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

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Abstract

Conflicting research suggests that deep brain stimulation surgery, an effective treatment for medication-refractory Parkinson's disease (PD), may lead to selective cognitive declines. We compared cognitive performance of 22 PD patients who underwent unilateral DBS to the GPi or STN to that of 19 PD controls at baseline and 12 months. We hypothesized that compared to PD controls, DBS patients would decline on tasks involving dorsolateral prefrontal cortex circuitry (letter fluency, semantic fluency, and Digit Span Backward) but not on other tasks (Vocabulary, Boston Naming Test), and that a greater proportion of DBS patients would fall below Reliable Change Indexes (RCIs). Compared to controls, DBS patients declined only on the fluency tasks. Analyses classified 50% of DBS patients as decliners, compared to 11% of controls. Decliners experienced less motor improvement than non-decliners. The present study adds to the literature through its hypothesis-driven method of task selection, inclusion of a disease control group, longer-term follow-up and use of Reliable Change. Our findings provide evidence that unilateral DBS surgery is associated with verbal fluency declines and indicate that while these changes may not be systematically related to age, cognitive or depression status at baseline, semantic fluency declines may be more common after left-sided surgery. Finally, use of Reliable Change highlights the impact of individual variability and indicates that fluency declines likely reflect significant changes in a subset of patients who demonstrate a poorer surgical outcome overall.

Keywords

Parkinson's disease; Deep brain stimulation; Reliable Change

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 et al., 2006). Aside from alleviating many of the core motor deficits and improving "on" time, DBS also reduces the potentially disabling drug-induced side effects that occur in approximately 40–50% of PD patients receiving levodopa therapy for at least 4–6 years (Ahlskog & Muenter, 2001). Leads contain

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four contacts, and unique stimulation settings can be determined and modified individually through changes in contact location, pulse width, frequency, and voltage. Because of DBS's unique features of reversibility and flexibility, it has in many parts of the world replaced ablative procedures and become the "standard" surgical treatment for PD. The mechanism of action has yet to be fully elucidated; however, high-frequency stimulation appears to regulate the abnormal basal ganglia-thalamocortical motor circuits and also seems to modulate and change neural activity output including both rate and pattern of activity (McIntyre, Savasta, Kerkerian-Le Goff, & Vitek, 2004).

Although the motor benefits are well documented and substantiated, research has shown that at least some patients undergoing DBS may exhibit specific cognitive declines (The Deep Brain Stimulation for Parkinson's Disease Study Group, 2001). Supportive of this observation was a recent meta-analysis that reported cognitive problems occurring in approximately 41% of patients who underwent bilateral STN DBS (Temel et al., 2006). Despite the recent increase in interest in non-motor effects of DBS surgery, the cause, types, and predictors of these cognitive side effects have not yet been adequately uncovered. Performance decrements following DBS surgery have been documented on a variety of tasks, including verbal fluency, memory, attention, executive functioning, and also language (Parsons, Rogers, Braaten, Woods, & Tröster, 2006; Voon, Kubu, Krack, Houeto, & Tröster, 2006). In addition, there remains little agreement on which variables are predictive of post-DBS cognitive declines. Studies have implicated a handful of disparate factors that may predict post-surgical declines in cognitive performance, and these factors include age, side of surgery, and various pre-operative patient attributes such as poor cognitive status, depressive symptomatology, apathy, neuropsychiatric conditions, disease duration and/or severity, and dopaminergic related psychosis (De Gaspari et al., 2006; Funkiewiez et al., 2004; Perriol et al., 2006; Smeding et al., 2006). However, predictors of decline vary across studies, and many investigations have failed to identify any factors that directly relate to cognitive outcome. Conflicting findings related to the prevalence, patterns, and risk factors of post-DBS declines may also relate to differences in neuropsychological testing batteries, variation in time to follow-up, as well as specific methodological limitations, including small sample sizes, failing to include a non-surgical control group, and an exclusive focus on group mean differences.

In the present study we sought to address what we perceive to be two critical methodological issues apparent in the extant literature. These issues included the failure to include a non-surgical control group and the bias to exclusively focus on group mean differences. We believe the inclusion of a disease control group is essential in this type of research because the neurodegenerative process of PD itself leads to cognitive changes that may not be attributable to the surgical intervention, and also because nearly all serial neuropsychological research is influenced by practice effects (the tendency for patients to perform better on a measure simply as a result of their taking it twice). While approximately 25–30% of PD patients will manifest a full-blown dementia syndrome, those patients who fail to develop dementia per se will commonly evidence a pattern of cognitive impairments involving attentional set shifting, memory retrieval, and visuospatial abilities and directed verbal fluency problems, and these features are commonly observable even in early disease stages (Aarsland, Zaccai, & Brayne, 2005; Cooper, Sagar, Jordan, Harvey, & Sullivan, 1991; Muslimovic, Post, Speelman, & Schmand, 2005). However, comparisons with a control group can reduce the influence of these important confounds on the interpretation of study findings.

Woods et al. (2006) reviewed 30 studies examining cognitive effects of STN DBS and recommended that future efforts be directed toward examining the significance of effects at the individual level, not just group differences. One validated method for characterizing

individual changes in performance over time uses a Reliable Change Index (RCI), which can control for both the imprecision of a measurement instrument, and also for expected practice effects when attempting to determine scores due to chance (Chelune, Naugle, Lüders, Sedlak, & Awad, 1993; Jacobson & Truax, 1991). Unlike traditional statistical approaches that examine group mean scores to determine the nomothetical statistical rarity of post-test scores, the RCI method determines the statistical significance of individual changes in performance, thereby allowing for the differentiation of group differences that result from small changes in the majority of a sample versus those due to relatively large changes in a subset of a sample.

Unlike previous exploratory studies of cognitive outcome following DBS that have analyzed large neuropsychological batteries, the present study involved tasks selected in a hypothesis-driven manner, based on evidence for their activation of dorsolateral prefrontal cortex related circuitry. One hypothesis for cognitive changes following DBS involves current spread from high-frequency stimulation (HFS) into subregions of GPi and STN that are involved in the associative basal ganglia-thalamocortical loop, and that are directly adjacent to the sensorimotor subregions targeted for implantation (Sudhyadhom et al., 2007). The cortical target area for the primary associative loop is the dorsolateral prefrontal cortex, and HFS may differentially affect the associative and limbic basal ganglia-thalamocortical loops (Alexander, DeLong, & Strick, 1986). This current spread may be one explanation for abnormal clinical performance on neuropsychological measures. Adding further support to this theory is that imaging studies of HFS show that cerebral blood flow in the cortical areas representing non-motor loops is activated during cognitive tasks (Haegelen et al., 2005; Limousin et al., 1998; Schroeder et al., 2003; Sestini et al., 2002). Additive to this hypothesis of current spread are the known physiological properties of non-motor subregions of GPi and STN that under variable stimulation parameters may exert different and also differential effects on motor behaviors as well as cognition (Temel, Blokland, Steinbusch, & Visser-Vandewalle, 2005). Evidence from human studies supports this notion and has shown preliminarily that high-frequency stimulation results in motor improvement in PD, but may also have concomitant cognitive deterioration, whereas low-frequency stimulation seems to enhance cognitive performance in the context of motor worsening (Wojtecki et al., 2006). Modifying stimulation parameters therefore change the extent to which non-motor features are expressed (Francel et al., 2004).

The primary aims of the present study were to test the hypothesis that cognitive declines associated with DBS surgery manifest in diminished performance on neuropsychological tasks shown to involve the dorsolateral prefrontal cortex (DLPFC), and to determine the significance of individual performance changes in the DBS group using Reliable Change. Finally, we sought to explore the relationship between patient as well as surgical variables and post-operative cognitive decline.

METHOD

Participants

The study participants included 41 patients with idiopathic PD who were being followed by the Movement Disorders Center (MDC) at the University of Florida, and who signed informed consent to participate in a quantitative measures research database. All patients were Caucasian, and two identified themselves 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 22 individuals who underwent unilateral DBS surgery in right STN (*N*=3), left STN (*N*=7), right GPi (*N*=5), or left GPi (*N*=7). The PD control group comprised 19 individuals who

were followed over time without undergoing DBS surgery. The primary inclusion criterion for the control group was the occurrence of two neuropsychological evaluations approximately 1 year apart without prior or intervening surgery. Many of these patients were eligible for DBS and received surgery at our center at a later date, while others declined for personal reasons.

All patients included in this study were between the ages of 50 and 75. Of the 25 patients identified through the database as meeting inclusion criteria for the DBS group, 3 were excluded in order to render the DBS and control groups more comparable on the variable of age. On average, these three patients were 51.67 years old (range 51–52), and they did not significantly differ from the remaining 22 DBS patients with regard to their level of education, severity of motor symptoms, or disease stage. Patients were excluded from either group if they evidenced dementia, as defined by scores below 25 on the Mini-mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) or 130 on the Mattis Dementia Rating Scale (DRS-2; Mattis, 2001), had undergone previous DBS or ablative procedures, received bilateral DBS surgery, or their electrodes were misplaced.

Procedures

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 during this visit as a measure of depression severity. Motor functioning was assessed using the Unified Parkinson 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).

Neuropsychological measures were chosen based on their documented propensity to engage dorsolateral prefrontal cortex circuitry, as revealed by convergent evidence from neuropsychological and neuroimaging studies. Descriptions of the tasks are provided in Table 1 and included speeded verbal fluency tasks (Controlled Oral Word Association Test and Animals) and a measure of working memory (Digit Span Backward). Intrinsic word generation to letters has been shown to activate several prefrontal subregions, including Brodmann's areas (BA) 4, 6, 44, and 45 (Amunts et al., 2004;Baldo, Schwartz, Wilkins, & Dronkers, 2006;Costafreda et al., 2006;Friston, Frith, Liddle, & Frackowiak, 1991). In addition to engaging left dorsolateral prefrontal cortex, semantic fluency may also rely on its right homologue (Szatkowska, Grabowska, & Szymanska, 2000). Manipulating number strings in working memory has shown to activate several prefrontal areas, including BA 6, 9, 44, and 46, and compared with the forward portion, Digit Span Backward selectively activates dorsolateral prefrontal cortex (Hoshi et al., 2000;Owen, 2000;Tsukiura et al., 2001). We also examined performance on a vocabulary knowledge test and a measure of visual confrontation naming, which involve less dorsolateral prefrontal cortex circuitry engagement.

RESULTS

Group characteristics

Table 2 compares demographic, cognitive, mood, and disease-related data on the two groups. Patients ranged in age from 53 to 74 and were in general well educated. Their motor

symptoms were moderately severe when they were assessed "*on*" medications with the motor portion of the UPDRS, and they were in the middle stage of PD as defined by the Hoehn & Yahr scale. As shown in Table 2 there were no significant differences between groups on any of these variables. The groups also scored similarly on the two cognitive screening measures (i.e., DRS-2 and MMSE) and a self-report measure of depressive severity (i.e., BDI-II).

Duration of parkinsonian symptoms, per patient self-report, was approximately 138.5 months for the DBS group (*SD*=63.9, range 52–319 months) and 76.5 months for the PD controls (*SD*=69.1, range 21–310 months). This difference in self-reported symptom duration (i.e., 62 months) was significant, $t(39)=-2.98$, $p=.005$, $r=.43$. In addition, DBS patients' motor symptoms were more severe than those of PD controls when patients were assessed "*off*" medications with the UPDRS-III (DBS group *M*=43.4 vs PD control *M*=30.8), $t(36)=-3.85$, $p<.001$, $r=.54$.

High-resolution post-operative CT scans were obtained for all DBS patients, and these scans were fused to pre-operative MRIs in order to accurately measure lead locations. Coordinates of the active electrode contact for each of the four targets were calculated relative to the AC-PC line, and means are shown in Table 3.

Group differences in cognitive performance over time

Mean scores of the DBS patients and PD controls tested at baseline (Time 1) and at Time 2 across each of the five cognitive tests are shown in Table 4. In order to allow comparisons between the measures, Digit Span Backward and Vocabulary scaled scores were converted to T-scores before their inclusion in analyses. To test the first prediction that, compared to a control group, DBS patients would decline only on tasks with greater dorsolateral prefrontal cortex involvement, a separate repeated-measures analysis of variance (ANOVA) was conducted for each of the five dependent variables (COWAT, Animal Fluency, Digit Span Backwards, BNT, Vocabulary). For each ANOVA, the between-participants factor was Group (DBS, PD controls) and the within-participants factor was testing Time (Time 1, Time 2). As shown in Table 5, results revealed no significant main effects of Group or Time for any of the five cognitive tests with the exception of a significant main effect of time for semantic fluency such that on the whole, patients performed more poorly at post-test ($p=.04$).

Significant Group × Time interactions were detected for the two fluency tasks: letter fluency, $F(1, 39)=10.27$; $p=.003$; $\eta_p^2=.21$, and animal fluency, $F(1, 39)=6.35$; $p=.02$; $\eta_p^2=.14$. Using the method of simple main effects described by Winer, Brown, and Michels (1991) to decompose these interactions, we conducted Bonferroni-adjusted post-hoc comparisons to evaluate the DBS versus control group differences separately for each occasion. As shown graphically in Figure 1a, DBS and PD control patients did not differ at baseline testing on the measure of letter fluency; however, the DBS patients produced significantly fewer words than PD controls at follow-up testing ($p=.03$). Similarly, we compared the Time 1 versus Time 2 differences separately for DBS and control patients. The DBS patients' post-surgery scores on letter fluency were significantly lower than their baseline scores ($p=.001$), while control patients' pre- and post-test scores did not differ significantly. For semantic fluency (Figure 1b), similar procedures revealed that DBS and PD control patients did not differ at baseline or at follow-up testing. However, DBS patients' post-surgery scores were significantly lower than their baseline scores ($p=.002$), while control patients' pre- and post-test scores did not differ significantly.

Because DBS patients and PD controls differed significantly on two key disease variables (i.e., disease duration and UPDRS-III "*off*"), these analyses of variance were re-run using these variables as covariates (ANCOVAs). Results revealed a trend for the Group × Time interaction to persist for letter fluency, $F(1, 34)=3.86$, $p=.058$, $\eta_p^2=.10$; however, the interaction was no longer significant for semantic fluency, $F(1, 34)=2.2$, $p=.15$, $\eta_p^2=.06$. No other main effects or interactions approached significance in either of the ANCOVAs. In order to further explore possible relationships between these baseline disease variables and changes in verbal fluency, Pearson correlations were calculated. Letter fluency change scores did not correlate with disease duration ($r=-.15$; $p=.51$) or UPDRS-III "*off*" ($r=-.099$; $p=.68$). Similarly, Animal fluency change scores did not correlate with disease duration ($r=.097$; $p=.67$) or UPDRS-III "*off*" scores ($r=.11$; $p=.66$).

In order to investigate the possibility that observed cognitive changes might be related to changes in dopaminergic medications following DBS surgery, Pearson correlations between changes in levodopa equivalent dosages (LEDs) and changes on fluency measures were calculated. Changes in LED did not correlate with performance changes on letter ($r=-.28$; $p=.24$) or semantic ($r=-.11$; $p=.66$) fluency. Because there was a trend for STN and GPi subgroups to differ in LED change ($p=.07$), such that STN patients experienced a mean reduction of 233.45mg as compared to a mean increase of 359.77mg in the GPi group, these correlations were also conducted separately for these subgroups. Among STN patients neither letter ($r=.12$; $p=.79$) nor semantic ($r=-.21$; $p=.62$) fluency change correlated with LED change. Among GPi patients LED change did not correlate with semantic fluency change ($r=-.17$; $p=.62$), but there was a trend for LED change to negatively correlate with change in letter fluency ($r=-.55$; $p=.08$).

Because using normative T-scores can artificially reduce error variance as well as introduce error variance when normative data are based on different samples not uniformly corrected for the same demographics, we also ran these nomothetic analyses on raw fluency scores with relevant demographics (i.e., age and education) as covariates. The results were virtually identical. The Group × Time interactions were still significant for both letter, $F(1, 37)=8.29$; $p=.007$; $\eta_p^2=.18$, and semantic, $F(1, 37)=4.50$; $p=.04$; $\eta_p^2=.11$, fluency, and no main effects or interactions involving either covariate were identified.

Reliable Change results

To examine the significance of individual changes in performance on the two cognitive tests for which Group × Time interactions were identified, (i.e., letter and semantic fluency), we calculated Reliable Change Indexes (RCIs) that were corrected for practice effects using previously described formulas 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*" on a measure if the difference between their obtained and predicted scores exceeded the RCI for the particular cognitive test. Consistent with the majority of previous literature using RCIs, 90% confidence intervals were chosen. The results were as follows. Two (11%) PD control patients evidenced significant decline on one fluency measure, and none showed decline on both measures. In contrast, 11 (50%) DBS patients evidenced significant decline on one or both fluency measures. Specifically, 7 DBS patients declined on only one measure (3 on letter fluency and 4 on semantic fluency) and 4 DBS patients declined on both.

Next, Pearson chi-square tests were conducted in order to assess the significance of the proportional differences between the number of decliners in the DBS and PD control groups. In addition, phi values were obtained to index effect sizes. There was a significant and

moderate association between having surgery and declining on at least one verbal fluency measure, $\chi^2(1)=7.34$, $p=.007$, Phi=.42. Finally, the odds of declining were calculated separately for DBS patients and PD controls, and these were used to calculate odds ratios. Compared to patients who did not undergo surgery, DBS patients had 8.3 times greater odds of experiencing significant decline on at least one measure of verbal fluency. Looking at letter and semantic fluency individually, DBS patients had 8.4 times greater odds of declining on letter fluency and 10.3 times greater odds of declining on semantic fluency, compared to PD controls.

Variables related to post-DBS cognitive change

To determine the relationship between variables identified as risk factors by previous studies (i.e., age, baseline cognitive status, baseline depression status, side of DBS surgery) and changes in performance on the verbal fluency tasks, two linear regressions were conducted. For both regressions these four variables were regressed on performance change (post-test T-scores minus pre-test T-scores) on letter fluency or semantic fluency, respectively. The model was not significant in predicting change in performance on letter ($R^2=.097$; $p=.81$) or semantic ($R^2=.38$; $p=.11$) fluency. Despite the non-significance of the latter model, it was noted that the predictor *side* was significantly related to change in semantic fluency performance ($\beta=-.57$; $p=.01$). On average, patients who underwent surgery to their *right* brain experienced a negligible *increase* in performance of 0.88 points, while patients who underwent surgery to their *left* brain experienced a substantial *decrease* in performance of 14 points; this difference was moderate and significant, $t(20)=3.16$; $p=.005$; $r=.58$. Of the eight patients who underwent surgery to the right brain, only one experienced a significant decline on the measure of semantic fluency, according to the RCI analyses. In contrast, 8 out of the 14 patients who underwent left-sided surgery experienced significant decline on this measure. Pearson chi-square tests for the significance of these differences revealed a significant association between side of surgery and semantic fluency decline, $\chi^2(1)=4.20$; $p=.04$; Phi=.44.

In order to investigate other possible differences between DBS patients who experienced significant declines in verbal fluency and those who did not, a series of exploratory independent samples *t*-tests were conducted. Because the method of Reliable Change does not correct for baseline differences, these tests compared patients classified as decliners and non-decliners based on RCI analyses on a variety of baseline disease indicators (i.e., UPDRS "*on*" and "*off*," disease duration) and change (i.e., Time 2–Time 1 Hoehn & Yahr stage, UPDRS "*on*" and "*off*," levodopa equivalent dose, BDI-II) variables. Due to the relatively small number of patients and the exploratory nature of these comparisons, *r* values were calculated as an index of effect size in order to clarify results. As shown in Table 6, none of the baseline characteristics examined was significantly different between the groups, but there was a trend for the groups to differ on side of surgery. Namely, 9 out of the 11 decliners had undergone surgery to the left brain, $t(18.82)=-1.83$; $p=.08$; $r=.39$. With regard to patients' motor changes, decliners and non-decliners differed significantly on changes in their UPDRS scores when they were assessed both "*on*," $t(19)=-2.87$; $p=.01$; $r=.55$, and "*off*" medication, $t(17)=-2.20$; $p=.04$; $r=.47$, and effect sizes for these differences were moderate. On average, non-decliners experienced a reduction of 6.5 points when assessed "*on*" medications and a reduction of 15.1 points when assessed "*off*" medication. In contrast, decliners experienced an increase of 3.1 points when assessed "*on*" medications and a reduction of only 5.7 points when assessed "*off*" medications. Decliners and non-decliners did not significantly differ in changes in LED.

DISCUSSION

Cognitive changes identified in the present study

The present study documented selective cognitive declines on letter and semantic fluency in patients assessed 1 year after undergoing unilateral DBS, when compared to a group of PD patients who did not undergo surgery. Declines specific to the DBS group were not identified on a measure of working memory (Digit Span Backward) or on measures of semantic knowledge (Vocabulary, Boston Naming Test). These findings are in line with the majority of previous studies, which have documented fluency declines (Castelli et al., 2006; De Gaspari et al., 2006; Funkiewiez et al., 2004; Gironell et al., 2003; Rothlind, Cockshott, Starr, & Marks, 2007; Smeding et al., 2006; Voon et al., 2006). However, reports of working memory changes after surgery, which we did not find, conflict with other studies (Hershey et al., 2004; Morrison et al., 2004; Saint-Cyr, Trepanier, Kumar, & Lang, 2000). The absence of a working memory deficit in this and in some previous studies may be at least partially explainable by the fact that verbal fluency tasks and Digit Span Backward differ in both the neural networks engaged (Baldo et al., 2006; Crosson et al., 2003; Jonides et al., 1998) as well as the nature of the cognitive abilities assessed. The fluency measures are timed tasks, while patients are allowed to respond at their own pace in the Digit Span task. Thus, the former tasks may be more sensitive to PD bradyphrenia, or an overall slowing of information processing, which affects patients' response output.

Alternatively, the finding that DBS patients declined on verbal fluency but not on a working memory task may reflect a different mechanism underlying cognitive decline following surgery. Group-specific declines on fluency measures may result not from current spread within subcortical target structures, but rather from direct damage to frontal areas along the electrode trajectory. Several studies have documented similarly impaired cognitive performance both with stimulators turned "*on*" and "*off*," and such findings have been interpreted as providing evidence that cognitive declines after surgery may not be related to high frequency stimulation per se (Daniele et al., 2003; Morrison et al., 2004). However, most studies employed a relatively short "wash-out period" separating the "*on*" and "*off*" conditions, and the effects of stimulation may have persisted well beyond the point at which stimulators were turned off (Kern & Kumar, 2007). Other studies have reported the opposite finding that impairments were most prevalent in the "*on*" stimulation condition (Hershey et al., 2004; Jahanshahi et al., 2000; Pillon et al., 2000). Future research is needed to clarify these conflicting findings.

Another proposed explanation for post-DBS declines lies in changes in dopaminergic medications after surgery, particularly in patients undergoing STN DBS (Funkiewiez et al., 2004). In the present sample, LED reductions did not account for observed fluency changes, which mirrors findings of other authors (Rothlind et al., 2007). We did not identify relationships between LED and fluency changes, and decliners and non-decliners did not differ in LED change. Commensurate with previous reports of a greater medication reduction after STN DBS (Vitek, 2002), we identified a trend for STN but not GPi patients to experience a reduction in LED. While changes on neither fluency measure correlated with change in LED among STN patients, there was a trend for letter fluency to *negatively* correlate with change in LED, among GPI patients and this correlation was moderately sized. Increasing dopaminergic drugs after surgery seemed to be related to worse letter fluency performance after surgery. In so far as increased LED may reflect a less positive surgical outcome, these findings provide a very preliminary indication that patients performing worse on letter fluency measures may not have had as successful a surgery.

The importance of individual variability

An important contribution of the present study to the literature on DBS-related cognitive changes lies in its use of Reliable Change. This well-established method for defining true, functional change within an individual may represent the most important information for the clinician. Since group comparisons rely on performance means that do not describe individual variability, one cannot draw definitive conclusions about the ubiquity of an effect using an exclusively inferential approach. To date, only one published study using RCIs to analyze cognitive effects of DBS surgery for PD exists. This report featured a shorter (6 months) follow-up period, and the authors only studied patients undergoing bilateral implantation in the subthalamic nucleus and not unilateral as in our series (York et al., 2008).

In the present study, RCI analyses support the view that group-specific cognitive declines likely reflect large and meaningful declines in a subset of patients rather than negligible effects in most or all patients. Specifically, significant cognitive declines were found in 50% of the DBS patient group, as compared to only 11% in the control group. Researchers have posited that even when results suggest stable cognitive functioning overall in group studies, individual changes can vary greatly (Dujardin, Defebre, Krystkowiak, Blond, & Destée, 2001). The value of the idiographic approach from a methodological standpoint is highlighted by the present study, which identified a substantial proportion of individual decliners but relatively meager effect sizes (i.e., η_p^2=.21 and .14) using inferential statistical procedures. Similarly, York et al. (2008) reported verbal fluency declines only at the trend level when conducting group comparisons but found that 40% of patients evidenced significant declines on their measures of semantic fluency and 26% on letter fluency. Significant changes may be underestimated or overlooked when relying purely on a nomothetic approach, and an idiographic approach can provide additional essential answers to a research question.

Factors related to post-surgical cognitive decline

None of the hypothesized variables (i.e., age, baseline cognitive status, baseline depression score, surgery side) was found to be significantly associated with performance changes on the measure of letter fluency in the present study. Moreover, only side of surgery was associated with performance on semantic fluency. While effect sizes indicate that the absence of significance for many predictors is reliable, it should be noted that the regression analyses used to address this aim were underpowered. Previous research attempting to identify predictors of cognitive decline after DBS surgery has been largely unsuccessful in documenting a linear relationship between baseline variables and cognitive outcome (Ory-Magne et al., 2007; Parsons et al., 2006; Voon et al., 2006). In the present study no patients in the DBS group were over the age of 70, and only patients in whom dementia was vigilantly ruled out were included as per the protocol for candidate selection. The resultant limited range most likely accounts for the lack of association between age or baseline cognitive functioning and post-surgical cognitive changes in our study.

The hypothesis that patients undergoing left-sided surgery would experience greater cognitive declines was supported by our data in that undergoing surgery to the left brain was significantly associated with decline in semantic fluency, and there was a trend for more patients who declined on at least one measure to have undergone surgery to their left brain. The vast majority of the literature on DBS cognitive outcomes has not addressed this question of laterality, as most reports are on simultaneous or closely staged bilateral procedures. Rothlind et al. (2007) reported that in a group of patients undergoing staged bilateral DBS to either GPi or STN, performance on the Animal Fluency Test declined more in patients whose initial surgery was to their left, as opposed to the right. In addition, many

researchers have documented greater declines in a variety of cognitive tests, including fluency, following left-sided ablative procedures (Cahn et al., 1998; McCarter, Walton, Rowan, Gill, & Palomo, 2000; Obwegeser et al., 2000; Tröster, Woods, & Fields, 2003). The finding that side of surgery predicted greater semantic fluency, but not letter fluency, declines following DBS likely resulted from the fact that although similar, semantic fluency requires adequate knowledge of the attributes that define a semantic category. Because semantic fluency tasks are considered more sensitive to the breakdown in the structure of semantic knowledge, they are thought to rely on the overall integrity of the whole left hemisphere (Jurado, Mataro, Verger, Bartumeus, & Junque, 2000). It is important to note that virtually all of the tasks employed in this and previous studies are verbal and preferentially engage the left hemisphere. Therefore, while it appears that left-sided DBS is associated with decline in these select tasks, we cannot generalize these findings to other tasks, and future researchers should seek out tasks that may be more sensitive to right-brain dysfunction (e.g., Tower of London).

Comparisons between patients classified as decliners and non-decliners using Reliable Change revealed that while these patients did not differ on any baseline measures, decliners failed to show the degree of motor improvement experienced by non-decliners. Specifically, scores on the UPDRS motor examination, which quantifies the severity of PD-specific motor symptoms, improved more in those DBS patients who did not show cognitive decline. In addition, there was a trend for increasing LED, a possible indication of less positive surgical outcome, to correlate with worsening letter fluency performance among GPi patients. Thus, patients who decline cognitively after DBS surgery may be those who show a poorer response to surgery in general. It is possible that slight variations in lead placement in a subset of patients led to their obtaining less motor benefit due to inadequate stimulation in sensorimotor subregions and concomitant increased stimulation in associative subregions.

The implication that cognitive deficits are related to a lack of motor improvement is not prevalent in the literature; however, most studies have merely dismissed this explanation in light of overall cognitive declines that appear in the context of motor improvements in the same group of patients. The logic in using group comparisons to address this question is flawed in that averaging outcomes might mask associations that exist in individual patients. While this approach tests for a systematic relationship between motor and cognitive changes, it does not examine motor changes in a particular patient who experiences a significant decline. One group that attempted to characterize the relationship between motor and non-motor outcome by comparing patients who were stratified based on relatively arbitrary cut-offs failed to identify an association between cognitive decline and poor motor response (Perriol et al., 2006). However, these authors only assessed patients using a global measure of cognition (DRS-2).

Study limitations and suggestions for future research

The present study suffers from several important limitations. First, the sample used in the present study lacked racial and ethnic diversity, as 39 out of the 41 patients were Caucasian, and only one patient in each group (DBS and PD control) was Hispanic. This likely reflects both the limited diversity of the patient population at this center as well as the relatively lower incidence of PD among African Americans (Van Den Eeden et al., 2003). In addition, the sample comprised a relatively small number of patients in general. A recent meta-analysis highlighted how widespread and problematic this limitation is in the extant literature on post-DBS cognitive morbidity and recommended a sample size of at least 48 patients (Woods et al., 2006). The present study attempted to address this limitation by using RCIs to capture individual changes that may have been masked by group averaging.

The present report presents data on a relatively small cognitive battery. Only five measures were selected for analysis in accordance with the specific hypotheses set forth, and this consideration reflects the theory-driven study design that contrasts with much of the literature, which has an exploratory approach. Recent studies have identified other tests that may be sensitive to post-DBS changes, and we are currently conducting analyses to investigate such findings in our sample.

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, and they were experiencing more severe motor dysfunction when assessed "*off*" medication. These important differences make it impossible to completely rule out the possibility that our finding of DBS-specific cognitive declines relates to group differences in variables related to the disease process. Indeed, including the variables UPDRS "*off*" and disease duration as covariates in the analyses of variance reduced the significance of the Group × Time interaction effect to the level of a trend for letter fluency and rendered it non-significant for semantic fluency. However, no main effects were found for either of these variables, and the power of the co-varied analyses was so low as to make it impossible to draw conclusions. Additionally, correlational analyses identified no significant associations between verbal fluency change and either UPDRS "*off*" or disease duration, and there were no significant differences between decliners and non-decliners on either variable. Thus, while the data do not seem to suggest that the identified DBS-specific cognitive changes are more related to disease duration or severity than to surgery, it is not possible to completely elucidate their relative contributions.

A strength of the present study was its inclusion of a PD control group. While the ideal PD control group would be one that is wait-listed to have DBS surgery, methodological and ethical issues related to the availability and recognized efficacy of DBS make such a group difficult to obtain. To date, no controlled studies in the extant literature have adequately resolved this problem. In many studies, groups were not matched on at least one important disease variable (Smeding et al., 2006; York et al., 2008), or had very small sample sizes (Gironell et al., 2003; Moretti et al., 2003; Morrison et al., 2004).

It should be noted that the present study was unable to address differences in outcome related to surgery site (i.e., GPi vs STN). This question is important for determining the ideal site for individual patients and should be investigated with larger samples and randomization protocols. An ongoing NIH-funded study at the University of Florida is currently addressing the topic of DBS surgery site in relation to outcome and laterality.

Conclusions

The present study adds to the literature through its use of Reliable Change to highlight the impact of individual variability in outcome as well as the clinical and research value of a combined nomothetic and idiographic approach. Results indicated that fluency declines reflected significant changes in a subset of DBS patients that was proportionally larger than that of controls. In addition, the findings provide solid evidence that declines in semantic fluency is associated with left-sided DBS, which has not been clearly demonstrated in previous studies. Finally, the present study suggests that while fluency changes are not systematically related to the patient characteristics of age, baseline cognitive status, or pre-operative depressive symptomatology, they may appear more commonly in those patients who demonstrated a less robust surgical outcome. Further research is needed to investigate this important finding and its implications. In addition, future studies should aspire to longer follow-up in order to determine the persistence and stability of deficits. More attention should be directed toward investigating the real-world significance of DBS-related cognitive

changes. Since the relationship between neuropsychological tests and everyday functioning is likely moderated by other factors such as depression levels and social support, researchers should be cognizant of these variables when drawing conclusions (Chaytor, Temkin, Machamer, & Dikmen., 2007; Okun et al., 2008). Tests of everyday functioning and patient and caregiver self-report measures could be developed to address this question.

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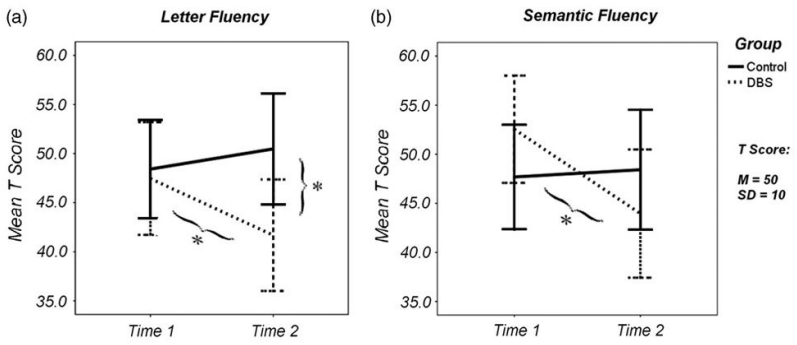

Figure 1.
Control versus DBS patients' scores on letter and semantic fluency tests at times 1 and 2.

Table 1

Neuropsychological measures

	Tests involving dorsolateral prefrontal cortex
Semantic Fluency Animals	*The Animal Fluency Test* (Animals) – Involves producing exemplars of a semantic category (i.e., animals) during a 60-second period. DV = total number of words, converted to T-scores based on norms adjusted for age, education, and gender (Heaton, Miller, Taylor, & Grant, 2004).
Letter Fluency COWAT	*Controlled Oral Word Association Test* (COWAT; Benton, Hamsher, & Sivan, 1994) – Involves producing words beginning with a specified letter of the alphabet (e.g., "f", "a", etc.) over a 60-second period; Total of three trials with one letter per trial; DV = total number of words converted to a T-score according to norms adjusted for age, education, and gender (Heaton et al., 2004).
Working Memory Digit Span Backward	Digit Span Backward (Wechsler Adult Intelligence Scale, 3rd edition; Wechsler, 1997) – Involves listening to a string of numbers and repeating in the reverse order. DV = total number of correct trials converted to scaled scores based on age-based norms.
	Tests with less involvement of dorsolateral prefrontal cortex
Visual Confrontation Naming BNT	*Boston Naming Test* (BNT; Kaplan, Goodglass, & Weintraub, 1983) – 60-item version, involves naming visually presented objects; DV = total correct items converted to T-scores based on age, education, and gender-based norms (Heaton et al., 2004).
Vocabulary WASI	*Vocabulary* (Wechsler Abbreviated Scale of Intelligence; Wechsler, 1999) – requires patients to provide verbal definitions of a series of words that increase in difficulty, and 0, 1, or 2 points are possible on each trial, depending on the depth and accuracy of response. Scores representing total points obtained were converted to scaled scores based on age-based norms provided in the testing manual.

Table 2

Surgical patients versus disease controls at baseline

	Controls	DBS	*t*	*df*	*p*
Age (years)	64.6 (6.6)	61.4 (5.0)	1.76	33.25	.09
Education (years)	15.4 (3.0)	14.0 (2.3)	1.67	39	.10
Male/Female	12/7	18/4	1.32	34.30	.20
Months with symptoms	76.5 (69.1)	138.5 (63.9)	−2.98	39	.005
Hoehn & Yahr stage	2.4 (.4)	2.2 (0.3)	1.84	30.82	.08
UPDRS “*on*”	25.3 (8.5)	22.9 (8.0)	0.89	36	.38
UPDRS “*off*”	30.8 (8.3)	43.4 (11.5)	−3.85	36	<.001
BDI-II	9.2 (8.6)	10.1 (8.2)	−0.29	35	.77
MMSE (raw)	28.3 (1.9)	29.0 (1.1)	−0.59	39	.12
DRS-2 (raw)	138.6 (3.5)	138.0 (4.4)	0.50	39	.62

DBS=Deep Brain Stimulation, UPDRS=Unified Parkinson Disease Rating Scale; BDI-II=Beck Depression Inventory, 2nd edition, MMSE=Mini-Mental State Examination; DRS-2=Dementia Rating Scale, 2nd edition.

Table 3

Means and standard deviations of coordinates of active electrode contacts relative to the anterior commissure/posterior commissure line

	X	Y	Z
Right STN (*N* =3)	13.4 (0.8)	−0.5 (3.7)	−1.8 (1.5)
Left STN (*N* =7)	−11.6 (0.7)	−1.5 (1.5)	−1.2 (1.3)
Right GPi (*N* =5)	20.6 (0.7)	4.5 (1.1)	−0.2 (1.9)
Left GPi (*N* =7)	−22.1 (1.5)	2.1 (1.6)	−0.3 (1.6)

STN=Subthalamic nucleus; GPi=Globus Pallidus internus.

Table 4

T-scores on specific cognitive tests at times 1 and 2

	Controls	DBS	*t*	*df*	*p*
Vocabulary					
Time 1	58.0 (7.9)	55.5 (6.7)	1.06	39	.29
Time 2	57.1 (13.1)	54.4 (8.0)	0.79	37	.43
BNT					
Time 1	55.5 (10.8)	53.6 (11.1)	0.55	39	.59
Time 2	55.8 (11.9)	53.7 (12.7)	0.53	38	.60
Digit Span Backward					
Time 1	51.9 (13.5)	51.5 (7.6)	0.10	39	.92
Time 2	50.1 (8.6)	49.7 (6.0)	0.18	39	.86
COWAT					
Time 1	48.4 (10.4)	47.5 (12.9)	0.26	39	.80
Time 2	50.5 (11.7)	41.7 (12.8)	2.28	39	.03
Animal Fluency					
Time 1	47.7 (11.0)	52.5 (12.3)	−1.32	39	.19
Time 2	48.4 (12.7)	44.0 (14.7)	1.03	39	.31

DBS=Deep Brain Stimulation; BNT=Boston Naming Test; COWAT=Controlled Oral Word Association Test; T-scores: Mean=50; Standard Deviation=10.

Table 5

Repeated-measures analyses of variance

	SS	MS	*F*	*p*	Effect size (η^2_p)	Power
Vocabulary						
Group	154.53	154.53	1.18	.28	0.03	0.19
Error (between)	4827.26	130.47				
Time	32.94	32.94	0.95	.34	0.03	0.16
Group × Time	0.25	0.25	0.01	.93	0.00	0.05
Error (within)	1287.68	34.80				
BNT						
Group	79.33	79.33	0.31	.58	0.01	0.09
Error (between)	9861.23	252.85				
Time	1.04	1.04	0.05	.82	0.00	0.06
Group × Time	0.16	0.16	0.01	.93	0.00	0.05
Error (within)	790.35	20.27				
Digit Span Backward						
Group	1.37	1.37	0.01	.92	0.00	0.05
Error (between)	4841.62	127.41				
Time	75.27	75.27	1.71	.20	0.04	0.25
Group × Time	0.47	0.47	0.11	.92	0.00	0.05
Error (within)	1670.48	43.96				
COWAT						
Group	485.42	485.42	1.86	.18	0.05	0.27
Error (between)	10178.19	260.98				
Time	70.55	70.55	2.32	.14	0.06	0.32
Group × Time	312.16	312.16	10.27	.003	0.21	0.88
Error (within)	1185.41	30.40				
Animal Fluency						
Group	0.79	0.79	0.003	.96	0.00	0.05
Error (between)	10103.65	259.07				
Time	314.45	314.45	4.50	.04	0.10	0.54

	SS	MS	*F*	*p*	Effect size (η_p^2)	Power
Group × Time	443.52	443.52	6.35	.02	0.14	0.69
Error (within)	2725.50	69.89				

SS=Sum of Squares; MS=Mean Squares; BNT=Boston Naming Test; COWAT=Controlled Oral Word Association Test.

Table 6

Baseline and change score comparisons in decliners vs non-decliners

	Decliners	Non-decliners	*t*	*df*	*p*	*r*
Baseline characteristics						
Age	61.8 (5.0)	61.0 (5.3)	−0.37	20	.71	.08
BDI-II	11.5 (9.6)	8.3 (6.2)	−0.84	18	.41	.19
DRS-2	137.5 (4.9)	138.4 (4.1)	0.42	20	.68	.09
UPDRS "*on*"	22.6 (6.9)	23.2 (9.2)	0.16	20	.87	.04
UPDRS "*off*"	40.4 (10.9)	46.4 (11.8)	1.18	18	.25	.27
Disease duration (months)	139.5 (70.1)	137.5 (60.5)	−0.07	20	.95	.02
Levodopa equivalent dose	1026.6 (304.7)	1189.7 (717.9)	0.69	13.76	.50	.18
Left/Right	9/2	5/6	−1.83	18.82	.08	.39
Change variables						
Hoehn & Yahr stage	0.4 (0.6)	0.1 (0.3)	−1.66	11.42	.12	.44
UPDRS "*on*"	3.1 (6.0)	−6.5 (8.9)	−2.87	19	.01	.55
UPDRS "*off*"	−5.7 (11.0)	−15.1 (7.6)	−2.20	17	.04	.47
BDI-II	3.0 (9.4)	−0.2 (6.2)	−0.89	18	.39	.21
DRS-2	−5.6 (5.9)	−3.7 (5.9)	0.74	20	.47	.16
Levodopa equivalent dose	284.1 (884.3)	−46.6 (504.6)	−1.02	17	.32	.24

BDI-II=Beck Depression Inventory, 2nd edition; DRS-2=Dementia Rating Scale, 2nd edition; UPDRS=Unified Parkinson Disease Rating Scale.