Different Mechanisms of White Matter Abnormalities in Attention-Deficit/ Hyperactivity Disorder: A Diffusion Tensor Imaging Study

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Objective: Literature regarding white matter (WM) abnormalities in attention-deficit/ hyperactivity disorder (ADHD) is sparse and inconsistent. In this article, we shed more light on WM microstructure in ADHD, its association with symptom count, and the familiality of WM abnormalities in ADHD. **Method:** Diffusion tensor imaging (DTI) was performed in a large sample of individuals with ADHD (n = 170), their unaffected siblings (n = 80), and healthy controls (n = 107), aged 8 to 30 years. Extensive categorical as well as dimensional data regarding ADHD status and symptom count were collected. A whole-brain voxelwise approach was used to investigate associations between ADHD status and symptom count and WM microstructure, as measured by fractional anisotropy (FA) and mean diffusivity (MD). **Results:** Individuals with ADHD showed decreased FA and decreased MD in several widespread, non-overlapping brain regions. In contrast, higher ADHD symptom count was consistently associated with increased FA and decreased MD in the ADHD group. Unaffected siblings resembled individuals in the ADHD group with regard to decreased FA but had MD similar to that in healthy controls. Results were not confounded by socioeconomic status, the presence of comorbidities, or a history of medication use. **Conclusions:** Our results indicate widespread disturbances in WM microstructure in ADHD, which seem to be driven by 2 different mechanisms. Decreased FA in ADHD may be due to a familial vulnerability to the disorder, whereas a second mechanism may drive the association between ADHD symptom count and both higher FA and lower MD. Such different mechanisms may play an important role in the inconsistencies found in the current literature. J. Am. Acad. Child Adolesc. Psychiatry, 2014;■(■):■–■. **Key Words:** ADHD, DTI, connectivity, siblings, WM microstructure

Neuroimaging studies suggest that alterations in structural and functional brain connectivity might (partly) underlie behavioral symptoms of attention-deficit/ hyperactivity disorder (ADHD).[1] Diffusion tensor imaging (DTI), a technique often used to measure structural brain connectivity, allows quantification of the microstructural properties of brain white matter (WM) by measuring diffusivity of water molecules. Commonly used DTI parameters include fractional anisotropy (FA) and mean diffusivity (MD), which rely on the direction and strength of water diffusion, respectively.[2,3] FA is often interpreted as indicative of axonal integrity and organization, whereas MD is generally associated with changes in the intercellular space. It should be noted, however, that although diffusion parameters are overall quite sensitive to tissue properties such as axonal orientation, axonal density, and myelination, no DTI measure is specifically sensitive to a given property.[4]

Converging evidence from DTI studies in ADHD points toward a widespread pattern

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of WM disturbances throughout the brain in ADHD.[5-7] However, the current literature is limited by a great heterogeneity in findings in terms of the location and direction of abnormal FA and MD values. Part of this heterogeneity may be caused by differences in sample characteristics (e.g., different age ranges, comorbidities, or diagnostic methods) and research methods (e.g., multiple comparison or head movement correction). However, it is unlikely that such factors could explain why FA and MD values have been found to be both lower and higher in ADHD across different studies. Hence, it is currently difficult, if not impossible, to draw conclusions regarding the location and severity of WM disturbances in ADHD, and to interpret these disturbances in terms of underlying microstructural abnormalities.

Over the past decade, the view on ADHD psychopathology has shifted from a categorical, qualitative disease definition to a more dimensional, quantitative view, in which symptoms lie on a continuum from normal to abnormal behavior, with ADHD as a clinical disorder on the extreme.[8] Consistent with this view, it should be expected that ADHD-related neurobiological abnormalities are also quantitative rather than qualitative in nature, and that they are associated with the number of ADHD symptoms. Hence, studying the brain correlates associated with dimensional measures of ADHD may provide a more powerful approach than examining the neurobiology of categorical distinctions.[9] Studies investigating dimensional associations between ADHD and WM microstructure are sparse and inconsistent. Three studies found correlations between behavioral measures of ADHD and FA or MD values in some of their regions of interest (ROIs),[10-12] suggesting that the behavioral symptoms of ADHD are associated with WM pathology. One of these studies found a negative relationship between FA in the cerebellum and inattention in patients with ADHD.[10] A second study found a positive relationship between MD in the forceps minor and inattentive symptoms across the 3 groups that they examined (ADHD, unaffected siblings, and healthy controls),[11] and the third study reported a positive correlation between FA in the sagittal stratum and total ADHD symptomatology across individuals with ADHD and healthy controls.[12] Notably, these studies differ greatly in location and in the direction of their findings and are thus difficult to integrate. Other studies that investigated the association between dimensional measures of ADHD and DTI parameters reported negative results.[10,11,13,14] To our knowledge, no studies have adopted a whole-brain voxelwise approach to explore the association between ADHD symptom count and WM abnormalities throughout the whole brain.

A virtually unexplored issue is the familiality of WM abnormalities in ADHD, which can be investigated by including unaffected siblings. If WM abnormalities reflect a familial vulnerability to the disorder, unaffected siblings are expected to show WM abnormalities similar to those of their affected siblings, although possibly to a lesser extent. To date, only 1 DTI study has included unaffected siblings of individuals with ADHD.[11] The authors found no disturbances in FA in the group with ADHD, but MD was elevated in individuals with ADHD as well as in their unaffected siblings in the superior longitudinal fasciculus, forceps minor, and anterior thalamic radiation, giving support for the first time to the idea of a heritable component in WM abnormalities in ADHD.

The current study aimed to explore microstructural properties of WM brain tissue in children, adolescents, and young adults with ADHD. By using a large, carefully and extensively phenotyped sample, a more robust image of WM pathology in ADHD should emerge. Inclusion of unaffected siblings allowed us to investigate the familiality of WM abnormalities in ADHD. In addition, a whole-brain analysis using a dimensional approach was used to investigate whether inattentive and hyperactive-impulsive symptoms were associated with WM abnormalities in ADHD. Based on the current literature, widespread WM abnormalities in ADHD were expected to be found. However, because of the high heterogeneity of previous findings,[7] no specific hypotheses were formed regarding the location and direction of expected effects.

METHOD

Participants

A full description is provided in previous work by van Ewijk *et al.*[15] In short, participants originally took part in the Dutch part of the International Multicenter ADHD Genetics (IMAGE) study,[16] and were re-invited for the current follow-up study between 2009 and 2012 (NeuroIMAGE study; also see www.neuroimage.nl). Inclusion criteria were age 5 to 30 years, European white descent, IQ $\geq$70, and no epilepsy, neurological disorder, or known genetic disorder (such as fragile