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Deviant white matter structure in adults with attention-deficit/hyperactivity disorder points to aberrant myelination and affects neuropsychological performance

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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) in childhood is characterized by gray and white matter abnormalities in several brain areas. Considerably less is known about white matter microstructure in adults with ADHD and its relation with clinical symptoms and cognitive performance. In 107 adult ADHD patients and 109 gender-, age- and IQ-matched controls, we used diffusion tensor imaging (DTI) with tract-based spatial statistics (TBSS) to investigate whole-skeleton changes of fractional anisotropy (FA) and mean, axial, and radial diffusivity (MD, AD, RD). Additionally, we studied the relation of FA and MD values with symptom severity and cognitive performance on tasks measuring working memory, attention, inhibition, and delay discounting. In comparison to controls, participants with ADHD showed reduced FA in corpus callosum, bilateral corona radiata, and thalamic radiation. Higher MD and RD were found in overlapping and even more widespread areas in both hemispheres, also encompassing internal and external capsule, sagittal stratum, fornix, and superior lateral fasciculus. Values of FA and MD were not associated with symptom severity. However, within some white matter clusters that distinguished patients from controls, worse inhibition performance was associated with reduced FA and more impulsive decision making was associated with increased MD. This study shows widespread differences in white matter integrity between adults with persistent ADHD and healthy individuals. Changes in RD suggest aberrant myelination as a pathophysiological factor in persistent ADHD. The microstructural differences in adult ADHD may contribute to poor inhibition and greater impulsivity but appear to be independent of disease severity.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common childhood psychiatric disorder with an estimated prevalence around 5.3% in childhood that persists through adolescence reaching a prevalence of up to 4.9% in adults (Simon et al., 2009). ADHD is associated with global and regional brain volume reductions. Meta-analytic findings show reductions in total cerebral volume, in frontal lobes, cingulate cortex, and corpus callosum; in addition, robust evidence exists for decreased gray matter volume in subcortical areas (Ellison-Wright et al., 2008; Frodl and Skokauskas, 2012; Nakao et al., 2011; Valera et al., 2007). Differences in subcortical structures such as the putamen and caudate seem to disappear with increasing age (Castellanos et al., 2002; Nakao et al., 2011). Moreover, longitudinal studies show a delay in the age by which peak cortical thickness is reached in ADHD patients (Shaw et al., 2007), which has led to the suggesting that ADHD may be the outcome of a maturational lag that eventually normalizes (Rubia, 2007). More recent results of longitudinal studies indicate, however, that reductions in basal ganglia, which were detected in childhood, persisted into adolescence (Shaw et al., 2014). Cross-sectional studies in adults with ADHD also point to persistent gray matter reductions in subcortical volumes (Frodl et al., 2010; Onnink et al., 2014; Proal et al., 2011; Seidman et al., 2011) as well as in cortical areas (Ahrendts et al., 2011;

Abbreviations: ADHD, Attention-deficit/hyperactivity disorder; DTI, Diffusion tensor imaging; TBSS, Tract-based spatial statistics; FA, Fractional anisotropy; MD, Mean diffusivity; AD, Axial diffusivity; RD, Radial diffusivity; ROI, Region of interest; SAD, Sustained attention dots; SART, Sustained attention to response task.

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Amico et al., 2011; Biederman et al., 2008; Makris et al., 2007; Seidman et al., 2006, 2011), and in cerebellar regions (Proal et al., 2011; Seidman et al., 2011).

Over the last decade, the focus of neuroimaging research has widened from studies of regional volume alterations to studies of altered white matter connections within and among several neural networks (Konrad and Eickhoff, 2010). Advances in diffusion tensor imaging (DTI) allowed non-invasive investigation of white matter tracts connecting cortical and subcortical regions (Thomason and Thompson, 2011). DTI probes both the microstructural organization and the myelination of white matter through measuring the diffusion of water molecules in the tissue (Beaulieu, 2002; Le Bihan et al., 2001). Commonly used parameters are fractional anisotropy (FA) and mean diffusivity (MD), which reflect the preferential directionality of water diffusion along white matter tracts and the magnitude of diffusion, respectively (Le Bihan et al., 2001). Although decreased FA is a characteristic of impaired white matter integrity, its exact neurobiological meaning is not fully understood (Beaulieu, 2002).

Impaired white matter integrity has been found in numerous psychiatric disorders including major depressive disorder (Korgaonkar et al., 2011), bipolar disorder (Barysheva et al., 2013), schizophrenia (Mandl et al., 2013) and ADHD. A meta-analysis in children, adolescents, and adults with ADHD provided evidence of microstructural abnormalities in areas such as the anterior corona radiata (ACR), forceps minor, bilateral internal capsule, and cerebellum (van Ewijk et al., 2012). This meta-analysis only included hypothesis-free whole-brain voxelwise (VBA) approaches and could not provide directionality of findings (e.g., higher or lower FA in ADHD). Hypothesis-driven region of interest (ROI) studies reported that ADHD is in general associated with lower FA in the corpus callosum (Cao et al., 2010), cerebellum (Bechtel et al., 2009), and in several fronto-striatal tracts (Hamilton et al., 2008; Pavuluri et al., 2009; Shang et al., 2013; Wu et al., 2014). Some studies revealed that ADHD patients had *higher* FA (de Zeeuw et al., 2012; Silk et al., 2009; Tamm et al., 2012) in fronto-striatal regions when compared with healthy controls. A recent study found clusters of decreased FA and MD in most of the major white matter tracts and concluded that white matter alterations are a wide-ranging rather than localized feature in children and adolescents with ADHD (van Ewijk et al., 2014). Analyses using graph theory in combination with whole-brain DTI (e.g., brain connectomics) revealed similarly that, in children and adolescents with ADHD, decreased white matter connectivity in fronto-striatal circuits extended to a larger brain network which encompassed additional cortico-cortical, subcortical, and cerebellar circuits (Hong et al., 2014). The few available DTI studies of adult ADHD patients to date showed decreased FA in tracts such as the cingulum bundle (Makris et al., 2008), the inferior longitudinal fasciculus (ILF) (Konrad et al., 2012), the superior longitudinal fasciculus (SLF) (Cortese et al., 2013; Makris et al., 2008), and the corpus callosum (Dramsdahl et al., 2012). Although the current ADHD literature lacks longitudinal DTI studies, decreased FA has been reported in persistent *and* remitted adult patients with ADHD in comparison with healthy controls. These persistent findings were observed in areas including the corona radiata, sagittal stratum, the retrolenticular internal capsule, and the SLF (Cortese et al., 2013). Conversely, another study found that remitted adult patients did not differ significantly from controls, while patients with persistent ADHD had decreased FA in the uncinated and inferior fronto-occipital fasciculi (Shaw et al., 2015).

Decreased FA is typically accompanied by increased MD values in studies of ADHD. Increased MD is related with decreased cellular density (Alexander et al., 2007) and may reflect abnormalities in ADHD more sensitively than FA (de Luis-Garcia et al., 2015; Lawrence et al., 2013). Moreover, decreased FA might result from increased radial diffusivity (RD) and/or reduced axial diffusivity (AD) (Alexander et al., 2007). While the biological correlates of those measures are not yet entirely clarified, decreases in AD are currently thought to indicate axonal damage or degeneration, and increases in RD with minimal changes in AD are thought to indicate increased freedom of cross-fibre diffusion and possibly decreased myelination (Alexander et al., 2007; Song et al., 2002). Reporting changes in RD and AD could potentially help elucidate the FA findings in studies of ADHD. In the ADHD childhood literature, reports on RD have shown the entire range from increased RD (Helpern et al., 2011; Nagel et al., 2011) to decreased RD (Silk et al., 2009), and one study reported no change in RD (Tamm et al., 2012). Increased AD (together with an increased FA) has been reported in two childhood studies (Silk et al., 2009; Tamm et al., 2012). A recent study in adult ADHD patients suggested that reductions of FA were driven by changes in RD rather than AD (Shaw et al., 2015).

In addition to case–control comparisons, some studies investigated the behavioural implications of changed white matter variation in patients with ADHD by looking at its association with clinical symptoms or cognitive measures. Although findings in the ADHD literature are heterogeneous and complex, most studies have found that increasing symptom severity was associated with decreased FA (Ashtari et al., 2005; Nagel et al., 2011; Shang et al., 2013), but also with higher FA (Peterson et al., 2011; van Ewijk et al., 2014). In an adult ADHD study, attentional performance correlated with FA and MD in the right SLF, and measures of impulsivity correlated with FA in right orbitofrontal fibre tracts (Konrad et al., 2010).

Taken together, there is strong evidence for wide-spread white matter differences in ADHD patients compared to controls, and these may be related to ADHD symptomatology and cognitive functioning. Findings in the ADHD literature differ in precise location and directionality, which makes comparison of studies difficult. This is likely due to differences in sample characteristics (e.g., gender, age ranges), small sample sizes, and methodological differences (e.g., use of VBA versus ROI approaches). Relative to childhood and adolescent ADHD studies, there are few DTI studies in adult patients, and those are hampered by small sample sizes and by the use of ROIs instead of whole-brain approaches (except for the study by Cortese et al. (2013)). In adult ADHD, only few studies investigated AD and RD (Shaw et al., 2015), associations with ADHD symptomatology (Dramsdahl et al., 2012; Shaw et al., 2015), and cognitive performance (Konrad et al., 2012). Therefore, an overall picture of white matter pathology in adult ADHD is currently lacking.

In this study, we used DTI to comprehensively compare white matter variation in adults with ADHD and healthy controls. We investigated values of FA, MD, AD, and RD using tract-based spatial statistics (TBSS), which is a whole-skeleton voxel-by-voxel analysis (Smith et al., 2006). Within the ADHD group, we investigated associations of FA and MD with clinical symptom scores and cognitive measures. These cognitive measures were selected to cover prominent cognitive domains commonly affected in adults with ADHD (e.g., working memory, attention, inhibition, and delay discounting/impulsivity). Based on the current literature, we expected to find (a) widespread decreases of FA and increases of MD and RD in ADHD, and (b) associations of FA with symptom severity and cognitive performance.

2. Materials and methods

2.1. Subjects and procedure

In total, 216 individuals (107 patients with persistent ADHD, 109 healthy controls) from the Dutch cohort of the International Multicentre persistent ADHD CollaboraTion (IMpACT) (Franke et al., 2010) participated in this study. The patients and an age-, gender-, and IQ-matched group of healthy controls were recruited through the Department of Psychiatry of the Radboud University Medical Center and through advertisements.

Patients were included if they met DSM-IV-TR criteria for ADHD in childhood as well as adulthood, as assessed by a psychiatrist. At the time of inclusion into the study, participants were assessed using the Diagnostic Interview for Adult ADHD (DIVA) (Kooij, 2010). This