Neuropsychologia 47 (2009) 3203–3209

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Behavioral effects of subthalamic deep brain stimulation in Parkinson's disease

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ARTICLE INFO

Article history:
Received 9 March 2009
Received in revised form 18 June 2009
Accepted 30 July 2009
Available online 5 August 2009

Keywords:
Executive dysfunction
Behavior
Apathy
Disinhibition
Cognition

ABSTRACT

To date, few studies have utilized standardized measures to assess the neurobehavioral changes that can accompany deep brain stimulation (DBS) of the subthalamic nuclei (STN) for the treatment of Parkinson's disease (PD), yet behavioral changes are the most debated among practitioners. We evaluated behavior with the Frontal Systems Behavior Scale (FrSBe), which includes a large-scale normative sample for self- and collateral ratings and is particularly relevant to PD with subscales assessing Apathy, Disinhibition, and Executive Dysfunction. Data were collected from 16 (11 males) PD patients. All FrSBe subscale scores increased significantly when retrospective preoperative scores and current (postoperative) scores were compared. Self- and collateral FrSBe ratings were not significantly correlated with each other, though for both scores at least half of the group met criteria for a clinically significant level of symptoms postoperatively. No significant correlations were seen for collateral current FrSBE ratings with cognitive or motor variables. Higher self-ratings of behavior characteristic of apathy were related to higher self-ratings of depressive symptoms, and to a smaller decrease in antiparkinsonian medications following surgery. We propose that the standardized assessment of behavioral aspects of executive dysfunction adds information that is largely dissociable from the motor and cognitive assessment of function in PD patients undergoing STN DBS. In future, prospective standardized measurement of behavior may allow for better prediction of which patients will experience significant behavioral issues postoperatively.

1. Introduction

Both Parkinson's disease (PD) and its treatment impact frontal–striatal systems, circuitry that is critical for behavioral regulation (Frank, Scheres, & Sherman, 2007). While deep brain stimulation (DBS) of the subthalamic nuclei (STN) is one of the most effective treatments for PD motor dysfunction (for review see Limousin & Martinez-Torres, 2008), it is thought to adversely affect behavior and executive function in some patients (for review see Voon, Kubu, Krack, Houeto, & Tröster, 2006). Although the behavioral effects of STN DBS are widely debated both in the literature (see for example Tröster, 2008 commentary) and among practitioners, only the cognitive impact of STN DBS has been well-studied using standardized measures. To date, few reports have utilized standardized measures to assess neurobehavioral changes despite a call for such measurement nearly a decade ago (Trépanier, Kumar, Lozano, Lang, & Saint-Cyr, 2000).

Previous reports of behavioral executive dysfunction issues following surgery have been largely descriptive. One publication reported results of a standardized measure for a small selected sample of patients (Saint-Cyr, Trépanier, Kumar, Lozano, & Lang, 2000). A recent paper (Smeding et al., 2006) administered the Dysexecutive Questionnaire (DEX; Wilson, Alderman, Burgess, Emslie, & Evans, 1996); however, normative data are not available for this measure. The prevalence of papers on cognitive outcomes of STN DBS and the absence of papers focused on standardized assessment of behavior is particularly notable given that cognitive and behavioral measures purported to tap executive functions are readily dissociable (e.g., Reid-Arndt, Nehl, & Hinkebein, 2007; Shallice & Burgess, 1991; Vriezen & Pigott, 2002). Indeed, success on a standardized measure of problem solving or mental flexibility may fail to capture real-world behavioral consequences of executive dysfunction. Given the potential impact of behavioral changes on the functioning of the individual, and consequently their family, reliable and valid assessment of behavior is critical.

The choice of behavioral measures is far narrower than the choice of cognitive measures of frontal system functioning. Of the behavioral measures, The Frontal Systems Behavior Scale (FrSBe; Grace & Malloy, 2001) stands out as particularly relevant to PD. The FrSBe consists of 46 items, each of which falls into one of three subscales: Apathy, Disinhibition, or Executive Dysfunction. Zgaljardic and colleagues have previously emphasized how well these subscales map onto the frontal–striatal circuitry relevant to PD (Zgaljardic, Borod, Foldi, & Mattis, 2003). Psychometrically, the

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doi:10.1016/j.neuropsychologia.2009.07.022

Table 1
Preoperative patient characteristics: demographics, function, and medication levels.

Patient	Sex	Age at surgery (years)	Education (years)	UPDRS II on medication	UPDRS III on medication	Levodopa equivalent dose (mg/day)
1	Male	56	16	5	12	1701.9
2	Male	53	12	10	38	975.9
3	Female	41	10	9	17	2502.1
4	Male	48	12	11	47	1602.3
5	Female	53	11	10	19	900.0
6	Male	45	16	4	25	1302.3
7	Male	59	12	2	9	1500.0
8	Male	59	20	11	20	1551.9
9	Male	48	12	11	22	1000.0
10	Female	56	16	10	17	1450.0
11	Male	60	18	5	20	2051.9
12	Male	56	18	10	20	1150.0
13	Female	60	11	7	21	875.6
14	Male	63	16	7	11	1225.9
15	Female	55	12	10	18	751.5
16	Male	63	12	3	14	1733.3
Mean		54.7	14.0	7.8	20.6	1392.2
SD		6.4	3.1	3.1	9.7	469.4

FrSBe distinguishes itself from other measures with its large-scale normative sample for self- and family ratings and demonstrated validity for the assessment of behavior disturbances associated with damage to the frontal–subcortical circuits (Malloy & Grace, 2005). For these reasons we chose the FrSBe to provide quantitative assessment of post-operative behavioral functioning in PD patients who had undergone STN DBS surgery. Our primary objective was to explore the utility of the FrSBe in characterizing behavioral disturbance in this population. Secondly, we examined the relationship between FrSBe scores, mood, motor function, and cognitive measures. Finally, we sought to determine the relationship between self- and family reports of behavior.

2. Methods

2.1. Patients

A total of 23 patients underwent bilateral STN DBS for treatment of idiopathic PD in our clinic between January 2002 and December 2006. All patients underwent preoperative neuropsychological evaluations that are detailed below. Methods for bilateral insertion of DBS into the STN have been described previously (Hutchison et al., 1998). We performed staged implantation with the worse brain side operated on first, followed about 1 month later by second side surgery. Reasons for exclusion from this study were death unrelated to surgery (3), patient relocation (4), and incomplete neuropsychological data (2; e.g. non-English speaking patients); some patients had more than one reason for exclusion. Participants remaining were 16 (11 males) English speaking PD patients. Patient demographics and preoperative characteristics are shown in Table 1. A family member of each patient provided surrogate control data for the self-ratings. This study was undertaken with ethics approval to collect information on routine care for all neuromodulation patients. Patients provided informed, written consent.

2.2. Assessments

2.2.1. Motor function

Unified Parkinson's Disease Rating Scale (UPDRS) evaluations were conducted in the Movement Disorders Clinic a few months prior to the first implantation ($M = 3 \pm 3$ months) in both medication ON and practically OFF states (after withdrawal of medications for at least 8 h) and again 12 months postoperatively ($M = 13 \pm 1$ months) in 4 states (Medication OFF/Stimulation OFF, Medication OFF/Stimulation ON, Medication ON/Stimulation OFF, Medication ON/Stimulation ON). Only best ON states (medication preoperatively and medication plus stimulation postoperatively) and the OFF state (no treatment) were used for analysis, in order to examine the usual functional state of each patient, and evaluate the degree of improvement produced by the surgery. Scores from the UPDRS part II (activities of daily living; ADL) and UPDRS part III (motor) subscales were entered into the analysis. The levodopa equivalent dose was calculated as per the method of Chen, Garg, Lozano, and Lang (2001) using the medications taken at the time of the motor evaluations.

2.2.2. Cognitive function

Baseline neuropsychological assessments were performed an average of 7 months prior to the first side surgery ($SD = 6$ months) with follow-up assessments an average of 16 months ($SD = 4$ months) after this surgery. Although a range of cognitive domains were assessed, for the present study we focused on measures of executive function due to the particular relevance of these functions to PD, STN DBS, and the FrSBe. Phonemic and semantic fluency were measured using the letters "FAS" and the category "animal," respectively (Strauss, Sherman, & Spreen, 2006). Problem solving aspects of executive function were assessed with the Wisconsin Card Sorting Test (WCST; Heaton, Chelune, Talley, Kay, & Curtis, 1993). Although a number of scores are generated for the WCST, the percentage of error responses was chosen as the outcome measure because preliminary analysis demonstrated a high degree of correlation between all scores generated for this test and this score provided a measure of overall performance. The above-described cognitive scores were corrected for age and education using established normative samples and subsequently converted to *z* scores. An estimate of premorbid intelligence was made from the North American Adult Reading Test (NAART; Blair & Spreen, 1989). In addition, mood was assessed pre- and postoperatively during neuropsychological evaluations with the Beck Depression Inventory-II (BDI II; Beck, Steer, & Brown, 1996).

2.2.3. Behavioral function

FrSBe questionnaires were administered after completion of STN DBS surgery (average latency = 40 months, $SD = 23$, range = 13–78). Each of the 46 items on the FrSBe describes a behavior, and the frequency of the behavior is rated from 1 (*Almost never*) to 5 (*Almost always*). Each item falls onto one of three subscales: Apathy (14 items), Disinhibition (15 items), and Executive Dysfunction (17 items). The FrSBe is designed such that ratings are made retrospectively prior to an event (surgery in the present study) and as well as for current behavior. As well, the FrSBe has separate forms for patient self-reports and family reports with the same items, using either first or third person references to behaviors, respectively. Aside from one patient who had a sibling respond, spouses of patients provided the family report. Patient and family FrSBe reports were administered at the same time, but without communication between the patient and their family member during completion of the questionnaire. In addition, during the session in which they completed the FrSBe, patients also completed a BDI II to determine whether depression was contributing to item endorsement on the FrSBe. Using the normative data supplied by the test publisher for age, education, sex, and respondent (self or family member), all FrSBe ratings were converted to *T* scores. As per guidelines in the FrSBe manual, *T* scores equal to or greater than 65 are considered clinically significant in terms of the level of symptom severity; symptom severity increases with increasing scores.

2.3. Statistical analysis

Analyses were conducted using SPSS 15.0. All change variables were calculated as Post-STN DBS–Pre-STN DBS. A Shapiro–Wilk test identified several variables that were not normally distributed; as a result Spearman's rho (r_s) was used for the correlational analysis. To balance the number of correlations conducted with the exploratory nature of the study, significance for the correlational analysis was set as $p < .01$ ($r_s(14) \geq .623$). For paired comparisons of pre- and post- surgical scores, paired t-tests were used to compare normally distributed variables and Wilcoxon signed rank tests were used for non-normally distributed variables with significance set at $p < .05$ after correction for multiple comparisons.

3. Results

3.1. Pre- and postoperative comparisons

3.1.1. Motor and cognitive variables

Changes in non-FrSBe variables are summarized in Table 2. Motor scores on the UPDRS improved when scored on treatment