Abnormal connectivity pattern of fronto-striatal-thalamic circuits of patients with Tourette syndrome based on probabilistic tractography.

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Introduction: Abnormal connectivity pattern involving the fronto-striatal and fronto-thalamic circuitry has been implicated as the pathophysiologic mechanism causing involuntary motor and vocal tics in patients with Tourette syndrome (1). In this study using diffusion tensor imaging (DTI) and probabilistic tractographic technique (2), we assessed the pattern and quantified the strength of connectivity of the caudate and the thalamus to various cortical regions, including the frontal cortex.

Material and Method: We studied sixteen subjects with Tourette syndrome (TS) (age range: 7 – 18 years, mean age: 11.6 ± 2.1 years, 14 boys, 2 girls) and compared them with ten age matched normal controls (NC) (age range: 7 – 18 years, mean age: 13.2 ±3.5 years, 8 boys, 2 girls) using DTI acquired on a 3T MRI Scanner. Diffusion data consisted of 55 diffusion sensitized images (b=1000 [s/mm^2]) and one T_2W reference image (b=0 [s/mm^2]) in each of the 35–40 slices that covers whole brain. Images were further processed using FSL (ver 4.01) (FMRIB, Oxford, UK, http://www.fmrib.ox.ac.uk/fsl/) for brain extraction, probability distribution function (pdf) of individual voxels (with one fiber model per voxel), spatial registration of the diffusion data with MNI152 template image, and tractography. Based on the segments of the MNI templates, we segmented the cortical hemisphere including the cerebellum into eight cortical and subcortical targets (Frontal, Parietal, Occipital, Temporal, Insular, Cerebellum, Lentiform nuclei and Thalamus), and we subdivided the frontal cortex into 11 frontal-cortical targets (Cingulate, Paracingulate, Precentral, Middle frontal, Orbitofrontal, Superior frontal, subcallosal, Frontal pole, Frontaloperculum, Inferior frontal parsoperculum, and Inferior frontal parstriangularis). MNI standard template regions were transformed to the individual subject's diffusion space to be used as seed and target regions. Following the tractography procedure, they were transformed back to the MNI standard space for further comparison across subjects. Target based classification for caudate seed (CS) and thalamic seed (THS) were performed bilaterally to the ipsilateral hemisphere targets (with 5000 samples, step length of 0.5, and curvature threshold of 0.02). Connectivity scores of the seed regions were expressed as the sum of each individual seed voxel values. These values are defined by the number of samples reaching a particular target as a proportion of the total number of samples reaching any target regions within the target group (hemispheric or frontal). Preliminary statistical analysis involved all (8 hemispheric, and 11 frontal) target regions. However, subsequent analysis involved target region with only connectivity scores value > 10. Repeated measure analysis of covariance was performed separately for the two seed structures (CS, THS). Side and target are entered as within-subject variables, TS and NC as between-subject variables, and age at the time of MRI acquisition as covariate.

Results: With CS, frontal (257±19), lentiform nuclei (43±5), and thalamic (190±10) targets (Fig 1A) showed high connectivity scores (Figure 1A). Similarly with THS, caudate (313±20), lentiform nuclei (105±16), frontal (234±19), parietal (87±6), occipital (13±6), temporal (49±5), and cerebellum (77±11) targets showed high connectivity scores (Fig 1B). Among the frontal targets (figure 1C) CS showed high connectivity scores with the frontalpole (280±20) precentral gyrus (20±2), superior frontal gyrus (37±7), and subcallosal cortex (56±4), and the THS (fig 1D) showed high connectivity scores with the frontalpole (326±2), precentral gyrus (142±7), and superior-frontal gyrus (119±10). Furthermore, significant 2-way interaction between frontal targets and groups (NV, TS) was seen for caudate seed (p = 0.04) and thalamic seed (p=0.078). As illustrated in the figure(c,d) both the caudate and the thalamic seeds showed significantly decreased connectivity scores to the frontal pole target which represent the anterior dorsolateral frontal cortex. Although the connectivity scores to the frontal pole were decreased in both left and right sides, no significant interaction was noted between the left and the right sides.

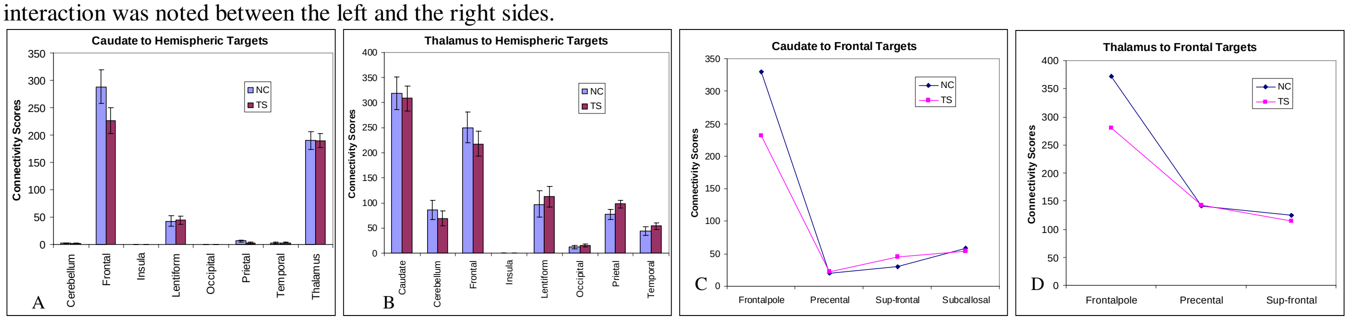

Figure: Connectivity scores of the caudate seed regions (A) and the thalamic seed regions (B) to the ipsilateral hemispheric targets and the connectivity scores of the caudate seeds regions (C) and the thalamic seeds regions (D) to the ipsilateral frontal targets. All values were expressed as Estimated Marginal Means.

Discussion: Our results showed abnormal connectivity patterns among components of the fronto-striato-thalamic circuit using seed regions at both the caudate and the thalamus and targeting the anterior dorsolateral frontal cortex in patients with Tourette syndrome in agreement with morphopmetric MRI on basal-ganlgia (3, 4)) and thalamus (5) of TS patients. Our results provide further evidence of the involvement of the fronto-striato-thalamic circuit in TS.

References: (1) Peterson et al., Arch Gen Psychiatry 2003; (2) Behrens TEJ, *NeuroImage*, 2007; (3) G Garraux, et al. Ann Neurol 2006; (4) Gerard J of Psychosomatic Research (2003): (5)Lee et al. Acta Psychiatr Scand 2006.