Comparative study of anatomical connectivity of prelemniscal radiations in healthy subjects and Parkinson´s disease patients

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TARGET AUDIENCE: Neuroimaging researchers, Neurosurgeons, Medical doctors.

PURPOSE: The subthalamic prelemniscal radiations (Raprl) have been proposed as a neurosurgical target for deep brain stimulation (DBS) for the treatment of Parkinson´s disease (PD) and essential tremor since 1970´s[1] and has been proven to be a superior target for ameliorating tremor and rigidity than any other target.[2] Despite its clinical usefulness, the anatomic connectivity of the Raprl remains unknown. This work aims to (1) characterize the anatomic connectivity of Raprl in healthy subjects and in PD patients and (2) to identify differences in the fiber populations that conform the Raprl using high angular resolution diffusion MRI and probabilistic tractography.

METHODS: The Institutional Review Board approved the protocol and all subjects signed a written informed consent according to the Declaration of Helsinki. Images from 12 healthy subjects and 6 PD patients were acquired using a 3Tesla Philips Achieva TX scanner. Diffusion- weighted images (DWI) were acquired using 120 unique diffusion- gradient directions with a b value of 2000 s/mm^2 and 4 volumes with b=0 s/mm^2 (voxel size of 2x2x2mm^3), in addition to T1 and FLAIR-T2 volumes with voxel resolutions of 1x1x1 mm^3. Total scan time was around 1 hour per subject. Constrained spherical deconvolution (CSD)[3] was performed, followed by the creation of track-density images (TDI)[4] based on 1 million tracks seeded homogeneously throughout the white matter using MRtrix (Brain Research Institute, Melbourne Australia), resulting in final resolution of the TDI was of 0.2x0.2x0.2mm^3; these images were crucial for the accurate visualization of the different subthalamic structures (Raprl, zona incerta, subthalamic nucleus (STN) and red nucleus), which were manually segmented based on the Schaltenbrand- Wahren atlas and were not readily discernible on the anatomical images. Next we seeded 50,000 streamlines at the level of the segmented Raprl, and used spherical-deconvolution informed filtering of tractograms (SIFT)[5] to improve the accuracy of probabilistic tractography. Finally, tracts were virtually dissected according to targets defined automatically by the co-registration of subject-specific labels according to the Desikan-Killiany Atlas as provided by Freesurfer (v. 5.3). The number of streamlines interconnecting the Raprl to each target was tabulated and differences between groups were assessed by Students t-test.

RESULTS: Probabilistic tractography demonstrated connectivity of the Raprl with distinct cortical and subcortical structures. All subjects showed connectivity with orbitofrontal cortex (OFC), motor and premotor cortex, thalamus, globus pallidus (GP), cerebellum and pedunculopontine nucleus (PPN). In 87.5% of healthy subjects GP showed connectivity with the contralateral dorsal brainstem in a region that corresponds to the location of the contralateral PPN, the same connectivity pattern is present in 83.3% of PD patients. The number of reconstructed streamlines obtained showed differences between groups in the connectivity to bilateral pallidum (GPleft mean=15621(sd=7018) and 10384(3736) for patients and controls, respectively, p=0.017 and GPright mean=14228(7080) and 10692(2818), p=0.045) and in bilateral thalamus (Thalamus left mean=31850(16069) and 40977(4348), p=0.02 and Thalamus right mean=36419(15131) and 42169(3557), p=0.006) (Table 1). Fiber bundles that conform Raprl seem to be intermingled in the posterior subthalamic area, but as they extend beyond and enter the posterior limb of internal capsule they show a clear spatial organization, with the tracts organized, according to their targets, from anterior to posterior as follows: 1) orbitofrontal cortex, 2) GP 3) supplementary motor area and 4) primary motor cortex and cerebellum (Figure 1).

DISCUSSION: In view that more than one third of white matter voxels contain crossing fibers[6], the use of DTI sequence resulted inadequate in studying fiber composition of a small area with multiple fibers. In contrast, CSD allowed the determination of the orientation of fiber tracts in the Raprl, an area through which several fiber bundles funnel. The order of fibers that passes through Raprl when they are above the subthalamic area is reproducible across all the 18 hemispheres studied and provide evidence of a clearly spatial arrangement of fibers. In the present study the thalamus is shown as the structure with the densest connections to Raprl. However, it must be noted that its spatial location, relatively close to the location of Raprl, may influence these results. In addition, streamlines were allowed to continue their trajectory after entering a target region, hence thalamus connectivity may be overrepresented due to streamlines passing through it on their way to the cortex or other targets. SIFT allows to reconstruct pathways in which the streamlines densities can be visualized as proportional to fiber densities in basis to CSD. This new imaging processing technique could give an approach of the characteristic of the subjacent tissue and could suggest micro- structural differences between groups as presented in this work. The differences between groups in the number of reconstructed streamlines for the thalamus and GP show that PD is a disorder characterized by changes in BG connectivity and involves degeneration of white matter tracts.[7] Although the differences of reconstructed streamlines between groups for GP could suggest a compensatory role of these projections. Classical tracer studies in monkeys described interconnections between the basal ganglia and cerebellum.[8] The present work support the idea that efficacy of Raprl DBS relies on interference of cerebellar-thalamic-BG connections. PD patients that have undergone Raprl-DBS show an improvement on gait that also occurs after unilateral GP-DBS[9], which could be explained because of the bilateral connections from Raprl to PPN through fibers crossing the midline at lower midbrain.

CONCLUSION: Probabilistic tractography based on TDI and CSD allows the visualization of Raprl this could be useful for planning neurosurgeries of posterior subthalamic area. Connectivity of Raprl replicates in humans invasive tracer studies from phylogenetic ancient species. Our findings provide new insights into subthalamic anatomic connectivity that allow explaining clinical benefits obtained with Raprl-DBS in PD patients.

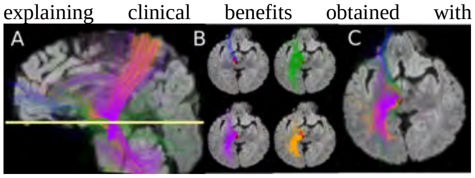

Figure 1. A: Sagittal T2FLAIR view of a representative healthy subject with Raprl probabilistic tractography overlay. Tracts from OFC in blue, the ones related to GP in green, cerebellar fibers in purple and anatomic connectivity with primary motor cortex in orange. The white line represents the level of axial views presented in B and C, that contains the same color coded pathways and also at midbrain are the segmentations of STN in pink, Raprl in yellow and Red nucleus in red.

Target area	Healthy subjects	Parkinson´s disease
Frontal pole left	313 (132)	357 (229)
Frontal pole right	573 (238)	361 (221)
Pallidum left	10384 (3736)	15621 (7018)*
Pallidum right	10692 (2818)	14228 (7080)*
Precentral left	5636 (1159)	4205 (1019)
Precentral right	5798 (1449)	4795 (1233)
Thalamus left	40977 (4348)*	31850 (16069)
Thalamus right	42169 (3557)*	36419 (15131)
Cerebellum cortex contralateral left	4615 (1783)	4828 (932)
Cerebellum cortex contralateral right	4924 (2083)	5253 (849)

Table 1. Mean and standard deviation of streamlines.

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