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ORIGINAL ARTICLE

Evidence of improved immediate verbal memory and diminished category fluency following STN-DBS in Chinese-Cantonese patients with idiopathic Parkinson's disease

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Abstract The present study investigated the neuropsychological effects of bilateral deep brain stimulation (DBS) on subthalamic nucleus (STN) in Chinese-Cantonese patients with idiopathic Parkinson's disease (PD). Twenty-seven patients were prospectively recruited from the Movement Disorder Clinic at the Hong Kong Prince of Wales Hospital. Neuropsychological evaluations were performed at baseline, 6 and 12 months following the DBS procedure. Assessment battery included standardized tests on global cognitive function, verbal memory, non-verbal memory, confrontation naming, visuospatial organization, attention and executive functions. Anxiety and depressive symptoms were measured by two self-reported questionnaires. Results demonstrated diminished performance on a category fluency task that occurred at 6 months post-operatively and persisted at 12-month re-evaluation; 29.6–33.3 % of patients showed reduction of more than 1 SD (standard deviation) at post-operative measure. Conversely, performance on an immediate recall task in a verbal memory test was found to improve significantly at the same time point and persisted through 12 months after surgery; 22.2–25.9 % showed an improvement ($\geq$1 SD). Psychologically, anxiety symptoms were statistically decreased and the significant reduction occurred at 12 months after surgery. Patients who reported a moderate to severe level of anxiety reduced from 51.9 to 18.5 %. Our findings concurred with most evidences on the effects of STN-DBS on verbal fluency; on the other hand, we demonstrated improvement of immediate verbal memory that warranted further investigation.

Keywords Parkinson's disease · Deep brain stimulation · Neuropsychology · Cognitive function · Memory · Category fluency

Introduction

Although bilateral deep brain stimulation of the subthalamic nucleus (STN-DBS) has been accepted as an effective treatment of motor symptoms in Parkinson's disease (PD), its reported effects on non-motor symptoms, including cognitive functions and mood, are highly varied and even conflicting in some reports [1–3]. The most consistent findings are reductions in verbal fluency and improvements in self-reported symptoms of depression [1]. Significant declines in verbal fluency (phonemic and semantic) that are persistent and evident after 3 years of DBS procedure are reported in up to 30–50 % of patients. Nevertheless, changes in global cognitive functioning, memory, attention and executive function are less common. Post-operative severe and global cognitive decline are seen in less than 1–2 % of patients [1]. In this prospective study, we aimed to evaluate the effects of STN-DBS on

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cognitive, anxiety and mood functions in Chinese-Cantonese patients with idiopathic PD.

Methods

Subjects

All patients with a clinical diagnosis of PD (Queen Square Brain Bank Criteria) who received bilateral STN-DBS were prospectively recruited at the Prince of Wales Hospital, a teaching hospital of the Chinese University of Hong Kong between 2009 and 2013. Ethic committee approval and written informed consent were obtained.

Assessments

Patients were evaluated at three time points: baseline, 6 months after and 12 months after the STN-DBS procedure as part of their regular clinical care by a clinical psychologist specialized in neuropsychology subspecialty. All patients were assessed at their optimal functioning (Drug ON at baseline and Drug ON and DBS ON at post-operation).

A total of eight neuropsychological tests were included. Global cognitive function was assessed using the Montreal Cognitive Assessment Hong Kong version (HK-MoCA) with a total score between 0 and 30 [4]. The Chinese Auditory Verbal Learning Test (CAVLT) was used for verbal memory [5]. This test included five repeated learning trials with a score for total immediate recall (range from 0 to 75); a score for immediate recall following interference (range from 0 to 15); and a score for a 30-min delayed recall (range from 0 to 15). Non-verbal memory was measured by Benton Visual Retention Test (BVRT) with 10 items of line drawings with progressive complexity, patients were required to recall from memory after a 10 s of exposure for each drawing (Administration A) [6]. The total score ranges from 0 to 10. Three parallel forms were used, all patients was assessed with Form C at baseline, Form D at 6-month post-operation and Form E at 12-month post-operation. Confrontation naming was examined using the Chinese modified version of the Boston naming test (BNT) [7] with 30 items and a maximum score of 30. Visuospatial organization ability was measured by the Hooper visual organization test (HVOT) [8]; the test consists of 30 line drawings of simple objects that have been cut into pieces and rearranged. Patients were required to name what each object would be if the pieces were put back together with a score range between 0 and 30. Executive functions and attention were measured by digit span test (DST) [5], Stroop test Chinese victoria version (ST) [5] and a category fluency test [9]. The Stroop test Chinese victoria version requires patients to name the color of each item on three task boards as quickly as possible. Each board contains 24 items presented in 6 rows with 4 items in a row. The three boards include one with colored dots, one with common Chinese words printed in color, and one with color words printed in color that are not corresponding to the words. Different from the original Stroop color and word test developed by Golden [10], reaction time in millisecond was measured for each task board and the patients are required to finish all 24 items on each board. Unlike most verbal fluency measures used in the West, phonemic fluency is not measurable in the Chinese language. This is because Chinese characters map onto phonology at the monosyllable level; there is no parts in a character that has phonological elements such as phonemes. Hence, semantic (category) fluency is used among Chinese-Cantonese and we include two trials, one for living things (animal) and the other non-living things (transportation). Patients were required to name as many items without repeat within a 60-s time limit for each category. Sum of the two trials was regarded as a category fluency total score. All patients were assessed at three time points using the identical version (except for BVRT that three parallel versions were used) and procedure of neuropsychological assessment.

Mood and anxiety symptoms were measured by the Beck Depression Inventory-II (BDI-II) [11] and Beck Anxiety Inventory (BAI) [12]. Baseline motor assessments (UPDRS Part III) were performed at "OFF" drug condition (after an interruption of anti-parkinsonism medication of at least 12 h) and in the best "ON" drug condition (after resumption of anti-parkinsonism medication). In the post-STN-DBS motor assessments, both Drug OFF and DBS OFF and Drug OFF and DBS ON were evaluated.

Statistical analysis

Scores at baseline, 6- and 12-month post-STN-DBS were compared using Friedman's test. Post hoc analysis was conducted using separate Wilcoxon Signed Ranked Tests with Bonferroni adjustment. Spearman rank correlation analysis was performed to test the within group changes of all neuropsychological test scores, and between changes of neuropsychological test scores, changes of motor functioning (UPDRS III scores), age at surgery, age at disease onset and disease duration. Clinical values were expressed as mean ± standard deviation (SD). A p value of <0.05 was considered statistically significant, except for the post hoc tests, a p value of <0.017 was set as significant level after adjustment. Post-operative change was determined by change of standard z scores, a criterion of equal to or more than ± 1.0 standard deviation (SD) was used to define individual post-operative improvement or decline. Data were analyzed using the Statistical package for social sciences (IBM SPSS, 21.0 version) [13].

Results

Baseline characteristics

Thirty patients with Parkinson's disease who received bilateral STN-DBS were recruited; three were excluded from analysis due to violation of the assessment protocol. Baseline characteristics and neuropsychological scores are summarized in Table 1. Of the 27 patients, 18 (66.7 %) were male. Their mean age was 55.3 (6.10) years with a range between 39 and 63. The mean age at disease onset was 45.37 (9.81) years with a mean of 10.12 (3.82) years of disease duration. They had a mean of 10.72 (5.34) years of full-time education. No major adverse events related to surgery occurred. At baseline measure, all patients had an above clinical cut-off score for HK-MoCA, indicating an intact overall cognitive function in all patients. Seven (25.9 %) and 14 (51.9 %) patients reported a moderate to severe level of depression and anxiety, respectively, according to standardized clinical cut-off [11, 12].

Effects of STN-DBS on neuropsychological functions

Neuropsychological test scores are summarized in Table 2. Consistent with most studies, the total number of words generated from the two category fluency trials (animal and transportation) was significantly diminished after bilateral STN-DBS [$\chi^2(2) = 8.52$, $p = 0.014$]. Post hoc analysis showed that the first statistically significant reduction occurred from the baseline to the post-operative 6-month evaluation ($Z = 2.558$, $p = 0.011$). Differences between the two post-operative measures were not significant, indicating that the reduction occurred at 6 months persisted through 1 year after the DBS procedure. Significant post-operative change as defined by the criterion of z score change equal to or more than $\pm$ 1.0SD was observed in 10 (37.0 %) patients in both the 6- and the 12-month post-operative assessment. In the 6-month post-operative evaluation, 8 (29.6 %) had a significant decline while 2 (7.4 %) had an improvement. After 12 months of the DBS procedure, 9 patients (33.3 %) had a significant decline from baseline while 1 patient (2.7 %) improved.

Table 1 Demographic characteristics at baseline

	Bilateral STN-DBS ($n = 27$)
Sex (M/F)	18/9
Age (years)	55.53 ± 6.10
Age at onset (years)	45.37 ± 9.81
Disease duration (years)	10.12 ± 3.82
Full-time education (years)	10.72 ± 5.34

All patients generated more items in the animal than the transportation fluency tasks at all three time points of measurements (Table 2). We found discrepancy on the effects of STN-DBS on animal and transportation fluency. There was a significant reduction on animal fluency after bilateral STN-DBS [$\chi^2(2) = 10.25$, $p = 0.006$]. The pattern of post-operative reduction was similar to the reduction of total category fluency as described above; that the first significant change occurred from the baseline to the 6-month post-operative evaluation ($Z = 2.657$, $p = 0.009$), such effect had persisted at 1 year post-operative evaluation. Interestingly, there was no significant change on transportation fluency at any post-operative time points of measurements [$\chi^2(2) = 5.52$, $p = 0.063$].

Performance on an immediate recall subtest of a verbal memory task (CAVLT), which requires learning and immediate recall of a word list for 5 times, was found to have a significant improvement [$\chi^2(2) = 7.14$, $p = 0.028$] post-operatively. Post hoc analysis demonstrated that the first statistically significant change occurred at 6 months after the DBS procedure ($Z = -2.760$, $p = 0.006$). Similar to the pattern of changes in category fluency, no difference was found between the two post-operative measures, suggesting that the changes detected at 6 months had persisted. Seven (25.9 %) and 6 (22.2 %) patients had a significant improvement at 6 and 12 months after surgery. Conversely, 1 (2.7 %) and 2 (7.4 %) experienced a significant decline at the two time points of measures, respectively. No statistically significant change was detected for a recall trial after interference and a delayed recall trial in the CAVLT.

There were no statistically significant pre- and post-operation differences on test scores in other neuropsychological tests including test for global cognitive function (HK-MoCA), non-verbal memory (BVRT), expressive naming (BNT), visuospatial function (HVOT), attention and executive function (ST, DST).

Psychologically, anxiety level was significantly reduced post-operatively [$\chi^2(2) = 10.78$, $p = 0.005$], while the severity of depressed symptoms remained steady. The first significant reduction of anxiety was found to occur from 6- to 12-month post-operative evaluation ($Z = 2.622$, $p = 0.009$) according to post hoc analysis. Unlike the cognitive changes reported above, no significant changes occurred from baseline to 6-month evaluation in anxiety level. At 12 months, 5 (18.5 %) and 6 (22.2 %) patients reported a moderate to severe level of anxiety and depressive scores, respectively, compared with 14 (51.9 %) and 7 (25.9 %) at baseline.

Motor scores (UPDRS III) were improved by an average of 63.1 % at 6 months and 62.2 % at 12 months following the STN-DBS procedure. Correlation analysis showed no statistically significant relationship within actual change scores on neuropsychological tests, and between

Table 2 Results of neuropsychological tests and motor assessment at baseline, 6 months after and 12 months after STN-DBS

	Baseline M ± SD (score range)	6 months M ± SD (score range)	12 months M ± SD (score range)	*p* value
Global cognitive function				
MoCA	26.32 ± 2.32 (20–30)	26.56 ± 2.77 (18–30)	27.16 ± 2.82 (20–30)	0.083
Attention and working memory				
Digit forward span	8.20 ± 1.29 (6–11)	8.12 ± 1.30 (6–11)	8.24 ± 1.61 (4–13)	0.930
Digit backward span	4.76 ± 1.51 (3–8)	4.60 ± 1.50 (2–7)	4.96 ± 1.39 (3–8)	0.183
Stroop test dot trial RT	15.63 ± 3.59 (10.34–25.08)	16.62 ± 4.59 (9.53–25.98)	17.18 ± 4.59 (10.32–28.30)	0.125
Stroop test word trial RT	19.04 ± 5.44 (9.32–32.33)	19.92 ± 5.49 (12.00–38.37)	20.33 ± 6.55 (11.19–35.94)	0.125
Verbal memory				
CAVLT				
Total immediate recall	41.76 ± 9.37 (25–60)	46.36 ± 8.87 (26–65)	47.32 ± 11.08 (25–65)	0.028*
Recall after interference	9.04 ± 2.92 (3–14)	9.36 ± 2.69 (3–14)	9.20 ± 3.06 (3–13)	0.709
Delayed recall	8.76 ± 3.28 (3–14)	9.44 ± 3.27 (2–14)	8.96 ± 3.67 (3–15)	0.700
Non-verbal memory				
BVRT	6.81 ± 1.33 (4–9)	6.33 ± 1.56 (4–10)	6.10 ± 1.51 (3–9)	0.099
Expressive verbal naming				
BNT	22.35 ± 2.33 (21–30)	23.54 ± 3.96 (17–29)	22.97 ± 2.98 (20–30)	0.912
Visuospatial ability				
VOT	19.53 ± 5.21 (12.5–29.0)	20.64 ± 4.75 (13.5–28.5)	19.22 ± 3.99 (12.0–29.5)	0.875
Executive function				
Stroop test color–word trial RT	32.74 ± 9.99 (20.22–68.69)	33.65 ± 12.27 (18.14–67.10)	32.70 ± 10.02 (19.24–53.00)	0.852
Category fluency (animal)	17.60 ± 4.24 (12–27)	16.00 ± 3.74 (11–24)	15.28 ± 3.78 (10–26)	0.006*
Category fluency (transportation)	11.64 ± 2.25 (7–16)	10.76 ± 2.57 (6–16)	10.56 ± 2.90 (6–16)	0.063
Category fluency total	29.24 ± 5.21 (21–40)	26.76 ± 5.62 (18–39)	25.84 ± 6.43 (17–42)	0.014*
Anxiety symptoms				
BAI	16.92 ± 6.54 (0–17)	13.75 ± 6.30 (1–12)	9.96 ± 6.69 (0–12)	0.005*
Depressive symptoms				
BDI-II	13.50 ± 6.59 (0–19)	12.00 ± 5.59 (0–11)	11.83 ± 6.41 (0–11)	0.347
Movement (UPDRS part III)				
Drug OFF	43.68 ± 12.85 (14–68)	na	na	na
Drug ON	14.28 ± 8.30 (3–31)	na	na	na
Drug OFF and DBS OFF	na	43.08 ± 13.63 (21–75)	44.33 ± 12.79 (22–66)	na
Drug OFF and DBS ON	na	16.08 ± 8.52 (3–33)	16.50 ± 9.28 (4–39)	na

The results are expressed as mean ± standard deviation (SD) and minimal and maximum score range in brackets. *p* values expressed as results of Friedman's test, a $p < 0.05$ was considered statistically significant

na not applicable, *HK-MoCA* Montreal cognitive assessment Hong Kong version, *CAVLT* Chinese auditory verbal learning test, *BVRT* Benton visual retention test, *BNT* Boston naming test, *HVOT* Hooper visual organizational test, *UPDRS* unified Parkinson's disease rating scale (Part III), *BDI-II* beck depression inventory-II, *BAI* Beck anxiety inventory, *RT* reaction time in millisecond

neuropsychological test scores, changes of motor functioning (UPDRS III scores), age at surgery, age at disease onset and disease duration.

Discussion

In this prospective study among PD patients with STN-DBS, we reported evidence of diminished category fluency and improved immediate recall in a verbal memory test that occurred at 6-month post-operative measure and persisted after 12 months of the DBS procedure. No patient showed a global cognitive decline after surgery. Psychologically, anxiety symptoms were significantly reduced at 12 months post-operatively, while level of depressive symptoms remained steady.

Diminished category fluency has been recognized as a cognitive risk following STN-DBS in PD and our findings concurred with most published evidences [1, 14–16]. Despite the consistency, the mechanism leading to this decline remains under-investigated. The neural correlates of verbal fluency have been demonstrated in healthy subjects that the process of word generation induces activation of the left-sided fronto-temporal network, including the middle frontal gyrus and the anterior cingulate cortex [17]. Some neuroimaging and lesion studies have suggested that semantic-based word retrieval (category fluency) is mediated primarily by temporal cortex, whereas the frontal region is more critical for phonemic-based word retrieval (phonemic fluency) [18]. Therefore, it has been believed that the microlesion effect along the placement of the electrode might affect verbal fluency [19], particularly phonemic fluency that relies more on the frontostriatal network where the electrode passed through [20]. In a recent study, it was demonstrated that long-term outcome of phonemic fluency following STN-DBS correlated with early decline synonymous of microlesion [20]. Nevertheless, some other studies have showed the role of prefrontal cortex in category fluency as well. In a study using SPECT, Cilia et al. demonstrated that decline in category fluency performance after STN-DBS was significantly associated with hypoperfusion clustered in the dorsolateral prefrontal cortex (middle frontal gyrus, BA 9), the anterior cingulate cortex (BA 33) and the ventral part of the caudate nucleus on the left hemisphere [21]. In the present study, we demonstrated diminished category fluency after STN-DBS in total word generation for living (animals) and non-living (transportation) things among Chinese-Cantonese-speaking population where only category (semantic) fluency was measurable due to the language structure. These findings contributed knowledge to existing evidence of a decline in verbal fluency after STN-DBS in a highly different language system that relies on semantic word retrieval. Further investigations on the neural correlates among Chinese-Cantonese populations are worthwhile.

When living (animal) and non-living (transportation) items were analyzed separately in our data, all patients generated more items in the animal than the transportation fluency task. Significant post-operative reduction of fluency was only found on animal items; ability on word generation of transportation was unaffected. This preliminary finding demonstrated the possibility of category-specific decline in fluency items in patients who received STN-DBS. In fact, previous research demonstrated that patients with brain damage of various etiologies showed a dissociation of performance for living and non-living things [22–24]. For instance, patients with herpes simplex encephalitis who had bitemporal damage were found to have impaired performance in naming and/or recognizing living things but not non-living things [25]. In contrast, a patient with a left temporal lobe lesion showed a reverse pattern of performance [26]. It has been hypothesized, with emerging evidences from neuroimaging studies, that the category dissociation might be related to the different anatomical correlates for naming/processing of living and non-living things that demand different neural networks. Giussani et al. conducted a study with 50 patients who underwent linguistic tasks in awake surgery procedures with brain mapping. Although their results showed that there were high individual differences in the localization and organization of word categories retrieval, they found statistically significant representation of neural structures for naming of non-living things in the left posterolateral temporoparietal cortex [27]. As reduction on verbal fluency has been consistently established in patients who have PD treated with STN-DBS, it would be worthwhile to delineate the nature of such reduction to include investigation on category-specific changes in future studies.

Compared with the effects of STN-DBS on verbal fluency, its effects on memory are less established. There were studies that reported post-operative decline in a task of episodic verbal memory 3 months after the STN-DBS procedures in patients with PD [28, 29]. On the other hand, a study in Korea among PD patients who received STN-DBS ($n = 46$) showed that more patients had a post-operative improvement in an immediate recall memory task (13–15 %) than a decline (3–10 %), but more patients had a decline (24–31 %) instead of an improvement (3–13 %) in a delayed recall memory task [14]. The present study found significant improvement in an immediate recall task of a verbal memory test that occurred at 6 months following the STN-DBS procedures and such changes persisted at 1 year post-operatively. This finding was preliminary and should be interpreted cautiously together with the methodological limitations in the study. Since an alternate parallel form of the verbal memory test was not available in the locally validated version, the improvement might likely be attributable to practice effect. Nevertheless, this could not explain why such improvement did not occur in other trials in the same task (e.g., immediate recall following interference, delayed recall task) or in the other neuropsychological tests. Since the STN-DBS contributed to motor improvement on both a statistical and a clinical levels, the overall reduction of motor disturbances might possibly allow patients to have an improved concentration and motivation to engage in the repeated process of learning (five learning trials for the immediate recall tasks), contributing to a better performance in a test setting. However, this hypothesis could not be tested unless a parallel version of the CAVLT was used, or/and similar pattern of improvement to be showed in other neuropsychological tests that specifically aim at assessing such ability, e.g., test on sustained attention, test on verbal encoding ability.

The present study was the first to report the neuropsychological abilities following STN-DBS in Chinese-Cantonese patients with idiopathic PD, although there were several limitations that needed to be addressed. First, we acknowledged the lacking of statistical power in the study therefore findings should be regarded as preliminary and exploratory. The study also lacked a control group which left the confounding of time effect unanswered. Further study with controlled group and adequate statistical power are necessary. Furthermore, we did not include a neuropsychological test of executive functioning specifically aimed at assessing problem-solving and set-shifting abilities, which were common cognitive deficits in this group of patient. In addition, collaboration across sites is important to improve recruitment and enhance generalizability. Finally, we suggest that the measurement approach to outcomes in future studies should be optimized to include neuroimaging studies, neuropsychological tests, a patient-compiled quality of life instrument as well as a mood questionnaire.

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Conflict of interest The authors declare that they have no conflict of interest.

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