Putative Links Between Fronto-Striato-Thalamic Pathways And Behavioral Phenotype In Children with Tourette Syndrome.

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Introduction: One of the prevailing theories in Tourette syndrome (TS) is that many of its symptoms (motor and vocal tics) co-existing with obsessive compulsive disorder, attention-deficit/hyperactivity disorder, (and other behavioral disturbances), can be accounted for by abnormalities within the fronto-striato-thalamic (FST) circuitry [1]. The purpose of this study was to determine, using probabilistic fiber tracking, whether abnormal connectivity of the FST circuit underlies the morphological changes reported previously in subcortical structures of patients with TS, and to correlate changes in the FST circuit with neurobehavioral measures.

Materials and Methods: Eighteen children (mean age 11.3 ± 2.4 years) diagnosed with TS and 12 healthy control children (mean age 12.2 ± 4.1 years) underwent diffusion tensor MRI (DTI). A spin-echo EPI double RF refocusing pulses and parallel imaging (factor of 2) was acquired in axial plane with sensitization gradients (b = 1000 [s/mm^2]) applied in 55 non-collinear directions and a T2W scan (b = 0 [s/mm^2]). The frontal cortex was segmented into 11 frontal-cortical targets: cingulum, para-cingulum, precentral, middle frontal, orbitofrontal, superior frontal, subcallosal, anterior dorsolateral frontal cortex, frontal operculum, inferior frontal pars operculum, and inferior frontal pars triangularis. Target based classification for caudate nucleus and thalamic seeds were performed bilaterally to the ipsilateral hemisphere targets. DTI were processed using FSL software (http://fmrib.ox.ac.uk/fsl/) to extract the brain, to determine probability distribution function (*pdf*) of individual voxels, to perform spatial registration of the diffusion data with MNI152 template images, and tractography [2]. Group differences in regional connectivity scores (CS) were assessed statistically using a two-tailed contrast, namely, testing for an increased or a decreased probability of a particular voxel in the seed ROI to connect to a frontal target region (k) using the following equation:

$$CS(k) = \sum_{j=1}^{N} \left(\frac{S_{jk}}{\sum_{t=1}^{n} S_{jt}} \right)$$

N = number of voxels in seed ROI;
n = number of voxels in target ROI;
S = score relative to pixel,
k = index of target ROI

Each participant (patients) underwent measures of tic severity, attention-deficit/hyperactivity disorder, and obsessive-compulsive disorder to evaluate associations between Tourette syndrome specific (tics) and comorbid symptoms based on Diagnostic and Statistical Manual of Mental Disorders IV-TR [3] and diffusion tensor imaging metrics.

Results: Significant 2-way (groups x targets) interaction (p = 0.029) was observed for the caudate nucleus seeds. Simple effects tests showed that the TS group had significantly lower probability of connection between caudate nucleus (fig 1A) and anterior dorsolateral frontal cortex (ADLF) on the left (p=0.038), with a trend for decreased connectivity on the right (p=0.12). There was also a trend for increased connectivity in the TS group between the caudate seed and the right subcallosal target (p=0.054). The overall test for the thalamic seed (fig 1C) revealed a trend for a group x target interaction (p=0.078). Follow up simple effects tests showed that none of the targets reached significance for differences between the TS and control groups. Obsessive-compulsive behavior was negatively associated with connectivity score of the caudate nucleus and ADLF (p=0.01) in the left hemisphere. Obsessive-compulsive behavior was also positively associated with connectivity score for the subcallosal gyrus (p=0.009) and for the lentiform nucleus (caudate nucleus seed; p=0.008).

Discussion: Our findings demonstrate negative correlation between obsessive-compulsive behavior and connectivity of the FST circuitry (between the caudate nucleus and anterior dorsolateral frontal cortex bilaterally, and between the caudate and subcollosal gyrus). These indicate not only aberrant connectivity of these pathways in subjects with Tourette syndrome [4,5], but also to test putative links between these pathways and behavioral phenotype in this disorder [6]. These microstructural and morphologic findings support the notion that the primary disturbances in FST circuit are centered on neural projections into or out of the caudate nucleus.

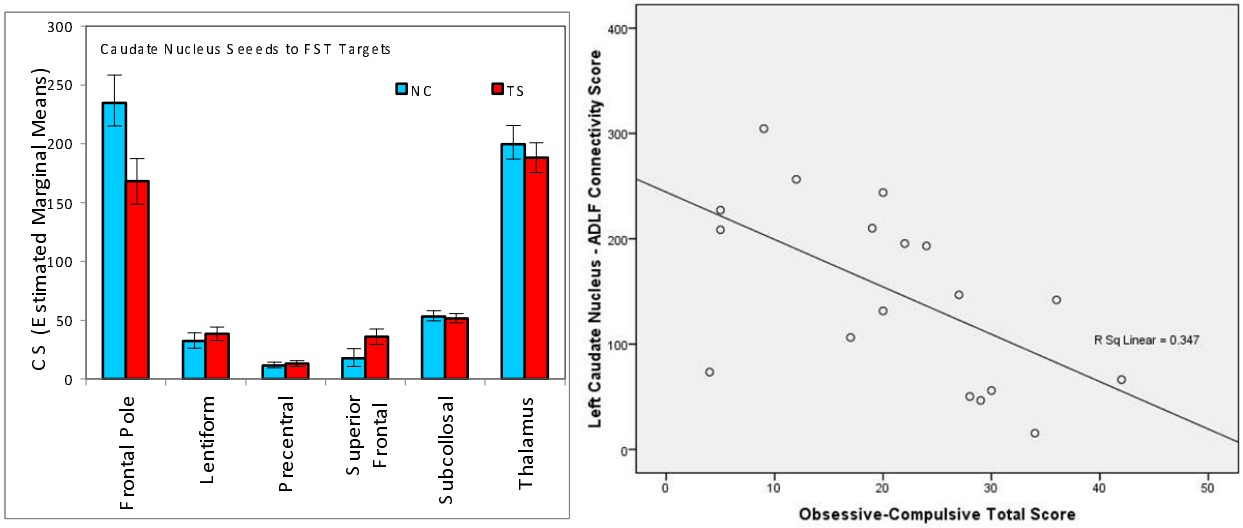

Figure1: A) Estimated marginal means (controlling for age) of the connectivity scores emanating from the caudate seed regions and targeting the cortical areas where values were expressed with standard error, (B) the correlation of the connectivity scores of the left caudate nucleus to ADLF with the obsessive compulsive totla score..

References: *[1] Rauch S, et al.. Advances in Neurology. (2001); [2] Behrens T et al., MRM (2003); [3] American Psychiatric Association (2000); [4] Makki M et al., Mov Disorder J (2008); [5] Singer HS, Neurologic Clinics (1997); [6] Osmon DC et al., Behav Modif (2005).*