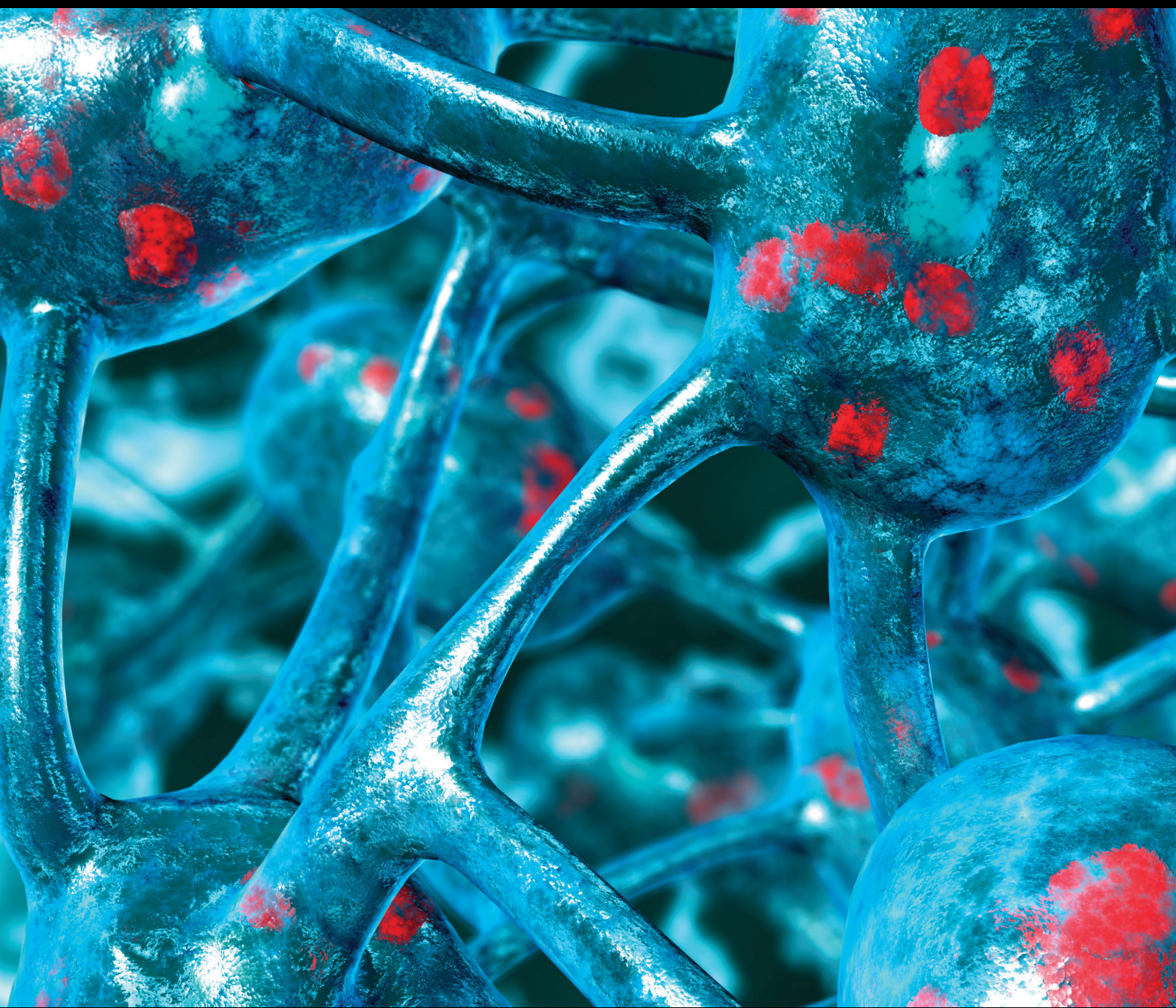
Parkinson's Disease

Behavioral and Emotional Dysfunction in Parkinson's Disease

Lead Guest Editor: Matteo Bologna
Guest Editors: Aristide Merola and Lucia Ricciardi



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Editorial

Behavioral and Emotional Dysfunction in Parkinson's Disease

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Alongside the major interest for Parkinson's disease (PD) motor symptoms, in recent years, there has been increasing attention to PD-associated nonmotor symptoms. Behavioral and emotional dysfunctions have been identified as major determinants of health-related quality-of-life impairment, frequently affecting PD patients since the very first stages of the disease or even before the onset of classical motor symptoms [1, 2, 3]. Despite their major impact on the quality of life, behavioral and emotional disorders may be under-recognized and untreated in PD.

Although the exact pathogenesis of behavioral and emotional disorders associated with PD remains to be clarified, several mechanisms have been identified. Because of the complex role of basal ganglia in processing a wide range of motor and nonmotor information [4, 5], dysfunction in these structures is thought to play a key role in generating behavioral and emotional disorders in PD. Other mechanisms, however, include dopaminergic and nondopaminergic dysfunctions of several pathways at the subcortical and cortical levels, including the limbic system [6, 7].

It is worth considering that PD affects over 6 million people worldwide and that this number is projected to double by 2040 [8]. The need for expanding the knowledge on behavioral and emotional dysfunctions represents, therefore, a key priority for clinicians and researchers and is crucial to the effective treatment of these disturbances.

This special issue was specifically designed to focus on three main critical areas, namely, (a) evidence of PD-associated behavioral and emotional dysfunctions, (b) neural correlates and pathophysiological aspects of behavioral and emotional dysfunction associated with PD, and (c) clinimetric assessment and screening instruments for PD-associated behavioral and emotional dysfunctions.

From the initial analysis of thirteen papers submitted by international researchers, seven were identified as the most relevant and peer-reviewed by experts in the field. The following is a short summary of the major findings of each of these papers.

Imaging genetics is a novel-integrated research method which combines different techniques in the attempt to disentangle the relationship between genetic factors and brain functions or structures. By using this experimental approach, Y. Zhi et al. further investigated the pathophysiological basis of depression in patients. The authors employed resting-state functional magnetic resonance imaging and tested the dopamine receptor D3 gene polymorphism. They found that the D3 gene Ser9Gly polymorphism was associated with more severe anhedonia in PD patients. They discussed the possible role of the frontal areas, namely, the right inferior occipital gyrus, lingual gyrus, and fusiform gyrus, in generating depressive symptoms in PD. The association between genetic variants imaging phenotypes and different clinical manifestations of nonmotor symptoms should be further explored in future studies.

Hallucinations are common disturbances in patients with PD. Previous studies have mainly investigated the neural correlates of well-formed visual hallucinations in PD patients with advanced disease. By contrast, less is known

about patients in the early stages of the disease and about minor hallucinations. C. M. Sawczak et al. investigated the contribution of the attention networks in generating minor hallucinations in PD. In their neuroimaging study, the authors demonstrated a thicker cortex in both the dorsal and ventral attention networks. It is noteworthy to remark, however, that prior work showed the opposite result, i.e., grey matter reductions in PD. Therefore, the available data so far indicate a variable pattern of cortical thickness alterations associated with hallucinations in PD. Further investigations and longitudinal studies are warranted to better define the neural correlates of PD psychosis.

Even though the decline in motor performance is the most prominent feature of PD progression, the relationship between movement abnormalities and nonmotor symptoms, including a deficit in motivation, is far from being understood. In their original study, M. Kojovic et al. tested the effect of monetary incentive on movement speed in PD patients treated with STN-DBS and dopaminergic medications. The results indicate that motivational modulation of movement speed may be enhanced as a direct consequence of DBS rather than dopaminergic treatment. The results may be relevant for future and innovative rehabilitation programs.

In their viewpoint paper entitled "Motor and nonmotor symptoms of PD; antagonistic pleiotropy phenomena derived from α-synuclein evolvability?," Y. Takamatsu et al. discuss nonmotor symptoms, including depression and anxiety, in PD and other synucleinopathies in an evolutionary perspective. The authors also discuss possible implications related to novel therapeutic strategies.

Mounting shreds of evidence suggest that people with PD perform poorly on tests assessing the ability to infer the beliefs, desires, and intentions of others. All these functions fall under the umbrella term of "Theory of Mind" (ToM). In their original paper, J. A. Foley et al. reveal that apparent impairment observed on ToM tests in PD patients is explained by altered executive functions. Among these, the authors report deficits in inhibition, likely due to neuropathological, metabolism, or connectivity changes of the frontal lobe in PD. The results highlight the importance of accurate neuropsychological testing in PD patients.

Proper assessment of behavioral and emotional dysfunctions in PD is a challenging issue, in both clinical and research contexts. For these purposes, various scales exist; however, their reliability and validity are not always tested in specific populations where contextual, social, and environmental factors may significantly influence the outcome measure. Thus, psychometric properties of the clinical scales have been often studied in different pathologies and in different settings. P. Massai et al. investigated the internal consistency, test-retest reliability, and construct and discriminant validity of the Geriatric Depression Scale (GDS) in Italian people with PD. Their results demonstrate that GDS is reliable and valid in Italian patients to quantify depression in PD.

With an estimated prevalence of ~3–42%, impulse control behaviours (ICB) and disorders (ICD) represent one of the most significant nonmotor health problems in patients with PD. Questionnaire for Impulsive-Compulsive Disorders in PD (QUIP) is the most commonly used screening instrument for ICD in PD patients. E. Maréchal et al. translated the QUIP into Flemish to develop a useful screening instrument for ICD in the Belgian population. They used a translation-backtranslation method. The results of this pilot study suggest that the validity of the questionnaire is similar to the original version. The authors emphasize the role of a proper screening instrument for the detection of ICB and ICD in the people with PD.

We believe that this special issue will contribute to raise interest in several aspects related to behavioral and emotional dysfunction in PD. We aimed to highlight original research findings from a broad perspective. We hope that this special issue might inspire future and novel research approaches to tackle some of the unsolved, and still controversial, issues highlighted in the various studies.

In conclusion, we would like to thank all the authors, the reviewers, and the editorial board members for their effort in constructing this special issue on behavioral and emotional dysfunction in PD.

Conflicts of Interest

The editors declare that they have no conflicts of interest regarding the publication of this special issue.

Matteo Bologna
Aristide Merola
Lucia Ricciardi

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Research Article

Impairment in Theory of Mind in Parkinson's Disease Is Explained by Deficits in Inhibition

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Objective. Several studies have reported that people with Parkinson's disease (PD) perform poorly on tests of 'Theory of Mind' (ToM), suggesting impairment in the ability to understand and infer other people's thoughts and feelings. However, few studies have sought to separate the processes involved in social reasoning from those involved in managing the inhibitory demands on these tests. In this study, we investigated the contribution of inhibition to ToM performance in PD. *Methods*. 18 PD patients and 22 age-matched healthy controls performed a ToM test that separates the ability to infer someone else's perspective from the ability to inhibit one's own. Participants also completed a battery of standard measures of social and executive functioning, including measures of inhibition. *Results*. The PD patients performed worse on the ToM test only when the inhibitory demands were high. When the level of inhibition required was reduced, there were no significant group differences. Furthermore, executive impairments in PD patients were limited to measures of inhibition, with disadvantages associated with poorer ToM performance in this group. *Conclusions*. This study provides convincing evidence that the apparent impairment observed on ToM tests in PD is explained by deficits in inhibition.

1. Introduction

Several studies have reported that people with Parkinson's disease (PD) perform poorly on tests assessing the ability to infer the beliefs, desires, and intentions of others [1–3]. These functions fall under the umbrella term of "Theory of Mind" (ToM), considered essential for the development and maintenance of successful social relationships [4].

ToM has been separated into cognitive and affective components [5]. Cognitive ToM is the ability to identify others' beliefs and intentions, and affective ToM is the ability to empathise with others' emotional states. In PD, there are reports of impairments in both [1, 2], but these have been inconsistent [6–8], with some reporting impairment only in cognitive ToM [7–11] or advanced disease [8]. The variation in results appears to depend upon the specific measure used and severity of PD in the cohort tested [12]. This would suggest that the incidental processing demands of the individual tests may be contributing to the observed variation.

This variation may be, at least in part, explained by the varying demands that each test places upon executive function. Although the precise role of executive function in

performance on ToM tests remains debated, some have argued that ToM is simply the reflection of "domain-general" executive functions within a social realm [13]. Alternative accounts have construed ToM as a specialised process, involving dedicated or "domain-specific" ToM computations, distinct from executive functions [14–16]. Others still have suggested that performance on ToM tests involves both domain-general executive functions and domain-specific ToM processes [17].

There are reports of a double dissociation between ToM and executive functions: impaired ToM with preserved executive functions [14, 18, 19] and preserved ToM with impaired executive functions [20, 21], suggesting separability of function. However, this apparent independence may betray an insufficiently broad assessment of the range of functions underpinned by executive control [22]. In particular, there is mounting evidence to suggest that the executive function of inhibition is crucial for performance on ToM tests. Several studies have found inhibition to be highly correlated with and predictive of performance on ToM tests in children [23–25] and adults [26]. In keeping with this, closer inspection of the aforementioned reports of preserved ToM with impaired executive functions reveals that this occurred in the presence of intact performance the Stroop Colour Word Test of inhibition [20] or in the absence of any measure of inhibition [21].

Samson and colleagues [27, 28] argue that standard tests of ToM lack the capacity to identify the specific cognitive function underlying impaired performance. For example, a canonical test of ToM is the "false belief" test. During this test, participants are asked to listen to a story in which a character hides an object and then leaves the room. When this character is outside of the room, a second character moves the hidden object to a new location. Participants are then asked where the first character will think the object is. Samson and colleagues argue that in order to answer this question correctly, participants must first inhibit their own knowledge of where the object is (self-perspective) in order to focus on the first character's false belief (other-perspective). This necessitates high demands upon attentional and inhibitory functions.

The neuropsychological profile of PD is characterised by deficits in attentional and executive function, most notably in inhibition [29–33]. Speed of processing is also reduced [34–36]. As PD progresses, other cognitive domains become increasing affected, with additional impairments in memory and visual processing [37, 38]. Thus, it remains unclear how much of the apparent impairment on ToM tests in PD may be explained by deficits in more general cognitive abilities, and particularly the executive function of inhibition.

The aim of the current study is to assess ToM abilities in PD when controlling for incidental inhibitory demands. In order to do this, we designed a false belief test based upon that described by Samson and colleagues [27, 28, 39], which directly manipulates the level of inhibition involved. In addition, we also assessed participants on standard ToM and cognitive tests, including several measures of executive functioning, including inhibition, and measures of mood, in order to investigate the relationship between these and performance on the experimental measure.

2. Methods

2.1. Participants. A total of 18 patients with idiopathic PD and 22 healthy age-matched controls took part in this study. All patients were recruited from the National Hospital for Neurology and Neurosurgery, Queen Square, London. All fulfilled Queen Square Brain Bank criteria for PD and had no diagnosis of dementia. All patients were receiving dopaminergic medication and tested under their usual medication conditions. The healthy controls were recruited amongst patients' spouses or relatives or through local advertisement. No participant had significant neurological or psychiatric history. The characteristics of the two groups are shown in Table 1.

The research was done in accordance with the Helsinki declaration and the Institute of Neurology Joint Research Ethics Committee UCLH, NHS Trust Research and Development Directorate.

2.2. Procedure. All of the patients and healthy controls completed the following assessments.

2.2.1. ToM Test: High and Low Inhibition Conditions. This test was adapted from Samson and colleagues [27, 28, 39]. In our version, participants completed 12 trials in each condition (high and low inhibition), presented in a pseudorandomized order. The high inhibition condition is similar to a classical false belief test. Here, the participant is shown a woman seeing an object placed inside one of three identical boxes. She leaves the room and in her absence, the location of the boxes is swapped. The woman then returns, and the participant is asked where she will look for the object. In order to answer correctly, the participant must not only infer the woman's false belief but also inhibit their own perspective of knowing the true location of the object.

In the low inhibition condition, the participant sees the woman looking inside the three boxes but is not shown which of the boxes contains the object. The woman then leaves the room, and as before, the location of the boxes is swapped. The woman then returns and offers the participant a clue about the location of the object by pointing to one of the boxes. The participant is then asked where she will look for the object. In order to answer correctly, the participant must infer the woman's false belief to choose the box she has selected. Crucially, in this condition, the participant does not have to inhibit knowledge of the object's true location. Thus, for each trial, the participant is asked where the woman will look for the object, assessing the participant's ability to infer a false belief. The participant is also asked where is the true location of the object, as a control measure to assess comprehension.

We modified the original test in two ways. Firstly, the original videos used only young actors. As there is evidence of an "own-age bias" in face processing [40–42], the videos were re-shot to include older actors. Secondly, as the original

Table 1: Characteristics of PD patients and healthy controls.

	PD patients ($n = 18$)	Age-matched controls ($n = 22$)
Gender (male)	10, 55.6%	9, 40.9%
Age (years)	63.83 ± 10.73	63.81 ± 7.09
NART predicted IQ	117.94 ± 6.64	119.41 ± 5.33
Age of onset (years)	57.56 ± 10.70	—
Duration of illness (years)	6.11 ± 3.07	—
Dopamine dosage (mg)	655.15 ± 450.34	—

test involved choosing between only two boxes, it invoked a binary response choice and required a great number of trials per condition to reduce the influence of chance, with an administration time of at least two hours. In the present study, the number of boxes was increased to three, allowing a reduction in the number of trials and administration time. When the correct answer could have been one of two possible locations, a response indicating either or both locations was accepted. Each question therefore had a maximum possible score of 12.

2.2.2. Standard Measures of ToM and Social Cognition. ToM was assessed using the Reading the Mind in the Eyes Test, Revised Version (RMET; [43]). On this test, participants were shown the eye regions of actors and asked to identify their mental state from one of the four possible responses. Social cognition was also assessed using the Ekman 60 Faces [44]. Participants were shown the faces of 10 actors and asked to identify the emotion expressed from one of six possible responses: happiness, sadness, disgust, fear, surprise, and anger.

2.2.3. Executive Functioning. Executive functioning was assessed using measures of attentional flexibility, updating of information in working memory, and inhibition of prepotent responses respectively. Attentional flexibility, or set-shifting, was assessed using the Plus/Minus test [45] and the Brixton Spatial Anticipation Test [46]. Updating of information in working memory was assessed using the Digit Span subtest from the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III; [47]). Inhibition of prepotent responses was assessed using the Stroop Colour Word Test [48], the Hayling Sentence Completion Test [46], and the Elevator Counting with Distraction subtest from the Test of Everyday Attention [49]. In addition, measures of phonemic (FAS; [50]) and semantic (animals; [50]) verbal fluency were also used.

2.2.4. Background Cognitive Tests. Other cognitive tests administered included the Story subtests from the Adult Memory and Information Processing Battery [51] and the Symbol Digit Modalities Test [52].

2.2.5. Mood. Mood state was assessed using the Hospital Anxiety and Depression Scale (HADS; [53]) and Apathy Evaluation Scale (AES; [54]).

2.3. Statistical Analysis. Mean and standard deviations were calculated for each of the variables. Normality of distribution was assessed using the Kolmogorov–Smirnov test and, if significant, by examining the z-scores for skewness and kurtosis. Homogeneity of variance was assessed using Levene's test. Unless otherwise stated, all data met the assumptions of normality and homogeneity of variance. It was not possible to conduct a mixed analysis of variance because of insufficient homogeneity of variance despite square root transformation. Therefore, scores were compared between groups using t-tests for related samples and independent t-tests, or Wilcoxon signed-ranks and Mann–Whitney analyses, as appropriate, corrected for multiple comparisons. Scores were also analysed using Pearson's correlational, principal components, and multiple regression analyses to explore the relationships between performance on measures of ToM and executive functioning, corrected for multiple comparisons where appropriate. All tests were conducted using IBM SPSS Statistics Data Editor version 24.

3. Results

3.1. Participants. The two groups were matched in age ($t(28.38) = -0.01$, $p = 0.09$), gender ($\chi^2(1) = 0.85$, $p = 0.27$), and NART Predicted Full Scale IQ ($t(37) = 0.77$, $p = 0.45$).

3.2. ToM Test: High and Low Inhibition Conditions. Mean performance on the ToM test in the two groups is shown in Table 2.

3.2.1. False Belief Test. As shown in Figure 1, Wilcoxon signed-rank tests revealed that the PD patients performed worse in the high inhibition condition than in the low inhibition condition ($Z = -2.40$, $p < 0.05$). There was no such difference in the healthy controls ($Z = -0.91$, $p = 0.37$).

Mann–Whitney tests revealed that the PD patients performed significantly worse than the healthy controls on the false belief test in the high inhibition condition ($U = 57.00$, $p < 0.001$). There were no significant group differences in the low inhibition condition ($U = 153.00$, $p = 0.60$).

3.2.2. True Location Test. Wilcoxon signed-rank tests also revealed that both groups performed worse on the true location test in the low inhibition condition than in the high inhibition condition (age-matched: $Z = -3.13$, $p < 0.01$; PD: $Z = -2.74$, $p < 0.01$).

Table 2: Performance on the ToM test in the two groups (mean ± SD).

Test	Condition	PD patients ($n = 18$)	Healthy controls ($n = 22$)
False belief	High inhibition	8.78 ± 2.53	11.55 ± 0.69**
	Low inhibition	11.06 ± 1.83	11.68 ± 0.58
True location	High inhibition	10.11 ± 1.64	11.52 ± 0.68*
	Low inhibition	7.56 ± 2.94	9.19 2.34

* $p < 0.01$; ** $p < 0.001$.

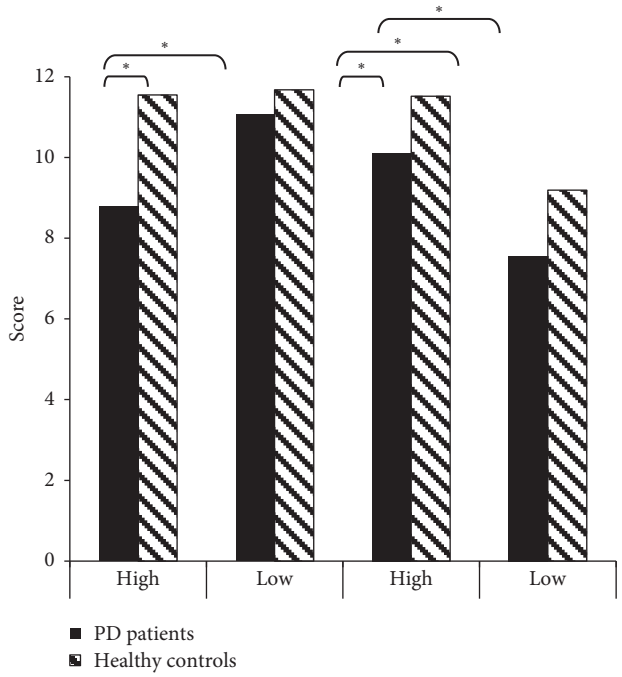

Figure 1: Performance on the ToM test in high and low inhibition conditions in the two groups.

Mann–Whitney tests revealed that the PD patients performed significantly worse than the healthy controls on the true location test in the high inhibition condition ($U = 88.50$, $p < 0.01$). There were no significant group differences in the low inhibition condition ($U = 124.00$, $p = 0.69$).

3.3. Standard Measures of ToM, Social Cognition, and Executive Function. Mean scores on the standard measures of ToM, social cognition, and executive function are reported in Table 3.

Independent t-tests revealed no significant group differences in performance on the Ekman (t (36) = −0.96, $p = 0.34$). However, PD patients performed significantly worse than the healthy controls on the RMET test (t (37) = 3.15, $p < 0.01$). The PD group also performed significantly worse on one measure of executive functioning only, namely, the Hayling (t (27.63) = 14.13, $p < 0.01$).

3.4. Background Cognitive Tests and Mood. Scores on the background cognitive tests and measures of mood are reported in Table 4.

Independent t-tests revealed that the PD patients performed significantly worse than healthy controls on both AMIPB immediate (t (35) = 3.85, $p < 0.001$) and delayed story recall (t (32.64) = 3.08, $p < 0.01$). There were no other significant group differences. There were no significant group differences in mood scores.

3.5. Relationship between ToM and PD Disease Characteristics. Pearson correlations were conducted to investigate the relationship between the PD patients' performance on the ToM test and their PD disease characteristics (dopamine dosage and disease duration). This revealed that higher dopamine dosages were associated with poorer performance in the high inhibition condition of the false belief test ($r = -0.50$, $p < 0.05$). There were no other significant associations.

3.6. Relationship between ToM and Executive Functioning. A principal components analysis with varimax rotation was also conducted to determine the relationship between the performance on the false belief test and measures of executive function. As shown in Table 5, this analysis extracted four independent factors. The first factor comprised scores on tests tapping inhibitory functions, namely, the false belief test in the high inhibition condition, the Stroop, Hayling, and Elevator Counting with Distraction tests, as well as the Brixton and both measures of verbal fluency to a lesser extent. The second factor reflected primarily working memory, with performance on the False Belief test in the low inhibition condition, Digit Span, and the Brixton and FAS fluency to lesser extents. The third factor only involved the set-shifting test of Plus/Minus ratio, whereas the fourth factor reflected its associations with the False Belief test in the low inhibition condition and verbal fluency.

Pearson correlations were also conducted to explore further the relationship between ToM and executive functioning. These revealed that performance on the false belief test in high inhibition condition correlated with performance on the Hayling ($r = 0.52$, $p < 0.01$) and Elevator Counting with Distraction tests only ($r = .61$, $p < 0.001$). Performance in the low inhibition condition was not associated with performance on any measures of inhibition or executive function. There were also no significant correlations between performance on the object location control test in either condition and performance on any measure of executive functioning.

Multiple regression analysis revealed that performance on the Hayling and Elevator Counting with Distraction tests was a significant predictor of performance on the False Belief

Table 3: Performance on the standard measures of ToM, social cognition, and executive functioning in the two groups (mean ± SD).

		PD patients ($n = 18$)	Healthy controls ($n = 22$)
Social Cognition	Ekman	49.42 ± 5.34	47.91 ± 4.30
	RMET	23.59 ± 3.28	26.77 ± 3.01*
Inhibition	Stroop—total	85.83 ± 19.49	91.53 ± 17.83
	Hayling—total scaled score	16.35 ± 2.12	18.70 ± 1.22*
	Elevator counting with distraction	7.65 ± 3.02	8.94 ± 1.21
Set-shifting	Plus/Minus ratio	1.38 ± 0.27	1.43 ± 0.17
	Brixton—overall score	4.44 ± 2.50	4.95 ± 2.54
Updating	Digit span: forwards and backwards	7.65 ± 3.02	8.94 ± 1.21
Fluency	FAS—total	40.00 ± 14.25	40.95 ± 10.80
	Animals—total	19.06 ± 4.25	21.60 ± 2.58

* $p < 0.01$; RMET: reading the mind in the eyes test, revised version.

Table 4: Performance on the background cognitive tests and mood assessments in the two groups (mean ± SD).

	PD patients ($n = 18$)	Healthy controls ($n = 22$)
AMIPB story immediate	27.94 ± 7.23	38.80 ± 9.51**
AMIPB story delayed	24.00 ± 6.94	34.29 ± 12.22*
AMIPB story retained	85.49 ± 9.76	90.41 ± 9.05
SDMT	40.12 ± 8.37	44.71 ± 5.82
HADS—anxiety	7.53 ± 3.64	5.19 ± 3.23
HADS—depression	4.00 ± 2.30	3.52 ± 2.80
Apathy	25.67 ± 3.37	24.50 ± 5.61

* $p < 0.01$; ** $p < 0.001$. AMIPB: Adult Memory and Information Processing Battery; SDMT: Symbol Digit Modalities Test; HADS: Hospital Anxiety and Depression Scale.

Table 5: Principal component analysis (with varimax rotation) for underlying factors on tests of executive function and false belief.

	Factor 1	Factor 2	Factor 3	Factor 4
False belief—high inhibition	0.81			
False belief—low inhibition		0.67		0.52
Stroop—total	0.81			
Hayling—overall score	0.77			
Elevator counting with distraction	0.82			
Plus/minus ratio			0.80	0.44
Brixton—overall score	0.67	0.47		
Digit span: forwards—backwards		0.65		
FAS—total	0.45	−0.58		0.42
Animals—total	0.61			0.42

test in the high inhibition condition ($F_{2,27} = 10.28$, $p < 0.001$). Together, the two tests accounted for 39.0% of the variance.

4. Discussion

The current study found that patients with PD performed significantly worse than age-matched healthy controls on two measures of ToM: our ToM test and RMET. At first glance, this finding lends support to the suggestion that, in PD, there is an underlying deficit in the ability to infer the beliefs, desires, and intentions of other people, consistent with other studies [1, 2] [7–9, 11, 12]. However, the main aim of the present study was to determine how much of this apparent impairment may be explained by the incidental processing demands that ToM tests incur, most notably in inhibition. Full neuropsychological testing revealed that the PD patients demonstrated impairment in executive functions and specifically in inhibition. Although PD patients demonstrated lower scores on all tests of executive functions, performance was only significantly reduced on one test of inhibition: the Hayling. This supports previous findings that PD is characterised by deficits in executive function and particularly inhibition [29–33]. Strikingly, when we manipulated our ToM test to reduce the level of inhibition required, there were no longer any group differences in performance. Further analyses also revealed that performance on the high inhibition condition of the ToM test was negatively correlated with greater impairment on measures of inhibition and, indeed, performance on the ToM test was predicted by performance on measures of inhibition. Furthermore, factor analysis confirmed that performance on the high and low inhibition conditions dissociated, with performance on the high inhibition condition loading upon inhibition, whereas performance on the low inhibition condition loaded upon working memory.

These findings suggest that, in PD, there is no impairment in ToM per se but rather the executive functions that support performance on ToM tests are diminished: deficits in inhibition underlie the impairment in ToM. This finding may help explain the inconsistency observed on tests of social cognition in both the current and previous studies. For example, although patients performed poorly on the RMET and the experimental measure of ToM, there were no significant group differences in recognising facial emotional expressions on the Ekman. Emotion recognition is thought to be a close correlate of social cognition [55] and impaired performance which is a diagnostic marker of frontotemporal dementia [56]. The preservation of emotion recognition affirms our finding that deficits in social cognition are not constitutional to PD, but rather reflect the incidental demands of the tests used. One previous study that reported emotion recognition deficits found, rather counterintuitively, performance to be worse in those with less advanced PD, but who were unmedicated at time of testing [57]. Other studies have also

shown little correlation between performance on this test and severity of motor symptoms [58]. This suggests that the proposed deficit in emotion recognition is not an inherent trait of PD, but rather a state-based epiphenomenon, with performance on such tests likely reflecting their incidental processing demands. Indeed, Bull et al. [59] found that performance on the RMET test was disrupted when participants were required to perform a secondary task involving inhibitory processing. This disruption was not witnessed when the secondary task involved other executive functions, namely, working memory or switching, nor when the task did not require attribution of mental states. Thus, this test's apparent reliance upon inhibitory processing may explain why our PD patients were impaired on this test.

The finding that there are only ToM deficits in PD when the ToM test places greater demand upon inhibition supports previous findings of a relationship between ToM performance and executive function [8, 12]. For example, Eddy et al. [60] also found that people with PD demonstrated less impairment on ToM tests when the executive load was reduced. Specifically, they found that performance on longer, but not shorter, verbal tests of ToM was associated with verbal working memory. In contrast with the current study, they argue that working memory and executive functioning deficits do not wholly explain ToM performance. It is important to note, however, that they omitted to include a measure of inhibition in this experiment. In an additional experiment, they did include measures of inhibition but failed to find any significant group differences in either inhibition or ToM, supporting the argument that performance on these is intrinsically linked in PD.

Anderson et al. [61] also reported the preservation of social cognition in PD, with poor performance tests of social cognition only occurring in the context of greater executive dysfunction. They propose that when faced with an everyday social problem, people with PD may have greater difficulty inhibiting any previously unsuccessful problem-solving strategies, resulting in the generation of fewer viable alternatives and reliance upon prepotent responding. Our study extends this finding to provide evidence that poor performance on tests of ToM tests in PD is explained by deficits in inhibition. The impact of executive load may also explain why the PD patients also performed worse on the control question within the ToM test. As the original [28] test was modified to include three rather than two boxes, the control question may have inadvertently become more challenging and involve greater processing demands.

It is important to note that overall cognitive load cannot account for the PD deficits in the high inhibition condition. The most challenging subtest on our ToM test appears to have been the true location test in the low inhibition condition, with both participant groups performing significantly worse on this subtest than in the high inhibition condition. Yet, no significant group differences were found here, supporting the suggestion that it is the deficits in inhibition that lead to the PD-specific impairments on the false belief task.

Our findings are in keeping with the known neuropathology of PD. Studies have repeatedly shown that PD is characterised by reductions in frontal lobe volume, metabolism, and connectivity [62–64]. Frontal areas are known to be critical for inhibition [65–67], with right frontal areas particularly involved in the inhibition of one's own perspective [28, 68]. The frontal lobe is also thought to be involved in ToM [69]. However, frontal lobe damage does not necessarily result in impairments in ToM [20] and inhibition is increasingly recognised as important for ToM [23, 24] and Doenyas et al. [26]. Therefore, we argue that our patients' deficits on our tests of ToM may be explained by their impairments in inhibition associated with the known frontal lobe damage in PD.

A limitation of our study is the small sample size. All previous research using this methodology has been limited to single cases or very small case series [27, 28, 39], and therefore, although our patient group size is modest, we hope it will provide a first step towards larger patient group studies.

Future research may wish to expand upon our methodology to include a further control condition that would not require the inference of a false belief, but rather assess the ability to follow the object being moved. This would provide a vigilance control condition enabling better isolation of the cognitive processes involved in the false belief task. However, increasing the number of conditions would necessitate a longer administration time and possibly increase testing fatigue.

In conclusion, this study shows that deficits observed on ToM tests in PD may be explained by deficits in inhibition. Poor performance on these tests therefore does not indicate impairment in social cognition, but more likely deficits in managing the complex processing demands that these tests involve.

Data Availability

The neuropsychological data used to support the findings of this study are restricted by the Institute of Neurology Joint Research Ethics Committee UCLH in order to protect patient privacy. Data are available from the corresponding author for researchers who meet the criteria for access to confidential data.

Conflicts of Interest

The authors declare that there are no known conflicts of interest.

Authors' Contributions

Sharon Abrahams and Lisa Cipolotti contributed equally to this work.

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Research Article

Increased Cortical Thickness in Attentional Networks in Parkinson's Disease with Minor Hallucinations

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Hallucinations are common in Parkinson's disease (PD). Based on functional brain MRI data, hallucinations are proposed to result from alterations in the dorsal attention network (DAN), ventral attention network (VAN), and default mode network. Using structural MRI data from Parkinson's Progression Markers Initiative (PPMI), we examined cortical thickness in these networks in PD patients with ($n = 30$) and without ($n = 30$) minor hallucinations who were matched on multiple clinical characteristics (e.g., age, sex, education, cognitive diagnosis, MoCA score, medication, disease duration, and severity) as well as healthy controls ($n = 30$) matched on demographic variables. Multivariate analyses revealed mild hallucinations to be associated with thicker cortex in the DAN and VAN, and these effects were driven by the left superior precentral sulcus and postcentral sulcus for the DAN and by the right insular gyrus for the VAN. While these findings may seem at odds with prior work showing grey matter reductions, our patients are in earlier stages of the disease than those in other studies. This is consistent with an inverted U-shape pattern of cortical thickness alterations in other neurodegenerative diseases and warrants further investigations in longitudinal studies tracking brain correlates of PD psychosis progression.

1. Introduction

Hallucinations are common in Parkinson's disease (PD) and follow a spectrum of severity (for review, see [1]). In their minor form, they consist of feeling someone's presence, passage hallucinations in one's peripheral vision, or increased frequency of visual illusions. With disease progression, well-formed visual hallucinations (e.g., people or animals) are experienced and insight is progressively lost leading to delusions. Importantly, hallucinations predict both dementia and nursing home placement in PD [2]. Neural correlates of PD-related hallucinations remain unclear. One model proposes that they develop due to dyscoordination of attentional brain networks in the context of ambiguous visual percepts [3, 4]. Specifically, alterations in the goal-directed, top-down, dorsal attention network (DAN) render it unable to correct erroneous interpretations of ambiguous visual stimuli by the stimulus-driven, bottom-up, ventral attention network (VAN) [5] and the default mode network (DMN) which mediates internally generated thoughts [6]. Normally, activity in the DAN and VAN are coupled and are anticorrelated with that of the DMN, but in PD with hallucinations, these relationships are altered. DAN activity and its connectivity with the VAN and visual regions are reduced, while connectivity within and between the DMN and VAN is increased [4].

To date, alterations in these networks are partially supported by structural neuroimaging findings. PD-related hallucinations have been associated with reduced grey matter volume in regions of the DAN (e.g., superior and inferior parietal lobules), the VAN (e.g., right insula), and DMN (e.g., hippocampus) [7], as well as atrophy in various components of the visual pathway [8, 9]. However, these

findings are inconsistent across studies possibly due to small samples and variability in methodologies. Most structural MRI studies also investigate PD patients with well-formed visual hallucinations at relatively late stages of the disease. One exception is a study demonstrating cortical thinning in the supramarginal, superior frontal, and lateral occipital gyri in a small patient group with well-formed visual hallucinations early in the disease course, but showing no alterations in patients with minor hallucinations (MH) [2]. Interestingly, although these findings were not interpreted in the context of the attentional network dysregulation model, the three regions showing cortical thinning are part of the DAN, VAN, and DMN [10]. In contrast, although hippocampal atrophy was found in advanced PD with well-formed hallucinations [11], increased volume was found in patients with MH [12]. In the present study, we address these conflicting results by investigating cortical thickness alterations in the VAN, DAN, and DMN in recently diagnosed PD patients with MH (PDMH) compared to PD patients with no hallucinations (PDnH), who were matched on multiple demographic and clinical variables, and healthy controls (HC). Based on the attentional network dysfunction model, we hypothesized that the PDMH group would demonstrate cortical thickness alterations in these networks.

2. Methods

2.1. Participants. Data used in the preparation of this article were obtained from Parkinson's Progression Markers Initiative (PPMI) database (http://www.ppmi-info.org/data). For up-to-date information on the study, visit http://www.ppmi-info.org. Each participating PPMI site received approval from an ethical standards committee on human experimentation before study initiation and obtained written informed consent for research from all individuals participating in the study. We extracted T1-weighted structural MRI, along with clinical and demographic data for 90 individuals (30 HC; 30 PDnH; 30 PDMH). The presence of MH was defined by a score of "1" on question 1.2 of the MDS-UPDRS on at least three consecutive visits (each at 6-month intervals). This, combined with review of participants' medical history confirming the absence of schizophrenia-spectrum disorder and of current dementia, is consistent with diagnostic criteria for PD-related psychosis, excluding dementia with Lewy bodies [13, 14]. Conversely, the PDnH patients reported no hallucinations on all visits to date. The groups were matched, participant-by-participant for age, sex, education, PD severity (MDS-UPDRS Part III and Hoehn and Yahr), whether they took PD medications, and cognitive diagnosis (i.e., mild cognitive impairment (MCI) versus intact, determined by PPMI investigators based on clinical interviews and cognitive testing; neuropsychological data are presented in Supplementary Materials (available here)). PD groups were also matched for levodopa-equivalent daily dose (LEDD) and MoCA scores. Demographic and clinical characteristics are shown in Table 1. For the PDMH group, MRI scans were selected from visits at the closest time point from their MDS-UPDRS. Scans for other groups were selected based on participant age, matched to the PDMH group.

2.2. Preprocessing and Cortical Thickness Measurements. T1-weighted structural MRI scans were acquired on 3T scanners using Sagittal 3D MP-RAGE or 3D FSPGR with an approximate 1 mm isotropic voxel size (see ppmi.org for details on cross-sites quality control and standardization). Cortical reconstruction and volumetric segmentation were performed using FreeSurfer-v4.5 (http://surfer.nmr.mgh.harvard.edu) [15]. Preprocessing included intensity normalization, skull stripping, registration to standard space, smoothing, delineation of pial, white matter, and grey matter surfaces with manual corrections, and parcellation of the cortex into 150 regions of interest (ROIs). We extracted each participant's cortical thickness for 31 ROIs defined by matching FreeSurfer parcellations [15] to peak MNI coordinates of key nodes of the DAN, DMN, and VAN identified by Yeo et al. [10]. Following visual inspection, we added two FreeSurfer parcellations to the DMN and removed one from the VAN to improve the spatial extent overlap between our network coverage and that of Yeo et al. (Supplementary Materials (available here) for network renderings, MNI coordinates, and corresponding FreeSurfer labels). We used bilateral ROIs for the DAN (superior precentral sulcus, posterior sulcus, superior parietal lobule, and anterior occipital sulcus) and DMN (superior frontal sulcus, angular gyrus, middle temporal gyrus, anterior cingulate cortex, superior frontal gyrus, parahippocampal gyrus, dorsal posterior cingulate cortex, and precuneus), and right hemisphere ROIs for the VAN (supramarginal gyrus, planum temporale, anterior middle cingulate, margin of the cingulate sulcus, and short insular gyrus), as it is known to be right-lateralized [5, 16]. Estimates of hippocampal volume were also extracted, given that this subcortical structure is part of the DMN and showed mixed findings in PD with hallucinations [1, 7].

3. Statistical Analysis and Results

3.1. Demographics and Clinical Measures. Using ANOVAs to compare the three groups (Table 1), there were no significant differences in age ($F_{(2,89)} = 0.084$, $p = 0.919$) or education ($F_{(2,89)} = 0.688$, $p = 0.505$) but the groups differed on the MoCA ($F_{(2,89)} = 9.221$, $p < 0.001$); post hoc tests (with Bonferroni corrections) revealed that HC performed better than the PDMH ($p < 0.001$) and PDnH ($p = 0.02$) groups, but the two PD groups did not differ ($p = 0.455$). Within PD, t-tests revealed that the PDMH and PDnH groups did not differ significantly on LEDD ($t_{(27)} = 0.424$, $p = 0.675$), disease duration ($t_{(58)} = 1.702$, $p = 0.094$), or disease severity as measured by the MDS-UPDRS Part III ($t_{(58)} = 1.685$, $p = 0.097$). Similarly, a median test showed no significant difference between PD groups on Hoehn and Yahr ($p = 0.347$). Chi-squared tests showed no differences between PD groups in medication types (Levodopa: $\chi^2 = 1.926$, $p = 0.165$; DA agonists, $\chi^2 = 2.308$, $p = 0.129$; other PD medications, $\chi^2 = 1.002$, $p = 0.317$; antipsychotics,

Table 1: Demographic and clinical characteristics.

	HC ($N = 30$)		PDnH ($N = 30$)		PDMH ($N = 30$)		p value	Post hoc
Demographics								
Age (years)	63.2	(9.5)	62.7	(8.1)	63.7	(9.7)	0.919	
Male, n (%)	19	(63)	19	(63)	19	(63)		
Education (years)	16.0	(2.9)	15.1	(3.1)	15.6	(2.9)	0.505	
Clinical								
Years since diagnosis	—	—	1.7	(1.1)	2.3	(1.4)	0.094	
MDS-UPDRS Part III	—	—	21.0	(10)	25.7	(11.3)	0.097	
Hoehn and Yahr, median (range)	—	—	2	(1–3)	2	(1–3)	0.347	
Dyskinesia present, n (%)	—	—	1	(3)	0	(0)	0.313	
REM sleep behaviour disorder, n (%)	—	—	9	(30)	15	(50)	0.114	
Medication for PD, n (%)	—	—	12	(41)	17	(57)	0.240	
Levodopa, n (%)	—	—	7	(23)	12	(40)	0.165	
DA agonist, n (%)	—	—	2	(7)	6	(20)	0.129	
Other, n (%)	—	—	4	(13)	7	(23)	0.317	
LEDD (mg)	—	—	370.2	(225.5)	410.9	(273.9)	0.675	
Antipsychotic medication (quetiapine), n (%)	—	—	0	(0)	1[a]	(3)	0.313	
Duration of hallucinations (years)	—	—	—	—	1.23	(0.66)	—	
Cognition								
Cognitive state (intact: MCI)	30 : 0		20 : 10		20 : 10		—	
MoCA	28.1	(1.8)	26.5	(2.3)	25.7	(2.5)	<0.001	HC > PDnVH and PDMH

Notes: demographic, clinical, and cognitive characteristics of our sample. Mean and standard deviation (parentheses) except where otherwise noted. ANOVAs were conducted for each measure and, if significant ($p \leq 0.05$), group differences were ascertained through post hoc testing. DA = dopamine; LEDD = levodopa equivalent daily dosage; MCI = mild cognitive impairment; MoCA = Montreal Cognitive Assessment. [a]Quetiapine 25 mg initiated 6 years prior to the scan date to treat anxiety.

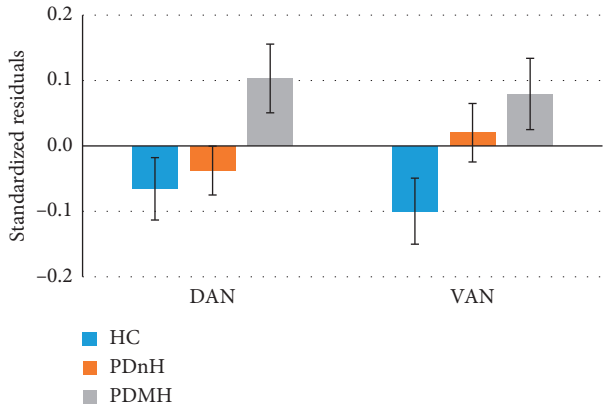
$\chi^2 = 2.069$, $p = 0.15$), presence of dyskinesia ($\chi^2 = 1.017$, $p = 0.313$), or presence of REM sleep behaviour disorder ($\chi^2 = 2.500$, $p = 0.114$).

3.2. Cortical Thickness. To correct cortical thickness measurements, we regressed out age, sex, and a proxy measure of brain volume (pBV = white matter + subcortical grey matter + cerebrospinal fluid) and the resulting standardized residuals were used in our primary analysis. The pBV excluded cortical grey matter to avoid controlling for the measure we are interested in (cortical thickness). The corrected standardized residuals were used as the dependent variables in mean-centered task partial least square (PLS) analyses [17] (see [17] for PLS review and tutorial). PLS is a multivariate technique that analyzes the covariance between a design matrix (i.e., group membership) and a data matrix (i.e., cortical thickness residuals). We performed separate analyses for the DAN, VAN, and DMN. A matrix of correlations between these two matrices was computed and used as the input for a singular value decomposition, which identifies latent variables that best explain the variance in the data. p values for the latent variables are obtained via comparison to a null distribution generated by randomly permuting the data matrix 1000 times and computing new correlations with the design matrix each time. Next, 500 bootstraps were performed by randomly resampling participants with replacement, which allowed calculation of the standard error of the salience of each ROI within the latent variables. As this is done in a single step in this multivariate technique, correction for multiple comparisons is not necessary.

Significant latent variables were identified for the DAN ($p = 0.039$, explained covariance = 75.5%) and the VAN ($p = 0.027$, explained covariance = 69.7%), but no significant latent variable was identified for the DMN. Linear contrasts revealed that cortical thickness was greater in the DAN among PDMH patients compared to the other two groups and thicker in the VAN among PDMH compared to HC. Bootstrap ratios (BSRs) and MNI coordinates for the ROIs in each network are shown in Figure 1. BSRs are roughly proportional to z-scores but should be interpreted as confidence intervals. In the present study, we consider BSRs ≥ 1.96 to be statistically significant; this corresponds to a 95% confidence interval. The most salient ROIs contributing to the group differences in the DAN were, as defined by the FreeSurfer Atlas [15], the left superior precentral sulcus and left postcentral sulcus (BSRs = 2.82 and 2.1, respectively) and in the VAN, the right short insular gyrus (BSR = 2.63). The peak MNI coordinates of these FreeSurfer ROIs correspond to canonical DAN and VAN areas identified in Fox et al. [18] seminal paper [18] as the frontal eye fields, inferior parietal lobule, and insula, respectively. We also compared groups' hippocampal volumes including age, sex, and intracranial volume as covariates of no interest in ANCOVAs. There was no effect of group in left ($F_{(2,89)} = 1.831$, $p = 0.167$) nor right hippocampal volume ($F_{(2,89)} = 0.429$, $p = 0.653$).

4. Discussion

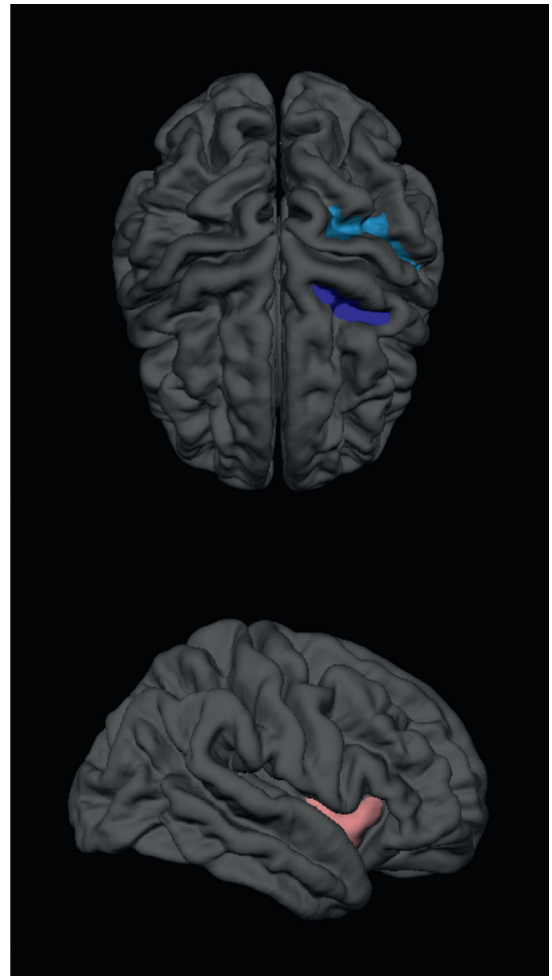
Our data partially support our predictions that individuals with early PD and MH exhibit cortical thickness alterations



(a)

ROI	Coordinates			Bootstrap ratio
	x	*y*	*z*	
DAN				
Left superior precentral sulcus	−27	−9	50	2.82*
Left postcentral sulcus	−37	−36	41	2.1*
Left superior parietal lobule	−19	−58	59	1.63
Left anterior occipital sulcus	−42	−68	0	−0.28
Left inferior precentral sulcus	−43	3	27	1.69
Right superior precentral sulcus	27	−9	52	1.79
Right postcentral sulcus	37	−35	42	1.27
Right superior parietal lobule	18	−54	60	1.04
Right anterior occipital sulcus	43	−65	4	−0.64
Right inferior precentral sulcus	43	4	27	1.71
VAN				
Right supramarginal gyrus	57	−32	31	0.01
Right planum temporale	58	−35	15	0.41
Right anterior middle cingulate	10	15	36	0.59
Right margin of the cingulate sulcus	14	−38	46	0.79
Right short insular gyrus	36	9	−2	2.63*

(b)



(c)

Figure 1: Group difference in cortical thickness. (a) Linear contrasts for each PLS network analysis. (b) Central MNI coordinates of the FreeSurfer parcellations and bootstrap ratios (BSRs) for all ROIs within the DAN and VAN. Asterisks indicate the most salient ROIs (BSR ≥ 2) contributing to each pattern. (c) Most salient ROIs in the DAN (dark blue = left frontal eye fields; light blue = left inferior parietal lobule) and VAN (orange = right insula). DMN is not depicted as no significant latent variable was found.

in attentional networks. Specifically, we found that the PDMH group had thicker cortex in the DAN compared to PDnH and HC groups, and this effect was driven by the left superior precentral sulcus and postcentral sulcus. We also found the PDMH group to have thicker cortex in the VAN compared to HCs, and this effect was driven by the right short insular gyrus. We did not find any group differences in cortical thickness in the DMN cortical ROIs nor in hippocampal volume. Others have found PD hallucinations to be associated with either reduced [2, 11] or increased [12] hippocampal volume; these mixed findings may be attributable to differences in hallucination duration or severity, as we will discuss shortly.

The presence of alterations in the VAN and DAN is consistent with the attentional dysfunction model of PD hallucinations [3, 4]. Our results of increased rather than decreased cortical thickness may seem at odds with studies showing reduced grey matter volume and cortical thinning in some brain areas affiliated with the DAN and VAN [2, 7]. However, similar findings of increased thickness/volume have been documented in PD patients with MH in the hippocampus and in other regions such as the parahippocampal gyrus and orbitofrontal cortex [12].

First, several methodological differences may contribute to these discrepancies. We used a multivariate technique and an ROI approach, which may allow detection of more subtle effects than whole-brain univariate analyses. We also used cortical thickness analyses, whereas most previous studies used VBM which is less specific in that it conveys information about a combination of grey matter measures (surface area, cortical folding, and cortical thickness) [19]. Importantly, our PD sample has a short disease duration with only MH while other studies involve PD with longer disease duration and well-formed visual hallucinations. Thus, it is possible that thicker cortex manifests early in the disease before giving way to atrophic processes, following an inverted U-shape function. A similar rationale was provided to explain increased hippocampal and cerebellar volumes in PD patients with MH [12]. Such an inverted U-shape function is seen in other

conditions such as prodromal Alzheimer's disease (AD). For instance, temporal and parietal structural changes in presenilin-1 mutation carriers follow a nonlinear trajectory with regional increases in presymptomatic period followed by decreases over time [20, 21]. We argue this inverted U-shape model potentially can explain the discrepancy between the present and previous work showing reduced, rather than increased, grey matter in the right insula in PD hallucinations [2]. The average disease duration of Shine et al.'s [3] PD hallucination sample was 6.7 years, which is approximately three times that of our PDMH sample. If grey matter alterations in PD hallucinations do indeed follow an inverted U-shape trajectory as the pathology progresses, then our finding and Shine et al.'s can be reconciled. Additionally, this increased cortical thickness in the VAN and DAN may reflect a trait or risk factor for the development of hallucinations. Interestingly, increased cortical thickness in different brain regions including the insula and inferior parietal lobule has been reported in individuals with schizophrenia who experience auditory hallucinations [22], which was interpreted as a dysregulation in cortical development. Similarly, increased cortical thickness in the superior parietal lobule has also been documented in patients with bipolar disorders with a lifetime history of auditory hallucinations [23].

One limitation of the present study is the reliance on a single item from the MDS-UPDRS scale (item 1.2) to determine the presence or absence of MH. Although the requirement of three consecutive (spaced at 6-month intervals) negative ratings in the PDnH and positive ratings in the PDMH minimizes possible false-negative and false-positive classification errors, respectively, this item does not provide detailed information on the qualitative nature and diversity of the minor hallucinations experienced. This is a common criticism of studies on PD-related psychosis. As a result, recently developed structured interviews have been validated and used in PD research to characterize hallucinations and their related features in more details. Some of these instruments only focus on well-formed hallucinations (e.g., North-East Visual Hallucinations Interview (NEVH I) [24] and Scale for Assessment of Positive Symptoms adapted for PD (SAPS PD) [25]), but a recent adaptation also surveys minor hallucinations (e.g., enhanced SAPS PD (eSAPS-PD) [26]). Although the PPMI study does not include such instruments, their integration in future research will certainly enhance our understanding of hallucinations in PD and underlying neural substrates.

5. Conclusion

In sum, we provide evidence for cortical thickness alterations in attention networks in recently diagnosed PD patients experiencing MH, which supports the attentional dysfunction model of PD hallucinations. Our data also suggest that the course of cortical changes may not follow a linear trajectory but rather an inverted U-shape function, as in prodromal AD, and future work should involve within-subject longitudinal investigations of the progression of psychosis to test this notion.

Data Availability

All data were collected by Parkinson's Progression Markers Initiative (PPMI) and are available, upon request, online (https://www.ppmi-info.org/access-data-specimens).

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Supplementary Materials

The Supplementary Materials contain additional data on neuropsychological assessments, as well as a detailed description of how structural brain networks and ROIs were identified. (*Supplementary Materials*)

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Research Article

The Association between DRD3 Ser9Gly Polymorphism and Depression Severity in Parkinson's Disease

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More and more evidence suggests that dopamine receptor D3 gene (DRD3) plays an important role in the clinical manifestations and the treatment of Parkinson's disease (PD). DRD3 Ser9Gly polymorphism is the most frequently studied variant point. Our aim was to investigate the potential effect of DRD3 Ser9Gly polymorphism on modulating resting-state brain function and associative clinical manifestations in PD patients. We consecutively recruited 61 idiopathic PD patients and 47 healthy controls (HC) who were evaluated by clinical scales, genotyped for variant Ser9Gly in DRD3, and underwent resting-state functional magnetic resonance imaging. Based on DRD3 Ser9Gly polymorphism, PD patients and HCs were divided into four subgroups. Then, two-way analysis of covariance (ANCOVA) was applied to investigate main effects and interactions of PD and DRD3 Ser9Gly polymorphism on the brain function via amplitude of low-frequency fluctuations (ALFF) approach. The association between DRD3 Ser9Gly-modulated significantly different brain regions, and clinical manifestations were detected by Spearman's correlations. PD patients exhibited decreased ALFF values in the right inferior occipital gyrus, lingual gyrus, and fusiform gyrus. A significant difference in the interaction of "groups × genotypes" was observed in the right medial frontal gyrus. The ALFF value of the cluster showing significant interactions was positively correlated with HAMD-17 scores ($r = 0.489$, $p = 0.011$) and anhedonia scores ($r = 0.512$, $p = 0.008$) in PD patients with the Ser/Gly or Gly/Gly genotypes. Therefore, D3 gene Ser9Gly polymorphism might be associated with the severity of depression characterized by anhedonia in PD patients.

1. Introduction

The characteristic of PD neuropathology is a selective loss of dopaminergic neurons in the substantia nigra pars compacta [1], and orally administered levodopa is one of the standard treatments of PD. As dopamine receptors provide vital determinants of dopamine function [2], there is no doubt that polymorphisms in dopamine receptor genes have an effect on PD. There are five dopamine receptors (DRs) subtypes, of which DR1 and DR5 are composed of D1-like receptors, while DR2, DR3, and DR4 consist of D2-like receptors [3]. The most frequently studied variant point of the DRD3 is DRD3 Ser9Gly polymorphism [4]. Although the emerging fact demonstrates that DRD3 Ser9Gly polymorphism is closely associated with the clinical manifestations [4–8] and the treatment of PD [9, 10], the results were inconsistent. So intensive studies are needed to explore the role of DRD3 Ser9Gly polymorphism in PD.

Imaging genetics is an integrated research method which uses neuroimaging and genetics to evaluate the impact of genetic variation on brain function and structure [11], which has been widely used to investigate the effect of gene in several diseases such as PD [12], amnestic mild cognitive impairment (aMCI) [13], and major depressive disorder (MDD) [14]. Moreover, resting-state functional magnetic resonance imaging (rs-fMRI) allows studying spontaneous

brain activity in absence of task, which records changes of Blood Oxygenation Level-Dependent (BOLD) signal [15]. Therefore, rs-fMRI could be used as a platform to evaluate the gene function in the brain. Amplitude of low-frequency fluctuation (ALFF) which detects the spontaneous amplitude of low-frequency (0.01–0.08 Hz) BOLD signal is one of the most reliable and reproducible rs-fMRI parameters and effectively reflects the level of regional functional neural activity [16].

In this study, we were the first to use ALFF to investigate the potential effect of DRD3 Ser9Gly polymorphism on modulating resting-state brain function and associative clinical manifestations in PD patients.

2. Materials and Methods

2.1. Study Participants. According to the UK Parkinson's Disease Society Brain Bank Research criteria [17], 61 well-characterized idiopathic PD patients were consecutively recruited from the First Affiliated Hospital of Nanjing Medical University between June 2017 and February 2018. PD patients who were diagnosed of neurological diseases other than PD, other forms of parkinsonism such as atypical parkinsonism and secondary parkinsonism or combined with severe cognitive impairment (Mini-Mental State Exam (MMSE) score < 24) [18], were ruled out in this study. The diagnosis was confirmed by two experienced neurologists, Kezhong Zhang and Yongsheng Yuan, to ensure the reliability of the study. Moreover, we consecutively recruited 47 age- and gender-matched healthy controls without neurological disorders (including movement disorders, parkinsonism, neurodegenerative diseases such as dementias), psychological disorders, a family history of PD, cognitive impairment, or imaging abnormalities from local individuals who volunteered to participate in scientific studies by advertising. Participants with sever acute or chronic diseases, contraindications for MRI scans, or a recent history of using antidepressant, anxiolytic, or antipsychotic drugs were also excluded. All participants were East Asian individuals and lived in Jiangsu Province, China. To minimize conceivable pharmacological impacts on neural activity, MRI scans and clinical examinations were performed during off-state (at least 12-hour withdrawal of pharmacologic treatment for PD) in PD patients. This study was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University, and all participants provided us with written informed consent before participating in the experiment.

2.2. Clinical Assessment. The third part of the Unified Parkinson's Disease Rating Scale (UPDRS-III) [19] and the Hoehn and Yahr (H&Y) staging were applied to evaluate the motor severity in the PD group. Moreover, we used Tinetti Mobility Test [20] to assess the balance and gait of PD patients. Furthermore, we detected the severity of fatigue, depression, anxiety, and apathy in PD patients using the Fatigue Severity Scale (FSS) [21], the Hamilton Depression Scale (HAMD) [22], the Hamilton Anxiety Scale (HAMA) [23], and the Modified Apathy Evaluation Scale (MAES) [24], respectively. Cognitive functioning and executive functioning of PD patients were evaluated by the Mini-Mental State Examination (MMSE) and the Frontal Assessment Battery (FAB) [25]. Epworth Sleepiness Scale (ESS) [26] was used to assess the sleepiness of PD patients. As previous studies reported that DRD3 Ser9Gly polymorphism was associated with anhedonia in patients with major depressive disorder, we decided to measure anhedonia in PD patients to further explore the role of DRD3 Ser9Gly polymorphism in PD [27]. Anhedonia score was measured by a single anhedonia item in the HAMD scale. This item measured a dimensional construct including desire, effort, and consummatory pleasure [22]. Levodopa-equivalent daily dose (LEDD) was calculated according to the widely accepted method [28].

2.3. DRD3 Genotyping. The analysis was performed in a blinded manner by experts who had no knowledge of all participants. Ten milliliters of peripheral blood from the antecubital vein was collected to extract DNA. Then, DNA was genotyped for DRD3 rs6280 (Ser9Gly). MassARRAY TYPER 4.0 software (Agena, Inc) was used to process and analyze the data. χ^2 test was used to check Hardy–Weinberg equilibrium. Then, the subjects were divided into different subgroups (Ser/Ser carriers and Gly carriers).

2.4. Image Acquisition. All participants were scanned using a 3.0 Tesla Siemens MAGNETOM Verio whole-body MRI system (Siemens Medical Solutions, Germany) which was equipped with eight-channel and phase-array head coils by experienced doctors from the radiology department. Tight foam padding was used to minimize head motion. As the scanner made big noise, earplugs were used. Participants were instructed to keep awake, eyes closed and motion less. They also tried their best not to think about anything. Three-dimensional T1-weighted anatomical images were obtained using a volumetric 3D magnetization-prepared rapid gradient-echo (MP-RAGE) sequence (repetition time (TR) = 1900 ms, echo time (TE) = 2.95 ms, flip angle (FA) = 9°, slice thickness = 1 mm, slices = 160, field of view (FOV) = $230 \times 230\ mm^2$, matrix size = 256×256, and voxel size = $1 \times 1 \times 1\ mm^3$). Resting-state functional images were obtained using an echo-planar imaging (EPI) sequence (TR = 2000 ms, TE = 21 ms, FA = 9°, FOV = $256 \times 256\ mm^2$, in-plane matrix = 64×64, slices = 35, slice thickness = 3 mm, no slice gap, voxel size = $3 \times 3 \times 3\ mm^3$, and total volumes = 240).

2.5. MRI Data Preprocessing. Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk), the data processing assistant for resting-state fMRI (DPARSF, http://www.restfmri.net), and MATLAB were used to perform MRI data preprocessing. The preprocessing of MRI data included exclusion of the first ten volumes of each functional time course, slice timing correction, head motion correction, regressing out of nuisance variables, spatial normalization,

resampling of images into a spatial resolution of $3 \times 3 \times 3\,mm^3$, and spatial smoothening with a Gaussian kernel (full width at half-maximum = $4 \times 4 \times 4\,mm^3$). Nuisance variable included the white matter, cerebrospinal fluid, and Friston 24-parameter head motion. Participants with head motion of more than 2.0 mm of translation or 2.0° of rotation during the course of the scan were ruled out. In order to minimize temporal drifts and white noise, the resulting data were temporally bandpass filtered (0.01–0.08 Hz).

2.6. ALFF Analysis. ALFF values were calculated in the frequency range of 0.01–0.08 Hz using DPARSF. Briefly, the calculation steps included converting all voxels from the time domain to the frequency domain and averaging the square root of the power spectrum between 0.01 Hz and 0.08 Hz.

2.7. Statistical Analysis. The analysis of demographic and neuropsychological data was performed using the SPSS 20.0 statistical analysis software (SPSS Inc. Chicago, IL, USA). Continuous variables and categorical variables were shown as median (range) and percentage, respectively. Comparisons of demographic data (gender, age, and education) among groups were performed using chi-square tests and two-way analysis of variance (ANOVA). As many neuropsychological data were not normally distributed, Mann–Whitney U tests were used to compare clinical data across genotypes within the PD group. Chi-square test was used to test the Hardy–Weinberg Equilibrium (HWE) of the genotype frequencies. A significant threshold was set at $p < 0.05$.

A two-way analysis of variance (ANOVA: groups × genotypes; groups: PD and healthy controls; genotypes: Ser/Ser carriers and the Gly carriers) with gender, age, and education as nuisance variables was performed to determine the effects of group and genotype on ALFF (voxel-level $p < 0.001$, cluster size > 10 voxels, corresponding to a corrected $p < 0.001$ as based on Monte Carlo simulations) (http://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim.pdf). Post hoc tests were performed to further explore some statistical differences. Finally, we explored the relationship between the neuropsychological test scores and the ALFF values of the clusters which showed significant effect of groups or the interaction between groups and genotypes using Spearman's Rho to detect the correlation significance.

3. Results

3.1. Demographic and Neuropsychological Characteristics. The genotype frequencies for DRD3 Ser9Gly in the PD group and the healthy control group are displayed in Table 1, which did not deviate from Hardy–Weinberg equilibrium (PD group: $\chi^2 = 2.181$, $P = 0.140$; control group: $\chi^2 = 0.084$, $P = 0.772$). Other demographic and neuropsychological characteristics of participants are displayed in Table 2. There was no significant effect of diagnosis, genotype, or interaction between diagnosis and genotype for gender, age, or education. Moreover, there was no significant difference in clinical data including disease duration, H&Y stage, LEDD, UPDRS-III, MMSE, FAB, Tinetti Balance, Tinetti Gait, FSS, HAMA, Apathy, ESS between Ser/Ser carriers, and Gly carriers in the PD group. Nevertheless, the HAMD scores in PD with the Ser/Gly or Gly/Gly genotypes were significantly higher than PD with the Ser/Ser genotypes ($P = 0.012$). Furthermore, the anhedonia scores in PD with the Ser/Gly or Gly/Gly genotypes were significantly higher than PD with the Ser/Ser genotypes ($P = 0.004$).

Table 1: Genotype frequencies for DRD3 gene Ser9Gly in PD group and HC group.

Genotype	PD (frequency)	HC (frequency)	Total (frequency)
Ser/Ser	35 (57.4%)	20 (42.6%)	55 (50.9%)
Ser/Gly	25 (41.0%)	22 (46.8%)	47 (43.5%)
Gly/Gly	1 (1.6%)	5 (10.6%)	6 (5.6%)

Genotype frequencies for DRD3 Ser9Gly in the PD group ($\chi^2 = 2.181$, $P = 0.140$) and the HC group ($\chi^2 = 0.084$, $P = 0.772$) did not deviate from Hardy–Weinberg equilibrium. Abbreviations: DRD3, dopamine receptor D3 gene; PD, Parkinson's disease; HC, healthy control.

3.2. ALFF Data. Two-way ANOVA (Table 3): Main effect of group (PD, HC) was found in right occipital lobe (right inferior occipital gyrus/lingual gyrus/fusiform gyrus) ($F = 23.44$, $p < 0.001$, corrected) (Figure 1). The "groups × genotypes" interaction was observed in the right frontal lobe (right medial frontal gyrus) ($F = 23.02$, $p < 0.001$, corrected) (Figure 2). However, the main effect of gene (the Ser/Gly or Gly/Gly genotypes, the Ser/Ser genotypes) was not observed.

Post hoc tests: Post hoc tests were corrected by Bonferroni correction with a significant different $p < 0.0083$ (0.05/6 (number of pair-comparisons)). ALFF values in the brain regions of the right medial frontal gyrus were increased in the PD group with the Ser/Gly or Gly/Gly genotypes when compared to the Ser/Ser genotype ($p \leq 0.001$) while decreased in the control group with the Ser/Gly or Gly/Gly genotypes when compared to the Ser/Ser genotype ($p = 0.001$). ALFF values in the right medial frontal gyrus were lowest in PD patients with the Ser/Ser genotype among four subgroups (Figure 3).

3.3. Correlation Analysis. ALFF values in the right medial frontal gyrus affected by interactions between groups and genotypes were positively correlated with HAMD-17 scores ($r = 0.489$, $p = 0.011$) (Figure 4) and anhedonia scores ($r = 0.512$, $p = 0.008$) (Figure 5) in the Gly carriers in the PD group, while it had no association with HAMD-17 scores or anhedonia scores in the other group. There was no significant correlation between ALFF values in the right medial frontal gyrus and UPDRS-III, MMSE, FAB, Tinetti Balance, Tinetti Gait, FSS, HAMA, Apathy, and ESS scores ($p > 0.05$) within each group.

4. Discussion

This study was the first to investigate the potential effect of DRD3 Ser9Gly polymorphism on modulating resting-state brain function in idiopathic PD patients and healthy

Table 2: Demographic data of participants.

Items	PD		HC		p
	Ser/Ser (n = 35)	Ser/Gly or Gly/Gly (n = 26)	Ser/Ser (n = 20)	Ser/Gly or Gly/Gly (n = 27)	
Gender (male/female)	22/13	19/7	10/10	19/8	0.372[a]
Age (years)	68 (44–81)	65.5 (49–88)	64.5 (52–72)	63 (55–72)	0.119[b]
Education (years)	11 (6–20)	12 (5–17)	12 (5–22)	12 (5–16)	0.845[b]
Disease duration (years)	4 (0.25–13)	3.125 (0.5–20)	NA	NA	0.930[c]
H&Y stage	2 (1–3)	2 (1–3)	NA	NA	0.424[c]
LEDD (mg/day)	375 (0–1025)	400 (0–837.5)	NA	NA	0.965[c]
UPDRS-III	22 (8–48)	22 (5–40)	NA	NA	0.815[c]
MMSE	29 (26–30)	29 (24–30)	NA	NA	0.477[c]
FAB	16 (10–18)	16 (10–18)	NA	NA	0.489[c]
Tinetti Balance	14 (4–16)	14 (3–16)	NA	NA	0.555[c]
Tinetti Gait	9 (2–12)	8.5 (4–12)	NA	NA	0.959[c]
FSS	28 (9–55)	26 (8–57)	NA	NA	0.569[c]
HAMD-17	2 (0–16)	4.5 (1–21)	NA	NA	0.012[c,*]
HAMA	7 (1–18)	9 (2–24)	NA	NA	0.270[c]
Apathy	14 (2–36)	17.5 (1–32)	NA	NA	0.310[c]
ESS	5 (0–14)	4.5 (0–11)	NA	NA	0.282[c]
Anhedonia score[&]	0 (0–2)	1 (0–4)	NA	NA	0.004[c,*]

Abbreviations: PD, Parkinson's disease; HC, healthy control; H&Y stage, Hoehn and Yahr stage; LEDD, levodopa-equivalent daily dose; UPDRS, Unified Parkinson's Disease Rating Scale; MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; FSS, Fatigue Severity Scale; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; ESS, Epworth Sleepiness Scale; NA, not applicable. Values except gender were expressed as median (range). [a]Chi-square tests. [b]Two-way analysis of variance (ANOVA). [c]Mann–Whitney U tests. [&]Anhedonia score was measured by a single anhedonia item in the HAMD scale. $^*P < 0.05$ was considered significant.

Table 3: Groups × genes ANOVA of ALFF.

Brain region	Peak MNI coordinates (mm)			Peak F value	Clusters size (mm^3)
Main effect of groups					
Right inferior occipital gyrus/lingual gyrus/fusiform gyrus	36	−90	−21	23.44	1377
Main effect of genotypes					
None					
Groups × genotypes interaction					
Right medial frontal gyrus	6	33	42	23.02	486

Two-way factorial analysis of covariance (ANCOVA: groups × genotypes; groups: PD and HC, genotypes: Ser/Ser carriers and the Gly carriers) was performed, adjusting for age, gender, and education. A corrected threshold by Monte Carlo simulation was set at $P < 0.001$; Abbreviations: PD, Parkinson's disease; HC, healthy control; ALFF, amplitude of low-frequency fluctuations; MNI, Montreal Neurological Institute.

controls. Moreover, we used sensitive clinical scales to carry out detailed clinical assessments, so we could further explore the relationship between DRD3 Ser9Gly polymorphism and associative clinical manifestations in PD patients.

DRD3 is located in 3q13.31 and mainly expresses in the ventral striatum and the globus pallidus where it regulates both dopamine release and clearance from extracellular space by the dopamine transporter (DAT) [29]. The DR3 is more selectively associated with the limbic areas of the brain which receives its dopamine input from the ventral tegmental area and plays an important role in cognitive, emotional, and endocrine functions [9]. Recently, some studies reported that DRD3 Ser9Gly polymorphism was associated with impulse-control disorders in PD patients, but their results were inconsistent [4–6]. Rajan et al. found that DRD3 Ser9Gly polymorphism is associated with aberrant decision-making under uncertainty in PD patients without active impulse-control disorders [7]. Goetz et al. observed that there was a higher frequency of the Gly allele in the hallucinators [8], while Wang et al. reported that no significant difference was found between hallucinators and nonhallucinators in the DRD3 Ser9Gly genotypic or allelic distributions [2]. Differences in the methods used for the assessment, the size of the samples studied, and the severity of the disease may lead to the discrepancy in the results. Moreover, the Gly/Gly group and the Gly/Ser group respond worse to pramipexole than the Ser/Ser group [9, 10]. Recent large meta-analyses suggest that DRD3 Ser9Gly polymorphism had no relationship to increased susceptibility to PD [30], indicating that DRD3 Ser9Gly might be a minor gene locus in the occurrence of sporadic PD. Hence, the main effect of DRD3 Ser9Gly in PD is alterations in some brain regions function instead of the susceptibility to disease. That is to say, exploring the association between genetic variants and clinical manifestations is more meaningful than exploring the association between genetic variants and the susceptibility to disease. Imaging genetics is a new method to study association between genetic variants and imaging

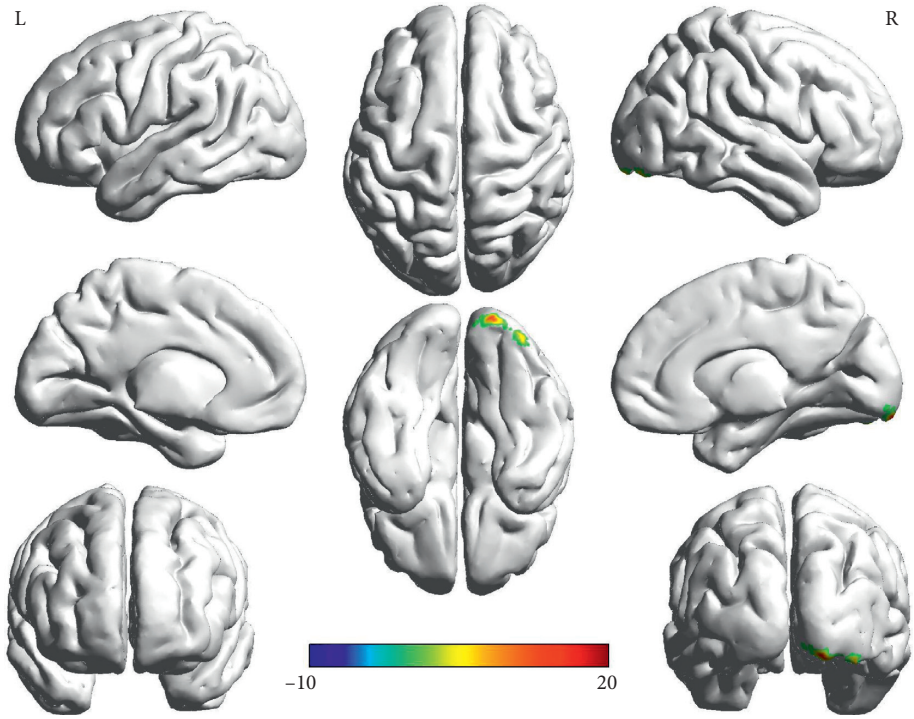

Figure 1: Main effect of groups on ALFF in PD and HC found in the right occipital lobe (right inferior occipital gyrus/lingual gyrus/fusiform gyrus). The finding was obtained via two-way factorial analysis of covariance (ANCOVA: groups × genotypes; groups: PD and HC, genotypes: Ser/Ser carriers and the Gly carriers) adjusting for age, gender, and education. A corrected threshold by Monte Carlo simulation was set at $P < 0.001$. The color bar indicates the F values from ANCOVA. Abbreviations: PD, Parkinson's disease; HC, healthy control; ALFF, amplitude of low-frequency fluctuations; R, right; L, left.

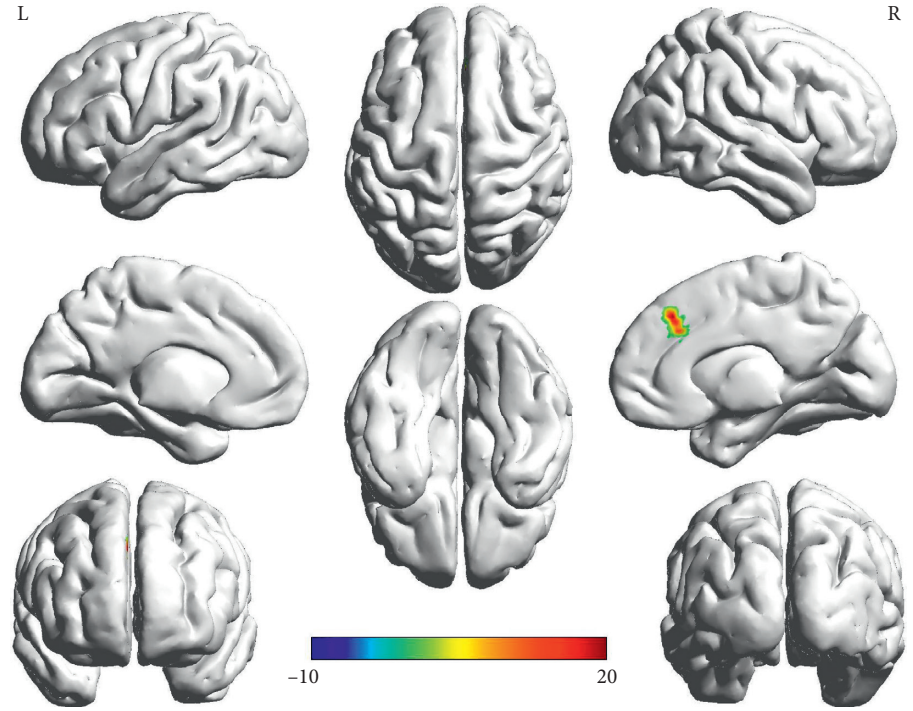

Figure 2: The interaction between groups and genotypes found in the right medial frontal gyrus. The finding was obtained via two-way factorial analysis of covariance (ANCOVA: groups × genotypes; groups: PD and HC, genotypes: Ser/Ser carriers and the Gly carriers) adjusting for age, gender, and education. A corrected threshold by Monte Carlo simulation was set at $P < 0.001$. The color bar indicates the F values from ANCOVA. Abbreviations: PD, Parkinson's disease; HC, healthy control; ALFF, amplitude of low-frequency fluctuations; DRD3, dopamine receptor D3 gene; R, right; L, left.

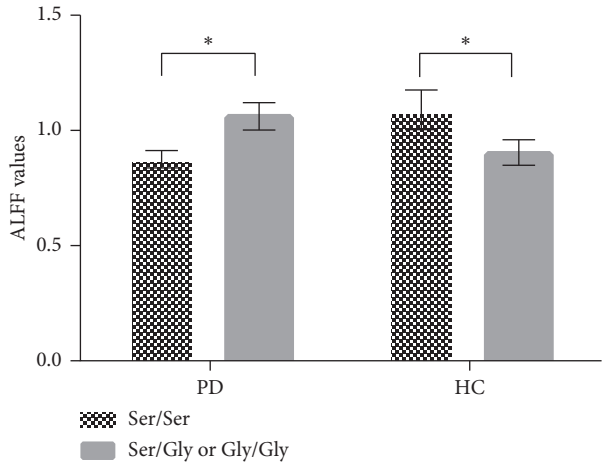

Figure 3: Post hoc tests of the interaction between groups and genotypes. Post hoc tests were corrected by Bonferroni correction with a significant different $p < 0.0083$ (0.05/6 (number of pair-comparisons)). ALFF values in the right medial frontal gyrus were increased in the PD group with the Ser/Gly or Gly/Gly genotypes when compared to the Ser/Ser genotype, while it was decreased in the control group with the Ser/Gly or Gly/Gly genotypes when compared to the Ser/Ser genotype. Abbreviations: PD, Parkinson's disease; HC, healthy control; ALFF, amplitude of low-frequency fluctuations; DRD3, dopamine receptor D3 gene. $^{*}p < 0.01$.

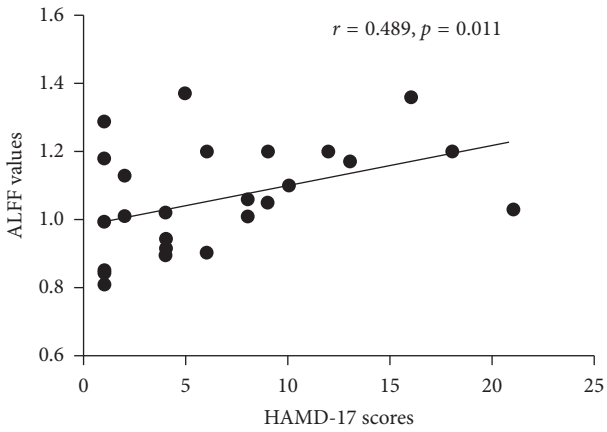

Figure 4: Correlation analysis between ALFF values in the right medial frontal gyrus and HAMD-17 scores. ALFF values in the right medial frontal gyrus affected by the interaction between groups and genotypes were positively correlated with HAMD-17 scores ($r = 0.489$, $p = 0.011$) in the Gly carriers in the PD group. Abbreviations: PD, Parkinson's disease; ALFF, amplitude of low-frequency fluctuations; HAMD, Hamilton Depression Scale.

phenotypes and further explore the association between genetic variants and clinical manifestations.

Our analysis in main effect of genotypes showed that there was no difference between Ser/Ser carriers and the Gly carriers in resting-state brain function, regardless of the disease status. Interestingly, a significant difference in the "groups × genotypes" interaction was observed in the right medial frontal gyrus, which demonstrated that there were differential effects of DRD3 Ser9Gly polymorphism in PD patients and healthy controls. Hence, both genetic factors

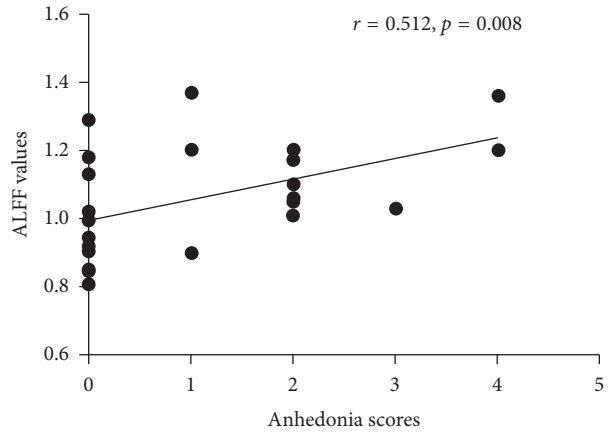

Figure 5: Correlation analysis between ALFF values in the right medial frontal gyrus and anhedonia scores. ALFF values in the right medial frontal gyrus affected by the interaction between groups and genotypes were negatively correlated with anhedonia scores ($r = 0.512$, $p = 0.008$) in the Gly carriers in the PD group. Abbreviations: PD, Parkinson's disease; ALFF, amplitude of low-frequency fluctuations.

and physical conditions should be taken into considerations to clarify a pathogenic role of DRD3 Ser9Gly polymorphism in PD. What is more, ALFF values in the right medial frontal gyrus were lower in Ser/Ser carriers than the Gly carriers in the PD group, while ALFF values in the right medial frontal gyrus were lower in the Gly carriers than Ser/Ser carriers in the HC group. This phenomenon indicated that PD patients with the Ser/Gly or Gly/Gly genotypes might potentially show evidence of functional brain abnormalities. Moreover, the ALFF value of the cluster showing significant interactions had relationships to HAMD-17 scores and anhedonia scores in PD patients with the Ser/Gly or Gly/Gly genotypes. HAMD-17 is a 17-item clinician-rated instrument developed to quantify the severity of depression, which has become one of the most widely used outcome measures in depression [31]. Therefore, DRD3 Ser9Gly polymorphism might be associated to the severity of depression characterized by anhedonia in PD patients with the Ser/Gly or Gly/Gly genotypes.

It has been widely reported that the Gly carriers are more common and anhedonic than Ser/Ser carriers among patients with major depressive disorder [27, 32, 33], indicating that DRD3 Ser9Gly polymorphism is implicated in the pathogenesis of depression. Compared with the Ser-9 variant, the Gly-9 variant has a significantly higher binding affinity for dopamine and exhibits higher cAMP inhibition and MAPK signal duration than Ser-9 variant [34], which attenuates the function of the D3 receptor [9]. The higher affinity of the glycine autoreceptor is linked to the decrease of the extrasynaptic dopamine concentration under conditions of tonic dopamine release [33], which leads to the change of the neural circuit underlying reward-related mechanisms (the cortico-limbic-striatal circuits) [35]. As shown in Figure 2, the activated brain region of the "groups × genotypes" interaction in the right medial frontal gyrus is located in the right medial prefrontal cortex

(mPFC). In both humans and animals, mPFC is a critical node in a distributed neural network which regulates many cognitive and limbic functions [36]. Previous studies suggest that the chronic mPFC overactivity stably suppressed natural reward-motivated behaviors and induced specific new brainwide functional interactions, which predicted the degree of anhedonia in individuals [37]. Moreover, mPFC is an important part of the reward-related neural circuit [38]. Therefore, we speculated that PD patients with the Ser/Gly or Gly/Gly genotypes had a deficiency in the reward-related neural circuit which led to anhedonia.

It must be acknowledged that our study had some limitations. Firstly, we integrated individuals with the Ser/Gly or Gly/Gly genotypes into a single group because of small sample size, which might have an adverse effect on the observation of "gene effect". Secondly, our study was a cross-sectional study and longitudinal studies are needed to further assess the progress of disease in the same participants. Thirdly, we ignored dopamine receptor genes other than DRD3 and did not study the gene-gene interaction. Fourthly, our study did not include some essential clinical symptoms such as impulse-control disorders, aberrant decision-making, hallucinations, and behavioral addictions which might be associated with DRD3 Ser9Gly polymorphism in PD patients [4–8]. Fifthly, the right medial frontal gyrus is engaged in many other cognitive functions [36, 39]. We excluded patients with cognitive impairment due to a consideration that their self-reporting on the questionnaire was likely unreliable. As a result, we could not carry on cognitive-related tests to further judge whether ALFF values in the right medial frontal gyrus affected has relationship to cognitive functions or not. Last but not least, we chose to evaluate anhedonia by one item of the HAMD rather than a specific questionnaire validated in PD patients, which was inaccurate. Therefore, a longitudinal research which has a larger sample size studies more clinical manifestations, includes patients with cognitive impairment, evaluates anhedonia by a specific questionnaire, and uses multimodal techniques is needed in the future.

5. Conclusions

The present study was the first time to demonstrate that the right medial frontal gyrus activation related to DRD3 Ser9Gly polymorphism is associated with the occurrence and the severity of depression in PD, in particular in a type of depression characterized by anhedonia, which might play a key role in the pathogenesis of depression in PD. Therefore, the right medial frontal gyrus activation related to DRD3 Ser9Gly polymorphism could be a biomarker for the occurrence and the severity of depression in PD. However, whether new biological measure could be invented to treat depression in PD patients with the Ser/Gly or Gly/Gly genotypes according to our findings or not needs further studies to judge. Furthermore, imaging genetics as a new promising approach was available to study the relationship between gene polymorphisms and the complicated clinical manifestations in PD.

Data Availability

The data are available to qualified investigators on request to the corresponding and senior authors.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

Authors' Contributions

Yan Zhi, Yongsheng Yuan, and Qianqian Si contributed equally to this work.

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Research Article

Impulsive-Compulsive Behaviours in Belgian-Flemish Parkinson's Disease Patients: A Questionnaire-Based Study

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Background. Impulsive-compulsive behaviours (ICB) are a potentially harmful group of behavioural symptoms among the nonmotor aspects of Parkinson's disease (PD). *Objective*. To develop and perform partial validation of a Belgian-Flemish version of the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP) as a screening instrument for ICB in PD patients. *Methods*. Using a translation-backtranslation method, we developed a Belgian-Flemish version of the QUIP, which was subsequently completed by 88 PD patients. QUIP-positive patients were invited for a semistructured diagnostic interview. *Results*. A positive QUIP score for one or more ICB was observed in 37 patients (41%). In 15 patients (17%), a positive QUIP score for one or more impulse control disorders (ICD) was noted: pathological gambling in 1, hypersexuality in 8, compulsive shopping in 5, and compulsive eating in 8 patients. A positive QUIP score for punding, hobbyism, and/or walkabout was observed in 30 patients. The semistructured diagnostic interview was performed in 22 QUIP-positive patients. The diagnosis of ICB was confirmed in 6 patients, suggesting a positive predictive value of 27% for the Belgian-Flemish version of the QUIP. *Conclusions*. We have developed a Belgian-Flemish version of the QUIP, which can be used as a screening questionnaire for ICB in PD patients. Our data suggest that sensitivity is high, specificity is low, and validity of the questionnaire is similar to the original version. We confirm the necessity of additional clinical assessment of QUIP-positive patients to ascertain a diagnosis of ICB.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative brain disorder and affects approximately 1% of the population above the age of 60 years in industrialized countries [1]. Besides motor symptoms, PD patients can experience several nonmotor problems. Impulse control disorders (ICD) are a subgroup of behavioural symptoms among the nonmotor aspects of PD. These potentially devastating neuropsychiatric symptoms are characterized by failure to resist an impulse, drive, or temptation to perform an act that is harmful to the subject or to others [2]. Typical ICD in PD patients are pathological gambling (PG), hypersexuality (HS), compulsive eating (CE), and compulsive shopping (CS). In addition, compulsive behaviours, such as punding, hobbyism, and walkabout (PHW), can be observed. A particular form of behavioural disturbance is the dopamine dysregulation syndrome (DDS), in which patients develop an addictive behaviour towards dopaminergic medication. We will use the umbrella term of impulsive-compulsive behaviours (ICB) to cover the classical impulse control disorders (ICD) as well as other typical compulsive behaviours in PD patients (punding, hobbyism, and walkabout).

The prevalence of ICD in PD patients ranges from 3.5% to 42.8% [2–11]. No significant difference in prevalence was observed between drug-naïve PD patients and healthy controls [3, 12], suggesting that PD itself is not a major risk factor. The most important risk factor for developing ICD is probably the use of dopaminergic drugs, in particular dopamine agonists (DA). Higher DA dosage and longer treatment duration were associated with a higher prevalence of ICD in a longitudinal study in PD patients [13]. Additional risk factors for ICD have been reported, including male gender, younger age, levodopa therapy, personal history of smoking, preexistent history of ICD symptoms, personality profile characterized by impulsiveness and novelty-seeking, history of depression, history of substance abuse, and familial history of gambling [2, 3, 10, 14–16].

Weintraub and coworkers have validated the QUIP (Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease) as the screening instrument for ICB in PD patients [17]. We have translated the QUIP into Flemish in order to have a useful screening instrument for ICB in the Flemish-speaking patient population.

2. Methods

We have sent questionnaires by postal mail to 216 PD patients attending the outpatient clinic of the Antwerp University Hospital. All patients had a clinical diagnosis of Parkinson's disease according to the NINDS criteria [18] and absence of dementia was documented. The QUIP is a brief self-completed screening questionnaire. The first section assesses the following ICD: gambling, hypersexuality, and compulsive buying and eating behaviours. The second section assesses other compulsive behaviours (punding, hobbyism, and walkabout). The last section questions compulsive use of dopaminergic medication. Positive answers for each disorder are added, which leads to a maximum of five points for each of the ICD and DDS, and three points for punding, hobbyism, and walkabout.

The QUIP was translated from English to Flemish by one member of the study team. Subsequently, two different team members independently translated this first Flemish version into English. The back-translated versions were compared to the original version and any discrepancies were modified after discussion among the team members. The patients were invited to complete the QUIP and an additional questionnaire to obtain information on sociodemographic status and personal and familial medical history. Both questionnaires were completed by the patient and, if available, with help of the caregiver.

The QUIP-positive patients were invited for a more extensive interview, which was performed by one of the investigators. This semistructured interview was based on validated criteria, such as the DSM-IV criteria for gambling and binge eating [19], the Voon criteria for hypersexuality [20], and the Mc Elroy criteria for compulsive shopping [17, 21], and a standardized semistructured questionnaire was used. Three different investigators performed the diagnostic interviews, but the final interpretation was made by only 1 of those 3 investigators to reduce inter-rater bias.

We calculated levodopa equivalent daily dosage (LEDD) in milligrams according to the following conversion factors: immediate release levodopa x1; levodopa controlled release x0.75; entacapone x0.33; tolcapone x0.5; ropinirol x20; rasagiline x100; amantadine x1; levodopa-carbidopa intestinal gel x1.10; pramipexole x100; rotigotine x30; selegiline x10 [22].

Statistical analysis was performed using IBM SPSS version 20. Categorical variables were compared using Pearson's chi-squared test. Significant differences of continuous independent factors between groups were analysed using nonparametric tests. A receiver operating characteristic (ROC) curve was plotted for each ICB in the present study. We have compared the calculated area under the curve (AUC) in the present study with the analysis, which was reported for the original QUIP [17]. The sensitivity and specificity were also compared for each ICB, based on the validated cutoff values of the original questionnaire.

2.1. Compliance with Ethical Standards. All activities involving human participants in this study were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Antwerp University Hospital Ethics Committee (reference number 11/45/343). Informed consent was obtained from all individual participants included in the study for collection of questionnaire and medical data.

3. Results

Completed questionnaires were obtained from more than one-third of the patients (88/216 patients), resulting in a response rate of 40.7%. The demographic and clinical features of the patients are presented in Table 1.

The mean age was 70.2 ± 9.2 (range: 44–85 years). The patients had a mean disease duration of 10.2 ± 6.8 (range: 1–43 years), and the mean age of onset was 60.2 ± 10.8 (range: 30–85 years). The majority of the patients (73/85; 86%) was treated with oral levodopa therapy, and slightly more than half of the patients (43/85) were treated with dopamine agonists. Mean levodopa equivalent daily dosage (LEDD) was 615 ± 353 (range: 100–1779 mg). Twenty (20/85) patients (23.5%) reported a history of mood disorder. In 13/85 patients (15.3%), a history of drug and/or alcohol abuse was noted. A familial history of mood disorder and drug and/or alcohol abuse was observed in 5/85 and in 16/85 patients, respectively.

QUIP scores, indicative for the probable presence of one or more ICB, were obtained in 37/88 patients (40.9%). In fifteen patients (17%), a positive QUIP score for one or more ICD was observed: PG in 1/88 (1.1%), HS in 8/88 (9.1%), CS in 5/88 (5.7%), and CE in 8/88 patients (1.1%). Punding, hobbyism, and/or walkabout (PHW) were present in 30/88 (34.1%) patients. We invited the QUIP-positive patients (37/88) for a more extensive interview. Fifteen (15/37) patients did not complete the confirmatory diagnostic interview and were excluded from further analysis.

Table 1: Clinical characteristics of complete study population, QUIP-positive, and QUIP-negative patients.

	Total $N = 88$	QUIP-positive $N = 36$	QUIP-negative $N = 52$
Age (years)	70.2 ± 9.2	68.3 ± 9.2	71.5 ± 9.1
M/F ratio	1.3	1.8	1.1
Onset age (years)	60.2 ± 10.8	57.4 ± 10.6	62.1 ± 10.7*
Disease duration (years)	10.2 ± 6.8	10.9 ± 6.0	9.7 ± 7.3
Married	74/87 (85.1%)	29/36 (82.9%)	45/52 (86.5%)
Higher education	29/86 (33.7%)	10/35 (28.6%)	19/51 (37.3%)
Smoking (current or past)	26/87 (29.9%)	10/35 (28.6%)	16/52 (30.8%)
History of mood disorder	20/85 (23.5%)	10/35 (28.6%)	10/50 (20.0%)
History of substance abuse	13/85 (15.3%)	7/35 (20.0%)	6/50 (12.0%)
Familial history of mood disorder	5/85 (5.9%)	4/35 (11.4%)	1/50 (2.0%)
Familial history of substance abuse	16/85 (18.8%)	9/35 (25.7%)	7/50 (14.0%)
Levodopa-induced dyskinesia	39/82 (47.6%)	13/33 (39.4%)	26/49 (53.1%)
Levodopa	73/85 (85.9%)	30/35 (85.7%)	43/50 (86.0%)
Dopamine agonist	43/85 (50.6%)	21/35 (60.0%)	22/50 (44.0%)
LEDD (mg)	615 ± 353	671 ± 418	575 ± 298

M/F ratio: male/female ratio; QUIP: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease; LEDD: levodopa equivalent daily dosage. Continuous variables are shown as mean ± standard deviation; categorical or binary variables are shown as proportion and percentage; variables were compared between QUIP-positive and QUIP-negative groups. * $p < 0.05$.

The positive predictive value of the Belgian-Flemish version of the QUIP was therefore calculated in the subgroup of 73 patients, excluding the 15 patients who did not complete the diagnostic interview. In this subgroup of 73 patients, a positive QUIP score was obtained for HS in 7/73 (9.6%), for CS in 3/73 patients (4.1%), and for CE in 7/73 patients (9.6%). In 18/73 patients (24.7%), a positive QUIP score for punding was observed, and in one patient, a positive score for DDS was documented. One patient (1/73; 1.4%) who scored negative on the QUIP (and thus was not invited for the interview) was diagnosed with PG on a follow-up visit with his treating neurologist.

Among the patients who completed both the QUIP and the diagnostic interview, a correct diagnosis of ICB was confirmed in 6/22 patients. The Belgian-Flemish translation of the QUIP therefore results in a positive predictive value (PPV) of 27% for the detection of ICB and a PPV of 33.4% for the detection of ICD (Table 2). The semistructured interview was only performed in QUIP-positive patients. Therefore, we cannot make any statement concerning false-negatives, and no valid conclusions can be inferred regarding sensitivity, specificity, and negative predictive value (NPV) of the Belgian-Flemish QUIP.

4. Discussion

We developed a Belgian-Flemish translation of the QUIP using a translation-backtranslation method. We conducted a study in 88 PD patients using this questionnaire. In 40.9% of the patients, the presence of an ICB was suggested, whereas in 17% of the patients, a positive QUIP score for an ICD was obtained. These numbers are generally in line with the reported prevalence of ICB and ICD in previous studies, using the QUIP [2, 9, 14, 23–28].

Twenty-two QUIP-positive patients participated in a semistructured diagnostic interview. The diagnosis of ICB or ICD was confirmed in 6 of these patients. A positive predictive value of 27% was calculated for the detection of ICB by the QUIP in our study population, which is in accordance with studies using the English QUIP version. If we assume that all QUIP-negative patients would also have tested negative in the semistructured interview, we obtain a sensitivity of 100% and specificity of 76% for the Belgian-Flemish version of the QUIP. These test characteristics are in accordance with the original English questionnaire [17]. We agree that in clinical practice, QUIP-positive patients should be further assessed in order to confirm the diagnosis of ICD/ICB [12, 25].

The most prevalent ICD in our study population was hypersexuality, which was also the most frequently observed ICD in a recent review paper grouping 11 different studies [29]. The majority of QUIP false-positives were found in the punding/hobbyism/walkabout (PHW) group. According to the QUIP results, 34.1% of the patients suffered from PHW. The semistructured interview confirmed a diagnosis of punding in only 4.1% of the patients, whereas hobbyism and walkabout were confirmed in none of the patients. This observation could be partly explained by misinterpretation of the questions concerning hobbyism and walkabout. Furthermore, we should also keep in mind that the true ICD/ICB frequency in our study may remain underestimated, due to hesitation from patients and/or caregivers to acknowledge the presence of a potentially socially stigmatizing behavioural disorder. There was no systematic collection of information from caregivers or significant others, which also might contribute to this underestimation.

Our study has several other limitations, the most important one being the initial small sample size, partly due to a relatively low response rate (40.7%), as well as a low rate of patients completing the diagnostic interview (59.4%). The semistructured confirmatory diagnostic interview was only performed in QUIP-positive patients. Therefore, we were not able to perform a reliable calculation of the sensitivity, specificity, and negative predictive value for the Flemish

Table 2: Calculation of PPV and speculative calculation of AUC, sensitivities, and specificities of the Flemish translation of QUIP in comparison to the original version validated by Weintraub and coworkers [17].

	N	AUC (ref. value original)	Cutoff	Sensitivity (ref. value original)	Specificity (ref. value original)	PPV (ref. value original)
All ICB (ICD + PHW + DDS)	73	0.881*(0.85)	—	1 (0.96)	0.76 (0.73)	0.27 (0.62)
All ICD	73	0.841*(0.88)	—	0.8 (0.97)	0.88 (0.79)	0.34 (0.53)
Gambling	73	0.493	2	0 (0.91)	0.98 (0.97)	0 (0.71)
Hypersexuality	73	0.971*	1	1.0 (1.0)	0.94 (0.89)	0.43 (0.47)
Compulsive shopping***	73	—	1	—(0.8)	—(0.89)	—(0.33)
Binge eating	73	0.846**	2	0.75 (0.86)	0.94 (0.89)	0.43 (0.26)
Punding, hobbyism, or walkabout	73	0.893**	1	1 (0.6–0.96)	0.79 (0.9–0.97)	0.17 (0.43–0.61)
DDS***	73	—	—	—	—	—

ICB: impulsive-compulsive behaviours; ICD: impulse control disorders; PHW: punding, hobbyism, and walkabout; DDS: dopamine dysregulation syndrome; AUC: area under the curve; PPV: positive predictive value. * $p < 0.01$; ** $p < 0.05$; ***no presence of this disorder was detected in our study population.

QUIP version. We can assume that these test characteristics are likely to be comparable with the original version. We observe a rather small percentage of true ICB in our population (6/73; 8.2%) in comparison with the majority of the previously reported studies [9, 12, 14, 23–28, 30]. The observed prevalence of ICB in a population can affect the calculated PPV and NPV of the questionnaire.

Differences in prevalence reported in literature should be interpreted with care. Not all studies used a semistructured interview to verify whether QUIP-positive patients fulfilled diagnostic criteria.

Our translation of the QUIP can be used as a screening instrument for ICB/ICD in the Dutch/Flemish-speaking PD patient population. The data of this pilot study suggest that the validity of the questionnaire is similar to the original version.

Data Availability

The data used to support the findings of this study are restricted by the Institutional Review Board of the Antwerp University Hospital according to local regulations, in order to protect patient privacy. Data are available, by contacting the corresponding author, for researchers who meet the criteria for access to confidential data.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Enhanced Motivational Modulation of Motor Behaviour with Subthalamic Nucleus Deep Brain Stimulation in Parkinson's Disease

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Background. Motivational improvement of movement speed in Parkinson's disease (PD) is observed in life-threatening situations and has been empirically demonstrated in experimental studies using reaction time paradigms. *Objectives*. To address two clinically relevant questions: first, if in PD, motivational modulation through provision of monetary incentive on a sorting task that approximates performance on everyday life tasks affects movement speed. Second, how this effect is compared between PD patients treated with medication or subthalamic deep brain stimulation. *Methods*. We used the Card Arranging Reward Responsivity Objective Test that shares component processes with everyday life tasks to compare reward responsivity of movement speed in 10 PD patients with STN-DBS, 10 nonoperated medicated PD patients, both OFF and ON their usual medications/stimulation, and 11 age-matched healthy controls. *Results*. Despite longer disease duration and more severe motor symptoms, STN-DBS PD patients with the stimulator turned ON showed greater improvement of movement speed with the prospect of monetary incentive compared to both medicated PD patients and healthy participants. *Discussion*. The effect of monetary incentive on movement speed in PD patients is more pronounced with STN-DBS than dopaminergic medications, suggesting that motivational modulation of movement speed may be enhanced as a direct consequence of STN stimulation.

1. Introduction

Motivational factors are known to influence motor behaviour in Parkinson's disease (PD), as evident in extreme situations of emotional and physical arousal/stress associated with improved mobility through the phenomenon known as paradoxical kinesis [1–3]. There is also supporting laboratory evidence for the motivational impact of monetary incentive on movement initiation speed, as both PD patients and healthy participants improve reaction times when offered small monetary incentive [4–6]. Nevertheless, little is known about motivational modulation of movement speed beyond life-threatening situations characteristic of paradoxical kinesis or the strict experimental conditions of reaction time studies. Specifically, it is unclear if motivational modulation of movement speed has an impact on bradykinesia in PD in common real-life situations and how this may be affected by various treatments. In the present study, we used a psychomotor task, the Card Arranging Reward Responsivity Objective Test (CARROT) [7] to compare the

effect of monetary incentive on movement speed between PD patients with STN-DBS, nonoperated PD patients on dopaminergic medication and age-matched healthy participants.

2. Methods

2.1. Participants. We studied 10 PD patients with bilateral deep brain stimulation of the subthalamic nucleus (STN-DBS PD: 9 male, mean age 58, range: 39–78), 10 non-operated PD patients treated with dopaminergic medications (MED PD: 6 male, mean age 60.5, range 50–70), and 11 age-matched healthy participants (5 male, mean age 61, range: 51–70). None of the patients had pathological gambling or other impulse control disorders, as assessed by the question related to dopamine dysregulation syndrome of MDS-UPDRS scale (Question 1.6). The clinical characteristics of the participants are given in Table 1. The study was approved by the local ethics committee, and written informed consent was obtained from all participants.

2.2. Experimental Design. PD patients were studied in the OFF and in the ON conditions, on 2 occasions separated by a week. For the OFF condition, MED PD and STN-DBS PD were studied after overnight withdrawal of medications, and in addition, STN-DBS PD patients had the stimulator turned OFF. For the ON condition, medicated PD patients took their usual dopaminergic treatment, while STN-DBS PD patients were studied with the stimulator turned ON, but without medications, in order to capture isolated effects of DBS. To control for potential familiarisation with the task, the healthy participants also completed the experiment twice. In PD patients, the order of ON and OFF sessions was counterbalanced, with half of the patients within each PD group being first tested in OFF and the other half in the ON state.

The severity of motor symptoms in PD patients was assessed with the motor section of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [8], in OFF and ON conditions (Table 1). Participants were screened for depression, apathy, and cognitive impairment using the Beck Depression Inventory (BDI) [9], the Marin Apathy Scale (MAS) [10], and the Mini Mental State Examination (MMSE) [11], respectively (Table 1).

2.3. Experimental Task. The Card Arranging Reward Responsivity Objective Test (CARROT) is a psychomotor task designed to measure incentive motivation, and it quantifies the extent to which participants increase speed of card sorting when offered a small financial incentive [7, 12–14]. Participants are given a stack of cards, each showing five single digits between 1 and 9 (one number in each corner and one number in the centre), of which one of them is 1, 2, or 3. The aim of the task is to sort cards as quickly as possible into stacks of 1, 2, and 3 piles on whether one of the numbers on the card is 1, 2, or 3. The participants completed three trials. The first was a baseline trial (T1) in which the participant was required to sort 60 cards as quickly as possible, to measure individual baseline speed. For trials T2 and T3, a stack of 100 cards was provided. In T2, the instruction was to sort cards as rapidly as possible within the individualised time limit for each participant measured in T1. T3 was the rewarded trial, and the participant was told that he/she would receive a 10p reward for every five cards sorted, with a 10p coin placed on the table in full view after every fifth card. The participants were not told in advance that they would be offered a reward in the third trial. Time was measured by experimenter with a stopwatch. The number of cards sorted in T2 indicates nonrewarded speed (NRSPEED), while the number of cards sorted in T3 indicates rewarded speed (REWSPEED). The reward responsiveness index (RRI) measures any increment of REWSPEED relative to NRSPEED, that is, RRI = REWSPEED−NRSPEED.

Table 1: Clinical characteristics of participants.

	STN-DBS PD	MED PD	HP
Disease duration (years)	14 (1.5)	4.8 (1.6)	—
Total motor UPDRS	OFF 41.6 (4.9) ON 21.9 (2.3)	OFF 30.4 (3) ON 15.3 (2.1)	—
LED	320 (40)	393 (44)	—
MAS	38.5 (2.2)	32.2 (2.8)	30.1 (1.5)
BDI	8.8 (1.2)	10.7 (1.4)	5.8 (1.6)
MMSE	29.1 (0.5)	29.5 (0.2)	29.8 (0.1)

Data are given as a mean and standard error within the brackets. Abbreviations: STN-DBS PD, PD patients on STN DBS; MED PD, medicated PD patients; UPDRS, Unified Parkinson Disease Scale; LED, L-Dopa Equivalent Dose in milligrams; MAS, Marin Apathy Scale; BDI, Beck Depression Inventory; MMSE, Mini Mental Status Examination.

2.4. Statistical Analysis. One-way ANOVAs were used to test differences in age distribution and differences on MAS, BDI, and MMSE scales between the 3 groups of participants. To compare UPDRS scores, we used repeated measures ANOVA (rmANOVA), with the between-subject factor PD group (STN-DBS PD vs. MED PD) and the within-subject factor condition (OFF vs. ON). To assess if the repetition of the task in HP affected performance, we performed rmANOVA, with two within-subject factors: session (1st vs. 2nd) and reward (NRSPEED vs. REWSPEED). To assess differences between groups in RRI, we used ANOVAs with the between-subject factor group (3 levels: STN-DBS PD vs. MED PD vs. HP) and the within-subject factor condition, which was for PD patients OFF vs. ON and for HP 1st vs. 2nd session. Post hoc Tukey tests with corrections for multiple comparisons were used to further analyse significant main effects or interactions. The associations between demographic data, clinical motor scores, BDI, MAS, and MMSE on the one hand and RRI on the other hand were examined with Pearson correlations.

3. Results

3.1. Clinical Scales. There was no difference in age between the two groups of PD patients and healthy participants ($F(2, 28) = 0.5$; $p = 0.61$). Disease duration was significantly

longer ($p < 0.001$) in STN-DBS PD compared to MED PD. As expected, both groups of PD patients had higher total motor UPDRS in the OFF vs. ON conditions (F (1, 19) = 67 $p < 0.001$). Moreover, STN-DBS PD patients had a higher total UPDRS score compared to MED PD patients both in OFF and ON conditions, as revealed by the significant factor group (F (1, 19) = 4.7 $p = 0.04$), but the nonsignificant group x condition interaction (F (1, 19) = 0.5; $p = 0.5$). For MAS, ANOVA revealed a significant effect of the factor group (F (2, 28) = 4.1; $p = 0.027$), due to higher apathy scores in STN-DBS PD compared to HC ($p = 0.027$). For BDI, the ANOVA revealed significant effect of the factor group (F (2, 28) = 3.4; $p = 0.05$), due to higher BDI scores in MED PD vs. HCs ($p = 0.04$). There was no difference in MAS and BDI between STN-DBS PD and MED PD ($p = 0.13$ and $p = 0.5$, respectively).

3.2. The CARROT. All but one patient (one MED-PD patient in the OFF state) completed both assessment sessions. For each group, the time taken to sort 60 cards in T1, the mean number of cards sorted in the nonrewarded trial T2 and in the rewarded trial T3, and RRI and percentage of improvement in T3 relative to T2 are given in Table 2.

For healthy participants, rmANOVA revealed no significant effect of session (F (1, 10) = 2.4; $p = 0.16$) or reward (F (1, 10) = 2.3; $p = 0.15$) and no significant 2-way interaction session x reward (F (1, 10) = 1.3; $p = 0.3$), indicating that repeating or familiarisation with the task did not influence the performance. For RRI, ANOVA revealed no significant main effect of the factor group (F (2, 27) = 1.8; $p = 0.2$) or the factor condition (F (1, 27) = 1.2; $p = 0.3$), whereas the group x condition interaction was significant (F (2, 27) =3. 9; $p = 0.03$). Post hoc Tukey analysis revealed this was due to higher reward responsiveness in STN-DBS ON vs. MED PD ON ($p = 0.03$) and STN-DBS ON vs. HP ($p = 0.03$ and $p = 0.03$ for STN DBS ON vs. 1st session HP and STN DBS ON vs. 2nd session HP, respectively), while there were no other significant differences (Figure 1).

3.3. Correlations. The patients' age, disease duration, UPDRS scores or BDI, MAS, and MMSE scores did not have any noteworthy correlations with RRI.

4. Discussion

To study motivational modulation of movement speed in Parkinson's disease, we used the CARROT. This psychomotor task shares strategies with several daily life tasks that require organisation by specific rules, such as sorting clothes by colour for washing, arranging books by topic, or keeping the groceries in the kitchen by compartments. Therefore, the CARROT may be better suited than reaction time experimental paradigms to understand motivational modulation of movement speed that occurs in common life circumstances. Previous studies in healthy participants found that enhancement of speed with monetary incentive on the CARROT correlates with individual differences in appetitive motivation, while in patient populations, the CARROT was shown to be sensitive to change in the motivational state with treatment of apathy [7, 12, 13].

The main result of our study is that STN-DBS PD patients with stimulation turned ON (but no additional dopaminergic medications) improved the movement speed with the prospect of monetary incentive to a greater extent than medicated PD patients and the healthy participants. This effect was present despite longer disease duration and more severe motor impairment for STN-DBS compared to medicated PD patients and despite higher levels of self-reported apathy compared to healthy participants.

The role of the basal ganglia (BG) is to make a selection of movements based on converging information from motor, associative, and limbic circuits [15]. Within BG, STN is a relay nucleus of the indirect pathway and receives direct cortical input via the hyperdirect pathway. Apart from the motor input originating from the motor cortex and the supplementary motor area, the STN receives inputs from associative and limbic cortical and subcortical structures, including the prefrontal cortex, ventral tegmental area, basolateral amygdala, the thalamus, and the ventral *pallidum* [16–20]. The information transmitted through the cortico-STN hyperdirect pathway reaches the basal ganglia output structures before information translated through the direct and indirect corticostriatothalamocortical pathways, suggesting that one of the role of the STN may be in integrating various associative and limbic information related to motor behaviour, before the final output for motor action is sent out from the basal ganglia [21]. In this view, the STN serves as a node to translate motivation into motor action, by processing limbic information that influences motor behaviour [20]. Several studies have reported behavioural changes after STN DBS in patients with PD, and there is evidence to support that these are derived from modulation of limbic-processing neurons within the STN [22–25]. STN DBS in PD has been associated with emergence of explosive-aggressive behaviour [26, 27], mania, and hypomania [28, 29], while accidental lesions of the STN may result in various symptoms of behavioural hyperactivity such as hypersexuality, eurphoria, and impulsivity [20, 30–32]. There is also neurophysiological evidence to support alteration of the limbic and associative circuits following STN DBS. In PD patients, 18F-FDG PET (performed before and 3 months after surgery) showed metabolic changes in several cortical regions that are part of limbic and associative circuits [33, 34]. Using intraoperative fMRI during high frequency STN stimulation in PD patients, blood oxygen level-dependent signal changes were observed not only in the motor circuitry but also in the limbic circuitry, including cingulate and insular cortices [35].

The results of the present study add to the line of evidence linking STN-DBS or STN lesions (which are assumed to have roughly similar inactivation effects as stimulation of the hyperactive STN in human PD) to heighten incentive motivation [36–38]. For example, increased sensitivity to food reward cues associated with postoperative weight gain has been documented after STN-DBS in PD patients [39, 40]. We have previously shown in the same group of PD patients that monetary incentive improves reaction times

Table 2: Number of sorted cards in Trials 1, 2, and 3, reward responsivity index, and percentage of improvement with rewarded trial.

		T1	T2	T3	RRI	% of improvement*
STN-DBS PD	OFF	128.2 (20.3)	59.3 (3.8)	61.5 (3.4)	2.2 (2.3)	4.8 (4.3)
	ON	87.2 (8.5)	62.8 (2.1)	71 (2.6)	8.2 (1.6)	13.3 (2.8)
MED-PD	OFF	72.8 (5.8)	67.1 (1.9)	68.8 (2)	1.8 (1.2)	2.7 (1.9)
	ON	68.5 (3.6)	65.4 (1.9)	66.7 (1.6)	1.3 (1.4)	2.3 (2.2)
HP	First	55.2 (3.7)	66.2 (1.4)	69.4 (2.1)	3.1 (1.3)	4.6 (1.9)
	Second	53.5 (4.2)	63.8 (1.3)	68.5 (1.5)	2 (1.8)	3.2 (2.9)

Data are given as a mean and standard error within the brackets. Abbreviations: STN-DBS PD, PD patients on STN DBS; MED PD, medicated PD patients; T, trial; RRI, reward responsivity index; *% of improvement in the rewarded trial relative to the nonrewarded trial.

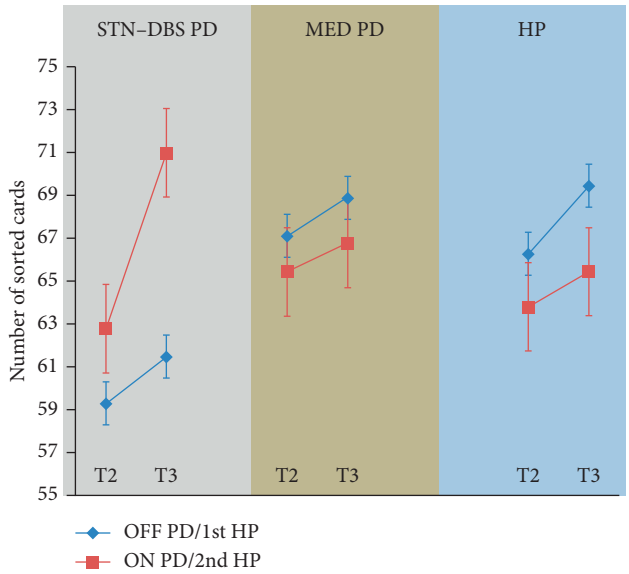

Figure 1: Nonrewarded speed (NREWSPEED) in T2 and rewarded speed (REWSPEED) in T3 are showed for STN-DBS PD patients and MED PD patients in OFF and ON conditions and for first and second experiments for healthy participants. The slope represents RRI, that is, REWSPEED–NRSPEED. PD patients with STN-DBS ON have higher RRI compared to medicated PD patients ON ($p = 0.03$) and to healthy participants ($p = 0.03$).

irrespective of patients being off or on medication or STN-DBS [5, 6]; however, only patients treated with STN-DBS (with stimulation turned on) were capable to further improve initiation time with higher reward magnitude, suggesting enhanced incentive motivation as a result of STN stimulation [6]. Interestingly, our STN-DBS PD patients with stimulation ON showed relatively larger improvement of movement speed with reward than healthy participants. One explanation is the "ceiling effect," as healthy participants could have already reached their near to maximal speed in the nonrewarded trial (note that instructions for the nonrewarded trial were to sort out cards as quickly as possible). Percentage of improvement in the rewarded trial in our group of healthy participants was around 4% which is in line with previous studies on healthy subjects [13].

Our results show dissociation between the deficient motivation represented by self-reported apathy (as measured by MAS) and experimental modulation of movement speed in response to small monetary incentive. This contra-intuitive effect may be possibly related to impulsivity. Some animal experimental studies suggest that higher reward sensitivity in STN-lesioned animals is associated with increased impulsivity [36, 37, 41] and studies in PD patients using the STN DBS ON vs. OFF methodology found that STN DBS in PD patients is associated with inhibitory deficit over anticipatory responses [6, 42]. Nevertheless, as our study was not designed to monitor anticipation errors, we cannot provide evidence to support the latter hypothesis.

5. Study Limitation

The main limitation of the study is the relatively small number of participants in each group. However, use of a repeated measures design allowed us to detect within-subject changes of movement speed between nonrewarded and rewarded trials in different motor conditions (ON vs. OFF medication or stimulation), increasing the statistical power. A repeated measures design may, however, be a source of a potential bias, since the participants repeated the CARROT twice and thus became familiarised with the task. Since in the second session participants knew they would be performing a rewarded trial, hypothetically they could strategically slow their performance on the nonrewarded trial in order to improve more in the rewarded trial. However, we believe that repetition of the task did not affect the results. First, we did not detect any differences between nonrewarded and rewarded trials in first and second sessions in healthy participants. Second, we counterbalanced the ON and OFF conditions in PD patients. Finally, there are previous studies that have successfully used the CARROT repeatedly in the same participants, in order to detect the effect of various measures on reward responsiveness [13, 14].

6. Conclusions

We have demonstrated, using a psychomotor CARROT task, that PD patients with STN-DBS ON (and no dopaminergic medications) showed greater improvement of movement speed with the prospect of monetary incentive compared to medicated PD patients and age-matched healthy participants. This suggests that motivational modulation of movement may be enhanced and be directly related to STN stimulation. This finding may be relevant for incorporating

reward cues into rehabilitation programmes for patients after STN-DBS treatment.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Review Article

Motor and Nonmotor Symptoms of Parkinson's Disease: Antagonistic Pleiotropy Phenomena Derived from α-Synuclein Evolvability?

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Lewy body diseases, such as Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA), are associated with a wide range of nonmotor symptoms (NMS), including cognitive impairment, depression and anxiety, sleep disorders, gastrointestinal symptoms, and autonomic failure. The reason why such diverse and disabling NMS have not been weeded out but have persisted across evolution is unknown. As such, one possibility would be that the NMS might be somehow beneficial during development and/or reproductive stages, a possibility consistent with our recent view as to the evolvability of amyloidogenic proteins (APs) such as α-synuclein (αS) and amyloid-β (Aβ) in the brain. Based on the heterogeneity of protofibrillar AP forms in terms of structure and cytotoxicity, we recently proposed that APs might act as vehicles to deliver information regarding diverse internal and environmental stressors. Also, we defined evolvability to be an epigenetic phenomenon whereby APs are transgenerationally transmitted from parents to offspring to cope with future brain stressors in the offspring, likely benefitting the offspring. In this context, the main objective is to discuss whether NMS might be relevant to evolvability. According to this view, information regarding NMS may be transgenerationally transmitted by heterogeneous APs to offspring, preventing or attenuating the stresses related to such symptoms. On the other hand, NMS associated with Lewy body pathology might manifest through an aging-associated antagonistic pleiotropy mechanism. Given that NMS are not only specific to Lewy body diseases but also displayed in other disorders, including amyotrophic lateral sclerosis (ALS) and Huntington's disease (HD), these conditions might share common mechanisms related to evolvability. This might give insight into novel therapy strategies based on antagonistic pleiotropy rather than on individual NMS from which to develop disease-modifying therapies.

1. Introduction

It is well established that synucleinopathies, including PD, DLB, and MSA, are characterized by a number of NMS, such as cognitive impairment, depression and anxiety, sleep difficulties, gastrointestinal disturbance, and autonomic failure. Because some NMS occur in the prodromal disease stages, NMS are both mechanistically and therapeutically important [1, 2]. Recently, in this field, there has been great interest in better understanding NMS, a topic which has

been prominently reviewed [3–9]. Nevertheless, the mechanisms which underlie NMS in neurodegenerative diseases remain obscure.

Accordingly, the main objective of this paper is to discuss how NMS might be involved in the pathogenesis of synucleinopathies and related disorders. Given that a variety of NMS often occur during the course of multiple neurodegenerative conditions, it is predicted that NMS might be triggered by multiple pathologic factors, including protein aggregation and inflammation. One possibility then would be that NMS might be passive phenomena as a result of neurodegeneration. Yet, an alternative and nonmutually exclusive possibility is that NMS might be a consequence of evolvability [10], whereby NMS information might be transgenerationally delivered to offspring encoded in APs, such as αS and Aβ, perhaps preventing the stresses relevant to NMS in offspring. On the other hand, NMS may manifest as symptoms of aging-associated neurodegenerative disease through an antagonistic pleiotropy mechanism in the parental brains. Finally, we propose that a better understanding of this hypothetical view would facilitate development of a therapy strategy against NMS in synucleinopathies.

2. Motor and Nonmotor Symptoms in Synucleinopathies

In PD and related synucleinopathies, treating motor signs and symptoms due to the degeneration of dopaminergic neurons in the substantia nigra has long been the focus of disease management. However, in recent years, because of increased clinical recognition and relevance to patient life quality, the nonmotor aspects of such disorders have attracted increasing interest. Clinically, NMS consists of four domains: neuropsychiatric (e.g., depression, anxiety, apathy, hallucinations, and dementia), autonomic (e.g., constipation, orthostatic hypotension, urinary changes, and sweating abnormalities), sleep (e.g., insomnia, sleep fragmentation, excessive daytime sleepiness, rapid eye movement, sleep disorder, and restless leg syndrome), and sensory dysfunction (e.g., pain and olfactory dysfunction) [11–13]. Such diversity of NMS may be consistent with the widespread distribution of αS pathology in the gut [14, 15] as well as brainstem and neocortex in PD brain [16], in which multiple populations of aminergic neurons may be affected, including serotonergic and noradrenergic neurons. Thus, the classic Parkinsonian motor syndrome is now regarded as but one unitary symptom type among many disparate symptoms of the synucleinopathies.

3. Are NMS Passive Phenomena?

Overall, it would appear possible that similar to motor symptoms (MS), NMS might be passive phenomena in response to amyloid fibrils and inflammation during the progression of PD and other disorders, including ALS and HD [17–20]. Indeed, such a view is supported by the results of studies in animal models. For instance, we also observed that transgenic (Tg) mice expressing DLB-linked P123Hβ-synuclein (βS) developed progressive neurodegeneration, as characterized by axonal swelling, astrogliosis, and behavioural abnormalities. Interestingly, expression of the memory abnormality (~6 months of age on water maze testing) was more prominent compared with the motor deficits (~12 months of age on the rotarod treadmill test) [21] (Figures 1(a) and 1(b)). Furthermore, P123HβS mice exhibited depression-like behaviors as assessed by locomotor activity (~6 months) and the nest building test (~6 months) [22] (Figures 1(c) and 1(d)). Collectively, this suggested that motor deficits were preceded by NMS, such as memory dysfunction and depression-like features. Similarly, hyperactivity and depression-like behaviors were observed in A53TαS Tg mice [23] and a tauopathy mouse model [24]. Since APs are constitutively expressed using artificial promoters, such as thy-1, prion promoter, and calmodulin kinase IIα, in Tg mice models of neurodegenerative diseases [21, 23, 24], it is presumed that the accumulation of protofibrillar APs, including P123HβS, αS, and tau, may interfere with signal transduction and transcription, eventually leading to the manifestation of neurobehavioral phenotypes such as depression.

There, however, would seem to be little evolutionary advantage for the passive association of NMS with neurodegenerative diseases in aging. Distinct from other organisms, humans are characterized by an extended postmenopausal senescence due to stable nutritional supply and an absence of predators [25]. Although nature remains biologically indifferent to the human condition during postreproductive time of life, a recent study suggests that the "grandmother effect" in humans may be evolutionarily beneficial because nursing of their first grandchild by a grandmother is beneficial to their daughter to encourage birth of a second grandchild [26]. From this perspective, if NMS are simply passive phenomena following neurodegeneration features, such as accumulation of toxic aggregates of APs and inflammation during aging, this would be evolutionarily not advantageous and might have been selected out in evolution.

4. NMS as Active Phenomena Dependent on Evolvability and Antagonistic Pleiotropy

One might wonder as to why NMS have not been eliminated through natural selection. Indeed, it was recently described that both MS and NMS were observed in 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine-treated marmosets, a nonhuman primate model [27]. Considering that NMS by themselves are rather consequences that are severely disabling for patients in aging and cannot transgenerationally be delivered to offspring, we predict that NMS might be linked to some physiologically beneficial effects during development and/or reproductive stages. Notably, such a view is reminiscent of the evolvability of APs such as αS and Aβ in the brain [10]. Based on the heterogeneity of protofibrillar forms of APs in terms of structure and cytotoxicity, we proposed that APs might act as vehicles to deliver information regarding diverse biological stressors [10]. Mechanistically, we speculate that αS, a monomer of which is unstable due to its intrinsically disordered nature [28], might become more stable through oligomerization,

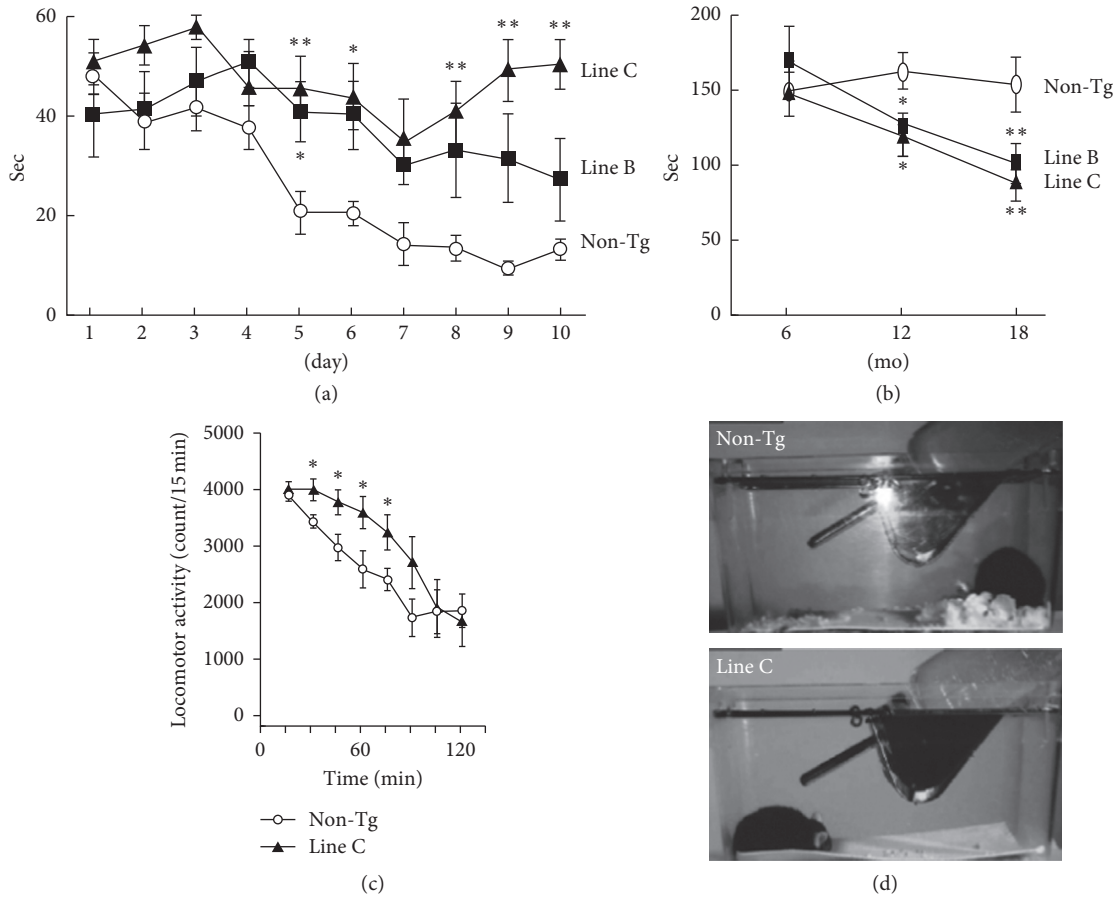

Figure 1: Altered behaviors observed in a DLB model mouse (a and b). Tg mice expressing DLB-linked P123HβS were characterized by memory disorder (~6 month: by the water maze test) (a) and being more prominent than motor deficits (~12 month: by the rotarod treadmill test) (b). See Reference [21] for the details. (c and d) The P123HβS mice exhibited depression-like behaviors as assessed from the results of the locomotor activity (6~10 month) (c) and the nest building test (6~10 month) (d). See Reference [21] for the details. Reprinted with permission from References [21, 22].

leading to formation of diverse strains of protofibrils. Such stable αS protofibrils may be feasible for transgenerational transmission to the offspring.

In this way, information regarding both MS and NMS might be integrated into the evolvability of αS (Figure 2). Presuming that NMS-related information is transgenerationally transmitted to offspring through evolvability of αS, it would benefit offspring. Yet, on the other hand, αS aggregates may also cause neurodegenerative disease and associated NMS through an antagonistic pleiotropy mechanism during aging. Thus, evolvability would be an epigenetic phenomenon in which APs transgenerationally transmit such information to offspring to cope with future stressors affecting the offspring's brain. It is predicted that NMS might be active phenomena related to evolvability.

5. Modulation of NMS Evolvability by Other Factors

Because αS pathology is promoted by other APs, such as Aβ [29] and tau [30], it is likely that evolvability of these molecules might also positively affect the evolvability of αS (Figure 2). Furthermore, βS is also of particular interest because the evolvability of αS may be positively and negatively regulated by wild-type and mutant βS, respectively [21, 31]. Similarly, since γ-synuclein (γS), the third member of the synuclein family of peptides [32, 33], may be involved in the regulation of αS evolvability because γS is associated with neuritic pathology, such as in dystrophic neurites and spheroid structures, in the brains of sporadic cases of PD, DLB, and neurodegeneration with brain iron accumulation type 1 [34, 35]. Furthermore, it was shown that the formation of aggregates and deposits of γS is facilitated after its oxidation at methionine 38 [36]. Collectively, it is possible that all synuclein family peptides might cooperate in NMS-related αS evolvability.

Moreover, aggregation of αS was also shown to be influenced by apolipoprotein E (apoE), a major Alzheimer's disease (AD) risk factor, with apoE4 having the most robust stimulatory effect compared with other isoforms (E2 and E3). Since apoE4 binds to Aβ and promotes fibrillization, we previously suggested that evolvability of Aβ might be enhanced by apoE4 [25]. Similarly, other apolipoproteins, such as ApoJ, and ApoA1, might also associate with αS to modify

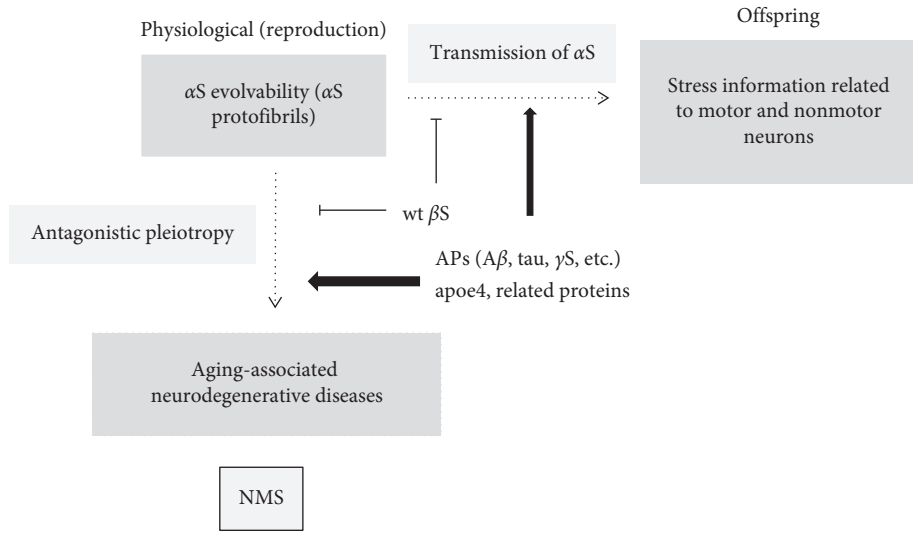

Figure 2: Schematics of the motor and nonmotor symptoms in neurodegenerative diseases and amyloid evolvability in the human brain. Hypothetically, stress information derived from both motor and nonmotor neurons might be integrated into diverse structures of αS protofibril strains that are transgenerationally transmitted to offspring during reproduction as a physiological phenomenon. On the other hand, the αS protofibrils may manifest as neurodegenerative disease associated with NMS through an antagonistic pleiotropy mechanism during the postreproductive senescent period. Both processes are stimulated by various proteins, including Aβ, tau, γS, and apoE, but are suppressed by wild-type βS.

evolvability [37, 38]. Notably, the importance of membrane lipids, such as raft, in α-synucleinopathies has been previously described [39]. Thus, it is tempting to speculate that the pathological role of membranous functions in α-synucleinopathies in aging might reflect the regulation of αS evolvability by the membrane in development/reproduction.

In addition, there has been increasing interest in transgenerational epigenetic inheritance in which various epigenetic factors like DNA methylation, histone modifications, and regulatory RNAs have been described [40]. Therefore, it is possible that some of these epigenetic factors are involved in regulating αS evolvability (Figure 2).

6. Therapeutic Implication

Notably, some NMS such as cognitive and neuropsychiatric features, [1] as well as constipation and other gastrointestinal symptoms [2], often are expressed in the prodromal disease stage of neurodegeneration. Since recent studies suggest that disease-modifying therapy (DMT) for neurodegenerative diseases should be initiated at earlier stages, NMS may be important from both the mechanistic and therapeutic standpoints.

As discussed, NMS might be either passive phenomena during the course of neurodegeneration or an active phenomena derived from evolvability through antagonistic pleiotropy. In the former case, neuropathogenic factors, such as fibrils and inflammation, are presumed to be situated upstream of NMS. Although therapeutic strategies are thought to target those neuropathogenic factors, no DMT has thus proven effective in relieving NMS. Alternatively, each nonmotor symptom might be individually targeted. For instance, dysfunction of hypothalamic-pituitary-adrenal axis (HPA), a central regulatory system underlying stressors [41], has been implicated in contributing to depressed mood and anxiety, in patients with depression [42]. In this context, it was shown that deletion of corticotropin-releasing factor receptor type 1 (CRFR1) mitigated the amyloid-β pathology in a mouse model of AD, lending support to the notion that suppressing the HPA axis through CRFR1 antagonism may be an effective therapeutic strategy against AD [43]. Given that CRFR1 in the brain is involved in the regulation of endocrine, behavioural, autonomic, and visceral in response to stress [44], the suppression of CRFR1 signaling might also be effective for other neurodegenerative diseases with NMS conditions. Also, pharmacological approaches, such as NMDA antagonists and dopamine agonists might be effective for some NMS such as depression [45, 46].

Yet, if the alternate explanation is the case, more unconventional therapeutic strategies might be employed. For instance, in addition to targeting neuropathogenic factors, such as fibrils and inflammation, disease-modifying strategies would focus on antagonistic pleiotropy rather than on the individual NMS. Currently, the mechanism underlying antagonistic pleiotropy is unclear. In this regard, however, it is noteworthy that a recent study revealed pleiotropic associations of allelic variants in a 2q22 region with risks of major human diseases, such as vascular disease, cancer, and neurodegenerative disease, and mortality [47], suggesting a possibility that the serine/threonine TGFβ/activin receptor-signaling pathways might be involved in the regulation of antagonistic pleiotropy. In support of this view, importance of the serine129 with phosphorylates αS has been well characterized in PD [48]. In particular, accumulation of αS serine129 phosphorylation in Lewy bodies is a hallmark of the pathogenesis in PD [49]. The similar is the case of tau in AD although involvement of both

serine/threonine kinases and tyrosine kinase has been described [50, 51]. If this view is the case, modification of the TGFβ/activin receptor-signaling pathways could be therapeutically effective for the entire symptoms, including both MS and NMS in neurodegenerative diseases and perhaps other aging-associated chronic diseases. Further investigations are warranted to test this intriguing possibility.

7. Conclusions

Although increasingly clear that NMS are important early biomarkers as well as targets for disease-modifying therapy for synucleinopathies, such as PD, DLB, and MSA, the mechanisms by which NMS are involved in the pathogenesis of the disease have not been fully understood. We hypothesized that stress information derived from both MS- and NMS-relevant neurons might be integrated into the diverse structures of αS protofibrils and are transgenerationally transmitted, which is probably beneficial to ward against forthcoming stressors in offspring, i.e., evolvability.

However, in parental brain, αS protofibrils might manifest later in life associated with aging-associated neurodegenerative disorders through the antagonistic pleiotropy mechanism. Therefore, our theory implies that NMS, because they are derived from the physiological phenomenon of evolvability, are not selected by evolution. It further introduces a new framework that antagonistic pleiotropy might be a valid therapeutic target for disease-associated NMS.

Although the concepts of amyloid evolvability and the antagonistic pleiotropy phenomena derived from amyloid-like proteins in neurodegenerative diseases are intriguing, such a theory requires further experimental validations and at present is far from explaining the complex pathophysiology of NMS in PD. Thus, further investigations are definitely warranted to demonstrate our hypothesis.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

MH conceived the study, and MH, YT, and GH wrote the paper. All authors have read and approved the manuscript.

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Research Article

Reliability and Validity of the Geriatric Depression Scale in Italian Subjects with Parkinson's Disease

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Introduction. The Geriatric Depression Scale (GDS) is commonly used to assess depressive symptoms, but its psychometric properties have never been examined in Italian people with Parkinson's disease (PD). The aim of this study was to study the reliability and validity of the Italian version of the GDS in a sample of PD patients. *Methods*. The GDS was administered to 74 patients with PD in order to study its internal consistency, test-retest reliability, construct, and discriminant validity. *Results*. The internal consistency of GDS was excellent ($\alpha = 0.903$), as well as the test-retest reliability (ICC = 0.941 [95% CI: 0.886–0.970]). GDS showed a strong correlation with instruments related to the depression ($\rho = 0.880$) in PD ($\rho = 0.712$) and a weak correlation with generic measurement instruments ($-0.320 < \rho < -0.217$). An area under the curve of 0.892 (95% CI 0.809–0.975) indicated a moderate capability to discriminate depressed patients to nondepressed patient, with a cutoff value between 15 and 16 points that predicts depression (sensitivity = 87%; specificity = 82%). *Conclusion*. The GDS is a reliable and valid tool in a sample of Italian PD subjects; this scale can be used in clinical and research contexts.

1. Introduction

Parkinson disease (PD) is characterized by motor and nonmotor symptoms. Bradykinesia, tremor at rest, and rigidity are the cardinal motor manifestations of PD [1]. Nonmotor symptoms include gastrointestinal dysfunctions, sleep disorders, cognitive disorders, and neuropsychiatric disturbances. Depression has been found to be more frequent in PD patients than in age-matched healthy controls or in patients with other chronic medical conditions [2, 3]. For example, major depression may be found in up to 20% of PD patients [4]. To measure the level of depression, it is crucial that clinicians and researchers have access to reliable and valid instruments. A recent systematic review about depression tools in PD patients recommended the use of the Hamilton Depression Inventory as a rating scale, which takes into consideration the judgment of the clinician or the caregiver, and the Geriatric Depression Scale (GDS), that considers the patient's point of view, for the screening and measurement of the degree of perceived depression in patients with PD [5].

The GDS [6], composed by 30 items, was developed to evaluate the level of depressive symptoms over the past week. It was transculturally adapted in several languages [7–9], and it has proven to be reliable and valid in subjects with dementia [10–13], stroke [14–17], rheumatoid arthritis [18], and psychiatric disorders [19, 20]. In PD, several studies showed that GDS has good psychometric properties, a high internal consistency (Cronbach's alpha = 0.92) [21], an excellent test-retest reliability (intraclass correlation coefficient = 0.89 [95% CI 0.83–0.93]), and a minimal detectable change of 5.4 points [22]. Taking into account the validity, the GDS showed good correlations with the Beck Depression Inventory ($r_s = 0.62$, $p < 0.05$) and with mood related items

of the Unified Parkinson's Disease Rating Scale ($r_s = 0.38$, $p < 0.05$) [23], and moderate correlations with the 17-item Hamilton Depression Rating Scale ($r = 0.54$, $p < 0.001$) [24]. Recently, the GDS was used in an Italian sample of geriatric patients, and this study confirmed the good psychometric properties of GDS [25]. As the measurement properties of an instrument are affected by the disease investigated and by the contextual factors, for a reliable and valid use of the instrument in Italian subjects, the GDS should be validated also in the target population to which the questionnaire will be administered. No study has assessed the psychometric properties of GDS in Italian patients with PD. Therefore, the aim of this study is to assess the reliability and the validity of the GDS in a sample of Italian PD patients, using the Classical Theory Test.

2. Methods

2.1. Subjects. Seventy-four (older than 18 years) patients with clinically diagnosed PD were consecutively recruited through a convenience sample in the Rehabilitation Unit of San Giovanni Battista Hospital, Polyclinic Italia, and in the Department of Neurosciences, Sapienza University of Rome. Patients with cognitive impairment (Mini-Mental State Examination score <23 points) and problems with reading and understanding the Italian language were excluded. All subjects gave their informed consent [26, 27] to participate in the study, and the research was conducted according to the principles of Declaration of Helsinki.

2.2. Outcome Measures

2.2.1. Geriatric Depression Scale. This scale assesses the depressive symptoms [6]. The version used in this study was composed by 30 items that investigated different aspects of the depression over the last week. Each item is rated by a dichotomous score (yes = 1; no = 0), and some items (Item numbers 1, 5, 7, 9, 15, 19, 21, 27, 29, and 30) presented a reverse score (yes = 0; no = 1). The total score is given adding the item scores, and it ranged from 0 (no depression) to 30 (maximum depression) points. The Italian version used in this study demonstrated to be reliable and valid [25].

2.2.2. Hospital Anxiety and Depression Scale. This scale measures the level of depression and anxiety [28]. It is composed by 14 items divided in two subscales: 7 items investigate depressive symptoms, and the other 7 measure anxious symptoms. Subjects respond to each item on four-level ordinal score (0 = no symptoms; 3 = maximum symptoms); therefore, the total scores may vary between 0 and 21 points for each subscale. The Italian version of the scale was used in this study [29].

2.2.3. Parkinson Disease Questionnaire. This questionnaire assesses the impact of parkinsonian symptoms in the life of these patients in the past month [30]. It contains 39 items that examine 8 domains through separately scored subscales: mobility (10 items), activities of daily living (6 items), emotional well-being (6 items), stigma (4 items), social support (3 items), cognition (4 items), communication (4 items), and bodily discomfort (3 items). A 5-point level score is attributed to each item (0 = never; 1 = occasionally/rarely; 2 = sometimes; 3 = often; 4 = always). A total score ranging from 0 (indicating best health status) to 100 (indicating worst health status) was calculated by summing the score of each item, both for the 8 subscores and for the total score. The Italian version used in this study was recently evaluated [31] and revealed good psychometric properties.

2.2.4. Short Form 36-Health Survey Questionnaire (SF-36). This is a 36-item questionnaire measuring the patient's health status in the past four weeks [32]. The total score ranges from 0 to 100 with higher scores indicating a better condition. The Italian version is considered to be a valid and reliable tool [33].

2.2.5. Barthel Index. This well-known test measures the disability on the ADLs [34]. It is composed of 10 items including feeding, bathing, grooming, dressing, bowel and bladder control, toilet use, transfers (bed to chair and back), mobility, and stairs climbing. Three ordinal level scores are attributed to each item (0, 5, or 10; 15 points for items regarding transfers and mobility) to assess whether the patient can perform the various activities independently, with assistance or whether they are totally dependent from others. The total score is generated summing each score, and it varies from 0 (total dependence) to 100 (total independence). The Italian version was administered in this study [35, 36].

2.3. Procedures. Four clinicians (three occupational therapists and one physical therapist) screened all patients for their recruitment. Once enrolled, these clinicians collected demographic and clinical variables and administered the outcome measure to all patients. In order to study the test-retest reliability, the GDS was readministered after seven days. To assess the discriminant validity, a physician diagnosed the depression in this sample. According to DSM-5, patients were diagnosed with depression if they had at least five depressive symptoms including "depressed mood" and "loss of interest or pleasure" for at least two weeks [37].

2.4. Statistical Analysis. Descriptive statistics was used to analyze the sample characteristics; in particular, mean ± standard deviation (SD), median with 25th and 75th percentiles, and frequency with percentage were calculated for intervallic, ordinal, and categorical data, respectively.

The reliability of GDS was assessed in terms of internal consistency and test-retest reliability. Internal consistency was determined calculating Cronbach's alpha [38]: for values closer to 1, the internal consistency is higher. Alpha was considered excellent if >0.9, good if >0.8, and acceptable if >0.7 [39]. Test-retest reliability was calculated by the intraclass correlation coefficient (ICC) with a 95% confident interval (CI). ICC values greater than 0.75 are a minimum

requirement to use the instrument in group measurements [40]; ICC values greater than 0.90 are considered essential for the use of the instrument in individual measurements [41].

The construct validity of the GDS was studied calculating the Pearson correlation coefficient (ρ) when comparing the GDS with the other administered instruments. The following ranges were considered in order to interpret the results: $\rho > 0.70$ = strong correlation, $0.50 < \rho < 0.70$ = moderate correlation, and $e\ \rho < 0.50$ = weak correlation [42].

In order to study the discriminant validity, the receiving operating characteristic (ROC) curve was created, and the area under the curve (AUC) was calculated. The closer the AUC value is to 1.0, the greater the instrument's ability to distinguish depressed and nondepressed patients. An AUC higher than 0.75 confers to the tool a moderate discriminative validity; while an excellent one is demonstrated by a value ≥0.90.

For all statistical analyses, the α value was set at 0.05, and SPSS statistical software program, version 18.0 for Windows (SPSS Inc., Chicago, IL, USA), was used.

3. Results

3.1. Sample Characteristics. Seventy-four patients (44 males; 30 females) with PD were included in this study. The demographic and clinical characteristics of the patients studied are reported in Table 1.

3.2. Internal Consistency. The internal consistency for the total GDS score was excellent ($\alpha = 0.903$).

3.3. Test-Retest Reliability. Test-retest reliability was assessed in a subsample of 35 patients. Excellent reliability was observed for the GDS total score (ICC = 0.941 [95% CI: 0.886–0.970]).

3.4. Validity. Pearson's correlation coefficient values are reported in Table 2. Taking into account the comparisons between GDS and the other instrument related to depression (HADS) and PD (PDQ-39), Pearson coefficient ranged between 0.712 and 0.880, indicating a strong correlation. On the other hand, regarding the comparisons between GDS and generic measurement instrument (Barthel Index and SF-36), the correlation coefficient varied from −0.320 to −0.217, showing a weak correlation.

Regarding the discriminant validity, the AUC showed a value of 0.892 (95% CI 0.809–0.975), indicating a moderate capability to discriminate depressed patients to nondepressed patient. The score with the best sensibility and specificity that predicts depression is between 15 and 16 (sensitivity = 87%; specificity = 82%) (Figure 1).

Table 1: Main demographic and clinical characteristics of the sample ($N = 74$).

Variables	Values
Age (years)[a]	66.9 ± 9.7
Gender[b]	
(i) Male	44 (59.5%)
(ii) Female	30 (40.5%)
Depression[b]	
(i) Presence	23 (31.1%)
(ii) Absence	51 (68.9%)
Medications prescribed to depressed subjects (N=23)[b]	
(i) Antidepressant	11 (47.8%)
(ii) Anxiolytic	10 (43.5%)
(iii) No medications	2 (8.7%)
Educational level[b]	
(i) Primary	9 (12.2%)
(ii) Secondary	17 (23%)
(iii) High school	33 (44.6%)
(iv) Degree	13 (17.6%)
(v) Not reported	3 (4.1%)
Employment[b]	
(i) Employed	13 (17.6%)
(ii) Not employed	4 (5.4%)
(iii) Retired	57 (77%)
Marital status[b]	
(i) Married	56 (75.6%)
(ii) Unmarried	17 (23%)
(iii) Not reported	1 (1.4%)
Time since PD diagnosis (years)[a]	7.8 ± 5.6
Hoehn and Yahr stage[c]	3 (2; 3)
Setting[b]	
(i) Department	20 (27%)
(ii) Ambulatory	53 (71.6%)
(iii) Day-hospital	1 (1.4%)
MMSE score[c]	29 (27.25; 30)
HADS-A score[c]	7 (4; 10)
HADS-D score[c]	7 (4; 10)
HADS total score[c]	15 (10; 20)
GDS total score[c]	13 (6; 19)
PDQ-39 subscale score[c]	
(i) Mobility	17.5 (7.5; 25.75)
(ii) Activities of daily living	10 (4; 15.75)
(iii) Emotional well-being	9 (5; 14)
(iv) Stigma	4 (2; 8)
(v) Social support	1 (0; 3.75)
(vi) Cognition	5 (2; 8)
(vii) Communication	3 (1.25; 6)
(viii) Bodily discomfort	4 (2; 7)
PDQ-39 total score[c]	59 (31.25; 76)
SF-36[c]	95 (86.25; 102)
Barthel Index[c]	85 (75; 95)

Data are expressed as [a]mean ± standard deviation, [b]frequency with percentage, or [c]median with 25th and 75th percentiles. MMSE: Mini-Mental State Examination; HADS-A: Hospital Anxiety and Depression Scale of Anxiety; HADS-D: Hospital Anxiety and Depression Scale of Depression; GDS: Geriatric Depression Scale; PDQ-39: Parkinson's Disease Questionnaire; SF-36: Short Form 36-Health Survey Questionnaire.

4. Discussion

The use of a reliable and valid instrument is essential in clinical practice and when measuring specific outcomes [43]. Several questionnaires are available to measure depression in patients with PD [5]. The psychometric properties of GDS have been extensively studied in different pathologies and in different settings. To our knowledge, however, no study assessed the psychometric properties of GDS in Italian

Table 2: Pearson's correlation coefficient for each comparison.

	HADS-A	HADS-D	Total HADS	PDQ	SF-36	Barthel Index
GDS	0.799*	0.800*	0.880*	0.712*	−0.320**	−0.217

* $p < 0.01$; ** $p \leq 0.5$. HADS-A: Hospital Anxiety and Depression Scale of Anxiety; HADS-D: Hospital Anxiety and Depression Scale of Depression; GDS: Geriatric Depression Scale; PDQ-39: Parkinson's Disease Questionnaire; SF-36: Short Form 36-Health Survey Questionnaire.

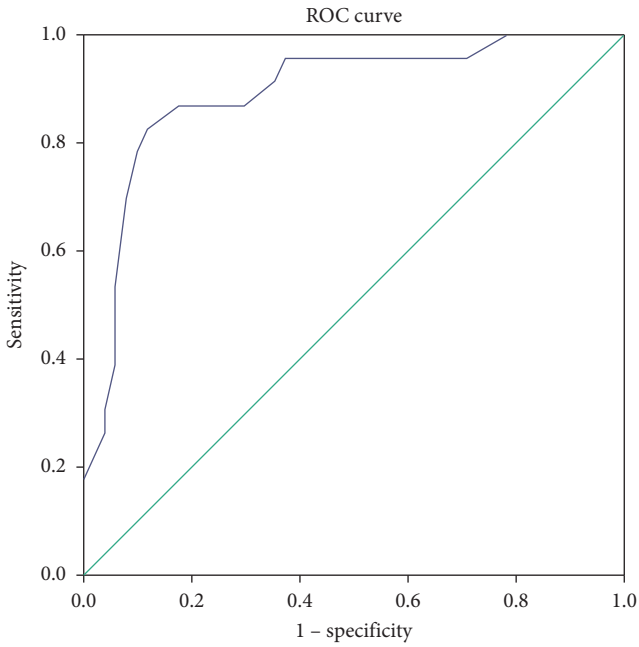

Figure 1: Receiving operating characteristic curve.

patients with PD. Studying the measurement properties in the context in which the instrument will be administered is crucial because these properties can be influenced by various contextual, social, and environmental factors [44]. The results of our study show that GDS is a reliable and valid instrument in Italian patients with PD.

The internal consistency assessed by calculating Cronbach's alpha (equal to 0.903) was excellent. The results obtained in the PD patients we studied are similar to those obtained in patients with different clinical conditions. For example, Cronbach's alpha was found to be 0.876 in a study on 294 geriatric patients [45] and 0.90 in 888 depressed and nondepressed elderly subjects [46].

We demonstrated an excellent test-retest reliability of the questionnaire (ICC = 0.941). The results obtained in our sample of PD patients are similar to those found in a cohort of 75 Chinese subjects with PD (ICC = 0.89 [95% CI 0.83–0.93]) [22].

The construct validity was investigated through the correlations between the GDS and other validated questionnaires. In particular, a strong construct validity was obtained through correlations with HADS (both with anxiety and depression) and PDQ-39. On the other hand, a weak correlation was found when the GDS was compared with the Barthel Index and the SF-36. The strong correlations between GDS and HADS can be explained because these two scales intend to measure the same variable, that is, the depression; these results are in line with previous studies that obtained similar correlations with questionnaires related to depression—Beck Depression Inventory ($r_s = 0.62$, $p < 0.05$) [23] and Hamilton Depression Rating Scale at 17 items ($r = 0.54$, $p < 0.001$) [24]. Conversely, the low correlation found with SF-36 and Barthel Index may be explained because both the Barthel Index and the SF-36 are generic instruments.

Finally, the discriminating validity was studied through the ROC curve in order to identify the best sensitivity and specificity of the cutoff value that can distinguish depressed and nondepressed patients. The cutoff value of 15–16 points showed a sensitivity of 87% and a specificity of 82%. Comparing our results with those obtained in other studies is not easy considering the different patient populations and the different settings; for example, the study by McDonald et al. showed a cutoff value of 9–10 points [24] and the study by Ertan et al. [7] a cutoff value of 13–14.

This study presents limitations that need to be taken into account. The design of the study did not allow the assessment of some fundamental psychometric properties such as content validity and responsiveness.

In conclusion, this study shows that GDS can be used in clinical practice as a valid measurement instrument in order to quantify depression in patients with PD.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Consent

Informed consent was obtained from all individual participants included in the study.

Disclosure

All authors have no commercial associations or disclosures that may pose or create a conflict of interest with the information presented within this manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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