White Matter Abnormalities in Tourette Syndrome Extend Beyond Motor Pathways

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Introduction. Tourette syndrome (TS) is a neuropsychiatric disorder with the cardinal symptoms of motor and vocal tics [1-2]. We investigated white matter abnormalities in Tourette patients using diffusion tensor imaging (DTI), Tract-Based Spatial Statistics (TBSS) [3] and correlation analysis.

Methods. DTI data from 19 adult Tourette patients and 19 age- and sex-matched healthy volunteers were acquired on a 1.5T scanner (SonataVision, Siemens) using a twice–refocused spin-echo diffusion-weighted EPI sequence (resolution=(2 mm)^3, TR = 11000ms, TE=89ms, FOV 256×208mm^2, b=800s/mm^2, 30 non-collinear directions). The acquisitions were repeated three times. Analysis of the data was performed using FSL [4]. After corrections for EPI distortions and subject motion effect, fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity and axial diffusivity maps were calculated. Voxelwise statistical analysis of these maps was carried out using TBSS [3]. Gender was included as covariate. All voxel-wise group comparisons were performed using two-sample T-tests. A statistical threshold t>3, P < 0.05, corrected for multiple comparisons with Threshold-Free Cluster Enhancement (TFCE) was used for this analysis [5]. Identification of the abnormal white matter tracts revealed by TBSS was based on the ICBM-DTI-81 white-matter labels atlas and JHU white-matter tractography atlas [6-7].

Additionally, in order to determine a potential influence of comorbidities in Tourette patients, data from one subsample of Tourette patients (4 women, 11 men) with no comorbidities were compared to an age-matched healthy control group (5 women, 10 men).

Analysis of correlations between mean the FA values and the Yale Global Tic Severity Scale (YGTSS) score as well as between the FA values and the subscores for motor and vocal tic was performed.

Results. TS patients in comparison to healthy controls showed a significant reduction of FA in the corticospinal tract, the corpus callosum and long association fibre pathways such as the inferior fronto-occipital fascicle and the superior longitudinal fascicle as well as in the uncinate fascicle. An increase in radial diffusivity was detected in patients in the corpus callosum, corticospinal tract, and superior corona radiata. FA decreases are compared to increased radial diffusivity in Figure 1.

In the whole Tourette sample there was no significant correlation between FA values and total YGTSS scores. In the subsample without comorbidites significant correlations were detected between the YGTSS subscore motor and vocal tics and the mean FA value in the right and left anterior thalamic radiation (left r=0.56, P=0.04, right r= 0.64, P=0.02). The YGTSS motor score correlated significantly in the right corticospinal tract with the mean FA value (r=0.57, P=0.04) and reached trend level for the corticospinal tract (r=0.52, P=0.07). Further significant correlations were depicted between the right and left uncinate fascicle and the combined vocal and motor tic score (right r=0.6, P=0.03. left r=0.58, P=0.04) as well as with the motor score alone (left r=0.59 P=0.03, right r=0.56, P=0.05). In addition, the FA-value for the forceps minor correlated significantly with the motor and vocal tic score (r=0.65, P=0.02) as well as with the motor score only (r=0.67 P=0.01). With the total YGTSS score there is a significant correlation with the FA-values in the right cingulum (r=0.58, P=0.04) as well as the forceps minor (r=0.55, P=0.05) and the right uncinate fascicle (r=0.55, P=0.05) and left uncinate fascicle at trend level (r=0.49, P=0.09).

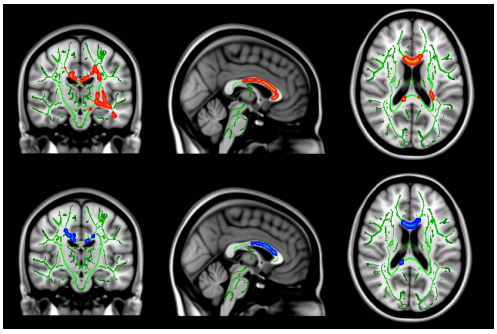

Figure 1. FA reductions in TS patients are displayed in the upper row in red. Alterations overlap to a large degree with the increases in radial diffusivity which are depicted in blue in the lower row. Background: mean tract skeleton (green) and MNI 152 brain. (MNI coordinates: x= -1, y= -17, z=19).

Discussion and Conclusion. DTI analysis in our adult TS sample shows a decrease of FA and increase in radial diffusivity in the corticospinal tract. There are widespread changes (reduced FA and increased radial diffusivity) in the anterior and posterior limb of the internal capsule. Our results indicate that TS is not restricted to motor pathways alone but affects association fibres such as the inferior fronto-occipital fascicle, the superior longitudinal fascicle and fascicle uncinatus as well. In the subsample of TS patients without comorbidities there is a significant correlation with the FA values in the right corticospinal tract (total corticospinal tract at trend level) and the YGTSS motor tic score. The combined motor and vocal YGTSS score as well as the motor score itself correlates significantly with the FA values in the right and left thalamic radiation. In agreement with our hypotheses, the corticospinal tract as the main motor pathway is affected in TS and the degree of alterations correlates with symptoms severity in the subgroup of TS without comorbidities. Our results show reduced FA values in all sub-regions of the corpus callosum and confirms the altered interhemispheric connectivity in TS. The alterations in the corpus callosum in our data are associated with TS itself, not with the comorbidities, as the results of the subsample without comorbidities indicate. In summary, reduced FA and increased radial diffusivity in adult Tourette patients affects different systems and brain regions. The pathologic pattern reaches beyond the corticospinal tract and affects interhemispheric connections such as the corpus callosum as well as intrahemishperic long associations fibre tracts. The affection of limbic structures such as the uncinate fascicle and its close correlations with the motor and vocal tic score indicates that alterations in Tourette syndrome reach beyond the motor system. The alteration pattern of decreased FA and increased radial diffusivity might indicate a deficit in myelination as the underlying pathophysiologic principle.

References: 1. Leckman 2003, Brain Dev. 2. Albin, Mink 2006, Trends Neurosc. 3. Smith et al. 2006, NeuroImage. 4. Smith et al. 2004, NeuroImage. 5. Smith, Nichols 2009, NeuroImage. 6. Wakana et al. 2004, Radiology. 7. Hua et al. 2008, NeuroImage.