Clinically applicable delineation of the pallidal sensorimotor region in patients with advanced Parkinson's disease: study of probabilistic and deterministic tractography

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OBJECTIVE Deep brain stimulation (DBS) is an effective procedure in improving motor symptoms for patients with advanced Parkinson's disease (PD) through the use of high-frequency stimulation. Although one of the most commonly used target sites for DBS, sensorimotor regions of the globus pallidus interna (GPi) have yet to be thoroughly described with advanced neuroimaging analysis in vivo for human subjects. Furthermore, many imaging studies to date have been performed in a research setting and bring into question the feasibility of their applications in a clinical setting, such as for surgical planning. This study compares two different tractography methods applied to clinically feasible acquisition sequences in identifying sensorimotor regions of the GPi and the subthalamic nucleus (STN) in patients with advanced PD selected to undergo DBS.

METHODS Seven patients with refractory PD selected for DBS were examined by MRI. Diffusion images were acquired with an average acquisition time of 15 minutes. Probabilistic and deterministic tractography methods were applied to each diffusion-weighted data set using FSL and MRtrix, respectively. Fiber assignment was performed using combined sensorimotor areas as initiation seeds and the STN and GPi, separately, as inclusion masks. Corticospinal tracts were excluded by setting the cerebral peduncles as exclusion masks. Variability between proposed techniques was shown using center of gravity (CoG) coordinates.

RESULTS Deterministic and probabilistic corticopallidal and corticosubthalamic pathways were successfully reconstructed for all subjects across all target sites (bilaterally). Both techniques displayed large connections between the sensorimotor cortex with the posterolateral aspect of the ipsilateral GPi and the posterolateral aspect of the ipsilateral STN. The average variability was 2.67 mm, with the probabilistic method identifying the CoG consistently more posterior and more lateral than the deterministic method.

CONCLUSIONS Successful delineation of the sensorimotor regions in both the GPi and STN is achievable within a clinically reasonable timeframe. The techniques described in this paper may enhance presurgical planning with increased accuracy and improvement of patient outcomes in patients undergoing DBS. The variability found between tracking techniques warrants the use of the probabilistic tractography method over the deterministic method for presurgical planning. Probabilistic tractography was found to have an advantage over deterministic tractography in its sensitivity, in accurately describing previously described tracts, and in its ability to detect a larger number of fibers.

<https://thejns.org/doi/abs/10.3171/2018.7.JNS18541>

KEYWORDS diffusion-weighted imaging; deep brain stimulation; sensorimotor regions of the globus pallidus interna; probabilistic tractography; fronto-striato-subthalamic-pallidal network; functional neurosurgery

ABBREVIATIONS CoG = center of gravity; CSD = constrained spherical deconvolution; DBS = deep brain stimulation; DTI = diffusion tensor imaging; FDT = FMRIB Diffusion Toolbox; FMRIB = Functional Magnetic Resonance Imaging of the Brain; FOD = fiber orientation distribution; GPi = globus pallidus interna; GPU = graphics processing unit; MPAGE = magnetization-prepared rapid acquisition gradient echo; PD = Parkinson's disease; ROI = region of interest; STN = subthalamic nucleus; UPDRS = Unified Parkinson's Disease Rating Scale.

SUBMITTED February 23, 2018. **ACCEPTED** July 16, 2018.

INCLUDE WHEN CITING Published online December 14, 2018; DOI: 10.3171/2018.7.JNS18541.

DEEP brain stimulation (DBS) involves the implantation of electrodes that apply high-frequency electrical stimulation to targeted subcortical structures. Over the past 2 decades, DBS has been a well-established treatment option for patients suffering from movement disorders.¹⁶ Stimulation of the subthalamic nucleus (STN) or globus pallidus pars interna (GPi) has provided significant improvement in motor function in patients with Parkinson's disease (PD) by reducing dyskinesia and motor fluctuations in tremor, rigidity, and bradykinesia.^{9,23}

Follett et al. compared 24-month outcomes for patients who had undergone bilateral stimulation of the GPi and STN and found that patients with PD had similar improvements in motor function after either pallidal or subthalamic stimulation.¹⁴ Stimulation of the GPi has been found to reduce medication side effects, leading to better drug tolerance.²⁴ Furthermore, available data comparing cognitive performances following DBS suggest that risk of cognitive decline is lower in GPi DBS when compared to STN.^{17,27,29} Despite the lack of evidence that neurostimulation of the STN provides better outcomes,⁸ this nucleus is more commonly targeted for DBS.^{14,41} Imaging research has followed suit, with the majority of the literature published focusing on the connections involving the STN.²² Patriat et al. were able to parcellate the functional territories of the GPi into motor, associative, and limbic regions using tractography-based parcellation. The authors claimed that "the consistency, validity, and clinical relevance of our findings have the potential for improving DBS targeting, by increasing patient-specific knowledge of subregions of the GPi to be targeted or avoided, at the stage of surgical planning, and later, at the stage when stimulation is adjusted."³¹ Because individualized treatment planning based on identification of sensorimotor regions of the nuclei has the potential to improve outcomes in patients with DBS,⁴⁰ there remains a need for the identification and delineation of pallidal pathways, specifically the sensorimotor regions of the GPi. Unfortunately, our current understanding of the somatotopic organization of the GPi in humans is limited and a more detailed map of the individual regions of the GPi is desirable for understanding both the effects of DBS and clinical outcomes.^{5,35,36}

Diffusion imaging is a commonly used MRI method to noninvasively trace white matter tracts and map structural connections of the human brain.¹ Diffusion-sensitized imaging utilizes two magnetic gradients as a means of visualizing the microstructural organization of white matter.²⁶ Diffusion-based tractography has become a useful tool to better visualize and understand activated pathways associated with PD.¹⁵ Algorithms have been developed to generate 3D representations of axonal fibers based on the direction of the major eigenvector of diffusion commonly known as tractography.¹⁹ Tractography methods use local diffusion orientations to determine pathways between distinct brain regions using two different diffusion model fittings. In general, tractography methods can be classified into deterministic and probabilistic categories. Deterministic tractography assumes a single fiber orientation for each voxel, producing one streamline per seed voxel. Probabilistic tractography, however, assumes a distribution of fiber orientations, and produces multiple stream-

line samples per seed voxel drawn from a probability distribution of the orientation estimates (Fig. 1).¹¹ Although deterministic methods of diffusion tensor imaging (DTI) are more commonly used to visualize tracts for clinical purposes, a major limitation of deterministic tracking is in its inability to accurately represent crossing fibers, kissing fibers, and fanning fibers in image voxels containing more than one fiber orientation, which have been estimated to comprise 90% of all voxels.²¹ More advanced diffusion models, such as the constrained spherical deconvolution (CSD) method, may more accurately track voxels containing multiple fiber orientations. Advanced tracking methods provide more anatomically plausible tracts, and may provide more valuable information for neurosurgical planning.⁶ This technique is not commonly used in a clinical setting, as the computations needed for probabilistic tractography are generally much more demanding than deterministic tractography algorithms.¹¹ Recent studies, however, have compared tensor-based deterministic methods to advanced probabilistic methods in patients selected for STN DBS and have shown that the CSD-based probabilistic method provides more consistent tractography results when compared to deterministic-based methods.^{32,38} At the same time, these studies were limited by creating target maps only in the region of the STN³² and failed to implement scan times with a duration appropriate for a clinical setting. It has been suggested that fiber pathways reconstructed with CSD are more consistent with known neuroanatomy than those reconstructed with deterministic models, and may better connect pathways in the complex fiber architecture of white matter.²⁵

This study evaluates the use of both deterministic and probabilistic tractography methods to delineate three pathways involved in the mediation of DBS treatment effects: the hyperdirect, direct, and indirect pathways. This is the first study to reconstruct not only cortico-STN hyperdirect pathways, but also corticopallidal pathways, using a clinically feasible processing pipeline as well as clinically feasible scan times.

Methods

Participants

In this retrospective single-center study, a total of 7 patients with PD (3 men and 4 women, ranging in age from 69 to 78 years old) selected for DBS were scanned prior to surgery. The study was approved by the IRB of Thomas Jefferson University. All patients had a diagnosis of advanced idiopathic PD according to standard clinical criteria. All patients underwent motor examinations (Unified Parkinson's Disease Rating Scale [UPDRS]-III) before and after image-guided, image-verified DBS under general anesthesia without microelectrode recordings. Based on clinical protocols, 2 patients underwent DBS implantation into the bilateral STN while the remaining 5 patients underwent placement of DBS neurostimulators into the bilateral GPi. Detailed patient characteristics for this main study are presented in Table 1.

Image Acquisition

All DBS candidates underwent preoperative MRI ex-

FIG. 1. A: Degree of anisotropy. **B:** Deterministic fiber tracking; the fiber path across voxels is inferred based on a single diffusion orientation per each voxel. **C:** Probabilistic fiber tracking; tractography generated based on a probability distribution of diffusion orientations within each voxel.

aminations for surgical planning consisting of T1-weighting scans (with and without gadolinium), T2-weighted scans, and proton density-weighted images; diffusion imaging sequences were also acquired for tractography. All acquisitions were performed on a 3.0-T Philips Achieva MR machine with a 32-channel head coil. To eliminate movement artifact, all patients were scanned under a standardized general anesthetic.

T1-weighted structural scans based on magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequences were acquired for trajectory planning. The T1-weighted imaging parameters used were: TR 7.0 msec, TE 3.0 msec, flip angle 9°, matrix size 512 × 512, FOV 25 cm, slice thickness 1.0 mm, and voxel size 1.0 × 1.0 × 1.0 mm³. The T2-weighted and proton density-weighted images were acquired for determining the targets of DBS. A dual spin echo sequence was acquired with the following parameters: TR 5.24 seconds, TE₁ 16 msec, TE₂ 80 msec, matrix size 256 × 256, slice thickness 2.0 mm, spatial resolution 2.0 × 2.0 × 2.0 mm³, and FOV 24 cm. Diffusion-weighted images were acquired axially in the same anatomical location prescribed for the T1-weighted images. The following parameters were used: 32 diffusion-encoding directions, b = 850 sec/mm², TR 12,000 msec, TE 83 msec, matrix size 128 × 128, slice thickness 2.0 mm, and voxel size 1.8 × 1.8 × 2.0 mm³. The average acquisition time was 15 minutes for diffusion-weighted images, with a total scan time of approximately 50 minutes.

Manual Segmentation

For each patient, the GPi and STN were manually segmented using ITK-SNAP (<http://www.itksnap.org>) by the senior author (C.W.) on the T2-weighted and proton density-weighted scans, respectively. The FreeSurfer analysis suite (<http://surfer.nmr.mgh.harvard.edu>) was used to automatically parcellate cortical regions of T1-weighted images based on patient anatomy (see Fig. 3, T1-weighted data). Supervision of FreeSurfer segmentation by the se-

nior author (C.W.) was performed for the cortical segments of each patient to generate accurate patient-specific parcellation of the motor, supplementary motor, and sensory areas. The GPi, STN, and cortical regions of interest (ROIs) were coregistered to the b0 image obtained from the diffusion scan using the FLIRT (the Functional Magnetic Resonance Imaging of the Brain [FMRIB] Linear Image Registration Tool) rigid body technique with 6 degrees of freedom and nearest-neighbor method as a cost function. The volumes of all segmented ROIs and cortical seeds are shown in Table 2.

Diffusion Data Processing and Tractography

Diffusion images were corrected for eddy current distortion and motion-induced artifacts using the artefact correction in diffusion MRI (ACID) toolbox (<http://www.diffusiontools.com/>). Fiber assignment was performed using the selected cortical areas as initiation seeds and the GPi and STN as an inclusion mask. ROIs were manually drawn over the cerebral peduncles of each individual subject's b0 image, and used as an exclusion mask, to ensure corticospinal tracts were not included.

TABLE 1. Patient information for response to DBS and disease severity studies

Variable	Mean ± SD	Range
Age (yrs)	70.4 ± 7.2	59.1–78.8
Disease duration (yrs)	8.2 ± 2.1	5.7–10.6
UPDRS-III*		
Preop	29.6 ± 13.9	15–48
Postop	15.8 ± 4.9	11–23
Follow-up (mos)	3.5 ± 2.5	1.1–7.3

There were 3 women and 4 men in the study.
* Preoperative medication-ON UPDRS-III and postoperative medication-ON DBS-ON UPDRS-III scores were recorded.

TABLE 2. Volume of STN, GPi, and cortical seeds

Case No.	STN (cm ³)		GPi (cm ³)		Cortical Seeds (cm ³)
	Lt	Rt	Lt	Rt	
1	0.16	0.14	0.44	0.66	3.34
2	0.18	0.15	0.46	0.43	2.33
3	0.16	0.16	0.52	0.54	2.17
4	0.13	0.15	0.59	0.42	2.79
5	0.15	0.15	0.51	0.44	3.54
6	0.16	0.15	0.51	0.45	2.87
7	0.15	0.16	0.53	0.49	1.90
Mean $\pm$ SD	0.16 $\pm$ 0.015	0.15 $\pm$ 0.007	0.51 $\pm$ 0.049	0.49 $\pm$ 0.086	2.71 $\pm$ 0.61

The MRtrix toolbox (<https://github.com/jdtournier/mrtrix3>) was used to analyze the diffusion sensitized data set, generate fiber orientation distribution (FOD) estimates, and create deterministic-based track density maps using a CSD model. Probabilistic fiber tractography was performed by the Diffusion Toolbox (FDT) of the FMRIB Software Library. Distributions of fiber orientation were estimated for each voxel based on the BEDPOSTX tool of FDT, computing two crossing fibers per voxel.

Deterministic track density maps and probabilistic maps of sensorimotor regions of the left and right STN and GPi were created. The number of tracts passing through a given voxel were counted and mapped as a numerical value for both tracking methods. Using the manual parcelations of the basal ganglia structures, we created track density images to represent the number of sensorimotor pathways passing through a given ROI.

Track Density Analysis

In order to compare deterministic and probabilistic tracking solutions, the center of gravity (CoG) of the track density maps of both targeted regions (STN and GPi) was calculated for each patient. For deterministic tractography, the track density map was generated based on whole-brain streamline tractography using FOD (Fig. 2). Within the targeted regions of the STN and GPi, the weighted pixel intensities of the track density maps were multiplied by their corresponding coordinates. The sum was then divided by the total pixel intensity of the track density image of each ROI to find the gray level-weighted CoG. The Euclidean distance was measured between the CoG of deterministic and probabilistic methods. Additionally, to compare the relative location of fiber tracts across each patient in the cohort, the distance between each tracking solution CoG and the centroid of the target nucleus itself was measured, with the latter serving as a reference point across patients. The standard deviation was calculated across the x-y-z axes for the entire cohort. A dice coefficient statistic was used to compare the sensorimotor regions as defined by each tracking solution. The full processing pipeline is shown in Fig. 3.

Results

Processing Time

The estimated processing time for probabilistic fiber

tracking ranged from 8 to 10 hours, whereas total processing time for deterministic fiber tracking was estimated to take approximately 5 minutes on a Linux machine with 4 Intel Xeon E5-2697 Processors.

Delineation of the Sensorimotor Regions of the STN and GPi

Deterministic and probabilistic methods successfully reconstructed pathways between the sensorimotor cortex and the ipsilateral STN (left and right) across all patients. Both methods were able to detect pathways between sensorimotor areas and the ipsilateral GPi (left and right) for all patients. The probabilistic method detected an average of 200% more pathways connecting the cortical areas to the targeted regions, throughout all structures. Both tracking solutions defined the sensorimotor region within the posterolateral aspect of the ipsilateral STN, and within the posterolateral aspect of the GPi (Fig. 4).

Track Density of Target Regions

The overlap between the probabilistic and deterministic track density maps within the defined target regions varied considerably between patients; however, the probabilistic method detected a significantly larger portion of fibers for the STN and GPi when compared to the deterministic method, indicating greater sensitivity of the probabilistic method. Overall, the average difference between probabilistic and deterministic tractography CoG was 2.67 mm. These values are certainly on a relevant order of magnitude for stereotactic trajectory planning. According to the Schaltenbrand-Wahren brain atlas, both the STN and GPi are approximately 4–5 mm in width.³⁷ As such, this discrepancy can mean the difference between targeting the lateral or medial portion of the nucleus. In the realm of DBS, a target difference of 2 mm can certainly make a clinical difference, particularly if the electrode is implanted closer to the structures that will result in stimulation-related side effects.³³ Intraoperatively, trajectories are typically adjusted by 2 mm, depending on microelectrode recordings or intraoperative findings.

Both tracking solutions detected the tract CoG in the posterior and lateral portion of the target nucleus (Table 3). Specifically, the deterministic method yielded a tract CoG 0.17–2.09 mm lateral to the target centroid, which was more medial than the probabilistic derived targets,

FIG. 2. Extraction of deterministic track density map: FOD estimation performed by CSD technique (A), whole-brain streamline tractography using FOD (B), and track density map based on the streamline tractogram (C). Probabilistic map seeded in the sensorimotor areas; each voxel has a value representing the connectivity value between that voxel and the seed voxel; crossing fibers and fiber orientation are indicated by green and red lines (D).

ranging from 0.53 to 4.09 mm lateral. This difference was also seen in the y-direction, with deterministic tracking solutions detecting the tract CoG more anteriorly, ranging between 0.13 and 0.87 mm, while the probabilistic method detected fibers relatively more posteriorly within the nucleus, located between 0.61 and 2.27 mm from its centroid. Finally, for the z-direction, probabilistic tracking detected more fibers located superiorly within the STN, and slightly inferiorly in the left GPi. Deterministic tracking lacked sensitivity to detect differences between solutions and the centroid of the nucleus in the z-direction for all examined structures.

Discussion

In this study, the sensorimotor regions of the STN and GPi in patients selected for DBS were delineated based on deterministic and probabilistic fiber tracking techniques. These results, in part, replicate previous work done by Petersen et al., where both tractography methods were used to identify connections between the ipsilateral cortical motor areas to only the STN.³² In addition to inclusion of the GPi, a larger patient cohort and a more feasible acquisition time was used in the present study, which increases the clinical applicability for trajectory planning in centers that use either nucleus (STN and/or GPi) as a target for DBS.

Pathophysiology of PD

Although a detailed review of the literature regarding

the pathophysiology of PD is beyond the scope of this study, it is instructive to review the role that the GPi and STN are thought to play in this disease, particularly if we are to better understand the white matter structures being visualized with tractography. Findings suggest that neurons of the internal segment of the GPi and the STN are hyperactive in PD and may contain pathways which, when imbalanced, abnormally activate output nuclei and inhibit thalamic neurons projecting to the cortex.²⁰ Cortically initiated activity from voluntary movement is suspected to be regulated by a dichotomy of direct and indirect pathways from the striatum to major output structures of the basal ganglia.⁹ Output neurons of the direct pathway include the substantia nigra pars reticulata and GPi, which are responsible for an increase in locomotor activity and movement. The indirect pathway causes a reduction of locomotor activity and movement through the disinhibition of glutamatergic neurons of the STN.³ In this model, PD may be explained as an imbalance between the direct and indirect pathway transmission from the striatum to the basal ganglia output nuclei.²⁰

Excitatory projections to the STN from several cortical areas have been termed the “hyperdirect pathway.”²⁸ This corticosubthalamopallidal hyperdirect pathway conveys excitatory effects from motor-related cortical areas to the globus pallidus, bypassing the striatum, which decreases conduction time for signal propagation.²⁰ The hyperdirect pathway is thought to be responsible for the mediation of inhibition that occurs shortly before the time of reaction

FIG. 3. The full processing pipeline: preprocessing, segmentation, tractogram extraction, and analysis.

FIG. 4. Anatomical location of track density of probabilistic tractography in the left and right STN and GPi in coronal (A) and sagittal (B) views. Maximum fiber density was detected in the posterosuperolateral aspect of the ipsilateral STN and the posterolateral aspect of the GPi.

to external stimuli.^{12,27,38} It is suggested that the hyperdirect pathway can broadly inhibit motor programs so that signals through the direct pathway may be able to adjust the selected motor program.^{2,12} It is because of these relationships that motor portions of the GPi or STN are most commonly targeted in the surgical treatment of PD.^{30,34,39,41}

The direct pathway projects directly to the GPi, whereas the indirect pathway projects first to the globus pallidus externus, which then connects to both the GPi and STN. The hyperdirect pathway is unique as it bypasses the striatum and connects the cortex directly to the STN, which then sends excitatory projections to the GPi.

Detection of Sensorimotor Regions in the GPi and STN and Exclusion of Corticospinal Tracts

One of the major goals of this work was to detect the location of pathways passing through the GPi and STN with the intent to improve presurgical trajectory planning. By setting the cerebral peduncles as an exclusion mask, all pathways originating in the sensorimotor regions and terminating in the spinal cord or brainstem were eliminated.

We have been careful not to distinguish connections to the GPi as either direct, indirect, or hyperdirect connections, as it is uncertain whether or not the tracts identified first pass through other regions of the fronto-striato-sub-

thalamic-pallidal network. Both probabilistic and deterministic techniques appeared to connect the sensorimotor cortices with the posterolateral aspect of the GPi and the posterosuperolateral aspect of the ipsilateral STN. This is in accordance with work by Ewert et al., where the GPi and STN were segmented into sensorimotor, associative, and limbic functional zones in non-PD patients, based off of diffusion-based tractography.¹³ Similarly, it has been found that grouped motor, premotor, and sensory areas filled the posterior third of the GPi, which has been described previously as the sensorimotor domain and is a common target for DBS.^{5,10} The posterosuperolateral region of the STN is analogous and has been identified as the sensorimotor functional zone.^{7,26}

Probabilistic Versus Deterministic Tracking

Across all subjects and for all target regions, deterministic fiber tracking reconstructed smaller and more variable streamlines when compared with probabilistic tracking. This variability is clearly appreciated when examining the dice coefficient values (Table 4) for the overlap between track density maps of the GPi, being as low as 0.40 overlap. Furthermore, the Euclidean distance between the two tracking solutions averaged 2.08 mm for the GPi. While less variability was observed in the confined target region of the STN, a difference between probabilistic and deterministic was still observed, averaging 1.67 mm. This finding implies that the differences between the two tracking methods are still relevant even when considering a smaller target region. Overall, the average difference between probabilistic and deterministic tractography CoG was 2.67 mm. These values are certainly on a relevant order of magnitude for stereotactic trajectory planning. According to the Schaltenbrand-Wahren brain atlas, both the STN and GPi are approximately 4–5 mm in width.³⁷ As such, this difference can mean the difference between targeting the lateral or medial portion of the nucleus. In the realm of DBS, a target difference of 2 mm can certainly make a clinical difference, particularly if the electrode is implanted closer to structures that will result in stimulation-related side effects. Intraoperatively, trajectories are typically adjusted by 2 mm, depending on microelectrode recordings or intraoperative imaging.

When comparing the distances between the centroid of the targeted nucleus and the CoG of the tracking solutions, a consistently higher standard deviation was observed from the CoG for deterministic tracking, suggesting both higher sensitivity and precision of the probabilistic method. Similar to the work by Petersen et al.,³² our results demonstrate probabilistic tracking to be a consistently more reliable and accurate method for presurgical trajectory planning.

While our results delineated sensorimotor regions in the posterosuperolateral portion of the STN and posterolateral portion of the GPi (Fig. 3), in 1 patient the difference between probabilistic and deterministic tracking was significantly larger in the left GPi (13.85 mm) compared to other subjects (0.16–4.31 mm). Given the abnormal concentration of the tracts in the anterior portion of the GPi produced by the deterministic method, it is likely that this illustrates an incorrect representation of the sensorimotor region. This outlier (Fig. 5, yellow arrow) further empha-

TABLE 3. Coordinate deviation of tracking solutions from the CoG for each of the segmented anatomical nuclei averaged across all patients

Method	x (mm)*	y (mm)†	z (mm)‡	Angle (°)
Lt STN				
Deterministic	-0.34	-0.25	0.00	0.25
Probabilistic	-0.53	-0.61	0.43	0.36
Rt STN				
Deterministic	-0.71	-0.84	0.00	0.24
Probabilistic	-0.78	-1.09	0.43	0.31
Lt GPi				
Deterministic	-2.18	-0.34	0.00	0.83
Probabilistic	-3.18	-1.74	-0.14	2.15
Rt GPi				
Deterministic	-4.17	-1.75	0.00	0.67
Probabilistic	-4.09	-2.27	0.00	0.66

The angle represents the angle of the Euclidian distance vector calculated between the deterministic and probabilistic CoG, and the CoG of the segmented anatomical nucleus, defined in image space.

* + = anterior; - = posterior.

† + = medial; - = lateral.

‡ + = superior; - = inferior.

sizes the limitations of deterministic tractography and the increased accuracy of its probabilistic counterpart.

Ultimately, targeting the motor subregion of the nucleus has been shown to yield improved motor outcomes in DBS for PD.⁴ As such, we believe that the differences between deterministic and probabilistic tracking methods are significant enough to warrant the increased processing requirements, particularly because situations may arise where the formed tractography yields unusable results.

Clinical Application

The use of advanced imaging techniques to accurately demonstrate white matter tracts in a 3D manner is useful in neurosurgery for both decision making and neurosurgical planning.¹⁸ While a number of studies have demonstrated this utility, the time required for image acquisition often limits the clinical applicability of advanced diffusion imaging methods. As such, we aimed to develop an imaging pipeline capable of accurate white matter tracking while maintaining a short acquisition time. Our diffusion-weighted images, with a spatial resolution of $2.0 \times 2.0 \times 2.0$ mm³ and 32 directions, were acquired in merely 15 minutes. Previous work conducted in reconstructing STN projections using probabilistic tractography have used longer scan times to achieve high-resolution DTI with an acquisition time of approximately 1 hour and 30 minutes.³² While a lengthy scan time may be a minor inconvenience in a research setting, the duration of the acquisition would not be feasible in a routine clinical setting. Currently no probabilistic methods of tractography are commercially available packages cleared for clinical use. This work builds the argument for increasing the availability of advanced diffusion methods for use in a clinical setting.

TABLE 4. Difference in target regions' CoG coordinates between tracking methods

Case No.	CoG Coordinates of Track Density (image space)		Euclidean Distance (mm) Btwn Both Tracking Solutions*	Dice Coefficient
	Deterministic	Probabilistic		
1				
STN Lt	62.4, 69.4, 25.5	62.0, 69.6, 25.5	1.63	1.00
STN Rt	63.2, 57.1, 25.5	62.9, 56.5, 25.5	2.74	0.98
GPI Lt	63.2, 74.6, 29.5	63.0, 75.1, 29.5	2.11	0.83
GPI Rt	62.8, 50.9, 28.0	62.7, 50.7, 28.0	1.06	0.67
2				
STN Lt	55.3, 70.5, 39.5	55.0, 70.6, 39.5	1.18	1.00
STN Rt	55.9, 57.7, 39.0	56.2, 57.7, 39.5	2.21	0.98
GPI Lt	57.5, 74.0, 42.5	57.1, 75.2, 42.5	4.92	0.63
GPI Rt	59.0, 54.2, 42.5	59.3, 53.9, 42.5	1.46	0.83
3				
STN Lt	63.7, 71.1, 35.0	63.6, 71.1, 35.0	0.22	1.00
STN Rt	62.2, 58.9, 34.5	62.2, 58.9, 34.5	0.33	1.00
GPI Lt	68.8, 72.0, 36.5	66.1, 74.2, 37.0	14.44	0.40
GPI Rt	65.0, 56.0, 38.0	64.5, 55.4, 38.0	3.10	0.84
4				
STN Lt	59.1, 71.0, 39.5	58.8, 71.0, 39.5	0.41	0.94
STN Rt	60.1, 58.0, 40.5	59.7, 57.7, 40.5	0.16	0.98
GPI Lt	61.5, 75.1, 43.0	61.7, 75.3, 43.0	1.40	0.61
GPI Rt	62.8, 54.1, 45.5	62.6, 53.5, 45.0	1.71	0.67
5				
STN Lt	65.1, 70.0, 34.0	63.7, 71.3, 34.0	2.86	0.95
STN Rt	63.6, 57.1, 34.5	62.8, 56.6, 34.5	2.28	0.93
GPI Lt	64.9, 74.8, 38.5	64.6, 75.2, 38.5	2.34	0.86
GPI Rt	65.8, 54.1, 40.0	64.9, 52.8, 39.5	2.39	0.76
6				
STN Lt	62.4, 70.3, 38.5	62.8, 70.6, 39.0	2.64	0.97
STN Rt	62.5, 57.0, 39.0	62.9, 57.1, 39.0	1.52	1.00
GPI Lt	64.8, 74.1, 41.0	64.9, 74.1, 41.0	0.20	0.71
GPI Rt	63.7, 52.5, 40.5	64.7, 52.9, 41.0	4.61	0.68
7				
STN Lt	64.6, 68.6, 40.0	64.3, 68.9, 40.0	1.72	1.00
STN Rt	64.7, 57.3, 41.0	64.7, 57.3, 41.0	0.16	1.00
GPI Lt	67.9, 70.7, 44.5	68.0, 71.0, 44.5	1.48	0.75
GPI Rt	65.2, 53.5, 44.0	65.1, 53.4, 44.0	0.65	0.73

All coordinates have been reported in image space with the diffusion image serving as the reference. A dice coefficient of 1 indicates a perfect overlap, whereas a dice coefficient of 0 indicates no overlap.

* The GPI median ($\pm$ SD) was 2.08 ± 3.69 mm, whereas the STN median was 1.67 ± 1.90 mm. The total average distance was 2.67 mm.

Limitations and Future Work

Although a shorter acquisition time is desirable for clinical feasibility, the resulting low resolution of our DTI data creates a limitation when performing sensitive and accurate fiber tractography. The processing time for the creation of the track density maps, consisting of both manual and automated segmentation, FOD estimation, and whole-brain tractography, is associated with a substantial expenditure of time, which can be inefficient when working within a clinical timeframe. Probabilistic

tracking required up to 10 hours of processing time on a typical computer processor. Such processing could be incorporated into the workflows of surgeons who routinely plan their trajectories prior to the day of surgery, but would not be able to accommodate those who routinely perform stereotactic planning immediately prior to the surgical procedure. That being said, in their identification of the subthalamic region stimulation clusters, Akram et al. were able to successfully delineate fiber orientations using a graphics processing unit (GPU).² In the future,

FIG. 5. Cross-sectional view of probabilistic and deterministic track density maps of direct cortico-GPi pathways within the STN and GPi (left and right). The sensorimotor region is most concentrated in the posterosuperolateral portion of the STN, and the posterolateral portion of the GPi. Note that in case 3 (yellow arrow) the deterministic method inaccurately detected the CoG to be anterior in the GPi.

technological advances in processing capabilities such as GPU processing will help shorten processing times and consequently allow for greater adoption of these tracking techniques in the preoperative clinical setting. GPU-based data processing hardware is becoming more available in radiology settings.¹⁸ In either scenario, however, personnel with expertise in probabilistic tractography would be needed to process diffusion data accordingly.

A significant amount of research remains to be undertaken for the clinical use of tractography-based DBS targeting. First, the current study is limited by its small sample size. Second, to better understand the clinical relevance of tractography-based DBS targeting, clinical outcomes must also be considered. We intend to analyze the relationship between track density maps and electrode placement to quantify the effect of electrode placement on clinical outcomes. This will involve the calculation of the volume of tissue activation, calculated from the programming parameters, so as not to overlook the effect contacts adjacent to the nucleus might have on cell bodies as well as axons within the white matter outside of the nucleus.² The aim of this future study will be to associate overlapping stimulation sites within the STN and GPi with different connectivity patterns for maximum improvement in UPDRS-III scores.

We hope that our efforts will allow us to better understand the anatomical relationships and networks in PD. Because tractography illustrates connections without providing insight into the directionality, or number of connections between ROIs, it is possible that a portion of the fibers detected individually in the GPi and STN track density maps may pass through additional structures. In the future the use of additional inclusion and exclusion regions after performing tractography may allow for successful delineation of the direct, indirect, and hyperdirect pathways. By doing so, a better understanding of these three pathways and their contribution to disease progression and severity may be gleaned.

Conclusions

The results of this study demonstrate probabilistic tractography as a more reliable tractography method when compared to the deterministic-based method, in both the regions of the STN and GPi. Analysis of the results of probabilistic and deterministic tractography for both the STN and GPi indicates that probabilistic tracking is a more robust method for accurate stereotactic presurgical planning. Furthermore, we have demonstrated the ability to detect sensorimotor regions of the GPi and STN within a clinically applicable timeframe, presenting the opportunity for the integration of advanced neuroimaging methods for presurgical planning.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Muller, Alizadeh, Mohamed, Trieu, Wu. Acquisition of data: Alizadeh, Mohamed, Riley, Pearce, Liang, Romo, Wu. Analysis and interpretation of data: Muller, Alizadeh, Pearce, Wu. Drafting the article: Muller, Alizadeh, Wu. Critically revising the article: Muller, Alizadeh, Mohamed, Pearce, Trieu, Romo, Wu. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Muller. Statistical analysis: Muller, Alizadeh, Wu. Administrative/technical/material support: Mohamed, Riley, Liang, Sharan, Wu. Study supervision: Mohamed, Riley, Sharan, Wu.

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