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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