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COGNITIVE DECLINES AFTER UNILATERAL DEEP BRAIN STIMULATION SURGERY IN PARKINSON'S DISEASE: A CONTROLLED STUDY USING RELIABLE CHANGE, PART II

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Abstract

Deep brain stimulation (DBS) surgery, an effective treatment for medication-refractory Parkinson's disease (PD), may also lead to selective cognitive declines. In this continuation of a report by Zahodne et al. (2009), we compare cognitive performance of 24 PD patients who underwent unilateral implantation of the globus pallidus internal segment (GPi) or subthalamic nucleus (STN) to that of 19 PD controls. We used group statistical comparisons as well as Reliable Change Indexes (RCIs) to examine performance on measures of memory, processing speed, executive function, and visuospatial perception at baseline and 16 months after surgery. Significant between-group differences were noted on a psychomotor processing speed task. However, a significantly higher proportion of DBS patients than controls demonstrated reliable individual decline on a word list recall task (HVLT-R) and on several processing speed tests. Reliable improvements were noted on tests of visuospatial functioning. There was variability in individual outcome on executive functioning tests, with a small proportion of DBS patients demonstrating reliable decline and some demonstrating reliable improvement. Use of Reliable Change highlights the occurrence of individual variability, revealing declines and improvements in a small proportion of unilateral DBS patients that were not evident upon group comparison. These findings must be interpreted in light of group-level differences between the PD control and DBS patients on demographic and disease-related factors.

Keywords

Parkinson's disease; Deep brain stimulation; Reliable Change

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INTRODUCTION

Deep brain stimulation (DBS) surgery in the globus pallidus internus (GPi) or subthalamic nucleus (STN) is regarded as an effective treatment for well-selected patients suffering from medication-refractory Parkinson's disease (Pahwa, 2006). Aside from alleviating many of the core motor deficits and increasing the amount of time for which patients derive benefit from their dopaminergic medication, DBS also reduces the potentially disabling drug-induced fluctuations that occur in approximately 40–50% of PD patients receiving levodopa therapy for 4 or more years (Ahlskog & Muentner, 2001). However, cognitive effects of DBS have been reported in approximately 41% of bilateral STN DBS patients (Temel et al., 2006). A meta-analysis of 28 STN DBS studies reported significant, albeit small, declines in verbal memory and executive functioning, and moderate-sized declines in verbal fluency (Parsons, Rogers, Braaten, Woods, & Troster, 2006; Voon, Kubu, Krack, Houeto, & Troster, 2006).

More recently, researchers have begun to examine the significance of effects at the individual level using methods such as the Reliable Change Index (RCI) to control for both the imprecision of a measurement instrument and for expected practice effects when a test is administered on multiple occasions (Chelune, Naugle, Lüders, Sedlak, & Awad, 1993; Jacobson & Truax, 1991). Two studies applying RCI analyses to bilateral STN DBS patients have documented individual-level declines on tests of memory, verbal fluency, and executive function. York et al. (2008) derived 95% confidence intervals from an evaluation of 28 PD control participants tested on two occasions. Applying these confidence intervals to 23 bilateral STN DBS patients tested before and 6 months following surgery, the authors found that a significantly greater proportion of DBS patients than PD controls declined on delayed list learning (13%), letter fluency (26.1%), Trail Making Test B (57.1%), and the Stroop Color-Word Test (36.8%). Higginson et al. (2009) derived confidence intervals from a sample of 62 PD patients (Troster, Woods, & Morgan, 2007) and applied them to 22 bilateral STN DBS patients. A greater proportion of DBS patients than controls declined on the learning trials of the CVLT (15.8%), letter fluency (22.2%), and animal fluency (5.6%).

In a previous report we investigated cognitive changes at the group and individual levels, as well as predictors of cognitive decline, in a sample of patients who had undergone unilateral DBS to the STN or GPi (Zahodne et al., 2009). We tested the hypothesis that DBS patients would demonstrate statistically significant group declines relative to PD controls on tasks involving dorsolateral prefrontal cortex circuitry (letter fluency, semantic fluency, and Digit Span Backward) but not on other tasks (Vocabulary, Boston Naming Test). We also hypothesized that a greater proportion of DBS patients would fall below Reliable Change Indexes (RCIs) on the dorsolateral prefrontal tasks. The sample included 22 unilateral DBS patients and 19 PD control participants. We detected statistically significant declines in the DBS group compared to controls on letter and animal fluency. Reliable change analyses using 90% confidence intervals indicated that a greater proportion of DBS patients (50%) than controls (11%) exhibited decline on one or both fluency measures. Those surgical patients who declined on verbal fluency tasks experienced less motor improvement than those who did not decline. Surgery to the left brain was associated with significantly increased odds of decline on semantic fluency than surgery to the right brain.

In the present study we extend our previous investigation to include other neuropsychological outcomes. We use the same participant sample with the addition of two DBS patients. Specifically, we use group comparison and RCI analysis to investigate performance following unilateral STN or GPi DBS relative to PD control patients using measures of memory, processing speed, executive function, and visuospatial perception. We predict that our findings will extend those of Zahodne et al. (2009) and of other studies

employing reliable change methodology (Higginson et al., 2009; York et al., 2008), such that tasks engaging frontal-subcortical circuitry (processing speed, executive function, word retrieval in delayed recall tasks) will be diminished after unilateral DBS surgery.

METHOD

Participants

The study participants included 43 patients with idiopathic PD who were being followed by the Movement Disorders Center (MDC) at the University of Florida and who provided informed consent to participate in a quantitative measures research database. Of these patients 41 were Caucasian, and 2 identified as Hispanic. All patients had previously undergone extensive neurological screening by fellowship-trained movement disorders specialists in order to establish a definitive diagnosis of idiopathic PD based on UK Brain Bank criteria (Hughes, Daniel, Kilford, & Lees, 1992). The PD DBS group comprised 24 individuals who underwent unilateral DBS surgery in right STN ($N = 3$), left STN ($N = 8$), right GPi ($N = 5$), or left GPi ($N = 8$). The side of surgery was determined based on which side of the body exhibited the most troublesome symptoms. Of the DBS patients, 15 underwent surgery as part of their enrollment in a clinical trial of cognitive and mood effects of STN versus GPi DBS conducted at the University of Florida Movement Disorders Center (COMPARE trial), and their targets were determined based on randomization (11 GPi, 4 STN). The targets for the remainder of the DBS group were determined based on clinical judgment (7 STN, 2 GPi). High-resolution post-operative CT scans were obtained for all DBS patients, and these scans were fused to pre-operative MRIs in order to verify that leads were placed accurately. The PD control group comprised 19 individuals who were followed over time without undergoing DBS surgery. Inclusion/exclusion criteria are described in our previous report (Zahodne et al., 2009).

Procedure

Motor, mood, neuropsychological, and demographic data were obtained from the IRB-approved MDC research database. All patients underwent neuropsychological evaluation through the University of Florida Clinical and Health Psychology Clinic, and were taking their normal dopaminergic medications at the time of assessment. In addition to a comprehensive cognitive battery, the 21-item self-report Beck Depression Inventory (BDI-II) (Beck, Steer, & Brown, 1996) was administered as a measure of depression severity. Motor functioning was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn, Elton, & Committee, 1987) and the Hoehn & Yahr Stage Scale (Hoehn & Yahr, 1967). The DBS patients underwent all screening procedures as part of a 2-day evaluation for DBS candidacy, and control patients underwent similar evaluations as part of their normal clinical care through the UF MDC (Okun et al., 2004). The DBS group underwent neuropsychological testing an average of 16.4 months ($SD = 6.5$) after surgery.

Previously we reported the neuropsychological outcome of verbal fluency (Controlled Oral Word Test and Animals), working memory (Digit Span Backward), vocabulary knowledge, and visual confrontation naming (Boston Naming Test) (Zahodne et al., 2009). In the present study we examined performance on the remaining tests from our neuropsychological battery, including tests of memory, processing speed, executive function, and visuospatial perception. These tests included the immediate and delayed recall trials as well as the delayed recognition portion of Hopkins Verbal Learning Test-Revised (HVLT-R) (Benedict, Schretlen, Groninger, & Brandt, 1998), the immediate and delayed recall trials from the Logical Memory subtest of the Wechsler Memory Scale-III (Wechsler, 1997), the Trail Making Test (Strauss, Sherman, & Spreen, 2006), the Stroop Test (Golden, 1978), the Judgment of Line Orientation Test (Benton, Sivan, Hamsher, Varney, & Spreen, 1994), and

the Benton Facial Recognition Test (Benton, Sivan, Hamsher, Varney, & Spreen, 1983). Scores for all tests were converted to *T*-scores, based on appropriate normative correction, for analysis.

Group characteristics

Table 1 compares demographic, cognitive, mood, and disease-related data for the two groups. Independent samples *t*-tests were used to compare normally distributed data, and Wilcoxon's signed rank tests were used for those variables that were not normally distributed. The motor symptoms of both groups were moderately severe when assessed "on" dopaminergic medications with the motor portion of the UPDRS, and patients were in the middle stage of PD as defined by the Hoehn & Yahr scale. The groups also scored similarly on the two cognitive screening measures (DRS-2 and MMSE) and a self-report measure of depressive severity (BDI-II). The difference in self-reported symptom duration between the two groups was significant, $t(41) = -3.2, p = .003$. In addition, DBS patients' motor symptoms were more severe than those of PD controls when patients were assessed after 12-hour withdrawal from dopaminergic medications ("off" medications), $t(37) = -3.5, p = .001$, and DBS patients also had higher levodopa equivalent dosages before surgery, $t(35) = -5.1, p < .001$. Although not statistically significant, the controls also had a higher education level. Additionally, the DBS group had proportionately more men than the controls. We also compared baseline characteristics for target (STN vs GPi) and side (left vs right). Because there were no differences for the two surgical targets or surgical sides on any baseline characteristics, these data are not displayed.

RESULTS

Group differences in cognitive performance over time

Table 2 displays mean neuropsychological scores for both groups at Time 1 and Time 2. An initial series of independent samples *t*-tests revealed no significant baseline differences in performance on any of the measures. In order to examine group-level performance on the neuropsychological tests, we carried out multivariate repeated measures analysis of variance (MANOVAs). To minimize Type I error, separate MANOVAs were conducted for the dependent variables of specific cognitive domains: memory (DVs=HVLT-R total recall, HVLT-R delayed recall, Logical Memory immediate recall, and Logical Memory delayed recall), processing speed (DVs=Trail Making Test Part A, Stroop Word Reading), executive function (DVs = Trail Making Test Part B, the Stroop Color-Word subtest), and visuospatial perception (DVs = Facial Recognition Test, Judgment of Line Orientation test). The MANOVAs included a within-participants factor of testing session (Time 1 versus Time 2), and a between-participants factor of group (DBS versus control). Any significant interaction effects were decomposed and followed up with univariate ANOVAs to determine if the significant effects could be localized to one particular neuropsychological test.

Mean scores of the DBS patients and PD controls from Time 1 and Time 2 across each of the cognitive tests are shown in Table 2. Heterogeneity of variance, which could not be stabilized by square root transformation, was apparent for the Logical Memory Delay condition and the Facial Recognition Test. A significant main effect of Time was noted only for the visuospatial MANOVA, $F(1, 40) = 5.68; p = .022; \eta_p^2 = 0.12$, such that all participants (regardless of group) demonstrated lower scores on the visuospatial measures (i.e., Benton Facial Recognition Test, JLO) at Time 2 compared to Time 1. Univariate follow-up ANOVAs revealed a significant main effect of time for the JLO, $F(1, 40) = 4.97; p = .032; \eta_p^2 = .11$, such that all patients had lower scores at Time 2 compared to Time 1. There was no effect of time and no interaction effect for the Facial Recognition Test.

A significant Group $\times$ Time interaction was detected for the processing speed MANOVA, $F(1, 36)=5.61$; $p=.024$; $\eta_p^2=0.13$. Bonferroni-adjusted post-hoc comparisons revealed that the DBS and PD control patients did not differ at baseline testing on the composite measure of processing speed; however, the DBS patients performed significantly lower than PD controls at follow-up testing ($p=.025$). Similarly, the DBS patients' post-surgery scores on processing speed were significantly lower than their baseline scores ($p=.041$), while control patients' pre- and post-test scores did not differ significantly.

Finally, univariate follow-up ANOVAs were conducted to determine whether the processing speed changes could be localized to one of the processing speed DVs. For Trail Making Test Part A, there was a significant Group $\times$ Time interaction, $F(1, 40)=6.11$, $p=.018$, $\eta_p^2=0.13$. Because DBS patients and PD controls differed significantly on three key disease variables (disease duration, UPDRS-III "off" scores, and pre-surgical levodopa equivalent dosage), we examined whether these variables might be significantly related to the change in Trail Making A scores (Time 2 – Time 1). A correlation analysis suggested that these three variables were not significantly related to the outcome—disease duration: $r=.032$, $p=.84$; UPDRS-III "off" : $r=-.18$, $p=.29$; pre-surgical levodopa equivalent dosage: $r=-.083$, $p=.63$. For the Stroop Word Reading Test there was a significant main effect of time such that both groups declined from Time 1 to Time 2, $F(1, 37)=4.30$, $p=.045$, $\eta_p^2=0.10$, but the Group $\times$ Time interaction was not significant, $F(1, 37)=2.34$, $p=.14$, $\eta_p^2=0.059$.

Reliable Change results

We calculated Reliable Change Indexes (RCIs) corrected for practice effects using formulas previously described by Jacobson and Truax (1991). The RCIs and practice effects for each measure were calculated separately using the standard error of the difference in the PD control group. Patients were classified as "decliners" or "improvers" on a measure if the difference between their obtained and predicted scores exceeded the RCI for the particular cognitive test. Following the methods employed by Higginson et al. (2009), binomial tests were conducted in order to assess the significance of the proportional differences between the numbers of decliners/improvers in the DBS group compared to the control group. Binomial tests were employed due to small expected cell frequencies. Alpha was set at 0.01 due to multiple analyses and two-tailed p -values were used.

Results of reliable change analyses are shown in Table 3. A significantly greater proportion of DBS patients than controls demonstrated reliable decline from Time 1 to Time 2 on the HVLT-R immediate and delayed recall tests, Trail Making Test Part A, Stroop Word test, Trail Making Test Part B, and Stroop Color-Word test. A significantly greater proportion of DBS patients than controls demonstrated reliable *improvement* from Time 1 to Time 2 on Stroop Color-Word and the Judgment of Line Orientation Test.

DISCUSSION

In a previous report investigating 22 PD patients who underwent unilateral DBS surgery to the STN or GPi and 19 PD control participants, we detected statistically significant declines in the DBS group on letter and animal fluency tests (Zahodne et al., 2009). Reliable change analyses using 90% confidence intervals indicated that a greater proportion of DBS patients (50%) than controls (11%) exhibited individual-level decline on one or both fluency measures. There were no group or individual-level differences for the other tests studied (Digit Span Backward, Boston Naming Test, Vocabulary). In the present study we extended our previous investigation to include other neuropsychological outcomes including measures of memory, processing speed, executive function, and visuospatial perception. We used the

same participant sample with the addition of two DBS patients. We predicted that our findings would extend those of Zahodne et al. (2009) and of other studies employing reliable change methodology (Higginson et al., 2009; York et al., 2008), such that tasks engaging frontal-subcortical circuitry (processing speed, executive function, word retrieval in delayed recall tasks) would be diminished after unilateral DBS surgery.

Cognitive changes identified in the present study

Using inferential statistical testing, the present study documented cognitive declines on psychomotor processing speed in PD patients who underwent unilateral DBS implantation compared to age-matched PD controls. The decline in psychomotor processing speed was specific to the Trail Making Test Part A, and was not accounted for by group differences in disease severity. This finding is consistent with other studies demonstrating group declines in processing speed following unilateral (Rothlind, Cockshott, Starr, & Marks, 2007) as well as bilateral surgery (Saint-Cyr, Trepanier, Kumar, Lozano, & Lang, 2000).

The importance of individual variability

Using a 90% confidence interval derived from 19 non-surgical PD control patients, we examined rates of individual decline and improvement following unilateral DBS surgery. The DBS group demonstrated a significantly greater proportion of reliable decline on the Trail Making Test Parts A and B, the immediate and delayed recall portions of the HVLTR, and the Word Reading portion of the Stroop test. The DBS group demonstrated a significantly greater proportion of improvement on the Judgment of Line Orientation Test. There was some variability in outcome for the Stroop Color-Word test, with a small proportion of DBS patients demonstrating reliable decline and a small proportion demonstrating reliable improvement. Thus, we identified a significant proportion of individual decliners and improvers on tests for which no group differences were apparent according to inferential statistical procedures. Although a minority of DBS patients demonstrated these reliable changes, it is evident that clinically significant changes on a variety of tests may be overlooked when relying purely on a nomothetic approach.

Study limitations and suggestions for future research

The present study suffers from several important limitations. First, the sample comprised a relatively small number of patients, and power was reduced further by missing data points for some of the tests. The present study attempted to address this limitation by using RCIs to capture individual changes that may have been masked by group averaging. However, because a large number of tests were conducted to determine whether differences existed between the proportions of individuals demonstrating decline or improvement, the potential for elevated Type I error remains a concern.

In addition to the above issues, our DBS group included four subgroups (left/right, STN/GPi). Particularly in the context of low power, we cannot definitively determine if DBS in general was associated with the reported declines or if the observed changes were limited to one of the DBS surgical conditions. Additionally, of the 24 DBS patients, 9 were targeted for STN or GPi based on clinical judgment, whereas the remaining patients were randomized to those conditions. Substantially more clinically assigned patients were assigned to STN versus GPi, potentially introducing systematic variance for patients who were assigned rather than randomized to a target. Clinical decisions generally involved the selection of STN for medication reduction and selection of GPi if there were cognitive or behavioral concerns.

A final important limitation of the present study lies in its failure to more fully match DBS and PD control groups. Compared to control patients, DBS patients reported having PD

symptoms for a longer period of time, they were experiencing more severe motor dysfunction when assessed “off” medication, and they had higher dopaminergic medication requirements at Time 1. Although not statistically significant, the control group also had a higher education level. Finally, there was a greater proportion of males in the DBS group than the control group. These important differences make it impossible to completely rule out the possibility that our finding of DBS-specific cognitive declines results from group differences in variables related to the disease process or to demographic factors. The two PD groups did not significantly differ in their performance on baseline cognitive measures, and no significant correlations were detected between the relevant baseline variables that differed between the two groups and Trail Making A change scores. However, an absence of differences cannot be definitively inferred in the context of low power.

Conclusions

The present study adds to a previous report using the same sample of participants (with the addition of two DBS participants to the present report) that documented group- and individual-level decline on verbal fluency tests (Zahodne et al., 2009). In the present study significant between-group differences were detected for a psychomotor processing speed task, but a significantly higher proportion of DBS patients than controls demonstrated reliable individual decline on a word list recall task and on several processing speed and executive function tests. Taken together, these reports highlight the occurrence of declines on tasks relying on frontal-subcortical circuitry, at least in a subset of the unilateral DBS patient sample examined. In the present study reliable improvements were also noted on tests of visuospatial functioning and executive function. Future studies should address the real-world significance of DBS-related cognitive changes and potential reasons for variability in outcome. Additionally, this study does not clarify whether observed cognitive effects are due to stimulation- or surgery-related factors. Thus, future studies should investigate specific surgery- and stimulation-related mediators of cognitive improvement/decline following DBS surgery.

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Table 1

Baseline demographic data

	PD control (N= 19)	DBS (N=24)
Age	64.7 (6.6)	61.7 (4.9)
Education (yrs)	15.4 (2.9)	14.1 (2.6)
Gender	12M, 7F	20M, 4F
Evaluation interval (months)	16.1 (7.0)	20.1 (6.3)
Duration of symptoms* (months)	76.5 (69.1)	141.2(60.2)
UPDRS on	25.3 (8.5)	22.1 (8.1)
UPDRS off*	31.2(8.3)	42.8 (11.3)
Hoehn-Yahr stage (on)	2.4 (0.44)	2.1 (0.28)
LED*	337.0 (233.8)	1110.0 (533.5)
DRS-2 raw	138.6 (3.5)	137.6 (4.6)
MMSE	28.3 (1.9)	28.9 (1.2)
BDI	9.2 (8.6)	9.8 (7.6)

UPDRS, Unified Parkinson's Disease Rating Scale; LED, levodopa equivalent dose; DRS, Dementia Rating Scale; MMSE, Mini-Mental State Evaluation; BDI, Beck Depression Inventory.

* Indicates significance ($p < .05$).

Table 2

Cognitive outcome for the DBS and PD control groups

	Time 1		Time 2	
	Control	DBS	Control	DBS
<i>Memory</i>				
HVLT-R Immediate	47.8 (11.7)	42.6 (12.5)	48.0 (12.0)	37.9 (11.4)
HVLT-R Delay	41.8 (16.4)	42.2 (13.8)	44.3 (13.8)	37.2 (12.9)
HVLT-R Recognition	46.6 (10.3)	45.0 (5.2)	42.3 (14.0)	42.2 (12.5)
LM Immediate	47.4(13.1)	47.6 (8.7)	48.9 (9.5)	48.3 (11.3)
LM Delay	48.8 (13.8)	48.9 (8.5)	50.1 (12.3)	53.2 (7.3)
<i>Speed of Processing</i> [*]				
Trail Making A [*]	41.8 (11.5)	42.7 (11.5)	45.7 (9.5)	39.3 (12.7)
Stroop Word ⁺	45.5 (5.6)	43.4 (8.3)	44.9 (5.9)	39.7 (9.2)
<i>Executive Function</i>				
Trail Making B	39.7 (14.4)	39.2 (9.8)	41.2(16.2)	35.2 (12.7)
Stroop Color-Word	46.2 (10.4)	43.9 (9.8)	45.5 (10.0)	41.5 (9.7)
<i>Visuospatial</i> ⁺				
JLO ⁺	52.3 (12.5)	48.4 (11.9)	48.5 (13.9)	44.2 (12.3)
FRT	51.7 (9.9)	47.8 (11.5)	47.2 (17.0)	45.6 (8.7)

Values are mean *T*-scores (*SD*).

HVLT-R, Hopkins-Verbal Learning Test–Revised; LM, Logical Memory; JLO, Judgment of Line Orientation; FRT, Facial Recognition Test.

^{*} Indicates significant group $\times$ time interaction ($p < .05$).⁺ Indicates significant main effect of time ($p < .05$).

Table 3

Percentage of patients demonstrating reliable change based on 90% confidence intervals

Domain/Test	PD control		DBS	
	Decline	Improve	Decline	Improve
<i>Memory</i>				
HVLT-R Immediate	0	5.3%	20.8% *	8.3%
HVLT-R Delay	0	10.5%	25.0% *	4.2%
HVLT-R Recognition	10.5%	5.3%	13.0%	17.4%
LM Immediate	5.3%	10.5%	4.3%	0
LM Delay	0	10.5%	4.3%	8.7%
<i>Speed of Processing</i>				
Trail Making A	0	5.3%	8.7% *	0
Stroop Word	0	5.6%	9.5% *	0
<i>Executive Function</i>				
Trail Making B	5.3%	5.3%	9.1% *	0
Stroop Color-Word	0	0	19.0% *	9.5% *
<i>Visuospatial</i>				
JLO	5.3%	5.3%	17.4%	26.1% *
FRT	10.5%	0	0	4.2

90% RCI criterion refers to the amount of change in a *T*-score necessary from before to after surgery to be classified as a clinically significant change.

HVLT-R, Hopkins-Verbal Learning Test-Revised; LM, Logical Memory; JLO, Judgment of Line Orientation; FRT, Facial Recognition Test.

* Indicates significant difference in proportion of DBS patients demonstrating decline/improvement relative to control group proportions ($p < .01$).