Altered Diffusion Tensor MRI Indices of frontal cortical and basal ganglia in Children with Tourette Syndrome Assessed by Voxel-Based Analysis Study.

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Introduction: Tourette syndrome (TS) is a chronic, childhood-onset neuropsychiatric illness characterized by motor and vocal tics. It frequently co-occurs with obsessive-compulsive disorder (OCD), attention-deficit/hyperactivity disorder (ADHD), or other social and behavioral disturbances. Although the neurobiological abnormalities underlying TS remain unknown, various biochemical, neuroimaging, neurophysiological, and genetic studies suggest a role for the basal ganglia and related thalamic and cortical regions [1,2]. MRI studies of TS patients have reported volume reductions in the putamen, the globus pallidus, and the lenticular nuclei [3]. Volumetric changes have also been reported in frontal cortex [3,4], hippocampal gyrus [5], palladium [6], left mesencephalon [7], and caudate nucleus [8]. We investigated interhemispheric brain asymmetry of children with TS, by applying voxel-based analysis (VBA) of diffusion tensor imaging indices maps. We hypothesized the presence of abnormal diffusivity in frontal and subcortical brain regions assessed in vivo using diffusion tensor MRI.

Material and Method: Twenty children diagnosed with TS (age range=[6.3, 18] years, mean age 11.7 ±3.1 years, 17 boys and 3 girls) and 33 healthy control children (age range: [6.0, 17.6] years, mean age = 13.1 ± 3.2 years, 17 boys and 16 girls) underwent DTI on a 3T scanner. DTI sequence was performed in 36 to 40 axial slices with 6 diffusion sensitization gradients (b = 1000 [s/mm^2]) applied in non-collinear directions and a T_2W reference scan (b = 0 [s/mm^2]) averaged 6 times. Double radio-frequency refocusing pulses and parallel imaging capability (ASSET factor of 2) were applied to reduce eddy-current and geometric distortion derived from echo-planar imaging. Acquired images were processed using *DTIstudio* software (H. Jiang and S. Mori; Johns Hopkins University; http://cmrm.med.jhmi.edu) to create map of parallel (λ_1), middle perpendicular (λ_2) and minor perpendicular (λ_3) diffusions, apparent diffusion coefficient (ADC), and fractional anisotropy. Data were processed using the statistical parametric mapping software (SPM2, http://fil.ion.ucl.ac.uk/spm), to test for regional structural differences on a voxel-wise basis between groups of subjects [11]. Correction of residual eddy-current and field inhomogeneity distortions was performed first and non diffusion images were warped to EPI using an algorithm based on Markov random fields. Selected regions of interest (ROIs) included a composited frontal region (Brodmann areas: 9,10,11,44,45, 46, and 47) and caudate nucleus, putamen and globus pallidus. Each of the 5 maps (λ_1, λ_2, λ_3, ADC, and FA) was warped to the resulting non diffusion set, and a template was created from the 53 subjects. The normalized, segmented, and unmodulated images were smoothed using a 12-mm FWHM isotropic Gaussian kernel [12]. Group differences in regional (λ_1, λ_{23}, ADC and FA) maps were assessed statistically using four separate 2 (structure) x 2 (group) x 2 (side) multivariate analyses (MANCOVA), with age and gender as covariates. Follow up test was performed if (side x group) or (side x group x structure) interaction was < 0.1.

Results: In the frontal lobe we observed a significant 2-way interaction (side x group) for λ_1 *(p= 0.04),* and for ADC *(p = 0.038).* Follow up tests revealed significantly increased λ_1 on the left side *(p=0.023),* decreased λ_1 in the right side *(p=0.048),* and increased left > right asymmetry in ADC on the left side of TS patients as compared to controls *(p=0.038).* There was no significant difference in FA between the two groups. With regard to group differences in the basal ganglia, results revealed a significant 3-way interaction (*side x group x region = 0.06*) for λ_{23}. Follow up tests revealed a decrease across basal ganglia regions on the left as compared to controls (*p=0.037*). Additionally, there was a significant decrease in FA of the left palladium of the TS group compared to controls (*p=0.021*). Finally, we found significantly decreased λ_1, in the bilateral thalamus of TS patients compared to controls.

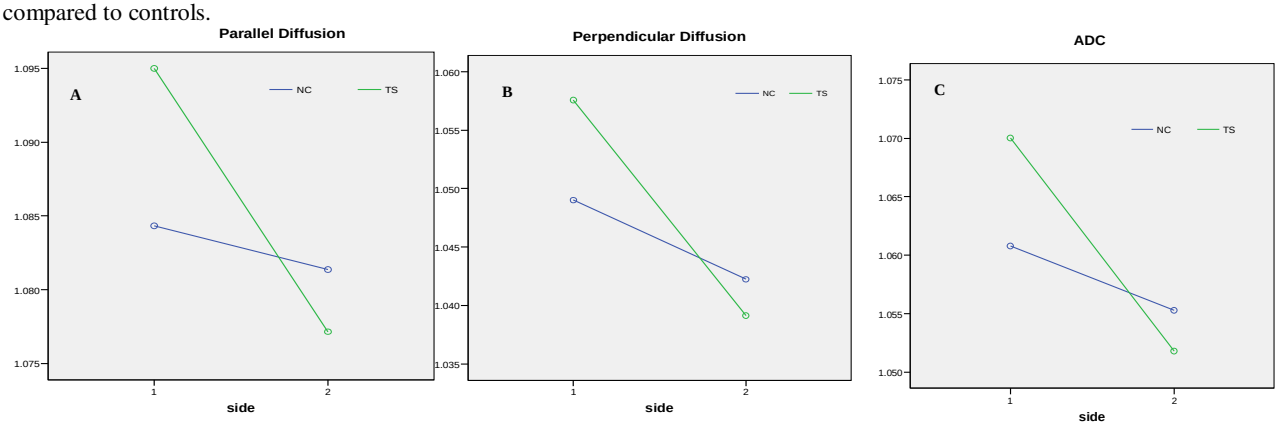

Figure 1: A) the frontal-lobe of TS patients showed a significant increase in parallel diffusion on the left side (side =1) and significant decrease on the right side (side = 2) compared to NC group. The same pattern was observed in perpendicular diffusion (B). Therefore, we measured significant increase of ADC on the left side, and significant decrease on the right side of TS group compared to NC group (C).

Discussion: Previous studies have shown abnormal gray matter morphology in the brains of TS patients, particularly in regions comprising the fronto-striato-thalamic circuit. Our results extend these findings by providing direct evidence for abnormal white matter integrity in component regions of this circuit in TS patients, thus further supporting a role for this circuit in TS. Future studies will use DTI tractography in order to further examine fronto-striatal and fronto-thalamic tracts in patients with TS.

References: 1) Leckman and Riddle, Neuron, 28:349-54, 2000; 2) Rauch et al, Adv Neurol, 85:207-24, 2001; 3) Peterson et al, Arch Gen Psych, 58:427, 2001; 4) Fredericksen, Neurology, 58:85-9, 2002; 5) Ludolph AG, Br J Psychiatry 2006 May; 188:484-5; 6) Peterson B et al., Arch Gen Psych 2003; 7) Garraux et al., Annals of Neurology 2006; 8) Bloch et al., Neurology 65 2005; 9) Fredericksen, Neurology, 58:85-9, 2002; 10) Kates et al., Psychiatry Res 116:63-81, 2002; 11) Ashburner J, Friston KJ. Neuroimage 2000;11:805– 821; 12) Friston, 1995; Worsley, 1996.

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