White Matter Microstructure in Subjects With Attention-Deficit/Hyperactivity Disorder and Their Siblings

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Objective: Previous voxel-based and regions-of-interest (ROI)–based diffusion tensor imaging (DTI) studies have found above-normal mean diffusivity (MD) and below-normal fractional anisotropy (FA) in subjects with attention-deficit/hyperactivity disorder (ADHD). However, findings remain mixed, and few studies have examined the contribution of ADHD familial liability to white matter microstructure. **Method:** We used refined DTI tractography methods to examine MD, FA, axial diffusivity (AD), and radial diffusivity (RD) of the anterior thalamic radiation, cingulum, corticospinal tract, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, forceps major, forceps minor, superior longitudinal fasciculus, and uncinate fasciculus in children and adolescents with ADHD (n = 56), unaffected siblings of ADHD probands (n = 31), and healthy controls (n = 17). **Results:** Subjects with ADHD showed significantly higher MD than controls in the anterior thalamic radiation, forceps minor, and superior longitudinal fasciculus. Unaffected siblings of subjects with ADHD displayed similar differences in MD as subjects with ADHD. Although none of the tested tracts showed a significant effect of FA, the tracts with elevated MD likewise displayed elevated AD both in subjects with ADHD and in unaffected siblings. Differences in RD between subjects with ADHD, unaffected siblings, and controls were not as widespread as differences in MD and AD. **Conclusion:** Our findings suggest that disruptions in white matter microstructure occur in several large white matter pathways in association with ADHD and indicate a familial liability for the disorder. Furthermore, MD may reflect these abnormalities more sensitively than FA. J. Am. Acad. Child Adolesc. Psychiatry; 2013;52(4):431-440. **Key Words:** attention-deficit/hyperactivity disorder (ADHD), diffusion tensor imaging, fiber tractography, fractional anisotropy, mean diffusivity.

Attention-deficit/hyperactivity disorder (ADHD) is characterized by age-inappropriate hyperactivity-impulsivity and/or deficits in attention.[1] ADHD affects approximately 5% of children worldwide,[2] at a high cost to affected individuals and society.[3] Prior studies suggest that ADHD is associated with widespread neural structural and functional deficiencies, where frontostriatal networks are particularly implicated.[4] Children with ADHD may also exhibit abnormalities in brain connectivity, as suggested by findings of lower ADHD-related functional connectivity,[5] lower white matter (WM) volumes,[6] and abnormalities in WM microstructure.[7,8]

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WM microstructure can be measured in vivo with diffusion tensor imaging (DTI), which estimates the directional diffusion of water molecules along axonal pathways.[9] One DTI measure is fractional anisotropy (FA), which quantifies the directionality of diffusion. Higher FA values reflect increased axonal integrity,[10] more myelination,[10,11] and increased homogeneity of fiber orientations.[10] Another DTI measure is mean diffusivity (MD), which provides a measure of average diffusivity. Larger MD values indicate more diffusion[9] and may reflect myelin breakdown,[12] decreased cellular density,[10,12] or increased extracellular volumes.[10,12] More specificity regarding the neurobiological determinates of altered white matter structure may be gained from examining axial diffusivity (AD) and radial diffusivity (RD). AD is the diffusion parallel to the axonal fibers, whereas RD is the average diffusion

perpendicular to axonal fibers.[13] Decreases in AD may reflect axonal damage[14] and/or axonal pruning,[15] whereas increases in AD may indicate neurofibril damage.[16] Increases in RD are believed to reflect myelin injury and/or decreased myelination.[13,14]

Previous studies examining white matter microstructure in ADHD have reported spatially diffuse differences in FA. However, the regions examined and the direction and significance of results have varied across studies even for overlapping pathways (reviewed in van Ewijk *et al.*[8]). Both ADHD-related decreases[17–23] and increases[24–26] in FA have been observed in projection pathways including the cerebellar and cerebral peduncles, cortical spinal tract (CST), internal capsule, and corona radiata. Likewise, although some studies report lower FA within association fibers such as the cingulum, fornix, inferior fronto-occipital fasciculus (IFO), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), posterior thalamic radiation, and uncinate fasciculus (UF),[17,18,20,27,28] others have shown regional increases of FA in these fiber pathways in ADHD relative to controls.[19,26,27,29,30] These discrepancies may reflect differences and/or limitations of analysis approaches. That is, whereas some studies have focused only on specific regions providing limited information, others have used whole-brain voxel-based approaches that may be more sensitive to registration errors potentially heightened by morphometric differences between groups.[6,31] Moreover, most studies have investigated relatively small samples of varying demographic and clinical characteristics, making it difficult to reconcile findings. Most prior studies have also not benefited from the use of higher angular resolution data that may allow for more precise estimates of FA and other diffusion metrics.[32] Notwithstanding, a recent meta-analysis of nine voxel-based studies showed more prominent ADHD effects in the cerebellum, forceps minor, internal capsule, and SLF, although directionality was not reported.[8] Whereas fewer studies have examined differences in MD between controls and subjects with ADHD, the majority of studies report higher MD in ADHD, with MD differences particularly noted in the internal capsule, SLF, and UF.[20,21,27,30] Only three studies to date have examined differences in AD and RD, with approximately equal numbers finding higher or lower AD in ADHD, and higher or lower RD in ADHD.[20,26,30]

To clarify prior findings we thus took advantage of higher-resolution DTI data and a more refined streamline tractography approach to examine FA and MD differences in nine major WM tracts (the anterior thalamic radiation [ATR], cingulate gyrus portion of the cingulum (henceforth referred to as the cingulum), CST, IFO, ILF, forceps major, forceps minor, SLF, and UF) in 64-direction DTI data in 56 children and adolescents with ADHD and 17 controls. In addition, as ADHD and white matter microstructure have both been shown to have a hereditary component,[33,34] and as unaffected siblings of children with ADHD have shown similarities in brain structure[35] and brain activity[36–38] with respect to their siblings with ADHD, we included a group of 31 related siblings without ADHD. We hypothesized that subjects with ADHD and their unaffected siblings would display MD and FA differences relative to controls in a number of tracts including the CST, forceps minor, and SLF. Post hoc analyses addressed differences in AD and RD in pathways showing FA or MD effects, and associations with clinical symptomology and/or executive functioning.

METHOD

Participants

Subjects with ADHD, unaffected siblings, and control subjects (all between the ages of 6 and 18 years) were recruited from the community or referred to the study by their physicians or through other ongoing studies of ADHD at the University of California, Los Angeles (UCLA). All children were evaluated for ADHD and other psychiatric diagnoses based on an interview with the primary caretaker, usually the mother, using a semi-structured diagnostic interview, the Kiddie-Schedule for Affective Disorders and Schizophrenia–Present and Lifetime version (K-SADS-PL)[39] and a direct interview with the child if 8 years of age or older. Parent ratings on the Swanson, Nolan, and Pelham, Version IV (SNAP-IV) Rating Scale[40] were used to supplement the diagnostic interviews. All interviews were conducted by clinical psychologists or highly trained, master's degree–level interviewers with extensive experience in psychiatric diagnoses. To assess cognitive functioning, subjects completed the Block Design and Vocabulary subtests of the Wechsler Intelligence Scale for Children, third edition (WISC-III)[41] or the Wechsler Adult Intelligence Scale, third edition (WAIS-III),[42] and parents completed the Behavior Rating Inventory of Executive Function (BRIEF).[43]

Probands and their siblings were included in the study if they met full diagnostic criteria for ADHD.

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