Patient-specific analysis of the relationship between the volume of tissue activated during DBS and verbal fluency

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ARTICLE INFO

ABSTRACT

Deep brain stimulation (DBS) for the treatment of advanced Parkinson's disease involves implantation of a lead with four small contacts usually within the subthalamic nucleus (STN) or globus pallidus internus (GPi). While generally safe from a cognitive standpoint, STN DBS has been commonly associated with a decrease in the speeded production of words, a skill referred to as verbal fluency. Virtually all studies comparing presurgical to postsurgical verbal fluency performance have detected a decrease with DBS. The decline may be attributable in part to the surgical procedures, yet the relative contributions of stimulation effects are not known. In the present study, we used patient-specific DBS computer models to investigate the effects of stimulation on verbal fluency performance. Specifically, we investigated relationships of the volume and locus of activated STN tissue to verbal fluency outcome. Stimulation of different electrode contacts within the STN did not affect total verbal fluency scores. However, models of activation revealed subtle relationships between the locus and volume of activated tissue and verbal fluency performance. At ventral contacts, more tissue activation inside the STN was associated with decreased letter fluency performance. At optimal contacts, more tissue activation within the STN was associated with improved letter fluency performance. These findings suggest subtle effects of stimulation on verbal fluency performance, consistent with the functional nonmotor subregions/somatotopy of the STN.

Introduction

Deep brain stimulation (DBS) surgery, a well-accepted treatment for medication-refractory Parkinson's disease, improves the cardinal motor symptoms and reduces the complications that may accompany dopaminergic therapies (Pahwa, 2006). However, the underlying bases for these dramatic motor improvements are not fully understood. One technique to quantify the effects of DBS on the nervous system is to create patient-specific models of the spread of stimulation (Butson et al., 2007; Maks et al., 2009). Patient-specific models take into account the anatomical placement of the electrode in relation to the surrounding brain structures, the electrical signals generated by the DBS device, and the neural activation of affected cells. In turn, these models provide a means of relating DBS activation information to clinical outcome. Previous patient-specific modeling efforts focused on motor outcomes; however, cognitive outcomes represent another important aspect of DBS. Although DBS appears to be relatively safe from a cognitive standpoint, long-term declines in

speeded word fluency tasks have consistently been reported (Ardouin et al., 1999; Dujardin et al., 2000, 2001; Rodriguez et al., 2005; Saint-Cyr and Albanese, 2006; Saint-Cyr et al., 2000). Verbal fluency tasks require subjects to produce as many words as possible within 60 seconds, according to specific letters (Benton, 1968; Borkowski et al., 1967) or semantic categories such as animals or vegetables (Newcombe, 1969). Both tasks are time-limited, requiring self-generation of words under constrained search conditions. According to a meta-analysis of DBS outcome studies, significant declines on tests of verbal fluency reach moderate effect sizes (Parsons et al., 2006).

The extent to which stimulation contributes to verbal fluency declines has not been clearly determined. The findings of studies investigating stimulation alone (ON versus OFF stimulation studies) have been variable. At least one study has shown a decline in verbal fluency when PD patients were tested ON compared to OFF stimulation (Schroeder et al., 2003). Additionally, Wojtecki et al. (2006) showed better verbal fluency performance with low frequency compared to high frequency stimulation. Others have not discovered ON versus OFF stimulation differences (Jahanshahi et al., 2000; Morrison et al., 2004; Pillon et al., 2000; Witt et al., 2004). In two studies, investigators directly examined pre–post verbal fluency

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performance in relation to that obtained during ON and OFF stimulation conditions (Morrison et al., 2004; Pillon et al., 2000). In these studies, fluency was unaffected by bilateral DBS stimulation per se (ON–OFF comparison), but there was a decline in performance following DBS surgery (pre–post comparison). In particular, Morrison et al. (2004) noted a decline in verbal fluency performance in an assessment designed to test the effects of surgery (presurgery compared to postsurgery OFF DBS) but not in the ON versus OFF stimulation condition (which assesses the effects of stimulation only).

A recent prospective randomized trial of DBS outcome, named the COMPARE trial, provides further support for surgery-related effects on verbal fluency performance in STN DBS (Okun et al., 2009). In this study, 52 subjects were randomized to receive unilateral STN or GPi DBS. At 7 months post-DBS, subjects were tested in four randomized/counterbalanced conditions: with stimulation of the contact providing *optimal* motor benefit, with stimulation of the contacts *ventral* and *dorsal* to that, and *off* DBS). Forty-five subjects (23 GPi and 22 STN) completed the protocol. Comparison of verbal fluency performance at each of the DBS testing conditions to pre-DBS performance showed a deterioration of letter fluency in the STN group, especially when *off* DBS. The persistence of deterioration in verbal fluency in the *off* STN DBS state suggested a surgical rather than a stimulation-induced effect. This observation and those reported earlier suggest that the decline in verbal fluency following DBS may have more to do with the surgical intervention than the effects of stimulation. However, further studies are needed, particularly studies involving direct examination of the effects of stimulation.

The STN is thought to contain separate functional subregions, which presents an important consideration when targeting stimulation. Movement-related cells have been observed to be segregated within the dorsolateral STN in both the human (Rodriguez-Oroz et al., 2001; Theodosopoulos et al., 2003) and nonhuman primate (DeLong et al., 1985; Matsumura et al., 1992; Wichmann et al., 1994). DBS of the dorsolateral sensorimotor area is thought to result in the best motor outcome (Herzog et al., 2004; Richardson et al., 2009). In addition to the dorsolateral sensorimotor territory, primate studies have revealed functional territories of the STN consisting of a more central associative territory and a smaller medial limbic area (Parent and Hazrati, 1995; Yelnik, 2002). One explanation that has been proposed for verbal fluency declines following STN DBS surgery is that current spread to nonmotor regions of the STN affects cognitive functions (Saint-Cyr et al., 2000; Woods et al., 2002).

The present study employed computer modeling to depict the volume and location of activated tissue in the STN patients from the COMPARE trial. Our goal was to better characterize relationships between verbal fluency performance and stimulation of functional subregions of the STN. Although neurosurgeons generally attempt to target the lateral sensorimotor subregions of the STN, it is possible that electrical current may affect neural activity in the associative subregions which are directly adjacent to the sensorimotor subregions. Patient-specific DBS models provide an opportunity to quantify the spread of stimulation within the context of the STN anatomy and to address relationships between different stimulation conditions and clinical outcomes.

STN patients from the COMPARE study underwent verbal fluency testing in four randomized conditions (OFF stimulation and with stimulation of the optimal, dorsal, and ventral contacts) (Okun et al., 2009). Patient-specific DBS models were created for each stimulation condition (Butson et al., 2007). Four indices were generated from the patient-specific models, including (a) total volume of activated tissue (VTA), (b) volume of activated tissue within the STN, (c) volume of activated tissue outside of the STN (i.e., white matter), and (d) proportion of volume overlap of activated tissue within the STN (PVO–STN). We investigated whether these indices were related to verbal fluency performance with stimulation at each contact. We hypothesized that direct stimulation of the ventral region would have

adverse effects on verbal fluency performance, while stimulation of optimal or dorsal regions would either result in improvements or no change in verbal fluency performance.

Methods

Participants

The present study drew STN patients from the COMPARE clinical trial conducted at the University of Florida (Okun et al., 2009). The trial recruited 52 individuals with a diagnosis of idiopathic PD to undergo surgery for DBS of the STN ($N = 26$) or GPi ($N = 26$) as well as 10 PD control subjects who did not undergo surgery. Before DBS, all participants underwent intensive baseline screening that included a diagnosis of PD by strict UK Brain Bank criteria, consultation with a neurology movement disorders specialist for medication optimization, consultation with a movement disorders neurosurgeon, a complete neuropsychology profile, and a psychiatry consultation.

Inclusion criteria for the clinical trial consisted of (1) Hoehn and Yahr stage II or worse when "off" medication; (2) intractable, disabling motor fluctuations, dyskinesias, or freezing episodes; (3) age between 30 and 75 years; (4) unsatisfactory clinical response to maximal medical management (with trials of both higher and lower doses of antiparkinsonian drugs); (5) a stable and optimal medical regimen of antiparkinsonian drug therapy for at least 3 months before surgery; and (6) right-handedness.

Exclusion criteria included the following: (1) clinically significant medical disease that would increase the risk of developing pre- or postoperative complications (e.g., significant cardiac or pulmonary disease, uncontrolled hypertension); (2) evidence of secondary or atypical parkinsonism as suggested by the presence of a history of stroke(s), encephalitis, exposure to toxins or neuroleptics, neurological signs of upper motor neuron disease, cerebellar involvement, supranuclear gaze palsy, or significant orthostatic hypotension; (3) MRI scan with significant evidence of brain atrophy (i.e., enough atrophy to suspect a possibility of complications such as subdural hematoma, as determined by the neurosurgeon) or other abnormalities (e.g., lacunar infarcts or iron deposits in the putamen); (4) dementia as evidenced by impairment in two neuropsychological domains and impaired or borderline neuropsychological function in one additional domain; and (5) a major psychiatric disorder on the *Structured Clinical Interview for DSM-IV* (*SCID-IV*) including current major depression.

Seven months after unilateral DBS implantation, patients underwent neuropsychological and motor testing. Testing for the study was performed with stimulation at the clinically defined optimal contact (the one yielding the best improvement in motor symptoms upon UPDRS motor examination and the one selected by the clinical team to use for long-term stimulation) as well as with stimulation of the dorsal and ventral contacts and OFF stimulation. Testing was conducted off medications (withdrawn 12 hours before testing). The order of the testing conditions was chosen by a computer-generated random sequence. Aside from the DBS programmer, all investigators were blind to the sequence of conditions. There was a standardized 10-minute delay from the time of setting the stimulator to the time of testing to allow the patients time to adjust to each of the new settings.

Forty-five subjects (23 GPi and 22 STN) completed the clinical trial protocol. After initial DBS activation, repeated follow-up evaluations were performed, as needed, until the optimal chronic stimulation parameters and adjunctive PD medication regimen were determined. The present study analyzed each STN patient who had all the necessary data for model creation and good agreement between the intended stereotactic DBS electrode implantation location and the location determined from postoperative CT. Patient demographic characteristics are shown in Table 1. The measured lead locations from computed tomography/magnetic resonance imaging fusion and

Table 1
Demographic and disease characteristics of the study participants. Means (± standard deviation) are shown.

	STN DBS
Age	59.8 (10.0)
Gender (% male)	69.2
Disease duration (years)	13.3 (4.0)
Hoehn and Yahr "off" stage (percent)	2: 8.3
	2.5: 29.2
	3: 37.5
	4: 25.0
	5: 0.0
Mean LED before surgery	935.9 (373.9)
Preoperative "on" UPDRS III score	22.5 (8.2)
Preoperative "off" UPDRS III score	45.2 (12.6)
Mini-Mental State Exam (max: 30)	28.0 (1.8)
Dementia Rating Scale (max: 144)	136.5 (7.0)
Beck Depression Inventory (max: 63)	10.4 (5.9)
Verbal fluency task Scores (raw)	
Letter	38.1 (11.7)
Semantic	18.3 (4.7)

LED—levodopa equivalent dosage.

the mean chronic deep brain stimulation parameters are described by Okun et al. (2009).

Verbal fluency tasks

Verbal fluency tasks consist of *letter fluency* and *semantic fluency*. *Letter fluency* tasks require subjects to rapidly produce words beginning with a particular letter of the alphabet, excluding proper nouns and the same word with a different suffix (Benton et al., 1994). The test allows 60 seconds to generate words beginning with a particular letter. *Semantic fluency* tasks require subjects to rapidly produce words belonging to a particular category (e.g., animals). For each testing session, the total number of words produced under each of three letter conditions and one semantic condition was recorded. Alternate forms of the verbal fluency tasks (i.e., different letter combinations and different semantic categories) were employed to minimize practice effects. The order of the four stimulation testing conditions was randomized, and the alternate forms were counter-balanced across the testing conditions.

Imaging and surgical procedure

Each patient received four MRI scans on the day before surgery: a three-plane localizing scout, a T1-weighted 3D magnetization-prepared rapid acquisition gradient echo (MP-RAGE), a 3D T2-weighted fluid-attenuated inversion recovery (FLAIR), and a T1-weighted 3D FGATIR (Sudhyadhom et al., 2009). The last three scans were each single-volume whole brain scans. All scans were acquired on a clinical Siemens Allegra 3-T MRI using a quadrature birdcage head coil. The total scanning time for all four scans was 30 minutes. On the morning of the operation, a Cosman–Roberts–Wells (CRW) head ring was applied under local anesthesia, and a high-resolution stereotactic head computed tomography (CT) scan was performed.

During the surgical procedure, microelectrode recording (MER) techniques were used to develop a 3D map of the target structures. For each MER pass, cellular activity was recorded at millimeter intervals beginning at 30 mm above the selected target and at submillimeter intervals as the microelectrode approached the target region. At each

interval, the encountered region was determined by the recording neurologist (Dr. Okun) based on the sound and appearance of the recording and the depth at which it was observed. Each determination was represented in real time as a color-coded point overlaid on an individual patient's MRI at the corresponding stereotactic coordinates. In addition to single cell recordings, cellular firing in response to passive motion and sensory stimulation was used to delineate the somatotopic organization of the target structure. MER passes were translated into a linear map of structure and somatotopy that was then overlaid on the patient's MRI. A final decision, based on this aggregate map, was made as to the best location to place the permanent DBS electrode. The decision-making process took into account both electrode tip location within the target region and the electrode's proximity to regions near the target that might result in side effects when stimulated. Recording data from the MER passes were saved in a spreadsheet for later use in development of the patient-specific DBS models.

Patient-specific DBS models

Each patient-specific DBS model was generated at the University of Florida (UF) with the use of a modified version of Human Cicerone v1.2 that was able to account for the CRW frame system (Miocinovic et al., 2007). The stimulation predictions were generated at the Cleveland Clinic Foundation (CCF) using a diffusion tensor-based finite element model of the neural activation induced by DBS (Butson et al., 2007). Each patient-specific DBS model included coregistration of the magnetic resonance images (MRI), computed tomography (CT) scans, a 3D brain atlas, neurophysiological microelectrode recording (MER) data, DBS electrode, and the volume of tissue activated (VTA) for each clinically evaluated stimulation parameter setting (Fig. 1).

Creation of each patient-specific DBS model followed a step-by-step procedure. First, the preoperative CT image with the stereotactic frame was loaded into the software (Fig. 1A). A virtual replica of the frame fiducial system (CRW frame) was positioned within the context of the CT scan, thereby defining the stereotactic coordinate system relative to the imaging data. The preoperative CT scan was then coregistered with the preoperative MRI scan. The next step consisted of scaling and positioning 3D anatomical representations of nuclei of interest (e.g., subthalamic nucleus, globus pallidus, thalamus, etc.) (Fig. 1B). The anatomical nuclei were originally positioned within the context of the MRI based on the stereotactic definition of the AC and PC points. However, the atlas was typically translated, rotated, and/or scaled along the anterior/posterior, dorsal/ventral, and medial/lateral axes to enable the most accurate match possible with the MRI.

The stereotactic location of each intraoperative MER data point was entered into the model. The microelectrode recording locations were displayed in Cicerone as small spheres and color-coded according to the anatomical structure they represented. Once MER data were entered, the 3D brain atlas of anatomical nuclei was further adjusted via 9 degrees of freedom. The goal was to use the anatomical information provided in the preoperative MRI along with the neurophysiological information provided by the MER tracks to achieve the best possible fit. In situations where both MER and MRI data could not be maximally accommodated, the MER data took precedence. This decision was justified because the overriding goal was to orient atlas surfaces as accurately as possible with respect to the patient's DBS electrode, and the relative position of the MER data was the basis for the surgical DBS electrode placement.

Completion of the preceding steps produced an anatomical model of the DBS electrode placement in accordance with the patient's preoperative MRI scan and MER data (Fig. 1C). This anatomical model of electrode placement was checked against the postoperative CT scan to verify correspondence between the surgically intended placement and the final resting place of the electrode relative to the skull. Many factors can impact discrepancies between these two measures of
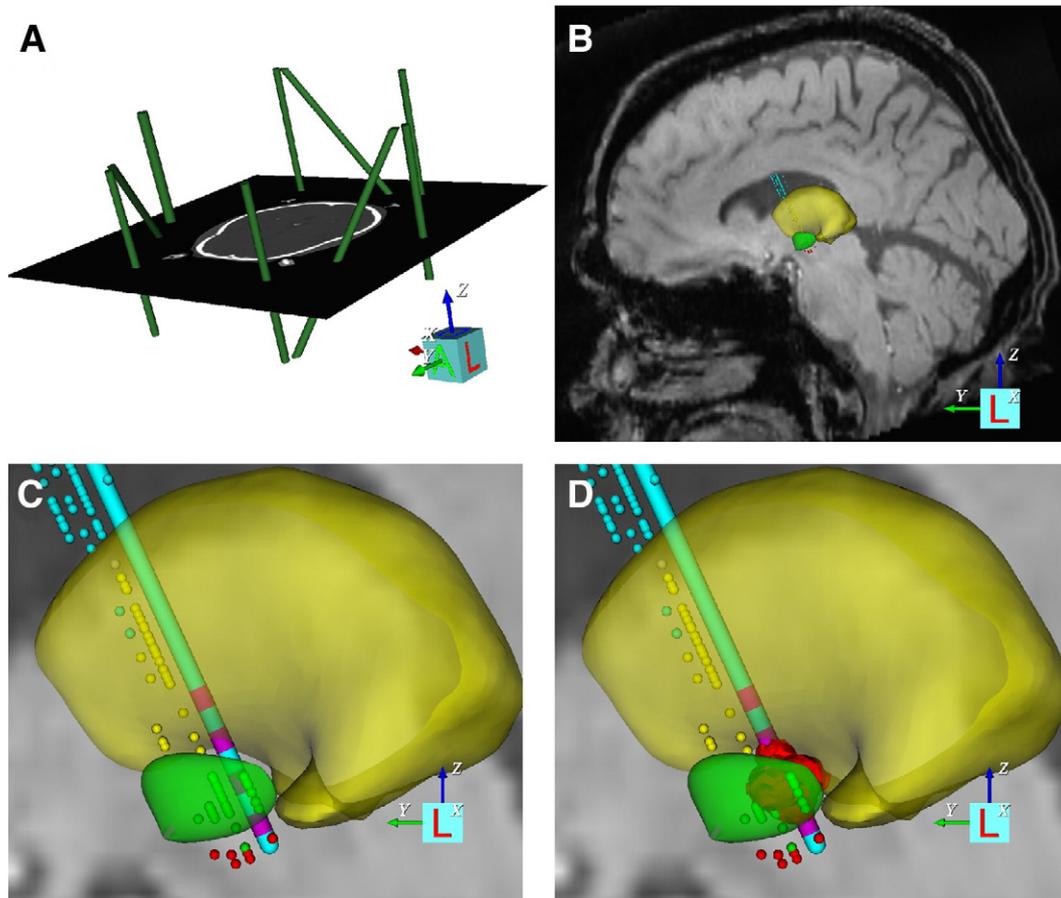
Fig. 1. Patient-specific DBS model. (A) The CRW stereotactic coordinate system (green imaging fiducials within the context of the pre-operative CT) was defined relative to the imaging data. (B) Microelectrode recording data were entered into the model (thalamic cells, yellow dots; subthalamic cells, green dots; substantia nigra cells, red dots), and a 3D brain atlas was fitted to both the neuroanatomy and neurophysiology (yellow volume, thalamus; green volume, subthalamic nucleus). (C) The implanted DBS electrode location was defined in the model. (D) The VTA (red volume) for each clinically evaluated stimulation parameter settings was calculated.

electrode placement (brain shift, lead migration, etc.) that are beyond the scope of this study. Nonetheless, 3 of the 22 patients we analyzed had poor correspondence, even when considering the errors associated with image registration. Therefore, these 3 subjects were excluded from further analysis.

The next step in the process was to calculate the volume of tissue activated (VTA) for each stimulation parameter setting evaluated in each patient. This was accomplished by transferring the patient-specific anatomical models from UF to CCF and then performing the DBS neural activation calculations using the DBS model described by Butson et al. (2007). The 3D atlas surfaces used in Cicerone were originally fitted to a diffusion tensor atlas brain image (DTI brain atlas) (Wakana et al., 2004). This DTI brain atlas represents the basis for the Butson et al. (2007) 3D finite element model of the electric field generated by DBS. The fitted 3D brain atlas surfaces used in each patient's anatomical model, and their corresponding electrode location, were reverse transformed into the context of the DTI brain atlas and calculations of the volume of tissue activated (VTA) were performed (Maks et al., 2009). The VTA can be interpreted as a region where the axons that pass through the volume will generate propagating action potentials at the stimulation frequency (Fig. 1D). The VTA methodology used in Butson et al. (2007) is principally applicable to monopolar stimulation. Two subjects from the COMPARE trial were clinically programmed with bipolar stimulation; these two subjects were excluded from the analysis in this study.

The patient-specific DBS models generated quantitative predictions on the spread of stimulation for each clinically evaluated stimulation parameter setting (Fig. 2). The specific predictions consisted of the total VTA and the VTA that occurred inside and outside of the STN. Finally, there may be some variation in total volumes of the STN between patients because the brain atlas was scaled to fit the nuances of each patient. Thus, we calculated the VTA as a proportion of the total STN volume (i.e., proportion of VTA overlap with the STN, PVO–STN).

Results

Patient-specific DBS models were created and analyzed for 17 of the 22 STN DBS patients in the COMPARE trial (Okun et al., 2009). Three patients were excluded because of discrepancies in their postoperative electrode location, and two patients were excluded due to their use of bipolar stimulation settings. Nine of the 17 patients underwent left STN DBS and 8 underwent right DBS. Fig. 2 displays examples of patient-specific models for a patient with left STN DBS and a patient with right STN DBS.

Relationship of the VTA to verbal fluency performance

Verbal fluency indices of interest included the total words generated in both letter and semantic conditions. Verbal fluency indices are expressed as standardized residual change scores with stimulation (dorsal, ventral, or optimal contact) relative to OFF stimulation. Positive values reflect higher-than-predicted scores with stimulation; negative values reflect lower-than-predicted scores. Standardized residual change scores were chosen over raw change scores to control for baseline differences in verbal fluency
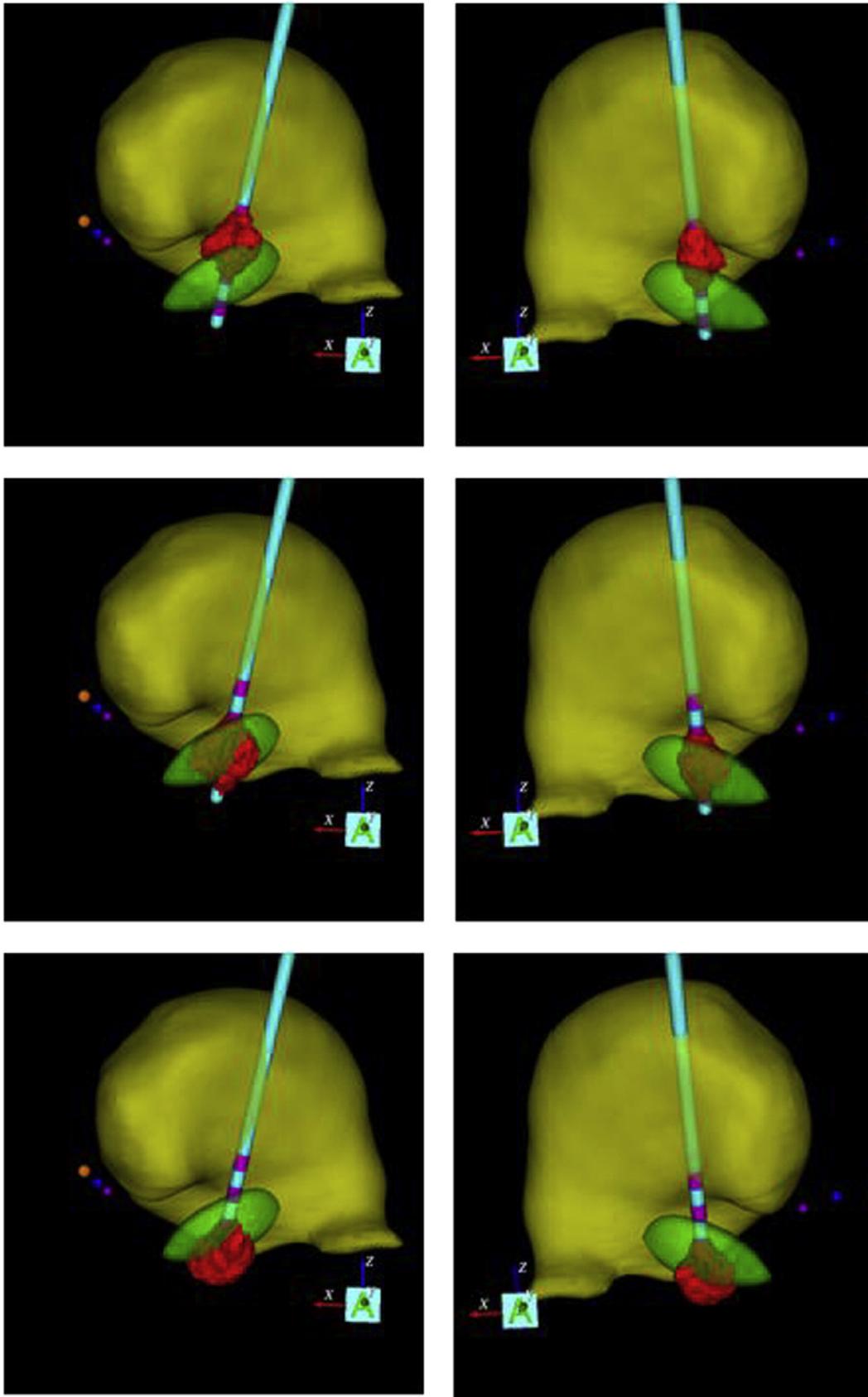
Fig. 2. Coronal view of two patient-specific DBS models. The left and right columns show patients with their DBS electrode implanted in their left or right hemisphere, respectively. The red volumes of activation generated by DBS at the dorsal, optimal, and ventral electrode contacts are displayed in each column. Anatomical nuclei (yellow volume—thalamus; green volume—STN) are also depicted relative to the AC (yellow sphere), PC (purple sphere), and MCP (blue sphere).

performance. Mean standardized residual change scores for each of the stimulation conditions are displayed in Table 2. Univariate ANOVAs revealed that there were no differences in verbal fluency performance among the three electrode contacts [letter fluency: $F(2,56) = 0.043$, $P = 0.96$, $\eta p^2 = 0.01$, power $= 0.06$; semantic fluency: $F(2,56) = 0.03$, $p = 0.97$, $\eta p^2 = 0.01$, power $= 0.05$].

Mean values for patient-specific DBS modeling indices at each of the three contacts are shown in Table 3. Spearman's correlations were conducted to examine the relationship between verbal fluency performance and these modeling indices because the data were not normally distributed. Correlation coefficients are shown in Table 4, and the significant relationships are displayed as scatter plots in Fig. 3. With optimal stimulation, there was a positive correlation between the VTA inside the STN and letter fluency change scores. That is, larger VTA inside the STN for optimal stimulation was associated with improved letter fluency performance relative to OFF stimulation. This relationship remained at trend level after removal of the outlier apparent in Fig. 3 (Spearman's $\rho = 0.44$, $p = 0.10$). Additionally, at optimal contacts, letter fluency change scores were positively correlated with the total VTA and the percent of VTA overlap with the STN. The relationship between letter fluency change scores and the total VTA remained at trend level after removal of the outliers apparent in Fig. 3 (Spearman's $\rho = 0.50$, $p = 0.06$).

With ventral stimulation, there was a negative correlation between the VTA inside the STN and letter fluency change scores. That is, more VTA inside the STN for ventral stimulation was associated with worse letter fluency performance relative to OFF stimulation. This relationship remained significant after removal of the outlier apparent in Fig. 3 (Spearman's $\rho = -0.60$, $p = 0.024$).

Discussion

Declines in verbal fluency tasks following STN DBS are thought to be due, in part, to a surgical/lesional effect (Morrison et al., 2004; Okun et al., 2009; Pillon et al., 2000). There is a lack of existing evidence in the literature supporting stimulation effects on verbal fluency performance. Indeed, in the present study, total verbal fluency output did not differ with stimulation of each of four conditions (dorsal, ventral, optimal, off). It must be noted that testing ON stimulation reveals the effect of stimulation as well as surgery and is not purely a measure of stimulation. Nevertheless, relationships between tissue activation and letter fluency performance were detected in the present study through the use of patient-specific stimulation models. Specifically, with ventral stimulation, a larger volume of tissue activated (VTA) inside the STN was associated with worse letter fluency performance relative to the OFF stimulation condition. On the other hand, with optimal stimulation, more VTA inside of the STN was associated with better letter fluency performance relative to the OFF stimulation condition.

Verbal fluency and DBS

Despite previous observations that the predominant effects underlying DBS-associated verbal fluency declines were lesional (Morrison et al., 2004; Okun et al., 2009; Pillon et al., 2000), the data from this study suggest that there may be additional stimulation-

Table 3
Mean (standard deviation) values for volume of tissue activated (VTA) variables (mm³).

	VTA in the STN	VTA outside STN	Total VTA	PVO–STN
Dorsal (N = 17)	9.06 (16.52)	56.65 (37.91)	65.71 (29.72)	0.18 (0.33)
Optimal (N = 17)	29.78 (21.47)	42.33 (31.96)	72.11 (32.94)	0.43 (0.33)
Ventral (N = 17)	36.39 (30.08)	22.17 (20.98)	58.56 (44.73)	0.63 (0.25)

induced effects depending on the locus and volume of activated tissue. However, the lack of support for stimulation effects may have to do with the nature of the testing procedure, and also whether stimulation was applied unilaterally or bilaterally. For instance, Alberts et al. (2008) tested bilateral STN DBS patients on a cognitive test (n-back) under single-task and dual-task conditions. The dual-task condition involved performing the cognitive task simultaneously with a motor task (force tracking) and was meant to better represent the conditions under which individuals performed cognitive activities in their daily lives. Under relatively simple dual-task conditions, there were no differences in cognitive or motor performance with unilateral or bilateral stimulation. As dual-task complexity increased, cognitive and motor performances were worse with bilateral compared to unilateral stimulation or when compared to OFF stimulation. These findings suggested that it is probably important to assess verbal fluency performance under conditions that may include increased task complexity, a dual-task paradigm involving a motor component, and bilateral stimulation. These more rigorous assessments may reveal that stimulation can directly affect cognition and specifically verbal fluency.

The patients in the present study underwent unilateral DBS surgery, which is important because it provided confidence that the behavior effects of DBS were the result of the single site of stimulation. However, sample size limitations prevented direct comparison of left and right DBS patient groups. Zahodne et al. (2009) showed in a larger sample size that left-sided surgery was associated with a greater risk for decline in semantic fluency performance when compared to right. Therefore, future larger studies should examine the relationship among laterality, tissue activation, and verbal fluency performance.

In the present study, the relationships of certain tissue activation indices were noted with letter fluency performance, but not with category fluency. It has been proposed that category fluency relies more on temporal lobe functioning and letter fluency more on frontal–subcortical structures (Baldo et al., 2006; Birn et al., 2009; Rascovsky et al., 2007). Given that many of the cortical afferents to STN originate from motor and frontal areas (Inase et al., 1999; Nambu et al., 1997), letter fluency may be more susceptible to STN stimulation effects than category fluency.

Table 2
Mean (SD) standardized residual change scores of verbal fluency performance at each of the three stimulation conditions relative to OFF stimulation. Negative values indicate lower than predicted scores obtained with stimulation relative to OFF stimulation, and positive values indicate higher than predicted scores.

	Optimal	Dorsal	Ventral
Letter fluency	0.17 (3.00)	−0.63 (2.57)	0.05 (3.46)
Semantic fluency	−0.09 (3.56)	−0.17 (3.67)	−0.73 (2.96)

Table 4
Spearman's ρ correlation coefficients for the relationship of verbal fluency performance with stimulation at different contacts to patient-specific modeling indices.

	VTA inside STN	VTA outside STN	Total VTA	PVO–STN
Letter fluency standardized residual change				
Dorsal (N = 14)	0.19	0.02	0.09	0.18
Optimal (N = 16)	0.54*	0.02	0.52*	0.51*
Ventral (N = 15)	−0.60*	0.57	−0.24	−0.31
Category fluency standardized residual change				
Dorsal (N = 14)	0.37	−0.42	−0.34	0.36
Optimal (N = 16)	0.42	−0.09	0.27	0.35
Ventral (N = 15)	0.10	−0.15	−0.06	0.18

Negative change values indicate lower than predicted scores obtained with stimulation relative to OFF stimulation, and positive values indicate higher than predicted scores.
* Significance at the $p < 0.05$ level.
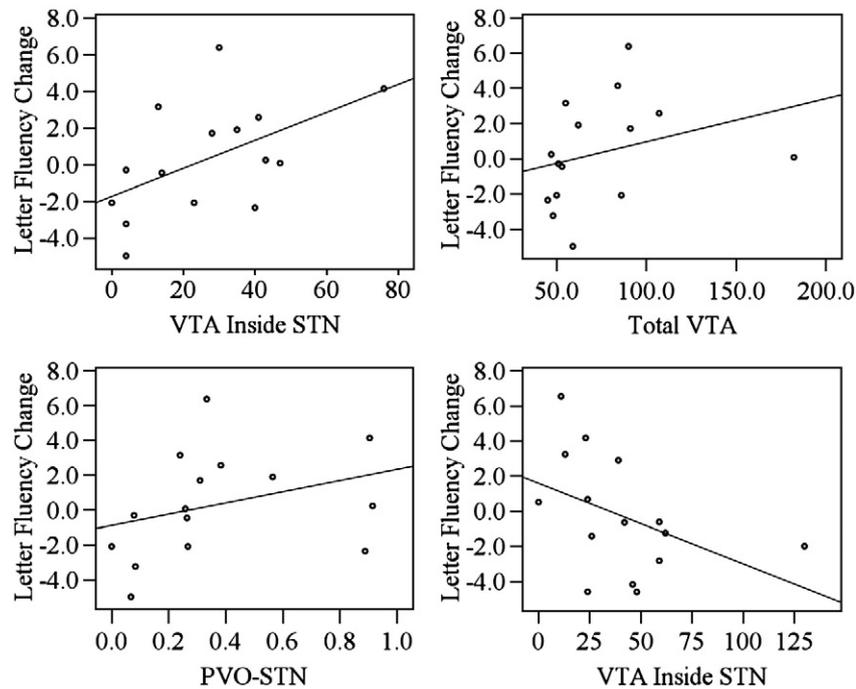
Fig. 3. Scatter plots of significant relationships between VTA indices and verbal fluency change scores relative to OFF stimulation. Negative change values indicate lower than predicted scores obtained with stimulation relative to OFF stimulation, and positive values indicate higher than predicted scores.

Subdivisions of STN

Observations of cognitive change following STN DBS (Parsons et al., 2006; Rothlind et al., 2007; Saint-Cyr et al., 2000; Smeding et al., 2006) have raised questions about whether cognitive effects result from spread of stimulation to neighboring subcortical structures or whether these changes can be traced to within the STN itself. Primate studies have revealed functional territories of the STN consisting of a dorsolateral sensorimotor area, a more central associative territory, and a smaller medial limbic area (Parent and Hazrati, 1995; Yelnik, 2002). The STN, as a primary relay in the indirect pathway, is thought to exert powerful excitatory action upon basal ganglia output structures through these separate functional subsystems (Parent and Hazrati, 1995). Our findings support the notion that functional subregions of the STN itself exert an influence on cognitive performance. In particular, activation in the ventral associative region resulted in negative effects on verbal fluency performance, while activation of the dorsolateral sensorimotor area, associated with the best motor outcome, was also positively associated with letter fluency performance. Thus, our findings were consistent with the known functional architecture of the STN.

York et al. (2009) also found supportive evidence for the hypothesis that the STN itself may be responsible for cognitive and behavioral change following DBS. They found that patients whose active electrodes were closer to the approximated STN seemed more likely to show verbal learning, memory, and verbal fluency declines at 6 months following surgery. However, they attempted to derive multiple comparisons on only 17 patients and, therefore, were underpowered to draw firm conclusions on the effects of trajectory and lead location to cognitive outcomes. Additionally, localization was performed by one rater using only imaging data and was not confirmed by physiology or any other measures. The methods of our study attempted to integrate a number of additional techniques (i.e., imaging data, intraoperative mapping data, and a 3D brain atlas) to better define the relative location between the electrode and the STN. Further, we utilized detailed predictions of the VTA to identify statistically significant relationships between STN DBS and verbal fluency.

Our findings may be relevant to the clinician charged with DBS programming. While previous research seems to indicate that it is the surgical procedure, and not stimulation per se that adversely affects verbal fluency performance, our findings indicate that there may be subtle effects of stimulation consistent with the STN's functional architecture. Stimulation within the region that yields optimal motor benefits may also yield the best outcome for verbal fluency performance. On the other hand, stimulation within the ventral associative region may have adverse effects on verbal fluency performance. Thus, if a patient demonstrates significant declines in verbal fluency performance following STN DBS surgery, it may be useful to evaluate whether optimal motor outcome is being achieved and to move one contact dorsally.

Limitations

The patient-specific DBS models used in this study relied on the most advanced neurostimulation prediction techniques currently available. However, DBS modeling technology is in its infancy and, therefore, has numerous limitations. For example, 3 of the 22 patients were excluded from analysis because their models revealed poor correspondence between the surgically intended placement and the final position of the electrode relative to the skull as revealed by CT scan. Many factors can impact discrepancies between these two measures of electrode placement (brain shift, lead migration, etc.), and further work is necessary to clarify their nature. It should also be noted that the coregistration of multiple images and atlas representations of the patient creates spatial variability that cannot be ignored. It is difficult to estimate the exact errors associated with our models, but we attempted to minimize coregistration error by using easily identifiable landmarks such as the AC/PC and intense visual inspection of our coregistration results. Another issue is that, outside of histological reconstruction, it is impossible to know the exact size, shape, and location of the STN in a given patient (Hardman et al., 2002; Nowinski et al., 2006; Yelnik et al., 2007). We relied on a 3D atlas volume to represent the STN in our analysis. Clearly, this simplifying assumption introduces some degree of error; however, we went to great efforts to fit each brain atlas to the

recorded neurophysiology and MRI neuroanatomy of each patient. The VTA prediction functions used in our patient-specific DBS models were derived from the activation of straight, relatively large diameter (5.7 μm) myelinated axons and may not be representative of the response of other neuron types surrounding the electrode (local projection neurons, local interneurons, afferent inputs, etc.). Given that myelinated axons are the most excitable neuron type to extracellular electrical stimulation (Ranck, 1975); our VTA predictions should be considered an upper limit in terms of stimulation spread. However, the stimulation predictions of our DBS models have been validated by both indirect (Butson et al., 2007) and direct (Miocinovic et al., 2009) measurements, and we have recently shown that prospective stimulation predictions from the models are capable of improving outcomes relative to traditional clinical DBS parameter selection (Frankemolle et al., 2010).

The present study contains a limited sample size, a problem inherent to many DBS outcome studies that limits the power to detect anything but very large effect sizes (Woods et al., 2006). Thus, our null findings may have been due to limited power. Additionally, we employed a 10-minute interval between the changing of stimulator settings and the onset of testing. This may have limited the ability to detect cognitive effects of stimulator settings, given that the time course of DBS effects is not entirely known.

In summary, the present study investigated stimulation effects on the verbal fluency task, which has been noted previously to consistently decline following STN DBS surgery. Stimulation of different electrode contacts within the STN did not affect total verbal fluency scores. However, models of activation revealed subtle relationships between the locus and volume of activated tissue and verbal fluency performance that were consistent with functional architecture of the STN. At ventral contacts, more tissue activation inside the STN was associated with worse letter fluency performance, but at optimal contacts, more tissue activation within the STN was associated with better letter fluency performance. Future studies should investigate stimulation effects on verbal fluency with regard to laterality, as well as to surgery-related factors such as the number of microelectrode passes. Future studies should also assess verbal fluency performance in the context of increased task complexity and dual task paradigms that more closely approximate daily functioning. These more stressful cognitive conditions will help to better characterize the contribution of the STN to cognitive performance.

Conflict of interest statement

Dr. Okun serves as a consultant for the National Parkinson Foundation, and has received research grants from NIH, NPF, the Michael J. Fox Foundation, the Parkinson Alliance, Medtronic peer reviewed fellowship training grants, and the UF Foundation. Dr. Okun has in the past received honoraria for DBS educational talks prior to 2010, but currently receives no support (since July 2009). Dr. Okun has received royalties for publications with Demos, Manson, and Cambridge (movement disorders books). Dr. Okun has potential royalty interest in the COMPRESS tool for DBS. Dr. Okun has participated in CME activities on movement disorders sponsored by the USF CME office.

Dr. Foote received research grants from NIH, NPF, Medtronic peer reviewed fellowship training grants, and the UF Foundation. Dr. Foote has in the past received honoraria for DBS educational talks prior to 2010. Dr. Foote has potential royalty interest in the COMPRESS tool for DBS. Dr. Foote has participated in CME activities on movement disorders sponsored by the USF CME office.

None of the other authors have any relevant conflicts of interest.

Acknowledgments

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