Abnormal Corticostriatal Pathway in Patients With Tourette Syndrome.

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Introduction: Tourette syndrome (TS) is complex neuropsychiatric childhood disorder characterized by involuntary non rhythmic movement and vocal symptoms called tic that are quite often associated with co-morbid neuropsychiatric comorbidities such as OCD, ADHD (REF). These tics and follow a waxing and waning pattern of severity and usually peak during the early second decade of life with many subjects (80%) showing a marked reduction of severity by the end of adolescence. Many evidences form postmortem and neuroimaging studies have implicated the involvement of fronto-striato-thalamic-cortical (FSTC) circuitry in the involvement of tic generation [1,2]. Tract Based Spatial Statistics (TBSS) is a well designed technique for the study of cerebral white matter (WM) which makes use of the intrinsic anisotropic property of the WM and projects the fractional anisotropy values of the WM tracts onto a virtual skeleton which runs at the median part of a WM tract [3]. In this present study we used TBSS to identify abnormalities in minor WM tract changes in children with TS (17 right handed, age = 11.6± 2.4 years, 14 males) and compared them to healthy controls (mean age: 12.3±3.2 years, 6 males).

Methods: Neurobehavioral measures for hyperactivity, attention, externalizing, internalizing, and obsessive and compulsive problems were also measured in TS children and for 15 of them the tic severity score or the period of one week prior to the MRI scan was noted according to the Diagnostic and Statistical Manual of Mental Disorders IV-TR [4]. Axial DT-MRI (> 34 slices, Voxel=0.85x0.85x3mm^3) were acquired on 3T scanner with 6 non-collinear diffusion sensitization gradients (b = 1000 [s/mm^2]) and 1 T2W, repeated six time and magnitude averaged. The entire image sets were affine corrected for motion and other imaging artifacts followed by extraction of the brain matter on the T2W images, using the Brain Extraction Tool (BET) (FSL software; FMRIB lab, Oxford UK) with a fractional intensity threshold of 0.35 [3]. The extracted T2W image were applied as a mask to both the FA and ADC images of all the participants and used as the input images for TBSS processing. The transformed FA images of all participants were averaged to create a mean FA image which was then used to create a skeleton image of the WM tracts by searching and labeling the skeleton voxels with maximum FA intensity along the perpendicular direction (breath) of the tract. This mean skeleton was later applied to the registered FA image of individual participants. Voxel-wise statistical analysis of individual skeleton images of both controls and TS children for both contrasts (controls > TS) and (controls < TS) was performed using nonparametric permutation test. Age was entered as a covariate, the cluster size threshold was > 3, the p-value of <0.05 for significance, after correcting for multiple comparisons. Skeletal voxels that were significantly different between the groups were isolated and labeled; these voxels were then expanded to include the full width of the WM tract which was then used as a mask permitting calculation of the mean FA and ADC values for the width of the tract for individual participants. These regional/tract values were then correlated with age, tic severity and neurobehavioral scores. The mean values from the regions identified from the TBSS analysis were noted for all the subjects and then correlated with tic severity and neurobehavioral scores. For Type I error associated with multiple correlations, the threshold significance for Pearson product moment correlation coefficient was set to p = 0.01, for correlations between neurobehavioral variables and DTI measurements.

Results: The main results of this investigation showed regions with increased water diffusivity (ADC) in parts of left external capsule (EC) and left subcolosal fasciculus (SC) (Figure 1). Furthermore, the mean ADC values measured from EC showed negative correlation with the tic severity score (r = -0.666, p = 0.007) (Figure 2).

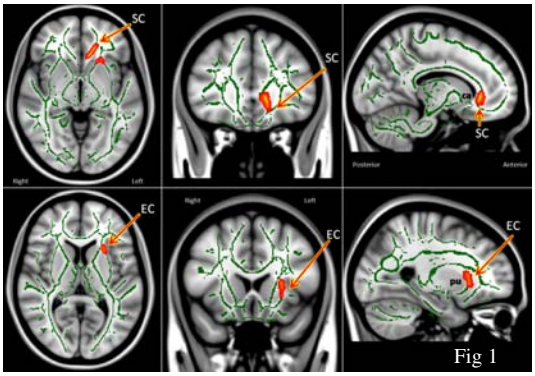
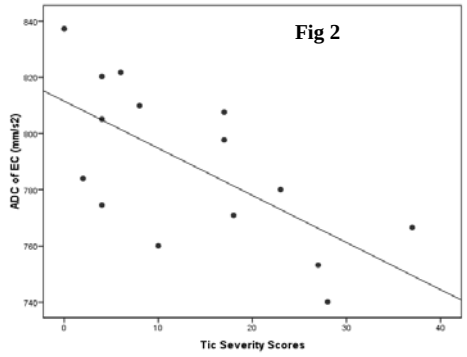


Fig 1: Increased ADC (arrows) identified in projections from cortex to basal ganglia. Subcallosal fasciculus (SC): projects from dorsal cortex to head of caudate, and the external capsule (EC) projects from ventral cortex to putamen.

Fig 2: Negative correlation between tic severity scores and ADC values of external capsule (EC)



Conclusions:The major findings of the present study were increased ADC values in the corticostriatal projection pathways including both the medial subcollosal fasciculs (SC) pathway and the lateral external capsule (EC) pathway of the left cortical hemisphere in children with TS. Also, the ADC values derived from the EC pathway showed significant negative correlation with the tic severity scores. One of the possible mechanism postulated in tic generation, is the involvement of cortio-striat-thalamo-cortical pathway. In a normal state, the frontal cortex has a normal tonic inhibition of the striatum through their inhibitory projections [5,6]. In subjects with TS this tonic inhibition from the frontal lobe could possibly be disturbed, leading to the disinhibition of the striatum causing the uncontrolled activation of the striato-thalamo-cortical pathway causing tics. This notion is supported by our finding where the diffusion abnormality in the corticostriatal projection pathway form the frontal cortex is strongly affected and correlated with the tic severity scores. These changes could be related to some specific neuronal injury in the frontal cortex, affecting the efferent axons from these neurons. These affected efferent axons from these neurons could show distal changes expressed as diffusion abnormality seen by us, in these white matter pathways.

References: [1] Behen ME et al., Mov Disord (2007); [2] Makki et al., J Child Neurol. (2008); [3] Smith SM et al., Neuroimage (2006); [4] American Psychiatric Association (2000); [5] Osmon and Smerz, Behav Modif (2005); [6] Singer and Minzer; Brain and Development (2003).