Medication with Stimulants Modifies the Mean Diffusivity in Children with Attention Deficit/Hyperactivity Disorder: a DTI Study

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INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is a very common psychiatric disorder for which the behavioral and cognitive symptoms are well known, as well as its response to treatment. However, the impact of this disorder on the brain neural structure has not been well stablished, and the effects of treatment on the white matter of the brain have not been sufficiently explored. Significantly, there is a considerable lack of agreement in the results of studies on the effects of ADHD using DTI.

In this abstract, we investigate the differences in the white matter structure between children with ADHD and age-matched normal controls, and analyze the effect of treatment on white matter connectivity using a recent tractography selection technique developed by the authors that provides increased robustness with respect to registration errors.

METHODS

30 healthy children (mean age is 8.5±1.6 y/o), 16 children diagnosed with ADHD who underwent no treatment (mean age is 7.6±1.4 y/o) and 30 children diagnosed with ADHD who were treated with methylphenidate (mean age is 8.9±1.4 y/o, at least 6 months of treatment without interruption) were recruited for the study. Exclusion criteria included left handedness and having been diagnosed with any other major psychiatric disorder. Data were acquired in a GE Signa 1.5 T MR unit at QDiagnóstica, Valladolid, Spain. The parameters of the acquisition protocol were the following: 25 gradient directions, one baseline volume, b=1000 s/mm^2, 1.015 × 1.015 × 3 mm of voxel size, TR=13,000 ms, TE=85.5 ms, 128 × 128 matrix, NEX=2, and 39 slices covering the entire brain. From the raw diffusion weighted images (DWIs) an algorithm based on the Otsu threshold[1] was executed to remove the image background as well as nonbrain structures such as the skull. Afterwards, tensors at each voxel were estimated using a least squares method[2]. From the tensor volume, whole-brain deterministic tractography was performed using Slicer 3.6 (http://www.slicer.org), using a Fractional Anisotropy (FA) mask thresholded at 0.2. Tractography parameters were as follows: minimum length of fibers = 10 mm, maximum length of fibers = 800 mm, stopping when linear measure = 0.1, stopping track curvature = 0.8, and integration step length = 0.5. Seed spacing was set to 2 mm.

Tractography selection based on geometrical constraints[3] was performed in order to extract the following fiber bundles: corpus callosum (CC), cingulate gyrus (CG), corticospinal tract (CORT), inferior frontoccipital fasciculus (IFO), inferior longitudinal fasciculus (ILF) and uncinate fasciculus (UNC). Fibers belonging to the corpus callosum were also separated into five different sectors[4]. Scalar measures were then computed from the tensor volume and averaged along each fiber bundle, including FA, Mean Diffusivity (MD), Tensor Mode (TM) and Linear Measure (LM).

Statistical analysis started by applying a Kolmogorov-Smirnov test to evaluate whether each scalar measure over each fiber bundle followed a normal distribution for each of the three groups. If the null hypothesis (the data follows a normal distribution) was rejected, the non-parametric Kruskal-Wallis test was performed to check whether the scalar measures from the three groups originated from the same distribution, and a parametric analysis of variance was performed otherwise. Finally, pairwise comparisons were made where statistically significant differences were found, using two-sample T-test or the Mann Whitney U test depending on the normality of the data.

RESULTS AND DISCUSSION

Significant differences in the MD were found between the three groups for the CORT, ILF, UNC and Section IV of the CC ($p<0.05$). No significant differences were found for other scalar measures or other fiber bundles. p-values are shown in Table 1 for these relevant cases, while boxplots depicting the medians and the interquantile ranges of MD are shown in Figure 1. Results indicate a decrease in MD in ADHD patients under treatment with respect to healthy controls (statistically significant for the ILF, UNC and CC, sect. IV) and also a decrease in MD in ADHD patients under treatment with respect to ADHD patients under no treatment (statistically significant for the CORT, ILF and CC, sect. IV). No significant differences were found, however, in ADHD patients under no treament with respect to healthy controls.

Only a few studies have analyzed changes in MD in ADHD patients, reporting an increase across several white matter areas with respect to healthy controls[5,6] While most DTI studies on ADHD in the literature have reported changes in FA in different regions or fiber bundles of interest within the white matter, they were conducted on older children, adolescents or adults. Besides, different anaylisis methods were employed, ranging from voxelwise analysis on FA volumes registered on a template to Tract-based Spatial Statistics (TBSS)[7]. To the best of our knowledge, the effects of stimulants on patients with ADHD were only studied by Ashtari *et al.* [8], with no significant differences found using a voxelwise analysis. Our results suggest that treatment with psychostimulants induces a significant decrease in the MD across several fiber bundles of the brain.

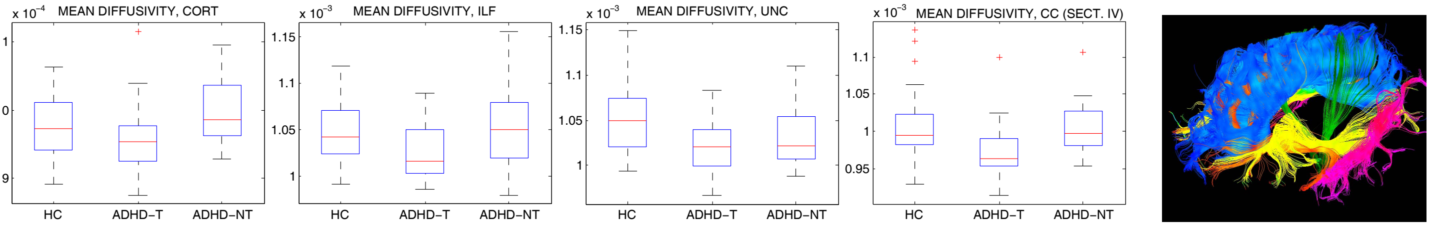

Figure 1. Boxplot of MD values averaged along fiber tracts where significant differences were found, for healthy controls (HC), ADHD patients under treatment (ADHD-T) and ADHD patients without treatment (ADHD-NT); (Right) Selected fiber tracts from a sample subject, depicted in different colours.

	CORT	ILF	UNC	CC (sec. IV)
Healthy Vs ADHD under treatment	0.2037	**0.0123**	**0.0004**	**0.0052**
Healthy Vs ADHD under no treatment	0.0708	0.7118	0.1064	0.9329
ADHD under treatment Vs ADHD under no treatment	**0.0106**	**0.0325**	0.2089	**0.0100**

Table 1. p-values from pairwise comparisons of MD values averaged along fiber tracts where significant differences were found. Statistical significant (marked in bold) was considered for $p<0.05$.

CONCLUSIONS

We have investigated the effect of ADHD and treatment with methylphenidate in the white matter connectivity of children using a tractography selection method that allows the robust extraction of several fiber bundles of interest. No significant differences were found in FA, TM and LM, but differences in the MD between ADHD patients under treatment and normal controls and between ADHD patients under treatment and drug-naive ADHD patients indicate that treatment with psychostimulants may modify the white matter connectivity. Based upon these preliminary results, further research is necessary in order to corroborate this important finding.

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