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In vivo characterization of the connectivity and subcomponents of the human globus pallidus

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ABSTRACT

Projections from the substantia nigra and striatum traverse through the pallidum on the way to their targets. To date, in vivo characterization of these pathways remains elusive. Here we used high angular resolution diffusion imaging (N = 138) to study the characteristics and structural subcompartments of the human pallidum. Our central result shows that the diffusion orientation distribution functions within the pallidum are asymmetrically oriented in a dorsal to dorsolateral direction, consistent with the orientation of underlying fiber systems. We also observed systematic differences in the diffusion signal between the two pallidal segments. Compared to the outer pallidal segment, the internal segment has more peaks in the diffusion orientation distribution and stronger anisotropy in the primary fiber direction, consistent with known cellular differences between the underlying nuclei. These differences in orientation, complexity, and degree of anisotropy are sufficiently robust to automatically segment the pallidal nuclei using diffusion properties. We characterize these patterns in one data set using diffusion spectrum imaging and replicate in a separate sample of subjects imaged using multi-shell imaging, highlighting the reliability of these diffusion patterns within pallidal nuclei. Thus the gray matter diffusion signal can be useful as an in vivo measure of the collective efferent pathways running through the human pallidum.

Introduction

The basal ganglia are a crucial forebrain network associated with many motor and non-motor functions, including reward processing, decision-making, and learning (Adam et al, 2013; Haber, 2003; Hollerman et al., 2000). Many aspects of basal ganglia function rely on dopaminergic inputs from the substantia nigra that serve as a modulatory signal for neurons in the subpallium (Haber et al., 2000). These dopaminergic inputs are conducted by a set of fiber bundles that originate in the pars compacta region of the substantia nigra, a portion of which migrate in a dorsolateral direction through the segments of the globus pallidus (Carpenter and Peter, 1972). While a majority of these projections pass through the pallidum and terminate on cells in the striatal nuclei (Carpenter and McMasters, 1964), a significant number of them also terminate in the inner and outer segments of the globus pallidus, forming the nigropallidal pathway (Cossette et al., 1999). Two other major fiber systems traversing through the globus pallidus project from the striatum, including the striatopallidal fiber systems, that form the canonical direct and indirect pathways, and the striatonigral fiber system. Breakdowns in these various pathways form the etiology of several neurodegenerative diseases. For example, axonal degeneration of the nigrostriatal pathway is the pathological hallmark of Parkinson's disease (Burke and O'Malley, 2013) while Huntington's disease is characterized by a loss of medium spiny neurons within the striatum that project to the globus pallidus (Reiner et al., 1988). Thus in vivo characterization of these basal ganglia projections has clear clinical implications.

One problem with characterizing both the nigral and striatal efferents is that they are largely embedded within the gray matter of several basal ganglia nuclei, primarily within the globus pallidus. The internal segment of the globus pallidus is the primary output of the basal ganglia network, sending projections that relay signals from upstream nuclei to the thalamus (Alexander et al., 1986). In primates it is comprised of the external segment (GPe), that serves as an inhibitory relay nucleus within the indirect pathway and the internal segment (GPi) that aggregates all information from all basal ganglia pathways. While primarily defined by their connectivity and neurophysiological profiles, the GPe and GPi are also distinguishable at the cellular level by differences in cell density, cell type, and morphology (Difiglia and Rafols, 1988; Eid et al, 2013; Hardman et al., 2002). One of the most salient differences is that the GPi has a much lower overall neuronal density (see Table 2 in Hardman et al., 2002). More importantly, given that the volume of the GPi is smaller than that of the GPe and that both nigrostriatal and striatonigral fibers pass through the globus pallidus on their way to their targets, the

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GPi also has a greater density of both nigrostriatal and striatonigral efferents than its external counterpart.

Despite the clear morphological differences, in vivo characterization of these critical nuclei and the efferents running through them remains elusive by MRI-based neuroimaging technologies, particularly conventional T1-weighted or T2-weighted imaging sequences used to estimate neuroanatomical structure. This is because T1-weighted and T2-weighted scans have limited power to characterize the microscopic structure of the GPe and the GPi. This limitation can be compensated by the recent advances in high angular resolution diffusion MRI which offers a non-invasive approach to study microscopic structure. For example, Behrens et al. (2003) used gradients of cortical connectivity to parcellate the nuclei of the thalamus and found robust correspondence to known histologically derived subdivisions. A further advantage of diffusion MRI is that it is able to detect microstructural differences in underlying cellular morphologies, including spatial asymmetry in axonal tracts. With these unique features, diffusion MRI has emerged as an increasingly popular tool for characterizing microstructural properties of neural tissue (Abhinav et al., 2014). While most commonly used to study structural subcomponents of large white matter fascicles (Bastiani et al., 2012; Fernández-Miranda et al., 2014; Wang et al, 2013), diffusion MRI has also been shown to be useful for characterizing differences in local connectivity and anisotropy of gray matter as well (Mang et al., 2012; Wiegell et al., 2003), including sensitivity to both neural and glial distribution patterns (Blumenfeld-Katzir et al., 2011).

Here we adopt an atlas-based approach to studying the orientation distribution functions of the water diffusion, termed spin distribution functions (SDF; Yeh et al., 2010) within the gray matter of the globus pallidus in a stereotaxic space. An SDF provides a nonparametric representation of the diffusion pattern that cannot be offered by conventional tensor-based analysis, thus allowing for characterizing and segmenting structural subcomponents. Unlike tensor-based metrics such as fractional anisotropy, SDFs can also be interpreted in voxels with crossing fiber pathways without violating any methodological assumptions, making them extremely useful in regions with complex microstructural architectures. Here we used data from two high angular resolution diffusion sequences, diffusion spectrum imaging (DSI) and multi-shell imaging (MSI), to examine the diffusion characteristics in the nigral and striatal efferents. The SDF patterns within pallidal voxels were first characterized in the DSI sample and replicated in the MSI sample as an independent validation data set. Along with characterizing the properties of the SDFs within the pallidum, we also examined whether there are reliable differences in the SDF patterns between the GPe and the GPi that allows for accurate segmentation based solely on diffusion properties. These findings may identify a clear potential for using high angular resolution diffusion MRI as a novel in vivo characterization of the microarchitecture of the human globus pallidus, including the nigral and striatal efferents that break down in various neurological pathologies.

Materials and methods

Participants and acquisition

Two separate types of diffusion imaging were used for our analysis.

Diffusion Spectrum Imaging (DSI: CMU-60 Dataset): Twenty-nine male and thirty-one female subjects were recruited from the local Pittsburgh community and the Army Research Laboratory in Aberdeen Maryland. All subjects were neurologically healthy, with no history of either head trauma or neurological or psychiatric illness. Subject ages ranged from 18 to 45 years of age at the time of scanning, with a mean age of 26 years (+/− 6 standard deviation). Six subjects were left handed (3 males, 3 females).
All participants were scanned on a Siemen's Verio 3T system in the Scientific Imaging & Brain Research (SIBR) Center at Carnegie Mellon University using a 32-channel head coil. We collected a 50 min, 257-direction DSI scan using a twice-refocused spin-echo EPI sequence and multiple q values (TR = 9916 ms, TE = 157 ms, voxel size = 2.4 mm^3, FoV = 231 × 231 mm, b-max = 5000 s/mm^2, 51 slices). Head-movement was minimized during the image acquisition through padding supports and all subjects were confirmed to have minimal head movement during the scan prior to inclusion in the template.

Multi-shell Imaging (MSI; HCP-80 Dataset): All multi-shell (MSI) data sets acquired from the Human connectome project at WashU-Minnesota Consortium (Q1 release). Thirty-six male and forty-two female subjects were scanned on a customized Siemens 3T "Connectome Skyra" housed at Washington University in St. Louis. Subject ages ranged from 22 to 36 years of age at the time of scanning, with a mean age of 29.44 (+/− 3.5 standard deviation). All subjects were healthy, with no history of neurological or psychiatric illness. The two subjects that have subsequently been found by the HCP to exhibit gray matter heterotopia have been excluded from this analysis. The HCP diffusion MRI session was acquired using a spin-echo EPI sequence and (TR = 5520 ms, TE = 89.5 ms, voxel size = 1.25 mm^3, FoV = 210 × 180, 3 shells of b = 1000, 2000, 3000 s/mm^2, 111 slices, 90-directions for each shell).

Diffusion MRI reconstruction

All images were processed with a q-space diffeomorphic reconstruction method described previously (Yeh and Tseng, 2011) using DSI Studio (http://dsi-studio.labsolver.org/). The SDFs were reconstructed to a spatial resolution of 1 mm^3. The white matter surface was rendered independently from an externally supplied 1 mm^3 resolution white matter template. The quantitative anisotropy (QA; Yeh et al., 2010) and fiber orientation of the three major fibers in each voxel were exported into a separate file for analysis.

SDF analysis

Masks of the inner and outer segments of the pallidum were manually drawn by identifying the internal medullary lamina in each hemisphere on the high resolution T1 ICBN MNI template. In each hemisphere, the GPe was drawn by including those voxels between the anterior and posterior limbs of the internal capsule, the putamen, and the internal medullary lamina (outer left in Fig. 2A). Similarly, the GPi was drawn by including the voxels between the internal medullary lamina, the posterior limb and genu of the internal capsule (inner left in Fig. 2A). All region of interest masks were drawn in MRICron (Rorden and Brett, 2000) and exported as NifTI images.

We then isolated the SDFs within each voxel of both region masks for analysis. For illustration, Fig. 2B shows a schematized version of a SDF illustrating three resolved fibers, with their independent magnitude (i.e., lengths, reflecting QA) and orientation. Two representative 3D SDFs from a voxel within the left GPi and a voxel within the left GPe are shown in Figs. 2C,D. For each voxel, we took three independent measures of the SDF structure: the primary fiber orientation, the number of resolved fibers across a range of QA thresholds, and the QA magnitude of the primary fiber. To generate the angular distribution histograms (Figs. 3,4), we used the circstat toolbox (Berens, 2009) and computed the circular mean of the voxel orientations across subjects. The internal capsule orientation (green arrows in Figs. 3,4) was calculated by averaging the primary fiber orientations across a 4 mm^3 voxel cube situated prominently within the internal capsule in the left and right hemispheres. For plotting purposes, a gaussian smoothing kernel was applied to the QA maps (Figs. 6A–D) for each subject (2 FWHM).