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# Relationship between white matter microstructure abnormalities and ADHD symptomatology in adolescents

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ABSTRACT

The present study sought to evaluate whether white matter microstructure abnormalities observed in a cohort of adolescents with attention-deficit/hyperactivity disorder (ADHD) have specific relationships with either or both Hyperactivity/Impulsivity and Inattentive ADHD symptom domains that would support a dimensional view of ADHD as adopted in the DSM-V. Diffusion tensor imaging (DTI) data were acquired on 22 adolescents diagnosed with ADHD. Multiple regression analyses were performed to determine whether scalar DTI measures in 13 tracts-of-interest demonstrated meaningful associations with Hyperactivity/Impulsivity or Inattentive symptom severity. Fractional anisotropy and radial diffusivity measures of white matter integrity exhibited significant linear relationships with Hyperactivity/Impulsivity and Inattentive symptom severity. However, only radial diffusivity in the right superior longitudinal fasciculus was specifically linked to Inattentive symptom severity and not Hyperactivity/Impulsivity symptom severity. Our results provide preliminary evidence that symptom domains in ADHD are linked to neuroanatomical substrates and confirm the value in examining ADHD from a dimensional perspective.



## 1. Introduction

The unresolved and long-debated (Lahey and Carlson, 1991; Cantwell, 1996; Sherman et al., 1997; Hudziak et al., 1998; Gomez et al., 1999; Neuman et al., 1999; Lahey et al., 2005; Nigg et al., 2005; Woo and Rey, 2005; Baeyens et al., 2006; Larsson et al., 2006; Volk et al., 2006) question whether the Inattention and Hyperactivity/Impulsivity symptoms of attention-deficit/hyperactivity disorder (ADHD) have shared versus distinct etiologies took a new turn when the fifth edition of the Diagnostic and Statistical Manual for Mental Disorders (American Psychiatric Association, 2013) replaced categorically distinct ADHD clinical subtypes with clinical "Presentations." This decision was based in large part on evidence that the subtypes have notable similarities (e.g., cognitive and academic dysfunction, treatment response), as well as the fact it better accounts for the within-patient instability of ADHD symptom expression over time (Willcutt et al., 2012). Although this diagnostic change seemingly endorses the idea that the different ADHD symptom types stem from common causal factors, there is as yet insufficient evidence for either distinctiveness or similarity of pathophysiology underlying the two ADHD symptom types to conclude they are the same or different. Some recent genetic evidence is strongly suggestive of differing ADHD symptom etiologies (e.g., Nigg et al., 2004; Larsson et al., 2006; Swanson et al., 2007). It is not yet known, however, what specific biological mechanisms might be linked to these differing genetic profiles. For instance, neuropsychological test performance, often useful to infer dysfunction in specific brain regions, shows more similarities than differences across hundreds of ADHD studies (Willcutt et al., 2012), differing perhaps only in a matter of degree of specific cognitive impairments.

One approach to identify distinct neurobiological abnormalities in ADHD subtypes would be to directly contrast Predominantly Inattentive and Predominantly Hyperactive/Impulsive DSM-IV-defined (American Psychiatric Association, 2000) ADHD patients using structural or functional neuroimaging. To date, however, there have been no studies that have directly compared brain structures in non-comorbid ADHD subtypes and only four studies that have directly compared brain function in non-comorbid ADHD subtypes (Solanto et al., 2009; Edel et al., 2013; McCarthy et al., 2013; Rodrak and Wongsawat, 2013). Functional studies typically demonstrate the existence of diffuse brain activity differences between Combined (ADHD-C) and Inattentive (ADHD-I) subtypes, almost entirely ignoring the Hyperactive-Impulsivity (ADHD-H) subtype. This strategy has an important drawback, because ADHD patients commonly present with a mix of the two symptoms types, frequently missing meeting

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ADHD "Combined Subtype" criteria by only one or two symptoms in either symptom domain. A useful way forward can be seen in another recent DSM-5 conceptual change that recognizes the importance of a dimensional perspective in psychiatry in general (e.g., McHugh and Slavney, 1998; Maser and Patterson, 2002; Haslam, 2003; Helzer et al., 2006a, 2006b, 2006c), and ADHD in particular. According to a dimensional perspective, differing profiles of severity (e.g., based either on the severity or the frequency of ADHD symptoms (Swanson et al., 2009) might reflect important etiological differences. Clear depiction of these abnormalities would be missed if one only considered the presence or absence of an arbitrary-numbered constellation of symptoms. A handful of promising studies already have attempted to link dimensions of ADHD symptom severity to brain abnormalities. For instance, in one study, higher ADHD Inattention predicted lower ADHD brain activation during all conditions of a Stroop Color-Word functional magnetic resonance imaging (fMRI) task (Depue et al., 2010). In contrast, there was no association of brain activation levels with Hyperactivity/Impulsivity symptom severity. Several studies of brain structure have linked Hyperactivity/Impulsivity severity to lower right ventral striatum volume (Carmona et al., 2009), greater amygdala volume (Frodl et al., 2010), and smaller posterior thalamus volume (Ivanov et al., 2010). Greater Inattention was associated with other brain region abnormalities, e.g., smaller right amygdala (Frodl et al., 2010) or larger right medial thalamus volume (Ivanov et al., 2010). While this limited evidence suggests that some forms of neurobiological impairment are linked to a specific dimensional severity continuum in ADHD, more work is needed – both to replicate initial findings and to extend them to other measures of brain structure and function. Moreover, dimensional studies of ADHD have yet to clearly identify shared neurobiological abnormalities between the two symptom types.

One aspect of brain structure that has not yet been examined from a dimensional perspective in ADHD is white matter microstructure, as measured by diffusion tensor imaging (DTI). DTI is sensitive to white matter axonal density, diameter, and organization and myelination (Gong et al., 2009). Characteristic changes, including increased axonal diameter and density and ongoing myelination, have been well documented in normal child and adolescent brain development (Snook et al., 2005; Eluvathingal et al., 2007; Lebel et al., 2008; Perrin et al., 2009), making DTI measures of white matter microstructure ideal for investigating how ADHD symptoms may manifest via abnormal development of white matter. To date, at least 15 studies have been published describing white matter connectivity abnormalities in ADHD (for review, see van Ewijk et al., 2012). However, this ever-growing growing number of studies has not yielded a consistent set of white matter tracts that are abnormal in ADHD. Of all available studies, ADHD abnormalities have been most often reported in the middle cerebellar peduncle, corpus callosum, internal capsule, corona radiata, cingulum bundle, superior longitudinal fasciculus, and inferior longitudinal fasciculus. These previous studies typically examined modest sample sizes, often of only a single DSM-IV subtype (typically Combined ADHD), or failed to distinguish among subtypes in their analyses. Only one DTI study to date has specifically examined dimensional white matter abnormalities in a mixed sample of Inattentive, Hyperactive-Impulsive, or Combined subtype ADHD children and adolescents related to the severity of Hyperactivity/Impulsivity (Hamilton et al., 2008), finding decreased fractional anisotropy in the bilateral corticospinal tract and superior longitudinal fasciculus in the ADHD cohort compared with the healthy controls. This study found no association between DTI measures and symptom scores as measured on the SNAP-IV symptom rating scales (Swanson, 1992), but the authors noted that their small sample size meant that the study was most likely unpowered to note anything other than the strongest effects. Another study examined a cohort of 96 neurologically normal 6-year-old boys and found that higher inattentive and hyperactivity/impulsivity ratings (as assessed using the Conners' Parent Rating Scale; Conners et al., 1998) were associated with reduced fractional anisotropy in a number of major white matter tracts including the right and left sagittal stratums, right posterior thalamic radiation, and the body and splenium of the corpus callosum (Qiu et al., 2012). While this latter study did not directly examine ADHD-diagnosed children, it linked white matter microstructure to ADHD symptoms and adds evidence for the validity of a dimensional framework for ADHD neurobiology.

The purpose of the present study was to evaluate whether ADHD white matter microstructure abnormalities have specific relationships with either (or both) major clinical domains of ADHD symptom severity (i.e., Hyperactivity/Impulsivity [ADHD-HI] vs. Inattention [ADHD-I]). Because so few previous DTI studies have considered neurobiological abnormality in ADHD from the perspective of dimensional severity, any evidence for unique relationships between white matter tract abnormality and severity of ADHD symptoms in either of the two DSM-IV ADHD clinical symptom domains would provide much needed biological validation of the proposed dimensional framework for ADHD. This would be a productive step in the direction of identifying any specific biological correlates shared by (or unique to) each symptom domain. Inherent in this argument is that the notion of severity – either ADHD or white matter microstructure – indexes the degree of severity or expression of a neurobiological abnormality unique to that symptom domain. Our approach was to examine a sample of youth representing a range of symptom severities (i.e., some without Hyperactive/Impulsivity, some without Inattentive, and others with varying degrees of each type of symptoms). Our analyses sought to show whether relationships between DTI-measured white matter microstructure and ADHD symptoms were either unique to one presentation or shared across both Hyperactivity/Impulsivity and Inattention. Although DTI fractional anisotropy (FA) is most commonly examined because it represents an effective summary measure of overall water diffusivity around white matter, recent research (e.g., Alexander et al., 2007; Thomason and Thompson, 2011) has indicated the value of concurrently examining additional scalar DTI measures (radial diffusivity, mean diffusivity, and axial diffusivity) that are believed to capture more specific aspects of white matter microstructural abnormalities.

## 2. Methods

### 2.1. Participants

Participants included 22 adolescents (18 males; four females) ages 12–18 (mean/SD age 15.0/1.9) diagnosed with ADHD (DSM-IV 314.00 or 314.01) who were recruited via community and physician referral as part of a National Institute of Mental Health (NIMH)-funded study of brain structure and function (K23MH070036). Because the purpose of this study was to examine dimensional relationships between ADHD symptom severity and brain structure and not to replicate the diverse previously identified ADHD white matter abnormalities, a non-ADHD comparison group was not included. The ADHD sample was specifically chosen because the study's recruitment criteria permitted a range of ADHD symptom severity. DSM-IV diagnoses were evaluated by the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (KSADS-PL; Kaufman et al., 1997) administered by experienced staff. The KSADS-PL was chosen over more typical measures, such as the SNAP or Conners' Parent Rating Scale, as while the latter two measures code symptoms using a summary score (e.g., 0 = definitely absent, …, 3 = definitely threshold) which arguably better captures conjoint measures of both number of symptoms and their degree of expression, such summary measures are typically highly correlated. Mean/SD ADHD Hyperactivity/Impulsivity symptoms were 6.1/2.3 (range 1–8); mean/SD ADHD Inattention symptoms were 7.2/1.8 (range 1–9). Roughly one-third of the sample were high on ADHD-I but low on ADHD-HI symptoms, another third was high on ADHD-HI but low on ADHD-I, and the final third was high on both ADHD-I and ADHD-HI symptoms. As per study criteria, none of the ADHD-diagnosed participants had any other current DSM IV-defined psychiatric comorbidity. Additionally, approximately one-third of participants reported regularly taking some sort of ADHD medication. As the DTI data were acquired as part of a larger study examining brain function in addition to brain structure, those participants currently taking ADHD