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Neuropsychological functioning following bilateral subthalamic nucleus stimulation in Parkinson's disease[☆]

C.E. Morrison [a,b,*], J.C. Borod [a,c], K. Perrine [b], A. Beric [b,d], M.F. Brin [a], A. Rezai [d], P. Kelly [b], D. Sterio [b], I. Germano [a], D. Weisz [a], C.W. Olanow [a]

[a] *Mount Sinai Medical Center, New York, NY, USA*
[b] *New York University Medical Center, New York, NY, USA*
[c] *Queens College and The Graduate Center of the City University of New York, New York, NY, USA*
[d] *Hospital for Joint Diseases, New York, NY, USA*

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Abstract

The cognitive effects of subthalamic nucleus (STN) stimulation in Parkinson's disease (PD) have been examined. However, there are no reported studies that evaluate, by incorporating a disease control group, whether neuropsychological performance in surgical patients changes beyond the variability of the assessment measures. To examine this issue, 17 PD patients were tested before and after bilateral STN stimulator implantation, both on and off stimulation. Eleven matched PD controls were administered the same repeatable neuropsychological test battery twice. Relative to changes seen in the controls, the surgery for electrode placement mildly adversely affected attention and language functions. STN stimulation, per se, had little effect on cognition. The STN DBS procedure as a whole resulted in a mild decline in delayed verbal recall and language functions. There were no surgery, stimulation, or procedure effects on depression scale scores. In contrast to these group findings, one DBS patient demonstrated significant cognitive decline following surgery.

Keywords: Parkinson's disease; Neuropsychological assessment; Cognition; Deep brain stimulation (DBS)

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* Corresponding author. Present address: Neuropsychology Service, NYU Comprehensive Epilepsy Center, 403 E, 34th Street, 4th Floor, New York, NY 10016, USA. Tel.: +1-212-241-4530.

E-mail address: c.morrison@med.nyu.edu (C.E. Morrison).

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Over the last decade, deep brain stimulation (DBS) has gradually come to be regarded as a safe and effective treatment for medically refractory Parkinson's disease (PD) (Gross & Lozano, 2000). Stimulation of the subthalamic nucleus (STN), in particular, has become very useful as it reduces the spectrum of PD motor symptoms (e.g., tremor, bradykinesia, rigidity, and levodopa-induced dyskinesia), often allows for a reduction in the dosage of antiparkinson medication (Moro, Scerrati, Romito, Tonali, & Albanese, 1999), and has been hypothesized to possibly slow disease progression (Rodriguez, Obeso, & Olanow, 1998). Although there is a rapidly growing literature regarding the motor benefits of STN DBS, the neuropsychological ramifications of this procedure are relatively understudied and the findings available in the literature have been mixed.

Looking at the short-term (3–6 months post surgery) cognitive effects of STN DBS, Ardouin et al. (1999b) reported on a series of PD patients who had undergone either bilateral STN ($n = 49$) or internal pallidum (GPi; $n = 14$) electrode placement. By comparing the presurgical baseline to the postsurgical stimulation-on condition in their combined sample, these investigators found a decline in verbal fluency and improvements on the Trail Making Test (TMT) parts A and B. Post hoc comparisons revealed that on both parts of the TMT, the subset of STN subjects improved whereas the GPi subjects remained the same across conditions. The investigators did not, however, include a measure that might separate the individual effects of the purely motor versus the cognitive components of this task. Depression scores also significantly improved in their STN group. After a similar postsurgical interval, Saint-Cyr and co-workers found that STN DBS adversely affected working memory, speed of processing, nonverbal learning, verbal and nonverbal memory, verbal fluency, and set-shifting, with older patients at particular risk for developing these cognitive impairments (Saint-Cyr, Trepanier, Kumar, Lozano, & Lang, 2000; Trepanier, Kumar, Lozano, Lang, & Saint-Cyr, 2000). Hariz et al. (2000) reported the case of a 53-year-old man with a 10-year history of PD and baseline moderate memory deficits who demonstrated cognitive deterioration postoperatively. This patient's new impairments were such that his ability to execute his activities of daily living was reduced, despite the marked motor improvement he experienced as a result of his bilateral STN DBS. Finally, in a small sample of PD patients who underwent unilateral STN DBS ($n = 3$), two of the three subjects demonstrated minimal cognitive change whereas the third subject declined in verbal fluency, verbal learning and memory, and executive functioning (Morrison et al., 2000b).

Assessment of cognitive functioning at longer follow-up intervals (9–12 months post surgery) has revealed more mixed findings. Some authors report no significant cognitive decline (Burchiel, Anderson, Favre, & Hammerstad, 1999; Limousin et al., 1998; Moro et al., 1999) or only isolated reductions in verbal fluency (Pillon et al., 2000) following bilateral STN DBS. Limousin et al., however, commented that although in most subjects, there was minimal postoperative cognitive change, one of their subjects who demonstrated baseline frontal lobe dysfunction, became even more impaired in this area following surgery. In contrast, the deficits described by Saint-Cyr et al. (2000) in their short-term follow-up evaluation largely persisted at the 12-month follow-up. Although learning ability recovered somewhat, performance on frontal lobe tasks either did not improve or continued to decline. It could be argued that the persistent deficits observed at long-term follow-up were related to Parkinson's disease progression, rather than to the DBS, per se. However, if this were the case, all studies with long-term follow-up data would note a similar decline in cognitive performance. As indicated above, other studies have not observed this pattern, suggesting that disease progression may not be the primary reason for the persistent reduction in performance following DBS surgery noted by Saint-Cyr et al. (2000).

The clinical findings mentioned above were the result of comparisons between baseline cognitive performance to performance in the stimulation-on condition. This comparison yields information about the overall cognitive effects of the DBS procedure, but does not allow for examination of the individual effects of DBS electrode placement or STN stimulation. There are, however, a few preliminary reports on the cognitive effects of high frequency STN stimulation where the stimulation-off and stimulation-on conditions were available and directly compared. The patient in the case report mentioned above, who demonstrated significant cognitive impairment postoperatively, did not improve on neuropsychological tests following initiation of STN stimulation (Hariz et al., 2000). In the larger sample ($n = 63$) reported by Pillon et al., bilateral stimulation of the STN improved psychomotor speed and working memory. For unilateral STN stimulation, stimulation per se had minimal effects on neuropsychological test performance (Morrison et al., 2000b). The latter authors, however, also compared the baseline condition to the stimulation-off condition and found that the cognitive decline noted in one of their subjects was largely the result of the surgery for electrode implantation rather than to STN DBS.

It is clear that the limited available data regarding the cognitive effects of STN DBS are not conclusive and that a more comprehensive experimental design is needed to fully evaluate the cognitive effects of multiple aspects of this surgery. In order to address this unmet need, the program for Neuropsychological Investigation of Deep Brain Stimulation (PNIDBS) was developed (Morrison et al., 2000b). The PNIDBS involves assessment of patients at baseline and following DBS surgery with stimulation both on and off. The program utilizes a battery of neuropsychological tests that were specifically selected because of their previously reported ability to detect impairment in PD, their assessment of several areas of cognitive functioning (i.e., attention, language, visuospatial, memory, and executive), repeatability, brevity, and minimal motor demands (only oral responses are required). In addition to utilizing the PNIDBS methodology, the present study made further efforts to control for test and subject variability. This was done by incorporating a PD control group into the study design. Inclusion of the disease control group allowed for evaluation of change in cognitive performance across surgical conditions in comparison to that seen in other similar PD patients who were tested multiple times with no surgery during the inter-test interval. This is a unique feature of the current study as a disease control group has not previously been utilized in studies evaluating cognition following DBS surgery.

With the above described clinical and experimental issues in mind, there were three primary objectives to the current study:

(1) To examine whether surgical implantation of chronically indwelling electrodes, independent of any effects DBS may have, results in a change in cognitive functioning (i.e., the Surgery Comparison);
(2) To assess cognitive changes that may result from chronically stimulating the STN (i.e., the Stimulation Comparison); and

(3) To evaluate the cognitive effects of the DBS procedure as a whole (i.e., the Procedure Comparison).

1. Methods

1.1. Subjects

Subjects were 28 individuals with idiopathic PD. Seventeen subjects underwent bilateral STN stimulator placement (15 simultaneous and 2 staged, i.e., sequential or serial placement, procedures; DBSPD). The DBSPD group consisted of nondemented (*M* Dementia Rating Scale, DRS; Mattis, 1988—score = 137.8 [5.6]) subjects of average intelligence (*M* National Adult Reading Test—Revised, NART-R; Blair & Spreen, 1989—score = 110.3 [8.2]) with moderate to severe idiopathic PD (*M* Hoehn & Yahr, 1967 stage—score = 3.3 [0.8]). Thirteen of the 17 DBS subjects were tested in all three experimental conditions, with four subjects declining to be tested in the stimulation-off condition. Two of the DBSPD subjects had a history of right-sided pallidotomy more than a year prior to entry into the present study. Although prior studies have found cognitive impairment following pallidotomy, much of the contemporary literature has found that right unilateral pallidotomy does not result in significant long-term cognitive changes (Cahn et al., 1998; Green & Barnhart, 2000; Rettig, York, Lai, & Jankovic, 2000; Schmand et al., 2000; Trepanier, Saint-Cyr, Lozano, & Lang, 1998). Therefore, the data from the two pallidotomy subjects were analyzed with those from the other surgical subjects.

Eleven subjects were included as demographically and clinically similar PD control (CPD) subjects. The CPD group consisted of nondemented (*M* DRS score = 136.8 [4.2]) subjects of average intelligence (*M* NART-R score = 103.5 [10.0]) with moderate to severe idiopathic PD (*M* Hoehn & Yahr, 1967 stage score = 3.3 [0.6]). None of the CPDs had a history of neurosurgery. The study was approved by the Institutional Review Board at the medical center, and written informed consent was obtained from all participants. Comparison of demographic and clinical characteristics between the DBSPD and CPD groups using independent *t* tests revealed that, overall, the two groups were well matched. See Table 1 for demographic and clinical characteristics, as well as results of group comparisons.

Table 1
Demographic and clinical characteristics of control and DBS subjects

Group	Gender	Age	Education (years)	Age at onset	Disease duration (years)	H & Y stage[a]	NART-R IQ	DRS total
DBSPD	13M/4F	59.9 (7.7)	15.4 (2.6)	48.9 (7.2)	10.8 (3.4)	3.2 (0.8)	110.3 (8.2)	137.8 (5.6)
CPD	10M/1F	62.7 (11.5)	13.8 (2.6)	52.8 (12.4)	10.0 (3.0)	3.3 (0.6)	103.5(10.0)	136.8 (4.2)
P value[b]		.45	.14	.30	.49	.29	.06	.63

[a] Hoehn and Yahr stage score (Hoehn & Yahr, 1967) assessed at baseline following a 12-h withdrawal of PD medications; DBSPD, deep brain stimulation Parkinson's disease subjects; CPD, Parkinson's disease patients that did not undergo surgery; NART-R, National Adult Reading Test—Revised (Blair et al., 1989); DRS, Dementia Rating Scale (Mattis, 1988).

[b] *P* value based on a *t* test comparing DBSPD and CPD subjects.

1.2. Procedure

In accordance with the procedure described in the PNIDBS (Morrison et al., 2000b), surgical subjects were tested in three conditions: baseline, postsurgically with stimulation off, and postsurgically with stimulation on. The second and third testing sessions took place an average of 13.3 (7.8) weeks postsurgically with a mean of 9.7 (7.7) days between the two postoperative conditions. During each of the postsurgical sessions, alternate equivalent versions of the test battery, administered on the presurgical day, were given. The order of the alternate forms of the three randomized test batteries was counterbalanced across subjects, as was the order of the postsurgical conditions (stimulator on or off first). Control PDs were tested twice (Time 1 and Time 2), with no surgical intervention during the inter-test interval. There was an average of 9.7 (7.4) weeks between sessions.

All subjects were asked to undergo cognitive testing following an overnight withdrawal of antiparkinson medications. In the current sample, five of the 17 surgical subjects were tested in all conditions following antiparkinson drug withdrawal. The remaining surgical subjects declined to undergo testing in the medication-off state due to the associated physical discomfort that could occur. Therefore, these subjects were tested in all conditions without a period of antiparkinson medication withdrawal. All CPDs consented to be tested following a 10–12 h withdrawal of their antiparkinson medications at both testing times.

The DRS and the NART-R were administered to subjects while they were on medications prior to the baseline/Time 1 condition. The neuropsychological test battery included in the PNIDBS (Morrison et al., 2000b) was utilized in the study conditions. The tasks were administered in a fixed order to minimize interference among tests. The following tests are included in the PNIDBS battery: Randt Memory Test (RMT)—Digit Span, Passages, and Pictures subtests (Randt & Brown, 1984); Brief Test of Attention (BTA; Schretlen, 1989); Hopkins Verbal Learning Test—R (HVLT-R)-modified administration[1] (Benedict, Schretlen, Groninger, & Brandt, 1998); Boston Naming Test (BNT)—short version (Mack, Freed, Williams, & Henderson, 1992); Verbal Fluency (Benton & Hamsher, 1989; for each condition, subjects were asked to generate words to one phonemic cue and one semantic cue; the phonemic cues used were the letters C, L, and P; the semantic cues were food, kitchen items, and occupations, with each cue randomized across conditions); Visual Form Discrimination Test (VFDT; Benton, Hamsher, Varney, & Spreen, 1983); Judgement of Line Orientation Test (JLOT)—short form (Woodard et al., 1997); Standardized Test of Direction Sense (STDS; Money, 1976); Odd Man Out Test (OMOT; Richards, Cote, & Stern, 1993); Stroop Color and Word Test (SCWT; Stroop, 1935); Alternating Verbal Fluency (Newcombe, 1969); and Geriatric Depression Scale (GDS; Yesavage et al., 1983).

The surgical procedure for placement of the electrodes was as follows. Utilizing standard methods of imaging and stereotactic techniques, the target coordinates were determined. Next, under local anesthesia, accepted methods of localization and stereotaxy were used to pass first a recording electrode and then a stimulation electrode until the target was reached (Germano

[1] Because PD patients have been observed to learn and process information slowly, two additional learning trials were added to more fully evaluate the learning curve. In addition, immediate and delayed cued recall trials were added.

& Heilbrun, 1998). The final coordinates for the implanted electrode were fine-tuned based on the patterns of microelectrode recordings and the effects of test stimulation (Weisz & Yang, 1998; Zonenshayn et al., 2000). The stimulator was implanted in a subclavicular, subcutaneous pocket under general anesthesia. Following surgery, stimulation parameters were adjusted on an individual basis by the treating neurologists so that maximum clinical benefit on motor symptoms was achieved.

1.3. Data analysis

Because of the unique nature of this data set, multiple statistical approaches were utilized. All statistical approaches were used to investigate the three separate objectives of this study. The first objective was to investigate the potential cognitive effects of electrode placement. This was done by comparing the presurgical baseline condition to the postsurgical stimulation-off condition (Surgery Comparison). The second objective was to examine the effects of chronic deep brain stimulation in the STN. To accomplish this, the stimulation-off and stimulation-on conditions were compared to each other (Stimulation Comparison). Finally, the third objective was to explore the overall cognitive effects of the DBS procedure as a whole. This was accomplished by comparing the presurgical baseline and stimulation-on conditions (Procedure Comparison). In each of these three comparisons, the goal was to investigate whether a greater degree of change occurred in the DBS group across conditions than that which occurred across the test–retest conditions of the PD control group. Postoperative motor data were not available for inclusion in this report. See Table 2 for a diagram of the study comparisons.

As data from multiple cognitive tasks with different point totals were combined for analysis (see below), it was necessary to employ a data transformation technique that would bring all the variables onto the same scale. An ideal method for data transformation would have been to utilize normative values to calculate z scores. However, appropriate published normative information is not available for many of the variables employed here, and the current study included a *disease* control group rather than a non-neurological control group. Therefore, in order to prepare the raw data for statistical analysis, the baseline scores from the entire sample (i.e., the 28 DBSPD and CPD subjects) were combined to generate means and standard deviations for each of the 22 cognitive variables. These baseline means and standard deviations were then used to standardize the data for each variable in each condition by generating z

Table 2
Diagram of the study comparisons

Comparison	PD group	Condition 1	Condition 2
Surgery	DBS	Baseline	Stimulation-off
	Control	Time 1	Time 2
Stimulation	DBS	Stimulation-off	Stimulation-on
	Control	Time 1	Time 2
Procedure	DBS	Baseline	Stimulation-on
	Control	Time 1	Time 2

Table 3
Mean standardized scores[a] (in standard deviation units) for each group in each condition

Neuropsychological variable	DBSPD Baseline ($n = 17$) Mean (S.D.)	DBSPD Stimulation-off ($n = 13$) Mean (S.D.)	DBSPD Stimulation-on ($n = 17$) Mean (S.D.)	CPD Time 1 ($n = 11$) Mean (S.D.)	CPD Time 2 ($n = 11$) Mean (S.D.)
Attention Composite Score	0.0 (2.6)	−1.1 (2.3)	−0.6 (2.8)	0.0 (2.0)	0.2 (2.2)
Digit span forward	−0.1 (1.0)	−0.4 (0.8)	−0.1 (1.1)	0.1 (1.0)	0.0 (1.0)
Digit span backward	0.2 (1.1)	−0.4 (1.1)	−0.1 (1.1)	−0.2 (0.9)	−0.4 (1.0)
Brief Test of Attention	−0.1 (1.2)	−0.4 (1.3)	−0.4 (1.2)	0.1 (0.7)	0.7 (0.8)
Language Composite Score	0.6 (2.2)	−0.6 (3.4)	−0.6 (2.7)	−1.0 (2.1)	−1.0 (2.5)
Phonemic fluency	0.2 (1.2)	−0.3 (1.5)	−0.2 (1.4)	−0.2 (0.6)	−0.1 (0.9)
Semantic fluency	0.1 (1.1)	−0.2 (1.4)	−0.6 (1.2)	−0.2 (0.8)	−0.1 (0.8)
Boston Naming Test	0.3 (0.8)	−0.1 (1.1)	0.1 (1.0)	−0.5 (1.1)	−0.7 (1.6)
Visuospatial Composite Score	−0.1 (2.0)	−1.2 (4.6)	0.0 (2.8)	0.1 (2.4)	−0.2 (2.8)
Visual Form Discrimination	0.0 (1.0)	0.0 (1.1)	0.1 (1.1)	0.0 (1.1)	0.3 (1.0)
Judgment of Line Orientation	−0.1 (1.1)	−0.5 (1.9)	−0.1 (1.1)	0.2 (0.9)	−0.1 (1.0)
Test of Direction Sense	0.0 (1.0)	−0.8 (2.2)	0.0 (1.1)	−0.1 (1.0)	−0.4 (1.4)
Learning Composite Score	0.3 (2.9)	−0.6 (3.8)	−0.9 (3.6)	−0.5 (1.7)	−0.2 (2.4)
RMT Story—immediate recall	0.1 (1.1)	0.4 (1.1)	−0.1 (1.1)	−0.1 (0.9)	0.21 (0.7)
HVLT-R[b]—total recall	0.2 (1.1)	−0.6 (1.7)	−0.6 (1.5)	−0.3 (0.7)	−0.4 (0.9)
HVLT-R—immediate cued recall	0.1 (1.0)	−0.4 (1.6)	−0.3 (1.4)	−0.1 (1.0)	0.0 (1.1)
Delayed Recall Composite Score	0.4 (2.8)	−0.1 (3.6)	−0.8 (3.4)	−0.6 (2.3)	−0.2 (2.6)
RMT story—delayed recall	0.1 (1.1)	0.2 (1.2)	−0.1 (1.1)	−0.2 (0.8)	−0.1 (0.9)
HVLT-R—delayed free recall	0.2 (0.9)	−0.2 (1.4)	−0.4 (1.3)	−0.2 (1.1)	−0.1 (1.0)
HVLT-R—delayed cued recall	0.1 (1.1)	−0.1 (1.3)	−0.3 (1.2)	−0.2 (0.9)	0.0 (0.9)
Recognition Composite Score	0.4 (2.8)	−0.1 (4.5)	0.1 (2.9)	−0.6 (2.1)	0.0 (1.7)
RMT pictures—immediate recognition	0.1 (1.3)	0.3 (0.4)	0.2 (0.5)	−0.1 (0.4)	0.1 (0.5)
RMT pictures—delayed recognition	0.1 (1.2)	0.2 (1.0)	0.0 (1.3)	−0.2 (0.4)	−0.1 (0.8)
HVLT-R recognition	0.2 (0.9)	−0.6 (3.7)	−0.2 (1.6)	−0.3 (1.2)	0.0 (0.9)
Executive Composite Score	−0.1 (3.3)	−1.2 (3.9)	−1.6 (3.9)	0.2 (2.2)	0.4 (1.5)
Odd Man Out Test	−0.1 (1.2)	−0.6 (2.2)	−0.7 (2.4)	0.1 (0.7)	0.1 (0.9)
SCWT-interference	−0.3 (1.0)	0.0 (1.0)	−0.1 (1.1)	0.5 (0.8)	0.5 (0.6)
Alternating fluency	0.0 (1.0)	−0.6 (1.1)	−0.7 (1.1)	0.0 (1.1)	0.3 (0.8)
HVLT-R—semantic clustering	0.3 (1.1)	−0.1 (1.0)	−0.1 (1.1)	−0.4 (0.6)	−0.4 (0.8)
Depression Score					
Geriatric Depression Scale[c]	10.9 (7.3)	8.8 (8.4)	9.4 (8.5)	10.0 (8.3)	10.8 (9.1)

[a] Baseline scores from the entire sample were combined to generate variable means and standard deviations for each of the 22 cognitive variables. These overall means and standard deviations were then used to standardize the data for each variable by generating *z* scores for each subject's raw score in all experimental conditions. DBSPD—deep brain stimulation Parkinson's disease subjects; CPD—Parkinson's disease patients that did not undergo surgery; RMT—Randt Memory Test (Randt and Brown, 1984); HVLT-R—Hopkins Verbal Learning Test—Revised (Benedict et al., 1998); SCWT—Stroop Color and Word Test (Stroop, 1935).

[b] Two additional learning trials were added, as well as immediate and delayed cued recall trials of the HVLT-R.

[c] Raw depression scale scores.

scores for each subject's raw score. A drawback of this method is the use of the subject's own baseline data in the development of *z* scores which are then used to make comparisons across conditions. However, the influence of this factor would appear to be systematic across conditions and is, therefore, not believed to have affected the ability to detect change in performance across conditions. It should be noted that this type of standardization procedure has been used previously in DBS research (Ardouin et al., 1999b).

Because of the relatively small sample sizes and the relatively large number of variables, cognitive domain composite scores were created in order to (a) increase the power of the analyses by reducing the number of dependent variables, and (b) broadly examine whether there were changes within particular cognitive domains for each of the three condition comparisons. To create the composite scores, variables were grouped into seven cognitive domains on an a priori basis (three variables per domain except for the executive domain where there were four), according to the cognitive function they are purported to reflect (i.e., attention, language, visuospatial, verbal learning, verbal recall, recognition memory, and executive). The following considerations were used in the assignment of the cognitive variables to each domain. In the development of the test battery (described in Morrison et al., 2000b) utilized in the current study, a comprehensive literature review was performed in order to select domains that would be most relevant for the study of cognitive deficits in PD and for this procedure. A methodological rationale for the assignment of each test variable to its particular cognitive domain was provided in an earlier paper (Morrison et al., 2000b). In addition, the test variable groupings were based on those described by authors (e.g., Lezak, 1995; Spreen & Strauss, 1998) who have drawn extensively from and summarized the vast neuropsychological assessment literature.

Next, on a subject-by-subject basis, the standardized scores for each variable within a domain were summed to create the composite scores. In order to evaluate performance on the individual tasks, the standardized scores for each of the 22 cognitive variables and the depression scores were also examined. The composite scores and the individual task variables served as dependent variables in both the primary and secondary analyses (described below). See Table 3 for a listing of group means of the standardized scores for all neuropsychological variables in each of the study conditions.

2. Results

2.1. Composite score analysis

The primary analyses included three two-way (2×2) mixed multivariate analyses of variance (MANOVAs), one for each of the comparisons (Surgery, Stimulation, and Procedure). The MANOVAs included one between-subjects factor (subject group: DBSPD and CPD) and one within-subjects factor (condition: Condition 1 and Condition 2). For the composite score MANOVAs, the seven composite scores served as dependent variables.

As the focus of this study was to investigate whether neuropsychological test performance changed following the DBS procedure beyond the inherent variability of the measures used, the secondary analyses included examination of the subject group (DBSPD and CPD) by condition (DBS—baseline, stimulation-off, and stimulation-on; controls—Time 1 and Time 2) interaction for the univariate analyses of variance (ANOVAs) for each composite score in each of the three comparisons (Surgery, Stimulation, and Procedure). These a priori selected univariate analyses were performed regardless of the significance of the MANOVA interaction effects.

2.1.1. Surgery comparison

In the primary analysis, none of the multivariate F tests for the Surgery comparison composite score MANOVA were significant. In the secondary analyses, the univariate subject group by condition interaction for the Attention Composite Score was significant ($F[1, 22] = 5.32$, $P = .031$). In this case, the PD controls did not change (Time 1 $M = -0.03[1.95]$; Time 2 $M = 0.24[2.21]$; $P =$ NS), while the DBS subjects declined (baseline $M = 0.01[2.56]$; stimulation-off $M = -1.14[2.31]$; $P = .03$) across conditions. In addition, there was a subject group by condition interaction for the Language Composite Score ($F[1, 22] = 4.14$, $P = .05$), wherein the controls again stayed the same across conditions (Time 1 $M = -0.96[2.08]$; Time 2 $M = -0.95[2.53]$; $P = NS$), while the DBS subjects declined (baseline $M = 0.62[2.23]$; stimulation-off $M = -0.60[3.44]$; $P = .031$).

2.1.2. Stimulation comparison

In the primary analysis, none of the multivariate F tests for the Stimulation comparison composite score MANOVA were significant. In the secondary analyses, none of the seven composite score subject group by condition univariate interactions for the Stimulation comparison were significant.

2.1.3. Procedure comparison

In the primary analysis, none of the multivariate F tests for the Procedure comparison composite score MANOVA were significant. In the secondary analyses, the Language Composite Score subject group by condition interaction was significant ($F[1, 26] = 4.07$, $P = .05$), wherein the controls did not change (Time 1 $M = -0.96[2.08]$; Time 2 $M = -0.95[2.53]$; $P = NS$) and the DBS subjects declined (baseline $M = 0.62[2.23]$; stimulation-on $M = -0.63[2.71]$; $P = .014$) across conditions. The Delayed Recall Composite Score subject group by condition interaction was also significant ($F[1, 26] = 4.24$, $P = .05$). In this case, the controls did not change (Time 1 $M = -0.59[2.28]$; Time 2 $M = -0.21[2.59]$; $P = NS$), and the DBS subjects declined (baseline $M = 0.38[2.78]$; stimulation-on $M = -0.81[3.37]$; $P = .036$) across conditions.

2.2. Analysis of individual scores by cognitive domain

In keeping with the preliminary nature of this study, an additional more detailed analysis was performed in the form of the cognitive domain analyses. When data reduction procedures are executed, as in the case of the composite scores described above, though the analysis is simplified, information regarding the details of each subject's performance on individual tasks is often lost. Therefore, the primary and secondary statistical approaches (see above) were also applied to the variables assigned to each cognitive domain. The primary statistical approach involved performing a MANOVA for each cognitive domain, using the standardized scores from the measures in that domain, for each of the three comparisons (Surgery, Stimulation, and Procedure). This allowed for examination of how the DBS subjects performed on the individual cognitive variables, in comparison to controls, while still performing a relatively parsimonious analysis. The structure of these MANOVAs was the same as that described for the composite score MANOVAs. The secondary analyses again involved reviewing the univariate subject group by condition interaction for each cognitive variable.

2.2.1. Surgery comparison

In the primary analyses, the Attention ($F[3, 20] = 3.43$, $P = .037$) and Verbal Learning ($F[3, 23] = 3.96$, $P = .023$) domain MANOVAs both yielded significant main effects for the Condition factor. Follow-up univariate analyses for the Attention condition main effect revealed that digit span backward performance declined across the conditions (baseline/Time 1 $M = 0.00$ [1.0]; stimulation-off/Time 2 $M = -0.40$ [1.06]; $P = .006$). There were no significant follow-up univariate analyses for the Verbal Learning condition main effect. The Attention ($F[3, 20] = 3.99$, $P = .022$) and Executive ($F[3, 20] = 3.76$, $P = .020$) domain MANOVAs both resulted in significant main effects of the subject group factor. Follow-up univariate analyses for the subject group main effect in the Attention domain MANOVA were not significant. Follow-up univariate analyses for the subject group main effect of the executive domain MANOVA revealed that the controls ($M = 0.49[0.67]$) performed better than the DBS subjects ($M = -0.21[1.0]$) on the SCWT-interference score ($P = .045$). The secondary analyses yielded no significant findings.

2.2.2. Stimulation comparison

In the primary analyses, none of the multivariate F tests for any of the Stimulation comparison cognitive domain MANOVAs were significant. For the secondary analyses, none of the univariate subject group by condition interactions were significant.

2.2.3. Procedure comparison

In the primary analyses, the Attention ($F[3, 24] = 3.94$, $P = .020$) and Executive ($F[4, 23] = 3.17$, $P = .033$) domain MANOVAs for the procedure comparison both resulted in significant main effects of the subject group factor. For the follow-up univariate analyses of the Attention variables, no significant results were obtained. Follow-up univariate analyses of the Executive variables found that the controls ($M = 0.49[0.67]$) performed better than the DBS subjects ($M = -0.23[1.05]$) on the SCWT-interference score ($P = .034$). The secondary analyses yielded one significant finding. The Brief Test of Attention subject group by condition interaction was significant ($F[1, 26] = 2.95$, $P = .037$). For this variable, the controls improved across conditions (Time 1 $M = 0.07[0.68]$; Time 2 $M = 0.71[0.79]$; $P = .014$), while the DBS subjects did not change (baseline $M = -0.05[1.18]$; stimulation-on $M = -0.35[1.19]$; $P = NS$).

2.3. Depression score ANOVAs

The depression scores were analyzed separately from the cognitive scores using a two-way (2×2) mixed design ANOVA, with subject group (DBSPD and CPD) as the between-subjects factor and condition (Condition 1 and Condition 2) as the within-subjects factor, for each of the three comparisons (Surgery, Stimulation, and Procedure). None of the univariate F tests for any of the three depression score ANOVAs (Surgery, Stimulation, and Procedure) were significant. See Table 3 for the mean raw scores for each group in each condition.

3. Discussion

This preliminary study sought to examine the cognitive effects of subthalamic nucleus deep brain stimulation. Though many groups are studying the motor effects of this procedure, there have been very few investigations of the cognitive effects of STN DBS. Using the methodology and neuropsychological test battery described in the PNIDBS (Morrison et al., 2000b), the individual effects of electrode placement (Surgery comparison), the effects of high frequency STN stimulation (Stimulation comparison), and the overall effects of the DBS procedure (Procedure comparison) were studied. The methodology utilized is relatively unique in that very few investigators have examined DBS subjects at baseline and postsurgically with stimulation both off and on. Furthermore, to date, there have been no studies that have evaluated, by incorporating a demographically and clinically matched disease control group, whether there is cognitive change following the DBS procedure beyond the inherent variability of the measures used to assess that change.

3.1. Surgery comparison

For the DBS group as a whole, although there was no effect on depression scale scores, the surgery for electrode placement appeared to have some adverse affects on isolated aspects of cognitive functioning. Specifically, there was a significantly greater degree of change in the surgical group than in the control group on the global indices of performance for attention and language measures. The pattern indicated that, in this sample, the surgery for electrode implantation adversely affected attention functions, specifically the combined performance on measures of attention span and mental tracking ability. Some aspects of expressive language ability were also adversely affected by the surgery. The Language Composite Score, which was derived from performance on measures of confrontation naming and of phonemic and semantic verbal fluency, also significantly declined in the surgical patients.

Although statistical analyses of the DBS subjects revealed only isolated areas of mild cognitive decline following surgery, a dramatic postsurgical decline occurred in one patient. This patient's decline was very obvious both behaviorally and by virtue of the fact that he was unable to complete most of the test battery with stimulation off at 12 weeks post implantation. Of the 16 tests attempted, he was only able to complete the Digit Span, RMT Picture Recognition, RMT Short Stories, BNT, and VFDT. He was unable to comply with the task demands on the remaining measures due to his cognitive impairments. A postoperative MRI on this patient revealed that the electrodes were located in the STN and that there was no evidence of hemorrhage or infarct.

In reviewing this subject's demographic, general intellectual, and clinical characteristics, as compared to the mean performance of the DBS group as a whole, on most variables, he was within one standard deviation from the group mean.[2] In two cases, however, he seemed to be different from the group (i.e., >1.5 S.D.). He was 14 years older (age 74 years) than the group mean at the time of surgery, and he was 12 years older than the group mean (age 61 years) at the time of his disease onset. This subject was also one of two individuals who had undergone staged implantation and was one of five subjects tested in all conditions following PD medication withdrawal. At this point, it is difficult to know if a single or multiple factors put him at risk for cognitive decline following the second procedure. The other subject in this study who underwent staged placement of his electrodes and the two subjects with a prior history of right-sided pallidotomy did not demonstrate the dramatic postsurgical changes that were noted in this individual. Previous DBS studies that have included subjects with a prior history of neurosurgery also have not reported global cognitive decline following DBS surgery (Heck, Steinvorth, Tronnier, & Fogel, 2000; Moro et al., 2000). However, as will be discussed below, the lack of identified decline may be due to the fact that most studies do not assess cognitive functioning in the stimulation-off condition.

In summary, for the group as a whole, mild decline was primarily noted in attention and language areas following electrode implantation. Given the trajectory of the electrodes as they pass through the brain (i.e., through frontal regions), it is not entirely surprising that aspects of these functions were somewhat adversely affected. One subject experienced significant decline following surgery, although the etiology of the change in this patient is not clear.

3.2. Stimulation comparison

The individual effects of STN stimulation did not affect neuropsychological test performance in the DBS group as a whole. In a study with a narrower focus, Ardouin et al. (1999a) found no change in “frontal” and attention composite scores between stimulation off and on conditions 3 months following DBS surgery. In contrast to these group findings, one individual in the present study demonstrated dramatic improvement when tested with stimulation on as compared to off. This individual was the subject described earlier who was not able to complete most of the test battery following the surgery for electrode implantation. When tested with stimulation on, he was able to complete nearly all of the tests, the one exception being the Odd Man Out Test. It is unclear why there was such a dramatic effect of stimulation in this one patient. It may be the case that cognitive change following the administration of STN stimulation is only observed in the severely cognitively impaired (i.e., recall that this patient was virtually untestable in the stimulation-off condition). However, there may be alternative explanations for this outcome. At the moment, there are no other reports describing this type of phenomenon in the literature.

On average, the number of depression symptoms reported by the surgical patients appeared not to be affected by STN DBS. In a similar vein, Heck et al. (2000) found no effect of STN stimulation on the number of “positive” and “negative” symptoms endorsed on an affect adjective checklist. Contrary to these findings, Bejjani et al. (1999) described a case where stimulation elicited a profound depression, which immediately resolved when stimulation was

[2] This patient had 14 years of education, had a Hoehn and Yahr stage score while off medications of 3, had a NART-R IQ of 103, and had a DRS total score at baseline of 131/144.

turned off. In that case, however, while the target of the electrodes was the STN, a postoperative MRI revealed that the electrode contact that elicited the effect was actually located in the substantia nigra.

To summarize, overall, there was no effect of STN stimulation on cognitive or affective functioning in the DBS PD group as a whole. There was, however, one subject who experienced striking cognitive benefit from STN stimulation.

3.3. Procedure comparison

The overall cognitive effects of the DBS procedure appeared to be minimal declines in memory and language functions. In terms of memory, delayed verbal recall was specifically affected by the procedure. This finding is contrary to a previous report of a trend for improvement in this function following the DBS procedure (Moro et al., 1999). As both reported and present samples were small, more extensive research is needed to determine exactly how long-term memory is affected by STN DBS. As in the case of memory, for language production, there were no changes in the control group but a significant decline in the DBS group across conditions. Decline in language production, specifically verbal fluency, has generally been one of the few consistent findings in studies of cognition following the STN DBS procedure (Alegret, Vallldeoriola, Junque, Vendrell, & Tolosa, 2000; Ardouin et al., 1999b; Moro et al., 1999).

Depression scores were not affected by the procedure as a whole. There were no significant changes in depression for the DBS subjects, as compared to controls, in the procedure comparison. Although one prior report noted improvement in mood at a 3-month assessment, this effect was actually lost at a 12-month follow-up (Ardouin et al., 1999b).

3.4. Conclusions

In the Surgery Comparison, the general pattern of findings suggested mild decline on attention and language measures. In the procedure comparison, mild declines in language and delayed verbal recall were observed. By contrast, in the stimulation comparison, there was very little cognitive change.

In contrast to these minimal changes in the group as a whole, one male subject demonstrated substantial cognitive decline following surgery and better than average cognitive improvement with STN stimulation. Although this subject demonstrated motor and cognitive benefit from STN DBS, his overall cognitive decline following the procedure was such that he had to move from an independent to an assisted living situation because of new difficulties with his ability to manage activities of daily living. There is one other case report in the literature of a 53-year-old man who demonstrated significant motor benefit but global cognitive decline following STN DBS (Hariz et al., 2000). Though the impaired subject from the present sample was older at the time of disease onset and at the time of surgery than the rest of our group, Hariz et al.'s (2000) case was much younger (by 21 years) than our subject at the time of surgery. Taken together, these data suggest that age may not be the primary or sole predictive factor for development of cognitive impairment following the DBS procedure.

As the present study, and many of the available reports in the literature, have found mild to no cognitive change in most subjects following STN DBS, it may be the case that, in general, the

DBS procedure in this brain nucleus has a limited impact on cognitive functioning. However, these conclusions must be viewed as preliminary. Because the current study was the first attempt, to our knowledge, to implement a rather complex study design, the sample size was somewhat small and may have limited the power of the data analyses. Future studies should include larger sample sizes to address this limitation.

Another issue to be considered is the brevity of the test battery that we employed, and hence the limited range of cognitive functions that could be tested. To make the battery feasible to administer to this patient population, aspects of each cognitive domain could not be tested comprehensively. However, for this type of research, a brief battery is ideal for these reasons. First, there are a limited number of standardized neuropsychological tasks that have multiple versions for repeated testing. Second, we have found that these patients do not tolerate long testing sessions, nor is it always possible to integrate many hours of neuropsychological testing with the motor function evaluations that patients undergo as part of ancillary research visits and clinical appointments. Despite the limitations of the PNIDBS battery, it is important to note that our findings were similar to those reported in other studies.

An additional issue is the composition of the subjects within the surgical group. Two subjects had staged, as opposed to simultaneous, electrode implantation; two subjects had a history of right-sided pallidotomy; and five subjects underwent all conditions following withdrawal from antiparkinsonian medication. Although previous reports have indicated that dopaminergic medications have very minimal effect on neuropsychological test performance in patients with moderate-to-severe PD (Girotti et al., 1986; Gotham, Brown, & Marsden, 1988; Morrison, Borod, Brin, & Olanow, 2000a), that subjects with a prior history of neurosurgery do not necessarily demonstrate cognitive decline following DBS (Heck et al., 2000; Moro et al., 2000), and that right-sided pallidotomy is not associated with long-term cognitive impairment (see discussion above), it is not clear how much variance these points might have contributed to the outcome of the current study.

The issue of differential practice effects as a result of the DBS surgical group having been tested one more time than the control group and the shorter inter-test interval in the postoperative conditions for the surgical group, as compared to that for the control group, may have also influenced the results of this study. However, the expected outcome of an increased practice effect advantage in the DBS group would have been greater improvement in the DBS subjects as compared to the controls. In contrast to this expectation, when there was change, the performance of the DBS subjects tended to decline relative to the controls. Therefore, potential differential practice effects between groups were not believed to be a significant issue in the outcome of this study.

Finally, other methodological factors, such as the final location of stimulating electrodes within the STN and the degree of motor benefit obtained from STN stimulation, may have added to the variance of performance within the surgical group. Unfortunately, it was not possible to collect postoperative MRIs on all subjects to verify that the electrodes were in the same area of the STN across subjects, and postoperative ratings on the degree of motor benefit each subject obtained from the procedure were not available. Another methodological factor to be considered is the differential effect various surgical approaches and techniques may have on outcome. Variable results across centers may be influenced by these issues as well.

As research in this area continues, each of these methodological and subject issues should be considered. Nonetheless, results from the current study further our understanding of the cognitive effects of DBS. Overall, the procedure appears to be fairly benign in terms of cognitive functioning, however, isolated areas of cognitive deficit may result following surgery. Physicians and patients will want to take this information under consideration when deciding whether to proceed with the surgery. In light of the findings from the current study, future studies should include assessment of functioning outside the neuropsychology laboratory by evaluating patients' activities of daily living and their ability to function independently.

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