White matter abnormalities in mesocorticolimbic network of drug naïve ADHD children by diffusion tensor imaging

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TARGET AUDIENCE: Neuro-radiologists and scientists interested in application of diffusion tensor imaging and/or childhood mental disorders

PURPOSE: Attention deficit/hyperactivity disorder (ADHD) is one common neurodevelopmental disorder characterized as behavioral problems as well as damaged cognitive functions. White matter (WM) abnormality had been studied with diffusion tensor imaging (DTI) in the past with small sample size and inconsistent results in various brain regions with underlying mechanism remaining unclear[1]. Present study aims to explore microscopic WM alternations in drug-naïve ADHD children in a relatively large sample size, more importantly, apart from the commonly used water diffusion parameters such as fractional anisotropy (FA), we also calculated radial diffusivity (RD) and axial diffusivity (AD) to help elucidate the possible mechanism of FA changes underlie pathophysiology of ADHD.

METHODS: We recruited 51 drug-naive ADHD children (mean age=10.1±2.3) and 51 matched healthy controls (mean age=10.9±1.8). The study was approved by local ethnical committee and written consent was obtained from parents of all the subjects. Conners' ADHD Scale-Parent Version as well as a set of neuropsychological test battery, including Wechsler Intelligence Scale, Stroop test, Visual memory test, Verbal fluency test and Wisconsin Card Sorting test was carried out to evaluate symptom severity and cognitive functions. MRI scanning was done via a 3-T MRI system to obtain the DTI data which were then put into FSL to generate FA, RD and AD maps of each subject. Voxel-based analysis of FA between two groups was done via two sample T-test in SPM8 with age and gender as covariates, threshold at p<0.001 (uncorrected) at voxel level with extent threshold of 100 contiguous voxels. After that, the resultant clusters were extracted as ROIs to correlate with clinical scores using spearman's correlation in SPSS 20.0. Moreover, RD and AD were also extracted from the ROIs for ANCOVA with age and gender as covariates (Bonferroni correction, p<0.025) between two groups.

RESULT: Compared with healthy controls, the ADHD children displayed lower scores in most domain of neuropsychiatric tests and yielded significant increased FA in left cingulum bundle (CB) (peak coordinates [-10,0,36], T=3.74, *Figure.1A*) and posterior-body of corpus callosum (CC) (peak coordinates [7,-13,29], T=3.42, *Figure.1B*). Further analysis revealed that patients showed significantly higher RD in left CB (Figure.1C) but lower AD in CC (Figure.1D). In ADHD group, the FA of left CB negatively correlated with total time in Stroop test (r=-0.285, p=0.042, *Figure.2A*) but positively correlated with right numbers (r=0.348, p=0.012, *Figure.2B*) and total numbers (r=0.386, p=0.005, *Figure.2C*) in verbal fluency test.

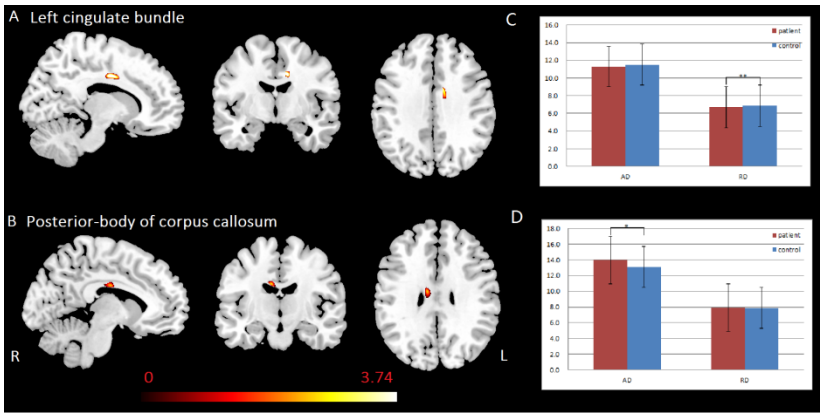

Figure.1 A and **B** are the results of two sample t-test showing FA increase between ADHD and controls (p<0.001). **C** and **D** show the results of ANCOVA comparison for AD and RD between two groups. * means p<0.05, **means p<0.025 (Bonferroni corrected)

DISCUSSION: Present study found FA increase in drug-naïve ADHD children in left CB and posterior-body of CC, both of which belong to mesocorticolimbic network that plays an important role in attentional processing ability [2]. Further ROI analysis revealed there may be different underlying mechanism for FA changes in two regions. Specifically, FA increase in CB regions was caused by increased RD while in CC region it was due to decreased AD. Since RD was thought to be modulated by myelin disruption whereas AD is more specific to axonal degeneration[3], we speculated that similar phenomena discovered by commonly used index such as FA may have different cellular alterations. The change of FA also correlated with scores for neuropsychiatric index seemed to indicate that higher FA value accompanies with better cognitive functions in patients group. But we have to notice that all the cognitive functions were still worse than that of normal controls. Thus we postulated that there might be some compensatory response in ADHD white matter.

CONCLUSION: Current study found increased FA with discrepant cellular alternating patterns in drug-naïve ADHD children in the regions of left CB and posterior-body of CC, while correlated with some cognitive function domains. However, given the complexity of cerebral white matter, future studies combined multiple modality techniques are needed to elucidate the FA alternations.

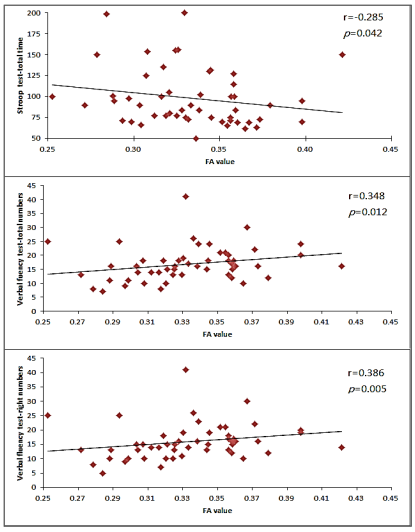

Figure.2 Results of correlation between FA and neuropsychiatric measurements in ADHD children

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