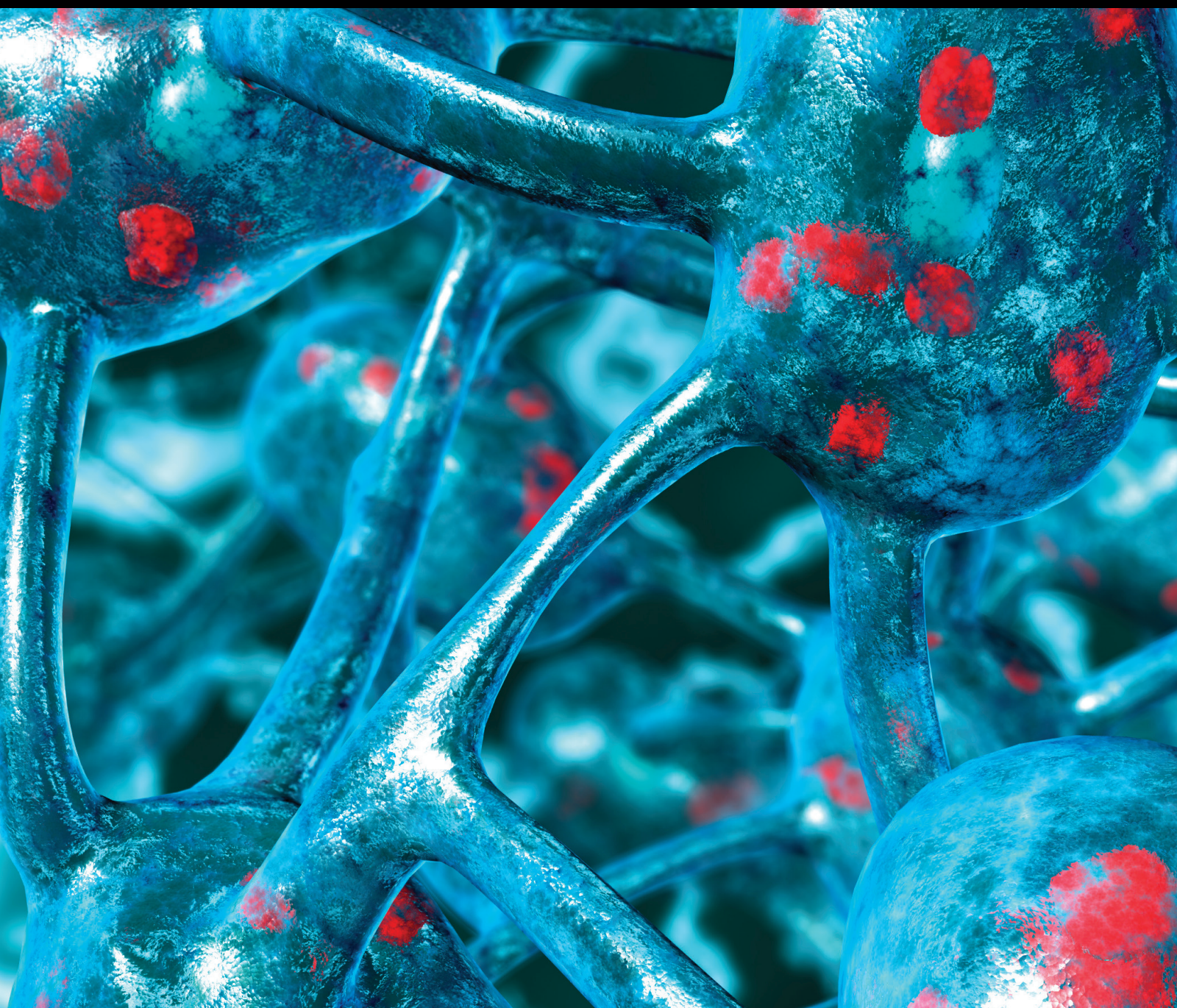
Parkinson's Disease

Cognitive Changes and Promotion in Parkinson's Disease

Lead Guest Editor: Xiao-Ping Wang
Guest Editors: Xi-Jin Wang, HaiBo Chen, Sarah D. Canning, and Xingguang Luo



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Editorial Board

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Editorial

Cognitive Changes and Promotion in Parkinson's Disease

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Parkinson's disease (PD) has been recognized as a multisystemic neurodegenerative disorder with typical motor symptoms, including static tremor, bradykinesia, rigidity, postural instability, and gait difficulty. In addition to the defining dopamine-related motor symptoms, however, increasing evidence has shown that PD patients often experience a series of nonmotor symptoms, including mood and behavior disorders, cognitive impairment, brain-gut-axis disorders, autonomic system failure, sensory symptoms, and sleep disturbances.

Cognitive impairment is one of the most devastating and common nonmotor symptoms of PD. People with PD exhibit more rapid decline in a number of cognitive domains, in particular, executive, attentional, and visuospatial domains, but also memory especially skill/implicit learning. As we all know, the underlying mechanism of motor symptoms of PD is depleted dopaminergic cells in the substantia nigra. In contrast, the pathophysiological basis of cognitive impairments in PD remains uncertain. Disrupted frontal-subcortical circuits due to dopaminergic neuron damage and wide deposition of α-synuclein, β-amyloid, and tau proteins might play a role. In K. Li et al.'s paper, they summarized rs-fMRI studies on cognitive function in PD and discuss the strong potential of rs-fMRI in this area. rs-fMRI can help reveal the pathophysiology of cognitive symptoms in PD, facilitate early identification of PD patients with cognitive impairment, distinguish PD dementia from dementia with Lewy bodies, and monitor and guide treatment for cognitive impairment in PD. In particular, ongoing and future longitudinal studies would enhance the ability of rs-fMRI in predicting PD dementia. In combination with other modalities such as positron emission tomography, rs-fMRI could give us more information on the underlying mechanism of cognitive deficits in PD.

Progressive supranuclear palsy (PSP) was first described as a progressive neurological disorder with motor, ocular, and cognitive features. Both PSP and PD are characterised by extrapyramidal syndromes, each of which can comprise symptoms of bradykinesia, rigidity, and/or postural instability. Clinically, it remains difficult to distinguish from Parkinson's disease (PD). In J. A. Foley et al.'s paper, they investigated whether the newly developed ECAS, designed to be used with people with even severe motor disability, was sensitive to the cognitive impairment seen in PD and PSP and able to distinguish between these two disorders. It is developed to be used with patients with even severe physical disability and thus may be suitable for detecting cognitive impairment in all motor disorders. Many of the subtests can be performed either orally or manually, with some measures corrected for motor speed, reducing the impact that physical disability may have performance on cognitive tests. It also allows the clinician to track cognitive impairment throughout the disease course, crucial for any longitudinal studies. ECAS is a quick, simple, and inexpensive test that can be used to support the differential diagnosis of PSP.

How to get cognitive training? There are two frequently used methods: standard or tailored. Standard cognitive

training involves cognitive tasks that are not customised to the individual's cognitive deficits, whereas tailored cognitive training is deficit specific. In B. J. Lawrence et al.'s paper, they examined whether standard cognitive training, tailored cognitive training, transcranial direct current stimulation (tDCS), standard cognitive training + tDCS, or tailored cognitive training + tDCS improved cognitive function and functional outcomes in participants with PD and mild cognitive impairment (PD-MCI). And the outcomes improved for the groups that received standard or tailored cognitive training combined with tDCS. Participants with PD-MCI receiving cognitive training (standard or tailored) or tDCS demonstrated significant improvements on cognitive and functional outcomes, and combining these interventions provided greater therapeutic effects.

Another method, bilateral deep brain stimulation of subthalamic nucleus (STN-DBS), has been proven to be effective in improving motor symptoms in Parkinson's disease (PD) patients. However, psychiatric changes after surgery are controversial. So in Y. Wang et al.'s paper, they specifically analyzed apathy following bilateral STN-DBS in PD patients using a meta-analysis. They found a significant difference between the presurgery stage and the postsurgery stage scores. STN-DBS seems to relatively worsen the condition of apathy, which may result from both the surgery target (subthalamic nucleus) and the reduction of dopaminergic medication. Thus, in J. A. Foley et al.'s paper, they examined the use of standardised neuropsychological assessment for the evaluation of surgical candidates and to identify risk factors for subsequent decline in cognition and mood. They concluded that neuropsychological assessment in a sample of patients undergoing DBS for PD is suitable for the screening of candidates and can identify baseline risk factors, which requires careful consideration before and after surgery.

This issue assembles exciting, distinguished observations into the state of the art and science, as well as emerging future topics, in this important interdisciplinary field. We hope that this special issue would attract a major attention of the peers. We would like to express our appreciation heart and soul to all of the authors and reviewers.

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Research Article

Standardised Neuropsychological Assessment for the Selection of Patients Undergoing DBS for Parkinson's Disease

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DBS is an increasingly offered advanced treatment for Parkinson's disease (PD). Neuropsychological assessment is considered to be an important part of the screening for selection of candidates for this treatment. However, no standardised screening procedure currently exists. In this study, we examined the use of our standardised neuropsychological assessment for the evaluation of surgical candidates and to identify risk factors for subsequent decline in cognition and mood. A total of 40 patients were assessed before and after DBS. Evaluation of mood and case notes review was also undertaken. Before DBS, patients with PD demonstrated frequent impairments in intellectual functioning, memory, attention, and executive function, as well as high rates of mood disorder. Post-DBS, there was a general decline in verbal fluency only, and in one patient, we documented an immediate and irreversible global cognitive decline, which was associated with older age and more encompassing cognitive deficits at baseline. Case note review revealed that a high proportion of patients developed mood disorder, which was associated with higher levels of depression at baseline and greater reduction in levodopa medication. We conclude that our neuropsychological assessment is suitable for the screening of candidates and can identify baseline risk factors, which requires careful consideration before and after surgery.

1. Introduction

Drug therapies for advanced Parkinson's disease (PD) can be unsatisfactory, with unwanted side effects, and/or insufficient control of disabling motor symptoms. Thus, there has been resurgence in interest in surgical treatments, with deep brain stimulation (DBS) now increasingly offered as an option. DBS is the chronic, high-frequency electrical stimulation of most usually the subthalamic nucleus (STN) or internal segment of the globus pallidus (GPi) [1], which is thought to alter the pattern of neural activity, with resulting beneficial effects upon motor function [2]. Its success relies heavily upon appropriate selection of candidates, which in turn relies in part upon neuropsychological screening [3, 4]. However, no standardised screening procedure currently exists, and it remains unclear what level of cognitive dysfunction precludes successful surgery. In this study, we discuss the limitations of existing presurgical protocols and evaluate the use of standardised neuropsychological assessment in a sample of patients undergoing DBS for PD. We describe patients' performance on this neuropsychological assessment before and after DBS and identify potential baseline predictors of after DBS decline, which warrant further investigation.

DBS has been shown to be relatively safe, with few negative events occurring during or following surgery, when performed on appropriate candidates [5]. However, STN DBS is thought to result in better improvements in motor control; there is some evidence to suggest that it also poses a greater risk of negatively affecting speech articulation, impulsive behaviours, and/or mood [6–10], and therefore, GPi DBS may be preferred for patients presenting with these difficulties. However, marked global cognitive deterioration

has also been reported [11, 12], and mild decline in verbal fluency has frequently been documented [13–30].

Decline in cognitive functioning following DBS has been found to be more common in patients who are older, especially above 70 years [29, 31], particularly affecting frontal executive functions [28]. Yet others have cautioned against a strict age criterion, as many people older than 70 can demonstrate good outcomes [32, 33]. Indeed, it has been reported that other factors, particularly cognitive performance, may be more useful as predictors of postoperative decline [3, 29, 34, 35]. Several studies have suggested that lower cognitive functioning at baseline is predictive of poorer cognitive outcome following surgery [36], perhaps because of lower "cognitive reserve" [35]. It has even been suggested that the presence of any cognitive deficits at baseline, particularly in executive function and memory, should serve as exclusion [36, 37]. However, PD is usually accompanied by at least mild cognitive deficits, particularly in executive function, and the evolution of a dementia is rather insidious, without any clear boundary features. Thus, it remains unclear what level of impairment should constitute a contraindication to surgery.

Despite the widespread agreement on the importance of appropriate screening and careful selection of surgery candidates, to the best of our knowledge no standardised neuropsychological assessment procedure currently exists. The Consensus on DBS for PD [38] published guidance on presurgical screening and selection of patients but did not provide a presurgical neuropsychological protocol. Rather, they listed an extensive range of neuropsychological domains to be assessed and tests commonly used. The tests listed ranged from very brief screens (including the MMSE) to very long and extensive batteries (such as the Wechsler Memory Scales and Delis–Kaplan Executive Functioning System). They stated that tests chosen should be reliable and valid, with adequate normative data for referencing performance. However, without any guidance on how to choose between the vast range of tests, nor how to interpret scores when deciding on suitability for surgery, it remains unclear how to use neuropsychological assessments to identify candidates suitable for DBS. Indeed, defining what constitutes unacceptable cognitive dysfunction remains the most controversial aspect of patient selection [2].

Moreover, there is scant official guidance. The British Psychological Society [39] recommends that candidates undergo presurgery neuropsychological evaluation but does not describe what this should consist of. The Australian guidelines [40] simply recommend that patients should be able to give a good account of themselves and capable of giving informed consent. Of course, even marked cognitive impairment may be masked by higher levels of cognitive reserve and/or fluctuating levels of attention and vice versa; gross physical and speech disability may mask intact cognition. Thus, the absence of any firm guidelines for the assessment and interpretation of cognitive performance clearly poses a significant hurdle for the appropriate selection of candidates for DBS.

In lieu of such guidance, several studies have relied upon brief cognitive screens only, such as the Mini-Mental State Examination (MMSE) [41]. This may be criticised for a number of reasons. Firstly, the MMSE comprises very few subtests that are sensitive to the typical cognitive dysfunction displayed in PD, namely, executive dysfunction [42–48] and cognitive slowing [49–52] and thus is insufficient for detecting cognitive impairment [53, 54]. Secondly, the MMSE suffers from significant ceiling and floor effects [55], so cannot capture very mild nor very severe cognitive dysfunction. Thirdly, MMSE scores are affected by age and education [56, 57], so that a low score in an older person with minimal formal schooling may present a false positive for dementia. Fourthly, an individual may attain a low MMSE score for a number of noncognitive reasons, including poor speech intelligibility, high levels of anxiety, fatigue, and distracting dyskinesia. Therefore, a low score on this test should not necessarily be used to preclude surgery.

Moreover, such brief screening tools do not permit scrutiny of the wider cognitive profile, important for confirming diagnosis. Many cases of "failed" DBS have been later found to have atypical Parkinsonian syndromes, known not to benefit from DBS [58]. Thus, there is a need to identify a suitable presurgical neuropsychological protocol, which is sufficiently sensitive to both the typical cognitive dysfunction displayed in PD and atypical cognitive decline, as seen in other Parkinsonian disorders and has clear guidelines for its interpretation.

In addition to changes in cognition, there are also a few reports of dramatic deterioration in mood and greatly increased apathy following DBS [22, 59–61], with an associated elevated risk of suicide despite successful reduction of motor symptoms [62, 63]. As such deterioration can clearly negate any potential benefits [64], it is essential that candidates at high risk of such postoperative decline are identified at baseline. Specifically, postoperative risk of suicide has been associated with higher levels of mood disorder, apathy, and/or family or social stress at baseline [65, 66]. This may not only reflect the additional stressor of surgery [67, 68] but also the direct effects of the stimulation itself [69] and any reductions in dopaminergic medication [70, 71]. As mood disorder is so prevalent in PD and may reduce with improvements in motor symptoms following surgery [35], it remains unclear what level of mood disorder should act as an absolute contraindication for DBS.

Thus, the aims of this study were to evaluate the use of our standardised neuropsychological protocol in the evaluation of patients undergoing DBS for PD in order to identify any contraindication for surgery and to be sensitive to changes following DBS.

2. Methods

2.1. Participants. A total of 40 patients (29 male, 11 female) who underwent DBS took part in this study. All patients had had a diagnosis of idiopathic PD for at least five years (according to Queen Square Brain Bank criteria), were younger than 70 years, and suffered from disabling motor complications despite optimal treatment. Each patient underwent multidisciplinary evaluation to decide on suitability for DBS. Formal levodopa challenge confirmed dopaminergic

drug responsiveness. A structural MRI was obtained to exclude surgical contraindications, such as advanced brain atrophy, white matter changes, or any other abnormality contraindicating surgery. Detailed neuropsychological and neuropsychiatric assessments excluded patients with significant cognitive impairment and/or psychiatric comorbidities. Contraindications for STN DBS included the presence of clinically relevant speech difficulties and cognitive impairment. The final decision regarding suitability for DBS and appropriate target for each patient was taken during a joint meeting of patient, immediate family, neurologist(s), and neurosurgeon(s).

Motor status was evaluated using part III of the Unified Parkinson's Disease Rating Scale (UPDRS-III). Prior to surgery, patients were assessed in the practically defined "off state" after overnight withdrawal of anti-Parkinsonian drugs and the "on state," following a levodopa challenge using a suprathreshold dose of oral levodopa. After DBS, motor assessments were sequentially performed under the following conditions, in open fashion: off medication/on stimulation (with stimulation switched on after 12 h medication withdrawal) and on medication/on stimulation (1 h after the administration of a routine dose of levodopa while stimulation was reintroduced). All medications before and after surgery were recorded, noting any dopamine agonist treatment, and levodopa-equivalent dosage was calculated (www.parkinsonsmeasurement.org). History of impulse control disorder was recorded by reviewing the medical notes and noting any mention of compulsive gambling, eating, shopping, or sexual behaviour before or after DBS.

All patients underwent assessment of neuropsychological and mood functioning before and after surgery, under optimal conditions. Thus, preoperatively, this was in the on medication and postoperatively on stimulation/on medication. The postoperative assessment was performed a mean of 19.60 months after surgery (range = 1–54; SD = 11.56). This broad range reflected the early recall of one patient following concern about cognition immediately following DBS, as well as later routine follow-up of cognitively intact patients after surgery.

The most appropriate DBS target was chosen on clinical grounds based on patient motor phenotype, imaging, and preoperative cognitive assessment. Twenty-eight patients underwent bilateral STN DBS and twelve bilateral GPi DBS.

2.2. Neuropsychological Assessment. The tests included general screening and IQ measures, as well as tests of specific cognitive functions. This was to enable both the quantification of any intellectual deficit and the elucidation of specific cognitive profiles. Thus, the measures included tests of general cognitive functioning, memory, language, visuoperceptual ability, attention, executive functions, and speed of processing. The tests chosen were considered to have acceptable test validity and reliability, as described below. The assessments took around two hours to complete and were as follows:

(1) The MMSE was used as a screening test of global cognitive functioning [41]. It is not sufficient as a measure of cognition in Parkinson's disease [53], but as the "gold standard" screening instrument, it permits easy comparison between studies.

(2) Vocabulary, similarities, arithmetic, and digit span subtest scores from the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) [72] were prorated to generate verbal IQ (VIQ). Picture Completion and Matrix Reasoning subtest scores were prorated to generate scores for nonverbal IQ (PIQ). The WAIS-III has been found to have good sensitivity and specificity for cognitive disorders [73] and good reliability for Parkinson's disease [74].

(3) The National Adult Reading Test-Revised (NART-R) [75] was used to estimate the premorbid level of intellectual functioning, by generating each patient's Predicted Full-Scale IQ (PFSIQ). The NART-R has very good interrater and test-retest reliability, and good validity, although suffers from a ceiling effect limiting prediction of IQ scores beyond 125.

(4) Memory was assessed using the following:

  (a) The Warrington Words and Faces Recognition Memory Tests (RMTs) [76] were used to assess recognition memory. The RMT correlates well with other measures of memory and has adequate reliability for patients with neurological disorders [77, 78].

  (b) The People and Shapes subtests from the Doors and People Test were used to assess verbal and visual recall memory (D&P) [79]. These tests have sufficient validity and reliability [80] and are recommended for assessing recall in PD [81].

(5) The Graded Naming Test (GNT) [82] was used to assess language. The GNT has good test-retest reliability and is well suited for detecting any gradual changes in performance over time [83]. Moreover, it is sensitive to cognitive impairment in Parkinson's disease [84].

(6) The Silhouettes subtest from the Visual Object and Space Perception Battery (VOSP) [85] was used to assess visuoperceptual functioning. This test has been validated as a test of object perception [86] and is sensitive to visuospatial impairment seen in PD dementia [87] and atypical PD [88].

(7) Elevator Counting and Elevator Counting with Distraction subtests from the Test of Everyday Attention (TEA) [89] were used to assess sustained and selective attention. These tests have high test-retest reliability and correlate with other measures of attention. Furthermore, these tests have been shown to be sensitive to Parkinsonian disorders, including Lewy body dementia [90].

(8) Executive functioning was assessed using the following:

  (a) FAS and Category subtests from the Delis–Kaplan Executive Function System (DKEFS) [91] were used to assess verbal fluency. The tests have been standardised and found to be sufficiently reliable [92].

(b) The Stroop [93] was used to assess verbal inhibition. It has high reliability [94] and is sensitive to cognitive deficits in PD [95].

(c) The Hayling and Brixton tests [96] were used to assess verbal suppression/strategy formation [97] and nonverbal set-shifting, respectively. They have moderate sensitivity and specificity for detecting executive dysfunction [98] and are sensitive to PD [99, 100].

(9) The Symbol Search and Digit Symbol Coding subtests from the WAIS-III [72] were used to assess processing speed. These tests have been shown to be sensitive to PD [101].

2.3. Mood Assessment. All patients were screened for mood disorder using the Hospital Anxiety and Depression Scale (HADS) [102] and the Apathy Evaluation Scale (AES) [103]. These tests have been validated for use in PD [104, 105].

2.4. Case Note Review. The case notes were reviewed by one clinical neuropsychologist (JAF) to identify any change in cognition, mood, or behaviour since DBS, as highlighted by the surgery team, neurologists, or nursing staff. Any mention of decline in memory, attention, perception, language, reasoning, mood, anxiety, depression, or motivation was recorded, along with number of months elapsed since surgery. As discussed before, any mention of a de novo impulse control disorder was recorded.

2.5. Statistical Analysis. Scores for each of the neuropsychological assessments were compared with published normative data. For each measure, patients were judged to be impaired if scores were ≤2 SD. When multiple measures were used, performance was classified as impaired when ≤2 SD on at least one of the measures used.

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. Baseline scores of the STN and GPi DBS groups were compared using t-tests or Mann–Whitney tests, as appropriate. Pre- and after DBS scores were compared using t-tests for related samples or Wilcoxon signed-ranks, as appropriate. Pearson's correlations, chi-squared analyses, and logistic regression techniques were used to detect any significant associations. All analyses were conducted using IBM SPSS Statistics Data Editor, version 19.

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.

3. Results

3.1. Patient Demographics. As shown in Table 1, the STN and GPi DBS patient groups did not significantly differ in terms of age, gender split, or premorbid level of intellectual functioning, as estimated by the NART. They also did not significantly differ in age at diagnosis, duration of disease, or history of impulse control disorder.

Table 1: Patient demographic characteristics.

	STN ($n = 28$)	GPi ($n = 12$)	p
Gender (male)	17	8	0.72
Age (at first assessment, years)	57.50 ± 7.32	61.33 ± 6.30	0.12
NART Predicted Full-Scale IQ	111.57 ± 11.08	103.42 ± 15.43	0.07
Age at PD diagnosis (years)	45.55 ± 7.80	48.60 ± 6.35	0.29
PD disease duration (years)	18.77 ± 6.12	19.00 ± 4.55	0.92
History of impulse control disorder (n, %)	9, 28.1%	1, 3.1%	0.08

3.2. Clinical Characteristics before and after DBS. At baseline, there were no significant differences between the STN and GPi DBS patient groups in UPDRS-III scores off or on medication, nor in baseline levodopa-equivalent dosage (as shown in Tables 2 and 3). STN DBS was successful in improving UPDRS-III scores off medication ($t(23) = 6.50$, $p < 0.001$), with a corresponding reduction in levodopa-equivalent dosage ($t(21) = 4.50$, $p < 0.001$). There was no significant difference in UPDRS-III scores on medication. In the GPi DBS group, there was no significant change in levodopa-equivalent dosage and change in motor performance was not examined because of insufficient collection of postsurgery motor performance data.

There were also no significant differences between the STN and GPi DBS patients groups in proportion of patients receiving dopamine agonist treatment before or after DBS.

3.3. Cognitive Performance before and after DBS. When baseline neuropsychological assessment scores were compared with published normative data, impairment was documented on at least one domain of cognitive function in 85% of all patients (STN: $n = 22$, 64.7%; GPi: $n = 12$, 100%). In both groups, impairments were frequently in intellectual functioning, memory, attention, and executive function (Table 4). The GPi DBS group also demonstrated frequent impairments in the additional domains of cognitive screen and speed. There was a significant association between DBS location and frequency of impairment, with the GPi group having more frequent impairments on the cognitive screen ($\chi^2(1) = 9.20$, $p < 0.05$), measures of memory ($\chi^2(1) = 5.80$, $p < 0.05$), executive function ($\chi^2(1) = 9.20$, $p < 0.05$), and speed ($\chi^2(1) = 9.20$, $p < 0.05$).

When investigated further, we found that the GPi DBS patients obtained lower baseline scores on tests of general intellectual functioning (VIQ: $t(38) = 4.24$, $p < 0.001$; PIQ: $t(38) = 2.33$, $p < 0.05$), recognition memory (RMT words: $U = 65.5$, $p < 0.05$; RMT faces: $t(37) = 3.74$, $p < 0.01$), attention (TEA EC with distraction: $t(37) = 2.76$, $p < 0.05$), and executive functioning (category fluency: $t(37) = 2.75$, $p < 0.05$; Stroop: $t(35) = 3.49$, $p < 0.01$; Brixton: $t(33) = 4.12$,

Table 2: Patient motor characteristics before and after DBS.

	STN			GPi		
	Before DBS ($n = 28$)	After DBS ($n = 24$)	p	Before DBS ($n = 11$)	After DBS ($n = 4$)	p
UPDRS-III off medication	48.68 ± 14.10	28.67 ± 9.99	0.00	50.73 ± 11.09	35.20 ± 15.32	—
UPDRS-III on medication	17.29 ± 7.967	15.83 ± 7.20	0.49	24.64 ± 10.97	20.75 ± 11.56	—

Table 3: Patient medication characteristics before and after DBS.

	STN ($n = 28$)			GPi ($n = 12$)		
	Before DBS	After DBS	p	Before DBS	After DBS	p
Levodopa-equivalent dosage (mg/d)	1321.82 ± 638.68	863.73 ± 583.92	0.00	1263.40 ± 971.08	1205.10 ± 626.68	0.81
Dopamine agonist treatment (n, %)	15, 46.9%	6, 18.8%	0.01	7, 21.9%	5, 15.6%	0.16

Table 4: Cognitive performance before DBS: proportion impaired in each domain.

Cognitive domain	STN ($n = 28$)	GPi ($n = 12$)	p
Screen	**1, 3.7%**	**5, 41.7%**	**0.01**
IQ	12, 42.9%	8, 66.7%	0.30
Memory	**9, 33.3%**	**9, 75.0%**	**0.04**
Language	1, 3.7%	3, 27.3%	0.07
Perception	2, 7.4%	1, 8.3%	1.00
Attention	5, 18.5%	4, 33.3%	0.42
Executive function	**4, 14.8%**	**8, 66.7%**	**0.01**
Speed	**2, 7.4%**	**4, 36.4%**	**0.05**

Results are given as number and percentage. Chi-squared significant group comparisons are indicated in bold.

$p < 0.01$). Thus, all subsequent analyses of cognitive performance were split according to site of DBS.

As shown in Table 5, there was a significant drop in phonemic and category fluency following both STN and GPi DBS. In the STN patients, there was also a significant decline in performance on Symbol Search, and in the GPi patients, there was also a decline in PIQ. There were also near-significant declines in Stroop performance and VIQ following STN DBS. There were no other significant or near-significant differences in cognitive performance following either STN or GPi DBS.

Case note review revealed mention of decline in cognitive function in 15% ($n = 6$) of patients after DBS (4 STN DBS, 14.3%; 2 GPi DBS, 16.7%). There was no significant association between DBS location and subsequent cognitive decline ($\chi^2(5) = 4.73$, $p = 48$). Number of months elapsed since surgery had a bimodal distribution, with two patients demonstrating marked decline immediately (STN and GPi DBS, resp.), but others demonstrating decline at least a year after surgery ($n = 4$, range = 13–72 months). When considering those who declined immediately, one demonstrated confusion and hallucinations immediately after GPi DBS surgery, thought to be associated with a urinary tract infection and which improved with appropriate treatment consistent with a diagnosis of delirium rather than dementia. However, the other deteriorated physically and cognitively after STN DBS (as confirmed by repeat cognitive assessment), without any subsequent improvement.

3.4. Predictors of Cognitive Decline following DBS. Pearson correlational analysis revealed no significant baseline cognitive, mood, or motor correlates of decline in phonemic fluency after either STN or GPi DBS. Greater decline in category verbal fluency following STN DBS was associated with higher levels of apathy ($r = 0.47$, $p < 0.05$) and levodopa-equivalent dosages at baseline ($r = -0.43$, $p < 0.05$) and greater change in cognitive speed, as indexed by change in performance on both Digit Symbol Coding ($r = 0.49$, $p < 0.05$) and Symbol Search ($r = -0.53$, $p < 0.01$). However, only the correlation between decline in category fluency and Symbol Search survived the Bonferroni adjustment for multiple comparisons. Greater decline in category fluency following GPi DBS was associated with worse UPDRS-III scores off medication at baseline ($r = 0.70$, $p < 0.05$), but this did not survive the Bonferroni adjustment.

There were also no significant baseline correlates of decline in Symbol Search after STN DBS. However, greater decline in PIQ following GPi DBS was associated with slower baseline performance on the Digit Symbol Coding subtest. There were no other significant predictors of decline following DBS.

In order to identify baseline predictors of the subsequent global and irreversible cognitive decline following STN DBS noted in the one patient, Crawford and Howell [106] single-case methodology was used. This revealed that this patient was significantly older (68 years) than the mean age (59.15 years) of the STN DBS patients who remained stable ($t = 1.86$, $p < 0.05$). Indeed, although the baseline neurology assessment revealed no atypical symptoms, it did raise concerns about the older age. MMSE performance was flawless, but the patient demonstrated mild baseline impairments in all domains, including language and visuoperceptual functioning. Indeed, this patient was the only patient to demonstrate baseline impairment in language and subsequently undergo STN DBS. Another patient also demonstrated baseline impairment in visuoperceptual and subsequently underwent STN DBS, which proved successful, but it is noted that this patient was younger (55 years) than the mean age of the STN DBS group.

When considering the remaining patients who demonstrated cognitive decline at least a year after surgery (as identified

Table 5: Cognitive performance before and after DBS: mean scores on each test.

Assessment	STN ($n = 28$)			GPi ($n = 12$)		
	Before DBS	After DBS	p	Before DBS	After DBS	p
MMSE (30)	28.64 ± 1.41	28.64 ± 1.68	1.00[a]	26.75 ± 3.14	25.75 ± 2.87	0.31[a]
WAIS-VIQ	111.21 ± 12.40	107.54 ± 15.93	0.05[a]	92.75 ± 13.10	92.67 ± 10.71	0.97[a]
Vocabulary (66)	51.57 ± 9.61	49.96 ± 10.00	0.13[a]	40.64 ± 15.02	37.27 ± 14.14	0.16[a]
Similarities (33)	**24.71 ± 4.51**	**22.75 ± 5.64**	0.02[a]	19.36 ± 5.43	18.36 ± 5.12	0.43[a]
Arithmetic (22)	**15.61 ± 2.94**	**14.04 ± 4.64**	0.01[a]	10.36 ± 2.94	9.64 ± 3.04	0.90[a]
Digit span (30)	**17.57 ± 4.15**	**16.43 ± 4.26**	0.04[a]	14.08 ± 3.09	14.00 ± 3.16	0.41[a]
WAIS-PIQ	106.37 ± 15.17	104.04 ± 19.57	0.50[a]	**93.64 ± 15.11**	**84.45 ± 12.91**	**0.01[a]**
Picture Completion (25)	17.96 ± 4.25	17.19 ± 4.86	0.33[a]	12.92 ± 3.66	11.33 ± 3.53	0.07[a]
Matrix Reasoning (26)	16.35 ± 5.61	15.31 ± 5.90	0.24[a]	11.10 ± 4.33	9.20 ± 4.21	0.09[a]
RMT-W (50)	46.81 ± 3.50	45.12 ± 5.35	0.10[b]	39.20 ± 9.45	40.30 ± 8.68	0.16[a]
RMT-F (50)	41.88 ± 4.13	41.08 ± 5.68	0.54[a]	33.60 ± 6.85	34.00 ± 7.92	0.80[a]
D&P People delayed (12)	7.21 ± 3.68	7.50 ± 4.30	0.59[b]	6.40 ± 4.65	5.60 ± 3.95	0.57[a]
D&P Shapes delayed (12)	10.50 ± 3.28	10.25 ± 2.82	0.22[b]	8.86 ± 3.63	7.43 ± 3.78	0.30[a]
GNT (30)	23.69 ± 3.42	23.69 ± 3.28	1.00[a]	17.91 ± 8.11	19.45 ± 6.65	0.34[a]
VOSP Silhouettes (30)	22.81 ± 3.25	21.92 ± 3.91	0.13[a]	20.82 ± 3.52	19.00 ± 5.88	0.41[a]
DKEFS FAS (SS)	**13.42 ± 4.89**	**11.54 ± 4.61**	**0.01[a]**	**10.92 ± 5.18**	**8.00 ± 4.88**	**0.01[a]**
DKEFS Category (SS)	**12.31 ± 4.21**	**10.00 ± 4.99**	**0.01[a]**	**8.50 ± 3.00**	**5.00 ± 3.30**	**0.01[a]**
Stroop (112)	91.81 ± 21.36	83.77 ± 22.94	0.06[a]	63.00 ± 20.44	58.50 ± 23.45	0.12[a]
Hayling (SS)	5.68 ± 1.07	5.32 ± 1.52	0.28[b]	4.60 ± 1.84	4.70 ± 1.83	0.89[a]
Brixton (SS)	4.91 ± 1.53	5.00 ± 2.28	0.83[a]	2.33 ± 1.66	2.56 ± 2.07	0.72[a]
TEA EC (7)	6.67 ± 0.96	6.75 ± 0.44	0.85[b]	6.50 ± 1.41	5.88 ± 1.55	0.26[b]
TEA EC-Distraction (SS)	9.91 ± 2.66	8.96 ± 2.92	0.15[a]	7.13 ± 3.14	5.75 ± 1.91	0.17[a]
WAIS-SS (SS)	**9.62 ± 2.25**	**8.46 ± 2.82**	**0.02[a]**	7.89 ± 3.33	6.11 ± 2.42	0.86[a]
WAIS-DSC (SS)	8.20 ± 2.52	7.48 ± 2.65	0.22	4.89 ± 2.67	4.67 ± 1.87	0.86[a]

Results are given as mean ± SD ([a]paired t-test; [b]Wilcoxon signed-rank). Significant differences are indicated in bold. MMSE: Mini-Mental Status Examination; WAIS-VIQ, PIQ: Wechsler Adult Intelligence Scale-Third Edition-Verbal IQ, Performance IQ; RMT-W, F: Warrington Recognition Memory Test for Words, Faces; D&P: Doors and People Test; GNT: Graded Naming Test; VOSP: Visual Object and Space Perception Battery; DKEFS: Delis–Kaplan Executive Function System; SS: scaled score; TEA EC, ECD: Test of Everyday Attention Elevator Counting, Elevator Counting with Distraction; WAIS-III SC, DSC: Wechsler Adult Intelligence Scale-Third Edition Symbol Search, Digit Symbol Coding.

Table 6: Mood scores before and after DBS.

Assessment	STN ($n = 28$)			GPi ($n = 12$)		
	Before DBS	After DBS	p	Before DBS	After DBS	p
HADS anxiety (21)	7.50 ± 3.23	6.27 ± 4.85	0.19[b]	8.55 ± 3.30	9.00 ± 4.12	0.69[a]
HADS depression (21)	6.15 ± 4.42	6.00 ± 4.04	0.86[a]	7.00 ± 3.85	7.73 ± 4.63	0.67[a]
Apathy (54)	10.75 ± 6.02	13.96 ± 11.16	0.15[b]	14.57 ± 6.71	20.86 ± 11.11	0.67[a]

Results are given as mean ± SD ([a]paired t-test; [b]Wilcoxon signed-rank).

in the case note review), no significant difference in demographics or cognitive performance at baseline was identified.

3.5. Mood before and after DBS. Baseline mood assessment revealed high rates of anxiety disorder ($n = 22$, 56.4%), depression ($n = 14$, 35.9%), and apathy ($n = 14$, 38.9%) but no significant association between frequency of mood disorder and subsequent DBS location. There were also no significant differences in anxiety, depression, or apathy mean scores between the two surgery groups after DBS (Table 6). Case note review indicated mention of mood and/or motivation disorder in a high proportion of patients following DBS (STN: $n = 17$, 60.7%; GPi: $n = 8$, 66.7%), documented a mean of 23.16 months (SD = 18.09) after surgery. There was no significant association between DBS location and likelihood of mood disorder and no significant difference in time since surgery between the two DBS patient groups.

Incidence of case note indication of cognitive impairment or mood disorder, as a function of time, is depicted in Figure 1.

One patient also developed de novo impulse control disorder, namely, hypersexuality, after GPi DBS.

3.6. Predictors of Mood Disorder following DBS. Patients who had subsequent mood disorder were found to have significantly higher baseline levels of depression ($t(36.65) = -0\ 3.56$, $p < 0.01$) and underwent a greater reduction in levodopa medication than those who did not ($t(30) = -3.43$, $p < 0.01$; Figure 2). There were no other significant baseline predictors of subsequent mood disorder, including DBS target.

Logistic regression confirmed these as significant predictors of subsequent mood disorder ($\chi^2(2) = 24.13$, $p < 0.001$), explaining 72.2% of the variance (Nagelkerke R^2). Significant and independent associations were found

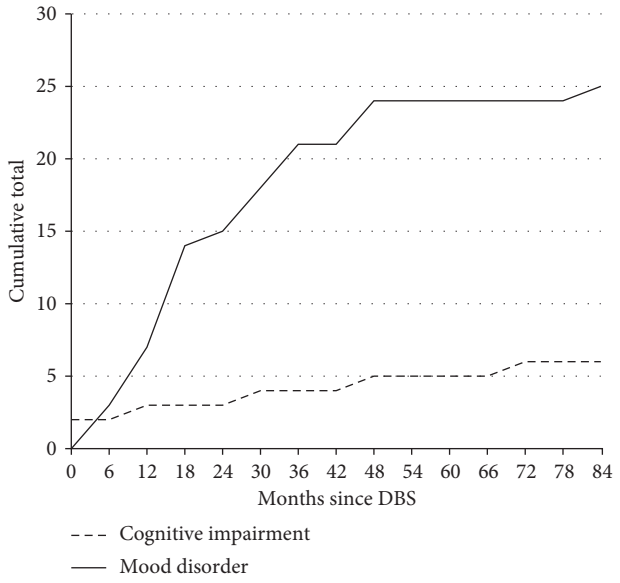

Figure 1: Cumulative cases of cognitive impairment and mood disorder as a function of time following DBS.

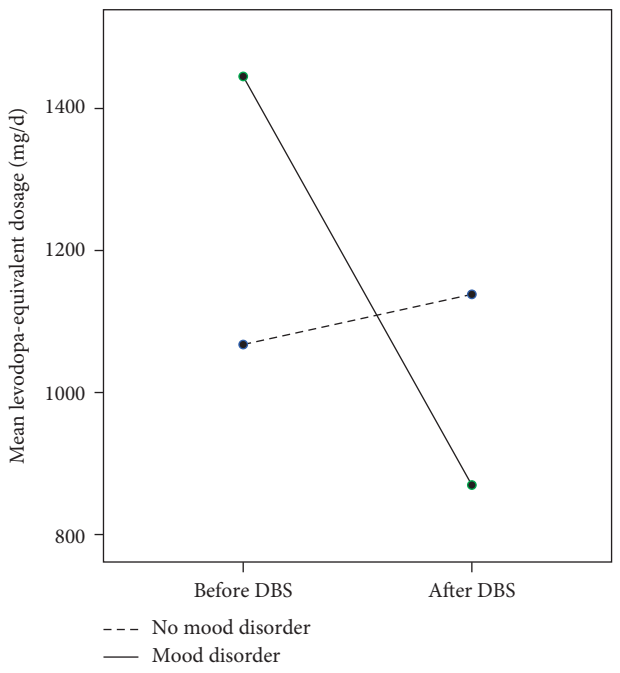

Figure 2: Mean levodopa-equivalent dosage of patients before and after DBS in patients split according to subsequent onset of mood disorder.

for both baseline depression ($p < 0.05$; odds ratio: 2.23; 95% confidence intervals: 1.17–4.25) and levodopa reduction ($p < 0.05$; odds ratio: 1.00; 95% confidence intervals: 1.00–1.00). Classification analysis revealed only one false negative.

The patient who developed impulse control disorder following GPi DBS did not experience a reduction in levodopa-equivalent dosage but rather an increase, with ongoing dopamine agonist treatment.

4. Discussion

Neuropsychological assessment is considered to be an important part of the screening for selection of candidates for DBS. However, to the best of our knowledge, no standardised assessment procedure currently exists, with many studies relying upon brief screening tools only. Neuropsychological screening should comprise tests with sufficient reliability and validity, which are sensitive to cognitive impairment and dementia in PD, able to disambiguate between PD and other disorders, including atypical Parkinsonian syndromes, and be sensitive to the changes in cognitive and mood functioning associated with DBS.

In this study, we examined the use of our standardised neuropsychological assessment in a sample of patients undergoing DBS for PD. Our assessment tested a wide range of neuropsychological domains, including general intellectual functioning, verbal and visual recognition and recall memory, language, visuoperceptual functioning, attention, verbal fluency, executive functioning, and speed of processing. The tests were all standardised, with adequate psychometric properties, easy to administer, and suitable for routine clinical services.

Our neuropsychological assessment was sensitive to the cognitive impairment found in PD. At baseline, we documented frequent impairments in intellectual functioning, memory, attention, and executive function, with more frequent impairments, as expected, in the GPi group. Indeed, only six of all DBS patients (15%) did not demonstrate impairment in at least one cognitive domain. Despite this only one patient demonstrated immediate and irreversible cognitive decline following DBS. This highlights the limitation of using the presence of any baseline cognitive impairment as an exclusionary criterion for DBS. As low test scores may reflect a number of cognitive and noncognitive variables, such as high levels of fatigue, low scores on any one test should not be used to preclude surgery.

Our neuropsychological assessment was also sensitive to the cognitive impairments that warrant caution before proceeding with DBS. In the patient who demonstrated immediate and irreversible global cognitive decline, single-case statistics revealed that this patient was significantly older than the mean age of those who remained stable and had greater deficits in language and visuoperceptual processing at baseline. Of course, this is a single case, and therefore, these results may not be generalizable, but this finding supports earlier reports that decline in cognitive functioning following DBS is more common in patients who are older [12, 28, 29, 34] and who have greater or more encompassing cognitive deficits at baseline [36, 68].

Although previous guidance on patient selection has tended to focus on memory impairment as a core contraindication for surgery [45, 124], PD patients often demonstrate patchy performance on tests of memory, likely reflecting the role of frontosubcortical-mediated cognition on memory functioning [107]. In our study, we observed common impairments in memory at baseline, but frank deficits in language and visuoperceptual processing were considerably less common and likely betrayed a greater level

of general cognitive impairment. Previous guidance has warned that lower cognitive functioning at baseline is predictive of poorer cognitive outcome, but hitherto, there have been no recommendations on what level of impairment should constitute a contraindication to surgery. Our data suggest that, when using the present neuropsychological assessments, caution must be advised if any deficits are revealed in language and/or visuoperceptual processing (scores <5th percentiles), particularly in patients who are older and under consideration for STN DBS.

Previous studies describing negative cognitive outcomes following DBS may have failed to identify such risk factors because of insufficient scrutiny of baseline cognitive performance. Previous reports of immediate and global decline following DBS have often stated that such deterioration has occurred despite satisfactory performance on neuropsychological testing at baseline [11, 12]). Closer examination reveals that such testing has often been limited to a few screening measures of cognitive function (e.g., the MMSE) or focused on executive function, rather than explicitly assessing the presence of impairment in others, more atypical domains, such as language and visual processing. For example, York and colleagues [12] report the immediate and global cognitive decline in one gentleman aged 73 years but limit discussion of baseline cognitive performance to MMSE only, which was notably intact with a score of 28/30.

In keeping with this, our patient who demonstrated immediate and permanent cognitive decline performed flawlessly on the MMSE and performed poorly on only two out of four tests of executive function but demonstrated unexpected impairments, most clearly in language and visual perception. This underlines the importance of a broad neuropsychological assessment, interrogating a wide range of cognitive domains, to reveal the full cognitive profile.

Our neuropsychological assessment was also sensitive to the changes in cognitive functioning associated with DBS. Pre- and after DBS assessments revealed that alongside improvements in the motor status and medication load are noted in the STN group at least, and our assessment detected significant declines in verbal fluency in both groups following DBS. This confirms the mild changes frequently noted in this cognitive function following DBS [18, 35].

Although the exact cause of verbal fluency decline remains unclear, it has been linked with reductions in self-generation [18, 22]. Accordingly, the present study found that greater decline in verbal fluency was associated with higher levels of apathy at baseline. Although this did not persist after the Bonferroni adjustment for multiple comparisons, several studies have described increases in apathy following DBS [16, 18, 22, 60, 108–110]. Such behavioural adynamia, as witnessed by the reduced fluency and increased apathy, may in part relate to changes in cognitive speed [29]. We found that reduction in fluency was significantly associated with greater changes on at least one measure of speed of processing. These changes did not seem to simply reflect withdrawal of dopaminergic medication [111, 112], as although reductions in verbal fluency were related to higher levels of baseline levodopa dosage and there was no correlation with change in dosage following DBS. It has also been suggested that the surgery itself may contribute to increases in apathy [60, 113], possibly caused by microlesions to the subthalamic area during implantation of the electrode [114].

Irrespective of the underlying mechanism, deterioration in verbal fluency can deleteriously affect activities of daily living and quality of life [115] and is correlated with reduced independence in everyday functional tasks [116]. Therefore, it is recommended that patients and their families are counselled about this significant risk before deciding to proceed with surgery, particularly those who present with higher levels of apathy at baseline.

In addition to this finding of reduced verbal fluency, our assessment detected declines in other aspects of cognitive functioning. Specifically, STN patients demonstrated significant slowing on the Symbol Search test and near-significant slowing on the Stroop and reduction in VIQ. GPi patients demonstrated significant reductions in PIQ. These findings confirm a slowing in the STN patients at least. In the absence of any other focal deficits, the heterogeneous reductions in performance on the WAIS (in both DBS groups) may also reflect the composite nature of this measure and the effortful, sustained, and speeded aspects of attentional functioning that it requires. Such reductions in speed of processing after DBS have rarely been discussed as most studies investigating cognitive changes have failed to include any measure of processing speed [115]. In previous studies, there have been conflicting reports of faster responding following STN DBS. However, further inspection suggests this may be due to a speed-accuracy trade-off [1, 117]. In our study, we have shown that deleterious changes in speed of processing are present, with likely important consequences for general intellectual functioning.

When considering the patients who went on to report cognitive decline at least a year after surgery (as identified by case note review), there were no significant predictors at baseline. This may suggest that the observed decline reflects the normal progression of the disease, rather than any preexisting vulnerability in the cognitive profile. It is important to recognise that the case note review was limited to qualitative and subjective comments only, precluding comment on the severity of any cognitive decline. However, the current findings do support previous studies which suggest that the risk of developing dementia following DBS is equivalent to that in medically treated patients [34, 118, 119]. This should be validated through future research that involves a medically treated control group.

Our study indicated no significant changes in mood or apathy, as measured by questionnaires, following DBS. However, case note review revealed a very high incidence of depression, anxiety, and/or apathy after surgery. These contrasting findings may be explained by the fact that assessment of mood relied upon self-reported symptoms of depression, anxiety, or depression, whereas case note review simply indicated clinicians' observations. Discrepancy between self- and proxy-ratings of mood in Parkinson's disease has been reported previously [45, 120, 125] and may be explained by patients' lack of insight and cognitive dysfunction [121].

Mood disorder emerging after DBS has been largely attributed to reduction in dopaminergic medications [111, 112]. Accordingly, we found that deterioration in mood was significantly correlated with reductions in levodopa medication, irrespective of DBS location. There was no association with discontinuation of dopamine agonists, suggesting that overall levodopa load was more important than the type of medication. These findings are in keeping with previous reports of mood disorder occurring as a nonmotor dopamine withdrawal syndrome after DBS [70, 112].

Furthermore, the chance of developing mood disorder, as identified in the case notes, was even higher in those who endorsed clinically significant levels of depression at baseline. This may suggest that those who have a preexisting vulnerability in mood are at high risk of developing profound mood disorder following DBS. Of course, the high incidence of mood disorder as noted in the case notes may simply reflect clinicians' recognition of (stable) low mood. However, its timing of onset and high incidence is consistent with several other studies [22, 59, 60, 122]. Therefore, we recommend careful and systematic longitudinal psychological follow-up for all PD DBS patients.

High levels of postoperative apathy or mood disorder can negate any improvement in quality of life [63, 126], but few studies have researched the presence of any baseline correlates of such decline. This study has found that a higher rating of depression at baseline is a predictor of poorer psychosocial outcome following DBS. We found high rates of depression, apathy, and anxiety in our patients at baseline, which may reflect elements of both reactive mood disorder and dysregulation of reward and motivation processing [123]. Indeed, previous research has suggested that mood disorder following DBS may reflect the effects of impaired extrastriatal dopaminergic pathways not sufficiently compensated for by STN stimulation [70]. Therefore, we would suggest that rather than excluding such patients from DBS, any dopamine withdrawal following surgery should be done cautiously.

One of our patients developed de novo impulse control disorder following GPi DBS. The onset of hypersexuality occurred in the context of increased levodopa dosages following surgery, with ongoing use of dopamine agonists. Our findings were of course limited to clinician ratings only and may have missed other cases. Future research should further investigate the incidence of impulse control disorder following DBS by using a semistructured interview, such as the QUIP [127]. Nevertheless, this case reflects the challenges of balancing treatment of motor and nonmotor symptoms in PD (cf. [128]).

4.1. Recommended Battery. Following our findings, we propose an abbreviated version of our neuropsychological protocol, suitable for routine clinical use. We recommend that this protocol includes our measures of current and premorbid intellectual functioning (prorated version of the WAIS-III, NART-R) to gauge overall level of intellectual decline; memory recognition and recall (RMT Words and Faces and D&P People and Shapes) to ensure cognitive profile is not amnestic and thus atypical for PD; language and visuoperceptual function (GNT and VOSP Silhouettes) to detect the identified red flags for DBS; verbal fluency (DKEFS FAS and Category) and another measure of executive function (Stroop) to determine severity of executive dysfunction; speed of processing (Digit Symbol Coding and Symbol Search); and measures of mood and behavioural functioning, targeting depression, apathy (HADS and AES), and impulse control disorder (using a measure such as the QUIP). Of course, analysis of neuropsychological performance should consider any relevant cultural or linguistic factors, and it may be appropriate to replace some of the present neuropsychological assessments with suitable substitutions for specific populations.

5. Conclusion

This study has presented a standardised neuropsychological assessment procedure suitable for the selection of appropriate candidates with PD for DBS and identified clear baseline risk factors for subsequent decline in cognitive functioning and mood.

Conflicts of Interest

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

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Review Article

Apathy following Bilateral Deep Brain Stimulation of Subthalamic Nucleus in Parkinson's Disease: A Meta-Analysis

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Bilateral deep brain stimulation of subthalamic nucleus (STN-DBS) has proven effective in improving motor symptoms in Parkinson's disease (PD) patients. However, psychiatric changes after surgery are controversial. In this study, we specifically analyzed apathy following bilateral STN-DBS in PD patients using a meta-analysis. Relevant articles utilized for this study were obtained through literature search on PubMed, ScienceDirect, and Embase databases. The articles included were those contained both pre- and postsurgery apathy data acquired using the Starkstein Apathy Scale or Apathy Evaluation Scale with patient follow-up of at least three months. A total of 9 out of 86 articles were included in our study through this strict screening process. Standardized mean difference (SMD), that is, Cohen's d, with a 95% confidence interval (CI) was calculated to show the change. We found a significant difference between the presurgery stage and the postsurgery stage scores (SMD = 0.35, 95% CI: 0.17~0.52, $P < 0.001$). STN-DBS seems to relatively worsen the condition of apathy, which may result from both the surgery target (subthalamic nucleus) and the reduction of dopaminergic medication. Further studies should focus on the exact mechanisms of possible postoperative apathy in the future.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease and is characterized by bradykinesia, rigidity, resting tremors, and postural instability [1]. In addition to these motor symptoms, PD patients also suffer from many nonmotor symptoms including mood and behavior disorders, cognitive changes, autonomic system-failure, sensory symptoms, and sleep disturbances [2–4]. Following long-term treatment using antiparkinsonian medications, the presence of dyskinesia and symptom fluctuations becomes a major therapeutic challenge. Thus, deep brain stimulation (DBS) has recently become a preferable surgical therapy to treat PD. The globus pallidus internus (GPi) and the subthalamic nucleus (STN) are the main targets of the stimulating loci [5]. Neurosurgeons implant the electrodes using an approach that combines intraoperative recording and stimulation. The targets are identified using preoperative magnetic resonance imaging and intraoperative electrophysiological recordings [6].

It has been well established that bilateral deep brain stimulation of subthalamic nucleus (STN-DBS) significantly improves the primary motor symptoms as well as some nonmotor symptoms, such as sensory symptoms and sleep disturbances [7, 8]. However, apathy, a common mood disorder in PD patients after bilateral STN-DBS, is controversial. Apathy has been described as a quantitative reduction in purposeful behaviors and self-generated voluntary actions [9], which cannot be attributed to any impairment of consciousness or any emotional or cognitive disorder [10]. Apathy is also known to significantly increase burden on caregivers and has negative effects on treatment and long-term outcome [11, 12].

Many studies have reported increases in apathy after STN-DBS [13–18], while others show opposite outcomes [19–21]. Neurologists cannot forecast this behavioral outcome when advising surgery to their patients and patients'

family. Therefore, we performed this quantitative meta-analysis with strict inclusion criteria to study the effect of bilateral STN-DBS on apathy and expected to draw a conclusion and provide useful reference for clinical practice.

2. Materials and Methods

2.1. Search Strategy. Literature searches of the PubMed, ScienceDirect, and Embase databases up to January 2017 were performed to identify relevant articles published in English. The search terms were ("bilateral deep brain stimulation" OR "bilateral subthalamic stimulation") OR (bilateral stimulation AND "subthalamic nucleus") AND ("Parkinson disease" OR "Parkinson's disease") AND "apathy". In addition, we searched the references of the identified studies to find other satisfactory studies. This task was completed by two reviewers independently. When disagreements arose, a third reviewer was consulted.

2.2. Inclusion and Exclusion Criteria. The inclusion criteria were the following: (1) Full-text publications written in English, (2) At least 10 patients in the study, (3) The patients were followed up for at least 3 months, (4) presurgery and postsurgery apathy data obtained through the Starkstein Apathy Scale or Apathy Evaluation Scale (The Starkstein Apathy Scale consists of 14 questions and was designed specifically for patients with PD. Scores range from 0 (least severe apathy) to 42 (most severe apathy). A score of 14 or greater indicates clinically significant apathy [22]. The Apathy Evaluation Scale contains 18 questions with scores ranging from 18 to 72, and a higher score is associated with a worse condition [23].), (5) The data were analyzed in the form of mean and standard deviation, (6) The missing data could be obtained using definite methods written in the Cochrane handbook [24].

The exclusion criteria were (1) reviews, meta-analysis, book chapters, letters to the editor, or case reports with no original data, (2) duplicate reports with identical data, (3) data from nonhuman species, and (4) insufficient original data.

2.3. Quality Assessment. Two reviewers evaluated the quality of the studies using the Methodological Index for Non-randomized Studies (MINORS). The MINORS covers 8 different areas, and each area is scored 0(not reported), 1 (reported but inadequate), or 2 (reported and adequate). A score greater than 10 indicates a good quality study [25].

2.4. Extraction. The data were extracted from the selected articles by two researchers independently, while differences were resolved by consulting a third reviewer. The following information was extracted: first author's name, year of publication, sample size, patient characteristics, time of following up, DBS programming, the state (on/off) in the postoperative evaluation, and the relevant presurgery and postsurgery apathy data.

2.5. Statistical Analysis. We combined the results of each article using standard meta-analytic methods to estimate the overall efficacy, tolerability, and safety of STN-DBS. STATA statistics software (Version 12.0, Stata Corporation, College Station, Texas 77,845 USA) was used to analyze available data. The data collected on apathy using the Starkstein Apathy Scale or the Apathy Evaluation Scale were considered continuous data. Since there were two scales used in our study, an estimate of the combined effect sizes utilizing standardized mean difference (SMD), that is, Cohen's d, was given, with a 95% confidence interval (CI). SMD, a standard statistic, was used to show the comparisons of presurgery and postsurgery change. This value reflects an intervention-induced change of the outcome on an average and is used as a summary statistic in meta-analysis when the studies were measured in different ways [26]. The Q-test and I^2-statistics were used to evaluate the degree of heterogeneity between studies. The fixed-effects model was employed if $I^2 < 50\%$; otherwise, the random-effects model was used [27]. Sensitivity analysis was performed by excluding each study and reanalyzing the remaining studies. Begg's test, which measures funnel plot asymmetry, was used to assess publication biases. A value of <0.05 for Begg's test was considered statistically significant publication bias [28].

3. Results

3.1. Characteristics of Eligible Studies. Overall, 86 articles were initially retrieved. After reviewing titles and abstracts, 29 articles, 4 case reports, 6 reviews, and 1 book chapter were excluded. After reading the full-texts of the remaining articles, 9 studies met all of our inclusion criteria and were picked up for this meta-analysis. Figure 1 shows the flow chart of the screening process.

All the included studies were follow-up type studies, with following up time ranging from 3 months to 17 months. The sample size was 253, and 111 patients (44%) were assessed using the Starkstein Apathy Scale, the others using the Apathy Evaluation Scale. All PD patients involved underwent bilateral STN-DBS and were evaluated in the state of drug on and drug on/stimuli on before and after surgery. The main areas studied are described in Table 1.

Table 2 shows the results from 9 included articles evaluated using MINORS analyses on 8 different areas. All studies had clearly stated aims, prospective collections of data, endpoints appropriate to the aim of the study, and follow-up periods appropriate to the aim of the study. Although not all trials had inclusion of consecutive patients and unbiased assessments of the study endpoint, the total scores show a good quality of each study.

3.2. Quantitative Synthesis. The heterogeneity between the included studies showed that $I^2 = 21.1\%$; therefore, the fixed-effects model was used to count the pooled SMD. Based on the comparison of preoperative and postoperative change, we found that there was a significant difference in the score between the presurgery stage and the postsurgery stage (SMD = 0.35, 95% CI: 0.17~0.52, $P < 0.001$) (Figure 2).

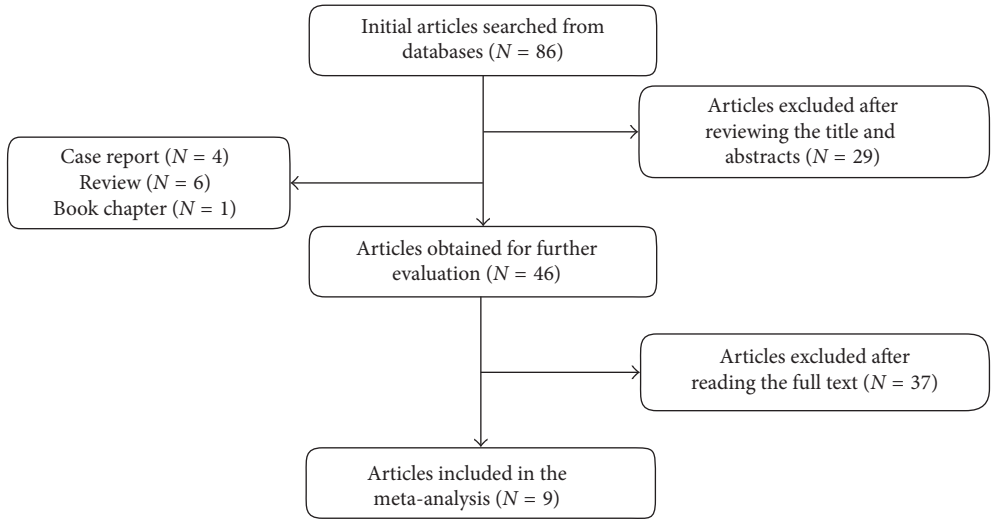

Figure 1: Flow chart of eligible articles.

Further subgroup analysis showed that follow-up did not have an effect on the condition of apathy ($p = 0.256$).

In the sensitivity analysis, each study was omitted by turns to show the influence of every article contributing to this meta-analysis. No significant alterations were found in the pooled SMD, which showed a high level of stability of this meta-analysis. Begg's test was used to assess publication bias, and the funnel plot was approximately symmetric, indicating that there was no publication bias(Figure 3).

4. Discussion

In recent years, bilateral STN-DBS has been performed widely in order to treat advanced PD patients. STN-DBS involves the application of electrical stimuli, with specific pulse amplitude, duration, and frequency to produce a functional lesion within the subthalamic nucleus [29]. Compared to the conventional pharmacotherapy, it can afford to decrease motor fluctuations, reduce "off" time, and show improvement in dyskinesia [30]. There are several meta-analyses examining the postoperative condition of PD patients. Tan et al. and Xie et al. reported that STN-DBS could improve Unified Parkinson's disease rating scale III (UPDRS-III) scores and quality of life (QOL) and allow recovery of verbal fluency [31, 32]. Many published meta-analyses have showed evidence for an adverse effect on cognition, depression and anxiety [33–35]. The present article is, to our knowledge, the first meta-analysis focusing on the effects of DBS on apathy.

Apathy is defined as a lack of motivation characterized by diminished goal-oriented behavior and cognition and reduced emotional expression [36]. The prevalence of apathy in PD varies from 17% to 70% depending on the sample populations, diagnostic criteria, and evaluation tools utilized [7]. PD caregivers live with a burden resulting from the apathy condition of patients, similar to the caregivers of other neurological disorders. Apathy also has negative effects on treatment and long-term outcome. Neurologists should carefully consider the target of choice for PD patients who are eligible for DBS as a means to overcome the adverse effect of long-term treatment of antiparkinsonian medication [11, 12]. Specifically, attention should be paid to the change in apathy following bilateral STN-DBS in PD as it has implications for treatment and care. The apathetic scales we used in this study are the Starkstein Apathy Scale and the Apathy Evaluation Scale: the former was designed specifically for PD patients and the latter is regarded as the most psychometrically robust apathy scale [37].

The present meta-analysis included 9 studies containing 253 PD patients comparing the differences in apathy between presurgery and postsurgery patients. Through strict methodological and statistical analysis, our data suggested that there was a statistical significant difference in the scores between the presurgery stage and the postsurgery stage (SMD = 0.35, 95% CI: 0.17~0.52, $P < 0.001$), which means that bilateral STN-DBS did seem to worsen the PD patients' apathetic condition. However, the subgroup analysis of the relationship between follow-up and the change in apathy score failed to support this conclusion ($p = 0.256$).

We were not able to draw a conclusion about the clinical significance of the finding. There are several limitations of this article. First, the studies included were all follow-up studies, not randomized controlled trails with control groups, which hindered us from analyzing whether the progression of PD played a role in the change of apathy, nor do levodopa equivalent daily dose (LEDD) or other confounding factors. Second, due to the limited sample size, the power that was used to detect a true difference between presurgery and postsurgery may be not strong. Additionally there were only a few studies in the subgroup analysis resulting in a low statistical power when analyzing the effect of follow-up on the condition of apathy.

STN-DBS seemed to worsen the condition of apathy regardless of the follow-up, and we attempted to unravel the

Table 1: Characteristics of the eligible studies.

Number	Author	*N*	Age	Disease duration	DBS programming	State in the evaluation	Scale	Follow-up	Preoperative score	Preoperative LEDD	Postoperative score	Postoperative LEDD
1	Houvenaghel et al. [21]	26	56.6 ± 7.4	11.47 ± 4.54	Bilateral STN-DBS	Drug on and stimuli on	AES	3 months	31.8 ± 7.0	1271.2 ± 555.6	31.2 ± 7.7	758.0 ± 407.79
2	Robert et al. [20]	44	56.3 ± 7.5	11.4 ± 4.1	Bilateral STN-DBS	Drug on and stimuli on	AES	3 months	31.4 ± 6.4	1280.8 ± 632.4	31.6 ± 7.1	889.9 ± 209.3
3	Lewis et al. [17]	27	61.1 ± 9.1	12.7 ± 6.7	Bilateral STN-DBS	Drug on and stimuli on	AES	1 year	34.04 ± 9.58	831.5 ± 425.91	37.44 ± 8.71	359.23 ± 264.46
4	Lewis et al. [18]	28	61.1 ± 8.9	12.43 ± 6.74	Bilateral STN-DBS	Drug on and stimuli on	AES	1 year	33.85 ± 9.71	832 ± 426	37.0 ± 8.91	359.3 ± 264.5
5	Lhommee et al. [16]	67	57.8 ± 7.2	10.5 ± 3.1	Bilateral STN-DBS	Drug on and stimuli on	SAS	1 year	6.2 ± 3.5	1026 ± 459	9.4 ± 4.5	284 ± 312
6	Chou et al. [19]	10	62.1 ± 6.5	9.1 ± 5.8	Bilateral STN-DBS	Drug on and stimuli on	SAS	6 months	13.2 ± 8.6	1164.9 ± 752.9	13.6 ± 7.4	567.9 ± 512.4
7	Drapier et al. [15]	17	56.9 ± 8.7	11.8 ± 2.6	Bilateral STN-DBS	Drug on and stimuli on	AES	3 months	37.2 ± 5.5	-	42.5 ± 8.9	-
8	Castelli et al. [14]	19	62.1 ± 4.2	14.7 ± 5.0	Bilateral STN-DBS	Drug on and stimuli on	SAS	17 months	11.6 ± 4.1	1192.5 ± 415.7	12.6 ± 5.3	571.6 ± 274.8
9	Drapier et al. [13]	15	59.7 ± 7.6	12.2 ± 2.8	Bilateral STN-DBS	Drug on and stimuli on	SAS	6 months	13.0 ± 6.5	1448 ± 400	18.8 ± 9.7	1127 ± 482

AES: Apathy Evaluation Scale; SAS: Starkstein Apathy Scale.

Table 2: MINORS scores of eligible studies.

Number	A	B	C	D	E	F	G	H	Total
1 [21]	2	0	2	2	0	2	2	1	11
2 [20]	2	2	2	2	0	2	2	1	13
3 [17]	2	0	2	2	0	2	1	1	10
4 [18]	2	0	2	2	0	2	2	0	10
5 [16]	2	0	2	2	0	2	2	1	11
6 [19]	2	0	2	2	0	2	2	1	11
7 [15]	2	0	2	2	0	2	2	1	11
8 [14]	2	2	2	2	0	2	2	0	12
9 [13]	2	0	2	2	0	2	2	0	10

A: a clearly stated aim; B: inclusion of consecutive patients; C: prospective collection of data; D: endpoints appropriate to the aim of the study; E: unbiased assessment of the study endpoint; F: follow-up period appropriate to the aim of the study; G: loss to follow-up less than 5%; H: prospective calculation of the sample size.

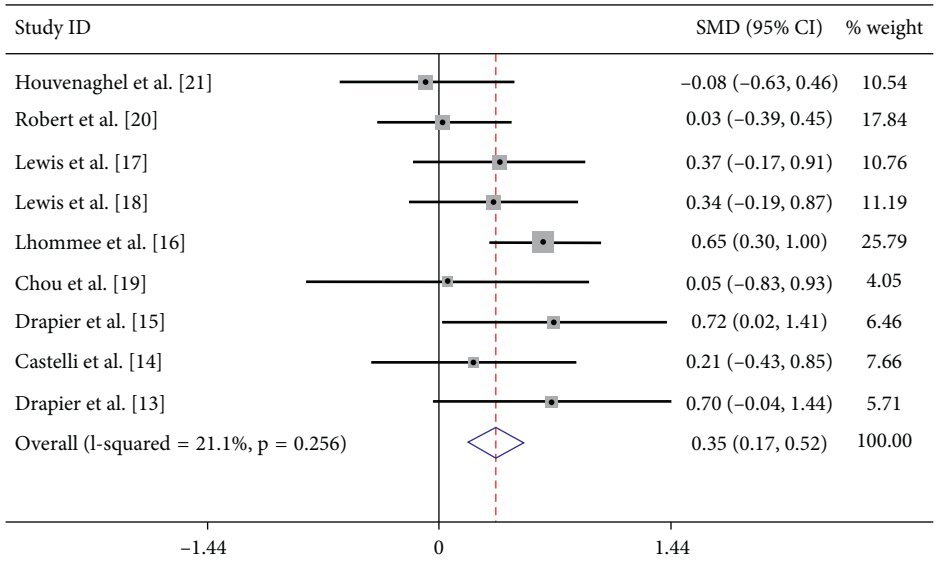

Figure 2: Forest plot for the change in apathy observed presurgery and postsurgery.

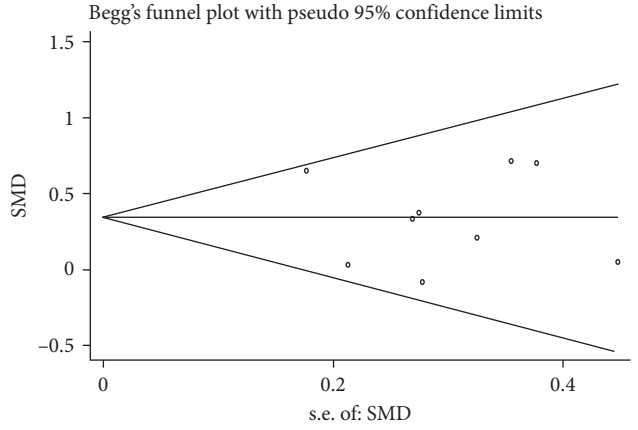

Figure 3: Funnel plot for publication bias in selection of studies.

reasons why some articles reported that apathy scores in PD were worsened after bilateral STN-DBS. The exact mechanisms of changes to apathy after surgery remain unclear.

Successful STN-DBS is accompanied by a decrease of dopaminergic medication at all times resulting from improvement of patients' motor symptoms, which suggests that a dopaminergic deficit may be an explanation for the pathogenesis of some forms of apathy [38]. Thobois et al. exposited that early postoperative apathy corresponds to a dopaminergic abstinence syndrome caused by a postoperative reduction in dopaminergic medication which discloses presynaptic degeneration of mesolimbic dopaminergic terminals [39]. Czernecki et al. performed a trial with ropinirole, a selective dopaminergic agonist (DA), showing that the reduction of dopaminergic medication may induce postoperative apathy [40]; however, the study had a small sample size. In another study, researchers found addition of DAs in the patients who suffered from more severe apathy after STN-DBS might lead to confusion rather than improvement [41]. Accounting for this, Carriere et al. wrote in their article that there were PD patients with either dopaminergic apathy (related to dopaminergic limbic denervation) or dopa-resistant apathy (related to striatal limbic atrophy), the latter of which may be related to more extensive spread of the disease [42].

Researchers did not make a conclusion about the exact relationship between post-DBS apathy and reduction of

dopaminergic medication after surgery. More studies pay attention to the operation targets to explain the apathic condition after STN-DBS. The STN is described to play an important role in each of the five corticobasal ganglia-thalamocortical circuits, each of which have specific motor, oculomotor, associative, or limbic functions [43]. There are three functional domains of STN: sensorimotor (dorsolateral), limbic (medial), and cognitive-associative (ventromedial) [44, 45]. Drapier et al. has reported that apathetic patients after surgery are stimulated more ventrally and internally in STN, as opposed to the nonapathetic patients who are stimulated closer to the dorsolateral area [13]. For other surgery targets, previous studies provided contrary outcomes in regards to the change between presurgery and postsurgery scores. Lozachmeur et al. found there was no significant difference between presurgery and postsurgery assessments for apathy when they chose GPi to be the target [46]. However, many studies have found that the STN-DBS is superior at reducing the LEDD compared to GPi-DBS [47–49]. The smaller reduction of dopaminergic medication after GPi-DBS may weaken the worse score after surgery when compared to the condition of STN-DBS. As mentioned above, we can speculate that both the surgery target (subthalamic nucleus) and the reduction of dopaminergic medication are involved in the apathetic condition after STN-DBS.

In conclusion, the condition of apathy seems to be worsened following bilateral STN-DBS in PD. Further studies should focus on the exact mechanisms of apathy following bilateral STN-DBS. Considering the limitations mentioned above, further studies with more specific information and larger sample sizes should be carried out, and caution should be taken in interpreting our findings.

Conflicts of Interest

The authors report no conflicts of interest in this work.

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Research Article

Sensitivity and Specificity of the ECAS in Parkinson's Disease and Progressive Supranuclear Palsy

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Disentangling Parkinson's disease (PD) and progressive supranuclear palsy (PSP) may be a diagnostic challenge. Cognitive signs may be useful, but existing screens are often insufficiently sensitive or unsuitable for assessing people with motor disorders. We investigated whether the newly developed ECAS, designed to be used with people with even severe motor disability, was sensitive to the cognitive impairment seen in PD and PSP and able to distinguish between these two disorders. Thirty patients with PD, 11 patients with PSP, and 40 healthy controls were assessed using the ECAS, as well as an extensive neuropsychological assessment. The ECAS detected cognitive impairment in 30% of the PD patients, all of whom fulfilled the diagnostic criteria for mild cognitive impairment. The ECAS was also able to detect cognitive impairment in PSP patients, with 81.8% of patients performing in the impaired range. The ECAS total score distinguished between the patients with PSP and healthy controls with high sensitivity (91.0) and specificity (86.8). Importantly, the ECAS was also able to distinguish between the two syndromes, with the measures of verbal fluency offering high sensitivity (82.0) and specificity (80.0). In sum, the ECAS is a quick, simple, and inexpensive test that can be used to support the differential diagnosis of PSP.

1. Introduction

It has now been over 50 years since progressive supranuclear palsy (PSP) was first described as a progressive neurological disorder with motor, ocular, and cognitive features [1]. Clinically, it remains difficult to distinguish from Parkinson's disease (PD) [2, 3], particularly in the early stages [4]. Even when using agreed criteria, the accuracy of diagnosis is not 100% [5]. As it has a significantly worse prognosis than PD, with a more rapid progression [6], early detection is crucial for enabling access to appropriate interventions and support, as well as identifying patients suitable for clinical trials. In the absence of any disease-specific biomarkers, there is a need for a quick, simple, and inexpensive test that can be used for the differential diagnosis of PSP.

Both PSP and PD are characterised by extrapyramidal syndromes, each of which can comprise symptoms of bradykinesia, rigidity, and/or postural instability [7]. Both disorders can feature eye movement abnormalities, and although the presence of the supranuclear vertical gaze palsy in PSP is diagnostically helpful, it is not universal [8, 9] and may be absent until quite late in the disease [10]. Although

both disorders are thought to feature some similar cognitive signs, there is evidence to suggest that the specific cognitive profile may be a useful distinguishing feature [11].

Early cognitive impairment is a feature of PSP, which may precede the motor or ocular signs [12]. The profile is mainly that of executive dysfunction [13] and cognitive slowing [14], with markedly reduced verbal fluency [15, 16]. Deficits in other domains, including memory [17], language [18–20], visuospatial [16, 18], and social cognition [21–23], have also been reported.

In contrast, early stages of PD are characterised by only mild deficits in executive functions [24–27], but with illness progression, there is evolution from a mild cognitive impairment (MCI) to dementia, with greater involvement of posterior-based visual functions [28–30].

Existing screens of cognitive functioning can be criticised for being insufficiently sensitive to the cognitive profile of both PD and PSP. For example, the most widely used cognitive screen, the MMSE [31], has no measure of verbal fluency. Both the MMSE and the Addenbrooke's Cognitive Examination [32] have inadequate assessment of executive function. Their ensuing ceiling effects give them a low detection rate for cognitive impairment in Parkinsonian syndromes [33–35]. The Frontal Assessment Battery [36] does assess verbal fluency and executive function but has no measure of memory, language, or visuospatial function. Similarly, the Dementia Rating Scale (DRS) [37] has no measure of language or visuospatial function. This reliance upon the executive functions reduces its ability to discriminate PSP from PD [38] or frontotemporal syndromes [39]. The DRS also has a lengthy administration time and requires specialised testing materials, impractical for routine bedside use. The Montreal Cognitive Assessment [40] does have a measure of verbal fluency but does not accommodate for physical disability. Indeed, none of the existing assessments were designed specifically for people with movement disorders, such as Parkinsonian syndromes. Tasks involving speaking, writing, or drawing can be influenced by motor symptoms such as tremor, rigidity, bradykinesia, apraxia, or dysarthria; thus, a genuine cognitive impairment might be sometimes difficult to distinguish from motor dysfunction and performance decrements exaggerated by physical disability.

The ECAS [41] was recently developed as a brief assessment for the identification of cognitive and behavioural changes in disorders characterised by prominent motor symptoms, such as amyotrophic lateral sclerosis (ALS). It was developed to be used with patients with even severe physical disability and thus may be suitable for detecting cognitive impairment in all motor disorders. Many of the subtests can be performed either orally or manually, with some measures corrected for motor speed, reducing the impact that physical disability may have upon performance on cognitive tests [42]. It also allows the clinician to track cognitive impairment throughout the disease course, crucial for any longitudinal studies.

The ECAS has been standardised using a sample of healthy controls, providing normative data for clinical use [41]. It has also been validated against other screening tools [43, 44] and extensive neuropsychological assessment [45]. It is available in English [41], German [46], Swiss German [46], Italian [44], and Chinese [47]. However, it remains untested whether the ECAS is also sensitive to the cognitive impairment observed in other progressive movement disorders. Thus, the aims of the present study were to determine firstly whether the ECAS is sensitive to the cognitive impairment seen in PD and PSP and secondly whether it is able to distinguish between these disorders, in order to support the differential diagnosis of PSP.

2. Methods

2.1. Participants. All patients were recruited from the National Hospital for Neurology and Neurosurgery, Queen Square, London. PSP patients (9 males and 2 females) were diagnosed using the NINDS-SPSP criteria [48] and had a mean illness duration of 3.73 years (range 1–11 years). PD patients (24 males and 6 females) fulfilled the Queen Square Brain Bank criteria for PD and had a mean illness duration of 5.67 years (range 0–14 years). All patients with PD-MCI were identified using the Movement Disorder Society Task Force guidelines [49], in which impairment (<2 SD) is present on at least two tests of cognitive functioning, either within or across different cognitive domains.

The healthy controls were those reported by Niven et al. [45]. They (26 males and 14 females) were recruited through the Psychology Department of the University of Edinburgh. No participant had significant neurological or psychiatric history.

The research was done in accordance with the Declaration of Helsinki and approved by the NRES Committee London-Queen Square and the University of Edinburgh's Department of Psychology Ethics Committee.

2.2. Measures. The ECAS is a 15–20-minute screen that includes assessment of the following domains: (1) fluency (free: words beginning with "S" and fixed: words beginning with "T" but with only four letters); (2) executive functions, separate from verbal fluency (Reverse Digit Span, Alternation, Inhibitory Sentence Completion, and Social Cognition); (3) language (Naming, Comprehension, and Spelling); (4) memory (Immediate Recall, Delayed Percentage Retention, and Delayed Recognition); and (5) visuospatial (Dot Counting, Cube Counting, and Number Location). Verbal fluency measures take into account the slowing of motor responses, by generating a verbal fluency index corrected for motor speed. Previously published ECAS normative data [41] were used to classify the abnormality of performance on each domain and calculate the total score out of a maximum of 136 (lower score indicating worse performance), with any scores <2 SD considered to be impaired.

Extensive neuropsychological testing was administered to assess the same domains (fluency, executive functions, language, memory, and visuospatial; Table 1). Mood was assessed using the Hospital Anxiety and Depression Scale [50], and patients were also assessed using the Apathy Scale [51].

Scores for the neuropsychological assessments were compared with published normative data. For each measure,

Table 1: Neuropsychological assessment.

Domain	Subdomain	Measures
Fluency		Phonemic verbal fluency index [42] (VFi): words beginning with "P" and "R"
Executive functions	Inhibition	Hayling Sentence Completion Test [52]: total unconnected errors (converted but not scaled); latency score (time taken to complete unconnected sentences minus time taken for connected sentences)
	Shifting and rule detection	Brixton Spatial Anticipation Test [52]: total number of errors
	Social	Reading the Mind in the Eyes–Revised [53]: total number of correct ones
Language	Naming	Graded Naming Test [54]
	Spelling	Graded Difficulty Spelling Test [55]
Memory		Adult Memory and Information Processing Battery [56]: immediate story recall; delayed story recall
Visuospatial		The Visual Object and Space Perception Battery [57]: cube analysis; number location

Table 2: Demographics of the participants.

	PSP patients		PD patients		Controls	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Age	66.82 (7.08)	53–77	63.33 (7.89)	50–80	62.70 (10.48)	39–88
Duration of symptoms (years)	3.73 (3.20)	1–11	5.67 (3.47)	0–14	—	—
Gender (female)	2	—	6	—	14	—
Education, mean years (SD)	15.27 (4.98)	10–26	14.33 (3.22)	9–23	12.25 (3.39)	9–25
HADS Depression	8.50 (5.50)	1–15	6.77 (4.39)	0–16	2.40 (1.81)	0–6
HADS Anxiety	8.50 (5.79)	2–17	9.17 (4.13)	3–18	4.83 (2.75)	0–11
Apathy	17.67 (12.04)	4–34	15.90 (10.26)	4–42	—	—

HADS: Hospital Anxiety and Depression Scale.

patients were judged to be impaired if scores were ≤2 SD. In the case where multiple measures were used, performance was classified as impaired when ≤2 SD on one of the two or two of the three measures was used.

2.3. Statistical Analyses. Data were analysed using SPSS v.19. Between-group comparisons were made using analyses of variance, and Pearson's and Spearman's correlations were used to detail the relationships between measures. Receiver operating characteristic (ROC) curve analyses were used to determine the relative sensitivity and specificity of the ECAS for the two patient groups.

3. Results

3.1. Demographics. Demographic details are given in Table 2. There were no significant group differences in age or education, and patients did not differ in symptom duration. There were significant group effects found for both HADS Anxiety (F (2, 75) = 13.04; $p < 0.001$) and Depression (F (2, 77) = 19.03; $p < 0.001$), with post hoc analysis revealing that patients had significantly higher burden of symptoms than healthy controls but no significant group difference between patient groups. There was no significant group difference in apathy scores between patient groups.

3.2. Performance on the ECAS. There was a significant effect of diagnosis on ECAS performance (Table 3). PSP patients had significantly lower total scores than PD patients and healthy controls, and PD patients had significantly lower total scores than healthy controls (all $p < 0.017$). There was a significant effect of diagnosis on all domains, except visuospatial. PSP patients performed worse than PD patients and healthy controls on fluency, language, executive function, and memory (all $p < 0.017$). PD patients performed worse than healthy controls on executive function only ($p < 0.017$).

When compared to published normative data, 81.8% ($n = 9$) of the PSP patients and 30.0% of the PD patients ($n = 9$) were impaired on the ECAS. PSP patients demonstrated most frequent impairments in fluency, language, and memory (each $n = 7$; 63.6%) and then executive function ($n = 6$; 54.5%) and visuospatial ($n = 3$; 27.3%). PD patients demonstrated most frequent impairments in language ($n = 9$; 30.0%), executive function and memory (each $n = 8$; 26.7%), and then fluency and visuospatial (each $n = 5$; 16.7%). There were no significant correlations between duration of symptoms and ECAS scores in either patient groups.

In order to investigate the specific nature of the impairment in both patient groups, individual domains were further investigated. In fluency, post hoc comparisons revealed a significant effect of diagnosis on both free fluency (F (2, 23.16) = 15.19; $p < 0.017$) and fixed fluency (F (2, 21.63) = 8.30; $p < 0.017$), with PSP patients performing worse than PD patients and healthy controls (all $p < 0.017$), but with no significant differences between PD patients and healthy controls. In language, there was a significant group effect on spelling (F (2, 76) = 10.58; $p < 0.017$), with PSP patients performing worse than PD

Table 3: ECAS scores of the participants.

	PSP patients		PD patients		Controls		F (df)	p
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range		
Total (max. 136)	85.09 (24.46)	54–126	109.87 (13.52)	78–126	120.61 (7.06)	100–132	17.44 (2, 22.09)[a]	<0.001
Executive function (max. 48)	29.27 (13.27)	9–46	36.93 (6.05)	19–44	42.11 (3.49)	33–48	12.56 (2, 22.22)[a]	<0.001
Language (max. 28)	23.18 (5.06)	15–28	26.67 (2.11)	19–28	27.50 (0.80)	25–28	5.76 (2, 21.01)[a]	<0.001
Fluency (max. 24)	8.18 (8.74)	0–22	18.73 (4.83)	6–24	20.74 (2.39)	12–24	12.37 (2, 21.91)[a]	<0.001
Memory (max. 24)	10.27 (6.90)	0–20	15.67 (4.25)	3–22	18.39 (2.53)	13–23	10.85 (2, 22.76)[a]	<0.001
Visuospatial (max. 12)	11.09 (1.87)	6–12	11.47 (1.04)	8–12	11.87 (0.67)	8–12	2.33 (2, 22.86)[a]	0.066

[a]Welch's adjusted F ratio.

Table 4: Neuropsychological assessment performance of participants.

		PSP patients		PD patients		Healthy controls		F (df)	p	Post hoc
		Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range			
Fluency	"P" VFi	10.90 (6.30)	2.37–19.67	4.13 (2.98)	0.96–14.50	3.68 (1.96)	1.52–9.33	22.65 (2.78)	<0.001	PSP < PD
	"R" VFi	14.16 (13.16)	2.50–41.00	4.12 (2.11)	2.00–9.50	3.65 (1.73)	1.72–9.33	22.37 (2.76)	<0.001	PSP < PD
Executive function	Hayling: B–A time	69.14 (86.55)	5–251	33.00 (28.04)	−3 to 126	34.88 (28.96)	−5 to 121	2.88 (2.73)	0.06	
	Hayling: errors	6.57 (5.56)	0–14	5.17 (5.89)	0–29	8.75 (9.17)	0–32	1.80 (2.73)	0.17	
	Brixton	38.43 (3.21)	35–43	34.54 (9.71)	16–50	35.08 (8.23)	15–47	0.59 (2.70)	0.56	
	Reading the Mind in the Eyes	20.50 (5.43)	14–29	23.93 (5.06)	13–35	26.35 (3.81)	17–34	5.72 (2.71)	<0.01	PSP < HC
Language	Graded Naming Test	20.64 (5.85)	9–26	23.20 (3.61)	13–29	24.15 (6.64)	14–57	1.71 (2.78)	0.19	
	Graded Difficulty Spelling Test	19.64 (8.44)	2–29	22.29 (6.01)	7–30	22.53 (4.50)	12–29	1.15 (2.76)	0.32	
Memory	Immediate Story Recall	24.45 (14.20)	0–41	27.04 (9.73)	7–49					
	Delayed Story Recall	23.64 (15.54)	0–40	25.46 (9.61)	7–46					
	Retention	80.16 (32.96)	0–111.11	93.92 (14.75)	62.50–136.00	94.49 (12.74)	58.82–12.27	3.12 (2.77)	0.05	
Visuospatial	Cube Analysis	8.91 (1.58)	6–10	8.83 (1.62)	5–10	9.63 (0.87)	5–10	23.61 (2.78)	<0.05	PSP < HC
	Number Location	8.45 (2.46)	2–10	9.20 (1.00)	7–10	9.43 (0.71)	7–10	2.90 (2.78)	0.06	

VFi: Verbal Fluency Index.

patients and healthy controls (both $p < 0.017$), but with no significant difference between PD patients and healthy controls. In memory, there was a significant group effect on immediate recall (F (2, 24.04) = 11.47; $p < 0.017$) and retention (F (2, 20.69) = 8.92; $p < 0.017$), but not recognition. PSP patients performed significantly worse than PD patients and healthy controls on both of these (both $p < 0.017$), but with no significant difference between PD patients and healthy controls. In executive functions, there were significant group effects on reverse digit span (F (2, 25.96) = 7.60; $p < 0.017$), alternation (F (2, 22.92) = 5.66; $p < 0.017$), and social cognition (F (2, 20.42) = 9.49; $p < 0.017$). Both PSP and PD patients performed significantly worse than healthy controls on reverse digit span and social cognition (all $p < 0.017$), but with no significant differences between patient groups. PSP patients performed significantly worse than PD patients and healthy controls on alternation ($p < 0.017$), but with no significant difference between PD patients and healthy controls.

3.3. Performance on Full Neuropsychological Assessment. Upon full neuropsychological assessment, there was a significant effect of diagnosis on fluency, executive function, and visuospatial domains (Table 4). Specifically, there were significant group differences on both measures of fluency, with PSP patients performing worse than PD patients and healthy controls. There were no significant differences between PD patients and healthy controls. In addition, PSP patients performed worse than healthy controls on the

Reading the Mind in the Eyes Test and Cube Analysis, but with no significant differences between PSP and PD patients, or between PD patients and healthy controls.

When scores on each of the neuropsychological assessments were compared with published normative data, there was a significant group difference in incidence of impairment in one domain only: fluency (χ^2 (1) = 7.61; $p < 0.001$). Nine of the 11 PSP patients (81.8%) were classified as impaired on at least one measure of verbal fluency, in comparison with only 33.3% ($n = 10$) of the 30 PD patients.

3.4. Diagnostic Accuracy of the ECAS for Cognitive Impairment in PD. Within the PD patients, a total of 17 (56.67%) met the criteria for PD-MCI. When PD and PD-MCI groups were compared, there were no significant differences in age, education, or symptom duration. However, on the ECAS, the PD-MCI group had significantly lower total scores (t (20.25) = 5.14; $p < 0.001$) and performed worse on executive function (t (23.83) = 3.02; $p < 0.01$), verbal fluency (t (22.52) = 3.26; $p < 0.01$), memory (t (28) = 3.09; $p < 0.01$), and visuospatial subscales (t (16.00) = 3.11; $p < 0.01$). On full neuropsychological assessment, the PD-MCI group also performed significantly worse on the Brixton Test (t (24) = 3.81; $p < 0.001$), Reading the Mind in the Eyes Test (t (26) = 2.75; $p < 0.05$), Graded Naming Test (t (28) = 4.32; $p < 0.001$), and Cube Analysis (t (20.69) = 2.801; $p < 0.05$).

ROC curve analysis revealed that the total score of the ECAS is able to discriminate between PD and PD-MCI with high sensitivity (88.2%) and 100% specificity, when using a threshold score of 112.50/136. The AUC is 0.93 (SE = 0.06; $p < 0.001$). Confidence intervals are 0.81 (lower bound) and 1.00 (upper bound). Indeed, all PD patients who performed in the impaired range on the ECAS fulfilled the diagnostic criteria for PD-MCI.

3.5. Diagnostic Accuracy of the ECAS for PSP. ROC curve analysis also revealed that the ECAS is highly specific (86.8%) and sensitive (91.0%) when discriminating PSP patients from healthy controls using a threshold score of 113.50/136. The AUC is 0.91 (SE = 0.67; $p < 0.001$). Confidence intervals are 0.79 (lower bound) and 1.00 (upper bound). All PSP patients who performed in the impaired range on the ECAS demonstrated impairment upon full neuropsychological testing, including impairment on at least one measure of verbal fluency.

3.6. Diagnostic Accuracy of the ECAS for Distinguishing between PD and PSP. The second aim of the study was to determine whether the ECAS is able to distinguish between PD and PSP, in order to support the early and accurate diagnosis of PSP. ROC curve analysis showed that the measure is able to discriminate between PD and PSP (when comparing all patients, irrespective of cognitive performance), with high specificity (76.7%) and sensitivity (72.7%), using a threshold score of 103.50/136 (Figure 1). The AUC is 0.80 (SE = 0.09; $p < 0.01$). Confidence intervals are 0.62 (lower bound) and 0.98 (upper bound). This generated three false negatives and seven false positives. The false positives were all patients who fulfilled the criteria for PD-MCI.

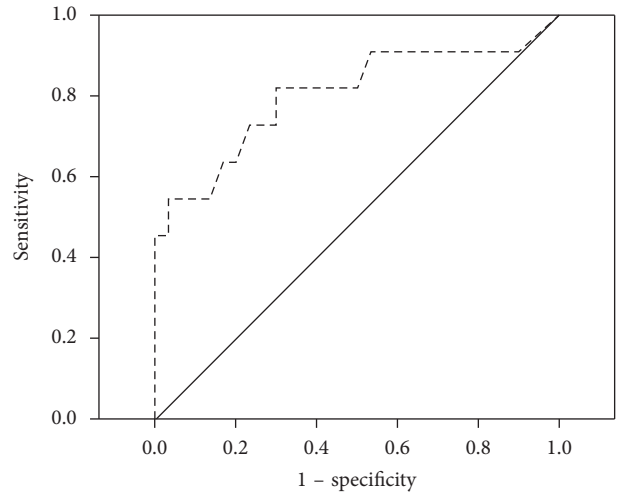

Figure 1: ROC curve depicting sensitivity and specificity of the ECAS, when comparing the PD and PSP patients (higher sensitivity scores indicate lower performance).

Within the ECAS, fluency was the best predictor of PSP, with high specificity (80.0%) and sensitivity (82.0%) using a threshold score of 17/24. The AUC is 0.84 (SE = 0.08; $p < 0.01$). Confidence intervals are 0.69 (lower bound) and 1.00 (upper bound). This generated two false negatives and six false positives (five PD-MCI and one PD). This is in contrast to when using the raw number of words generated in the two fluency tasks as a predictor, which has lower sensitivity (77.8%) and specificity (79.2%) when using a threshold score of 17.5.

4. Discussion

Our study has shown that the ECAS is sensitive to the cognitive impairment seen in PD. We found that 30% of PD patients were impaired on the ECAS, all of whom also demonstrated impairments upon full neuropsychological testing and fulfilled the criteria for PD-MCI. Indeed, ROC curve analyses revealed that the ECAS has excellent sensitivity and complete specificity for detection of PD-MCI. On the ECAS, PD patients demonstrated impairments in a number of domains but performed significantly worse than healthy controls on one domain only: executive function. PD-MCI patients also demonstrated deficits in language and visuospatial functioning. These findings confirm the greater involvement of posterior functions with more advanced Parkinson's disease [30] but also suggest that the pattern of impairment can be fairly heterogeneous, even involving language. This is in accordance with the findings of the MDS Task Force [49], who also report impairments in a range of cognitive domains, including language.

Our data also show that the ECAS is sensitive to the cognitive impairment in PSP. We found that 81.8% of PSP patients were impaired on both the ECAS and full neuropsychological testing, including at least one measure of

fluency. Again, ROC curve analyses confirmed that the ECAS total score gave excellent sensitivity and specificity for detection of PSP when compared with healthy controls. On the ECAS, PSP patients demonstrated the expected impairment in fluency, but also executive function, memory, and language. On extensive neuropsychological testing, PSP patients demonstrated impairments in fluency as well as executive function and visuospatial. The prominence of fluency and executive impairment on both the ECAS and full neuropsychological testing is in accordance with previous descriptions [13, 15, 16, 28], confirming that the ECAS is sensitive to the typical profile of cognitive impairment in PSP.

Importantly, we also found that the ECAS was able to distinguish between PD and PSP. ROC curve analysis revealed that the ECAS total score was sensitive and specific to PSP, with verbal fluency being the best discriminator. The ECAS was able to identify all PSP cases demonstrating cognitive impairment upon full testing. The few false positives mostly reflected PD patients with advanced cognitive impairment.

The strikingly reduced verbal fluency found on the ECAS and full testing confirms this as the cognitive hallmark of PSP. Importantly, the ECAS revealed this marked deficit even after accounting for the slowed motor speed. This contrasts with impairments in other cognitive domains, such as memory, which can improve by up to 50% given sufficient extra time [58, 59]. This impoverished verbal fluency, alongside the frequent family reports of reduced spontaneous speech and conversation initiation, likely reflects a cognitive adynamia beyond that of simple bradyphrenia but rather a more significant impairment in the generation of a "fluent sequence of novel thought" [19, 60]. This may reflect a deficit in novel thought generation and/or its appropriate sequencing [61]. Indeed, it has been argued that the akinesia in motor abilities, reduction of verbal fluency in cognition, and apathy in behaviour are all different manifestations of the same underlying disorder [62].

PSP patients also demonstrated impairments in other domains, which supports the findings of previous studies. In accordance with previous reports of poor delayed recall [17], our PSP patients displayed impaired verbal recall on the ECAS, with three of the seven PSP patients impaired on both the ECAS and full testing. Our patients also demonstrated language impairment, reflecting spelling difficulties, in accordance with previous studies [20, 63, 64]. Spelling was more impaired on the ECAS, perhaps because its spelling test comprises nouns, verbs, and compounds of low-to-medium frequency, with a longer mean length. In contrast, the spelling test used upon full testing contained mostly nouns of high-to-low frequency, with a shorter mean length. Our patients also demonstrated impaired visuospatial function, which supports previous findings [16, 18]. Nearly a third of PSP patients were impaired on the ECAS, with all of these also impaired upon full testing.

The PD and PSP patients both performed poorly on measures of social cognition. These findings echo previous reports of impaired performance on tests of theory of mind and social norms [22, 44, 65–67].

5. Conclusions

The ECAS captures the core cognitive deficit of reduced verbal fluency, as well as the wider cognitive profile of PSP. This may allow longitudinal testing to track progression as verbal fluency reaches floor. It was possible to use the ECAS with all the patients who took part in this study, despite often severe motor symptoms, indicating that it would be well tolerated in those with advanced disease. This suggests that the ECAS is suited for bedside use for detecting cognitive impairment in Parkinsonian syndromes and for distinguishing different cognitive profiles within these, in order to support differential diagnosis. Full neuropsychological assessment can then be used to further elucidate the specific clinical profile of each patient. Future research should examine its sensitivity for detecting cognitive impairment in other progressive movement disorders.

Conflicts of Interest

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

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Review Article

Resting State fMRI: A Valuable Tool for Studying Cognitive Dysfunction in PD

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Cognitive impairment is a common disabling symptom in PD. Unlike motor symptoms, the mechanism underlying cognitive dysfunction in Parkinson's disease (PD) remains unclear and may involve multiple pathophysiological processes. Resting state functional magnetic resonance imaging (rs-fMRI) is a fast-developing research field, and its application in cognitive impairments in PD is rapidly growing. In this review, we summarize rs-fMRI studies on cognitive function in PD and discuss the strong potential of rs-fMRI in this area. rs-fMRI can help reveal the pathophysiology of cognitive symptoms in PD, facilitate early identification of PD patients with cognitive impairment, distinguish PD dementia from dementia with Lewy bodies, and monitor and guide treatment for cognitive impairment in PD. In particular, ongoing and future longitudinal studies would enhance the ability of rs-fMRI in predicting PD dementia. In combination with other modalities such as positron emission tomography, rs-fMRI could give us more information on the underlying mechanism of cognitive deficits in PD.

1. Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative diseases. Traditionally, it has been regarded as a movement disorder characterized by the motor symptoms, such as bradykinesia, resting tremor, and rigidity. Up to now, it is well known that cognitive impairment is a common nonmotor symptom in patients with PD, even in the early stages or before motor symptom onset [1]. Furthermore, about 40% of the PD patients suffer from PD dementia (PDD) in cross-sectional studies [2]. In a longitudinal study, 83% of the PD patients developed dementia during the 20-year follow-up [3]. Despite the heavy burden caused by cognitive impairments in PD, we still lack effective treatments for cognitive symptoms in PD. Although acetylcholinesterase inhibitors could provide modest help, the progression of cognitive decline is inevitable [4].

The underlying mechanism of motor symptoms of PD is depleted dopaminergic cells in the substantia nigra [5]. In contrast, the pathophysiological basis of cognitive impairments in PD remains uncertain. Disrupted frontal-subcortical circuits due to dopaminergic neuron damage and wide deposition of α-synuclein, β-amyloid, and tau proteins might play a role [6, 7]. Various neurotransmitters including dopamine, acetylcholine, serotonin, and noradrenaline are involved [7]. A better understanding of the pathophysiology of cognitive impairments in PD can facilitate early identification and improved intervention for cognitive symptoms.

Functional MRI (fMRI) measures the blood-oxygen-level dependent (BOLD) signal in the brain, which is determined by the amount of oxyhemoglobin and deoxyhemoglobin and reflects neuronal activity. Resting state fMRI (rs-fMRI) estimates the brain BOLD signal while the subjects are awake without performing any specific task [8]. MRI is widely equipped by hospitals and research institutions; rs-fMRI is easy to perform and has an excellent safety profile compared to other imaging

modalities such as computed tomography (CT), positron emission tomography (PET), and single photon emission computed tomography (SPECT). Therefore, the application of rs-fMRI in neurological and psychiatric disorders has been rapidly increasing in the recent two decades. There are many approaches that can analyze the rs-fMRI data, including amplitude of low-frequency fluctuations (ALFF) and regional homogeneity (ReHo) which reflect local activity of individual regions or voxels, as well as seed-based functional connectivity (FC), independent component analysis (ICA), effective connectivity, machine learning, and graph theory-based analyses which measure the connectivity characteristics of different regions [8, 9]. rs-fMRI has been applied to investigate the pathophysiology of motor and nonmotor symptoms in PD, help early and differential diagnosis, predict disease progression, and guide treatment. In this review, we summarize recent developments of rs-fMRI studies on cognitive impairments in PD.

2. Uncovering the Pathophysiology of Cognitive Impairment in PD Using rs-fMRI

2.1. rs-fMRI Studies on PD Patients with Mild Cognitive Impairment (MCI) or Dementia. Cognitive activities rely on the coordination of various brain regions. Several networks have been established by rs-fMRI: the default mode network (DMN), the visual network, the sensorimotor network, the executive control network, and the frontoparietal network [10]. rs-fMRI is useful for improving our understanding of the mechanism of cognitive impairment in PD. Gorges et al. performed seed-based analyses on rs-fMRI in PD patients with and without MCI and healthy controls. Compared with the controls, PD patients without cognitive impairment had increased FC in multiple regions, while PD-MCI patients had decreased FC mainly within the DMN. The increased FC in PD patients without cognitive impairment might be a compensatory mechanism preceding PD-MCI [11]. Hou et al. conducted a study on drug-naïve PD patients with and without MCI and found FC reduction in both PD groups. In addition, compared with PD patients without cognitive impairment, PD-MCI patients had significantly reduced FC between DMN and the middle frontal and middle temporal gyri; within the DMN, PD-MCI patients had reduced FC between the anterior temporal lobe and inferior frontal gyrus. The FC alterations in the PD group were associated with attention/working memory and memory function [12]. Chen et al. studied the FC between posterior cingulate cortex and other regions of the bran in PD patients with and without MCI. They found decreased FC between the posterior cingulate cortex and the right temporal gyrus and increased FC between the posterior cingulate cortex and multiple brain regions in PD patients without cognitive impairment compared with healthy controls and reduced FC between the posterior cingulate cortex and several areas including bilateral prefrontal cortex, the left parietal-occipital junction, and the right temporal gyrus in PD-MCI patients compared with PD patients without cognitive impairment. The FC of the posterior cingulate cortex with other brain areas was associated with MoCA and MMSE scores in the PD patients [13]. Baggio et al. performed ICA and seed-based rs-fMRI analyses in PD patients without cognitive impairment, PD-MCI patients, and healthy controls. They found that PD-MCI patients had decreased connectivity between the dorsal attention network and the right frontoinsular regions, and this alteration was associated with attention/executive function. The DMN showed increased connectivity with medial and lateral occipito-parietal regions in PD-MCI patients, which was correlated with worse visuospatial/visuoperceptual abilities [14]. In another study by Baggio et al., graph theory-based analysis showed that PD-MCI patients had reduced long-range connections and increased local interconnectedness including higher measures of clustering, small-worldness, and modularity. The local interconnectedness was associated with visuospatial/visuoperceptual and memory functions in the PD patients [15]. Peraza et al. compared the intra- and inter-network changes in PD patients with and without MCI and found that PD-MCI patients had intranetwork impairments in the attention, executive function, and motor control networks compared with PD patients with normal cognitive function, as well as internetwork alterations in the visual perception together with the three above-mentioned networks [16]. Amboni et al. assessed the brain networks using ICA analysis in PD patients with and without MCI. Both PD groups showed impaired DMN connectivity, while the PD-MCI group showed impaired FC in the frontoparietal network. In addition, the decreased prefrontal cortex connectivity was associated with memory, visuospatial, and executive function [17]. Shin et al. compared the FC of PD-MCI patients with shorter and longer periods of motor symptoms before cognitive impairment using seed-based analyses and found that these two groups showed different characteristics of decreased FC in the DMN. Their findings implied that these two types might have different mechanisms and might help predict cognitive decline in future studies [18]. Lopes et al. investigated the brain network features of PD patients with different levels of cognitive function using the graph theory and network-based statistics. They showed that the functional organization decreased in accordance with the degree of cognitive impairment, and PD patients with cognitive impairment had reduced FC in the basal ganglia, ventral prefrontal, parietal, temporal, and occipital cortices [19]. The above studies confirmed the commonly impaired cognitive domains in PD, executive, attention, visuospatial function, and memory [7], and uncovered the impaired brain regions.

2.2. rs-fMRI Study on PD Patients without Cognitive Impairment. rs-fMRI is a sensitive imaging modality that can reveal dysfunction in cognition-related brain regions in PD patients with only subtle cognitive changes or even without cognitive symptoms. This property makes rs-fMRI a promising tool for the early identification of patients with a high risk for PDD. Lucas-Jimenez et al. used a seed-based FC analysis and showed reduced DMN FC in nondemented PD patients, and this FC change was correlated with lower verbal and visual memory and visual abilities in PD [20].

Manza et al. also used a seed-based approach to investigate the striatum FC in PD patients, the results showed that the stronger FC between the dorsal caudate and the rostral anterior cingulate cortex was associated with cognitive dysfunction (especially memory and visuospatial function) [21]. Muller-Oehring utilized a seed-based rs-fMRI and task fMRI and demonstrated that stronger putamen-medial parietal and pallidum-occipital FC than controls was associated with executive function and motor symptoms [22]. Tessitore et al. assessed the brain FC of cognitively unimpaired PD patients using the ICA analysis and found decreased FC within the DMN, and the FC changes correlated with memory, visuospatial, and attention/executive function [23]. Madhyastha et al. showed impaired brain network dynamic connectivity at rest in PD patients without cognitive impairment using factor analysis of overlapping sliding windows, and the factors in the dorsal attention network and frontoparietal task control network were correlated with patients' performance in attention examinations [24]. Luo et al. performed a graph theory-based analysis in drug-naive PD patients and found disrupted network organization in the PD patients at global, nodal, and connectional levels. Node centralities and connectivity strength were reduced mainly in the temporal-occipital and sensorimotor regions. Furthermore, the changed global network properties were associated with cognitive function [25]. In a group of rigidity-dominant drug-naive PD patients without cognitive impairment using a seed-based approach, Hou et al. found a decreased FC in DMN (especially the posterior DMN) and an increased FC in the anterior DMN in the PD patients, and increased FC of the anterior and ventral parts were negatively correlated with Hopkins verbal learning test-revised scores [26]. In a 3-year longitudinal study by Olde Dubbelink et al., the multivariate exploratory linear optimized decomposition into independent components analysis showed widespread reduction of FC in the PD patients compared with the controls. After 3 years, the FC in the PD patients decreased further on, and the FC changes were most prominent for posterior parts of the brain. The FC change over time was correlated with the alteration of global cognitive function, as well as perception, praxis and the spatial span subscores [27]. It is noteworthy that some patients in their study had dementia, and the cognitive performance of the PD patients was inferior to the controls at baseline [7]. In a study by Huang et al., left onset PD patients had worse performance in feedback-based associative learning than the right onset PD patients and the controls. In the left onset PD patients, the impaired cognitive function was associated with the ReHo in the right dorsal rostral putamen [28]. These studies showed that rs-fMRI was a sensitive tool detecting brain network abnormalities in PD patients without obvious cognitive impairment, and some motor symptom features implied higher risk for cognitive dysfunction in PD.

3. Combining rs-fMRI with Other Modalities

Until now, various methods have been applied in investigating neurological disorders, and each has its advantage and disadvantage. PET and SPECT using different radio ligands can display abnormalities of neurotransmitters in the brain and deposition of aggregated proteins such as α-synuclein, β-amyloid, and tau proteins in neurological disorders [29]. EEG has a very high temporal resolution. CSF laboratory examinations are able to detect the culprit protein and the degree of neurodegeneration [30]. Combining rs-fMRI and other modalities can deepen our understanding of the pathophysiology of cognitive dysfunction in PD. Madhyastha et al. used the "network kernel analysis" in PD patients and found widespread alterations in the correlations of network kernels in the PD patients, and the degree of network disturbance was associated with lower cerebrospinal fluid α-synuclein and amyloid-β_{42} levels. In addition, increased correlation of the insula with the DMN was associated with worse attentional function. Therefore, both α-synuclein and amyloid-β_{42} might play a role in disrupting cognitive-related brain regions [30]. Lebedev et al. combined a graph theory-based rs-fMRI analysis with ^{123}I-FP-CIT SPECT imaging. In their study, executive function was associated with dorsal frontoparietal cortical processing and sensory involvement, as well as the striatal dopamine transporter binding ratios. Memory performance was correlated with prefrontolimbic processing but not associated with nigrostriatal dopaminergic function. Their study confirmed that distinct from executive dysfunction, memory deficits in PD was not induced by dopaminergic insufficiency [31]. In future studies, integration of more CSF laboratory examinations, EEG/fMRI, and PET imaging utilizing more radio ligands including for other transmitters (cholinergic, serotonergic, norepinephrinergic systems, etc.) and abnormal proteins (such as α-synuclein, β-amyloid, and tau proteins) and laboratory examinations using other body fluids can promote our recognition of the underlying mechanism of cognitive impairment in PD.

4. rs-fMRI as a Diagnostic Tool

So far, most of the rs-fMRI studies in PD enrolled small numbers of patients. However, we can obtain preliminary consistent conclusions on the networks disrupted in PD and their relationship with cognitive dysfunction. We still need more evidence to apply rs-fMRI as a diagnostic tool in clinical practice. Abos et al. used a support vector machine method to distinguish PD patients with and without MCI with an accuracy of 80%, and the connectivity of the selected edges was correlated with memory and executive function in the PD patients [32]. Peraza et al. compared the brain network between patients with dementia with Lewy bodies and PDD using seed-based analyses. Their results implied that there might be subtle differences in attention and motor-related networks between these two disorders [33]. Borroni et al. performed rs-fMRI in patients with PD, PDD, and DLB using ReHo. PD and PDD patients had decreased ReHo in the frontal regions, while DLB patients had lower ReHo in the posterior regions [34]. Future studies enrolling large samples would pave the road for clinical diagnostic applications in PD.

5. Prediction of Cognitive Impairment in PD

Disease-modifying therapies targeting α-synuclein, β-amyloid, and tau proteins are under active investigation and are hopeful to be available in clinical practice in the near future. Early identification of PD patients with a high risk for dementia is critical for potential disease-modifying therapies. As far as we know, most of the studies using rs-fMRI for cognitive function in PD are cross-sectional. Only two studies explored the progression of cognitive impairment and brain network changes in a longitudinal design. However, they only enrolled small numbers of patients and had a short time of follow-up (1 and 3 years, resp.) [21, 27]. Ongoing prospective studies such as the Parkinson's Progression Markers Initiative (PPMI) would help answer the question of PDD prediction.

6. Evaluating and Assisting Intervention

rs-fMRI has been applied in the assessment of the effects of levodopa and cognitive rehabilitation in PD cognition. Simioni et al. tested the effect of levodopa on brain networks and cognitive function using seed-based and ICA analyses. Levodopa increased resting state FC between caudate and right parietal cortex (within the frontoparietal attentional network), and this effect was associated with improvement in working memory performance [35]. Diez-Cirarda employed a seed-based rs-fMRI analysis in a randomized controlled trial of cognitive rehabilitation in PD and showed increased FC between the left inferior temporal lobe and the bilateral dorsolateral prefrontal cortex in the rehabilitation group than the control group. Moreover, the increased FC was correlated with executive function in the treatment group [36]. Eighteen months later, they performed a follow-up examination of 15 patients in the rehabilitation group and found preserved effect of rehabilitation on both cognitive function and brain FC even after 18 months [37]. Cerasa et al. also evaluated the effect of cognitive rehabilitation using rs-fMRI. They employed ICA and SPM and showed improved attention/executive function together with the attention and central executive neural networks [38]. There are other studies evaluating the effect of varied interventions on the resting brain networks, but the associations with cognitive function has been less investigated [39–45]. In the future, rs-fMRI can play a more important role in evaluating treatment effects as well as guiding neuromodulation therapies.

In summary, rs-fMRI might be a useful tool for the exploration of underlying mechanism of cognitive dysfunction in PD and can help diagnose cognitive dysfunction in PD and assist treatments. More longitudinal studies using rs-fMRI and the combination of rs-fMRI with other modalities are needed.

Conflicts of Interest

All the authors declared no relevant conflicts of interest.

Authors' Contributions

Kai Li and Wen Su contributed equally to this work.

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Research Article

Cognitive Training and Transcranial Direct Current Stimulation for Mild Cognitive Impairment in Parkinson's Disease: A Randomized Controlled Trial

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This study examined whether standard cognitive training, tailored cognitive training, transcranial direct current stimulation (tDCS), standard cognitive training + tDCS, or tailored cognitive training + tDCS improved cognitive function and functional outcomes in participants with PD and mild cognitive impairment (PD-MCI). Forty-two participants with PD-MCI were randomized to one of six groups: (1) standard cognitive training, (2) tailored cognitive training, (3) tDCS, (4) standard cognitive training + tDCS, (5) tailored cognitive training + tDCS, or (6) a control group. Interventions lasted 4 weeks, with cognitive and functional outcomes measured at baseline, post-intervention, and follow-up. The trial was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR: 12614001039673). While controlling for moderator variables, Generalized Linear Mixed Models (GLMMs) showed that when compared to the control group, the intervention groups demonstrated variable statistically significant improvements across executive function, attention/working memory, memory, language, activities of daily living (ADL), and quality of life (QOL; Hedge's g range = 0.01 to 1.75). More outcomes improved for the groups that received standard or tailored cognitive training combined with tDCS. Participants with PD-MCI receiving cognitive training (standard or tailored) or tDCS demonstrated significant improvements on cognitive and functional outcomes, and combining these interventions provided greater therapeutic effects.

1. Introduction

There is a growing body of research examining mild cognitive impairment in Parkinson's disease (PD-MCI) and the potential of nonpharmacological interventions (e.g., cognitive training and noninvasive brain stimulation) for improving cognitive function in PD and PD-MCI [1].

There are two frequently used methods of computer-based cognitive training: standard or tailored. Standard cognitive training involves cognitive tasks that are not customised to the individual's cognitive deficits, whereas tailored cognitive training is deficit specific. Recent studies report improved cognition following standard and tailored cognitive training in PD. París et al. [2] examined whether standard multimedia and paper/pencil cognitive training improved cognitive functioning, quality of life (QOL), and activities of daily living (ADL) in PD. Compared to the control group, the trained group improved across all cognitive domains except language, but no improvement was found for QOL and ADL [2]. In a randomized controlled trial, Edwards et al. [3] examined whether standard computer-based cognitive training improved speed of processing in PD. There were significant improvements in speed of processing for those with mild/moderate PD [3]. For tailored cognitive training, Naismith et al. [4] examined the effect of two-hour sessions twice a week, which involved

psychoeducation and tailored computer-based tasks. Episodic memory and learning retention significantly improved posttraining [4]. Cerasa et al. [5] examined neurofunctional correlates between trained cognitive domains and synaptic plasticity of those domains in PD. Participants completed 12 hours of computer-based cognitive training tailored to their pretraining cognitive impairment(s). Compared to the control group, the training group demonstrated attentional improvements which increased neural resting state (fMRI) activity in the superior parietal and prefrontal dorsolateral cortices [5]. There is increasing evidence supporting standard and tailored cognitive training for cognition in PD, but it remains unclear which modality has greater therapeutic potential [6].

Transcranial direct current stimulation (tDCS) modulates neuronal activity by delivering low-intensity electrical currents to specific cortical regions [7]. Initial studies report improved cognition following tDCS in PD. Boggio et al. [8] demonstrated that 2 mA tDCS over left DLPFC improved working memory in PD, whereas 1 mA and sham tDCS provided no beneficial effects for cognition. Pereira et al. [9] examined whether 20 minutes of counterbalanced 2 mA tDCS over left DLPFC and left temporoparietal cortices immediately improved executive functions. In a randomized controlled trial of tDCS in PD, Doruk et al. [10] compared 2 mA tDCS applied over left (group one) or right (group two) DLPFC with sham stimulation (control group) for executive function. Compared to the control group, significant improvements in the Trail Making Test (Part B) were found for both tDCS groups immediately following the two-week intervention and at one-month follow-up [10]. These studies provide preliminary evidence that tDCS may improve cognitive function in PD, but more standardised clinical trials are required to substantiate these findings.

One recent study [11] combined cognitive training with tDCS simultaneously and reported a trend towards significant improvement in memory, but the lack of a control group limits interpretation of intervention effects. It remains unclear whether combining cognitive training with tDCS provides optimal conditions (stimulation and compensation) to elicit neuronal plasticity and improve cognition in PD and PD-MCI. The present study examined whether standard cognitive training, tailored cognitive training, tDCS, standard cognitive training + tDCS, and tailored cognitive training + tDCS improved cognitive function and practical outcomes in PD-MCI.

2. Methods

2.1. Study Design. This study was a parallel, randomized controlled trial conducted in accordance with CONSORT requirements (see Supplementary Table S1) [12]. Participants were randomized to one of six groups (5 intervention and 1 control) by a computer generated list using block randomization at a ratio of 1 : 1. Blinding is difficult to achieve in nonpharmacological trials, and so participants and researchers were not blinded to the interventions.

Participants in the standard or tailored cognitive training groups completed computer-based training for 45 minutes, 3 times per week for 4 weeks. Cognitive training was completed using the website version of Smartbrain Pro™ (http://www.smartbrain.net) in participants' homes. Participants in a tDCS group completed 20 minutes of stimulation, once a week for 4 weeks. Each session of tDCS was completed at Curtin University. All participants completed the same neuropsychological tests at baseline (week 0), post-intervention (week 5), and follow-up (week 12).

Curtin University's Ethics Committee provided approval (approval number: HR 189/2014), and this study was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR: 12614001039673). All participants provided informed consent, and participation was completed during participants' "ON" stage of medication.

2.2. Study Population. Participant recruitment and neuropsychological assessments were completed at Curtin University, Western Australia, in 2015. The following inclusion criteria applied: (1) participants diagnosed with idiopathic PD in accordance with the UK PD Brain Bank criteria, (2) presence of MCI in accordance with the Movement Disorder Society (MDS) PD-MCI Level II diagnostic criteria [13], (3) a stable response to antiparkinsonian medication at pre-intervention and during the course of the intervention, and (4) cognitive deficits that did not interfere with functional independence (i.e., UPDRS-II score less than 3). The following exclusion criteria applied: (1) presence of PD-Dementia, (2) recent history of brain surgery, (3) Deep Brain Stimulation (DBS) implant, (4) active skin disease on the scalp, (5) history of migraine or epilepsy, and (6) metal implants in the head/brain. 70 participants completed baseline neuropsychological assessments, with 42 meeting inclusion criteria (Figure 1). All participants completed their intervention and post-intervention neuropsychological assessments. Four participants (9.5%) did not complete follow-up assessments due to inability to travel due to disease progression ($N = 2$) and lack of time ($N = 2$).

2.3. Cognitive Training. Smartbrain Pro is an interactive computer-based training program designed to train each cognitive domain. Smartbrain Pro has been used in trials which have demonstrated improvements in cognitive functioning in Alzheimer's disease and PD [2, 14]. Smartbrain Pro was streamed directly from the Internet onto participants' home computers or onto Acer™ Aspire E3-112 portable computers via Optus™ E5251 Mini Wifi Modems (provided by the researcher). Performance was automatically monitored by the program to adjust individual difficultly levels for each activity. Participants in the standard cognitive training and standard cognitive training + tDCS groups completed a predetermined program comprising 10 activities, two activities per cognitive domain (see Supplementary Table S2). Participants in the tailored cognitive training and tailored cognitive training + tDCS groups completed activities which were individualized to their baseline neuropsychological test results. For example, a participant who demonstrated memory and executive function impairment at baseline completed only memory and executive function activities during cognitive training.

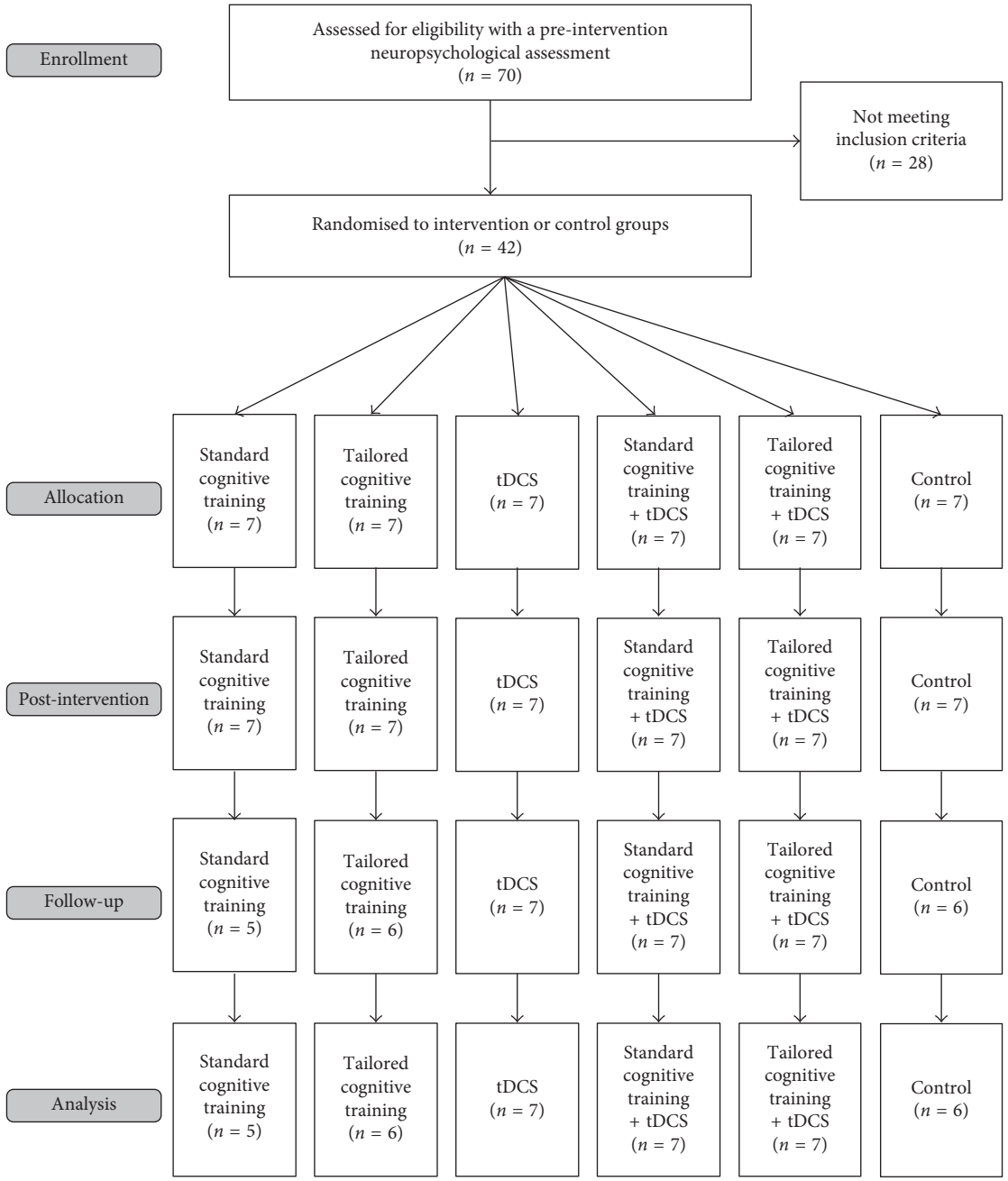

Figure 1: CONSORT flow diagram.

The activities themselves were the same as for the standard cognitive training, and normative data were used to define each participant's degree of cognitive impairment, as described in earlier work [15].

2.4. Brain Stimulation. tDCS is a noninvasive brain stimulation procedure delivering low-intensity electrical currents to specific cortical areas. For participants in the tDCS, standard cognitive training + tDCS, and tailored cognitive training + tDCS groups, stimulation sessions were scheduled for the same day and time each week for 4 weeks. During each session, participants received 20 minutes of constant current 1.5 mA stimulation over left dorsal lateral prefrontal cortex (LDPFC). tDCS was delivered using the TCT™ tDCS stimulator (http://www.trans-cranial.com/) and administered with two $50 \times 70\,\text{mm}^2$ sponge electrodes soaked in saline solution. The anode electrode was placed over F3 according to the 10–20 international system, and the cathode electrode was placed above the left eye. Executive function and attention/working memory are most frequently impaired cognitive domains in PD [15, 16] and associated with cortical activation of the left DLPFC [5]. Previous studies demonstrate improved cognitive functioning following tDCS over left DLPFC in PD [8, 9]. Left DLPFC was therefore targeted for tDCS in this study.

2.5. Control Group. Participants in the control group completed baseline, post-intervention, and 12-week follow-up neuropsychological assessments, but did not complete cognitive training or tDCS.

2.6. Neuropsychological Assessment. Neuropsychological assessments were conducted by doctoral researchers with extensive training and experience in administration, scoring, and interpretation of neuropsychological tests in PD. The following tests were selected in accordance with MDS Task Force [13] recommendations: (1) *executive function* was assessed using the Stockings of Cambridge (SOC) subtest from CANTAB™ and the Controlled Oral Word Association Task (COWAT) [17], (2) *attention and working memory* was assessed using the Letter-Number Sequencing (LNS) [18] and the Stroop (Colour-Word Interference) Test [19], (3) *memory* was assessed using the Hopkins Verbal Learning Test-Revised (HVLT-R) immediate recall subtest [20] and the Paragraph Recall test [21], (4) *visuospatial abilities* were assessed with the Judgement of Line Orientation (JLO) test [22] and the Hooper Visual Organisation Test (HVOT) [23], and (5) language was assessed using the Boston Naming Test-Short Form (BNT) [24] and the Similarities test [18]. Global cognition was assessed using the Parkinson's Disease—Cognitive Rating Scale (PD-CRS) [25] and the Mini-Mental State Examination (MMSE) [26]. Premorbid intelligence was assessed using the Australian version of the National Adult Reading Test (AUSNART) [27]. PD-MCI was classified as less than one standard deviation (SD) below normative scores on two or more neuropsychological tests [13]. Please refer to our earlier work [15] for a detailed description of our application of the MDS Task Force criteria for classification of PD-MCI in this study's sample of participants.

Activities of daily living (ADL) and quality of life (QOL) are impacted by cognitive impairment in PD, but few non-pharmacological trials have included these outcomes. ADL and QOL were assessed by the Unified Parkinson's Disease Rating Scale (Section II) [28] and the Parkinson's Disease Questionnaire-39 (PDQ-39) [29], respectively. Depression was included as a potential covariate and assessed using the Depression, Anxiety, and Stress Scale-21 (DASS-21) [30].

2.7. Data Analysis. Generalized linear mixed models (GLMMs) analysed outcome variables [31] in SPSS version 22.0. Separate GLMMs were run for each outcome variable to optimise the likelihood of convergence. To control the Type 1 error rate and conserve statistical power, outcome variables were grouped by cognitive domain (e.g., executive function and memory) and a more stringent alpha level was applied ($p < 0.025$) to interaction effects. Each GLMM was assessed for statistically significant Group × Time interaction effects, main effects of Time (per group), and pairwise contrasts. Statistically significant simple main effects of Group were not of interest for this study. Significant simple main effects of Group indicate a significant difference between group outcome scores at either pre-intervention, post-intervention, or follow-up time intervals. However, this study investigated whether there was a significantly different degree of *change* (over time) on outcome variables, between groups. Therefore, pre-intervention, post-intervention, or follow-up group differences provided no statistical evidence to support the effect of interventions (or no effect of the control group) on outcome variables. Effect sizes (Hedge's g) were calculated using the change score method and represent a comparison between each corresponding intervention group and the control group. Sample size was determined using G*Power 3. París et al. [2] and Naismith et al. [4] found moderate to large effect sizes for cognitive outcomes. To detect a moderate effect (power = 0.80 and $\alpha = 0.05$), 54 participants were required (9 per group).

3. Results

No data were missing at baseline. Little's Missing Completely at Random (MCAR) test showed data missing at post-intervention ($\chi = 23.80$, $p = 0.64$) and follow-up ($\chi = 40.34$, $p = 0.07$) were not systematically linked to included variables. Given that GLMMs account for missing data, means and standard deviations at post-intervention and follow-up assessments were slightly adjusted by each model and do not reflect the raw data at those time points. Refer to Supplementary Tables S3, S4, and S5 for raw neuropsychological test results.

Age significantly correlated with the HVLT ($r = -0.43$, $p = 0.004$), MMSE ($r = -0.43$, $p = 0.01$), and PD-CRS ($r = -0.37$, $p = 0.02$). Gender significantly correlated with the Stroop test ($r = 0.35$, $p = 0.03$). Years of education significantly correlated with Similarities ($r = 0.31$, $p = 0.04$) and MMSE ($r = 0.34$, $p = 0.03$). Premorbid IQ significantly correlated with Similarities ($r = 0.44$, $p = 0.003$), JLO ($r = 0.33$, $p = 0.03$), and MMSE ($r = 0.38$, $p = 0.01$). Disease duration significantly correlated with the HVOT ($r = -0.32$, $p = 0.04$). LED significantly correlated with Similarities ($r = 0.33$, $p = 0.03$). Depression significantly correlated with Similarities ($r = -0.39$, $p = 0.01$) and the PDQ-39 ($r = 0.59$, $p < 0.001$). Variables with significant correlations at baseline were included as covariates in corresponding GLMMs. An analysis of variance (ANOVA) of baseline demographic statistics indicated no statistically significant differences between groups (Table 1).

A significant interaction effect was observed for SOC, indicating a differential rate of improvement in executive function between groups ($F = 3.82$, $p < 0.001$). Significant improvements were identified for the standard cognitive training + tDCS group ($F = 10.73$, $p < 0.001$) and tailored cognitive training + tDCS group ($F = 12.00$, $p < 0.001$). No other groups improved on SOC, and no groups improved on the COWAT. Refer to Tables 2–4 for pairwise comparison statistics, effect sizes, and group baseline, post-intervention, and follow-up results.

For attention/working memory, a significant interaction effect was observed for the Stroop test ($F = 2.91$, $p = 0.003$). Significant improvements were identified for the tDCS group ($F = 4.06$, $p = 0.02$) and standard cognitive training + tDCS group ($F = 35.05$, $p < 0.001$). No other groups improved on the Stroop test. A significant interaction effect was observed for LNS ($F = 4.53$, $p < 0.001$). Significant improvement was identified for the tailored cognitive training group ($F = 6.62$, $p = 0.002$)

Table 1: Baseline demographic information for the intervention and control groups.

	Standard CT		Tailored CT		tDCS		Standard CT + tDCS		Standard CT + tDCS		Control		Group differences	
Outcome	*M*	SD	*M*	SD	*M*	SD	*M*	SD	*M*	SD	*M*	SD	*F*	*p*
Gender (%, ♀)	43% ($N = 3$)		57% ($N = 4$)		71% ($N = 5$)		71% ($N = 5$)		71% ($N = 5$)		57% ($N = 4$)		0.36	0.87
Age^{++}	68.14	8.69	65.57	5.20	72	6.45	63.57	15.68	67.43	6.37	72.29	6.21	0.80	0.56
Education^{++}	13.57	2.64	12.21	2.83	13.57	3.69	15.50	3.35	15.86	1.35	11.71	2.98	2.34	0.06
Premorbid IQ	103.29	6.96	107.21	12	108.21	5.83	111.96	4.37	111.08	3.59	103.64	7.53	1.76	0.15
Disease Duration^{++}	5.29	4.23	5.79	4.97	5.50	5.66	6.79	4.60	4.43	2.70	5.36	4.14	0.20	0.96
LED	295	313.40	383	178.62	573.29	586.25	350.71	322.37	464.29	358.78	292.88	274.51	0.64	0.68
DASS-D	2.29	2.56	1.29	1.50	3	2	3	5.07	3.29	4.11	2.71	3.15	0.34	0.89

M = mean; SD = standard deviation; *F* = ANOVA; *p* = level of statistical significance; *N* = number of participants; LED = levodopa equivalent dose; DASS-D = Depression, Anxiety, and Stress Scale (Depression subscale); IQ = intelligence quotient; CT = cognitive training; tDCS = transcranial direct current stimulation; ♀ = male gender; ++ = years.

Table 2: Standard cognitive training and tailored cognitive training group cognitive performance at baseline, post-intervention, and follow-up.

	Standard cognitive training						Pairwise comparison statistics					
	Baseline		Post-intervention		Follow-up		Baseline to post-intervention			Baseline to follow-up		
Outcome	*M*	SD	*M*	SD	*M*	SD	*t*	*p*	*g*[a]	*t*	*p*	*g*[a]
COWAT	38.86	13.89	44.14	11.40	42.20	13.60	1.81	0.07	0.70	1.31	0.19	−0.16
SOC	8.17	0.64	6.43	2.52	7.69	2.33	−1.90	0.06	−1.19	−0.51	0.61	−0.70
LNS	18.73	2.54	19.02	4.77	17.14	3.97	0.24	0.81	−0.04	−1.26	0.21	−0.42
Stroop test	33.83	6.20	36.11	6.76	36.16	5.31	0.82	0.42	0.35	1.67	0.10	−0.31
HVLT	22.08	5.41	26.94	5.35	27.44	2.33	3	0.003[b]	0.46	2.76	0.01[b]	0.44
Paragraph Recall	5	2.20	6.36	2.28	7.09	2.71	1.36	0.18	0.62	3.16	**0.002**[*]	0.93
BNT	14.14	1.72	13.86	0.98	13.60	1.17	−0.73	0.43	−0.55	−0.79	0.43	0.01
Similarities	22.14	3.05	23.71	3.31	21.89	1.17	1.51	0.25	0.28	−0.30	0.76	−0.70
JLO	25.61	3.39	24.90	4.35	20.61	3.42	−0.71	0.48	−0.08	−2.94	**0.004**[*]	−1.19
HVOT	24.49	3.76	25.21	3.45	26.07	2.96	0.84	0.40	0.06	1.38	0.17	0.36
MMSE	26.95	2.09	26.80	1.78	28.19	2.24	−0.19	0.85	0.41	0.86	0.39	−0.09
PD-CRS	89.42	10.28	96.13	9.12	100.09	8.94	1.42	0.16	0.44	2.29	0.02[b]	0.28
PDQ-39	24.20	10.07	20.68	10.76	25.60	9.95	−3.05	**0.003**[*]	0.24	0.71	0.48	0.06
UPDRS-II	0.96	0.77	0.73	0.74	0.85	0.74	−4.60	**0.001**[**]	0.33	−1.55	0.13	0.36
	Tailored cognitive training						Pairwise comparison statistics					
	Baseline		Post-intervention		Follow-up		Baseline to post-intervention			Baseline to follow-up		
Outcome	*M*	SD	*M*	SD	*M*	SD	*t*	*p*	*g*[a]	*t*	*p*	*g*[a]
COWAT	32.43	16.59	34.71	12.19	37.17	21.27	0.56	0.58	0.42	0.96	0.34	−0.07
SOC	6.43	2.33	6.55	2.07	5.26	2.84	0.14	0.89	−0.51	−0.98	0.33	−0.85
LNS	17.39	4.43	18.87	3.10	19.81	2.70	1.95	0.06	0.19	3.30	**0.001**[*]	0.30
Stroop test	31.89	9.01	35.17	10.65	31.83	9.49	1.42	0.16	0.34	−0.03	0.98	−0.51
HVLT	22.15	5.35	24.58	6.15	26.52	6.36	2.41	0.02[b]	0.05	2.93	0.004[b]	0.27
Paragraph Recall	5.64	2.20	7.36	3.50	7.23	3.21	2.21	0.03[b]	0.58	1.35	0.18	0.74
BNT	13.14	1.25	13.86	1.25	13.78	1.05	1.48	0.14	0.09	1.14	0.26	0.66
Similarities	22.11	2.47	23.71	3.31	22.72	1.52	−0.03	0.98	−0.36	0.51	0.61	−0.54
JLO	20.25	3.55	22.97	4.32	22.32	3.87	2.13	0.04[b]	0.49	1.94	0.06	−0.06
HVOT	20.37	3.76	23.22	3.45	23.19	5.35	3.35	0.001[b]	0.61	2.62	0.01[b]	0.65
MMSE	25.49	2.44	26.92	2.54	25.85	1.20	−2.70	0.01[b]	0.98	0.55	0.59	−0.45
PD-CRS	86.58	12.72	95.29	21.44	98.61	18.28	2.31	0.02[b]	0.39	3.64	0.001[b]	0.35
PDQ-39	21.41	7.39	18.09	5.19	18.21	8.65	−2.46	**0.02**[*]	0.26	−2.44	**0.02**[*]	0.30
UPDRS-II	0.68	0.32	0.80	0.40	0.71	0.27	0.88	0.38	−0.06	0.17	0.87	−0.24

M = mean; SD = standard deviation; *t* = t statistic; a = effect size computed using change scores with the control group, positive effect favours corresponding intervention group; b = not statistically significant due to nonsignificant main effect; [*] = $p < 0.05$; [**] = $p < 0.001$; tDCS = transcranial direct current stimulation; COWAT = Controlled Oral Word Association Test; SOC = Stockings of Cambridge; LNS = Letter-Number Sequencing; HVLT = Hopkin's Verbal Learning Test; BNT = Boston Naming Test; JLO = Judgement of Line Orientation; HVOT = Hooper's Visual Orientation Test; MMSE = Mini-Mental State Examination; PD-CRS = Parkinson's Disease—Cognitive Rating Scale; UPDRS-II = Unified Parkinson's Disease Rating Scale—Section II (ADL); PDQ-39 = Parkinson's Disease Questionnaire-39.

Table 3: tDCS and standard cognitive training + tDCS group cognitive performance at baseline, pos-tintervention, and follow-up.

	tDCS						Pairwise comparison statistics					
	Baseline		Post-intervention		Follow-up		Baseline to post-intervention			Baseline to follow-up		
Outcome	*M*	SD	*M*	SD	*M*	SD	*t*	*p*	*g*[a]	*t*	*p*	*g*[a]
COWAT	30.86	16.14	36	15.11	30.57	17.57	1.86	0.06	0.58	−0.17	0.86	−0.30
SOC	5.50	1.35	6.50	1.62	7	1.88	2.12	0.04[b]	−0.13	1.94	0.06	0.14
LNS	14.82	5.99	16.11	6.39	16.18	4.74	1.70	0.09	0.12	1.15	0.25	0.13
Stroop test	21.38	6.76	27.66	10.41	26.52	7.47	2.09	**0.04***	0.65	2.41	**0.02***	0.01
HVLT	20.33	8.27	25.33	6.28	23.33	7.45	4.45	0.001[b]	0.45	3.71	0.001[b]	0.03
Paragraph Recall	4	2.23	6.29	2.05	4.36	1.72	4.73	**0.001****	1.11	0.70	0.49	0.28
BNT	12.57	1.06	13.71	1.83	13.29	1.67	2.23	0.03[b]	0.30	1.63	0.11	0.65
Similarities	22.37	2.68	23.42	2.41	21.38	1.67	1.29	0.20	0.13	−0.76	0.45	−1.25
JLO	21.30	7.90	22.44	5.51	24.59	4.80	0.80	0.43	0.24	2.31	0.02[b]	0.18
HVOT	20.99	3.76	22.42	3.45	20.99	3.26	1.68	0.10	0.24	0.00	1	−0.01
MMSE	24.31	1.54	26.02	1.64	25.45	2.43	2.29	0.02[b]	1.36	1.84	0.07	0.55
PD-CRS	74.76	17.57	85.04	18.10	79.04	20.59	5.10	0.001[b]	0.53	1.51	0.14	−0.06
PDQ-39	23.04	8.45	18.09	5.19	18.21	8.65	−0.96	0.34	0.22	−1.11	0.27	0.37
UPDRS-II	1.27	0.56	1.06	0.66	1.23	0.66	−2.25	0.03[b]	0.32	−0.48	0.63	0.24
	Standard cognitive training + tDCS						Pairwise comparison statistics					
	Baseline		Post-intervention		Follow-up		Baseline to post-intervention			Baseline to follow-up		
Outcome	*M*	SD	*M*	SD	*M*	SD	*t*	*p*	*g*[a]	*t*	*p*	*g*[a]
COWAT	37.71	9.88	46.14	4.85	39.86	11.26	3.23	0.002[b]	1.33	0.44	0.66	−0.22
SOC	7.43	1.41	9.57	1.64	9.14	2.09	4.62	**0.001****	0.41	2.29	**0.02***	0.23
LNS	18.54	2.17	18.87	2.47	18.56	2.60	0.34	0.73	−0.04	0.01	0.99	−0.14
Stroop test	24.52	9.30	30.52	8.29	33.81	9.01	2.23	**0.03***	0.60	5.76	**0.001****	0.24
HVLT	26.51	4.08	28.51	5.10	29.94	4.85	1.43	0.16	−0.03	2.59	0.01[b]	0.09
Paragraph Recall	6	2.07	8.21	1.38	6.43	2.23	2.30	0.02[b]	1.29	3.25	0.002[b]	0.57
BNT	13.29	1.59	14.43	0.74	14	0.93	1.75	0.08	0.39	1.83	0.07	0.77
Similarities	21.59	2.49	23.51	1.72	21.02	2.31	2.70	**0.01***	0.59	2.02	0.06	−0.95
JLO	22.83	5.43	24.55	4.74	22.98	7	1.58	0.12	0.37	0.11	0.91	−0.23
HVOT	23.82	3.79	25.11	3.45	24.11	3.29	1.51	0.14	0.21	1.03	0.78	0.05
MMSE	27.02	1.72	26.87	1.30	27.73	1.33	−0.20	0.84	0.46	1.36	0.18	0.50
PD-CRS	87.08	16.93	98.79	13.03	94.94	18.02	5.30	0.001[b]	0.71	2.69	0.01[b]	0.10
PDQ-39	20.05	11.74	16.33	7.84	19.48	10.87	−1.82	0.07	0.27	−0.30	0.77	−0.09
UPDRS-II	1	0.48	0.62	0.53	0.77	0.32	−2.51	**0.01***	0.55	−1.74	0.08	0.51

M = mean; SD = standard deviation; *t* = t statistic; a = effect size computed using change scores with the control group, positive effect favours corresponding intervention group; b = not statistically significant due to nonsignificant main effect; * = $p < 0.05$; ** = $p < 0.001$; tDCS = transcranial direct current stimulation; COWAT = Controlled Oral Word Association Test; SOC = Stockings of Cambridge; LNS = Letter-Number Sequencing; HVLT = Hopkin's Verbal Learning Test; BNT = Boston Naming Test; JLO = Judgement of Line Orientation; HVOT = Hooper's Visual Orientation Test; MMSE = Mini-Mental State Examination; PD-CRS = Parkinson's Disease—Cognitive Rating Scale; UPDRS-II = Unified Parkinson's Disease Rating Scale—section II (ADL); PDQ-39 = Parkinson's Disease Questionnaire-39.

Table 4: Tailored cognitive training + tDCS and control group cognitive performance at baseline, post-intervention, and follow-up.

	Tailored cognitive training + tDCS						Pairwise comparison statistics					
	Baseline		Post-intervention		Follow-up		Baseline to post-intervention			Baseline to follow-up		
Outcome	*M*	SD	*M*	SD	*M*	SD	*t*	*p*	*g*[a]	*t*	*p*	*g*[a]
COWAT	32.14	9.22	36.29	8.45	35.86	11.50	1.74	0.08	0.70	1.77	0.08	−0.12
SOC	5.29	1.03	7	2.07	8.57	2.20	2.29	**0.02**[*]	0.19	3.86	**0.001**[**]	0.92
LNS	17.63	2.54	18.25	1.99	19.24	1.96	0.72	0.47	0.02	2.21	**0.03**[*]	0.22
Stroop test	29.95	11.50	30.66	6.97	32.38	7.10	0.18	0.86	0.14	0.87	0.39	−0.17
HVLT	21.04	2.70	24.90	2.28	25.19	5.30	5.21	0.001[b]	0.37	2.78	0.01[b]	0.22
Paragraph Recall	3.21	1.43	5.71	1.64	6.43	2.23	4.60	**0.001**[**]	1.36	3.25	**0.002**[*]	1.75
BNT	14	1.43	14.29	1.03	14.57	0.50	0.86	0.39	−0.18	−0.42	0.68	0.73
Similarities	22.89	3.18	26.03	2.25	20.75	2.20	3.73	**0.001**[**]	1.06	−2.15	**0.03**[*]	−1.58
JLO	22.33	7.71	22.47	6.31	22.04	7.13	0.12	0.91	0.06	−0.55	0.59	−0.28
HVOT	21.51	3.79	24.08	3.71	24.37	3.29	3.02	0.003[b]	0.54	2.76	0.01[b]	0.62
MMSE	26.37	1.99	26.51	1.38	26.37	1.54	0.21	0.84	0.61	0.00	1	0.19
PD-CRS	85.56	12.91	93.84	11.69	90.99	8.98	2.41	0.02[b]	0.51	2.66	0.01[b]	−0.02
PDQ-39	25.62	14.63	27.25	10.52	20.44	11.32	0.53	0.60	−0.14	−1.64	0.11	0.27
UPDRS-II	1.17	0.56	0.97	0.48	1.16	0.48	−1.47	0.14	0.34	−0.01	0.99	0.22
	Control						Pairwise comparison statistics					
	Baseline		Post-intervention		Follow-up		Baseline to post-intervention			Baseline to follow-up		
Outcome	*M*	SD	*M*	SD	*M*	SD	*t*	*p*	*g*[a]	*t*	*p*	*g*[a]
COWAT	30.14	15.45	27.43	9.94	36	19.16	−0.87	0.39	—	1.81	0.07	—
SOC	6	2.84	7.28	2.27	7.21	1.84	1.89	0.06	—	1.75	0.08	—
LNS	14.30	6.07	14.82	5.78	14.97	5.02	0.77	0.44	—	1.04	0.30	—
Stroop test	19.03	10.07	18.60	9.38	24.24	20.56	−0.34	0.74	—	0.86	0.39	—
HVLT	21.26	5.51	23.40	5.75	24.04	5.71	1.49	0.14	—	2.84	0.01[b]	—
Paragraph Recall	4.07	2.41	4.07	1.80	3.81	1.30	0.00	1	—	−0.36	0.72	—
BNT	12.43	1.99	13	1.76	11.87	1.84	3.06	0.003[b]	—	−0.87	0.39	—
Similarities	18.80	1.99	19.55	1.96	20.70	2.43	1.06	0.29	—	1.85	0.07	—
JLO	21.10	6.92	20.82	7.55	23.56	8.18	−0.37	0.71	—	1.38	0.17	—
HVOT	23.60	4.06	24.10	3.71	23.66	3.38	0.54	0.59	—	0.05	0.96	—
MMSE	24.38	2.07	24.38	2.16	25.82	2.31	−1.37	0.17	—	0.71	0.48	—
PD-CRS	76.50	19.35	77.50	14.81	82.22	20.21	0.33	0.74	—	3.21	0.002[b]	—
PDQ-39	24.02	14.52	23.76	14.92	24.59	11.81	−0.35	0.73	—	0.39	0.70	—
UPDRS-II	1.18	0.69	1.25	0.94	1.35	0.93	0.71	0.48	—	1.04	0.30	—

M = mean; SD = standard deviation; *t* = t statistic; a = effect size computed using change scores with the control group, positive effect favours corresponding intervention group; b = not statistically significant due to nonsignificant main effect; [*] = $p < 0.05$; [**] = $p < 0.001$; tDCS = transcranial direct current stimulation; COWAT = Controlled Oral Word Association Test; SOC = Stockings of Cambridge; LNS = Letter-Number Sequencing; HVLT = Hopkin's Verbal Learning Test; BNT = Boston Naming Test; JLO = Judgement of Line Orientation; HVOT = Hooper's Visual Orientation Test; MMSE = Mini-Mental State Examination; PD-CRS = Parkinson's Disease—Cognitive Rating Scale; UPDRS-II = Unified Parkinson's Disease Rating Scale—section II (ADL); PDQ-39 = Parkinson's Disease Questionnaire-39.

and tailored cognitive training + tDCS group ($F = 5.11$, $p = 0.01$). No other groups improved on the LNS.

For memory, a significant interaction effect was observed for Paragraph Recall ($F = 2.51$, $p = 0.01$). Significant improvements were identified for the standard cognitive training group, ($F = 5.24$, $p = 0.01$), tDCS group, ($F = 17.82$, $p < 0.001$), and tailored cognitive training + tDCS group ($F = 12.09$, $p < 0.001$). No other groups improved on Paragraph Recall, and no groups improved on HVLT.

For language, a significant interaction effect was observed for the Similarities test ($F = 3.25$, $p = 0.001$). Significant improvements were identified for the standard cognitive training + tDCS group ($F = 5.23$, $p = 0.01$) and tailored cognitive training + tDCS group ($F = 17.43$, $p < 0.001$). No other groups improved on the Similarities test, and no groups improved on the BNT.

For visuospatial abilities, a significant interaction effect was observed for JLO ($F = 3.76$, $p < 0.001$). However, a significant decline was identified for the standard cognitive training group ($F = 6.57$, $p = 0.002$). Therefore, no groups improved on JLO, and no groups improved on HVOT.

No groups improved on measures of global cognition (MMSE and PD-CRS).

For QOL, a significant interaction effect was observed for the PDQ-39 ($F = 2.96$, $p = 0.003$). Significant improvements were identified for the standard cognitive training group ($F = 7.21$, $p = 0.001$) and tailored cognitive training group ($F = 12.48$, $p < 0.001$). No other groups improved on QOL.

For ADL, a significant interaction effect was observed for the UPDRS-II ($F = 1.96$, $p = 0.04$). Significant improvements were identified for the standard cognitive training group ($F = 11.29$, $p < 0.001$) and standard cognitive training + tDCS group ($F = 3.40$, $p = 0.04$). No other groups improved on ADL.

4. Discussion

In support of the therapeutic potential of cognitive training and tDCS, differential rates of improvements in cognition, ADL, and QOL were observed across intervention groups. The control group did not improve on any outcome measures.

The standard cognitive training group improved on memory, ADL, and QOL. Previous standard cognitive training studies report improved memory [2] and ADL in PD [32], but this study is the first to report improvement in QOL. París et al. [2] used the same computer-based cognitive training program (Smartbrain Pro) and the same QOL outcome measure (PDQ-39), but their participants did not improve. This may reflect a ceiling effect as half the participants in París et al.'s [2] cognitive training group were identified as having normal cognition. Nonetheless, ADL and QOL are frequently impaired in PD and associated with cognitive decline [33, 34]. The current findings indicate that standard cognitive training improves ADL and QOL for those with PD.

The tailored cognitive training group improved on attention/working memory and QOL. One tailored cognitive training study has reported "attentional improvements," evidenced by increased neural resting state activity (measured by fMRI) in the superior parietal and prefrontal dorsolateral cortices following training [5]. The current study is the first to report improvements in QOL following tailored cognitive training in participants with PD or PD-MCI. Despite limited evidence in PD, a Cochrane review of cognitive training for people with mild to moderate dementia reported positive effects of cognitive training for QOL (and cognitive function) [35]. The positive results in dementia and in the current study indicate that future studies should explore the potential of tailored cognitive training to improve QOL in PD-MCI.

The tDCS group improved on attention/working memory and memory. Recent studies report significant improvements in attention/working memory in PD [8] and attentional/executive abilities [9, 10]. The current study is the first to demonstrate memory improvement following tDCS in PD-MCI. In accordance with the "dual syndrome hypothesis" [36], if participants in the current study had the APOE allelic genetic abnormality associated with memory deficits in the posterior cortex, the Scaffolding Theory of Ageing and Cognition [37] suggests that their impaired posterior cortical function may have led to compensatory activation of the prefrontal cortices (i.e., left DLPFC) to account for increased cognitive demand during complex tasks (i.e., neuropsychological assessments). Anodal tDCS may have therefore enhanced compensatory activation of the left DLPFC, leading to increased neural activity of frontal functions that were associated with improved memory performance in PD-MCI.

The standard cognitive training + tDCS group improved on executive function, attention/working memory, and ADL. Multiple uncontrolled studies combined standard cognitive training with tDCS, but the results vary. Biundo et al. [11] reported a decline in executive skills and improved attention and memory. Conversely, research in Alzheimer's disease paired repetitive transcranial magnetic stimulation (rTMS) with standard cognitive training and reported improved global cognition [38]. However, different methods of non-invasive stimulation, both anodal tDCS and high-frequency rTMS, increase cortical excitability to improve cognitive functioning [7]. In accordance with Mowszowski et al. [39], combining standard cognitive training with tDCS in the current study may have resulted in "positive plasticity" to alleviate cognitive deficits. Standard cognitive training may have stimulated and strengthened existing neural connections (synaptogenesis), while tDCS provided compensatory activation of a cortical region (left DLPFC) associated with higher-order cognition and functional improvement in ADL.

This is the first standard cognitive training and tDCS study to report language improvements in PD. Improved language abilities may be explained by the overlap between the language skills needed to complete the Similarities outcome test and those needed to complete the cognitive training program. During the language activities, participants finished sentences by selecting an appropriate word and determining the relationship between a group of words by applying a semantic category to those words. Successful completion of the Similarities test also involves application of semantic word categories to describe the most appropriate relationship between a set of words [18]. Participants in the standard cognitive training + tDCS group may have therefore trained and improved language skills that were most beneficial for

successful performance on the Similarities language test. There is mounting evidence indicating that some people with PD demonstrate language impairment [16, 40], and the current study suggests that combining standard cognitive training with tDCS may alleviate this deficit.

The tailored cognitive training + tDCS group improved on executive function, attention/working memory, and memory. Among studies that have examined these interventions independently, several reports improved executive function and attention/working memory in PD [5, 9]. The current study is the first to report memory improvements following tailored cognitive training and tDCS in PD. Memory impairment is common in PD and may predict progression to PD-Dementia [41]. Future clinical trials of tDCS and tailored cognitive training need to include standardised memory outcomes and interventions targeting memory impairment in PD.

The current study is also the first to report improved language abilities following tailored cognitive training and tDCS in PD. For the tailored cognitive training + tDCS group, language improvements were observed on the Similarities test, but not the BNT. The MDS Task Force classifies the Similarities test as a measure of language abilities [13]. However, the Similarities test is a subtest of the verbal IQ index of the WAIS battery and involves abstract reasoning [18]. Abstract reasoning is a higher-order cognitive ability associated with executive function and involves ordering, comparing, analysing, and synthesizing information [42]. When completing the Similarities test, participants need to describe in what ways are two concepts/words alike, which requires the use of abstract reasoning (an executive skill) to synthesise information related to both concepts/words. As a task requiring executive function, completing the Similarities test may involve increased activation of left DLPFC, which was also the target of tDCS for this group. Participants in this group also demonstrated impaired executive function (lowest baseline SOC score) and completed cognitive training tasks tailored to executive function skills. Pairing this form of tailored cognitive training with tDCS applied to left DLPFC may have increased cortical activity associated with improved performance on SOC *and* Similarities, tasks involving executive *and* language abilities. According to the theoretical model proposed by Kim and Kim [43], combining a stimulation and compensation-focussed intervention (tailored cognitive training) with another compensation-focussed intervention (tDCS) may have provided optimal conditions for neuronal plasticity, which led to improved performance across several cognitive domains.

There are limitations to the current study. Several outcomes did not improve across intervention groups, which may be due to a number of reasons. Despite selecting outcomes in accordance with MDS Task Force recommendations [13], a lack of sensitivity of some cognitive tests for detecting change in PD may have contributed to nonsignificant improvement for those tests (e.g., HVLT, BNT, and MMSE). [42] Researchers should consult compendiums of neuropsychological tests [42] to ensure that sensitive outcomes are included in future clinical trials. The cognitive training and tDCS parameters used in this study may have also impacted nonsignificant results. No improvements were observed for visuospatial abilities as measured by HVOT and JLO. These tests involve perceptual organisation (HVOT) and estimation of angled lines (JLO), but the visuospatial activities in the cognitive training interventions involved different visuospatial skills (e.g., identifying coordinates and time ranges on an analog clock). Furthermore, the tDCS in this study stimulated a cortical region (left DLPFC) that is not associated with visuospatial performance. Several studies report more dominant involvement of the right posterior hemisphere during completion of HVOT and JLO [44, 45]. It is therefore likely that the cognitive training tasks and site of tDCS were not conducive to improved visuospatial abilities. It is also important to note that two participants in the standard cognitive training group with high JLO scores at pre-intervention dropped out of the study preceding the follow-up assessment, which may account for this group's significant decline in JLO performance at follow-up. This study was also somewhat underpowered, which may have impacted nonsignificant outcome effects. Lastly, exposure was not matched between intervention groups. Participants allocated to the cognitive training groups (standard or tailored) completed 12 sessions of training. Whereas, participants in the cognitive training + tDCS groups completed 12 sessions of cognitive training *and* 4 sessions of tDCS. Completing both interventions exposed participants to a greater number of therapeutic sessions designed to improve cognition, which may have produced additive beneficial effects on neuropsychological outcomes. Future studies should account for these methodological parameters when exploring the therapeutic potential of cognitive training and tDCS in PD and PD-MCI.

5. Conclusions

This study provides evidence in support of cognitive training, tDCS, and cognitive training combined with tDCS for PD-MCI. The rate of participant attrition was low (<10%), and cognitive performance was measured in line with MDS Task Force recommendations for Level II diagnostic criteria of PD-MCI [13]. Overall, a greater number of outcomes improved for the groups that received standard or tailored cognitive training combined with tDCS. These findings suggest that cognitive training combined with tDCS may provide optimal conditions for neuronal plasticity, leading to improvements in cognition and functional outcomes for those with PD-MCI.

Conflicts of Interest

The authors declare no conflicts of interest.

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Supplementary Materials

Five tables are included in supplementary material. The CONSORT checklist is reported in Table S1. A summary of the cognitive training activities is reported in Table S2. Baseline, post-intervention, and follow-up neuropsychological test results are reported in Tables S3, S4, and S5, respectively. (*Supplementary Materials*)

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