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Original Research

Stimulation region within the globus pallidus does not affect verbal fluency performance

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ABSTRACT

Background: Subthalamic (STN) and globus pallidus (GP) deep brain stimulation (DBS) have been previously shown to be efficacious in the treatment of selected Parkinson patients with medication resistant motor fluctuations and/or tremor. Deep brain stimulation of the STN has been implicated with more cognitive and mood side effects as compared to GP DBS; however, more studies are needed to better understand possible target differences. Previously, Mikos et al. [1] reported worsening of verbal fluency depending on the stimulation location within the STN region.
Objective/hypothesis: The current study applied the methods used by Mikos et al. (2011) to a different sample of Parkinson patients who underwent GP DBS. Based on differences in the size and functional somatotopy between structures (GP 412 mm^3 vs. STN 167 mm^3), we hypothesized that there would be a less robust relationship between volume of tissue activated, fluency performance, and stimulation contact within the GP compared to what was reported in the STN.
Methods: Patient-specific DBS models were created and the volume of tissue activated within the GP was calculated. These data were correlated with patients' verbal fluency performance at dorsal, optimal, and ventral stimulation contacts.
Results: In contrast to STN findings, there was no significant relationship between stimulation location and fluency performance in patients who received GP DBS.
Conclusion(s): These results suggest that fluency may be less sensitive to stimulation location in the globus pallidus and thus there may be more flexibility in terms of DBS programming with GP DBS patients.

Introduction

Deep brain stimulation (DBS) is an efficacious treatment for medication refractory Parkinson's disease [2]. It has the potential to improve the various motor symptoms associated with Parkinson's disease, including tremor, rigidity, bradykinesia, and motor fluctuations and dyskinesias. Typically, DBS does not have a large effect on improving non-motor symptoms, such as emotional and cognitive dysfunction and these symptoms may significantly interfere with patients' quality of life and level of disability [3,4]. In

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some cases, non-motor symptoms actually worsen following DBS surgery, with the most common neuropsychological side effect reported as a decline in verbal fluency, though others have been described [5–7].

Notably, there are many variables that might define individual outcome for DBS surgery, including disease duration, symptom profile, staged vs. simultaneous double lead implant surgery, and the final neuroanatomical location and stimulation field generated by programming [8]. Traditionally, DBS for Parkinson's disease has targeted either the globus pallidus (GP) region or the subthalamic nucleus (STN) region. Some studies have suggested that the STN target has better implications for motor outcome in Parkinson's disease, with reduced bradykinesia [9] and a greater reduction in levodopa dosage post-surgery [9–11]. However, other studies have revealed that GP DBS results in similar motor outcomes [11,12] and perhaps better outcome in some cases due to an improvement in axial motor symptoms compared to STN targeted surgery (Follett 9-10).

Furthermore, there is evidence to suggest that GP DBS surgery may have some advantages as compared to STN DBS. While DBS surgery in general has been linked to improved quality of life in Parkinson's disease patients, Rodrigues et al. [13] showed that GP DBS (a combination of unilateral and bilateral patients) resulted in significant improvements in QOL that extended beyond improvement in the motor domain and included emotional and cognitive improvement. Zahodne et al. [14] went beyond that shown by Rodrigues et al. [13] by comparing patients who received unilateral GP DBS to those who underwent unilateral STN DBS. She showed that those who underwent GP surgery endorsed significantly greater QOL improvements compared to those who underwent STN surgery [14]. The reasons underpinning the differential improvement in QOL is unclear, but may be linked to increased cognitive dysfunction experienced by STN patients, levodopa reduction, and the addition of a second DBS lead [8].

It has been suspected that STN DBS may have a higher risk of cognitive decline post-surgery than GP DBS. Interestingly, reports have shown that some specific cognitive functions such as response inhibition decline, whereas others, such as cognitive flexibility, can actually improve [15]. However, one of the most consistent reports of cognitive decline post STN DBS has been in the domain of verbal fluency, particularly if more of the target region is activated by programming [8,9,12]. While the exact mechanism of cognitive changes following DBS is unknown, it is hypothesized that differences in clinical outcomes between STN and GP targeted surgeries may be due to differential stimulation of overlapping motor, associative, and limbic territories between the two structures [1,16]. Also, activation of multiple contacts or increasing the stimulation field in STN DBS may have a more detrimental result as compared to GP.

Deep brain stimulation surgeries for Parkinson's disease target the somato-motor regions within the STN and GP, but these structures also have internal divisions that are important for cognitive and limbic functions [16]. Although it is difficult to actually observe nuclear divisions within these small structures via current imaging technologies (MRI, PET), studies that use calbindin immunoreactivity methods have been able to demonstrate separate functional areas within these regions (both the GP and STN) [17–19]. One theory asserts that cognitive and emotional side effects resulting from DBS surgery are a result of spread of the electrical current to other non-motor territories, and to white matter tracts within the target location. While both the GP and the STN have non-motor subregions, the GP structure has the potential for less risk of non-motor territories being affected by DBS implantation/stimulation mainly because of its larger size (for a review, see Ref. [14]). The size hypothesis however, remains to be substantiated.

The GP is a structure of approximately 412 mm^3, approximately two and half times the size in volume of the STN, which is about 167 mm^3. Most of the volume of the GP has been hypothesized to be comprised of a sensorimotor territory (53%), which is located in the postero-ventral portion of the GP structure. The associative and limbic areas of the GP are thought to be proportionally smaller (29% and 18%, respectively), and located in the antero-medial region [17–19].

Mikos et al. [1] recently investigated the hypothesis that the volume of tissue activated (VTA) within different regions of the STN would differentially affect verbal fluency performance due to spread of activation into cognitive subregions of the STN. They utilized computer models of patient-specific DBS lead locations and VTAs at each DBS lead contact (ventral, optimal, and dorsal contact locations.) While there was not a significant difference in overall verbal fluency performance between lead locations, patient-specific DBS models revealed a subtle relationship between the VTA and verbal fluency performance that differed by stimulation location. Specifically, at ventral contacts, more tissue activation inside the STN was associated with decreased letter fluency performance, consistent with the non-motor functional somatotopy of the STN [1].

The aim of the current study was to use the methods previously implemented by Mikos et al. [1] in the STN to investigate the relationship between the VTA and verbal fluency performance at different contact sites within the GP. Like the Mikos study, the current investigation utilized the available data derived from patients who underwent unilateral GP DBS surgery as part of the NIH COMPARE clinical trial [12]. It was hypothesized that stimulation at different contacts (ventral, optimal, dorsal) in the GP would result in less robust relationships between verbal fluency performance and VTA than that reported in the STN study [1], since the differences in local spread of stimulation at each contact should be relatively small with respect to the proportionally larger somatomotor territory of the GP. We hypothesized that this would leave cognitive and limbic subregions of the GP less affected by stimulation.

Methods

Participants

The present study drew GP DBS patients from the available data from the NIH COMPARE clinical trial which was conducted at the University of Florida [12]. The trial recruited 52 individuals with a diagnosis of idiopathic PD who were randomized to undergo GP DBS ($N = 26$) or STN DBS ($N = 26$) as well as 10 PD control participants who did not undergo surgery. Before DBS, all participants underwent an intensive baseline screening that included a diagnosis of PD by strict UK Brain Bank criteria [20], consultation with a neurology movement disorders specialist for medication optimization, consultation with a movement disorders neurosurgeon, a complete neuropsychological profile, and a psychiatry consultation. A detailed list of inclusion and exclusion criteria is provided by Mikos et al. [1].

Seven months after unilateral DBS implantation, patients underwent neuropsychological and motor testing. Testing for the study was performed under four conditions, including one "off" stimulation condition and three "on stimulation" conditions. The latter occurred at one of 3 contact points – at the *clinically defined optimal* contact and at contacts *dorsal* and *ventral* to the optimal site. Table 1 contains the defined optimal, ventral, and dorsal cathode contacts for each individual as well as his/her stimulation settings and percent change in UPDRS scores from pre-op (off medications) to post-op (on optimal stimulation). Testing was

Table 1
Optimal, ventral and dorsal contacts and stimulation settings for each patient.

Patient id	Optimal cathode	Ventral cathode	Dorsal cathode	Anode	optimal voltage	optimal pulse	optimal frequency	UPDRS percent change (pre-operative vs. optimal stim)
273	2	1	3	4	2.4	90	135	−50
393	1	0	2	4	2.9	90	160	27.5
421	2	1	3	4	2.8	60	160	53.8
442	2	1	3	4	2	90	135	12
538	1	0	2	4	3.6	60	170	36.7
553	1	0	2	4	2.9	90	185	54.2
722	2	1	3	4	2.5	90	135	46.2
786	2	1	3	4	2.8	60	145	47.5
930	1	0	2	4	3.1	90	135	−37.1
1086	2	1	3	4	2.3	90	135	28.9
1621	2	1	3	4	2.6	60	185	28.3
2109	1	0	2	4	3	60	185	41
2166	2	1	3	4	3.2	90	135	46.2
2412	2	1	3	4	3.5	90	135	6.7
2488	2	1	3	4	2.5	90	160	34.4

conducted off medications (withdrawn 12 h before testing). The order of the testing conditions was chosen by a computer-generated random sequence. Aside from the person performing DBS programing, all investigators were blind to the sequence of conditions. There was a standardized 10 min 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.

The present study analyzed each GP DBS patient who had all the necessary data for model creation and who also had agreement (less than 4 mm discrepancy) between the intended stereotactic DBS electrode implantation location and the actual location determined from postoperative CT. The agreement between the electrode location data was necessary for the modeling techniques employed by the Cicerone DBS software tool [21]. Patient demographic characteristics are summarized in Table 2. Details regarding imaging and the surgical procedures have been previously reported by Mikos et al. [1].

Verbal fluency tasks

Verbal fluency tasks consisted of *letter fluency* and *semantic fluency*. *Letter fluency* tasks required participants to rapidly produce words beginning with a particular letter of the alphabet, excluding proper nouns and the same word with a different suffix [22]. The test allowed 60 s to generate words beginning with the target letter. *Semantic fluency* tasks require participants 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 for the four stimulation testing conditions was randomized, and the alternate forms were counterbalanced across the testing conditions.

Table 2
Demographic and disease characteristics of the study participants. Means (± standard deviation) are shown.

	GP DBS
Age	58 (5.04)
Gender (% male)	67%
Disease duration (years)	11.93 (4.28)
Hoehn and Yahr “off” stage (percent)	2: 21% 2.5: 0% 3: 79% 4: 0% 5: 0%
Mean LED before surgery	1111.65 (594.29)
Preoperative “on” UPDRS III score	19.13 (5.50)
Preoperative “off” UPDRS III score	39.00 (8.23)
Mini-mental state exam (max: 30)	28.53 (1.46)
Dementia rating scale (max: 144)	139.33 (3.64)
Beck depression inventory (max: 63)	12.27 (8.26)
Verbal fluency task scores (raw)	
Letter (pre-surgery)	40.5 (11.3)
(post-surgery, off-stimulation)	37.9 (11.4)
Semantic (pre-surgery)	19.3 (4.4)
(post-surgery, off-stimulation)	19.4 (5.3)

LED—levodopa equivalent dosage.

Patient-specific DBS models

Each patient-specific DBS model was generated with a modified version of Human Cicerone v1.3 that accounted for the CRW frame system [21]. An example of a patient-specific GP DBS model is shown in Fig. 1A and B. Each patient-specific DBS model included co-registration 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). These methods were employed for each clinically evaluated stimulation parameter setting. Creation of each patient-specific DBS model followed a procedure that was described previously in detail in the Mikos [1] report.

Ultimately, each of these models produced estimations of the volume of tissue activated (VTA) at each stimulation contact (optimal, ventral, and dorsal), inside and outside of the GP (Fig. 1D.) Because there was some variation in total volumes of the GP between patients, and because the brain atlas was scaled to fit the nuances of each patient, we calculated the VTA as a proportion of the total GP volume (i.e., proportion of VTA overlap with the GP, PVO—GP), consistent with the methods of Mikos et al. [1].

Results

Patient-specific DBS models were created and analyzed for 14 of the 22 GP DBS patients in the COMPARE trial [11]. Five patients were excluded because of technical issues in fusion of scans that failed to meet the strict standardized methods. Three patients were excluded due to misalignment of AC-PC coordinates with follow-up CT image, and these patients also did not meet strict standardization of the methods required for field modeling. There was no difference in clinical outcome of DBS surgery between those included and excluded in the analysis. Both groups showed a mean improvement of approximately 25% improvement in UPDRS

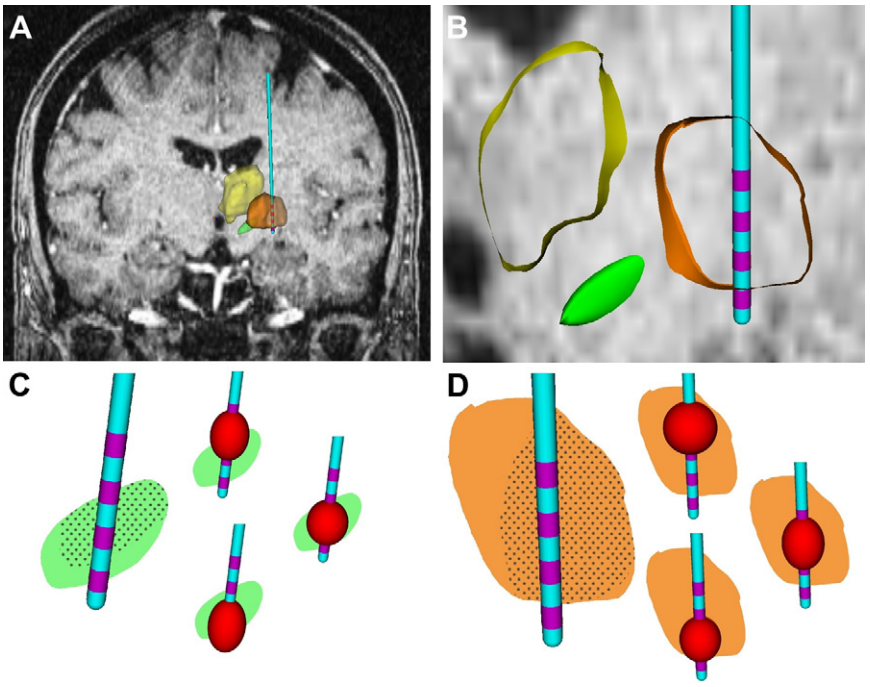

Figure 1. Patient-specific DBS model. All images display a coronal view of the left brain. A) Each patient model was developed from MRI and brain atlas data (yellow volume – thalamus; orange volume – GP; green volume – STN). B) clipped atlas volume in the plane of the GP DBS electrode. C) Example STN DBS patient from Mikos et al. (2011). Estimated sensorimotor region of the STN marked by stipple pattern, derived from Parent and Hazrati (1995). Dorsal, optimal, and ventral stimulation volumes tested in the patient are shown in red. D) Example GP DBS patient. Estimated sensorimotor region of the GP marked by stipple pattern, derived from Francois et al. (1994). Dorsal, optimal, and ventral stimulation volumes tested in the patient are shown in red. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

ratings. Six of the 14 patients underwent left GP DBS and 8 underwent right GP 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 the OFF stimulation condition. 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 (OFF stimulation) differences in verbal fluency performance. Mean standardized residual change scores for each of the stimulation conditions are displayed in Table 3. Non-parametric statistical tests were performed when the dependent variables were not normally distributed, as was the case for the standardized residual change scores and VTA indices. A Wilcoxon signed rank test showed that there was not a significant decline in verbal or semantic fluency from pre-surgery to post-surgery (off-stimulation) ($P > .26$). A Friedman's test revealed that there were no differences in verbal fluency performance among the three electrode contacts [letter fluency: $\chi^2[2] = 1.86$, $P = .40$; semantic fluency: $\chi^2[2] = 1$, $P = .61$]. Additionally, verbal fluency performance did not differ by side of DBS surgery (right vs. left.)

Mean values for patient-specific DBS modeling indices at each of the three contacts are shown in Table 4. Spearman's correlations were conducted to examine the relationship between verbal fluency performance and the modeling indices. Correlation coefficients are shown in Table 5. There were no significant relationships between magnitude and location of VTA and fluency performance relative to OFF stimulation, demonstrated in Figure 2.

Discussion

Analysis of verbal fluency performance of fourteen GP DBS patients tested on three stimulation settings (ventral, optimal, and dorsal) revealed no significant difference in letter or semantic fluency performance relative to off-stimulation settings, indicating that stimulation neither significantly improved nor hindered fluency performance post-GP DBS. Furthermore, there was no significant relationship between the volume of tissue activated within the GP and verbal fluency performance, regardless of the specific contact location on the GP DBS lead. This finding differs from that reported by Mikos et al. [1] who used only STN DBS patients from the same NIH COMPARE cohort. In a similar sized cohort ($N = 17$), Mikos showed a negative association between

Table 3
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	.09 (1.00)	.00 (.96)	−.01 (1.0)
Semantic fluency	−.05 (.98)	.00 (.96)	.12 (.90)

Table 4
Mean (standard deviation) values for volume of tissue activated (VTA) variables (mm^3).

	VTA in the GP	VTA outside GP	Total GP	PVO–GP
Dorsal ($N = 15$)	81.67 (23.64)	18.28 (29.36)	99.95 (20.36)	.05 (.01)
Optimal ($N = 15$)	70.89 (12.19)	6.32 (11.29)	77.21 (16.75)	.04 (.01)
Ventral ($N = 15$)	56.18 (22.08)	17.84 (19.97)	74.04 (27.86)	.03 (.01)

Table 5
Spearman's ρ correlation coefficients for the relationship of verbal fluency performance with stimulation at different contacts to patient-specific modeling indices.

	VTA inside GP	VTA outside GP	Total GP	PVO−GP
Letter fluency standardized residual change				
Dorsal ($N = 14$)	.28	−.19	.08	.11
Optimal ($N = 15$)	.19	.02	.00	.17
Ventral ($N = 15$)	−.38	.27	−.02	.27
Category fluency standardized residual change				
Dorsal ($N = 14$)	.03	.09	−.13	.22
Optimal ($N = 15$)	.22	−.11	.03	.02
Ventral ($N = 15$)	−.10	−.05	−.29	−.03

ventral STN stimulation and fluency performance. There was less of a negative influence of stimulation on fluency performance at optimal contacts. Target specific differences in STN vs. GP DBS could be important when tailoring a specific approach for an individual patient [8], especially in patients with known pre-DBS cognitive dysfunction.

The relative absence of relationship between the volume of tissue activated and fluency performance as assessed by contact location in the GP, unlike what was observed in the STN data, is likely related to the differential volumetric and somatotopic differences in properties of the two structures, though more data will be needed to confirm this hypothesis. Fig. 1C and D display examples of patient-specific VTA's within the STN (Fig. 1C) and the GP (Fig. 1D) and the relevant sensorimotor territory within the two structures. Mikos et al. [1] hypothesized and demonstrated a differential relationship between VTA and fluency at ventral, optimal, and dorsal contacts due to the functional somatotopy of the STN, which is comprised by a dorsolateral sensorimotor area, a central associative territory, and a small medial limbic area. These areas have been roughly divided into thirds of the total STN volume [23,24]. It is therefore relatively easy when applying STN DBS to spread current into non-motor regions.

The GP, however, is a much larger structure, approximately two and a half times the size of the STN [14], whose somato-motor territory (the target location of DBS surgery) occupies approximately 53% of its volume [17–19]. Thus, it is reasonable that small changes in contact locations on the DBS lead would result in minimal changes in fluency performance and that the resultant VTA would be minimally associated with fluency performance. The major reason for the lack of change in GP DBS is likely because the active stimulation contact remains largely within the desired somato-motor territory of the GP, leaving associative and limbic territories relatively unhindered. The size hypothesis however was not specifically tested by this study.

The data from this study, when combined with the Mikos work, has important clinical implications. It represents evidence that GP surgery (and stimulation) may impose less risk with respect to verbal fluency functioning, which could be an important pre-surgery consideration in cognitively at-risk patients. While cognitive deficits following STN DBS are subtle and do not necessarily interfere with activities of daily living [25], relatives of patients with STN surgery report a considerable increase in cognitive complaints [26] and GP patients report greater increases in QOL than STN patients [14].

The GP target is larger and predominantly comprised of a somato-motor territory, making it easier to stimulate without affecting other non-motor regions. Also, the clinician who programs the DBS stimulator post-surgery should have less worry about spreading the current, and using multiple contacts if necessary to enhance the individual patient outcome. The current data would suggest that post-GP DBS, a clinician programmer can shift to ventral or dorsal contact settings without affecting verbal fluency, and this may be different than the STN target.

Limitations

As is the case in many DBS studies, the current data is based on a relatively small sample size of 14 GP patients. Thus, null findings could be due to a lack of power. However, it is worth noting that this sample is comparable to the sample size of 17 analyzed in the study which employed the same methods in STN patients by Mikos et al. [1] which found a significant relationship between VTA and fluency performance which differed by DBS contact.

Eight patients were excluded due either an inadequate imaging fit or misalignment of AC and PC points that made field modeling impossible by strict criteria. The reason for these discrepancies is unclear and could have related to brain shift or lead migration, and also because we analyzed the data post-hoc from an existing data set that was not originally designed to be modeled. Additionally, while the Cicerone software represents a validated method for patient specific DBS lead location and stimulation spread analysis, it involves the co-registration and fusion of multiple images, including pre and post-operation CT scans, MRI images, and a 3D brain atlas. This process is complex and can introduce multiple sources of small error and we had to counteract the error by exclusion of patients with alignment discrepancies and intense visual inspection during each step of the modeling procedure. Future studies could be better designed to check alignments at the

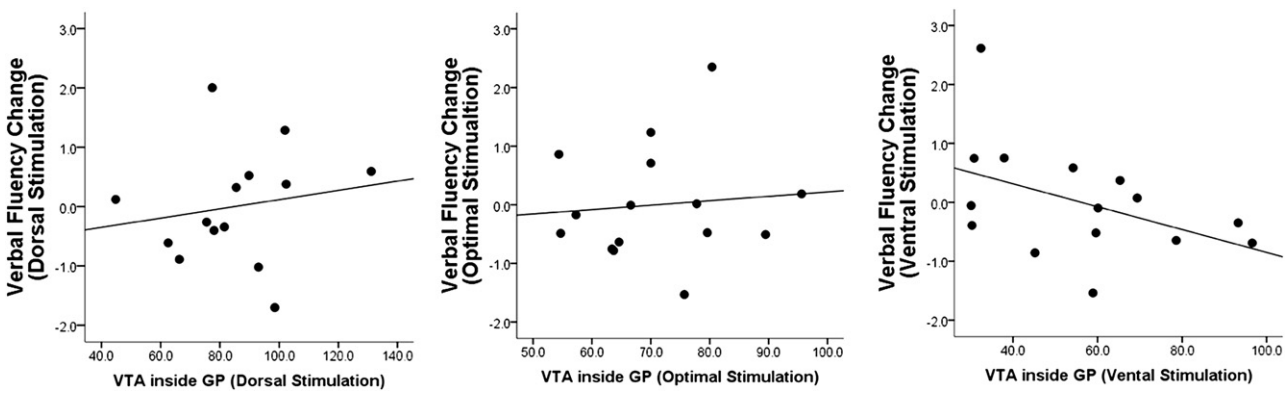

Figure 2. Scatter plots of VTA magnitude inside GP and verbal fluency change scores relative to OFF stimulation at dorsal, optimal and ventral contacts. The relationship between VTA and fluency performance did not differ by contact.

time of imaging to ensure a more complete data set. A more detailed description of other potential limitations related to this technology was previously provided by Mikos et al. [1].

Summary and conclusion

The current study employed methods used in a prior study of STN DBS patients and revealed no significant relationship between the GP volume of tissue activated and fluency performance, regardless of the DBS contact that was activated. This study adds important evidence to the literature that GP may impose less risk from cognitive standpoint, and that post-DBS there may be more flexibility in choosing settings to optimize DBS programming. Insights from this study and from other future studies should provide more information to facilitate patient-tailored decisions concerning DBS targets. These decisions should be based on the patient's disease profile and consider both motor and cognitive factors [8].

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