Advancing Pre-operative Targeting for Deep Brain Stimulation in the Globus Pallidus Internus: Functional Segmentation Based on Probabilistic Tractography

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Title of the study: Advancing Pre-operative Targeting for Deep Brain Stimulation in the Globus Pallidus Internus: Functional Segmentation Based on Probabilistic Tractography
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Funding Requested: Requested funding includes the costs for 2 MRI sessions per subject (20 total MRI sessions), subject compensation for time, and personnel effort costs. The remainder of data collection is performed as routine clinical care.

Abstract

DESCRIPTION: Parkinson's disease (PD) is a common neurologic condition affecting more than one million Americans alone with an estimated cost of $25 billion per year in the United States. Deep brain stimulator (DBS) has become the surgical treatment of choice. One such target for DBS is the globus pallidus internus (GPi). Current methods of DBS targeting pre-operatively rely on stereotactic methods that are based on standardized estimates of GPi structural anatomy. These methods fail to account for inter-individual anatomic variations in the functional anatomy.

The aim of the current study is the development of a novel imaging technique for segmenting the functional subdivisions of the GPi to provide a more precise pre-operative target for DBS placement. Rather than relying on standardized atlas-based targets, robust 3T MRI diffusion imaging will be obtained to provide a patient-specific functional target that would ideally outperform current methods leading to improved outcomes, fewer adverse effects, and decreased operating room times.

In the proposed pilot project, MRI data will be prospectively collected to show the feasibility of the segmentation algorithm and the potential relation to final lead positioning. Patients will be selected from those undergoing GPi DBS placement. This pilot data will serve as a basis for pursuing funding for a larger trial evaluating the prospective ability of the 3T targeting study to improve outcomes and decrease complications in GPi DBS placement. Improved outcomes and patient experience would be expected to further contribute to our facility as a center of excellence for treatment of movement disorders.

Research Plan

I. Specific Aims

The overall goal of this project is to provide feasibility data for a novel method of defining patient-specific functional anatomic targets for GPi DBS placement.

Aim 1. To evaluate the feasibility of a novel, clinically applicable 3 Tesla (3T) MRI protocol for functional segmentation of the GPi based on connectivity measures derived from MRI diffusion-weighted imaging.

a) Assess the ability of spatially localizing the motor functional representation within the GPi in individual subjects with a clinically feasible imaging protocol using widely available 3T MRI.

Aim 2. To determine the variation in degree of overlap between the traditional atlas-based target point and the derived MRI functional segments on pre-operative imaging

a) To better understand the relationship of the traditional target point and the functional segments, we will compare the degree of overlap. We hypothesize that the traditional target point will show variation between subjects in the degree of overlap with each functional segment suggesting inadequacy of structural targeting methods that are based on generalizations rather than patient-specific functional targets

Aim 3. To compile preliminary evidence for the role of a patient-specific, functional-based targeting protocol to replace potentially inaccurate atlas-based methods in treating Parkinson's disease that can be implemented on commonly available 3T MRI scanners

a) Based on the stimulation parameters used to achieve a satisfactory treatment response, a model of the volume of activated tissue will be generated. The degree of overlap between this volume of tissue will be assessed on both the pre-operative functional target and the original atlas-based target. We hypothesize that the volume of activated tissue will closely overlap with the functional segment most connected to the motor and pre-motor cortex.

b) Current data will be the basis for pursuing additional funding for implementing the 3T protocol in a larger patient cohort to further explore the potential role in treatment targeting

c) Eventual long-term goal will be acquisition of external funding for a clinical trial using the targeting sequence prospectively to assess the overall goal of this investigation: improving success rate and decreasing complication rate by addition of patient-specific functional targeting of the GPi.

II. Background and Significance

Parkinson's disease (PD) is a common, debilitating neurologic disease. Over one million people suffer from PD in the United States alone. Deep brain stimulation (DBS) has been shown to be an effective treatment option. One of the most frequent targets for DBS in PD is the globus pallidus internus (GPi).

One limitation of surgical (e.g., DBS) treatment for PD is the inability to identify functional brain targets pre-operatively. Current methods rely on atlas-based approaches or coordinate-based stereotaxy where a specific coordinate, based on larger landmarks, is presumed to be the approximate location of the targeted functional region in all patients. These targeting methods rely on standardized coordinates that do not account for known inter-individual variations in functional anatomy. In fact, it has been previously reported that 46% of patients

with poor response to DBS therapy have malpositioned DBS leads.[2] There is also disagreement in the choice of ideal atlas-based coordinates. Perhaps most concerning regarding all methods of structural localization is the assumption that brain function is predictable by brain structure. The validity of such assumption is questionable as it has been shown that brain functional localization may vary significantly from predictions based solely on structure. It is now well-known that pathologic changes in the brain can result in variations in the relationship of structure and function due to neural plasticity.

The idea of brain connectomics is a rapidly developing field of neuroscience. The ability to examine in vivo human brain functional connectivity has revealed new insight into many neurologic and neuropsychological conditions. To date, the clinical impact of connectomics has been limited. The origin of the current proposal was the belief that this emerging technology could be applied to a very specific problem in clinical medicine not well-addressed by current techniques. As such, this project would ideally serve as a model and further proof that such science can be currently translated into clinical medicine.

Only one prior study has attempted to provide GPi segmentation based on structural connectivity in normal subjects.[3] The authors found inconsistent results with the segmentation scheme. We believe our design to have advantages over this prior study for two primary reasons: (1) differences in the MRI data acquisition and (2) our selection of target regions for the segmentation. In contrast to this prior study, we have focused our target regions to better fit with the expected connectivity profile of the GPi based on known histologic data.

If the aims of this pilot are achieved, we will have sufficient evidence to show the feasibility of a clinically applicable MRI protocol for reliably localizing the patient-specific functional target within the GPi, rather than solely from a structural standpoint. By modifying inaccurate atlas-based methods, we hope to improve the accuracy of localization of the specific functional region of the GPi for treatment of PD that would be personalized to each individual patient.

Our long-term goals are to evaluate patient outcomes relative to our targeting methodology and subsequently pursue prospective clinical trials with the hypothesis that our connectivity-based targeting method increases success rates and decreases complications compared with traditional atlas-based methods. If our pilot is successful, we aim to pursue extramural funding for validation of the methodology in pre-operative targeting.

III. Progress Report and Preliminary Studies

The strategies utilized in the proposed project are similar to segmentation strategies previously applied to the human thalamus.[4] In previous work, we also have shown that the thalamus can be segmented based on probabilistic tractography measures to pre-defined cortical regions of interest. We have also illustrated that significant variation exists with regards to the functional localization of current atlas-based stereotactic targets within the thalamus (Figure 1). This work has yielded an accepted abstract at a national meeting and manuscript currently under review. The basic methodology utilized in prior work will be applied to the current project. Necessary modifications include re-defining the connectivity targets.

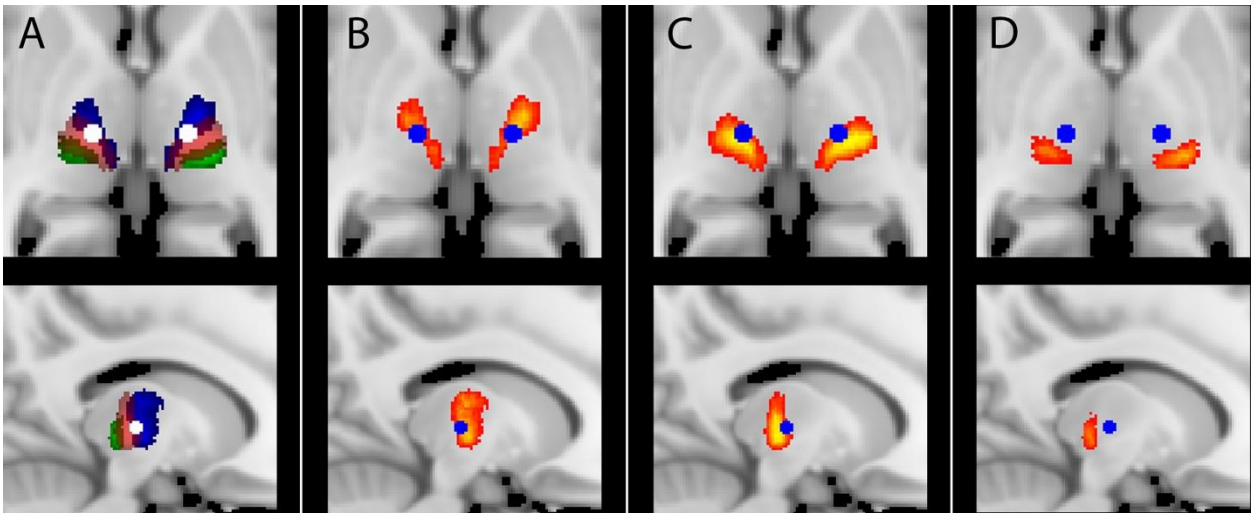

Figure 1. Axial (top) and sagittal (bottom) images of (A) the areas most connected to the supplementary motor area/premotor cortex (blue), primary motor cortex (red), and primary sensory cortex (green) compared to the coordinate-based ventral intermediate thalamic nucleus (Vim) deep brain stimulator target (white circle). Statistical heat maps for probability of connectivity to (B) supplementary motor area/premotor cortex, (C) primary motor cortex, and (D) primary sensory cortex relative to the coordinate-based Vim deep brain stimulator target (blue circle). (Heat map thresholds are 5-100%)

In addition, we have analyzed a small cohort of patients with GPi placement retrospectively (Figure 2). Unfortunately, the existing data is of insufficient quality to achieve the goals of the current project; however, this data does establish some feasibility of the proposed pilot.

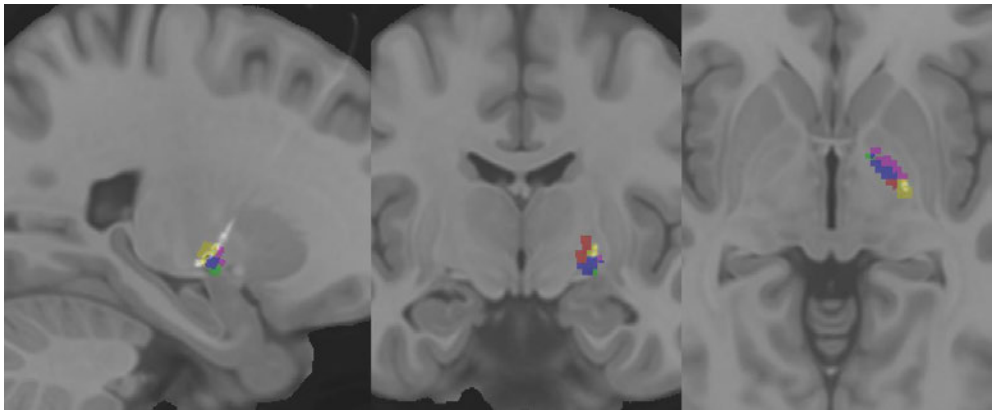

Figure 2. Sagittal, coronal, and axial images show segmentation of the globus pallidus internus. The DBS lead is positioned within the segment most connected to the primary motor cortex (yellow).

A foundation of success in the proposed project is the acquisition of high-quality data, as well as utilization of pre-processing and processing methodology that maximizes connectivity measures. I have gained significant experience in many of these methodologies, such as multiband EPI and connectivity analysis, as a co-investigator and the head of data quality and

acquisition in a grant utilizing the Human Connectome Project protocol (Human Connectome Project - Connectomes Related to Human Disease: Changes in Visual Cortical Connectivity Following Central Visual Field Loss. Project Number: U01-EY025858-01A1. PI: Kristina Visscher, Ph.D.).

Experience with the translation of advanced neuroimaging techniques to neurosurgical intervention is also beneficial to the proposed project. An understanding and appreciation of the limitations of various neuroimaging procedures in the clinical setting is essential for future adaptation to surgical guidance. In addition to my experience in clinical functional neuroimaging, I have authored or co-authored multiple papers in neurosurgical application of advanced neuroimaging techniques, including diffusion MRI.[5-10]

IV. Research Design and Methods

a. Study Design or Overview –Patients selected to undergo GPi DBS placement will be eligible for enrollment in the study. In addition to standard-of-care tests, subjects will undergo an MRI consisting of the proposed novel imaging protocol prior to placement of DBS. The patient will subsequently undergo standard-of-care therapy for DBS placement. Once the stimulator has been programmed post-operatively, the stimulation parameters and corresponding clinical changes will be collected and used to model the volume of activated tissue. The patient will additionally undergo a follow-up MRI used to localize the electrode within the brain to further localize the volume of activated tissue.

b. Study Subjects - Patients presenting to Mayo Clinic Neurosurgery identified to undergo deep brain stimulator placement in the GPi will be identified as potential subjects. Exclusion criteria for the proposed study would be any patient with contraindication to 3 Tesla MRI.

c. Sample Size – Due to the lack of any adequate preliminary studies, a sample size is estimated without statistical basis. A sample size of ten was chosen based on expected recruitment possibilities and sufficient size to prove feasibility and estimate power size for subsequent studies.

d. Data Collection –
Pre-Operative: Relevant clinical information will be collected including demographic data (age, gender), duration of Parkinson's disease, medication history, and a Unified Parkinson Disease Rating Scale (UPDRS) score. Pre-operative MRI will consist of a robust, multi-shell diffusion sequence at high resolution (1.5 x 1.5 x 1.5 mm voxel; b =1000, 2000; 64-directions, AP and PA phase encoding). Additional routine structural imaging consisting of T1-weighted MP-RAGE and FGATIR will also be obtained for purposes of identifying targets for segmentation.
Post-Operative: Clinical data will consist of post-treatment UPDRS score, complications related to DBS placement (e.g. infection, hemorrhage), and the stimulation parameters (voltage and contacts used) from the DBS programming to go with the tremor scoring. Stimulation parameters will also be recorded for any DBS programming that resulted in adverse effects, as well as the effect elicited. The patient will undergo an additional post-operative MRI using a T1 MP-RAGE sequence for purposes of localizing the final lead position.

e. Data Handling - All data will be collected in an anonymized fashion with unique coded identifiers for each subject. The identifier linking to the patient will be stored in a separate password-protected spreadsheet for purposes of collecting data at each of the timepoints in the study.

Clinical data will be tabulated within an Excel spreadsheet that is also password protected and recorded by anonymized ID. The imaging data will be downloaded from the MRI scanner on an encrypted drive and transferred to a password-protected and encrypted Mayo Clinic computer only accessible to the PI. Imaging data will be collected and stored without patient identifiers, only by unique study ID. Processing of the imaging data will be performed and saved on the computer.

f. Data Analysis - MP-RAGE structural scans will be coregistered to the diffusion data and automatically segmented into regions of interest using FreeSurfer software. Regions of interest will consist of: (1) prefrontal cortex, (2) supplementary motor area, (3) premotor cortex, (4) primary motor cortex, (5) putamen, (6) caudate, (7) thalamus, (8) globus pallidus externus, (9) pedunculopontine nucleus, and (10) subthalamic nucleus.

The diffusion data will be used to determine voxel-wise diffusion parameters using a Markov Chain Monte Carlo sampling in the FMRIB Software Library (FSL) "bedpostx" function. A multi-fiber approach (2 fiber orientations) using a multi-shell model will be used. To perform GPi segmentation based on structural connectivity, we will utilize a probabilistic tractography method by way of FSL's "probtrackx" to calculate probability of connection of each GPi voxel to the predefined volumes of interest (above). Each GPi voxel will then be assigned to the one target with the greatest number of propagated paths by using FSL's "find_the_biggest" function.

Using the MP-RAGE and FGATIR MRI data, the target point for DBS placement will be determined using current standard of care. The amount of overlap between this target and each of the GPi functional segments will be calculated.

The postoperative MRI scan will be coregistered to the pre-operative scans. The final location of the DBS lead will be calculated using LEAD-DBS software. Based on the stimulation parameters, the volume of activated tissue will be calculated with respect to lead localization. The amount of overlap between the volume of activated tissue (VAT) and each GPi segment will be calculated. Linear regression analysis will be performed to determine the degree of improvement in tremor score and degree of overlap between the VAT and each GPi segment. We hypothesize greater overlap between the VAT and GPi segment maximally connected to the primary motor cortex will result in a greater improvement in clinical improvement.

g. Feasibility and Time Frame – The expected timecourse for the study is one year. We would anticipate ~25 patients per year to be potential subjects based on historical figures of number of GPi DBS placements done at Mayo Clinic Florida. The timetable for each individual subject should be <6 weeks. Processing time for each subject is expected to be ~1 week. Since the study is incorporated into current standard-of-care clinical workflow (e.g.

imaging prior to surgery and followup imaging at time of return clinical visit), we anticipate high subject retention.

h. Strengths – The strength of the study lies in the robust diffusion sequence obtained by way of the recently released "multiband" diffusion MRI sequence. This allows a substantial improvement in resolution and data quality compared to traditional methods. Additionally, the prospective nature allows us to collect not only optimal therapeutic DBS stimulation parameters, but also those which produce unintended side effects. By capturing this additional data, it will help us to shed light on the cause of these unintended effects and potentially improve the pre-operative functional targeting. Lastly, the significant experience of the investigators in functional neuroimaging and deep brain stimulation is a significant benefit in preparing the study design and interpreting the data.

i. Limitation – One potential limitation lies in the study size. Since this is intended as a feasibility study, it may be expected that our results will not meet a statistical significance. Additionally, given the relatively low treatment failure rate for GPi DBS, we would expect few, if any, would have significantly poor outcomes which may limit our determination of the factors that produce such unfavorable results. Additionally, the lack of long-term followup limits our ability to identify patients with more long-term failures. This would be one goal of a follow-up study of larger scale.

V. Human Subjects

Detailed Description: Human subjects will be enrolled in the proposed study under the described inclusion and exclusion criterion. Maximal efforts will be used to minimize risk of exposure of PHI. The primary identifier recorded will be the patient medical record number. This data will be maintained in a secured location and key coded to the remaining data, which will be stored anonymously by coded subject ID. The study poses minimal risk to human subjects.

Population: The patient population consists of patients diagnosed with Parkinson's disease who are candidates for GPi deep brain stimulation. We anticipate 10 subjects total. No subjects will be included nor excluded based on any demographic data; however, we anticipate the population to be of older age by nature of the typical age of Parkinson's disease patients.

Research Materials: Research materials consist of routine clinical data that will be additionally recorded for research purposes. Data will also consist of MRI scans that will be obtained specifically for the purposes of this study.

Recruitment of Subjects: Subjects will be recruited from the Mayo Clinic Florida movement disorders clinic. Once patients have been identified as candidates for GPi DBS, they will be consented for enrollment in the study. Patients will be identified, recruited, and consented by Dr. Uitti in the Neurology clinic at the time of their consultation. The information provided to the subject will be a summary of the additional MRI scans to be performed as part of the study and their consent to collect relevant clinical information described. They will be advised that participation in the study is voluntary and will not affect

their clinical care. They will also be advised that participating in the study will provide no direct clinical benefits to them. Consent will be obtained as written and verbal consent with the patient. Ten subjects will be recruited.

Potential Risks: This study poses minimal risk to included subjects. The only test/procedure administered that is part of the study and not standard clinical care will be the acquisition of two routine MRI scans. Standard MRI screening precautions will be used to determine patient safety for the MRI environment. Any patients not meeting these standard guidelines will be excluded from the study.

Protection: The primary risk posed to subjects is the risk of MRI. Standard MRI precautions will be exercised to screen patients for any contraindication to MRI. Patients with any safety concerns will be excluded from the study.

Benefits: Subjects will not receive any direct benefit from participation in the study. The data acquired for the purposes of this study will not be used in their clinical decision-making. The benefits gained by the knowledge from our study have the potential of improving current targeting methods for deep brain stimulation and may improve patient outcomes, decrease complication rates, and decrease operating room time.

VI. Gender/Minority Mix

Patients of all demographics will be eligible for the study. No inclusionary or exclusionary criteria will be based on any demographic information.

VII. References:

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Study Activity	Wk 0	Wk 1	Wk 2	Wk 3	Wk 4	Mo 3	Mo 4-6	Yr 1	Off Study[c]
Informed consent	X								
History*	X					X			

Urine Pregnancy Test (SOC)			X			X			
Pre-Operative Brain MRI			X						
Surgery for DBS Placement			X						
Quality of Life Assessment	X					X		X	
Post-Operative MRI/CT						X			
DBS Programming Visit**						X	X (Optional)		
Adverse event evaluation	X								
* Age, Gender, Handedness, Medications, Disease Duration ** All programming settings will be collected throughout the duration of the study, including intra-operative and peri-operative programming/testing									