Differential Cognitive Effects of Unilateral Subthalamic Nucleus Deep Brain Stimulation for Parkinson's Disease

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Objective: The aim of this study was to investigate the cognitive effects of unilateral directional versus ring subthalamic nucleus deep brain stimulation (STN DBS) in patients with advanced Parkinson's disease.
Methods: We examined 31 participants who underwent unilateral STN DBS (left $n = 17$; right $n = 14$) as part of an National Institutes of Health (NIH)-sponsored randomized, double-blind, crossover study contrasting directional versus ring stimulation. All participants received unilateral DBS implants in the hemisphere more severely affected by motor parkinsonism. Measures of cognition included verbal fluency, auditory-verbal memory, and response inhibition. We used mixed linear models to contrast the effects of directional versus ring stimulation and implant hemisphere on longitudinal cognitive function.
Results: Crossover analyses showed no evidence for group-level changes in cognitive performance related to directional versus ring stimulation. Implant hemisphere, however, impacted cognition in several ways. Left STN participants had lower baseline verbal fluency than patients with right implants (t [20.66 = −2.50, $p = 0.02$]). Verbal fluency declined after left ($p = 0.013$) but increased after right STN DBS ($p < 0.001$), and response inhibition was faster following right STN DBS ($p = 0.031$). Regardless of hemisphere, delayed recall declined modestly over time versus baseline ($p = 0.001$), and immediate recall was unchanged.
Interpretation: Directional versus ring STN DBS did not differentially affect cognition. Similar to prior bilateral DBS studies, unilateral left stimulation worsened verbal fluency performance. In contrast, unilateral right STN surgery increased performance on verbal fluency and response inhibition tasks. Our findings raise the hypothesis that unilateral right STN DBS in selected patients with predominant right brain motor parkinsonism could mitigate declines in verbal fluency associated with the bilateral intervention.

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Non-motor cognitive symptoms cause overwhelming disability in patients with advanced Parkinson's disease (PD).[1] Ample evidence links PD with cognitive dysfunction, including declines in verbal fluency,[2,3] and PD is associated with increasing risk of mild cognitive impairment and dementia over time.[4] Cognitive changes following deep brain stimulation (DBS) surgery for PD versus best medical therapy generally describe acceptable safety and tolerability.[5,6] DBS at each of the major targets for movements disorders – subthalamic nucleus (STN), globus pallidus interna (GPi), and ventral intermediate thalamus (VIM) – improves motor symptoms but STN and GPi DBS are both associated with declines in semantic and phonemic verbal fluency.[7–11] To date, most DBS studies on cognitive function focus on changes after simultaneous or immediately staged bilateral surgeries with conventional ring-shaped electrodes at the STN target. Whether directional leads and/or implant hemisphere impact cognitive function is unclear.

DBS does not appear to increase dementia risk,[12] but bilateral surgeries for PD are associated with measurable declines in phonemic and semantic verbal fluency versus best medical therapy.[6,8] Although "mild" or "moderate" from the standpoint of psychometrics, fluent verbal communication is integral to negotiating occupational, social, and daily living activities, and DBS patients and their caregivers often complain about these functional declines when they occur. Changes in other domains of cognitive function following DBS are relatively understudied. Clear or consistent patterns of memory decline have thus far been elusive following STN DBS for PD,[5,6,13] although STN stimulation may adversely impact behavioral inhibition.[14,15] Further studies on changes in multidimensional cognition, therefore, are warranted in DBS patients, as the results could inform risk stratification in patients considering surgery and provide strategies to mitigate against potential declines. Furthermore, the impact of technological advances such as directional lead designs and potential closed-loop stimulation paradigms on cognitive function remains unclear.[16]

Language is perhaps the most well-recognized example of hemispheric brain lateralization,[17] and the motor manifestations of PD are often asymmetric, both at symptom onset and over time. Surprisingly, little is known about whether implant hemisphere impacts multidomain cognitive function.[18,19] Risk factors for cognitive declines after DBS surgery are incompletely understood.[5] Prior studies are often limited by low statistical power, inconsistent outcome measures, and variable inclusion/exclusion criteria.[5,20] Likely contributors include baseline cognitive performance, age, and stereotaxic microlesion effects (independent from direct effects of stimulation itself).[21,22] Staged bilateral surgeries appear to be associated with verbal fluency changes, regardless of which brain hemisphere was targeted initially.[23] The SUbthalamic Nucleus DirectionAL vs Circular Stimulation Study (SUNDIAL) is a randomized, double-blind, cross-over study examining the safety and efficacy of unilateral directional versus ring STN DBS for PD. Here we first contrasted within-participant changes in multidomain cognitive function with novel directional stimulation versus conventional ring DBS. We then stratified patients by implant hemisphere, hypothesizing that left versus right STN DBS might differentially impact verbal fluency and other cognitive functions after surgery.

Methods

Participants

We examined 31 PD patients (Table 1) who underwent unilateral STN DBS as part of a NIH-sponsored randomized, cross-over, double-blind clinical study (National Institute of Health BRAIN Initiative, clinicaltrials.gov NCT03353688). The United States Food and Drug Administration and the University of Alabama at Birmingham Institutional Review Board gave ethical approval for this work. All participants provided written informed consent prior to participation, only after a multidisciplinary committee recommended unilateral DBS at the STN target as part of routine care. For purposes of this study, DBS refers to the entire intervention (device implantation and microlesion effect, as well as neurostimulation). Inclusion required >30% improvement in the Movement Disorders Society – Unified Parkinson Disease Rating Scale (MDS-UPRDS) part 3 after administration of dopaminergic medications versus the "off" state (>12 hours off dopaminergic medication) during a pre-operative screening visit. Other inclusion criteria included ages 18–70 years old, Hoehn and Yahr classification >1, and a Dementia Rating Scale-2 score ≥130 (out of 144). Exclusion criteria included duration of PD <4 years, history of stroke or other significant neurological conditions, and diagnosis of a functional movement disorder based on consensus criteria. Three screen failures did not experience >30% improvement in UPDRS part 3 motor score "off" versus on medications, 1 scored >25 on the Beck Depression Inventory (BDI-II), and the multidisciplinary DBS committee eventually recommended the GPi rather than the STN target in another. One of 31 enrollees underwent an uncomplicated surgery and later voluntarily withdrew from the study.

TABLE 1. Participant Demographics

	Left STN			Right STN			
	n	Mean	SD	*n*	Mean	SD	*p*-Value
Age (years)	17	56.7	8.6	14	58.9	6.3	*0.145*
Age at disease onset (years)	17	49.3	8.6	14	50.8	6.7	*0.593*
Education (years)	17	16.1	2.6	14	15.2	2.3	*0.309*
Dementia Rating Scale	16	138.4	3.5	11	138.5	2.7	*0.989*
Beck Depression Inventory	17	7.5	5.1	13	9.3	6.3	*0.399*
Beck Anxiety Inventory	15	10.5	6.5	8	13	4.8	*0.313*
UPDRS motor off meds	17	51.5	11.8	14	46.2	14.4	*0.282*
UPDRS motor on meds	17	25.6	7.5	13	25.9	9	*0.915*
Hoehn & Yahr off meds	17	2.1	0.3	14	2.1	0.4	*0.843*
Hoehn & Yahr on meds	17	2	0	13	2	0	—
LEDD (mg)	17	1115.8	508.8	14	776.9	338.5	***0.035***
Baseline to surgery (days)	17	77.8	78.8	14	56.1	42.5	*0.338*
Handedness							
Right	15			11			*0.717*
Left	1			2			
Ambidextrous	1			1			
Sex							
Male	13			9			*0.729*
Female	4			5			
Race							
White	14			14			*0.255*
Black	1			0			
Asian	2			0			
Ethnicity							
Not hispanic or latino	17			14			—

Surgical Procedure and Stimulation Parameters

Motor symptom asymmetry is a defining clinical feature of PD. Our routine clinical practice is to treat the most severely affected hemibody with unilateral DBS, followed by staged surgery on the opposite side of the brain (when, and if, needed).[24–27] The same neurosurgeons (B.G., J.N.B.)kjm implanted a 1–3–3-1 directional lead (Boston Scientific Vercise DBS system, Natick MA, USA, FDA IDE# G170063) at the STN target under local anesthesia with the patient fully awake. Midazolam 1–2 mg is administered during the placement of the stereotactic frame. Pre-surgical brain MRI scans are co-registered with intraoperative O-arm CT images for STN targeting and to assess micro- and macroelectrode locations. The final DBS location is based on both awake electrophysiology recordings and the co-registered MRI and CT anatomic images. On average, there were 35.2 ± 21.5 days between lead implant and device activation. Participants were allocated to directional or ring stimulation at 2- and 4-month follow-up intervals in a double-blind fashion using block randomization in RedCap using an embedded randomization process. Regardless of directional or ring stimulation,

programming goals were to maximize improvements in PD motor symptoms. Per study protocol, post-operative head CT and brain MR images are acquired. Zero (0 of 31) participants experienced radiographic peri-electrode edema or clinically significant intracranial hemorrhage. Two participants had small, clinically imperceptible cortical hemorrhages, 1 associated with a left hemisphere implant and the other contralateral to a right hemisphere implant (etiology unclear). Neither demonstrated neuropsychological impairments as a result of these mini-hemorrhages, and post-operative surveillance showed radiographic resolution by 4 months.

DBS Programming

Our group has previously described the motor programming,[28] what follows is an overview. Four weeks post-implantation, participants arrived for monopolar review, completed in the off state (≥12 since their last administration of their PD medications) by experienced, certified movement disorders clinician. The programmer (M.W.) used a monopolar configuration with standard pulse width of 60 μs and a frequency of 130 Hz. For the duration of the study, the participant and researcher remained blinded. The directional DBS lead contains 4 rows with 8 total contacts (1–3–3-1 configuration). Doral and ventral rows have conventional ring-shaped contacts. The central rows have 3 directional contact segments (2 conventional rings, 6 directional contacts, 2 virtual rings). Randomization occurred *a priori* to reduce the likelihood of an order effect. We tested the therapeutic window following previously published methods.[29] The therapeutic window for each DBS configuration is defined as the ceiling value (i.e., 0.1 mA less than the current where the side effects were encountered) minus the floor (i.e., the current that provides significant improvement in cardinal signs). We delivered stimulation at the 50% midpoint of the therapeutic window at each DBS configuration during the monopolar review. Optimized settings for either ring or directional stimulation came from the most favorable responses from the initial and subsequent programming sessions.

Neuropsychological Assessments

All participants completed a standardized, comprehensive neuropsychological battery suitable for patients considering DBS.[25] Baseline screening assessments were discussed at a multidisciplinary DBS consensus conference prior to recruitment and enrollment. Coronavirus disease 2019 (COVID-19) emerged mid-trial, such that many encounters were converted to a telehealth format over a HIPAA-compliant 2-way video connection, consistent with standard clinical practices during the pandemic.[30,31] Whether in person or via telehealth, participants were in a quiet, distraction-free environment, and writing or note-taking was not allowed. Remote assessments utilized computer displays with sufficient screen area to allow easy viewing of DKEFS Color-Word Inhibition Test stimuli. All other tests did not require visual stimulus presentation. All testing neuropsychological testing occurred on dopaminergic medications.

We examined the following cognitive outcomes: *Dementia Screen*. Dementia Rating Scale (DRS-2)[32] served as a general cognitive screen at the pre-operative baseline encounter only. *Phonemic Verbal Fluency*. The F-A-S version was administered at the pre-surgery baseline assessment, and subsequent study visits alternated between the C-F-L and F-A-S versions.[33] Participants were asked to generate as many words as possible starting with a given letter over a 60-second period. *Immediate and Delayed Memory*. The Rey Auditory Verbal Learning Test (RAVLT)[34] is a 15-item word-list learning test. Outcomes were learning trials (1–5) total score and long-delayed recall number of words. Pre-surgery sessions used form AB, and visits 2, 3, and 4 used versions CB, Cr-AB, and Ge-AB, respectively. *Response Inhibition*. The Delis-Kaplan Executive Function System (DKEFS)[35] Color-Word Interference Test Trial 3 (Inhibition) evaluates response inhibition. Color naming, word reading, inhibition, and inhibition/switching were examined at each encounter, and the primary outcome for this study was time-to-completion for the inhibition trial in seconds. For all neuropsychological tests, raw scores were used for the primary analyses.

Statistical Analyses

R was used for all analyses (R Core Team, 2020; R Studio Team, 2021). Baseline continuous and categorical demographic variables were compared by implant hemisphere using Welch's 2-sample *t*-tests and chi-square tests (Table 1). To evaluate baseline cognition by implant hemisphere, Welch's 2-sample *t*-tests compared baseline cognitive function by implant hemisphere. To evaluate the effect of DBS on cognitive function over time, linear mixed effects regression (LMER) models estimated longitudinal change in cognitive function regardless of implant hemisphere. To evaluate potential effects of stimulation mode on cognitive function, OLS linear regression models regressed cognitive performance during directional stimulation on cognitive performance during ring stimulation, covarying for the order in which stimulation mode was presented to each patient. The intercept and slope were tested against $b = 0$ and $m = 1$, respectively, to determine if stimulation mode affected cognitive performance. To determine if unilateral DBS hemisphere differentially

impacts cognitive function after surgery, LMER models estimated longitudinal change in cognitive function by implant hemisphere, for both the raw cognitive scores and the percentage change from baseline. Raw score models included a random intercept by participant and percentage change models included a random slope by participant. All models included covariates for education level (years) and interaction terms for hemisphere by time. Percentage change models also included a slope covariate for baseline score. All models for the DKEFS Color-Word Inhibition Trial also included covariates for color naming speed and word naming speed. Age, visit type (telehealth versus in-person) and daily levodopa equivalent dose (LEDD) were tested as covariates to each model, and significant covariates were left in the models. Fixed effects were considered significant *a priori* with p-values of <0.05. DBS localization and STN reconstructions were completed using Brainlab (Munich, Germany) using previously published methods from our group.[36] Brainlab reconstructions were also used to determine if a DBS lead passed through, touched, or avoided the caudate nucleus. To render these images, we merged post-op CT scans with baseline MRI scans and rendered STN and leads in anterior commissure-posterior commissure (AC-PC) space with the XYZ origin [0, 0, 0] at the geometric center of each STN, rather than the midcommissural point.

Results

Baseline Demographics and Cognitive Performance

Age, age at disease onset, duration of disease, education, DRS-2 total, Beck Depression Inventory total, Beck Anxiety Index total, MDS-UPDRS part 3 score on and "off" medications, days from baseline screening to surgery, handedness, sex, race, and ethnicity did not differ by implant hemisphere (Table 1). Participants with predominant motor symptoms on the right body who received left STN DBS had higher LEDD at baseline. Participants with predominant symptoms on the left body who received right STN DBS displayed better preoperative verbal fluency function than those with left implants ($t(20.66 = -2.50$, $p = 0.02$). Response inhibition ($t(27.98 = 0.67$, $p = 0.51$), immediate recall ($t(22.74 = -0.57$, $p = 0.57$), and delayed recall ($t(28.97 = 1.25$, $p = 0.223$), did not differ by implant hemisphere at baseline. On average, the final cognitive assessment occurred at 253 days or 8 months after DBS surgery. Figure 1 displays the CONSORT participant flow diagram.

Cognitive Performance Following Unilateral STN DBS in either Hemisphere

When looking at the entire sample (pooling across hemispheres and ignoring directional versus ring stimulation configuration), unilateral STN DBS did not significantly impact verbal fluency, response inhibition, immediate recall, or delayed recall over an average follow-up duration of 8 months after surgery (Fig. 2A, Table 2). Inhibition processing speed was faster in patients who also performed DKEFS color naming ($p = 0.008$) and word naming ($p = 0.006$) faster. Older age was associated with slower inhibition processing speed ($p = 0.003$), and fewer immediate ($p = 0.004$) and delayed ($p = 0.002$) words recalled.

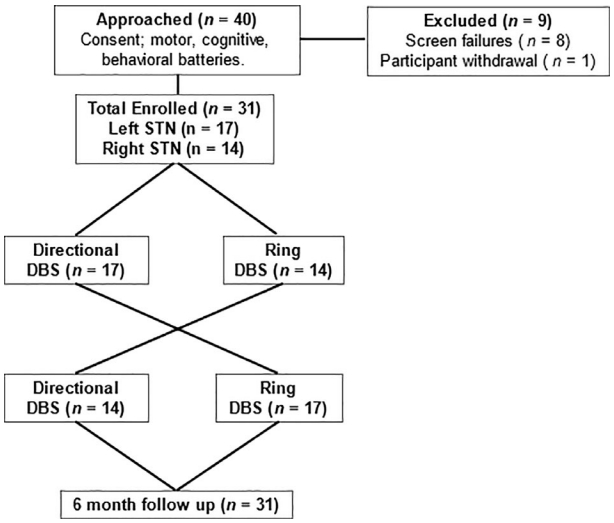

FIGURE 1: Participant CONSORT diagram.

Cognitive Performance by Stimulation Mode

Double-blind, randomized assessments of directional versus ring DBS showed no effect of stimulation mode on verbal fluency, response inhibition, or delayed memory (Fig. 2B, Table 3). Immediate memory performance statistically deviated from the unity slope ($m = 0.674$, $p = 0.027$) but not the y-intercept ($p = 0.421$). There was a bidirectional relationship for immediate recall with respect to directional stimulation, such that those with a higher percentage increase seemed to benefit from directional stimulation, while directional stimulation appeared to contribute to the lower percentage change from baseline performance. Presentation order of directional stimulation (i.e., at 2 or 4 months) did not impact verbal fluency, immediate, or delayed memory, but there was a modest order effect on response inhibition. Regardless of stimulation type, response inhibition performance was slightly better on the first stimulation modality than on the second ($p = 0.039$; ring-first y-intercept = 5.08% better on ring, directional-first y-intercept = 4.3% better on directional).

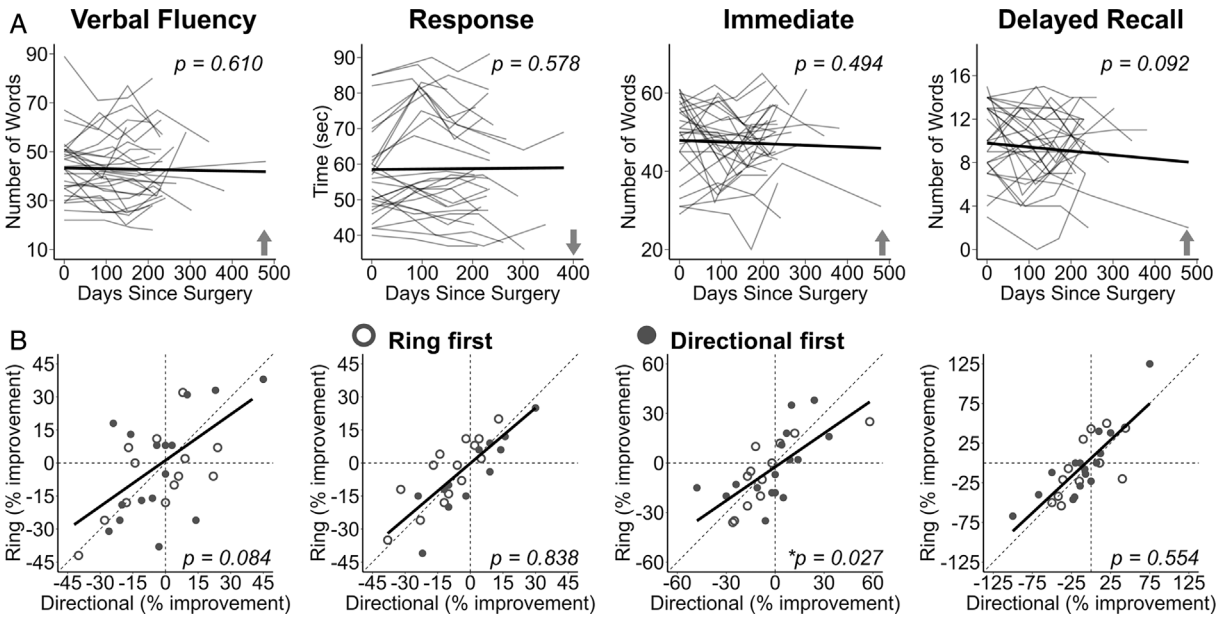

FIGURE 2: Cognitive performance following directional versus ring unilateral STN stimulation. (A) Gray lines indicate within-participant changes in cognitive performance over time after unilateral STN DBS, bold lines indicate sample means, arrows indicate direction of improved function, and *p*-values indicate the significance of the slope over time. (B) Unity plots contrast change in cognitive performance versus pre-op baseline during ring versus directional stimulation. Open circles indicate participants who were put on ring stimulation first during the double-blind stimulation randomization, and closed circles indicate participants who were put on directional stimulation first. *p*-Values indicate the significance of the slope. None of the y-intercepts were significant (verbal fluency: $p = 0.750$; response inhibition: $p = 0.874$; immediate recall: $p = 0.421$; delayed recall: $p = 0.273$)

Cognitive Performance by Implant Hemisphere

Implant hemisphere significantly affected longitudinal verbal fluency function (summary results in **Tables 4** and **5**). Following unilateral right-STN DBS, verbal fluency word count increased on average by 2.4 words ($p < 0.001$) and 7.6% from baseline ($p = 0.021$)

TABLE 2. Linear Mixed Effects Models of Overall Cognitive Performance following Unilateral STN DBS

Parameter	Verbal Fluency	Response Inhibition	Immediate Recall	Delayed Recall
Intercept	**43.351 (2.392)****	**31.196 (5.118)****	**47.862 (1.368)****	**9.851 (0.501)****
Age	—	**0.683 (0.211)***	**−0.494 (0.158)***	**−0.202 (0.059)***
Education (yr)	−0.387 (0.940)	−0.538 (0.647)	−0.220 (0.544)	−0.067 (0.174)
Color Naming Speed (s)	—	**0.456 (0.160)***	—	—
Word Naming Speed (s)	—	**0.572 (0.209)***	—	—
Change over time (days)	−0.003 (0.006)	−0.003 (0.006)	−0.004 (0.006)	−0.003 (0.002)
No. obs.	115	109	114	111
No. of groups: ID	31	30	31	30
Var: ID (Intercept)	149.30	61.80	43.640	4.101
Var: Residual	37.75	26.83	36.407	4.651

Note: Estimates are given in coefficient (SEM). The intercept indicates the score at baseline (0 days) for a patient with an average education level (15.7 yr) (and, for response inhibition, a patient with an average color naming speed (31.6 s) and word naming speed [22.2 s]). Asterisks indicate significant difference from zero.

*$p < 0.01$.

**$p < 0.001$.

TABLE 3. OLS Linear Regression of Cognitive Performance by Stimulation Mode

Parameter	Verbal Fluency	Response Inhibition	Immediate Recall	Delayed Recall
Intercept	−1.093 (3.392)	5.078 (2.495)	−2.350 (2.872)	5.625 (5.047)
Stimulation order	—	**−9.366 (3.752)***	—	—
Directional	0.670 (0.184)	0.967 (0.159)	**0.674 (0.134)***	0.918
Num. obs. (ID)	29	26	28	28
Adjusted R^2	0.305	0.714	0.455	0.617

Note: Estimates are the percentage change in cognitive performance on ring stimulation, given in coefficient (SEM). The intercept indicates the percentage change in performance on ring stimulation when the percentage change in performance on directional stimulation was 0. The directional slope indicates the strength of the relationship between the percentage change in performance on ring stimulation and the percentage change in performance on directional stimulation. Asterisks indicate significant difference from 0 for the intercept and from 1 for the slope.
*$p < 0.05$.

by 8 months post-op. Conversely, unilateral left-STN DBS yielded verbal fluency declines of 2.6 words ($p = 0.066$), or 9.5% versus baseline performance by 8 months post-operation ($p = 0.012$) (Fig. 3).

Response inhibition increased 6.2% from baseline by 8 months post-op following right unilateral STN DBS ($p = 0.032$) (Fig. 3). Regardless of implant hemisphere, response inhibition processing speed was faster in patients

TABLE 4. Linear Mixed Effects Models of Raw Cognitive Performance by Implant Hemisphere

	Verbal Fluency		Response Inhibition		Immediate Recall		Delayed Recall	
Parameter	Left STN DBS	Right STN DBS	Left STN DBS	Right STN DBS	Left STN DBS	Right STN DBS	Left STN DBS	Right STN DBS
Intercept	**37.381 (2.514)*****	**50.933 (3.775)*****	**37.906 (5.564)*****	32.019 (3.333)	**48.530 (1.868)*****	47.056 (2.817)	**10.660 (0.666)*****	8.896 (0.989)
Age	—		**−0.788 (0.204)*****		**−0.481 (0.161)****		**−0.186 (0.057)****	
Education (yr)	0.229 (0.715)		−0.867 [0.631])		−0.038 (0.490)		−0.003 (0.169)	
Color Naming Speed (s)	—		**0.379 (0.158)***		—		—	
Word Naming Speed (s)	—		**0.498 (0.204)***		—		—	
Change over time (days)	−0.015 (0.008)	**0.013 (0.012)***	0.003 (0.007)	0.014 (0.011)	−0.006 (0.009)	−0.002 (0.012)	−0.005 (0.003)	−0.003 (0.004)
No. obs.	115		109		114		111	
No. of groups: ID	31		30		31		30	
Var: ID (intercept)	79.64		55.37		31.04		3.62	
Var: Residual	35.71		25.24		36.17		4.62	

Note: Estimates are given in coefficient (SEM). The intercept indicates the score at baseline (0 days) for a patient with an average education level (15.7 yr) (and, for response inhibition, a patient with an average color naming speed (31.6 s) and word naming speed (22.2 s)). Asterisks indicate significant difference from zero (left STN DBS) or significant difference from left STN DBS estimate (right STN DBS).
*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.

TABLE 5. Linear Mixed Effects Models of Percentage Change Cognitive Performance by Implant Hemisphere

	Verbal Fluency		Response Inhibition		Immediate Recall		Delayed Recall	
Parameter	**Left STN DBS**	**Right STN DBS**	**Left STN DBS**	**Right STN DBS**	**Left STN DBS**	**Right STN DBS**	**Left STN DBS**	**Right STN DBS**
Intercept	−3.089 (2.536)	4.392 (3.809)	5.897 (6.298)	3.514 (2.464)	−0.742 (2.341)	−0.216 (3.509)	−4.977 (5.759)	1.320 (8.547)
Age	—		—		—		**−0.988 (0.466)***	
Education (yr)	0.087 (0.589)		0.126 (0.455)		−0.407 (0.590)		−0.022 (1.320)	
Color Naming Speed (s)	—		−0.079 (0.197)		—		—	
Word Naming Speed (s)	—		−0.326 (0.273)		—		—	
Change over time (days)	**−0.053 (0.020)****	**0.068 (0.033)*****	−0.052 (0.026)	**0.012 (0.029)***	0.031 (0.024)	0.039 (0.033)	**−1.145 (0.265)*****	−1.175 (0.070)
Days * Baseline value	**−0.004 (0.001)*****		0.001 (0.001)		**−0.006 (0.001)*****		**−0.037 (0.009)*****	
No. obs.	115		109		114		111	
No. of groups: ID	31		30		31		30	
Var: ID (days)	0.002		0.004		0.004		0.011	
Var: Residual	143.961		52.246		119.856		697.18	

Note: Estimates are given in coefficient (SEM). The intercept indicates the score at baseline (0 days) for a patient with an average education level (15.7 yr) and an average baseline score (and, for response inhibition, a patient with an average color naming speed (31.6 s) and word naming speed (22.2 s)). Asterisks indicate significant difference from zero (left STN DBS) or significant difference from left STN DBS estimate (right STN DBS).
*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.

who also performed faster on the DKEFS color naming ($p = 0.029$) and word naming ($p = 0.010$) tasks, and who were also younger ($p < 0.001$). Immediate recall did not significantly differ over time, nor was it affected by implant hemisphere (Fig. 3), but younger patients recalled more words ($p = 0.005$). Delayed recall declined by −1.8% from baseline by 8-months post-op following both left and right unilateral STN DBS (Left-STN DBS differs from zero, $p = 0.001$, right-STN DBS does not differ from Left-STN DBS $p = 0.835$), and younger patients recalled more words ($p = 0.003$) and recalled a higher percentage of words compared to baseline ($p < 0.001$).

A linear mixed model sensitivity analysis was performed where we looked at verbal fluency and response inhibition performances between the 2, 4, and 6-month post-operative visits, excluding the baseline performance. We found no significant differences in performance during this time period when baseline is excluded (Verbal Fluency: Left STN $p = 0.578$, right STN $p = 0.544$; Response Inhibition, left STN $p = 0.991$, right STN $p = 0.866$). This analysis indicates most of the cognitive change observed happens between the surgery and the first study visit, but our study was not designed to determine if this was purely a microlesion effect, a neurostimulation effect, or an interaction of the 2.

As seen in Fig. 4, in the right STN DBS patients, percentage change in verbal fluency was not related to change in quality of life (PDQ-8), sleep disturbance (PROMIS), or motor performance (UPDRS III total score, contralateral score, or midline score). In the right STN DBS patients, percentage change in inhibition speed was not related to change in quality of life (PDQ-8), sleep disturbance (PROMIS), contralateral motor control, or midline motor control (UPDRS III), but was positively correlated with percentage change in UPDRS III total score, such that more improvement on the UPDRS III is associated with greater increase (i.e., faster) response

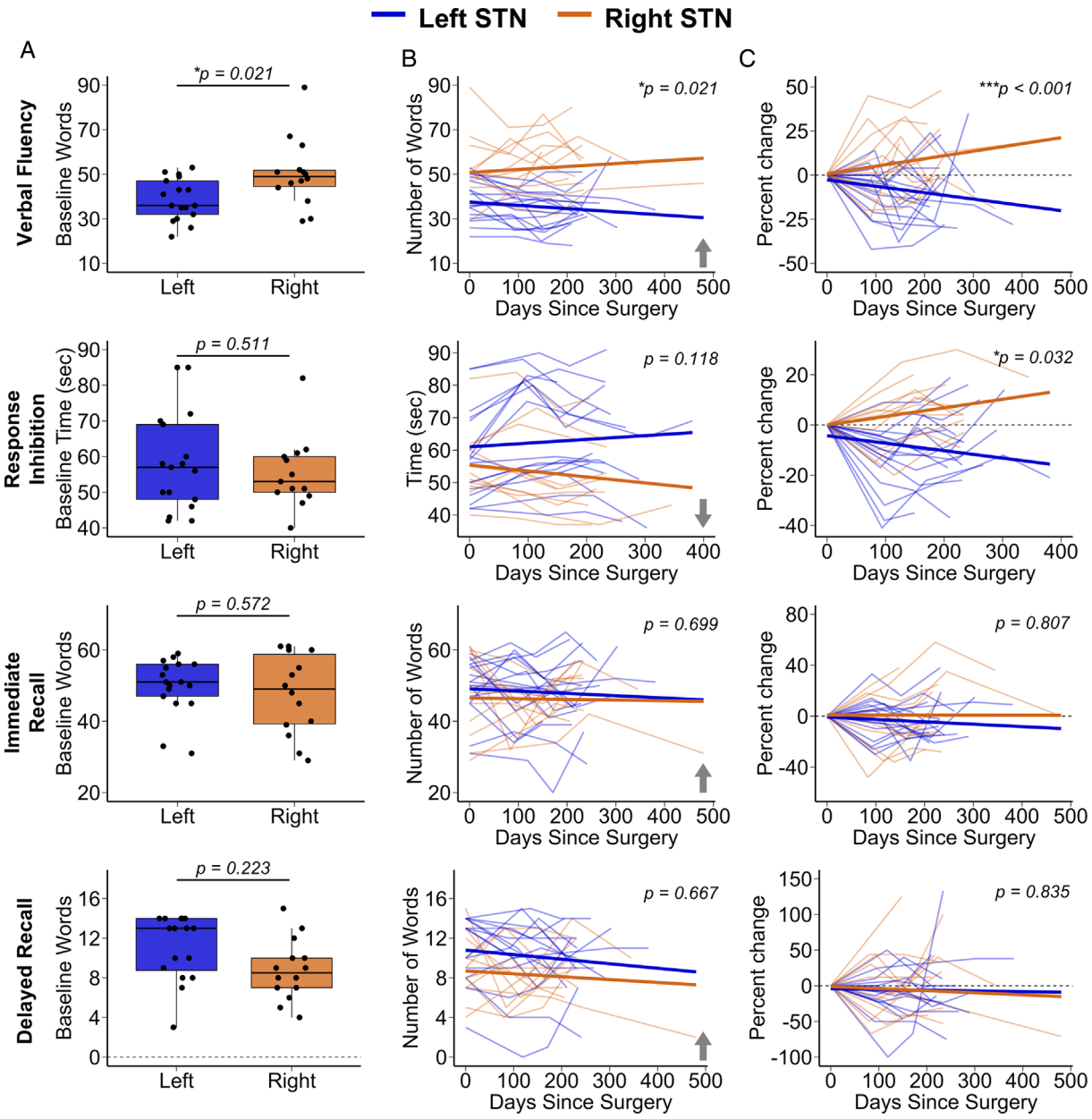

FIGURE 3: Baseline and longitudinal cognitive function in unilateral STN DBS patients. (A) Boxplots of baseline multi-domain cognitive performance by implant hemisphere. *p*-Values indicate significance between groups at baseline. (B, C) Line segments show within-participant changes in cognitive performance over time by implant hemisphere, and bold lines show group means. Higher verbal fluency and memory raw scores reflect increased output, while lower scores on response inhibition reflect faster performance. Percentage change is displayed as improved performance. *p*-Values indicate significant difference between groups in slopes over time.

inhibition speed. Also, percentage change in response inhibition in right STN DBS patients did not correlate with the percentage change in verbal fluency ($t(28) = -0.85081$, $p = 0.402$). As can be seen in Figure 4, DBS lead location is within or near the sensorimotor STN. While several may fall outside the STN, there is no bias toward the left or right hemisphere, and the distance outside of STN is within the standards of routine neurosurgical practice. Motor programming (MW) was consistent with expected STN benefits.

Verbal Fluency and the Caudate Nucleus. Several participants (6 of 20) have DBS leads that either touch or traverse the caudate (Fig. 4). As depicted, the participants where the caudate was traversed had the largest declines in verbal fluency at all post-operative time points, regardless of the implanted hemisphere.

Verbal Fluency and Electrode Placement. We examined this by stratifying our sample based on whether the stimulation site was inside versus outside the STN. A linear

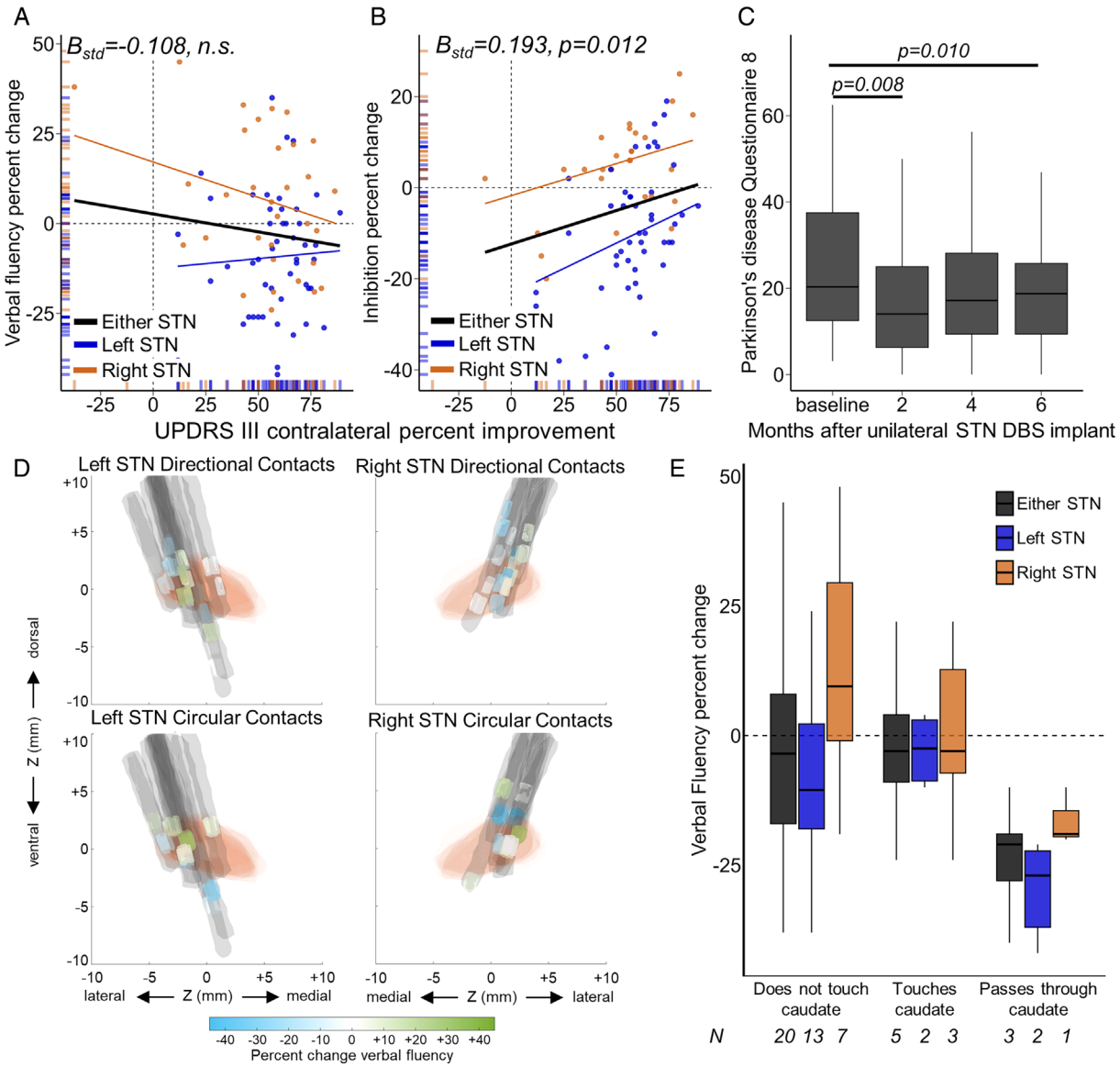

FIGURE 4: (A) There was no relationship between change in verbal fluency and change in UPDRS III, at the group level or by hemisphere. (B) Faster response inhibition relateds significantly to improvements in UPDRS III scores, both at the group level and within each hemisphere. (C) Quality of life, measured by the Parkinson's disease 8 questionnaire, improved after DBS. (D) BrainLab rendered schematic of lead locations relative to the geometric center of each participant's STN in AC-PC space. Pink indicates the overlaid individual STNs, and the color scale reflects improvements, declines, or stability in verbal fluency performance for the active contact at 12 months. (E) Verbal fluency performance as a function of whether the DBS lead passes through, touches, or does not touch the caudate nucleus. Multiple observations per participant allow boxplots for the few cases where the DBS lead passes through the caudate associated with decreased verbal fluency performance.

mixed effects regression estimated the fixed interaction and main effects of DBS hemisphere and whether an active contact intersected the STN on the verbal fluency percentage change from baseline. The model included random intercepts by participant and random slopes by participant across individual contacts. There was no significant interaction between DBS hemisphere and whether an active contact intersected the STN ($F(1,172.043) = 0.2848$, $p = 0.594$). There also was no significant main effect of whether an active contact intersected the STN ($F(1,172.043) = 2.291$, $p = 0.132$).

Functional Impairments in Verbal Fluency over Time

We evaluated the rates of clinical verbal fluency impairment by implant hemisphere at baseline and over the 8 months following unilateral STN DBS (Table 6). Here, impairment is defined as either 1 or 1.5 standard deviations below the

TABLE 6. Verbal Fluency Impairment by Implant Hemisphere across Clinical Thresholds[a]. [Color table can be viewed at www.annalsofneurology.org]

	Left STN		Right STN	
Time	***n* = 17**	***Proportion***	***n* = 14**	***Proportion***
16th percentile				
Pre-op baseline	4	23.5%	0	0.0%
2 mo	5	29.4%	2	14.3%
4 mo	5	29.4%	1	7.1%
8 mo	6	35.3%	0	0.0%
5th percentile				
Pre-op baseline	1	5.9%	0	0.0%
2 mo	2	11.8%	0	0.0%
4 mo	3	17.6%	0	0.0%
8 mo	1	5.9%	0	0.0%

[a]T-score corrected for age, sex, education.
Note: Impairment was defined as performance at or below the 16th or 5th %ile based on demographically adjusted T-scores. The color-scale (lighter-green to darker-green) reflects a higher rate of impairment for that particular cutoff.

50th percentile (i.e., the 16th and 5th percentiles, respectively) of a normative sample.[33] A proportion of left hemisphere implants had baseline and longitudinal verbal fluency impairments, whereas patients with right STN implants had little, if any, clinical impairments. Statistically significant group level verbal fluency declines do not uniformly impair all patients who receive unilateral left STN implants.

Discussion

Non-motor function is relatively neglected in research on DBS and other stereotactic functional therapies. Among various facets of cognitive function, declines in verbal fluency are the most common neuropsychological consequence of bilateral DBS for PD.[5,8,21,37–45] While verbal fluency function typically deteriorates with PD progression,[46] declines following bilateral DBS are more pronounced than with best medical therapy alone.[8,13,44] Here we found hemisphere-effects on cognition following unilateral STN DBS. Furthermore, double-blind, randomized crossover of directional versus ring stimulation showed no significant alterations in verbal fluency, response inhibition, and delayed memory based upon stimulation mode, and only a modest relationship with immediate recall.

Verbal fluency was impacted most strongly by implant hemisphere (and by extension motor symptom laterality). Participants who underwent unilateral DBS in the language dominant left hemisphere for predominant right body motor symptoms displayed worsened baseline and longitudinal verbal fluency at up to 8 months after surgery. In contrast, longitudinal verbal fluency increased in participants with right STN implants. Our findings therefore inform consent related to hemisphere-specific risk for verbal fluency declines following unilateral STN DBS, a safe and effective intervention for motor symptoms, medication reduction, and quality of life in patients with PD (Fig. 4C).[47–49]

These findings also raise two interrelated hypotheses regarding cognitive function in PD patients undergoing DBS. First, motor predominance in the language dominant left hemisphere is associated with measurable differences in the non-motor, cognitive phenotype of PD at the time of DBS evaluation. Second, unilateral rather than bilateral STN surgery, especially when the non-dominant right hemisphere shows motor predominance, is potentially a modifiable risk factor for declines in cognitive function associated with DBS. Both of these hypotheses should be investigated prospectively and/or in larger samples. Given that the target hemisphere for unilateral DBS is almost always dictated by motor symptom lateralization, changing the target hemisphere expressly to avoid cognitive symptoms would likely be unsatisfactory, as this would be contrary to the overall purpose of the intervention. However, our findings raise the question of whether selected PD patients with left hemibody symptoms (requiring either bilateral or right unilateral DBS), might be best served with a right unilateral DBS approach to minimize potential cognitive risk, while still providing adequate motor improvement. This question requires further research in an independent patient sample.

Our finding that motor symptom lateralization is associated with distinct cognitive phenotypes warrants further consideration in future studies. Motor symptoms of PD are asymmetric at onset and over the lifespan. Worse baseline verbal fluency in left STN implants suggest more extensive spread of synucleinopathy in non-motor circuits in the language dominant hemisphere prior to the DBS intervention.[50] Prior studies have found hemispheric asymmetry in dopamine transporter levels, cortical structure, and both motor and cognitive symptoms in people with PD.[51–53] Our study is consistent with these known manifestations of lateralization from other assessment modalities.[17,54,55] Regarding hemispheric specialization of language, our sample was overwhelmingly right-handed. While we did not formally evaluate language dominance with functional MRI or an

invasive Wada procedure, 95% of right-handed individuals display left hemisphere language dominance, whereas 70% of left-handed individuals display left hemisphere dominance, as well.[56] One possibility is that patients with variable degrees of right hemisphere language dominance might be adversely affected by right STN DBS, but inclusion of the small number of left-handed and ambidextrous participants in our sample did not impact our group-level findings.

Our findings of relative increases in verbal fluency following unilateral right STN DBS is novel. Furthermore, the magnitude of the verbal fluency declines following left STN implants in our sample is compatible with changes following bilateral STN DBS in larger cohorts.[8,23,40,43] Studies examining staged bilateral STN and GPi DBS and unilateral pallidotomy reported similar declines in verbal fluency following initial left but not right hemisphere targeting.[23] Moreover, patients with initial right hemisphere targeting who underwent staged left STN or GPi DBS experienced greater incremental declines in verbal fluency following the second procedure.[23] In the radiofrequency ablation literature, unilateral pallidotomy and thalamotomy studies report greater verbal fluency declines following left hemisphere procedures,[57,58] and one study reported a trend toward improved verbal fluency following right hemisphere pallidotomy with a smaller sample.[59]

In healthy adults, executive functions, including response inhibition performance, correlate with verbal fluency function.[60,61] Response inhibition and verbal fluency tasks also engage overlapping brain networks encompassing dorsolateral prefrontal cortex, anterior cingulate cortex, and basal ganglia, among others.[62] Our findings of faster response inhibition speed and improved verbal fluency following unilateral right STN DBS are consistent with these known relationships.[60] Notably, available literature on bilateral STN stimulation suggest that DBS worsens performance on response inhibition tests (e.g., the Stroop-Color Word Interference Tests, DKEFS Color-Word Inhibition).[14] These collective findings emphasize that DBS can alter this related but distinct aspect of cognitive function in addition to its more recognized effects on verbal fluency.

In contrast, we found no evidence for hemispheric differences in immediate memory recall, along with modest declines in auditory-verbal delayed recall regardless of implant hemisphere. A comprehensive meta-analysis of neuropsychological studies on STN DBS studies revealed small declines in auditory-verbal learning and memory (average random effect size = 0.21).[44] A more recent study also reported mild declines in auditory-verbal memory, but their sample consisted of only bilateral STN cases.[63] Although we found a similar patterns for declines in delayed memory following unilateral DBS, the effect size in our sample was comparatively smaller.

To our knowledge, this study is the first to characterize cognitive performance in response to directional brain stimulation. Directional DBS offers a wider therapeutic window than traditional omnidirectional stimulation,[64,65] and its greater spatial flexibility is typically preferred by patients at the STN target over time.[65] Prior studies suggest that stimulation location in the STN region might drive changes in cognitive function; therefore, novel directional stimulation fields might either perturb or mitigate such declines, depending on specific changes in the local stimulation field. Here we found no evidence that proximity of the stimulus to the STN impacted verbal fluency performance, yet stimulation yielded the expected ~50% improvements in contralateral motor function and qualify of life, both of which are compatible with results following bilateral DBS.[66,67] We saw no differences in verbal fluency, response inhibition, or delayed memory when comparing ring and directional stimulation, which suggests that unilateral ring and directional STN stimulation for motor symptoms both have overall favorable cognitive safety profiles.

Multiple factors in addition to hemispheric lateralization likely contribute to changes in verbal fluency after DBS surgery. In our sample, most of the cognitive changes occurred between baseline testing and the earliest follow-up at 2 months after surgery. Multiple studies including a large sham-controlled trial provide evidence that bilateral lead implant itself (prior to initiating stimulation) yields measurable declines in verbal fluency.[15,21] Regarding lead trajectory, our findings in a subset of 3 participants emphasize the potential importance of avoiding penetration of the caudate whenever possible, as described previously.[22] Another study found associations between verbal fluency declines and lateral entry points through the left superior frontal gyrus, but relatively little impact from traversing the caudate.[68] Other studies implicate lead location and stimulation frequency with changes in verbal fluency as well, emphasizing likely independent effects of stimulation itself.[40] Finally, PD itself is a progressive neurodegenerative disorder, with expected long-term cognitive declines over years regardless of the DBS intervention.

Neuronal mechanisms underlying changes in verbal fluency and other cognitive functions following DBS surgeries are unclear but likely involve disruption of basal-ganglia-thalamocortical networks. Single unit studies suggest functional roles for the STN in speech production,[69] and both animal and human studies have identified

monosynaptic pathways from prefrontal cortex and temporal lobe to STN.[70,71] Neuroimaging studies consistently support a role for the left inferior gyrus during verbal fluency tasks,[72,73] which has direct connections with dorsal STN.[71] Additionally, evoked potential studies suggest direct connections between STN and both inferior frontal gyrus and superior temporal gyrus and the opercular speech network.[70] Disruption or alteration of these aspects of network connectivity likely underlie changes in verbal fluency, response inhibition, and auditory-verbal memory retrieval in our sample.

Our study has strengths and some important limitations. Although we are aware of no prior studies of this size comparing hemispheric effects of unilateral DBS on cognitive function, our sample is still modest[20]; larger multicenter studies might detect additional or more subtle effects of unilateral DBS on cognitive function. Also, we did not directly contrast unilateral stimulation with either best medical therapy or bilateral DBS; therefore, inferences across studies should be interpreted with some caution. Regardless, we observed no significant group level changes in cognition in following unilateral STN DBS when implant hemisphere was removed from the statistical model. Additionally, including hemisphere in the model, we observed greater change in both verbal fluency and response inhibition following right STN DBS, which would not be expected in any case based on the prior literature on bilateral surgeries. Regarding these stronger performances, the effects were modest and might in part reflect practice effects on the tasks, but at the least they do not represent declines. Finally, while our study team was double-blinded to the stimulation parameters, patient and examiner were not blinded to implant hemisphere. That said, changes in cognitive function were noted at multiple time points and were generally consistent within individuals.

We conclude that unilateral directional and ring stimulation at the STN target are both safe and do not differentially adversely affect cognition in patients with PD. Our examination of unilateral rather than bilateral DBS surgery allowed the identification of hemisphere-specific changes in verbal fluency and executive function following unilateral STN DBS. Collectively, these findings raise the hypothesis that the unilateral intervention, particularly in the non-dominant hemisphere, might mitigate post-operative cognitive declines in selected patients. Future studies should prospectively contrast unilateral and bilateral DBS with best medical therapy to develop more personalized therapies to optimize both motor and non-motor function in patients with PD. Furthermore, additional studies are needed to shed light on how DBS interacts with brain networks involved in verbal fluency and other vital cognitive functions.[74]

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Author Contributions

Conception and design of the study: H.C.W., R.C.M., C.L.G., V.D.B. Acquisition and analysis of data: R.C.M., V.D.B., S.A.B., D.M., J.W.O., M.J.N., C.L.G., K.A.M., V.K., G.C., C.H., M.W., F.G.R., J.N.B., B.L.G., R.T.K., H.C.W. Drafting of the text and preparing the figures: V.D.B., S.A.B., R.C.M., D.M., J.W.O., H.C.W.

Potential Conflicts of Interest

Dr. Harrison Walker participates in data safety monitoring boards for 2 DBS studies. Dr. Kelly Mills has received honoraria from the Parkinson's foundation. The remaining authors do not report potential conflicts of interest.

Data Availability

Raw data can be obtained through the Data Archive for the BRAIN Initiative hosted by the University of South California (https://dabi.loni.usc.edu/dsi/1UXQYOCLCIOB).

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