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Evaluation of striatonigral connectivity using probabilistic tractography in Parkinson's disease

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ABSTRACT

The cardinal movement abnormalities of Parkinson's disease (PD), including tremor, muscle rigidity, and reduced speed and frequency of movements, are caused by degeneration of dopaminergic neurons in the substantia nigra that project to the putamen, compromising information flow through frontal-subcortical circuits. Typically, the nigrostriatal pathway is more severely affected on the side of the brain opposite (contralateral) to the side of the body that manifests initial symptoms. Several studies have suggested that PD is also associated with changes in white matter microstructural integrity. The goal of the present study was to further develop methods for measuring striatonigral connectivity differences between PD patients and age-matched controls using diffusion weighted magnetic resonance imaging (MRI).

In this cross-sectional study, 40 PD patients and 44 controls underwent diffusion weighted imaging (DWI) using a 40-direction MRI sequence as well as an optimized 60-direction sequence with overlapping slices. Regions of interest (ROIs) encompassing the putamen and substantia nigra were hand drawn in the space of the 40-direction data using high-contrast structural images and then coregistered to the 60-direction data. Probabilistic tractography was performed in the native space of each dataset by seeding the putamen ROI with an ipsilateral substantia nigra classification target. The effect of disease group (PD versus control) on mean putamen-SN connection probability and streamline density were then analyzed using generalized linear models controlling for age, gender, education, as well as seed and target region characteristics.

Mean putamen-SN streamline density was lower in PD on both sides of the brain and in both 40- and 60-direction data. The optimized sequence provided a greater separation between PD and control means; however, individual values overlapped between groups. The 60-direction data also yielded mean connection probability values either trending (ipsilateral) or significantly (contralateral) lower in the PD group. There were minor between-group differences in average diffusion measures within the substantia nigra ROIs that did not affect the results of the GLM analyses when included as covariates. Based on these results, we conclude that mean striatonigral structural connectivity differs between PD and control groups and that use of an optimized 60-direction DWI sequence with overlapping slices increases the sensitivity of the technique to putative disease-related differences. However, overlap in individual values between disease groups limits its use as a classifier.

Abbreviations: ADRC, Alzheimer's Disease Research Center; AFNI, Analysis of Functional NeuroImages; BET, brain extraction tool; DWI, diffusion-weighted imaging; FA, fractional anisotropy; FLAIR, fluid attenuated inversion recovery; FOV, field of view; FSL, Oxford Centre for Functional MRI of the Brain Software Library; GE, general electric; HY, Hoehn and Yahr; ICC, interclass correlation coefficient; IRB, institutional review board; LMPD, longitudinal MRI biomarkers in Parkinson's disease study; MD, mean diffusivity; MRI, magnetic resonance imaging; PD, Parkinson's disease; PET, Positron Emission Tomography; RD, radial diffusivity; ROI, region of interest; SD, standard deviation; SN, substantia nigra; SNR, signal to noise ratio; SPECT, single photon emission tomography; SPM, Statistical Parametric Mapping software; TE, echo time; TI, inversion time; TR, repetition time; TFCE, threshold-free cluster enhancement; UPDRS, Unified Parkinson Disease Rating Scale; VA, Veterans Affairs

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1. Introduction

Parkinson's disease (PD) is a common age-related neurodegenerative disease that is diagnosed on the basis of motor symptoms of resting tremor, bradykinesia, and rigidity, which are frequently asymmetrical at symptom onset. These motor symptoms are related to degeneration of dopaminergic neurons in the substantia nigra (SN) pars compacta that project to the striatum (caudate nucleus and putamen; Braak et al., 2003). Mammalian studies have shown that nigrostriatal projections arise from the ventral portion of the SN and ventral tegmental area, forming a broad bundle of axons that run through the brainstem tegmentum ventromedial to the red nucleus, the diencephalic prerubral field, and the dorsal and lateral hypothalamic area as well as medial portion of the internal capsule to distribute throughout the striatum (Moore and Bloom, 1978). Afferent connections from striatum to SN terminate mainly in the pars reticulata with a few fibers reaching the pars compacta (Parent, 1990).

Thus far, restorative treatments for PD, especially transplantation of fetal dopaminergic precursors into the striatum, have produced suboptimal results, in part due to lack of physiologic integration of the transplanted neurons into brain networks (Freed et al., 2001; Goren et al., 2005). As new treatments enter clinical trials, there will be a need for accurate biomarkers not only of dopamine cell survival but also of their function and connectivity (Palfi et al., 2002). Currently, the nigrostriatal pathway is best evaluated in vivo using Positron Emission Tomography (PET) or Single Photon Emission Tomography (SPECT) radiotracers that target dopamine metabolism, binding, or reuptake. These imaging methods are somewhat susceptible to floor effects (Karimi et al., 2013) and cannot evaluate the integration of dopamine-producing transplants into neural networks. Thus, the development of new non-invasive ways to measure striatonigral connectivity is highly desirable, if technically difficult. Such technical difficulties include limited spatial resolution of current imaging methods relative to the size of the nigrostriatal pathway, location of the pathway within the brainstem, which is susceptible to motion and misregistration errors, and abundance of large adjacent white matter bundles such as the corticospinal tract.

For this study, we used a hypothesis-driven approach to quantify structural connections between the putamen and SN from diffusion weighted imaging (DWI) data using probabilistic tractography. Unlike deterministic tractography, in which streamlines or “tracks” follow a single estimated orientation of the primary diffusion direction, probabilistic tractography also models error in the diffusion estimates. As a result, the directional orientation of vectors modeled probabilistically varies between samples, so not all samples will result in a streamline that reaches the target region. In gray matter regions where the isotropic (equal in all directions) component of diffusion is large and the anisotropic (directional) component small, there is greater variability in directional estimates such that few streamlines are generated. Nonetheless, probabilistic tractography is robust to noise since tracks that propagate in non-anatomic directions soon “die out” due to random orientations of fiber orientation estimates in the adjacent voxels (Behrens et al., 2003b), and less susceptible to signal drop out in areas of crossing fibers (Behrens et al., 2007). For the present study we compared results derived from two diffusion weighted imaging (DWI) sequences, a 40-direction sequence that has been used by our lab in other studies of aging and neurodegeneration (Ly et al., 2016), as well a 60-direction sequence with higher spatial and angular resolution, designed specifically for this project. The rationale for using two DWI sequences was to evaluate replicability of the technique, as well as to see if results from the optimized sequence would better separate PD and control groups. We hypothesized that PD patients would have lower structural connectivity between putamen and SN than their healthy counterparts.

2. Methods

2.1. Study participants

Forty Parkinson's disease (PD) patients and 44 age- and gender-matched controls were recruited as part of the VA-sponsored “Longitudinal MRI biomarkers in Parkinson's disease” (LMPD) study. Participants were recruited from local neurology clinics, through the University of Wisconsin Alzheimer's Disease Research Center (ADRC) recruitment database, and from local support groups. To be enrolled, PD participants had to meet UK Brain Bank criteria for Parkinson's disease (Hughes et al., 1992), be at least 45 years of age at symptom onset (to exclude most genetic causes of Parkinson's disease; Lucking et al., 2000), and be free of significant cognitive impairment (Mini Mental State Examination score of 27–30; Folstein et al., 1975). Exclusion criteria included clinically suspected “atypical” Parkinsonian syndrome, dementia, other central nervous system disease (multiple sclerosis, stroke, encephalitis), major psychiatric or medical disease, family history of PD in two or more first-degree relatives, and inability to hold anti-Parkinson medications for 12–18 h. The University of Wisconsin-Madison's institutional review board and the W.S. Middleton V.A. R. & D. committee approved this study and all participants provided written informed consent prior to participation.

2.2. Procedures

Study procedures included a structured interview to determine the nature and duration of motor, sensory, autonomic, and cognitive symptoms potentially related to PD, Unified Parkinson's Disease Rating Scale (UPDRS; Fahn and Elton, 1987) scoring by a movement disorders neurologist (C.G.), neuropsychological testing, and brain imaging. PD participants were off anti-Parkinson medications for 12–18 h prior to and during study procedures.

2.2.1. Image acquisition

Participants were scanned on a GE 750 Discovery 3T MRI system (GE Healthcare, Waukesha, WI) with an 8-channel phased array head coil. Two structural magnetic resonance imaging (MRI) sequences were acquired to define regions of interest for tractography. A high-resolution 3D Brain Volume Imaging (BRAVO) T1-weighted inversion-prepared sequence of repetition time (TR) = 8.2 ms, echo time (TE) = 3.2 ms, inversion time (TI) = 450 ms, flip angle = 12 degrees, field of view (FOV) = 256 mm, matrix = 256 × 256, slice thickness = 1.0 mm was acquired to define the putamen for precise hand tracing. A fluid-attenuated inversion recovery (FLAIR) sequence of TR = 6000 ms, TE = 124 ms, TI = 1867 ms, flip angle = 90 degrees, FOV = 256 mm, matrix = 256 × 256, slice thickness = 2.0 mm was acquired to provide contrast for defining the SN. DWI data were acquired with a diffusion-weighted echo planar imaging sequence with ASSET parallel imaging (undersampling R = 2 in the phase encoding direction), and higher order shimming prior to the acquisition of each sequence. For this project, we used two DWI protocols, a 40-direction sequence that has been used in prior ADRC studies (Ly et al., 2016), as well as an optimized 60-direction sequence with overlapping slices. The 40-direction (b = 1300 s/mm^2) diffusion weighted imaging (DWI) protocol included 52 contiguous, 2.9 mm thick axial slices of TR = 8000 ms, TE = 86.3 ms, FOV = 240 mm, matrix = 96 × 96 to yield 2.5 × 2.5 × 2.9 mm^3 resolution which was interpolated in-plane on the scanner to 0.94 mm voxels. The 60-direction (b = 1300 s/mm^2) DWI protocol included 55 overlapping 3.0 mm thick axial slices spaced every 1.5 mm, TR = 6500 ms, TE = 68.9 ms, FOV = 192 mm, matrix = 128 × 128 to yield 1.5 × 1.5 × 3.0 mm^3 resolution, which is upsampled to 0.75 × 0.75 × 1.5 mm voxels on the scanner. The thicker overlapping slices provided both higher signal to noise ratio (SNR) and finer spatial sampling than typical DWI sequences. Each DWI protocol included eight non-diffusion weighted volumes (b = 0). The