Psychiatry Research: Neuroimaging 202 (2012) 150–154

Contents lists available at SciVerse ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

# Diffusion tensor imaging reveals white matter abnormalities in Attention-Deficit/Hyperactivity Disorder

Leanne Tamm [a,*], Naama Barnea-Goraly [b], Allan L. Reiss [b]

[a] Center for ADHD, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States
[b] Center for Interdisciplinary Brain Sciences Research, Stanford University, Stanford, CA, United States

ARTICLE INFO

*Article history:*
Received 21 July 2011
Received in revised form 5 April 2012
Accepted 5 April 2012

*Keywords:*
Fronto-striatal abnormalities
Axial diffusivity
Diffusion tensor imaging
Fractional anisotropy
Attention-deficit/hyperactivity disorder

ABSTRACT

The specific brain structures or neural mechanisms underlying dysfunction in individuals with Attention-Deficit/Hyperactivity Disorder (ADHD) are not well established, particularly in regard to white matter (WM). Diffusion tensor imaging (DTI) was used to investigate WM in 12 adolescent males diagnosed with ADHD only and 12 typically developing controls (group matched; mean age = 15.64 years, SD = 1.15). In addition to fractional anisotropy (FA), we also examined axial and radial diffusivity (AD and RD) in an effort to help elucidate conflicting findings suggesting that *both* lower and higher FA values are characteristic of ADHD. Tract-based spatial statistics and voxel-wide analyses were conducted on the data utilizing a prefrontal mask to enable focus on fronto-striatal and prefrontal pathways. Adolescents with ADHD had significantly higher FA and AD values in fronto-striatal pathways compared with controls. No differences were observed for RD. These results contribute to the growing literature implicating prefrontal WM variations in neuropsychiatric disorders, and are consistent with findings suggesting a role for fronto-striatal pathways in ADHD pathophysiology.



## 1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a behaviorally defined disorder affecting approximately 3–5% of school-aged children (American Psychological Association, 1994). ADHD is characterized by problems with inattention, impulsivity, and hyperactivity causing significant impairment in multiple settings. Although behavioral and cognitive deficits in ADHD are well described, the specific brain structures or neural mechanisms underlying dysfunction in ADHD are not well established, in part because attention is a complex cognitive ability that involves multiple interconnected brain regions. Though the diagnostic construct of ADHD is heterogeneous with respect to genetic and environmental risk factors, these factors may converge at the level of aberrant neurodevelopment and functional neuroanatomy.

Most studies have focused on the contribution of cortical gray matter anatomy to brain function; however, in recent years, it has been recognized that white matter (WM) also makes an important contribution to cognition and emotion. WM comprises nearly half of the average human brain volume and plays a key role in development, aging, and many neurological and psychiatric disorders across the life span. In ADHD, anatomic MRI studies show decreased WM volume throughout the brain and, in particular, the prefrontal cortex (e.g., Krain and Castellanos, 2006). Significant decreases in WM volume have also been observed in children who are not medicated for ADHD (Castellanos et al., 2002). The cortical networks mediating cognitive function establish connectivity through WM pathways. Localized changes in cortical activation within the attentional network (e.g., frontal lobes) may result from anatomical variations of WM at various points in the network. Since higher order cognitive functions depend on intact communication between cortical areas through projection, association and commissural fibers (Skranes et al., 2007), investigating WM may elucidate our understanding of psychopathology.

Diffusion tensor imaging (DTI) is a magnetic resonance imaging (MRI) technique that provides information about WM microstructure in vivo. The myelin sheath and cell membrane restrict the diffusion of water perpendicular to the direction of the axons in WM, whereas water diffuses more readily parallel to the axons. This directional dependence of diffusion is quantified as anisotropy. Fractional anisotropy (FA) is a normalized measure of diffusion anisotropy and varies between 0 (equal diffusion in all directions) and 1 (highly directional diffusion), and is influenced by fiber coherence, myelin, extracellular diffusion, and axonal density (Sen and Basser, 2005). Axial diffusivity (AD, diffusion along the fiber) represents coherence of WM while radial diffusivity (RD, diffusion perpendicular to the fiber) is thought to be related to axonal myelination (Song et al., 2002). Although most ADHD studies report FA values, it has been argued that this may not be sufficient to characterize WM neuropathology (Alexander et al.,

* Corresponding author at: Division of Behavioral Medicine and Clinical Psychology, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave. MLC 10006, Cincinnati, OH 45229, United States. Tel.: +1 513 803 3176; fax: +1 513 636 0755.
*E-mail address:* leanne.tamm@cchmc.org (L. Tamm).

0925-4927/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.pscychresns.2012.04.001

2007). For example, WM neuropathology often causes FA to decrease, which may result from either increased RD and/or reduced AD (Alexander et al., 2007).

There is a growing literature investigating ADHD using DTI. The earliest of these studies focused on children with ADHD Combined Type versus normal controls (Ashtari et al., 2005). Results showed that children with ADHD had decreased FA in the right premotor, right striatal, right cerebral peduncle, left middle cerebellar peduncle, left cerebellum, and left parieto-occipital areas. FA values in the cerebellum were negatively correlated with inattentive symptoms. Recently, additional studies investigated children and adolescents with ADHD (ages 6–18). These studies reported lower FA values in the anterior corona radiata, anterior limb of the internal capsule, and superior region of the internal capsule (Pavuluri et al., 2009), corticospinal tract and superior longitudinal fasciculus (Hamilton et al., 2008), frontal and cerebellar WM (Kobel et al., 2010), bilateral frontolimbic and temporo-occipital WM, left cerebellar WM, right frontoparietal WM, right anterior and superior corona radiata, and left posterior corona radiata (Nagel et al., 2011), and forceps minor, the internal capsule, the corona radiata, the splenium of the corpus callosum, and the bilateral basal ganglia (Qiu et al., 2010) for children and adolescents with ADHD compared to controls. Lower FA values have been associated with low levels of functional magnetic resonance imaging (fMRI) activation in fronto-striatal regions associated with response inhibition in adolescents with ADHD and their parents (Casey et al., 2007). There have also been studies reporting higher FA values in various regions including the anterior corona radiata (Davenport et al., 2010), cingulum, uncinate fasciculus, inferior longitudinal fasciculus, and superior longitudinal fasciculus (Silk et al., 2008), right frontal lobe WM (Li et al., 2010), and right superior frontal gyrus and posterior thalamic radiation, and left dorsal posterior cingulate gyrus, lingual gyrus, and parahippocampal gyrus (Peterson et al., 2011) for children and adolescents with ADHD compared to controls.

Taken together, the DTI studies to date support a hypothesis of diffuse WM abnormalities in ADHD while differing in precise location and direction of differences, likely due to analytic techniques and heterogeneity in sample characteristics (gender, age range, subtype, medication status, comorbidities, etc.). There is particularly consistent evidence for FA disruptions in the superior longitudinal fasciculus and anterior corona radiata pathways critical to prefrontal cortical function (Liston et al., 2011). However, the direction of differences (increased FA versus decreased FA) varies by study.

Very few studies have reported on AD and RD in ADHD. Description of complementary scalars could help elucidate the differences in direction reported for FA in studies of ADHD. Abnormalities in WM structure in ADHD have been reported for mean diffusivity (an estimate of the magnitude of diffusion in WM pathways) with lower values in the posterior limb of the internal capsule and superior longitudinal fasciculus and higher values in the left frontolimbic WM, the latter were largely driven by increased RD in ADHD (Nagel et al., 2011). A cross-sectional study of development using diffusional kurtosis imaging, which investigates tissue microstructural integrity, suggested that adolescents with ADHD do not show expected age-related increases in radial or AD in the prefrontal cortex (Helpern et al., 2011). The finding was interpreted as consistent with studies suggesting developmental delays in brain maturation (Shaw et al., 2007).

In this study, we used DTI to investigate WM in adolescents with ADHD compared to typically developing controls. We investigated FA, AD, and RD using tract-based spatial statistics (TBSS). TBSS is a voxel-wise analytic tool implemented in FMRI Software Library (FSL, http://www.fmrib.ox.ac.uk/fsl/) which was specifically developed for the analysis of diffusion-weighted data. As such, it was designed to address shortcomings inherent in other voxel-wise analytic programs used for analyses of DTI data (e.g., Statistical Parametric Mapping, SPM) including the use of standard registration algorithms which are not optimal for use with diffusion-weighted data, arbitrary choice of smoothing kernel, partial volume effects, and the use of parametric statistics in data with an unknown distribution (Smith et al., 2007). TBSS addresses these issues by using nonlinear registration, projection into alignment-invariant tract representation (the "mean FA skeleton"), avoiding the use of smoothing and permutation statistics which do not require normally distributed data (Smith et al., 2007). Because most imaging studies report abnormalities in the fronto-striatal regions in ADHD and stimulant medication increases activation in these regions (Paloyelis et al., 2007), we focused on the striatum and adjoining frontal regions. Based on the literature, we hypothesized adolescents with ADHD would have aberrant white matter structure in fronto-striatal regions, and in particular the anterior corona radiata.

## 2. Methods

Fourteen adolescent boys diagnosed with ADHD Combined Type and 12 male controls participated. Informed consent and assent were obtained following procedures established by the Stanford Institutional Review Board. Subjects were recruited via mailings to local pediatricians, postings on the Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD) and Stanford Psychiatry web sites, flyers, etc. Participants were compensated for their time. ADHD diagnosis was determined via a structured interview conducted with the primary caregiver (Diagnostic Interview Schedule for Children Version 2.3 — DISC) (Lahey et al., 1996). In addition, the Conners' ADHD/DSM-IV Scale — Parent Version (Conners et al., 1998) was completed. Adolescents also completed the Conners' ADHD/DSM-IV scale, although this was not used to establish diagnosis. Typically developing controls were screened for neurological, developmental, and psychiatric disorders, and a family history negative for psychiatric disorders via interview with the primary caregiver and T-scores<65 on the Achenbach Child Behavior Checklist (Achenbach, 1991). Data from two participants in the ADHD group were excluded due to excessive movement. Demographic information for participants included in the analyses can be found in Table 1.

Participants were right-handed, and ranged in age from 14 to 18 (group matched; mean age = 15.64 years, *S.D.* = 1.15). Groups did not differ on IQ estimated from the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) or mathematic achievement screened with the Wide Range Achievement Test, Third Edition (Jastak and Wilkinson, 1993). The groups did differ on reading and spelling, however, with the ADHD groups performing more poorly than the controls. Four subjects in the ADHD group reported current use of stimulant medication; all were subjected to an 18-h washout before the scan. No other medication use was reported. Subjects did not drink caffeine at least 2 h before the scan. Of those reporting drug use (two in the ADHD group, one in the comparison group) and alcohol use (three in the ADHD group, six in the comparison group), a 3-week washout period for drugs (typically marijuana) and a 1-week washout period for alcohol were observed.

**Table 1**
Participant demographic characteristics.

| | ADHD ($n=12$) | Control ($n=12$) | Statistical test (2-tailed) |
|---|---|---|---|
| Age | 15.8 (1.5) | 15.6 (0.8) | $t(22)=0.34$, $P=0.74$ |
| Full scale IQ | 106.1 (10.8) | 111.6 (11.7) | $t(22)=-1.19$ $P=0.25$ |
| Reading | 104.6 (7.5) | 111.0 (5.7) | $t(22)=-2.37$, $P=0.03$ |
| Spelling | 95.7 (12.9) | 106.0 (10.4) | $t(22)=-2.15$, $P=0.04$ |
| Arithmetic | 100.6 (13.4) | 106.3 (15.5) | $t(22)=-0.96$, $P=0.35$ |
| Ethnicity | | | $\chi^2(2)=0.39$, $P=0.82$ |
| Caucasian | $n=10$ | $n=9$ | |
| Hispanic | $n=1$ | $n=1$ | |
| Other | $n=1$ | $n=2$ | |
| DSM-IV ADHD T-score | 82.9 (6.2) | 47.4 (9.7) | $t(21)=10.5$, $P<0.001$ |
| Alcohol use past month (number of times) | 0.83 (2.3) | 0.83 (1.3) | $t(22)=0.00$, $P=1.0$ |
| Illicit drug use past month (number of times) | 0.42 (1.0) | 0.50 (1.7) | $t(22)=-0.14$, $P=0.89$ |
| Comorbid diagnoses | | Not applicable | |
| Other disruptive behavior disorders | $n=6$ | | |
| Mood disorder | $n=2$ | | |
| Anxiety disorder | $n=3$ | | |
| Medication use | | Not applicable | |
| Adderall | $n=1$ | | |
| Ritalin | $n=3$ | | |

Note: Values are mean (standard deviation). ADHD = attention-deficit/hyperactivity disorder; IQ = intelligence quotient; DSM-IV = Diagnostic and Statistical Manual.