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THE IMPACT OF VOLUME OF TISSUE ACTIVATION ON CORTICAL-STRIATAL  
NETWORKS AND VERBAL FLUENCY DECLINES IN POST-DEEP BRAIN  
STIMULATION PARKINSON'S DISEASE PATIENTS

By

Alexander Luke Alley  
B.S., University of Louisville, 2020

A Thesis  
Submitted to the Faculty of the  
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For the Degree of

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University of Louisville  
Louisville, Kentucky

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A Thesis Approved on

April 22, 2022

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## ABSTRACT

### THE IMPACT OF VOLUME OF TISSUE ACTIVATION ON CORTICAL-STRIATAL NETWORKS AND VERBAL FLUENCY DECLINES IN POST-DEEP BRAIN STIMULATION PARKINSON'S DISEASE PATIENTS

Alexander Luke Alley

April 22, 2022

This study investigated the cortical-striatal networks of verbal fluency declines in 6-month, post-operative, deep brain stimulation Parkinson's Disease patients. Nine Parkinson's disease participants with implanted STN or GPi DBS systems were recruited for this study. Verbal fluency data was obtained from each patient preoperatively and 6-months post implantation. The stimulation-based volume of tissue activated area (VTA) of each target site (STN or GPi) was analyzed using Lead-DBS and Lead-Group. The white matter tracks intersecting each patient's VTA, terminating in the pre-SMA, SMA, caudate nucleus, and anterior cingulate were investigated and correlated with verbal fluency declines. We found statistically significant effects of DBS on verbal fluency, with a trend towards greater declines in the STN compared to the GPi. Verbal fluency declines were found to be the greatest in patients with more white matter tracts leading from the left hemisphere to the left caudate and bilaterally to the pre-SMA and SMA, and there were no correlations found between VF and the anterior cingulate.

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## INTRODUCTION

Parkinson's disease (PD) is the most common form of movement disorder and the second most common neurological disorder. Prevalence rates of PD in industrialized countries are estimated at 0.3% of the entire population and as high as 1% in people over 60 years of age, effecting upwards of five million people worldwide [1-4]. Its pathological hallmark is the loss of pigmented dopaminergic neurons in the substantia nigra pars compacta, leading to various motor symptomologies [5, 6]. These motor symptoms are manifested clinically by a triad of cardinal motor symptoms- rigidity, bradykinesia, and tremor, which become progressively worse as the disease advances. Dopaminergic medications are typically used for the frontline treatment of these motor symptoms in PD. Usually increasing the dosage of these medications is commonplace to combat these worsening symptoms [3]. However, the benefits of higher doses are offset by side effects, such as dyskinesia, motor fluctuations, confusion, and hallucination [7], creating the need for other treatment methods outside of medication.

Surgical treatments for PD were developed as a means to overcome difficulties associated with the medical management of motor complications in patients with advanced Parkinson's disease [8]. Deep Brain Stimulation (DBS) was historically used as a method to check the area to be lesioned in each functional target during a Pallidotomy [9]. Later it became an adjustable and reversible alternative procedure to stereotactic ablation [10]. Because of this, Globus Paladus internus (GPi) DBS was successfully introduced for the management of bradykinesia and rigidity [11]. Following the discovery of the key role that the Subthalamic Nucleus (STN) plays in the pathophysiology of PD [12], STN lesions were shown to improve parkinsonism and subsequently showed that STN DBS could become a successful surgical treatment site candidate for patients with PD [8, 13].

DBS for the treatment of PD is an efficacious treatment method for the reduction of PD motor symptoms. This treatment, however, can have deleterious effects on certain aspects of the patient's cognitive functioning. Specifically, most patients experience a decline in spontaneous word generation, or verbal fluency (VF) [14-28]. Deficits in verbal fluency are variably expressed and exacerbated in PD and following DBS surgery [16]. However, the specific effects that DBS has on cognition are not well understood [29]. While VF deficits are generally a part of PD symptomology prior to DBS surgery [30], the underlying cause of the worsening that occurs after DBS is still an area of active research [14].

While DBS is overall a generally safe treatment for PD, deficits in VF represent one of the most commonly reported side effects of DBS therapy when targets of either the STN or GPi are used [16, 44]. Causes of this effect across individuals and between targets are generally incomplete, however. Some patients do not show any, or marginal fluency deficits, whereas others can potentially show a dramatic reduction in VF [45]. Reductions in VF can lead to a negative impact on quality of life for PD patients and suboptimal clinical responses [16, 31-34]. The prospect of having short- or long-term complications, particularly cognitive changes, can negatively affect efficacy and enthusiasm for continued use of an intervention. Understanding what causes VF decline due to DBS might also help to optimize future DBS settings [16].

VF is generally tested with a task requesting the patient, within a minute, to name as many words as possible starting with a specific letter (F, A, or S), known as phonemic or letter fluency and/or stemming from a certain category (e.g. animals and boys names), known as semantic or categorical fluency) [35, 36]. Deficits in VF in turn come about from both linguistic and executive dysfunctions as it involves a multitude of cognitive processes including lexical search, memory retrieval, executive functioning, and response monitoring, inhibition, and selection [36, 37]. Among 21 studies looking into VF declines in PD patients with DBS, 16 reported data for phonemic VF (355 patients) and 16

reported data for semantic VF (355 patients) and found average effect sizes of moderate size (0.51 and 0.73) for both letter and categorical VF declines [33].

Action (verb) fluency is another form of fluency, similar to semantic and phonemic verbal fluency, but it requires the patient to rapidly generate as many verbs (i.e. “things that people do”) as possible in within one minute. Verb generation is primarily associated with the integrity of frontal-striatal-thalamo-cortical loops [38, 39], whereas noun generation is more dependent on the temporal and inferior parietal cortices [40, 41], with deficits in noun naming being linked to anterior and inferotemporal areas [42]. Action fluency may be more sensitive to frontal-basal ganglia loop pathophysiology than traditional noun fluency tasks, which is in line with the existing hypothesized neural dissociation between noun and verb retrieval [43].

The production of speech involves a complex interplay of motor and cognitive processes, and the decline of VF in PD patients undergoing DBS is theorized to be caused by changes in the basal-ganglia-thalamocortical network [33, 44]. Non-surgical contributors (ex- dopaminergic medication changes, pre-surgical disease variables, and various neuropsychological and physicals characteristics) do not seem to provide significant insight into the emergence of VF deficits post DBS [14, 24, 45-47]. There is, however, evidence for reductions in fluency tied to stimulation parameters. For example, clinically high frequency DBS (~160 Hz), in conjunction with both the location of the

electrodes within the target area and location of the volume of tissue activated (VTA) collectively, lead to increased rates of VF decline, implicating a direct role of stimulation and potential VTA induced white matter networks in VF declines [48-50].

There is some indication that fluency deficits may be greater when a STN target is used versus GPi, although mixed results have been reported with both targets and more research is warranted[48-50]. Also, concerns surrounding changes in frontal lobe related cognitive functions have been raised [24, 51-53] specifically with STN DBS. STN DBS may lead to improved motor conditions but concomitantly worsened emotional and cognitive measures (ie- anxiety, depression, apathy, and categorical fluency task) with little to no change in other cognitive functions [22]. Worsening in categorical fluency seems to be the most frequent cognitive decline reported after STN-DBS [22, 24, 54, 55]. This may be because the STN is a relatively small structure that is innervated with cortical projections from motor, associative and limbic areas [56, 57]. The frontal lobe related cognitive changes after DBS could be the result of modulation of the associative circuits [15]. Cilia et al., 2007 found that worsening fluency in STN-DBS was associated with decreased perfusion in the left dorsolateral prefrontal cortex, anterior cingulate cortex, and ventral caudate nucleus ( $p<0.01$ ). There are also indications that Pre-SMA and SMA could potentially be involved in the mediation of VF as well, notionally allowing the indirect effects of the DBS system on the cortex to modulate VF [58, 59]. VF declines with DBS GPi however, have received less attention and there is a lack of

research into the mechanisms that could explain the VF decline with GPi. The current study aims to determine how the field of stimulation and the upstream cortical circuitries modulated by the stimulation are related to fluency decline in STN and GPi which could offer new strategies for the mitigation of negative DBS cognitive side effects.

We predict that DBS will lead to a global VF decline and we will additionally explore the cortico-striatal networks associated with these VF declines because the indirect role that the cortex plays in the mediation of VF is unclear and has not been previously studied.



## METHODS

### Patient Cohort

**Table 1**

Demographics and clinical variables (means and standard deviation) for GPi and STN

Patients

	GPi (6)	STN (3)
Age (yrs)	57.2(11.4)	62.6(13.9)
Gender (M:F)	2:3	3:1
Education (yrs)	13.8(1.6)	12.8(1.0)
Disease Duration (yrs)	6.75(5.1)	9.25(3)

(Table 1) shows 9 participants total, recruited from the UofL Health system, which were included in this trial. Six of those patients were implanted with bilateral GPi DBS, and the remaining 3 patients were implanted with STN targets, 2 bilateral and 1 unilateral right STN. Patients were implanted with either Medtronic, Abbott, or Boston Scientific DBS systems. All patients were tested on VF both ON stimulation status and on dopaminergic medication, to best emulate patient at-home and day-to-day conditions. Imaging data of 8 of 9 patients consisted of multispectral preoperative MRI (T1 and T2 weighted) sequences and were also CT scanned postoperatively. One patient, however, underwent preoperative CT and postoperative CT imaging due to an MRI incompatible implanted medical device.

### **Verbal Fluency**

To obtain verbal fluency comparisons, participants were administered postoperatively either the Letter and Category tasks from the DKEFS Verbal Fluency assessment [60] or the Letter and Category tasks from the COWAT Verbal Fluency assessment [35], dependent upon the original VF assessment administered during the patient's initial preoperative neuropsychological assessment. These tests were used to measure Letter and Category fluency. All patients were additionally asked to participate

in an Action fluency [43] assessment post-operatively (only a subset of participants underwent preoperative Action fluency testing), where they generated a list of action words. The participants were tested both at time of initial evaluation of DBS implantation and again 6 months post-implantation.

Participants were instructed to generate as many words within 1 minute following a semantic, phonemic, and action category, such as “animal names”, “words that begin with the letter “f””, or “things that people do”, respectively. Participants were then given points for each unique word given and inversely were not given points for words with similar roots (“run”, “runs”, “running”) or for the same action with different subjects (“running fast” or “running slow”). Additionally, they were instructed to refrain from giving numbers and proper names of people and places. The order of fluency test administration was fixed across patients and consisted of Letter then Category, followed by Action.

### **Participant Imaging Co-registration & Electrode Localization**

Initial individual processing and registration of all the patients’ imaging and electrode localization were completed using Lead-DBS. Localizations were finalized using the default parameters of the Lead-DBS v.2 pipeline [61]. Linear co-registration of the preoperative MRI (or CT) imaging to the postoperative CT images were completed

using Advanced Normalization Tools (ANTs; <http://stnava.github.io/ANTs/>; [62]). If necessary, these normalized images were manually refined using 3D slicer ([www.slicer.org](http://www.slicer.org)). The preoperative scans were normalized into MNI (ICBM 2009b NLIN Asym; [63] space using ANTs and the “Effective: low variance” protocol with subcortical refinement within the Lead-DBS space [64]. Co-registration results were then manually checked using built-in tools that assist visual inspection- red wire-frame generation of the anchor modality, and further false-color overlays. Co-registration is a crucial step during electrode localization since the preoperative data is used to define overall anatomy and of postoperative data to define electrode locations [61].

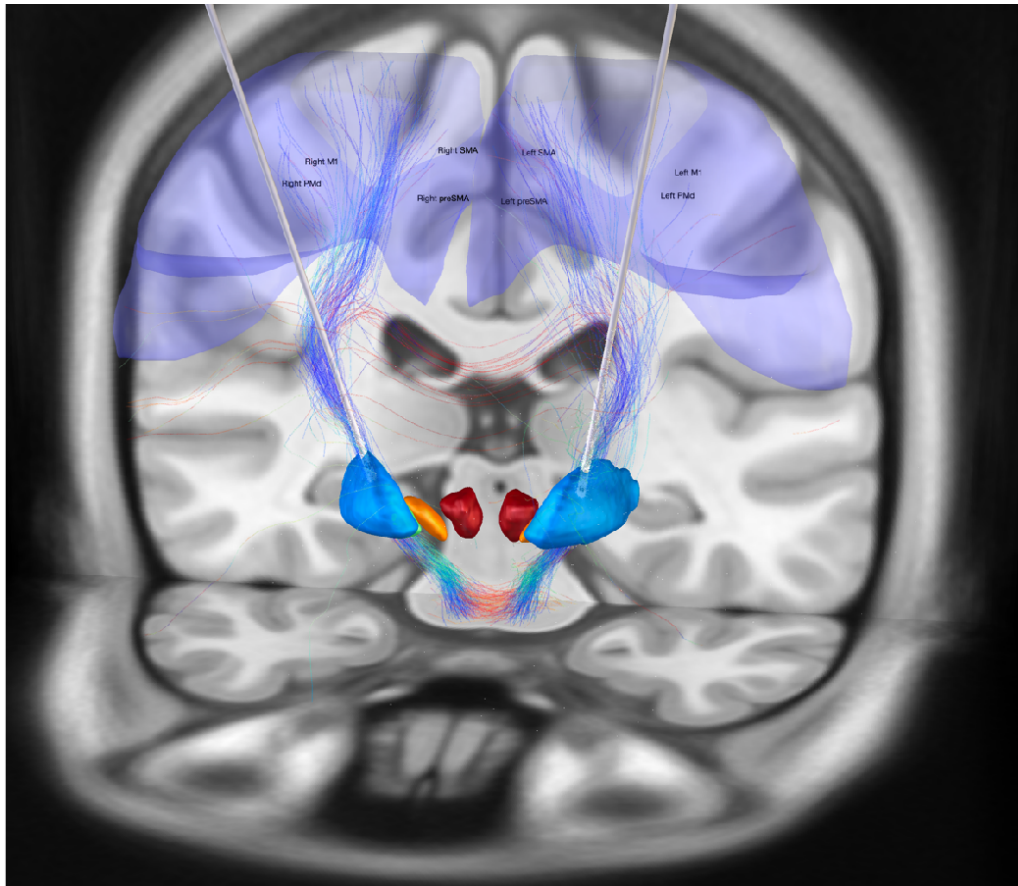
Normalization of individual patient anatomy to a template space creates an environment in which relation of electrode placement to anatomy and comparisons between patients and electrode centers are possible. These template spaces often allow the most likely location of anatomical structures to be better defined, and can then be used to project subcortical atlases or whole-brain parcellations [61] onto regions of interest. The patient-to-template-normalization in the primary default pathway of Lead DBS uses the Advanced Normalization Tools (ANTs) SyN [62], which employs a Four-Stage preset with subcortical refinement, and the Statistic Parametric Mapping (SPM) Unified Segmentation Method, which is based upon Tissue Probability Maps calculated from multispectral ICBM 2009b NLIN ASYM Space templates [65].

During surgery, air can potentially enter the skull after it is accessed and opened. This can ultimately lead to a nonlinear deformation of the brain in relation to the bone, called brain shift (pneumocephalus). This usually pushes the forebrain in the occipital direction because of the supine nature of the patient. When this is present during post-operative imaging, it can induce a discrepancy between the electrode placement and the anatomical structures compared to the preoperative imaging [66]. To combat this, Lead DBS uses a threefold linear registration stored internally and applies this to DBS electrode placement afterward [61, 67]. The PaCER toolbox [68] was used during the process of electrode placement reconstruction [61].

The VTA is a conceptual volume elicited by the electrical stimulation from the DBS device and is thought to produce additional action potentials due to the electrical stimulation of axons [69]. The SimBio/FieldTrip toolbox within Lead-DBS was used to estimate the VTA for each participant within this study using the stimulation parameters of each patient at the time of their postop VF testing. This toolbox uses a finite element method (FEM) approach, 4-Compartment model and Tetrahedral Mesh method [70]. The VTA is then used to estimate the further connectivity matrix of each patient. (Figure 2) shows, within 3D template MNI space, the registered electrodes, basal ganglia structures, VTA, white matter tracts and their terminating structures based upon the HMAT parcellation.

**Figure 1**

Localized and registered, using Lead-DBS, bilateral GPi DBS electrodes in MNI space with stimulation mediated VTA, activated white matter tracts, cortical & basal ganglia structures based upon the HMAT parcellation



## **Connectomic Analysis**

Six of the 9 patients were included in the connectomic analysis using the toolbox Lead Group, with the percentage change in VF scores included in the Lead Group GUI. Stimulation parameters were specified for each individual patient and was used to calculate the VTA using a FEM approach. Seeding from these VTA's provide an estimate of structural connectivity to other brain areas and was computed using Lead Group. A PD-specific connectome was then used, which was obtained from an 85-patient sample included in the Parkinson's Progression Markers Initiative (PPMI; [www.ppmi-info.org](http://www.ppmi-info.org)) database [71]. For the current analysis, fibers of the connectome were selected that traversed through the VTA and terminated in the distinct regions of the sensorimotor cortex, the Human Motor Area Template (HMAT) and the Automated Anatomical Labeling (AAL3) atlas. [72, 73]. These parcellation contains regions defining supplementary, and presupplementary motor areas (SMA/preSMA), anterior cingulate, and the caudate nucleus [5, 8, 79]. These intersections were measured and then correlated with VF declines.

## **Statistical analysis**

First, the effect of stimulation in the STN and GPi on letter and category fluency from pre- to post-DBS was compared. VF for each category was defined as a scaled score

(scaled score of the average word rate generated per minute). A one-way ANOVA was used, with Fluency Type (Category and Letter), and Session (Pre, Post), as the within-subject factors and DBS Target (STN, GPi) as the between subject's factor. A paired samples T-Test was also performed on the 5 patients who had both pre- and post-procedural Action fluency scores.

Second, the percentage of VF decline was calculated by taking the difference of the summed category and letter pre- and post-operative scores for each patient. This result was then correlated, using a Spearman's Rank-correlation, to the amount of VTA activated white matter fiber tracts that terminate within the right and left Pre SMA, SMA, Anterior Cingulate Gyrus, and the Caudate nucleus. Random permutation (x 5000) was conducted to obtain P-values.



## RESULTS

**Table 2**

DBS clinical stimulation parameters (means and standard deviations) for GPi and STN targets separated by left and right electrode leads

	GPi (6)		STN (3)	
	Left (6)	Right (6)	Left (2)	Right (3)
Amplitude (V)	4.0(1.1)	3.1(1.8)	2.9(1.4)	1.6(.57)
Pulse width (ms)	67.5(15)	67.5(15)	60(0)	60(0)
Frequency (Hz)	135(10)	135(10)	140(14.1)	128.8(2.5)

(Table 1) shows participant demographics and clinical variables. (Table 2) reports DBS stimulation parameters for both targets (means and standard deviations). PD patients with DBS STN and GPi targets were similar in age, gender, education, and disease duration.

## DBS effects on fluency

**Table 3**

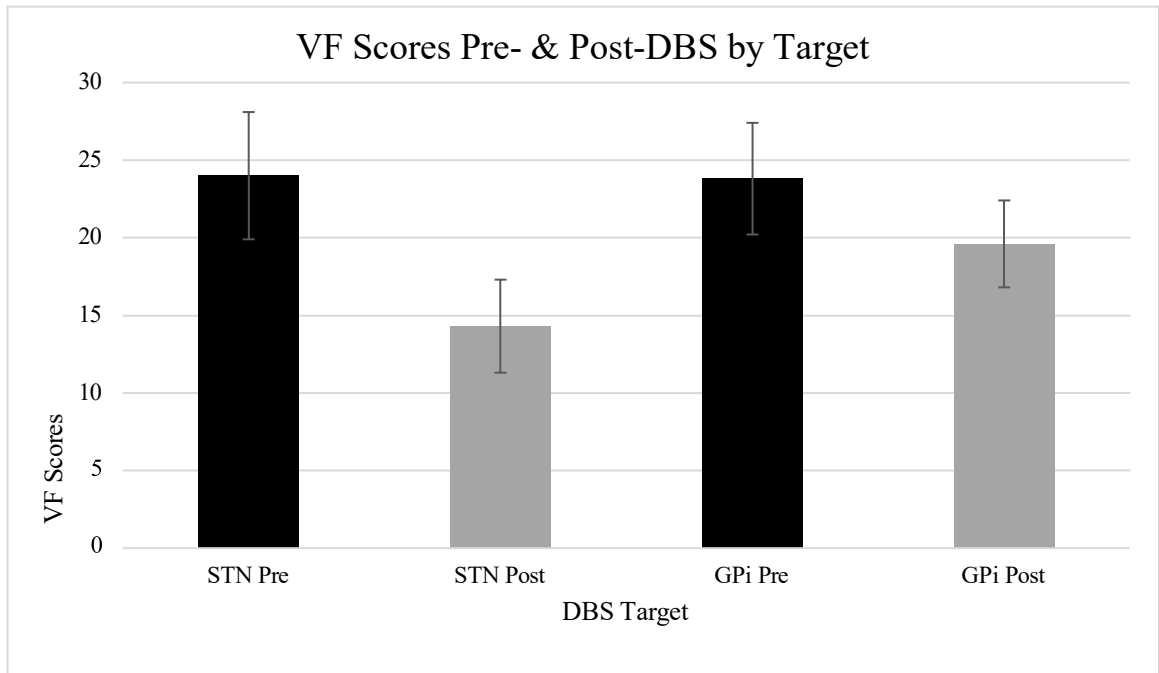
VF for Letter and Category types, dependent upon target, pre- and post-DBS

		STN		GPi	
Session	Fluency Type	Mean	Std. Error	Mean	Std. Error
Pre	Letter	11.0	2.2	12.2	1.9
	Category	13.0	1.9	11.6	1.7
Post	Letter	7.8	1.3	9.8	1.2
	Category	6.5	1.7	9.8	1.6

(Table 3) shows verbal fluency data for two of the VF types, Letter and Category, pre- and post DBS surgery dependent upon each target, STN and GPi. Verbal fluency was not found to vary by fluency type (Fluency Type,  $F(1,7) = 0.06$ ,  $p = .94$ ,  $\eta^2 = 0.01$ ), the production of letter-associated words (10.2) and category-related words (10.2) was comparable. A significant decrease in VF was discovered between pre- (12.0) and post-operative (8.5) testing (Session,  $F(1,7) = 25.32$ ,  $p = .002$ ,  $\eta^2 = .783$ ) (Table 5). There was a larger decline in STN VF (pre = 12.0 to post = 7.1) compared to GPi VF (pre = 11.9 to post = 9.8) from pre- to post DBS implantation, although this was not significant (Session x Target,  $F(1,7) = 4.0$ ,  $p = 0.08$ ,  $\eta^2 = .36$ ) (Table 4 and Figure 2). All other two- and three-way interactions between fluency types, session, and target were not significant ( $F$ 's < 2.9,  $p$ 's > .133,  $\eta^2$  < .29). Action fluency was not included in this analysis due to the inconsistency of presurgical testing and was calculated separately.

**Figure 2**

Average (Letter + Category) verbal fluency scores preoperatively compared to 6-month post DBS implantation



(Table 4) shows the VF for the third type, Action fluency. Due to only having preoperative Action VF data on 5 of the patients, these scores were ultimately not included in the ANOVA or the fiber count correlations. Consistent with both the Letter and Category fluency data, a decreasing trend was also observed with the Action VF data as well (pre= 9.0 to post= 6.8) (T(4) = report t value, p = 0.086).

**Table 4**

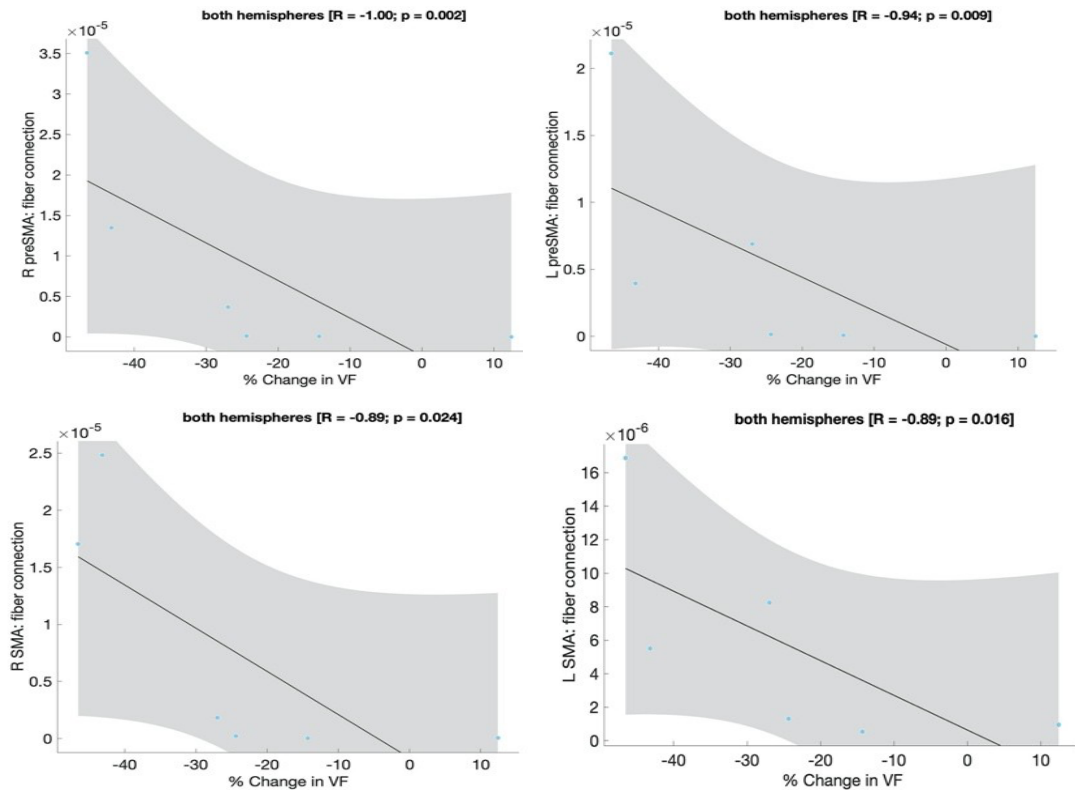
VF for Action fluency pre- and post-DBS

Session	Mean	N	Std. Deviation	Std. Error
Pre	9.0	5	2.9	1.3
Post	6.8	5	2.6	1.2

## Cortical areas impacted by DBS associated with post-operative change in fluency

**Figure 3**

Correlation of bilateral VTA intersected fiber counts and % change in VF for left and right SMA/PreSMA

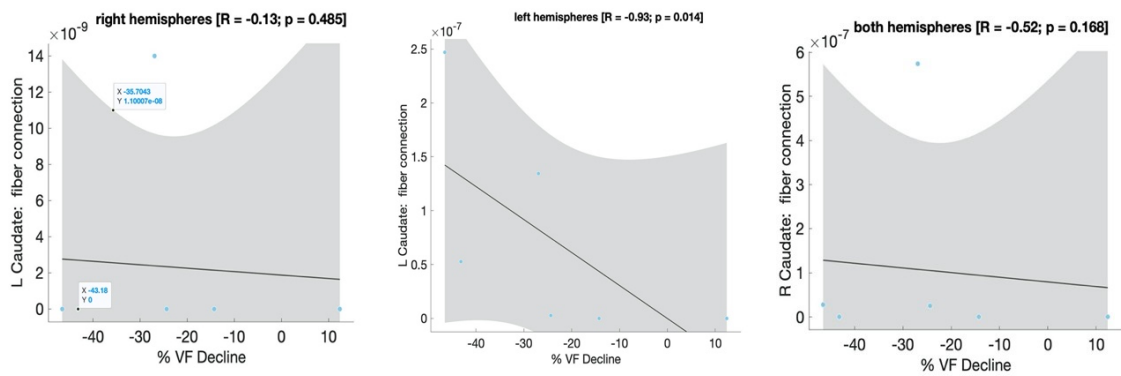


While the processing that takes place in Lead-DBS mainly serves to visually describe DBS effects about their anatomical sites of one patient, Lead-Group further provides specific statistical tests and ways to export metrics to run more elaborate statistical analyses between a participant group. For the purpose of this study, based on

the PPMI 85 connectome, fibers that were traversing through the VTAs of each patient were isolated and the ones terminating in each region defined by the HMAT and AAL3

**Figure 4**

Correlation of right and left hemisphere VTA intersected fiber counts and % change in VF for right and left caudate



parcellations were counted using Lead-Group. These several, primarily, cortical regions (Pre-SMA, SMA, Anterior Cingulate Gyrus, and Caudate Nucleus) were then correlated with the change in VF across the group. As can be seen in (figure 3), the greater the number of fibercounts connecting VTAs from both hemispheres to the R and L SMA & Pre-SMA is associated with larger VF decline ( $R > -0.89$ ,  $p < 0.02$ ). There were no connections to either the right or left anterior cingulate cortex in correlation to VF. Interestingly, the left caudate nucleus only showed fibers from the ipsilateral (left) hemisphere contributing to VF decline (L Caudate, L hemisphere:  $R = -0.93$ ,  $p = 0.01$ )

(L caudate, R hemisphere:  $R = -0.13$ ,  $p = 0.5$ ). There was no significant correlation found between either hemisphere's connection to the right caudate with VF declines ( $R = -0.52$ ,  $p = 0.1$ ). (Figure 4) shows the exact correlational curve for right and left caudate. (Table 5) shows all correlational, significance, fibercount, and VF values for each area and hemisphere.

**Table 5**

All correlational and p-values for each target area from each VTA hemisphere (R Hemisphere, L Hemisphere, Both hemispheres)

	VTA hemisphere		
	Both Hem.	R Hem.	L Hem.
L Caudate	Both Hem.	R Hem.	L Hem.
R	NOT SIG	-0.13	-0.93
p	NOT SIG	0.485	0.014
R Caudate	Both Hem.	R Hem.	L Hem.
R	-0.52	NOT SIG	NOT SIG
p	0.168	NOT SIG	NOT SIG
L Pre-SMA	Both Hem.	R Hem.	L Hem.
R	-0.94	-0.94	-0.94
p	0.009	0.008	0.011
R Pre-SMA	Both Hem.	R Hem.	L Hem.
R	-1.00	-1.00	-0.94
p	0.003	0.002	0.009
L SMA	Both Hem.	R Hem.	L Hem.
R	-0.89	-0.94	-0.89
p	0.016	0.004	0.014
R SMA	Both Hem.	R Hem.	L Hem.
R	-0.89	-0.93	-0.89
p	0.024	0.007	0.014

## DISCUSSION

The current study replicated previous findings regarding the deleterious effects that DBS has on category and letter verbal fluency (14,16, 22, 24, 44, 47-40, 50-52, 56-57). Like these prior studies, we discovered postoperative fluency declines in all fluency categories in PD patients, with some suggestion that STN VF declines may be more significant than GPi. Additionally, this study examined what VTA mediated cortical areas could be associated with global VF declines in DBS implanted PD patients.

### **Potential cortical mechanisms of VF decline**

Reductions in VF after DBS have been attributed to factors related to the surgical procedure (e.g. lesion effects) as well as to stimulation parameters [47, 74]. The aim of this study was to understand the role that clinically determined stimulation dependent VTA's have on their connected structures and ultimately VF declines following DBS implantation. Specifically, we investigated how the VTA created by the clinical stimulation settings modulates the white matter tracts to pre-SMA, SMA, anterior cingulate, and caudate that could potentially explain declines in VF. This study suggests that increasing activated white matter tracts leading to the left caudate nucleus (from the left hemisphere only), right and left pre-SMA and SMA (regardless of hemisphere of origin) relates to higher declines in VF.



The caudate nucleus is thought to be involved in various roles of higher neurological functioning. It functions not only in planning the execution of movement, but also in learning and memory [75]. Evidence suggests potential lateralized effects of DBS on axial motor symptoms as well as deleterious effects of left-sided DBS on language-related functions, specifically VF [76]. The declines we see associated with the left caudate nucleus from the left hemisphere DBS VTA, could be a potential explanation of the lateralized VF effects seen in PD DBS. Also, the VF declines seen generally related to the caudate could be explained due to the conceivable effects the DBS system could have on the executive functioning and memory retrieval tasks governed by the caudate.

VF declines related to the pre-supplementary motor area could be explained, similar to the caudate nucleus, by impacting the roles it has on executive functioning [77]. In addition, the frontal aslant tract, is a direct pathway connecting the Broca's area to the Pre-SMA [58]. Indirect influence on this tract via the DBS mediated VTA could potentially lead to the increases in VF decline seen here.

The SMA, specifically the medial portion, potentially has mechanisms for response sequence planning and response inhibition during VF performance. Effects of the DBS on this structure could potentially explain the VF declines seen as well. Future study could help to expand the current understandings of the role that these areas play in language. More specifically, by looking at the effects that DBS has on language subprocesses (word retrieval, generation and working memory) across the VTA based

cortical networks or through the experimental manipulations of the VTA (as associated circuits) to test the relative effect it may have on VF.

### **Limitations and future directions**

This study has several limitations and leaves room for further research and exploration. First, although we were able to explore the within-subject nature of the VF results, the small sample size (n=9) greatly limits the breath of our conclusions. The same conclusion holds true for the connectomics results as well. While we do find a statistically significant result of overarching verbal fluency decline and a greater trending VF decline in STN targeted patients, future studies with larger sample sizes are needed to confirm the robustness and strength of these relationships. A larger sample would provide not only a greater statistical power to investigate a combination of stimulation parameters in both DBS targets but would also allow the differentiation of target location between the connectomics. Also, employing actual DTI imaging, allowing for patient specific white matter analysis, instead of a generalized connectome, could provide more precise insight into the structures impacted by DBS induced VTA; this could be a direction for future study.

Second, this study is limited because it did not allow full experimental control over the variables, such as stimulation parameters and target location. A future prospective study with randomized DBS targets across patients, an equal number of

participants with STN and GPi targets and standardized stimulation parameters could overcome some of these issues.

In addition, we were not able to include the action fluency data alongside letter and category fluency in relation to the connectomics. This was due to the inconsistent nature of the preoperative neuropsychological testing completed at the inaugural start to the DBS program at UofL Health. The addition of action fluency to this data could provide further insight to differing mechanisms of VF aside from those that letter and category provide. In addition, the type of preoperative VF testing (COWAT vs DKEFS) in this case was inconsistent, leading to increased difficulties in a direct comparison of the two results. This again was due to the inconsistent nature of the preoperative testing conditions of each participant. A future study could correct for this using consistent preoperative testing measures for all patients, leading to a more direct comparison of VF results.

One other potential area of future study surrounding the indirect connectomic effects of DBS outside of VF could be its effects on motor outcome and ultimately be used to further optimize additional motor outcomes.

Furthermore, the participants in this study were in their optimal medication and stimulation state and did not include a post-op off stimulation/off medication state to dissociate potential lesion from stimulation effects. However, the growing body of research points to a stimulation induced cause of these cognitive decline (14-28). Also,

the lack of unilaterally implanted patients in this study did not allow us to separate the contribution of unilateral versus bilateral stimulation on VF changes.

## CONCLUSION

The current study shows a clear reduction in VF 6-months after surgical implantation of electrodes and shows a potential greater decline in VF with target areas of the STN over the GPi in patients with PD. Because of this stimulation there are other brain structures influenced, like the pre-SMA, SMA, and the caudate nucleus potentially causing the declines seen in VF. Clinically, including a fluency measure, in addition to motor function testing, during the process of defining and optimizing the DBS parameters during implantation could positively influence both motor and fluency outcomes

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