

## Visualization of the human basal ganglia and thalamic circuits in individuals using 7T MRI

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**Introduction:** Basal ganglia circuits are affected in neurological disorders such as Parkinson's disease (PD), essential tremor, dystonia and Tourette syndrome [1,2]. Subject-specific models of the structural and functional connectivity of these circuits are critical for elucidating the mechanisms of these disorders, and developing new treatments. Despite recent advances in neuroimaging techniques, insufficient resolution and sensitivity have limited progress toward a more complete description of the basal ganglia and thalamic connectivity in individuals. Here, we present a unique imaging and computational protocol designed to generate a comprehensive *in vivo* model of the structure and connections of the human basal ganglia. Capitalizing on the enhanced signal-to-noise ratio and enriched contrast of ultra-high-field (7T) MRI [3], detailed subject-specific representations of the basal ganglia structures and white matter pathways were obtained. Seven pathways were reconstructed and visualized for the first time in individuals. Parcellations of the basal ganglia (caudate nucleus, CN; putamen, Pu; external and internal globus pallidus, GPe/GPi; substantia nigra, SN; and subthalamic nucleus, STN) and thalamus (Tha) into sub-territories based on their distinct connectivity patterns are also presented. Our findings are supported by functional connectivity maps obtained from resting-state fMRI, and results from animal studies [4], histology, or group-averaged MRI population studies [5,6]. The new findings open new avenues of investigation into the movement and neuropsychiatric disorders, in individual human subjects.

**Method:** Four healthy subjects were scanned using a 7T MRI. One subject was scanned twice in two different days. The protocol included T1-weighted MRI (1 mm<sup>3</sup> voxel size), T2-weighted MRI (0.4x0.4x2 mm<sup>3</sup>) and susceptibility-weighted imaging (SWI; 0.4x0.4x1 mm<sup>3</sup>), high-angular resolution diffusion imaging (HARDI; 1.5x1.5x1.5 mm<sup>3</sup>, 128 diffusion gradients, b-value=1500s/mm<sup>2</sup> and 15 b<sub>0</sub> images), and resting-state fMRI (R-fMRI; 5 min acquisition with 150 time frames 1.5x1.5x1.5 mm<sup>3</sup>). A combination of T2, SWI and fractional anisotropy (FA) images was used to manually segment the seven regions of interest (ROI) in the five datasets. The exquisite level of details of 7T T2 and SWI data allows the clear differentiation of GPe, GPi, SN and STN. Fiber orientation mapping and probabilistic tractography [7] was performed to: 1) Identify the three-dimensional course of white matter pathways between ROIs; 2) Identify sub-territories within ROIs, based on the distinct probability of connection of each voxel. Seed-based analysis [8] of the R-fMRI data was performed to obtain activation maps of each ROI.

**Results:** Twenty-one pathways were studied. High reproducible patterns of connectivity were found across right and left hemispheres in each individual and across the five individual datasets (Fig. 1; pathways in white wireframe, Pu in red, SN in yellow, Tha in orange and GPi in green), and in agreement with previous results from human *post-mortem* and animal studies. Seven pathways (nigrostriatal, nigropallidal, nigrothalamic, subthalamopallidal, pallidothalamic, striatopallidal, and thalamostriatal) were successfully reconstructed and visualized (Fig. 1). A finer level of analysis was performed using a voxel-based approach to identify anatomical sub-territories of each ROI, and quantify the probabilities of these connections (Fig. 2; each color represents thalamic subdivisions strongly connected to the basal ganglia). We found a good spatial agreement between our structural and functional connectivity findings.

**Discussion:** Contrary to most existing studies, which are based on animal data, histology, or group-averaged MR imaging of human subjects, the data presented here was acquired in individual and living human subjects. Based on this data, we propose an updated description of the human basal ganglia and thalamic connectome, summarized in Fig. 3. The seven anatomical pathways we successfully visualized in individual living human subjects are highlighted in red. This fine mapping of the basal ganglia/thalamic connectome made possible by the techniques demonstrated here, may provide valuable pre-operative information about targeting specific structures and planning for deep brain stimulation surgery. This may, in turn, translate into improved clinical outcomes. Finally, this study provides new quantitative tools with which to investigate longitudinal alterations in basal ganglia and thalamic structure, and connectivity in patients and individual subjects with movement and neuropsychiatric disorders, allowing for investigations into structural and functional changes at the level of overall target shape, volume, sub-territory organization, and in the strength of connections—and the clinical significance of any such findings.

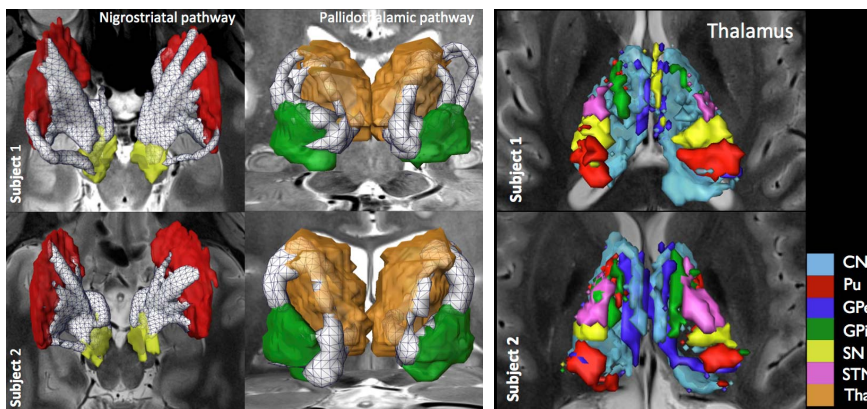


Figure 1 – White matter pathways reconstructions (white wireframe) from probabilistic tractography

Figure 2 – Thalamus parcellation based on white matter projections to the basal ganglia

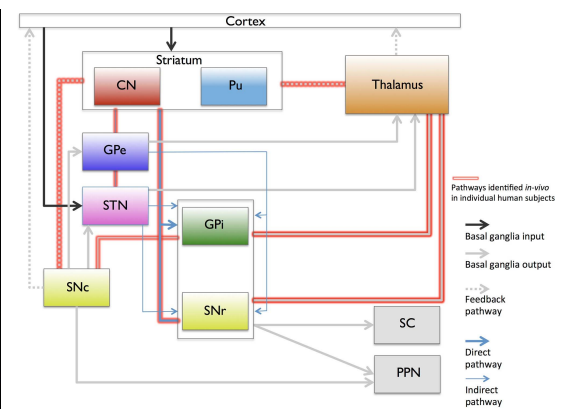


Figure 3 – Basal ganglia and thalamus circuits, and newly identified pathways *in vivo* in individual human subjects (red)

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