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The effects of deep brain stimulation of the pedunculopontine nucleus on cognition in Parkinson's disease and Progressive Supranuclear Palsy ☆

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ABSTRACT

Deep brain stimulation (DBS) of the pedunculopontine nucleus (PPN) is a relatively new treatment approach for the axial symptoms of Parkinson's disease (PD) and Progressive Supranuclear Palsy (PSP). The results concerning the clinical benefits are variable and inconsistent. The effect of PPN-DBS on limited aspects of cognitive function has been examined in a handful of mainly single or multiple case studies. The aim of this study was to investigate the effects of PPN-DBS for PD and PSP using a comprehensive battery of neuropsychological assessment covering the main cognitive domains. Five patients with PD and two patients with PSP who were consecutively operated at our centre with PPN-DBS were administered a neuropsychological battery of cognitive tests within one month prior to surgery and one year after surgery. The majority of tests of cognition showed no significant change from before to after surgery. The only aspects of cognition that showed reliable decline in a proportion of the patients were some indices of processing speed (Stroop colour naming control task, WAIS-III digit symbol) and category switching verbal fluency. Despite the small and heterogeneous sample, the results indicate that PPN-DBS is generally safe from a cognitive perspective.

1. Introduction

In Parkinson's Disease (PD) and progressive supranuclear palsy (PSP) cholinergic neurons of the pedunculopontine nucleus (PPN) degenerate [1]. Proposed motor functions of the PPN include locomotion [2] and voluntary movement [3]. PPN abnormalities in PD and PSP may be associated with the postural and gait impairments in these disorders. This is strengthened by a correlation between the degree of neuronal loss in the PPN and the severity of motor symptoms [4]. In the MPTP primate model of PD, 5–10 Hz low frequency stimulation of the PPN reversed akinesia [5]. Thus, the PPN was identified as a new DBS target for the treatment of the axial symptoms of PD and PSP. Clinical trials of low frequency PPN-DBS for motor symptoms have reported mixed results. The greatest improvement of axial symptoms was elicited by a combination of PPN- and STN-DBS [6] and unilateral PPN-DBS reduced freezing and falls [7]. Low frequency PPN-DBS improves Unified Parkinson's Disease Rating Scale scores on average by 33% [6].

Since PPN-DBS is a relatively new treatment, only a handful or studies have investigated its effects on cognitive function [8–11]. Most of these studies only included a limited neuropsychological battery. Three of the studies investigated acute stimulation on/off effects [12,13,14] and only four studies [8–11] examined the effects of PPN-DBS surgery by comparing and pre and post-operative cognitive performance, and two of these are single case reports. More importantly with the exceptions of two single case reports [8,10], the other studies examined the combined effects of PPN and STN-DBS. Therefore, the nature of any cognitive changes that can be solely attributed to PPN-DBS remains unclear. The aim of the present study was to identify the 'pure' or 'direct' effects of PPN-DBS on cognition and we examined the performance of 7 patients with PD or PSP who were consecutive referrals for PPN-DBS on a large neuropsychological battery before and one year after surgery.

2. Methods

2.1. Participants

Five patients (5 males) with the clinical diagnosis of Parkinson's disease based on the UK Brain Bank criteria and two patients with the clinical

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diagnosis of Progressive Supranuclear Palsy (1 male) based on the National Institute of Neurological Disorders and Society for PSP (NINDS-SPSP) criteria [15] were assessed. The mean age was 68.0 years (SD = 5.54; range 59–74). All had MRI-guided and MRI-verified PPN-DBS surgery, which was unilateral in 6 and bilateral in one case [16]. The demographic and clinical information for the sample at baseline are presented in Table 1. At the one-year follow-up assessment, low-frequency PPN stimulation remained switched on for the PD patients only; as the DBS had been switched off for the two PSP patients.

2.2. Design

Patients completed the neuropsychological assessment prior to PPN-DBS surgery and one year after surgery.

2.3. Neuropsychological assessment

An extensive neuropsychological test battery was used to assess all major cognitive domains with the main focus on executive function. The tests included were the Mini Mental State Examination, Dementia Rating Scale-2, National Adult Reading Test, Wechsler Abbreviated Scale of Intelligence, Wechsler Adult Intelligence Scale–III (WAIS-III) Working Memory Index (WMI) and Processing Speed Index (PSI), California Verbal Learning test, Delis-Kaplan Executive Function System Stroop colour-word interference, Trail making and verbal fluency subtests. All the tests were administered and scored according to standard procedures.

The Beck Depression Inventory [17] and the Starkstein Apathy Scale [18] were also administered.

2.4. Statistical analysis

Comparison of pre and post-operative scores were with the Wilcoxon test. For measures with significant change after surgery, the reliable change indices were calculated to determine the reliability of the change.

3. Results

3.1. Whole sample

The mean scores on the tests of cognitive function before and 12 months after surgery for the whole sample are presented in Table 2.

The analysis revealed a significant decline on the Initiation/Perseveration subscale of the Dementia Rating Scale-2 ($p = 0.038$), from before to after surgery. There was no effect of surgery on the other DRS-2 subscales.

On the California Verbal Learnin Test, the total number of words recalled on trials 1 to 5 were significantly lower after than before surgery ($p = 0.027$). There was no effect of surgery on the free and cued short and long delay recall trials, or the recognition trials or on the number of intrusion and repetition errors (all $p > 0.05$).

Performance on the colour naming condition of the Stroop colour word interference test was worse after PPN-DBS ($p = 0.017$). The effects of surgery on the word reading ($p = 0.058$) and switching/interference ($p = 0.058$) subtests approached significance, also suggestive of slowing of performance after surgery. However, there was no significant effect of surgery on the interference condition ($p = 0.16$). Wilcoxon tests did not show any significant effects of PPN-DBS surgery on the number of errors on the Stroop subtests.

The category switching verbal fluency task was worse after surgery both in terms of the number of correct words generated ($p = 0.009$) and the number of correct switches ($p = 0.01$). The effect of surgery on category verbal fluency and letter verbal fluency were not significant (both $p > 0.05$).

PPN-DBS surgery did not produce any significant change on the remaining tests, namely, the Trail making test, WASI current IQ, WAIS III Working Memory Index and Processing Speed Index (all $p > 0.05$). Similarly, there was no significant change from before to after surgery in mood or apathy.

3.2. PD patients only

Wilcoxon tests revealed a significant reduction from before to after PPN-DBS surgery for the total number of correct words (pre mean: 9.8 (SD = 2.95); post mean: 6.2 (SD = 2.59); $z = -2.04$; $p = 0.041$) and the total number of correct switches (pre mean: 9.8 (SD = 2.39); post mean 6.6 (SD = 2.3); $z = -2.03$; $p = 0.042$) on the category switching fluency test. The pre vs post-operative changes for the remaining tests were not significant (all $p < 0.05$).

3.3. Reliable change indices (RCI)

The RCIs for the neuropsychological tests which showed significant effects for the whole sample (or the PD patients only), were calculated. The RCIs for the Initiation/Perseveration subscale of the DRS-2 and the colour-naming subtest support the reliability of the significant post-operative decline reported above, as a decline was present in 66.67% of the patients. For the total number of correct words generated on the category switching fluency test, RCIs are supportive of a reliable change as 57.14%, of the patients showed a reliable decline at the post-operative assessment. Also, with the RCIs for the PD patients only, 4 out of 5 patients or 80% showed a reliable decline at the post-operative assessment on the category switching test. RCIs for the switching accuracy score on the category switching fluency test, suggest that only 42.86% of the patients had a reliable decline at the post-operative assessment. The RCI for the total number of words recalled across 5 trials on the California Verbal Learning Test is not consistent with a reliable change as only 33.33% of the patients showed a reliable decline at the post-operative assessment.

4. Discussion

This is the first study to investigate the cognitive effects of PPN-DBS in a sample of 5 PD and 2 PSP patients who had PPN-DBS surgery only, who were assessed before and one year after surgery on an extensive neuropsychological battery.

The results suggest that PPN-DBS surgery does not affect most aspects of cognitive function and is associated with a reliable decline of category switching verbal fluency and processing speed in a proportion of the patients. For the whole sample, the initial analysis indicated a significant

Table 1
Demographic and clinical information for the seven patients.

Patient	Age years	Gender	Years of education	Disease duration years	UPDRS/PSPRS	Operation side	MMSE	BDI	SAS
PD 1	71	M	17	21	20	R	30	2	7
PD 2	74	M	13	9	39	L	29	16	23
PD 3	70	M	19	17	23	L	29	12	6
PD 4	66	M	10	3	31	L	28	3	2
PD 5	73	M	10	11	16	B	27	19	21
PSP 1	59	F	16	2	30	L	30	33	18
PSP 2	63	M	10	8	44	L	27	2	8

M = Male; F = Female; PD = Parkinson's disease; PSP = Progressive Supranuclear Palsy; UPDRS = Unified Parkinson's disease rating scale; PSPRS = Progressive supranuclear palsy rating scale; R = Right; L = Left; B = Bilateral; MMSE = Mini Mental State Examination; BDI Beck Depression Inventory; SAS = Starkstein Apathy Scale.

Table 2
Means and standard deviations given in brackets for the neuropsychological tests before and 12 months after PPN-DBS surgery. Values represent scaled scores, unless indicated otherwise.

Neuropsychological test	N	Pre-operative assessment	N	Post-operative assessment	*p*-Value
Dementia Rating Scale-2 (DRS-2)					
Attention	6	12.33 (1.03)	6	11.17 (2.4)	0.135
Initiation/Perseveration[a]	6	7.5 (2.5)	6	5.67 (3.27)	0.038
Construction	6	9.5 (1.22)	6	10 (0)	0.363
Conceptualization	6	10.33 (3.2)	6	11 (1.1)	0.699
Memory	6	12 (1.55)	6	11.33 (1.86)	0.501
Total Score	7	9.71 (3.77)	7	8.29 (3.04)	0.093
National Adult Reading Test					
Premorbid Estimated Full scale IQ	7	107.29 (12.57)	7	109.86 (12.9)	0.179
Wechsler Abbreviated Scale of Intelligence					
Vocabulary[a]	6	48.5 (17.48)	6	42.5 (16.07)	0.410
Matrix reasoning[a]	6	54.33 (8.69)	6	51.83 (10.19)	0.120
Full scale IQ	6	103.5 (18.51)	6	97 (16.53)	0.316
California Verbal Learning Test-II					
Total recall trials 1 to 5[a]	6	54 (10.75)	6	49.5 (9.5)	0.027
Free short-delay recall[b]	6	9.17 (3.31)	6	8.67(3.2)	0.737
Cued short-delay recall[b]	6	10.33 (2.5)	6	10.83 (3.06)	0.415
Free long-delay recall[b]	6	9.67 (1.97)	6	9.83 (2.99)	0.842
Cued long-delay recall[b]	6	10.67 (2.94)	6	10.33 (2.8)	0.611
Total intrusions[b]	6	4 (3.58)	6	5.5 (5.39)	0.537
Total repetitions[b]	6	5.17 (3.82)	6	6.17 (4.26)	0.562
Yes/No Recognition Total correct[b]	6	15 (1.1)	6	15.5 (0.84)	0.203
Recognition false positives[b]	6	5.5 (5.92)	6	3.83 (3.87)	0.489
Forced choice recognition percentage correct	6	98.96 (2.55)	6	100 (0)	0.363
Wechsler Adult Intelligence Scale-III					
Digit Span	7	9.86 (1.86)	7	10.43 (2.07)	0.386
Letter-number sequencing	6	8.83 (3.06)	6	8.67 (3.27)	0.907
Arithmetic	7	9.71 (2.87)	7	10.29 (2.87)	0.172
Working Memory Index	6	98 (10.73)	6	98.5 (9.33)	0.276
Digit symbol	7	5.86 (1.77)	7	5.14 (2.34)	0.499
Symbol search	7	8.29 (2.29)	7	6.43 (2.51)	0.081
Processing Speed Index	7	78.57 (12.27)	7	73.43 (8.73)	0.411
Delis-Kaplan Executive Function System					
Colour Word interference-colour naming	6	5.5 (3.21)	6	2.83 (1.83)	0.017
Total errors[b]		0 (0)		0.17 (0.41)	0.317
Colour Word interference-word reading	6	6.5 (3.62)	6	4.5 (4.18)	0.058
Total errors[b]		0 (0)		0 (0)	1
Colour Word interference-inhibition	7	6.29 (3.09)	7	4.0 (3.65)	0.160
Total errors[b]		3.57 (3.41)		3.57 (2.94)	0.799
Colour Word interference-inhibition/switching	6	5.5 (3.51)	6	3.67 (3.44)	0.058
Total errors[b]		2.17 (3.54)		5.33 (3.67)	0.068
Trail making-visual scanning	6	5.5 (4.18)	6	3.83 (4.26)	0.195
Trail making-number sequencing	7	7.71 (4.82)	7	5.57 (3.46)	0.073
Trail making-letter sequencing	6	6.5 (4.42)	6	4.67 (3.72)	0.459
Trail making-number-letter sequencing	7	8.0 (4.83)	7	5.29 (5.38)	0.153
Trail-making-processing speed	6	7.5 (4.04)	6	5.17 (5.08)	0.252
Verbal fluency-letter	7	8.57 (3.78)	7	7.0 (3.0)	0.174
Verbal fluency-category	7	6.29 (2.87)	7	5.43 (2.37)	0.078
Verbal fluency-category switching (total correct)	7	8.57 (3.78)	7	5.86 (3.18)	0.009
Verbal fluency – category switching (switching accuracy)	7	8.57 (3.51)	7	6.14 (3.08)	0.01

[a] T-scores.
[b] Raw scores.

post-operative decline of the Initiation/Perseveration subscale of the DRS-2, the total number of words recalled on 5 trials of the CVLT, the colour naming control condition of the Stroop colour-word interference test and the number of both correct words and switches on the category switching fluency test. Reliable Change indices (RCIs) were calculated to estimate the proportion of patients, who had a reliable decline, improvement or no change on the cognitive tests. The RCIs suggested that for the whole sample, for the Initiation/Perseveration subscale of the DRS-2 and the colour naming condition of the Stroop colour-word interference test, 66.67% of the patients showed a reliable decline on both these tests. For the total number of correct words on the switching category verbal fluency test 57.14% of the whole group and 80% of the PD patients showed a reliable decline. However, despite the reliable decline in the initiation/perseveration subscale of the DRS-2 for the whole sample, it is important to note two important points. First, the change in this subscale and other subscales of the DRS-2 was not significant when considering only the 5 PD patients, thus indicating that the significant decline in the initiation/perseveration subscale was due to the two PSP patients. Second, even for the whole sample, the decline in the initiation-perseveration subscale of the DRS-2 was mainly due to a decline on the supermarket category fluency item of this subscale, with patients generating significantly fewer words after surgery.

The results need to be considered with caution, as they are based on a small number of patients, and a mixed sample of PD and PSP patients and no control groups were included. Nevertheless, the results indicate that the majority of tests of cognitive function do not show any change after PPN-DBS surgery.

Some previous studies of the effects of PPN-DBS surgery on cognition reported improvements in specific cognitive tests, including grammatical errors, attention, working-memory and verbal fluency [8,10,11]. The present findings are not consistent with these previous results, as no cognitive improvement was observed after PPN-DBS, and processing speed and category switching fluency declined post-operatively. However, the reliability of these cognitive improvements can be questioned as two of these studies

are single case reports [8,10] and the other sample had both PPN-DBS and STN-DBS [11].

Considering the interconnectivity of the PPN with the basal ganglia and the prefrontal cortex [19] it is possible that the decline in processing speed and category switching verbal fluency after PPN-DBS reflect disruption of the motor preparation and switching functions of the fronto-striatal circuits. This would be consistent with the finding that low frequency PPN stimulation induced increased glucose utilization in prefrontal regions [12,14]. On the basis of electrophysiological studies in animals performing a stop signal ask, it was proposed that the PPN may serve as an accelerating mechanism for the indirect basal ganglia pathway and may decrease striatal activity [20]. Thus, it is possible that in the present study PPN-DBS surgery had an impact on the patients' ability to inhibit habitual responses in order to produce controlled responses during performance of tasks such as the category switching verbal fluency test.

Our study was the first to use an extensive neuropsychological test battery to assess major cognitive domains in a sample of PD and PSP patients who had PPN-DBS only. The results indicate that PPN-DBS surgery is generally safe from a cognitive perspective, but may be associated with a decline of category switching verbal fluency and also processing speed in a proportion of the patients. Given our small and heterogeneous sample, these results require replication in a larger and more homogeneous sample of PD patients.

Declaration of competing interest

Nothing to declare.

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