White Matter Connectivity between Structures of the Basal Ganglia using 3T and 7T

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Abstract—Analysis of the basal ganglia has been important in investigating the effects of Parkinson’s disease as well as treatments for Parkinson’s disease. One method of analysis has been using MRI for non-invasively segmenting the basal ganglia, then investigating significant parameters that involve the basal ganglia, such as fiber orientations and positional markers for deep brain stimulation (DBS). Following enhancements to optimizations and improvements to 3T and 7T MRI acquisitions, we utilized Lead-DBS on human connectome project data to automatically segment the basal ganglia of 49 human connectome project subjects, reducing the reliance on manual segmentation for more consistency. We generated probabilistic tractography streamlines between each segmentation pair using 3T and 7T human connectome diffusion data to observe any major differences in tractography streamline patterns that can arise due to tradeoffs from different field strengths and acquisitions. Tractography streamlines generated between basal ganglia structures using 3T images showed less standard deviation in streamline count than using 7T images. Mean tractography streamline counts generated using 3T diffusion images were all higher in count than streamlines generated using 7T diffusion images. We illustrate a potential method for analyzing the structural connectivity between basal ganglia structures, as well as visualize possible differences in probabilistic tractography that can arise from different acquisition protocols. © 2021 The Author(s). Published by Elsevier Ltd on behalf of IBRO. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Key words: probabilistic tractography, Parkinson’s disease, basal ganglia, MRI, 3T, 7T.

INTRODUCTION

Basal ganglia structures such as the subthalamic nucleus (STN) and substantia nigra (SN) have been crucial targets for studying Parkinson’s disease. It has been well established that the death of dopaminergic neurons commonly occurs in the SN pars compacta of clinical Parkinson’s Disease patients (Galvan and Wichmann, 2008; Surmeier et al., 2017), which in turn contributes to the dysfunction of downstream nigrostriatal basal ganglia pathways related to movement disorders (Poewe et al., 2017; Guo et al., 2018). In order to directly observe the effects of dopaminergic neuronal death, studies have utilized MRI to produce images of the basal ganglia and identify biomarkers stemming from the disruption of dopaminergic output. Through the segmentation of basal ganglia using MRI, studies are able to compare volumetric differences and levels of iron accumulation in patient and control brain structures attributed to the effects of the neuronal disease. Additionally, studies have used MRI for precise planning of treatments such as deep brain stimulation (DBS) where knowing the accurate locations of STN (Kitagawa et al., 2005; Temel et al., 2006) and the globus pallidus internal (GPI) (Vidalhiet et al., 2005; Follett et al., 2010) for lead stimulation is necessary for optimal treatment outcome. As such, accurate segmentation for identifying key brain structures is a cornerstone method for studying effects of diseases and treatments using MRI.

Another avenue in which MRI is used for studying the brain is through diffusion MRI, where identifiable patterns of free-moving water molecules can be interpreted as myelinated axons running through white matter (Behrens et al., 2003; Sotiropoulos et al., 2016). Distribution models such as diffusion tensor are capable of modeling diffusion information into fiber orientations in voxels of MRI images, providing a distribution of fiber orientations for sampling streamline fibers (Behrens et al., 2007). As a result, the diffusion dependent streamline fibers can be observed for significant differences to simulate damage to white matter, which are often coupled by changes in diffusion (Tan et al., 2015; Kamagata et al., 2018). Various diffusion studies of Parkinson’s disease patients were able to find significant alterations in the diffusion tractography of the nigrostriatal tract, correlating
with disruptions to white matter integrity affected by loss of dopaminergic neurons (Zhang et al., 2015; Theisen et al., 2017).

For a closer look at white matter connectivity, diffusion tractography can also be filtered into specific streamline fibers that connect regions of interest (Kamagata et al., 2018). For example, filtering each subject’s nigrostriatal diffusion tractography by individual DBS stimulation sites can distinguish which brain structures show strong connectivity with clinically effective DBS stimulation sites (Van Hartevelt et al., 2014) in patients treated with STN DBS surgery. While this method can be a powerful tool in investigating the connectivity between brain structures, it relies on the accuracy and consistency of segmentation, as the patterns of white matter tracts that connect regions vary significantly depending on the locations of each region (Vanegas-Arroyave et al., 2016). Manual segmentations conducted by professionals may be the gold standard for achieving proper levels of segmentation accuracy, but various structural problems can occur if a study lacks manpower with prior anatomical experience in segmentation and if the study necessitates segmenting significant number of regions and images (Yaakub et al., 2020). As such, the use of segmentation software toolboxes for segmenting brain structures automatically and accurately can improve the accessibility of studies requiring segmentation.

For this study, we utilize Lead-DBS (Horn and Kühn, 2015), an open-source toolbox designed for providing precise locations of anatomical structures and electrode placement for DBS, to segment key structures involved in Parkinson’s disease, such as globus pallidus external (GPe), GPi, red nucleus (RN), STN, SN and striatum. Lead-DBS provides a multitude of automated atlas-based segmentation methods for segmenting regions and subregions of the brain not commonly done by other open-source toolboxes. We used Lead-DBS for its capability and accessibility in providing accurate and consistent results in automatically segmenting previously mentioned structures with minimal human interaction (Nowacki et al., 2018; Ewert et al., 2019). To observe the level of connection between each segmented structure, we utilized PROBTRACKX (Behrens et al., 2007) from the FMRIB software library (FSL) diffusion toolkit to generate probabilistic tractography between the segmented structures. Tractography was generated on both 3T and 7T to investigate how our streamline generation methodology behaves under change in field strength and acquisition. We aimed to describe a user-friendly methodology for automatically segmenting deep brain structures, then drawing probabilistic tractography between each segmentation as a preliminary study before evaluating similar relationships in other diseased subjects in future studies.

**EXPERIMENTAL PROCEDURES**

**Subjects**

Forty-nine female subjects from the WU-Minn HCP Young Adult 1200 Subjects dataset were used for this study (Van Essen et al., 2013). All subjects were young adults (age range: 22–35 years) and healthy, with no documented neuropsychiatric disorders, neurologic disorders or illnesses such as diabetes and high blood pressure.

**MRI acquisition protocols**

3T T1w, T2w, diffusion weighted, 7T diffusion weighted MRI data of all 49 female subjects were used for this study. 3T images were acquired using 3T Siemens Skyra scanner with a 100 mT/m gradient set and 32 channels head coil (Uğurbil et al., 2013).

3T T1w images were acquired using 3D MPRAGE sequence (echo time (TE) = 2.14 ms, repetition time (TR) = 2400 ms, inversion time (TI) = 1000 ms, flip angle (FA) = 8°, field of view (FOV) = 180 × 224 × 224 mm³, voxel size = 0.7 mm isotropic, bandwidth (BW) = 210 Hz/Px, acquisition time = 7 min 40 s).

3T T2w images were acquired using 3D T2-SPACE sequence (echo time (TE) = 565 ms, repetition time (TR) = 3200 ms, field of view (FOV) = 180 × 224 × 244 mm³, voxel size = 0.7 mm isotropic, bandwidth (BW) = 744 Hz/Px, acquisition time = 8 min 24 s).

3T diffusion weighted images were acquired using multiband spin-echo EPI sequence (echo time (TE) = 8.95 ms, repetition time (TR) = 5520 ms, flip angle (FA) = 78°, refocusing flip angle (rFA) = 160°, field of view (FOV) = 210 × 180 (RO × PE), matrix = 168 × 144 (RO × PE), slice thickness = 1.25 mm, 11 slices, 1.25 mm isotropic voxels, multiband factor = 3, echo spacing = 0.78 ms, bandwidth (BW) = 1488 Hz/Px, b-values = 1000, 2000, 3000 s/mm², 90 diffusion weighting directions, acquisition time = 9 min 50 s). Total scanning time was ~55 min.

7T diffusion images were acquired using 7T Siemens MAGNETOM scanner with a 70 mT/m gradient set and 32 channels head coil (Uğurbil et al., 2013). 7T diffusion images were acquired using multiband spin-echo EPI sequence (echo time (TE) = 71.2 ms, repetition time (TR) = 7000 ms, flip angle (FA) = 90°, refocusing flip angle (rFA) = 180°, field of view (FOV) = 210 × 210 mm (RO × PE), matrix = 200 × 200 (RO × PE), slice thickness = 1.05 mm, 132 slices, 1.05 mm isotropic voxels, multiband factor = 2, echo spacing = 0.82 ms, bandwidth (BW) = 1388 Hz/Px, b-values = 1000, 2000, 3000 s/mm², 65 diffusion weighting directions, acquisition time = 9 min 50 s). Total scanning time was ~40 min.

All images were minimally preprocessed beforehand through the HCP minimal preprocessing pipeline (Glasser et al., 2013). Through the pipeline, the T1w and T2w images were corrected for MR gradient nonlinearity-induced distortions and readout distortions then bias field corrected. The diffusion weighted images were normalized for b0 image intensity, then corrected for EPI distortions, eddy-current induced distortions, subject motion and gradient nonlinearity. More details on acquisition parameters and the preprocessing pipeline can be found in the WU-Minn HCP 1200 Subjects Data Release: Reference Manual, available at https://www.humanconnectome.org/.
Segmentation

Segmentation of GPe, GPi, RN, STN, SN, and the striatum was done through the default Lead-DBS pathway, excluding electrode localization and reconstruction (Horn et al., 2019). First, a bias-field correction step using the N4 algorithm was applied to T1w and T2w images (Tustison et al., 2010). Following the bias correction, the T2w images were co-registered to T1w images using SPM 12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12). Each co-registration was visually inspected using edge detection based wire-frames overlaid on each co-registered images generated by Lead-DBS. The co-registered images were then normalized to MNI template space using advanced normalization tools (ANTs) symmetric image normalization (SyN) (Avants et al., 2008). Then the DISTAL atlas, which consists of various anatomical structures optimized for the precise parcellation of STN and GPi in MNI space (Fig. 1), is warped back to each subject’s space through inverse normalization (Ewert et al., 2018). The results of segmentations were visually inspected by overlaying each inverse normalized area of interest on T1w and T2w images as shown in Fig. 2. The segmented regions of interest were used directly for diffusion tractography due to diffusion weighted images being preregistered to T1w structural images in HCP minimal preprocessing pipeline. The segmentations that were registered to each subject’s 3T and 7T b0 images were visually inspected by overlaying each registered segmentation onto its respective 3T and 7T b0 images. The segmentation pipeline was ran successfully on all 49 subjects with no need for manual tuning.

Probabilistic tractography

BEDPOSTX, a tool that models diffusion parameters in each voxel using Monte Carlo sampling, was run on preprocessed 3T and 7T diffusion weighted images (Behrens et al., 2007; Hernández et al., 2013). BEDPOSTX was run with 3 fibers per voxel, 3000 burnin, rician noise and gradient nonlinearities considered. Rician noise option was chosen for BEDPOSTX due to Gaussian models substantially underestimating mean FA and MD values in voxels compared to Rician models (Wegmann et al., 2017). PROBTRACKX was used to generate probabilistic tractography between each segmented left hemisphere structures using the diffusion parameters generated from results of 3T and 7T BEDPOSTX (Behrens et al., 2007; Hernández et al., 2013). Running PROBTRACKX generates two results: a streamline count, which represents number of streamlines generated from each seed structure that also pass through a target structure, and the 3D mesh of the probabilistic tractography simulating the shape of the streamlines. PROBTRACKX was run with 5000 samples per voxel, step size of 0.625 and curvature threshold of 0.2, with no exclusion or termination masks. Running BEDPOSTX commands for each subject’s 3T and 7T diffusion data, as well as PROBTRACKX commands for each basal ganglia waypoint connectivity were facilitated through custom bash scripts. The bash scripts were written to parse through multiple subject folders subsequently with the instructions to run identical BEDPOSTX commands with options defined by variables. Additionally, PROBTRACKX commands were called by the script repeatedly for every basal ganglia pair to calculate basal ganglia interconnectivity for each subject. Volumetric models of the generated probabilistic tractography were normalized to the MNI template using FSL FLIRT, then averaged between each subject. Numeric values of streamlines generated between the segmented structures were averaged then normalized by dividing each number by the voxel number of each seed mask due to the differences in total number of tractography seeds per mask (Calabrese et al., 2015).
RESULTS

The outlines of 3T and 7T automatic segmentations are overlaid on top of each respective T2 weighted MRI images in Fig. 1. PROBTRACKX with each basal ganglia structure pair generated two results: 3D mesh of the shape of probabilistic tractography, which allows for the visualization of pathways that connect the basal ganglia pair, and a waytotal number, which describes the total number of generated streamlines that were not rejected by the inclusion mask criteria. The 3D meshes of pathways between basal ganglia structures generated from 3T and 7T data are shown in Fig. 3. The averaged, normalized streamline counts and their average deviations between 3T and 7T segmented masks are shown in Table 1. Streamlines generated between each segmentation pair using 7T diffusion images were all lower in mean count than streamlines generated using 3T diffusion images. The comparison between streamline counts generated using 3T and 7T images are visualized through a connectogram in Fig. 4.

DISCUSSION

In this study, we segmented basal ganglia structures involved in DBS, then generated probabilistic tractography between the segmented structures. We obtained probabilistic tractography streamline counts between each structure pair using 3T and 7T diffusion images, first to test whether if our methods work on images with different acquisition protocol and field strength, and second to observe possible differences in streamline counts that can arise due to differences in acquisition protocol. Through automated methods, we were able to observe fiber counts and regions frequently used in studying the effects of diseases on deep brain structures.

There are several motivations for establishing a segmentation and tractography pipeline for MRI diffusion studies. Through automatic and efficient segmentation, many MRI images can be processed quickly with little manpower for annotating regions of interests (Yaakub et al., 2020). Coupled with diffusion images, the segmented areas can be quickly scanned for major diffusivity changes that can occur in neuronal diseases (Zhan et al., 2012). Neuronal changes frequently reported in PD studies can be observed through reconstructed streamlines that characterize the change in diffusivity of water molecules often seen in damaged neurons (Theisen et al., 2017; Koirala et al., 2019). While interpretation of streamline counts are difficult due to varying conditions (curvature, length) that can influence streamline generation, various studies have observed significant differences in probabilistic tractography of PD patients. A study observ-
ing the striatonigral pathway (pathway between the putamen, which is part of the striatum, and the SN) of control and PD subjects showed statistically significant reductions in tracts generated with probabilistic tractography (Theisen et al., 2017). Another study was able to observe reductions in structural connectivity of limbic structures associated with epilepsy using probabilistic tractography (Bonilha et al., 2012). As such, studies have reported evidence of reduced streamline counts that correlate with weakened white matter connectivity of the basal ganglia. The tractography generated in Fig. 3 represent specific white matter connectivity between structures of the basal ganglia and are known to be affected by degeneration of dopamine neurons in SN. Utilizing the methodology presented in this study can be useful in observing significant diffusion tractography changes of basal ganglia structures and for illustrating the changes that can occur in white matter of neurodegenerative patients.

A sample run of the tractography pipeline was run on 3T and 7T diffusion weighted images of 49 HCP subjects. Results showed higher streamline count generation between all segmented structures on 3T diffusion images than 7T diffusion images, as shown in Table 1 and visualized in Fig. 4. As shown in a previous study that compared the differences between 3T and 7T HCP fiber orientations, the lower angular resolution and angular contrast of the 7T diffusion acquisition has resulted in lower sensitivity for resolving fiber orientations as visualized in Fig. 5 (Sotiropoulos et al., 2016). Fiber orientation estimation with the 7T HCP diffusion image was shown to be spatially incoherent when compared to 3T fiber orientation estimation, with some voxels missing fiber crossings used in resolving streamlines (Sotiropoulos et al., 2016). Additionally, increased susceptibility to high iron concentrations of deep grey matter structures such as RN, SN and STN in 7T acquisitions may have contributed to increased inhomogeneities disrupting fiber orientation placement and streamline generation between segmentations (Pfefferbaum et al., 2010). As shown in Fig. 5, the lower number of resolved

![Fig. 3. Results of PROBTRACKX between key structures of Parkinson’s disease. 3D representations of both 3T (left) and 7T (right) segmentations and probabilistic tractography are displayed left of 2D representations. The colored masks in the 3D structures represent the segmented basal ganglia masks. The gray structures between the segmented masks represent probabilistic tractography generated between the segmented basal ganglia masks. The 2D figures consists of white masks, which represent the segmented basal ganglia masks, and red streamlines, which represent the generated probabilistic tractography between the segmented masks. From top to bottom, the connections are between: Striatum, GPe; Striatum, GPi; Striatum, SN; GPi, STN; GPe, STN; STN, SN. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)](image-url)
fiber orientations in lower angular resolution images can make it difficult to resolve streamline fibers between structures, especially if the fiber orientations that connect two structures are mostly missing. Therefore, the high number of streamline fibers can be attributed to the robust network of fiber orientations that can connect two regions of interest, and may be a quality of higher angular resolution images. Additionally, if more streamline fibers can be generated through probabilistic tractography, significant changes to white matter tractography from neuronal diseases or treatments resulting in the alteration of white matter diffusivity can be better illustrated especially if fiber branches that are only resolved in high angular resolution images show visible change.

There are limitations to consider regarding our results and methodology. First, the two acquisitions on 3T and 7T field strengths had different protocols with varying factors in addition to field strength and spatial resolution such as hardware, repetition time, gradient sets and bandwidth that could have affected the comparison. In order to conduct a proper comparison between 3T and 7T, such differences in protocol will need to be resolved. Second, the probabilistic tractography generated from 3T and 7T images were not tested against ground truths or compared to other tractography methods for overlap. As such, it is unclear from results whether tractography generated from 3T or 7T represent more valid results. However, we believe our methods can help contribute to calculating common fiber bundles that interconnect basal ganglia structures, similar to studies that have produced anatomical atlases of macroscale human structural connectomes (Yeh et al., 2018). Third, streamline generation can vary in count and shape depending on the options given to the PROBTRACKX program. It is possible that the options used in PROBTRACKX for streamline generation were either too harsh or too lenient,
causing irregularities in streamline count due to their sharpness of angles or the strength of fiber orientations.

Our study was able to visualize the structural connectivity between basal ganglia structures of the motor loop known to be affected by the degeneration of dopaminergic neurons using automated segmentation and probabilistic tractography. In addition, we generated probabilistic tractography using 3T and 7T HCP diffusion images as a preliminary study to observe whether streamlines change significantly in shape and count between two different acquisitions of the same subject. While this initial study showed lower mean streamline generation in 7T acquisitions, future studies with less differences in 3T and 7T protocol need to be done to draw a proper conclusion regarding the differences in basal ganglia streamline generation between 3T and 7T acquisitions. Additionally, future improvements on 7T acquisitions as well as algorithms to reduce inhomogeneity should also help improve streamline generation using 7T diffusion images (Möller et al., 2020). We also believe that future studies with Parkinson’s disease patients and controls can be done in the future to see if any significant differences in streamline connectivity between motor loop structures can be observed in Parkinson’s disease patients.

DATA AVAILABILITY

The open-source toolbox and code LEAD-DBS (Horn et al., 2019) used for segmentation are available for free at www.lead-dbs.org. SPM toolbox used for co-registration is available at https://www.fil.ion.ucl.ac.uk/spm/software/spm12. The toolbox and code for FMRIB’s software library (FSL v.6.0) which includes the BEDPOSTX and PROBTRACKX tools are available at https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL. The WU-Minn Human Connectome Project, 1200 Subjects Data Release dataset is publicly available at https://www.humanconnectome.org/. Script files used in this study are publicly available at https://github.com/jaehyukshim11/probTractxPipeline/.

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COMPETING INTERESTS

Authors report no competing interests.

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