition test. With each question, participants were asked to choose a correct answer without leaving any questions blank.

The accuracy of TOT responses was examined by a Goodman-Kruskal gamma correlation computed for each participant [31]. The gamma correlation measures the association between TOT reports and subsequent recognition performance. The assumption is that if one has the answer, but is unable to retrieve it for the moment, they are likely to be able to recognize it on a subsequent recognition test. Just like any other correlational measure, gamma correlation ranges from -1 to $+1$. The correlation of 0 indicates no association between TOT responses and recognition performance, whereas the correlation of $+1$ indicates the perfect association between TOT responses and recognition performance. It is difficult, if not impossible, to interpret the correlation of -1 . The gamma is computed based on four measures created by a 2×2 matrix consisting of TOT (yes or no) and recognition (yes or no). The four measures are frequency counts of (a) the items with TOT responses that are correctly recognized, (b) the items with TOT responses that were not correctly recognized, (c) the items without TOT responses that were correctly recognized, and (d) the items without TOT that were not correctly recognized. The gamma score is computed by the following formula, $\text{gamma} = (\text{ad} - \text{bc}) / (\text{ad} + \text{bc})$. This means that when the sum of the two products (ad and bc) is zero, the gamma score is undetermined, and therefore, we had to exclude these participants from the analysis. Four participants from the PD patient group (18.2%), five participants from the elderly control group (22.7%), and three participants from the college student group (6.5%) were excluded. Because the percentage of excluded participants was not greater in the PD patient group than in the elderly control group, we proceeded with this analysis.

3. Results

3.1. Timing Performance. Figure 1 shows the mean timing deviation from the cued metronome beat for the first, second, and third sessions for the PD patient, elderly control, and college student groups. As shown, the PD patients showed lower timing accuracy than the elderly control and college student groups. A 3 (group: PD patient, elderly control, and college student) \times 3 (session intervals: first, second, and third) mixed-design analysis of variance (ANOVA) was conducted, with group as a between-subjects variable and session interval as a within-subjects variable. Due to a computer failure to record data, one college student was excluded from the analysis. The results indicated that the main effect of group was significant, $F(2, 86) = 14.53$, $\text{MSE} = 12757.43$, $P = .0001$, and $\eta_p^2 = .25$. However, the main effect of interval, $F(2, 172) = 0.19$, $\text{MSE} = 1659.34$, $P = .83$, and $\eta_p^2 = .002$, as well as the group \times interval interaction, $F(2, 172) = 1.00$, $\text{MSE} = 1659.34$, $P = .41$, and $\eta_p^2 = .02$, was not significant. Fisher LSD tests comparing the three groups indicated that the PD patient group showed significantly lower timing

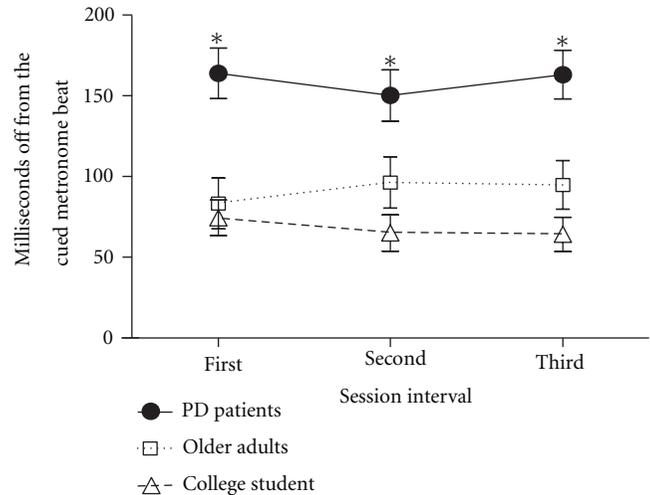


FIGURE 1: Motor timing performance (average of milliseconds off from the cued sound) for the first, second, and third sessions on the Groove for college students (open triangle), older control adults (open square), and Parkinson patients (filled circle). * $P < .05$ compared to college students.

accuracy ($M = 159.06$, $SD = 81.84$) than the elderly control ($M = 91.47$, $SD = 59.38$) and college student ($M = 67.87$, $SD = 58.58$) groups, with the latter two groups showing no difference from each other. It is also important to note that those PD patients who showed overall timing deficit had a greater proportion of their clapping responses occurring before the cued beat (indexed by % early responses) than the corresponding elderly control (≤ 70 years) and college student groups: $M = 80\%$, 69% , and 76% early responses, respectively, $F(1, 62) = 1.30$, $\text{MSE} = 255.7$, and $P = .03$.

3.2. Memory Performance. Figure 2 shows the mean proportion of (1) correctly recalled items, (2) incorrectly recalled items, and (3) correctly recognized items. Because the recognition test was a forced-choice test, the false alarm rate is the inverse of the mean correctly recognized items. As shown, all three measures showed comparable performance between PD patients and elderly control participants. These two groups, in turn, performed better than college students. A one-way between-subjects ANOVA was used to compare the three groups on each measure. For the correctly recalled items, the difference among the groups was significant, $F(2, 87) = 3.13$, $\text{MSE} = 0.29$, $P = .049$, and $\eta_p^2 = .07$. Fisher LSD tests showed that the difference between the PD patient ($M = .35$, $SD = .18$) and elderly control ($M = .35$, $SD = .17$) groups was not significant. Fisher LSD tests further showed that these two groups recalled a significantly greater number of correct answers than the college student group ($M = .26$, $SD = .16$). For the incorrectly recalled items (i.e., commission errors), the difference among the groups was significant, $F(2, 87) = 7.86$, $\text{MSE} = 0.003$, $P = .001$, and $\eta_p^2 = .15$. Fisher LSD tests showed that the PD patient ($M = .13$, $SD = .50$) and elderly control ($M = .14$, $SD = .06$) groups were not different from each other. The college student group ($M = .09$, $SD = .06$) showed significantly

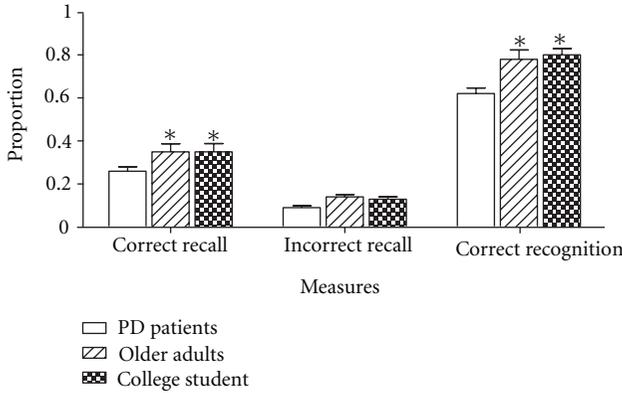


FIGURE 2: Recall and recognition performance expressed in proportion of the total number of general knowledge questions (30 questions) for college students (open bars), older adults (hatched bars), and Parkinson patients (stippled bars). * $P < .05$ compared to college students.

fewer incorrectly recalled items than the PD patient and elderly control groups. The correctly recognized items showed a similar pattern. The difference among the groups for correctly recognized items was significant, $F(2, 87) = 10.20$, $MSE = 0.03$, $P = .0001$, and $\eta_p^2 = .19$. Fisher LSD tests showed that the difference was not significant between the PD patient ($M = .80$, $SD = .15$) and elderly control ($M = .78$, $SD = .20$) groups. These two groups, in turn, outperformed the college student group ($M = .62$, $SD = .18$). These results indicated that memory performance was similar between the PD patient and elderly control groups. Both the PD patient and elderly control groups showed better performance than the college student group. PD patient group showed no evidence of memory deficiency on general knowledge questions.

3.3. Metamemory Performance. Figure 3 shows the mean proportion of (1) “do not know” responses, (2) correctly recognized items that participants said “do not know” (“do not know correct”), and (3) TOT responses across PD patients, elderly control participants, and college students. Figure 3 also shows TOT accuracy across the three groups, measured by Goodman-Kruskal gamma correlation between TOT responses and recognition performance [31, 62]. As shown, PD patients and elderly control participants showed similar performance on the “do not know” and “do not know correct” measures. For each measure, we conducted a one-way between-subjects ANOVA comparing the three groups. The results showed that the difference among the groups was significant for the “do not know” measure, $F(2, 87) = 5.61$, $MSE = 0.04$, $P = .005$, and $\eta_p^2 = .11$. Fisher LSD tests showed that the PD patient ($M = .36$, $SD = .22$) and elderly control groups ($M = .39$, $SD = .20$) made fewer “do not know” responses than the college student group ($M = .51$, $SD = .18$). No difference was found between the PD patient and elderly control groups. The results for the “do not know correct” measure revealed that the difference among the group was not significant, $F(2, 87) = 0.03$, $MSE = 0.01$, $P = .97$,

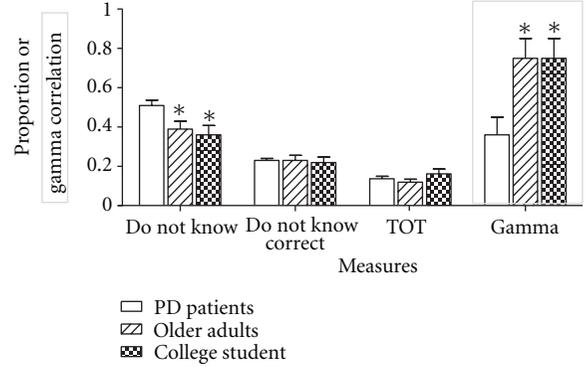


FIGURE 3: Do not know and TOT reports (in proportion to 30 general knowledge questions), TOT accuracy (gamma correlation), for college students (open bars), older adults (hatched bars), and Parkinson patients (stippled bars). * $P < .05$ compared to college students.

and $\eta_p^2 = .001$, indicating that the accuracy of “do not know” responses was similar among PD patients ($M = .22$, $SD = .12$), elderly control participants ($M = .23$, $SD = .12$), and college students ($M = .23$, $SD = .07$). Next, we analyzed the total number of TOT responses. The results showed that the difference among the groups was not significant, $F(2, 87) = 1.27$, $MSE = 0.01$, $P = .29$, and $\eta_p^2 = .03$, indicating that the PD patient ($M = .16$, $SD = .11$), elderly control ($M = .12$, $SD = .07$), and college student ($M = .13$, $SD = .09$) groups showed similar TOT responses (expressed as a proportion of total number of responses). Because the PD and elderly control groups showed higher recall than the college student group, TOT responses were conditionalized on unrecalled items (i.e., TOT plus “do not know” responses); that is, what proportion of unrecalled items participants responded with TOT responses? One-tailed planned t -tests were conducted because the literature indicated that elderly adults tend to experience TOT at a higher frequency than young adults [37, 63]. The results indicated that the difference between the PD patient ($M = .35$, $SD = .23$) and college student groups ($M = .22$, $SD = .13$) was significant, $t(66) = 2.99$, $P = .002$. The difference between the elderly control ($M = .28$, $SD = .24$) and college student groups also approached significance, $t(66) = 1.41$, $P = .08$. Because no difference was found between the PD patient and elderly control groups, $t(42) = 0.97$, $P = .34$, these two groups were combined and compared with the college student group. The difference was significant, $t(88) = 2.44$, $P = .01$, indicating that the older group ($M = .32$, $SD = .24$) showed a higher tendency of making TOT responses than the younger group ($M = .22$, $SD = .13$).

In terms of TOT accuracy, the groups differed on gamma scores, $F(2, 78) = 4.63$, $MSE = 0.19$, $P = .01$, and $\eta_p^2 = .11$. Fisher LSD tests showed that the gamma scores were similar between PD patients ($M = .72$, $SD = .44$) and elderly control participants ($M = .75$, $SD = .40$). The gamma score was significantly lower for the college student group ($M = .36$, $SD = .61$) than the PD patient and elderly control groups,

indicating that the accuracy of TOT responses was lower for the college student group than for the PD patient and elderly control groups. Recently, a question was raised as to whether gamma is the best measure of metacognitive accuracy. Benjamin and Diaz [64] recommend two alternative measures, signal detection (d_a) and G^* . Unfortunately, the former is not suitable for the present data because it requires at least a 2×3 contingency table. Furthermore, G^* discards those participants who showed perfect accuracy. In fact, using G^* , only six participants remained in the PD patient and elderly control groups because many participants in these groups were very conservative. Using the remaining participants, a one-way ANOVA did not show a difference among the groups, $F(2, 37) = 0.15$, $MSE = 1.07$, $P = .86$, and $\eta_p^2 = .01$. We also computed Hart difference score statistic (D) [65], which, according to Benjamin and Diaz, did better than gamma in their simulation. The results of a one-way ANOVA based on D also showed a nonsignificant difference among the groups, $F(2, 79) = 0.12$, $MSE = 0.07$, $P = .89$, and $\eta_p^2 = .003$. All these measures provided converging evidence that the PD patients did not show impairment in TOT accuracy.

To assess the effects of age and the amount of general knowledge on gamma correlation (i.e., TOT accuracy), an analysis of covariance (ANCOVA) was conducted using the age and the number of correctly recognized answers as variables. When the low, medium, and high knowledge groups were compared with age as a covariate, no difference was found among the groups, $F(2, 74) = 1.21$, $MSE = 0.30$, $P = .30$, and $\eta_p^2 = .03$. The difference was also nonsignificant when the young, middle, and old age groups were compared with general knowledge as a covariate, $F(2, 31) = 1.40$, $MSE = 0.14$, $P = .26$, and $\eta_p^2 = .08$. However, age as well as the number of correctly recognized answers significantly correlated with gamma score: age $r(78) = .26$, $P = .02$, and correctly recognized answer $r(78) = .24$, $P = .04$. Further, age was significantly correlated with the number of correctly recognized answers, $r(90) = .40$, $P < .001$. A linear regression showed that age and the number of correctly recognized answers jointly accounted for 9% of variance ($R^2 = .09$), $F(2, 75) = 3.58$, $P = .03$. However, neither alone significantly predicted TOT accuracy.

We also predicted that the MMSE score would be positively correlated with the TOT accuracy for the PD patients and elderly. The results showed that the correlation was nonsignificant for the PD patients, $r(18) = .24$, $P = .17$ (one-tailed) but significant for elderly, $r(17) = .43$, $P = .04$ (one-tailed). Combining the PD patients and elderly, the correlation was significant, $r(35) = .32$, $P = .03$ (one-tailed). In contrast, the correlation was much smaller for college students between the TOT gamma and the MMSE score, $r(43) = .07$, $P = .33$ (one-tailed). In summary, TOT accuracy and MMSE are related in PD patients and elderly, but not for college controls.

The strength of TOT states showed similar patterns. A mean TOT strength was computed for each participant using all TOT responses as well as using only TOT responses that were accurate (i.e., the ones that participants selected correct answers on the subsequent recognition test). Because both

analyses produced similar results, the results from the former analysis will be presented here. An attempt was also made to compute the mean strength of inaccurate TOT; however, due to a small number of these responses, we were unable to proceed with this analysis. A one-way between-subjects ANOVA comparing all three groups showed that the difference was significant, $F(2, 80) = 4.81$, $MSE = 12.52$, $P = .01$, and $\eta_p^2 = .11$. Fisher LSD tests showed that the elderly control group ($M = 13.37$, $SD = 4.66$) showed higher strength than the college student group ($M = 10.47$, $SD = 3.26$). The PD group ($M = 12.00$, $SD = 2.75$) was not different from either group. In sum, there was no evidence that PD patients had metamemory deficiency. Both the PD patient and elderly control groups performed similarly on all metamemory measures: frequency, strength, and accuracy of TOT.

Based on the hypothesis testing procedures reported above, there was no statistical difference between the PD and elderly control groups. However, the failure to reject the null hypothesis does not mean that the two groups are equivalent because the P value is “the probability of data given that the null hypothesis is true” rather than “the probability that the null hypothesis is true given the data” [66, page 372]. To further support the equivalence of the two groups, the procedure that would establish statistical equivalence, described by Tryon [66] and Tryon and Lewis [67], was performed for each memory and metamemory measure as follows. First, the 95% inferential confidence interval (ICI) was computed for each group based on the revised formula described by Tryon and Lewis [67, Equation 9, page 274]. If there is an overlap in 95% ICI between the PD and elderly control groups, the difference is not statistically significant. Then, the question becomes whether the two groups are equivalent or the decision is indeterminant. Second, the value of the delta (Δ) was set. This is the amount of difference between the two groups “that is considered to be inconsequential” based on “substantive grounds that have been established apart from the analysis at hand by professional consensus or other means” [67, page 273]. There is no fast and easy method of determining Δ ; however, for the purpose of the present investigation, we used the width of the 95% confidence interval (CI) for the elderly control group because if the PD group is equivalent to the elderly control group, the likely location of the population mean should be the same between these two groups. Third, the equivalence range (${}_eR_g^{2\alpha}$) was computed for each measure based on the procedure described by Tryon and Lewis. This range was based on 100 $(1 - 2\alpha)\%$ ICI, using the shrinkage factor ($E^{2\alpha}$). Equivalence between two groups is established when ${}_eR_g^{2\alpha} \leq \Delta$ [67, Equation 23, page 276]. The assumption is that the difference between the lowest and the highest ends of 90% ICI (based on both groups) should not exceed Δ . As shown in Tables 2 and 3, for memory performance and metamemory performance, respectively, statistical equivalence is demonstrated in all but the TOT measure. However, when the TOT responses were conditionalized on unrecalled items (i.e., proportion of TOTs in unrecalled items), Δ (.19) did not exceed ${}_eR_g^{2\alpha}$ (.21), indicating that the two means were equivalent.

TABLE 2: Shrinkage factors (E^α and $E^{2\alpha}$), confidence intervals (CI), inferential confidence intervals (ICI), ${}_eR_g^{2\alpha}$, and Δ for memory performance.

	Correct recall		Incorrect recall		Correct recognition	
	PD	Elderly	PD	Elderly	PD	Elderly
M	.35	.35	.13	.14	.80	.78
SD	.18	.17	.05	.06	.15	.20
SE	.04	.04	.01	.01	.03	.04
E^α		.69		.69		.69
$E^{2\alpha}$.69		.69		.70
95% CI	.27-.43	.28-.43	.11-.15	.11-.16	.73-.87	.69-.87
95% ICI	.29-.40	.30-.40	.11-.14	.12-.15	.75-.85	.72-.84
90% ICI	.30-.39	.31-.45	.11-.14	.12-.15	.76-.84	.73-.83
${}_eR_g^{2\alpha}$.09		.04		.11
Δ		.15		.04		.18

Note: $N = 22$; E^α is based on $100(1 - \alpha)$ and $E^{2\alpha}$ is based on $(1 - 2\alpha)$; ${}_eR_g^{2\alpha}$ is based on 90% ICI and Δ is based on 95% CI for the elderly group.

TABLE 3: Shrinkage factors (E^α and $E^{2\alpha}$), confidence intervals (CI), inferential confidence intervals (ICI), ${}_eR_g^{2\alpha}$, and Δ for metamemory performance.

	Do not know		Do not know correct		TOT number		TOT strength		Gamma	
	PD	Elderly	PD	Elderly	PD	Elderly	PD	Elderly	PD	Elderly
M	.36	.39	.22	.23	.16	.12	12.00	13.37	.72	.75
SD	.22	.20	.12	.12	.11	.07	2.75	4.66	.44	.40
SE	.05	.04	.03	.03	.02	.01	0.61	1.04	.10	.10
E^α		.69		.69		.70		0.70		.69
$E^{2\alpha}$.69		.69		.71		0.71		.69
95% CI	.26-.46	.31-.48	.17-.28	.18-.29	.11-.21	.09-.15	10.72-13.28	11.19-15.55	.50-.93	.55-.95
95% ICI	.29-.43	.33-.45	.18-.26	.19-.27	.13-.20	.09-.14	11.09-12.91	11.83-14.91	.57-.87	.61-.89
90% ICI	.31-.42	.34-.44	.19-.25	.20-.26	.13-.19	.10-.14	11.24-12.76	12.09-14.65	.60-.84	.63-.87
${}_eR_g^{2\alpha}$.14		.07		.09		3.41		.27
Δ		.17		.11		.06		4.36		.40

Note: $N = 22$ except that for TOT strength $N = 20$ for the PD group and $N = 20$ for the elderly group and for gamma, $N = 18$ for the PD group and $N = 17$ for the elderly group; E^α is based on $100(1 - \alpha)$ and $E^{2\alpha}$ is based on $(1 - 2\alpha)$; ${}_eR_g^{2\alpha}$ is based on 90% ICI and Δ is based on 95% CI for the elderly group.

4. Discussion

The present study investigated whether a form of metacognition, tip-of-tongue (TOT), was affected by Parkinson's disease (PD). Patients with PD showed lower motor response timing accuracy but uncompromised TOT performance, compared to both control groups. Both the PD patient and elderly control groups showed similar level on all TOT measures: frequency, strength, and accuracy, despite the fact that the PD patients showed significantly worse timing accuracy than the elderly control and college student groups. Further, general knowledge was uncompromised by PD on both recall and recognition tests; the PD patient group showed a similar level of performance to the elderly control group, which was higher than that of the college student control group.

A variety of neuropsychological studies have reported a deficit in the ability of PD patients to accurately perceive duration and correctly timed motor responses [56, 68]. Accordingly, it was expected that PD patients would show lower timing accuracy relative to controls (elderly and college

students) in performing the metronome timing task. The metronome timing task used in the present study involves several components of the working memory functions, including maintenance, manipulation, and monitoring of cognitive resource as related to timing interval, internal and external cues, and stimuli pacing [69, 70]. The present results agree with previous reports that PD patients have significantly worse motor timing than age-matched controls, suggesting that the brain regions affected in PD may play a direct role in such tasks [53]. In fact, a large number of studies have shown that human motor timing behavior is closely linked to the prefrontal cortex (PFC) and the basal ganglia activity, brain regions severely compromised in PD [54, 68, 71]. The present results are therefore consistent with the hypothesis that motor timing performance deficit in PD patients is closely related to a dysfunction of the prefrontal-basal ganglia circuits.

In contrast to the motor timing performance, there was no evidence that PD patients had deficiency in TOT metacognition. Both PD patients and elderly groups showed significantly greater TOT responses as well as TOT accuracy

than did college group, showing about 200% and 206% accuracy increase compared with college group, respectively. In fact, both the PD patient and elderly control groups performed similarly on all metamemory measures: frequency, strength, and accuracy of TOT. It has been suggested that TOTs are simply strong FOK experiences [72], but evidence that refutes this claim has been reported. For example, Widner et al. [31] using perseveration errors made during the Wisconsin Card Sorting Task, as an index of PFC functioning, reported that the TOT judgments were not related to PFC functioning. In their study, PFC functioning had an impact on FOKs, but did not impact TOTs. The present results are compatible with a view that the TOT and FOK are disparate cognitive processes subserved by different neural substrates. The results also support a notion that the activation of the localized specific brain regions including the right prefrontal and ACC regions may be closely associated with the neuropsychological processes involved in both TOT judgment and retrieval. PD patients in the present study did not show impairments in TOT experience, and, therefore, it is conceivable that these brain regions remained intact and functional. In fact, the present results revealed that the MMSE scores were positively correlated with TOT accuracy scores in PD patients and elderly, further supporting the view that PD patients in the present study did not have damage in frontal lobe areas associated with TOT metacognition as well as with certain aspects of cognitive control.

In addition, although PD is associated with emotional impairment [16, 73, 74], a feeling of imminence and emotional reactions [75–77] that often accompanies TOT experience appears to be unaffected in PD patients. Taken together, the present findings support the postulate that TOT metacognitive function may not be directly related to dopamine deficiency in PD patients, which influence the overall prefrontal executive networks, but perhaps is likely due to dysfunction within a localized specific neural network [29, 46]. Future research, such as fMRI morphometry, will be needed to further delineate the precise nature of metacognitive and associated neural function in normal subjects as well as PD patients. Elucidating and characterizing a specific neural function associated with unimpaired TOT metacognition in PD patients may have significant therapeutic and prognostic implications for PD and other dopamine-related disorders.

Uncompromised TOT metacognition among the PD patients may also depend on the nature of the memory task. In regard to another metacognitive measure FOK, some studies showed impaired FOK among PD patients [27, 78], whereas others showed intact FOK among PD patients [25, 26]. The disparate results are likely to be based on the difference in the nature of the memory task; that is, those studies that used an episodic memory task showed impaired FOK [27, 78], whereas those studies that used a semantic memory task showed spared FOK [26, 79]. Similarly, PD patients may show impaired TOT if the task is episodic in nature (e.g., paired-associate learning) rather than semantic in nature (e.g., general knowledge questions). In fact, in the present study, there was no evidence of impaired semantic memory by the PD patient group relative to both control

groups; both correct recall and recognition showed comparable performance between PD patients and elderly participants, both of which, in turn, performed much better than college students. The episodic, but not semantic [38, 39], memory is thought to involve context retrieval and executive control operations that are closely linked to prefrontal cortical (PFC) executive functions [27, 32, 80, 81]. Given this, the present results appear to be in line with the hypothesis that PFC deficit in PD patients is closely related to dysfunction of the episodic, but not semantic metacognition [27, 46, 82].

One weakness of the present study was that metacognitive control was not directly measured. That is, TOT is an indicator of metacognitive knowledge; however, how this knowledge is used to control retrieval might show impairment among PD patients. A future question should be whether participants would show longer retrieval time when they experience TOT. This question could be answered by measuring participants' response time in reporting TOT experience as well as response time associated with TOT resolution.

In regard to TOT and aging, it is well established that older adults experience more TOTs than younger adults, possibly due to age-related cognitive changes [37, 83]. The present results were consistent with these findings because when TOT responses were conditionalized on unrecalled items, older adults (PD patients and elderly control groups combined) showed a higher tendency of responding with TOT than the college student control group.

In terms of TOT accuracy, the present results were consistent with the incremental and metacognitive perspectives which argue for TOT accuracy increasing with aging as a result of knowledge culmination and memory network expansion [31, 84]. Conceivably, broader and stronger knowledge base in older adults including PD patients may have contributed to providing more familiar cues (the cue familiarity heuristics) and more target-related information (the accessibility heuristics) to increase the TOT accuracy [23, 26, 85]. This interpretation based on the increment view is consistent with the current data, in that the level of general knowledge (indexed by the number of correctly recognized answers), as well as age, covaried with TOT accuracy, suggesting that participants who had more knowledge were more likely to have more accurate TOT metacognitive judgments, regardless of age.

In regard to motor timing performance and the TOT metacognitive function, there was a dissociation between the accuracy of TOT judgments and the level of motor timing-related functioning. The results indicated that TOT accuracy (indexed by gamma correlations) was not affected by the level of motor timing accuracy (low- versus high-accuracy group) in any of the subject groups examined. There was also no correlation between motor timing accuracy and gamma correlation scores in any groups. The data indicated that TOT metamemory and motor timing performance may represent distinct cognitive functions, potentially mediated by functionally and structurally different systems from one another. To the extent that the motor timing abilities are related to the prefrontal cortical (PFC) function [68, 70],

our results suggest the possibility that TOT experiences are indeed different from other metacognitive processes that require PFC function, such as in FOK and prospective memory performance [27, 31, 43]. Consistent with this theme, both FOK metamemory and prospective memory are impaired in PD [14, 15, 25, 26]. Further study examining both FOK and TOT in the same PD patient group, however, is required before any concrete conclusions can be established. Nevertheless, based on the current data, it can be concluded that despite patients with PD showing significant motor response timing impairment (an index of prefrontal and working memory impairment), they were not impaired in their TOT metamemory performance compared to age-matched adults.

One caveat to above interpretations is that PD patients examined in the current study were ON anti-Parkinsonian medication, primarily dopaminergic agonists (DA). Despite inconsistent and incomplete reports on the effects of DA drugs on motor timing functions, [86], administration of DA agonist has been found to cause alterations in these functions including clock speed shifts to an earlier time, relative to the feedback time [52]. In the current study, PD patients displayed this effect with a greater proportion of clapping responses occurring early, relative to the cue (~16% greater shift to early responses), than did age-matched adults (80% and 69% early responses by PD and elderly, resp.). Consequently, it is difficult, if not impossible, to rule out the possibility that the null difference in TOT measures between the PD patient and elderly control groups might have resulted from an anti-Parkinsonian drug-related effect. More accurate and careful interpretation of current data must await further research that examines the effects of DA drugs on metacognition and motor timing learning in PD patients while ON or OFF medication.

In view of the previously reported association between metacognitive abilities with competence in problem solving and learning new skills [20, 87, 88], the present results appear to be relevant to efficiency in memory retrieval process and quality of life for PD patients [15, 43, 89]. Conceivably, PD patients without dementia could benefit from intervention strategies (e.g., implementation intention) that are based on metacognitive abilities (e.g., metacognitive knowledge, skill, and belief) in ways that will help promote qualities such as self-evaluation, self-monitoring, self-control, self-motivation, and everyday functional capability [88, 90–92]. Being in a TOT state is often frustrating experience, but it may be used as a cue or strategy (think some more immediately, think some more later, or look up the answer) to facilitate retrieval [57]. Accordingly, PD patients may be trained to use TOT states to select effective and appropriate retrieval strategies in ways that will help improve their overall cognitive functions.

The future investigation should also include metacognitive judgments that are made at encoding or judgments of learning (JOL), which is one's judgment that a given item is learned adequately enough for successful retrieval on a future test. Research has shown that JOLs are causally related to monitoring and control of the acquisition of to-be-learned materials [49, 93–95]. The issue is whether PD patients

would be able to use JOL for effective monitoring and control of their operations during acquisition. Previous studies have shown that frontal lobe damages would be likely to lead to impairment in JOL [96] even though no JOL impairment was found when medial prefrontal cortex was damaged [97]. Taken together, it could be predicted that JOL metacognitive function may also remain uncompromised in PD patients. If this is the case, it will confer unique opportunities for development of safer and more effective cognitive intervention strategies in patients with PD as well as other related neurodegenerative diseases. Given the close link between cognitively demanding tasks on postural and motor stability in PD patients [98, 99], further study into this issue is obviously critical to better understand the contribution of metacognitive abilities in the human memory retrieval process, as well as in the overall cognitive and motor functions. The present findings also provide further support to the existing literature on cognitive abilities, which are not as severely impaired as was once purported in PD, including selective attention, decision-making, verbal memory, and adaptive abilities [26, 100–103]. By fully understanding which cognitive neural functions are unimpaired in PD, more effective training strategies can be developed to improve patient's symptom management strategies and their quality of life.

5. Conclusions

The present findings, collectively, support the view that TOT metamemory judgment is not impaired in PD patients, and that varied metacognitive functions (TOT, FOK, and prospective memory) may be differentially affected by the disease. The findings also suggest potential implications of TOT metacognitive abilities related to memory retrieval processes as well as to general cognitive and motor functions in PD. Further study into this issue is obviously critical to the development of novel behavioral therapeutic options that may prove useful in enhancing memory function and overall quality of life in these patients.

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Review Article

Dopamine Agonists and Pathologic Behaviors

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The dopamine agonists ropinirole and pramipexole exhibit highly specific affinity for the cerebral dopamine D3 receptor. Use of these medications in Parkinson's disease has been complicated by the emergence of pathologic behavioral patterns such as hypersexuality, pathologic gambling, excessive hobbying, and other circumscribed obsessive-compulsive disorders of impulse control in people having no history of such disorders. These behavioral changes typically remit following discontinuation of the medication, further demonstrating a causal relationship. Expression of the D3 receptor is particularly rich within the limbic system, where it plays an important role in modulating the physiologic and emotional experience of novelty, reward, and risk assessment. Converging neuroanatomical, physiological, and behavioral science data suggest the high D3 affinity of these medications as the basis for these behavioral changes. These observations suggest the D3 receptor as a therapeutic target for obsessive-compulsive disorder and substance abuse, and improved understanding of D3 receptor function may aid drug design of future atypical antipsychotics.

1. Introduction

An association between neurodegeneration of the dopaminergic nigrostriatal system and the major motor symptoms of Parkinson's disease (PD) was first recognized in 1960 [1] after pioneering work by Arvid Carlsson showed that L-DOPA reversed the parkinsonian syndrome in rabbits induced by reserpine [2]. This observation led to the first trials of injected levodopa (L-dopa), a direct metabolic precursor of dopamine, to address motor symptoms associated with the disease. This treatment demonstrated transient success, but was impractical due to severe toxicities associated with the injections. Gradual titration of oral L-dopa was better tolerated, but was still associated with severe nausea and the requirement of higher doses of L-dopa due to peripheral consumption of the substrate. In the 1970s, compounding L-dopa with the peripheral dopa-decarboxylase inhibitor carbidopa very successfully addressed these shortcomings. Nausea and vomiting were reduced to such a degree that the medication adopted the trade name Sinemet (sine = without; emet = emesis). Compounded levodopa-carbidopa remains the mainstay of treatment for PD.

Dopaminergic agonists are synthetic analogues of dopamine. Apomorphine was suggested for the treatment of PD as early as 1884 [3], although the first article describing its effectiveness was not published until 1951 [4]. Bromocriptine was found to be effective in PD in 1974 [5]. Other ergotamine dopamine agonists including lisuride, pergolide, and cabergoline were subsequently found to be effective. In the 1990s, two nonergot dopamine agonists (DA), pramipexole and ropinirole, were granted approval for use in the United States. These have been adopted by many clinicians for a variety of reasons, including a more stable motor response, improved side-effect profile, and more convenient dosing schedule.

As DA medicines became widely used, unanticipated reports of poorly modulated risk taking began to emerge, and the link between these behaviors and the medications was recognized by the year 2000 [6, 7]. These took the form of compulsive gambling, hypersexuality, hyperphagia, and even hobbying or shopping that took on an obsessive-compulsive-type character. Examining the pharmacology of these medications and their specificity to the D3 dopamine receptors provides an opportunity to understand why these

pathological behaviors are not generally seen with levodopa, why tardive movement disorders arise in many patients taking typical (dopamine-targeting) neuroleptics, and why the recognition of DA-agonist-related pathological behaviors in PD patients may suggest potential therapeutic targets for similar behavioral problems that arise spontaneously in the general population.

2. Dopamine Receptors, L-Dopa, and Dopamine Agonists

Dopamine receptors have been divided into 5 different subtypes (D1–D5). Structurally, the D1 and D5 receptors are very similar, while the D2, D3, and D4 receptors are different from them. In particular, the D3 receptor has strong representation in the limbic system and its connections in the ventral striatum and is associated with cognitive, emotional, and endocrine functions [8].

L-dopa increases the availability of dopamine in the brain, without known specificity for a dopamine receptor subtype. In contrast, the dopamine agonists ropinirole, pramipexole, and pergolide exhibit high affinity for the D3 receptors [9–11]. The older dopamine agonist, bromocriptine, does not share this specificity and appears to have greater affinity for the D2 receptor [9].

This receptor specificity may have functional relevance to the increased rates of pathological behaviors, as the D3 receptor expression is particularly rich in limbic areas and often being coexpressed with D2 in regions serving sensory (sensory thalamic nuclei), hormonal (mammillothalamic tract), and association (amygdala) functions [12]. The D3 receptor appears to control the phasic, but not tonic, activity of dopaminergic neurons which may be induced by novelty or presentation of drug-conditioned cues in rodents [13–15]. These data seem to converge on an important role for the D3 receptor in modulating the physiologic and emotional experience of novelty, reward, and risk assessment and likely explain the relatively higher rates of pathological behaviors among patients taking DAs. Pathological behaviors associated with bromocriptine have not generally been observed, with a single case report in 2003 being the first time this association was noted [16]. This likely reflects the lower frequency of use and may also be understood in the context of bromocriptine lacking the D3 specificity of the more commonly utilized DAs. Animal models suggest that D3 receptor stimulation is also involved in the emergence of dopamine-induced dyskinesias [17, 18].

3. Pathological Behaviors

The most commonly reported pathological behaviors have been pathological gambling, hypersexuality, compulsive or binge eating, and compulsive shopping. Uncertainty remains regarding the overall frequency of DA-associated behavioral changes. Initial surveillance suggested very low rates—on the order of 2%–8% [19]. Subsequent structured-questionnaire ascertainment found higher rates, with a recent large questionnaire-based assessment reporting a rate of 13.6% [20].

This cross-sectional study assessed rates of pathologic gambling (9.9%), compulsive sexual behavior (4.4%), compulsive buying (7.2%), and binge eating (5.6%) among current DA users, with a total of 17.1% of current DA users exhibiting any pathological behavior. This compared to the significantly lower rate of pathological behaviors (6.9%) among subjects not using a DA for at least 6 months prior to enrollment.

Some authors argue that reliance on impersonal questionnaires or spontaneous patient reports likely results in incomplete ascertainment due to the sensitive and/or potentially embarrassing nature of these symptoms. Another recent report utilized physician-directed symptom elicitation and found pathological behaviors in 24% of patients using DA at therapeutic doses and in 30% of patients using “target” DA dosing [21]. Although involving a smaller population than some other reports, this paper highlights some difficulties in capturing behavioral changes with several patients exhibiting compulsive hobbying or computer use, and others having poor insight into their behavioral changes including a patient with compulsive gambling who perceived his behavior as “beneficial” due to net wins.

Emergence of pathological behaviors is very uncommonly seen among patients treated with L-dopa alone [22]. A large study utilizing structured interview assessment found pathological behaviors in 6.9% of subjects not currently taking a DA, although prior exposure to DA was not reported [20]. In previous reports, the DA with highest D3 affinity (pramipexole) appears to be more commonly implicated in pathological behaviors both in PD and in restless legs syndrome [23], but a large cross-sectional study found no difference between current use and risk for pathological behaviors between DAs [20]. Again, prior DA exposures and reasons for discontinuation were not reported.

The relationship between deep brain stimulation (DBS) of the subthalamic nucleus (STN) and impulse control disorders is complex, and it is the focus of several review papers [24, 25]. In general, a reduction in dopaminergic medication is seen after STN DBS, and with reduction or elimination of dopamine agonist therapy ICDs such as pathological gambling and others can improve [26–29]. However, several studies have noted *de novo* ICDs after DBS [30–32]. Interestingly, models of STN function [33] suggest that the STN modulates decision thresholds in proportion to reinforcement and decision conflict. Patients with STN DBS showed typical conflict-induced slowing in “win-win” computerized decision-making tasks with their DBS off, but 10 minutes after turning the DBS on, they exhibited less slowing and increased impulsive decision making in these same tasks [34]. Dopamine dysregulation syndrome (DDS) is a compulsive overuse of dopaminergic therapy. Preexisting DDS may or may not improve after STN DBS. Lim et al. found DDS remained unimproved or worsened in 12/17 patients after DBS, although this was a mix of STN and globus pallidus interna (GPi) DBS cases [32]. In the remaining 5/17 patients, DDS improved or resolved.

Discontinuation of the DA or significant adjustment in dosage is the mainstay of treatment intervention and appears to be required to achieve full remission or significant reduction in behaviors [35]. Even still, some patients exhibit

persistent pathological behaviors. A study examining psychosocial outcomes in patients having exhibited pathological gambling found persistent financial and marital stress as a consequence of these behaviors although full or partial resolution of the behaviors in all subjects followed [36].

Some authors group DA-associated behavior changes as disorders of impulse control, but careful examination of the behavioral issues reported in the medical literature and by our patients suggests a more complex behavioral derangement than a general disorder of impulse control. Patients appear to demonstrate a circumscribed obsessive-compulsion for a particular behavior. Most commonly, patients exhibit one particular obsession, but even in cases where two or more obsessions manifest, the more widespread injudicious decision making and excessive spontaneity that characterize a general disorder of impulse control are absent [20–23, 37, 38]. It may be that the neural systems mediating these pathologic behaviors are more closely aligned with punding (an intense fascination with meaningless movements or activities such as collecting, arranging, or taking apart objects), and one study suggested a strong relationship between punding and the expression of dyskinesias. Some studies suggest a D3 receptor-dependent response to L-dopa and dyskinesia, at least in monkeys [13].

Several recent studies have documented the importance of the brain circuits involved in reward and risky decision making, including, thalamic, striatal, and ventromedial frontal regions. Using fMRI, Reuter and colleagues compared pathological gamblers and control subjects and found that activation in regions such as the ventral striatum is inversely related to their pathological gambling severity, as if risks and rewards were less salient to pathological gamblers except at high enough magnitudes [39]. Another fMRI study had subjects play a game in which they decided to keep pumping up a virtual balloon or quit and collect reward points, with larger rewards associated with larger balloons [40]. Increased activation levels in insular, thalamic, striatal, and dorsolateral prefrontal regions bilaterally and medial prefrontal cortex/anterior cingulate regions correlated with increases in active risk taking. Functional imaging studies in PD patients have implicated similar brain regions [41, 42].

Voon et al. [38] studied PD patients with and without impulse control disorders (ICD) in a risk task involving a certain (e.g., +\$100) or an uncertain outcome (e.g., 50/50 chance of winning either \$200 or winning \$0) for both gains (+\$) and loss (–\$) domains. PD patients without impulse control disorders behaved more similarly to healthy controls while they were on DA medications, making substantially more risky choices when they were confronted with losses than with gains, thereby showing “loss aversion” [43]. These same patients made highly similar choices in the gain versus the loss domains without loss aversion when they were off DA medications. PD patients with ICD showed more risk taking in the gain domain whether on or off medication, a pattern that was opposite to those of the healthy controls and PD patients without ICD. Moreover, PD patients with ICD also showed higher sensitivity to risk when they were on DA medications, displaying a steeper drop in the number of risky choices as the value at stake became higher and

higher. In another study [44], PD patients without ICD were given the Iowa Gambling Task (IGT) while they were on or off medications. In this task, subjects chose between four decks of cards with various risk reward payoffs (i.e., risk disadvantageous (RD) decks with larger and frequent rewards but also infrequent large losses leading to long-term net losses, versus risk advantageous (RA) decks with smaller frequent rewards but also smaller infrequent losses leading to long-term net gains). PD patients off DA medications showed an appropriate decrease in choices for the risk-disadvantageous (RD) decks over trials. In contrast, PD patients on DA medications failed to show such outcome-contingent learning; instead, they kept on choosing the RD decks.

4. Implications for Other Disorders

Analogous behavioral changes arise spontaneously in the general population, where they are often termed “obsessive-compulsive disorder” or “addiction.” Obsessive-compulsive behaviors emerge in 30–50% of patients with Tourette syndrome [45], and recent PET imaging evidence suggests widespread dysregulation of extrastriatal dopamine response in subjects with Tourette syndrome relative to the response in control subjects [46]. As discussed above, this suggests a relationship between dysregulation of dopaminergic tone and obsessive-compulsive behavioral manifestations.

The mainstays of pharmacologic treatment for obsessive-compulsive disorder are antidepressant medications whose primary pharmacologic target is thought to be serotonin (5HT), a strategy that meets with varying success. Consideration of the interaction between 5HT and dopamine in the limbic system provides another perspective on how these medications may be mediating that success. Rodent studies implicate D2 and D3 receptor activity in models of obsessive-compulsive behavior and found that D2/3 agonism ameliorated these behavioral models [47, 48]. The emergence of similar behavioral drug-induced compulsive behaviors in PD patients with no history of such behaviors and that the prevalence of these behaviors appears to show a dose-dependent response adds further credence to the relevance of dopaminergic stimulation in idiopathic obsessive-compulsive behaviors. In addition to inhibiting reuptake of 5HT and norepinephrine, clomipramine acts as an antagonist at the D2 and D3 receptors, which may explain in part the efficacy of clomipramine in treating obsessive-compulsive disorder. Taken together, these observations suggest that modulation of specific dopaminergic receptors may hold promise for new medications directed against obsessive-compulsive behaviors.

Substance abuse literature suggests that liability to this disorder exists in 9–12% of humans. The D3 receptor does not appear to have a direct role in reinforcing the effects of drugs of abuse, but the role of the D3 receptor may be in processing novelty and in the environmental conditioning and associations that reinforce drugs of abuse, particularly those with psychostimulant effects. Initial studies in squirrel monkeys [49] and in rats [50] suggest an important role of the D3 and the closely related D2 receptor in mediating

drug-related discriminatory behaviors, but they provide no evidence of a role of these receptors in direct reinforcement. The studies also suggest a role for these receptors in reinstatement of drug-use behaviors in abstinent animals. Taken together, these data suggest a potential role for D2/D3 specific ligands in decreasing relapse rates in abstinent drug abusers.

5. Conclusion

In the brief time since DAs have been widely used for treatment of PD, an important association between higher doses of these medications and the emergence of pathologic behaviors has been recognized. As outlined above, the D3 specificity of these medications and over-representation of the D3 receptor [51, 52] likely account for both the lower incidence of dyskinesias and also for the emergence of these pathological behaviors. This observation has important consequences for the safe use and monitoring of PD patients taking DA-agonists. Although the anatomical underpinning of this neural connectivity is incompletely understood, this observation also suggests potential therapeutic targets for obsessive-compulsive disorder and possibly for substance-based addictions. Advances in understanding the roles of specific dopamine receptors may also help to guide drug design for future atypical neuroleptics that aim to reduce side effects while improving efficacy.

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Research Article

Web-Based Assessment of Visual and Visuospatial Symptoms in Parkinson's Disease

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Visual and visuospatial dysfunction is prevalent in Parkinson's disease (PD). To promote assessment of these often overlooked symptoms, we adapted the PD Vision Questionnaire for Internet administration. The questionnaire evaluates visual and visuospatial symptoms, impairments in activities of daily living (ADLs), and motor symptoms. PD participants of mild to moderate motor severity ($n = 24$) and healthy control participants (HC, $n = 23$) completed the questionnaire in paper and web-based formats. Reliability was assessed by comparing responses across formats. Construct validity was evaluated by reference to performance on measures of vision, visuospatial cognition, ADLs, and motor symptoms. The web-based format showed excellent reliability with respect to the paper format for both groups (all P 's < 0.001 ; HC completing the visual and visuospatial section only). Demonstrating the construct validity of the web-based questionnaire, self-rated ADL and visual and visuospatial functioning were significantly associated with performance on objective measures of these abilities (all P 's < 0.01). The findings indicate that web-based administration may be a reliable and valid method of assessing visual and visuospatial and ADL functioning in PD.

1. Introduction

Visual and visuospatial deficits are common in Parkinson's disease (PD) and negatively affect everyday functioning. The PD Vision Questionnaire was developed to document the prevalence of these impairments [1]. It revealed that the large majority of respondents in the mild to moderate stages of the disease endorsed at least one such symptom [2]. Numerous studies have shown that individuals with PD demonstrate visual and high-order spatial impairments on laboratory-based assessments that cannot be accounted for by motor or executive dysfunction. Visual impairments and in particular, reduced contrast sensitivity, are well established [3–7]. In regard to visuospatial abilities, PD patients are impaired on global/local processing [8], a skill independent of executive demands, as well as mental rotation, way finding, visual construction, visuospatial reasoning, and angle size

estimation [9–12]. Visual deficits have been linked to freezing of gait, an extremely debilitating motor symptom [2]. Further, PD-related visual and spatial abilities are predictors of the ability to drive, a visually mediated ADL [13–15] that is important to independent living. Considering their prevalence and negative functional impact, there is a critical need for further information on these underappreciated nonmotor symptoms.

A challenge to the assessment of a variety of aspects of PD is the burden of research participation when it must occur outside of an individual's home. Frequent office visits and distant travel have been identified as barriers to patient participation in PD research studies [16], raising the question of possible sample bias with respect to those individuals who have the time, motivation, and travel-related mobility to participate. Emerging data support the feasibility of Internet-based experimental tools for data collection from individuals

with PD. Internet-administered experimental tasks have been developed and found comparable to office- or laboratory-based assessments for a variety of disorders [17–19]. Although tremor, rigidity, and bradykinesia might be expected to impact computer use, in fact many people with PD use the Internet for socialization, information gathering, and leisure activities despite their motor symptoms [20]. One of the benefits of online assessment is the potential to enroll larger numbers of research participants and include a wider range of participants (in terms of age and motor severity) than are usually assessed.

In order to assess visual and visuospatial impairments, we created a web-based version of our vision questionnaire. To evaluate the feasibility, reliability, and construct validity of the online version, we included this measure in a broad assessment of visual perception, cognition, and daily functioning in PD.

2. Materials and Methods

2.1. Participants. Twenty-four individuals with PD (12 women), recruited from the outpatient clinic of the Parkinson's Disease Center in the Department of Neurology, Boston Medical Center and from Boston-area PD support groups, took part in the study as well as 23 healthy control adults (HC) (16 women) who were community volunteers. Methods were approved by the Institutional Review Board (IRB) of Boston University and the Committee on Research with Human Subjects at Memorial Hospital of Rhode Island. Written informed consent was obtained from participants prior to their inclusion.

The PD and HC groups did not differ with respect to age, education, or male:female ratio (Table 1). There were no group differences in binocular near or far acuity (near acuity: $\chi^2 [6] = 4.5$, $P's = 0.50$; far acuity: $\chi^2 [6] = 4.1$, $P's = 0.60$). Near acuity was 20/25 (median) for both groups and far acuity was 20/20 (median) for both groups. No participant was demented as indexed by scores on the modified Mini-Mental State Examination (mMMSE) [21]. A cutoff score of 27 was used for HC participants. A score of 25 was used for PD participants because this form of the MMSE is particularly sensitive to specific cognitive deficits found in PD without dementia, as it includes tasks assessing executive functioning (scores converted from a 57-point scale). Participants were interviewed about their medical history, including ophthalmologic health, to rule out other confounding and exclusionary diagnoses such as stroke, head injury, serious medical illness, and ocular/optical abnormalities. The majority of participants (18 PD, 21 HC) underwent a detailed neuro-ophthalmological examination to confirm the absence of ocular disease. Participants who did and did not complete the neuro-ophthalmological examination did not differ in regard to participant characteristics or results.

Diagnosis of idiopathic PD, side of disease onset, and disease duration were confirmed by medical history and assessment with the Unified Parkinson's Disease Rating Scale (UPDRS). Two participants were not available for UPDRS administration. A Hoehn and Yahr (H&Y) score for stage

TABLE 1: Participant characteristics.

	PD ($n = 24$) Mean (SD)	HC ($n = 23$) Mean (SD)	t value ^a	P 's value
Age	65.7 (8.8)	66.7 (9.5)	0.39	ns
Education (yrs)	16.5 (2.3)	16.5 (2.4)	0.03	ns
Male:female	12:12	7:16	1.9 ^b	ns
BDI	7.0 (5.2)	3.8 (4.2) ^c	2.3	0.03
BAI	8.0 (5.3)	2.4 (3.4) ^c	4.1	0.001
UPDRS—motor score	24.6 (9.8)	NA		
Disease duration (yrs)	7.0 (5.2)	NA		

^a t -values unless otherwise indicated; ^bchi-squared value, ^cdf = 21; MMSE: modified Mini-Mental State Examination, scores converted to standard MMSE range; BDI: Beck Depression Inventory-II; BAI: Beck Anxiety Inventory; UPDRS: Unified Parkinson's Disease Rating Scale; NA: not applicable; ns: not significant.

of motor disability was derived from the UPDRS motor section [22]. Participants were in the mild to moderate stages of disease severity (Stage 1 = 2; Stage 2 = 3; Stage 2.5 = 11; Stage 3 = 6). All PD participants were taking medication for their motor symptoms and were tested when motor response was at its optimum ("on" period). Of the 24 participants, 23 followed a medication regimen that included levodopa/carbidopa therapy ($n = 5$), levodopa/carbidopa in combination with a dopamine agonist ($n = 16$), or dopamine agonist only ($n = 2$). One participant was not taking levodopa/carbidopa or a dopamine agonist. Group characteristics are summarized in Table 1.

2.2. Assessment

2.2.1. PD Vision Questionnaire. Participants completed the 73-item Vision Questionnaire [2] twice: once in the standard paper format and once online. The paper format was administered first to all but five individuals for scheduling reasons. These five did not differ from the others in regard to participant characteristics or results. The average duration between repeat assessment was 1.5 months (SD: 1.2 months). Exact dates were not available for the paper questionnaires of three participants but the surveys were returned within about one month of the online assessment.

The online version of the questionnaire included several design features to improve Internet accessibility for participants with PD. Visual feature enhancement included large font (~ 0.5 cm in height) and an option for increased contrast (negative polarity, white lettering on a black background), as some have found this to enhance computer screen reading [19]. Drop-down options were oversized to reduce issues with manipulating the mouse due to tremor or rigidity (>2 cm \times 0.5 cm). To minimize the cognitive demands of the questionnaire, the format of each page was kept consistent in form, size, and location of information, and only one question was presented per page.

The PD Vision Questionnaire comprises three sections: *Visual and Visuospatial* symptoms, performance of visually mediated *Activities of Daily Living*, and *Motor* symptoms.

TABLE 2: Questionnaire feedback collected online.

Feasibility questions	PD ($n = 24$)	HC ($n = 23$)
Difficult to complete? (1: not at all, 9: very much)	83% ratings of 1 or 2	91% ratings of 1 or 2
	34% indicated <30	96% indicated <30
Time to complete questionnaire (in minutes)	58% indicated 30–60	4% indicated 30–60
	8% indicated 60–90	
Instructions easy to understand? (1: not at all, 9: very much)	77% ratings of 8 or 9	91% ratings of 8 or 9

Qualitative responses were not included in these analyses. Follow-up questions were not administered if the participant denied experiencing that particular symptom.

In order to evaluate the reliability and validity of the three content areas, summary scores for each section of the survey were created. Within each content area, severity ratings (Likert scale) of all questions administered to every participant were summed. The Visual and Visuospatial summary score comprised 14 items rated on a scale from one to nine, with “1” indicating the absence of the problem. The Motor summary score comprised 21 items rated on a 9-point scale. The ADL summary score comprised two scale items and 11 yes/no items reflecting the presence or absence of a problem (score of 1 for “yes” and zero for “no”). Seven of the ADL questions also had a “not applicable” response option, which was scored as zero. While this may underestimate the severity of ADL impairment, this approach was preferred to methods that might overestimate the degree of ADL impairment (e.g., number of responses endorsed positively divided by the number of questions answered). For six PD participants, one or more of the summary scores from the paper format of the questionnaire could not be calculated because of skipped responses to multiple items within a content area (Visual and Visuospatial $n = 1$, ADL $n = 1$, Motor $n = 4$). For PD participants with only a few missing responses, values were replaced with the mean for the PD group (3 or fewer respondents per item). For the paper questionnaire, each of the summary scores was calculated for the PD group whereas in the control group only the Visual and Visuospatial summary score was calculated, as most of the motor and activities of daily living items were not applicable to this group. In Section 3, reliability of the Visual and Visuospatial summary scores are reported for the control as well as the PD group.

2.2.2. Construct Validation. Visual abilities included contrast sensitivity and coherent motion perception [7]. Contrast sensitivity was assessed with the chart-based Functional Acuity Contrast Sensitivity Chart (FACT) (Vision Sciences Research Corp., San Ramos, CA) and a computer-based backwards masking task [7]. Visuospatial abilities assessed included determination of the midpoint of a horizontal line with the Landmark Test of Line Bisection [23], map reading with the Standardized Road-Map Test of Direction Sense [24], and angle size estimation with the Benton Judgment of Line Orientation Test (JLO) [25]. Subjective quality of life

and activities of daily living were assessed with the Parkinson's Disease Quality of Life Questionnaire-39 (PDQ-39) [26]. Motor symptoms were evaluated with the UPDRS [27].

2.3. Statistical Analysis. Group differences on continuous measures (e.g., age, education) were evaluated using t -tests, and on categorical variables using the chi-squared test. The reliability of the web-based survey (versus paper) and construct validity of the online survey were evaluated with Pearson correlations. Because many visual and visuospatial measures were used, composite scores were created to evaluate the construct validity of the visual and visuospatial summary score. Z -scores were derived for performance on vision tasks (Vision z -score: FACT contrast sensitivity [average log sensitivity across the five spatial frequencies], backwards masking [grey level] contrast sensitivity, and coherent motion perception [% coherent dot motion]), visuospatial tasks (Visuospatial z -score: Line Bisection [% of line], Road Map [total errors], JLO [total errors]), and the combined visual and visuospatial tasks (Visual and Visuospatial z -score), which were compared with the Visual and Visuospatial summary score from the Vision Questionnaire. Means (SDs) on the individual tests were as follows for PD and HC: FACT: PD: 1.5 (0.3), HC: 1.6 (0.2); backwards masking contrast sensitivity: PD: 124.8 (46.6), HC: 92.1 (8.1); motion perception: PD: 9.1 (4.8), HC: 8.4 (4.3); Line Bisection: PD: 14.4 (8.8), HC: 13.07 (5.7); Road Map: PD: 2.5 (4.0), HC: 3.1 (3.9); JLO: PD: 5.8 (4.3), HC: 4.6 (4.2). Because clinical and cognitive symptoms may differ in men and women with PD [28] and in PD patients with left versus right side of motor onset [10], we examined the results along these dimensions. Summary scores for the three construct areas did not differ with respect to gender (all P 's > 0.70) or body side of motor symptom onset (all P 's > 0.50). Accordingly, data were collapsed across these subgroups.

3. Results

3.1. Feasibility. We expected that 90% of participants would complete both the paper and the web-based questionnaire. This benchmark was surpassed with 100% completion. There was no difference between PD and HC in their ability to complete the online survey. Feedback indicated that the majority of participants rated the survey as easy to use and said that it could be completed within an hour (Table 2). The PD group took longer than the HC group to complete the

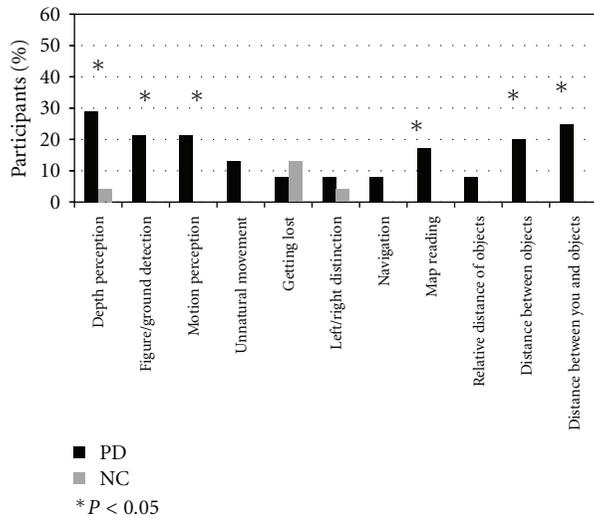


FIGURE 1: Percentage of PD and HC participants reporting impairment on the visual and visuospatial items from the web-based questionnaire.

questionnaire; the PD respondents had more questions to answer because there were items on PD-specific symptoms.

3.2. Visual and Visuospatial Abilities (PD and HC)

3.2.1. Prevalence. Self-reported visual and visuospatial deficits were prevalent in this sample with 15 PD participants (63%) compared to six (26%) of HC reporting at least one deficit ($\chi^2 = 6.3$, P 's < 0.01). A significantly greater percentage of PD than HC participants reported difficulties with depth perception, figure-ground discrimination, motion perception, map reading, and judging distances (all P 's < 0.05) (Figure 1).

3.2.2. Reliability. For the PD group there was a significant association between the Visual and Visuospatial summary scores derived from the online and the paper survey ($r = 0.71$, $P < 0.001$), suggesting good consistency across formats (Figure 2). This association was also observed for the control group ($r = 0.89$, $P < 0.001$). The percentage of individuals reporting specific visuospatial difficulties did not significantly differ between formats (all P 's > 0.10).

Validity of Web-Based Questionnaire (PD Only). With regard to construct validity, there was a highly significant negative association between the Visual and Visuospatial summary score from the web-based questionnaire and the z-score derived from performance on the objective visuospatial tests (composite score derived from Line Bisection, Road-Map, JLO) ($r = -0.59$, $P < 0.003$). That is, as self-reported visual and visuospatial impairments increased, performance on objective measures of visuospatial cognition was poorer. There were, however, no significant associations between the Visual and Visuospatial summary score derived from the questionnaire and the objectively based Vision z-score

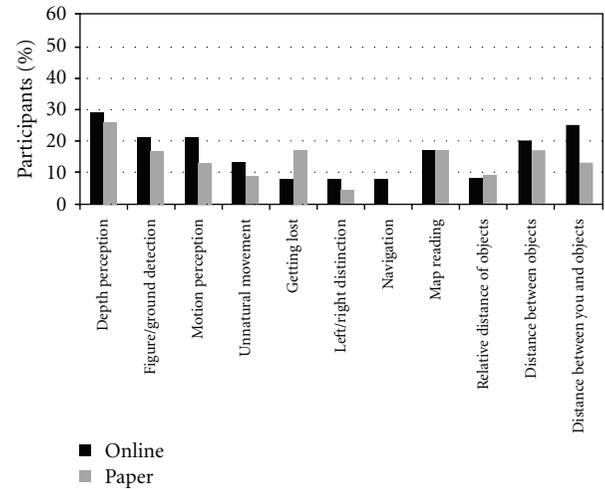


FIGURE 2: Percentage of PD participants reporting impairment on the visual and visuospatial items from the web-based versus paper-based questionnaires. There were no significant differences in item responding for the two formats (all P 's > 0.10).

(composite score from FACT contrast sensitivity, backwards masking contrast sensitivity, coherent motion perception), or combined Visual and Visuospatial z-score ($P > 0.30$).

Exploratory analyses were conducted to determine if responses to specific visuospatial items on the questionnaire correlated with corresponding performance on the objective measures. In view of the potential number of comparisons, analyses were limited to correlations between the objective visuospatial measures that comprised the Visuospatial z-score (Line Bisection, Road Map, JLO) and construct-related web-based questions. To correct for multiple correlations (seven per visuospatial task), significant associations were defined as $P \leq 0.007$ (alpha 0.05/7). Performance on each of Line Bisection and JLO was significantly correlated with a number of questions assessing self-reported high-order visuospatial abilities including navigation, map reading, and judging distances. Performance on the Road Map task was associated specifically with self-evaluated map reading abilities (Table 3). Overall, these findings provide support for the construct validity of the specific visuospatial items of left/right judgments, navigation, map reading, and estimating the distances between objects from the PD Vision Questionnaire.

3.3. Activities of Daily Living (PD)

3.3.1. Reliability. Excellent reliability across measures was indicated by the strong correlation between the ADL summary scores derived from online and paper versions of the survey ($r = 0.84$, $P < 0.001$).

3.3.2. Validity. Demonstrating construct validity of the ADL summary score, this score was significantly correlated with the ADL scale from the PDQ-39 ($r = 0.44$, $P < 0.05$) as well as the total PDQ-39 score ($r = 0.49$, $P < 0.05$).

TABLE 3: Content validation of visuospatial items.

Visuospatial items from questionnaire	Visuospatial tasks		
	Landmark N = 24	JLO N = 23	Road Map N = 23
Getting Lost	0.21	0.35	0.29
Left/Right decisions	0.54*	0.56*	0.41
Navigation	0.80*	0.56*	0.29
Map Reading	0.86*	0.60*	0.55*
Judging objects in relation to each other	0.75*	0.54	0.27
Determining the distance between objects	0.55*	0.58*	0.48
Estimating distance between you and objects	0.39	0.43	0.26

* Pearson correlation $P' s \leq 0.007$; Landmark: Landmark Test of Line Bisection; JLO: Judgment of Line Orientation.

3.4. Motor Symptoms (PD)

3.4.1. Reliability. There was a strong association between the Motor summary scores derived from the online and paper formats ($r = 0.80$, $P < 0.001$).

3.4.2. Validity. The self-reported Motor summary score and the UPDRS motor score were not significantly correlated ($r = 0.11$, $P = 0.62$). There was no association between the Motor summary score and the UPDRS motor score ($r = 0.17$, $P = 0.45$) even after conducting a partial correlation controlling for the duration of delay between UPDRS motor score rating and completion of the questionnaire (mean 7.4 months, SD 6.3 months). There was a significant correlation between the self-reported Motor summary score and the ADL section of the UPDRS ($r = 0.57$, $P < 0.01$), which evaluates functional and motor symptoms of PD through clinical interview with the participant.

4. Discussion

Our findings demonstrate the feasibility of using an online survey of visual and visuospatial abilities, ADL functioning, and motor symptoms by individuals with PD. Feasibility was also demonstrated in regard to self-evaluated visual and visuospatial abilities in healthy adults matched to the PD group for age, education, and other characteristics. Feedback from PD participants with mild to moderate disease severity and from HC indicated that the survey was easy to use and could be completed in a reasonable amount of time. All participants were able to complete both measures. The web-based assessment showed good reliability, comparable to other standard self-report measures of PD symptoms [29, 30]. Total Visual and Visuospatial summary scores did not differ between formats for the PD group ($P > 0.1$). The percentage of individuals with PD who reported difficulties on visuospatial items did not differ between formats (all $P' s > 0.10$). This result indicates that the formats have comparable sensitivity in regard to detecting visual and visuospatial impairments.

A greater percentage of the PD group than the HC group endorsed difficulties on most, but not all, of the visual and visuospatial items of the questionnaire. Non-endorsement of the “getting lost” item could indicate that individuals with

PD did not have difficulties in these areas. Alternatively, the results could reflect reluctance on the part of PD respondents to admit difficulties in aspects of functioning that might be associated with serious outcomes such as the potential loss of a driver's license. There is also the possibility that these individuals had minimal exposure to situations requiring these abilities—for example, if they drove or went for walks only infrequently, possibly owing to PD-related motor impairment.

In general, self-reported visual and visuospatial deficits were prevalent in this PD sample, consistent with previous reports [1, 2]. More PD participants than HC endorsed visual difficulties, including in depth perception, motion perception, and figure ground discrimination, as well as in higher-order visuospatial cognition such as map reading and estimating distances. While PD-related deficits on objective measures of these specific abilities have been previously documented [4, 12, 31], it is striking that these impairments were severe enough to be noticed by a significant portion of the PD participants during everyday tasks requiring visuospatial abilities.

In the PD group, the number and severity of self-reported visuospatial impairments were associated with poorer performance on a composite measure of objective tests of higher-order visuospatial cognition. As participants reported greater difficulties with navigation, map reading, and judging distances, they performed more poorly on content-related neuropsychological measures of visuospatial cognition. It appears that individuals with PD, as assessed in this sample (nondemented, with mild to moderate motor severity), are sensitive to and can accurately report their visuospatial impairments. These findings point to an association between performance on laboratory-based measures of visuospatial cognition and visuospatial behavior in everyday life. The lack of association between objective measures of visual functioning and self-reported deficits could reflect either the participants' insensitivity to visual changes or the ability of our objective measures to detect visual changes before they are severe enough to impact performance of visually mediated tasks.

The severity of ADL impairment, as indexed by the online questionnaire, was significantly correlated with the degree of impairment that the participants with PD reported

on the ADL scale as well as with the overall score of the PDQ-39, a commonly used measure of subjective quality of life [26]. These findings strongly suggest that web-based administration is a valid method of assessing difficulties with ADL functioning, which are frequently experienced by PD patients.

The Motor summary score of the web-based questionnaire was not correlated with the UPDRS motor score. It is possible that the restricted range of PD motor symptom severity in our sample (mild-moderate) might account for the absence of a significant association. One motivation for translating the questionnaire for online use is to capture the experience of PD participants with a broader range of disease severity than typically seen in research studies [12]. This includes individuals with more severe disease (H&Y 3+), which may prevent travel to a research setting or preclude lengthy in-laboratory assessments, as well as individuals with less severe disease (H&Y 1-2) who are still working and unable to take time out to participate. A second possible explanation for the lack of correlation between the survey's Motor summary score and UPDRS motor score is that in the former, the score is based on self-report whereas on the UPDRS the score is generated by an examiner. The lack of association between self- and examiner ratings of motor symptom severity also raises the possibility that our participants may not have viewed their motor symptom severity accurately, a finding that has been observed previously in patients with PD [32]. By contrast, the PD Vision Questionnaire Motor summary score was correlated with the UPDRS ADL score which, like the survey, reflects the participant's rather than the examiner's perspective. Participants may be more accurate in assessing their visuospatial and functional independence (ADLs), as these questions have better face validity than some of the motor symptoms assessed with the UPDRS. For example, unlike the spatial task of map reading, which patently assesses navigation abilities, many items on the motor scale of the UPDRS require evaluation of behaviors only rarely performed (e.g., tests of rapid alternating hand movements, force-induced loss of balance).

As the present study was conducted with a limited sample of participants, replication of our findings is needed to evaluate the stability of the reliability and validity associations. Larger samples would enable analysis by subgroups, which may be informative. For example, we recently reported that self-identified impairments in visual ADLs were more extensive in PD patients whose initial motor symptom was not tremor than in those whose initial symptom was tremor [33]. In particular, future work should focus on expanding the range of PD severity to include participants with milder and more severe motor impairment than were assessed here.

5. Conclusions

Internet-administered testing is a technology with the potential to increase participation in research and clinical trials by reducing the burden of engagement. Web-based administration may be especially useful in expanding the research pool of individuals with PD to include those who

are not able to participate in laboratory-based research because of time constraints or mobility issues. The high rating of ease of accessibility and ease of completion of our online questionnaire lends confidence to the supposition that many PD patients with more severe disease may be able to complete this measure. The inclusion of patients with a broader range of PD symptom severity, both milder and more severe, would lead to a more accurate characterization of PD-related motor and nonmotor symptoms, particularly of understudied visual and visuospatial impairments.

Conflict of Interests

The authors report no financial conflict of interest concerning the research related to the paper.

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