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Attention deficit/hyperactivity disorder and medication with stimulants in young children: A DTI study

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ABSTRACT

The relationship between attention deficit/hyperactivity disorder (ADHD) and white matter connectivity has not been well established yet, specially for children under 10 years of age. In addition, the effects of treatment on brain structure have not been sufficiently explored from a Diffusion Tensor Imaging (DTI) perspective. In this study, the influence of treatment with methylphenidate in the white matter of children with ADHD was investigated using two different and complementary DTI analysis methods: Tract-Based Spatial Statistics (TBSS) and a robust tractography selection method. No significant differences were found in Fractional Anisotropy (FA) between medicated, drug-naïve patients and healthy controls, but a reduced Mean Diffusivity (MD) was found in ADHD patients under treatment with respect to both healthy controls and drug-naïve ADHD patients. Also, correlations were found between MD increases and performance indicators of ADHD. These findings may help elucidate the nature of white matter alterations in ADHD, their relationship with symptoms and the effects of treatment with psychostimulants.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a very common neuropsychiatric disorder, with symptoms arising in childhood and often persisting during adult age (American Psychiatric Association, 2013). Although behavioral and cognitive aspects of ADHD are well-known, the specific pathophysiological mechanisms and changes in the brain structure and development in ADHD remain somewhat unclear. As with other neuropsychiatric disorders such as schizophrenia, neuroimaging studies in ADHD have increasingly focused on different aspects of brain connectivity during the last years. MRI anatomical studies showed decreased WM (white matter) volume throughout the brain in ADHD patients (Krain and Castellanos, 2006), particularly in the prefrontal cortex, while a growing number of fMRI studies have shown reduced activity in frontal regions and fronto-striatal networks in children and adolescent ADHD patients (Weyandt et al., 2013).

Diffusion Tensor Imaging (DTI) is an MRI modality that can provide additional information about brain connectivity. This neuroimaging tool enables in vivo quantification of the diffusivity of water molecules within tissue, providing information about the organization of the WM of the brain and the orientation of its fiber tracts. Water tends to diffuse preferentially along a direction parallel to WM tracts because the myelin sheath and cell membranes restrict the diffusion perpendicular to the direction of the axons. Thus, diffusion in WM tissue can be described through scalar measures that characterize different geometrical properties of the diffusion tensor. Fractional Anisotropy (FA) and Mean Diffusivity (MD) are most commonly employed, although other measures such as Tensor Mode (TM) and Linear Measure (LM) add complementary information about the nature of the anisotropy. LM is commonly employed in tractography algorithms, whereas TM has been employed in different studies on WM alterations (Douaud et al., 2011).

Tables 1 and 2 provide a comprehensive summary of the current literature in analysis of ADHD using diffusion MRI. Differences among previous studies stem from different patient groups and diverse analysis techniques. Although studies indicate that ADHD is associated with significant irregularities in white matter microstructure, especially in frontostriatal and selected corticocortical tracts, there is a considerable lack of agreement with respect to the nature, location and significance of these abnormalities. For instance, a decrease in the FA was reported in ADHD patients in multiple studies, while others described FA increases, sometimes along with simultaneous decreases in other WM

Abbreviations: ADHD, attention deficit/hyperactivity disorder; DTI, diffusion tensor imaging; TBSS, tract-based spatial statistics; FA, fractional anisotropy; MD, mean diffusivity; WM, white matter; TM, tensor mode; LM, linear measure; VBM, voxel-based morphometry; DSI, diffusion spectrum imaging; GTS, geometric tractography selection; HC, healthy children; ADHD-nT, ADHD who underwent no treatment; ADHD-uT, ADHD who were treated with methylphenidate; K-SADS-PL, kiddie schedule for affective disorders and schizophrenia, present and lifetime version; WISC-IV, Wechsler intelligence scale for children-IV; WPPSI, Wechsler preschool and primary scale of intelligence; DWIs, diffusion weighted images; CC, corpus callosum; CG, cingulum; CORT, corticospinal tract; IFO, inferior frontoccipital fasciculus; ILF, inferior longitudinal fasciculus; UNC, uncinate fasciculus; FWE, family-wise errors; TFCE, threshold-free cluster enhancement; CPT, Conners continuous performance test II.

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Table 1
Overview of DTI findings in ADHD patients in the literature, in chronological order (part 1). ACR, Anterior Corona Radiata; AD, axial diffusivity; ALIC, Anterior Limb of the Internal Capsule; ATR, anterior thalamic radiation; CC, corpus callosum; CG, cingulum; $D_{\parallel}$, axial diffusivity; $D_{\perp}$, radial diffusivity; DKI, Diffusion Kurtosis Imaging; DSI, Diffusion Spectrum Imaging; EC, External Capsule; FA, Fractional Anisotropy; GFA, Generalized Fractional Anisotropy; HC, healthy controls; IC, internal capsule; ILF, inferior longitudinal fasciculus; IFO, inferior frontoccipital fasciculus; $K_{\parallel}$, axial kurtosis; $K_{\perp}$, radial kurtosis; MCP, middle cerebellar peduncle; MD, Mean Diffusivity; MK, Mean Kurtosis; MTR, Magnetization Transfer Ratio; PBS, Pediatric Bipolar Disorder; PCR, Posterior Corona Radiata; PTR, posterior thalamic radiation; RD, radial diffusivity; SLF, superior longitudinal fasciculus; SCR, Superior Corona Radiata; SRI, Superior Region of the Internal Capsule; SS, Sagittal Stratum; PLIC, posterior limb of the internal capsule; TBSS, Tract-Based Spatial Statistics; UNC, uncinate fasciculus; VBM, Voxel-Based Morphometry; WM, white matter.

Study	N	Mean age	Analysis method	Main findings
Ashtari et al. (2004)	30	–	VBM (FA)	Less areas with reduced FA in medicated patients with respect to drug naïve patients
Ashtari et al. (2005)	33	9	VBM (FA)	Reduced FA in right premotor, right striatal, right cerebral peduncle, left middle cerebellar peduncle, left cerebellum, and left parieto-occipital areas
Chou et al. (2007)	32	13.6	VBM (FA)	Reduced FA in bilateral internal capsule, middle cerebellar peduncle and right cerebellum. FA increase in left parietal lobe, ventricle, corpus callosum and right parietal lobe
Casey et al. (2007)	60	48.4/17.3	Prefrontal cortex identified with fMRI, fiber tracking from adjacent areas	FA in right prefrontal fiber tracts correlated with both functional activity in the inferior frontal gyrus and caudate nucleus and performance of a go/no go task in parent–child dyads with ADHD.
Helpern et al. (2007)	17	16.08	DKI. Delineated prefrontal brain region (FA, MD, MK)	Absence of significant correlation of MK with age in ADHD, as opposed to control group. No differences in FA or MD
Hamilton et al. (2008)	33	11.8	ROI analysis using regions registered from SPM (Burgel et al., 2006)	Reduced FA in ADHD patients in corticospinal tract and superior longitudinal fasciculus
Makris et al. (2008)	29	40.8	VBM (FA)	Reduced FA in adults with childhood ADHD in cingulum bundle and superior longitudinal fascicle II
Silk et al. (2009b)	30	12.7	TBSS (Smith et al., 2006) (FA, MD)	Increased FA in WM white-matter regions underlying inferior parietal, occipito-parietal, inferior frontal, and inferior temporal cortex
Silk et al. (2009a)	30	12.7	Manually delineated ROIs	Different developmental changes in FA in the caudate nucleus
Pavuluri et al. (2009)	41	14.0	Manually delineated ROIs on specific fiber tracts (FA, MD)	Comparison of ADHD with PBD. Reduced FA in ACR in both PBD and ADHD relative to HC. Lower FA in ADHD relative to PBD and HC in ALIC and SRI. Increased ADC in ADHD relative to both PBD and HC in ACR, ALIC, PLIC, SRI, CG, ILF, and SLF
Bechtel et al. (2009)	34	10.9	VBM (FA) inside a cerebellum mask	Comparison of ADHD with combined epilepsy/ADHD and HC. Reduced FA in MCP in children with combined epilepsy/ADHD compared to HC and reduced FA in right MCP in children with developmental ADHD
Konrad and Eickhoff (2010)	–	–	Review	Convergent evidence for WM pathology and disrupted anatomical connectivity in ADHD
Li et al. (2010)	44	9.8	VBM (FA)	Increased FA in right frontal region
Konrad et al. (2010)	71	31.4	VBM (FA and MD)	Study in adults. Reduced FA and higher MD bilaterally in orbitomedial prefrontal WM and in the right anterior CG Increased FA bilaterally in temporal WM structures
Cao et al. (2010)	55	13.3	Manual delineation of CC in midsagittal slice	Reduced FA in the isthmus of the CC
Davenport et al. (2010)	55	14.96	VBM (FA)	Comparison of ADHD with schizophrenia and HC. Uniquely higher FA in left inferior and right superior frontal regions in ADHD. Lower FA in ADHD and schizophrenia patients than HC in left posterior fornix
Qiu et al. (2011)	30	12.93	VBM (FA)	Decreased FA in the forceps minor, the internal capsule, the corona radiata, the splenium of the corpus callosum, and the bilateral basal ganglia
Kobel et al. (2010)	26	10.7	VBM (FA)	Reduced FA left ACR, and in the right MCP. Increased FA in left temporo-occipital WM
Peterson et al. (2011)	32	11.2	VBM (FA) and ROI analysis (registered from atlas)	Increased FA in the right superior frontal gyrus and posterior thalamic radiation, and left dorsal posterior cingulate, lingual and parahippocampal gyrus
Liston et al. (2011)	–	–	Review	Studies indicate that ADHD is associated with significant irregularities in WM microstructure, especially in frontostriatal and select corticocortical tracts.

regions (Chou et al., 2007; Davenport et al., 2010; Konrad et al., 2010; Li et al., 2010; Peterson et al., 2011; Silk et al., 2009b; Tamm et al., 2012). There is, however, a number of factors that can contribute to the diversity of findings in ADHD using DTI, including differences in the age of the participants across different studies, the nature of the participants (ADHD patients vs controls, parent–child dyads, ADHD patients vs schizophrenia or epilepsy patients…), the WM analysis method (Voxel-Based Morphology, Tract-Based Spatial Statistics, manual delineation…) or the DTI measures employed, among others. Recently, Van Ewijk et al. identified two possible mechanisms with opposite effects on the FA: familiar vulnerability and ADHD symptom count (van Ewijk et al., 2014).

A growing number of recent studies have focused more on other parameters (besides FA) in order to investigate ADHD. Increased MD in ADHD patients has been reported in a number of cases (Konrad et al., 2010, 2012; Lawrence et al., 2013; Pavuluri et al., 2009), but decreases have also been found (van Ewijk et al., 2014). Nagel et al. reported both increases and decreases in this parameter (Nagel et al., 2011). Importantly, many studies have focused on adolescents or preadolescents, while fewer have reported results on children under the age of 10 (Ashtari et al., 2005; Li et al., 2010; Nagel et al., 2011).

With regard to the WM analysis method, most previous studies employed approaches based on Voxel-Based Morphometry (VBM), a technique that was originally designed for the analysis of T1 structural brain images (Ashburner and Friston, 2000; Wright et al., 1995) and is sometimes also referred to as VBA (Voxel-Based Analysis) (van Ewijk et al., 2012). Using this approach, each subject's volume is transformed into a standard space via registration, and then statistical analyses are carried out voxelwise in order to find differences among groups. Alternatively, an increasing number of studies have recently resorted to TBSS (Tract-Based Spatial Statistics), an analysis method designed to overcome the limitations of VBM by creating an invariant tract representation over which permutation statistics are performed (Smith et al., 2006). Recently, advanced imaging techniques such as DSI (Diffusion Spectrum Imaging) and Connectomics have been employed, with results pointing to altered WM connectivity in networks including frontal, striatal and cerebellar regions (Cao et al., 2013; Hong et al., 2014). Relationships have also been found between symptoms or continuous performance tests and impaired WM integrity (Cao et al., 2013; Lin et al., 2014; van Ewijk et al., 2014; Wu et al., 2014).

Increasing attention has been recently devoted to the acute and long-term effects of stimulants in the WM structure and functional connectivity. Castellanos et al. showed that treatment with methylphenidate may normalize WM volume reductions that occur in children with ADHD (Castellanos et al., 2002). Studies with fMRI provide evidence that methylphenidate has acute effects on brain functioning,