Abnormalities in the Microstructure of the Fronto-Striatal Fiber Pathways in Children with Attention-Deficit/Hyperactivity Disorder: Preliminary Results Using Diffusion Spectrum Imaging Tractography

Y-H. Wu[1], Y-C. Lo[2], S-F. S. Gau[3], and W-Y. I. Tseng[4,5]

[1]School of Medicine, National Taiwan University College of Medicine, Taipei, Taiwan, [2]Institute of Biomedical Engineering, National Taiwan University, Taipei, Taiwan, [3]Department of Psychiatry, National Taiwan University Hospital and College of Medicine, Taipei, Taiwan, [4]Department of Medical Imaging, National Taiwan University Hospital, Taipei, Taiwan, [5]Center for Optoelectronic Biomedicine, National Taiwan University College of Medicine, Taipei, Taiwan

Introduction Attention deficit hyperactivity disorder (ADHD) is a frequently diagnosed neuropsychiatric disorder in childhood, affecting 3%-10% of school-aged children worldwide. It is characterized by a developmentally inappropriate and pervasive expression of inattention, impulsivity and hyperactivity. To date, data from neuroimaging studies have provided important evidence implicating that white matter abnormalities play a role in the neuropsychogical dysfunction of ADHD. Deficits in neural circuits linking regions of the prefrontal cortex and the striatum (caudate nucleus and putamen) have been postulated to account for the core symptoms in ADHD. The fronto-striatal circuitry is involved in the ability to suppress inappropriate or irrelevant sensory or motor representations and to strengthen others. In this study, we focused on the caudate nucleus of the striatum and investigated four association fibers connecting the caudate nucleus to four regions of the prefrontal cortex (dorsolateral prefrontal cortex, medial prefrontal cortex, orbitofrontal cortex and ventrolateral prefrontal cortex) related to inhibition and cognitive control that might underlie the neuropsychopathology of patients with ADHD inferred from diffusion spectrum imaging (DSI) [Figure 1].

Materials and Methods Thirteen right-handed male children with ADHD, as well as thirteen age- and sex- matched healthy participants were examined using DSI. Images were acquired on a 3T MRI system with a 32-channel head coil (Tim Trio, Siemens, Erlangen, Germany). DSI was performed using a twice-refocused balanced echo diffusion echo planar imaging (EPI) sequence, TR/TE = 9600/130 ms, image matrix size = 80 x 80, spatial resolution = 2.5 x 2.5 mm^2, and slice thickness = 2.5 mm. 102 diffusion encoding gradients with the maximum diffusion sensitivity b_{max} = 4000 s/mm^2 were sampled on the grid points in the 3D q-space with $|q| \leq 3.6$ units [1]. DSI analysis was performed based on the relationship that the echo signal S(q) and the diffusion probability density function P(r) were a Fourier pair, i.e., $S(q)=FT\{P(r)\}$. The orientation distribution function (ODF) was determined by computing the second moment of P(r) along each radial direction. The intravoxel fiber orientations were determined by decomposing the original ODF into several constituent ODFs [2]. Further, those primary fiber orientations were used for tractography reconstruction. Generalized fractional anisotropy (GFA) at each voxel was quantified based on the shape of the original ODF [3]. Tractography was reconstructed using a streamline-based algorithm adapted for DSI data and the targeted tracts were selected by specific regions-of-interest. A method that projected the GFA onto a single mean path of a specific white matter tract, called mean path analysis, was used to analyze local changes in microstructure coherence along the individual tract bundles [4].

Results Children with ADHD showed significantly lower mean GFA values in the targeted fronto-striatal fibers, namely the dorsolateral prefrontal-caudate tract (left, *p*<0.001; right, *p*=0.042), medial prefrontal-caudate tract (left, *p*=0.002; right, *p*=0.016), orbitofrontal-caudate tract (left, *p*<0.001; right, *p*<0.001) and ventrolateral prefrontal-caudate tract (left, *p*=0.014; right, *p*=0.001) in both hemispheres compared with the healthy controls [Figure 2].

Discussion Using the DSI technique to investigate the integrity of white matter structural connectivity of the bilateral four targeted fronto-striatal fiber bundles, we found that children with ADHD had lower GFA values in the targeted fibers compared with healthy children. The finding is consistent with previous diffusion tensor imaging studies that showed decreased fractional anisotropy in prefrontal white matter and the striatum in ADHD [5]. Our finding implies a disruption in the normal pattern of structural connectivity in frontal-striatal brain regions in ADHD. It warrants further investigation of the correlations between GFA and the severity of clinical and neuropsychological symptoms using a larger sample.

References [1] V.J. Wedeen, *et al*., Magn Reson Med. 2005; 54:1377-86. [2] F.C.Yeh, *et al*., Proc ISMRM, 2008. [3] D.S. Tuch, Magn Reson Med, 2004; 52, 1358-1372. [4] W.Y. Chiang, *et al*., Proc ISMRM, 2008. [5] A. Konrad, *et al*., Eur J Neurosci. 2010 Mar; 31(5):912-9.
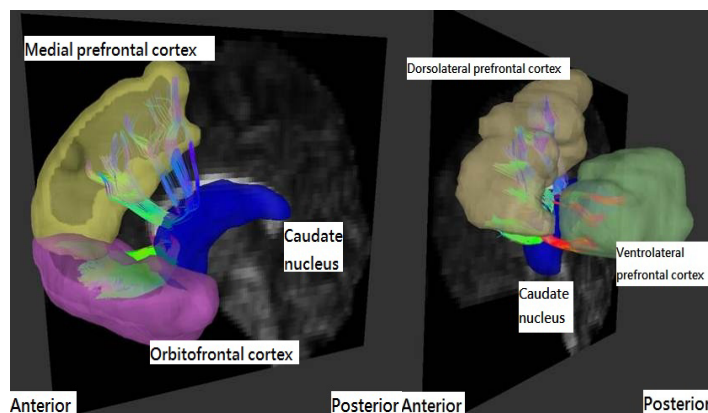

Figure 1 Four association fibers connecting the caudate nucleus to four regions of the prefrontal cortex (dorsolateral prefrontal cortex, medial prefrontal cortex, orbitofrontal cortex and ventrolateral prefrontal cortex) in the left hemisphere.
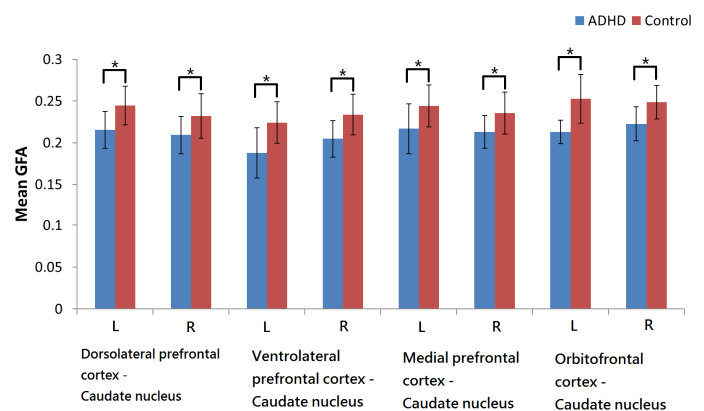

Figure 2 Lower GFA values of bilateral four fronto-striatal fibers in patients with ADHD compared with healthy participants.