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Phonemic verbal fluency decline after subthalamic nucleus deep brain stimulation does not depend on number of microelectrode recordings or lead tip placement

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ABSTRACT

Background: Evidence suggests that both motor improvement and decline in verbal fluency in Parkinson's disease (PD) patients undergoing deep brain stimulation (DBS) may be attributed to a lead implantation effect.
Objective: We investigated whether the number of microelectrode recording (MER) passes influenced either motor UPDRS scores just prior to stimulation initiation at 4 weeks or decline in verbal fluency 6–24 months after surgery.
Methods: We retrospectively analyzed 50 PD patients who underwent bilateral STN DBS. Off medication UPDRS III motor scores were obtained before surgery and before stimulation was initiated. Neuropsychological testing was completed pre- and post-operatively in 28 patients at a mean of 377 days. Coordinates of lead tip and active stimulation site were calculated.
Results: There was no improvement in off-medication UPDRS III motor scores at a mean 33.9 days following surgery, with mean change of 0.04 ± 10.48 ($p = 0.98$). There was no correlation between the number of MER passes and change in individual UPDRS motor score ($r = -0.0001$, $p = 1.0$). We observed significant decline in phonemic verbal fluency by 16% ($p = 0.003$) but it was not correlated with number of left hemisphere ($r = -0.15$, $p = 0.46$), or total number of passes ($r = -0.02$, $p = 0.94$) or coordinates of the lead tip or active stimulation site. There was a trend toward correlation with age ($r = 0.38$, $p = 0.07$).
Conclusions: Significant decline in phonemic verbal fluency did not correlate with surgical passes nor with location of the lead tip or active stimulation site. These data suggest that age may influence verbal fluency decline more than surgical technique.

1. Introduction

Deep-brain stimulation (DBS) of the subthalamic nucleus (STN) is a well-established effective treatment for Parkinson's disease patients suffering from motor fluctuations and dyskinesias [1–3]. PD patients may experience an improvement in motor function immediately after DBS lead implantation but before stimulation is initiated, sometimes referred to as a "microlesional effect" [4]. The mechanism underlying the microlesional effect is not completely understood but is usually attributed to microtrauma during lead placement and may be more prominent following STN lead placement compared to globus pallidus (GPi) lead placement [4–6]. DBS surgery typically employs microelectrode recordings (MERs) to localize the intended target prior to lead insertion [7,8]. Several studies have reported improvement in motor function immediately after microelectrode recordings and the effect may at least 6 months following lead implantation [4,5]. It has been suggested that a microlesional effect may be a positive prognostic indicator, correlated to motor improvement after chronic STN stimulation [4]. In other instances, the effect may mask delayed deterioration of axial motor function following DBS [6]. Taken together, these observations suggest that the microlesional effect is clinically significant and may have a longer duration than previously thought.

Simultaneously, there is consistent evidence that STN DBS may worsen certain aspects of cognition, particularly verbal fluency [9–12]. Recent evidence suggests that the effect may be at least partially related to the surgical procedure itself, as a decline in verbal fluency has been seen in both the on and off stimulation

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state [9]. These along with functional imaging studies support the idea that there may be lesional effects, such as edema, involving the frontostriatal system, as a result of lead implantation [13]. The degree of verbal fluency decline seems particularly more prevalent after STN DBS procedures relative to GPi DBS [9] and this may reflect the more medial trajectory possibly affecting pre-supplementary motor cortex (pre-SMA) and caudate regions thought to be involved in phonemic fluency [14]. In at least one study, the effect was more prominent when stimulating via contacts located more ventrally within the STN [9]. Therefore stimulation and surgical factors may both contribute to a decline in phonemic verbal fluency.

The goal of this single-center retrospective study of PD patients undergoing bilateral STN DBS was to investigate whether changes in motor function or verbal fluency could be correlated with specific surgical factors. We hypothesized that a greater number of MER passes would result in a greater degree of local injury and therefore would be associated with a larger microlesional effect on motor outcome. We also hypothesized that given evidence of verbal fluency impairment independent of stimulation, that some aspect of the lead implantation procedure itself (i.e. the number of MER passes) may be correlated with the degree of decline. We also explored whether differences in the location of the lead itself or the active contact correlated with decreases in verbal fluency post-operatively.

2. Methods

We analyzed data from all patients with PD undergoing bilateral STN DBS in our movement disorders center between January 2004 and December 2012. Approval for this retrospective study was obtained from the Beth Israel Deaconess Medical Center Institutional Review Board. All surgeries except one were performed by one neurosurgeon (E. P.), using a Leksell stereotactic frame and Model 3387 leads (Medtronic, Minneapolis, MN, USA) connected to either Activa SC or Soletra (Medtronic, Minneapolis, MN, USA) implantable pulse generators. Microelectrode recordings were made with Guideline System 3000A (Axon Instruments, FHC, Inc., Bowdoin, ME). Patients were excluded if they received only unilateral DBS, if they required lead removal, had prior leads in place, or if data were missing or unavailable from medical records. Patients were excluded from the motor outcome analysis if the time elapsed between the levodopa challenge clinic visit and the initial DBS programming visit was greater than 180 days. Patients were excluded from the cognitive outcome analysis if the time elapsed between neuropsychological testing was greater than 24 months.

A standard levodopa challenge was performed as part of the pre-operative workup 1–3 months prior to surgery. Patients' symptom severity was rated by a trained movement disorders specialist (L.C.S. or movement disorders trained fellow or nurse) employing the motor sub-score of the Unified Parkinson's Disease Rating Scale (UPDRS-III), in both the 'off medication state' (i.e. 12 or more hours after their last dose of antiparkinson medication) and the 'on medication state' (i.e. 1 h following their usual dose of medication with confirmation that the patient was experiencing their usual medication response). These represent the baseline 'off' and 'on' medication scores. Post-operatively, patients were examined in the off medication state prior to initiating stimulation.

In addition, subgroup analyses were performed on patients who worsened by more than 5 points and those who improved by more than 5 points on UPDRS score between the pre-operative and post-operative "off" assessments, which is the moderate clinically significant change in the motor UPDRS score [15]. Levodopa equivalent daily doses were calculated [2].

Neuropsychological testing was conducted in the on-medication state 1–5 months prior to surgery and in the on medication/on stimulation state 6–24 months after lead implantation. Testing included the Mattis Dementia Rating Scale (M-DRS), the Trailmaking Test, Parts A and B, Rey Verbal Learning Task (RAVLT), the FAS phonemic fluency task, Beck Depression Inventory, and subtests from the Wechsler Adult Intelligence Scale (WAIS). DBS stimulation parameters at the time of post-operative neuropsychological testing were obtained from the medical record. Postoperative CT or MRI was performed on patients within 24 h after surgery using a standardized and prospectively implemented protocol designed to reveal the DBS leads and the commissures at high resolution. Stereotactic MRI data was analyzed using a VoXim workstation (IVS Technology GmbH, Chemnitz, Germany). All image sets were computationally reformatted so as to be parallel to the anterior commissure–posterior commissure (AC–PC) line and orthogonal to the midsagittal plane. *x*, *y* and *z* coordinates of the actively stimulated contact points and of the electrode tip, were calculated using the mid AC–PC point as the reference unless otherwise stated. The target was placed at the lead tip, defined as the last axial slice where lead artifact was visible. From these images, each individual contact could be visualized and the coordinates were calculated from the active contact documented at the time of repeat neuropsychological testing. Pairwise correlation analysis and *t*-test were performed using Stata 11 (StataCorp, College Station, TX). Power to detect a correlation coefficient of 0.5 or greater using post-operative change in verbal fluency scores was 0.9 with an alpha of 0.05.

3. Results

Between January 2004 and December 2012, 70 patients underwent bilateral STN DBS at our center. Fifty patients met criteria for motor outcome analysis, and 28 patients had both pre- and post-operative neuropsychological test scores available for analysis. The characteristics of these patients are summarized in Table 1. The mean time between the pre-operative levodopa challenge visit and post-operative initial programming visit was 95.1 days (SD 31.9). The mean time between lead implantation and post-operative initial programming visit was 33.9 days (SD 12.7). The mean time between pre-operative and post-operative neuropsychological testing was 377 days (SD 196). The mean number of MER passes (right + left) during surgery was 4.3 ± 2.0 (range 2–9). The mean number of right passes was 2.3 ± 1.7 (range 1–7), and left passes was 1.9 ± 1.3 (range 1–5). Complications included symptomatic intracerebral hemorrhage ($n = 1$), asymptomatic intracerebral hemorrhage ($n = 3$), subdural hematoma ($n = 1$), and transient encephalopathy ($n = 8$).

3.1. Motor outcomes

We evaluated microlesional effect by comparing patients' pre-operative off medication UPDRS III score with their post-operative,

Table 1
Summary of baseline data for bilateral STN DBS patients.

	Mean ± SD (range)
N	50
Age, y	63.1 ± 8.5 (36–79)
M/F, %	42/23, 65% M
PD duration, y	11.8 ± 4.3 (4–23)
LEDD, mg	1312.7 ± 638.1 (375–3100)
UPDRS III off-medication, pre-op	37.1 ± 10.3 (19.5–74.5)
UPDRS III on-medication, pre-op	18.0 ± 8.3 (2.5–38)
UPDRS III off-medication, post-op	37.1 ± 12.5 (9–70)
Left MER passes	1.9 ± 1.3 (1–5)
Right MER passes	2.3 ± 1.7 (1–7)