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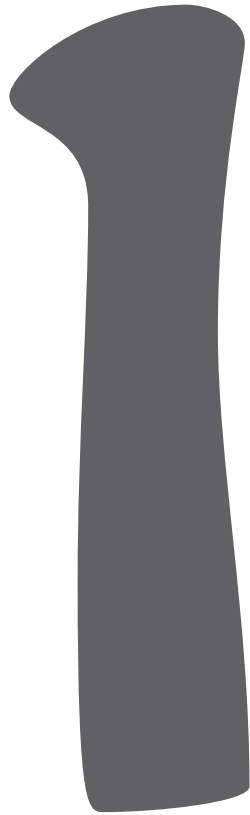
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Introduction

Parts of this chapter are adapted from:

Van Ewijk, H. & Oosterlaan, J. (2014). Attention-Deficit/Hyperactivity Disorder. In: Blaney, P. H., Krueger, R. F., Millon, T. (Eds.), *Oxford Textbook of Psychopathology*. Oxford, United Kingdom: Oxford University Press.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Attention-Deficit/Hyperactivity Disorder (ADHD) is a highly prevalent neurodevelopmental disorder. ADHD is characterized by persistent and age-inappropriate levels of inattention, hyperactivity, and/or impulsivity, occurring in multiple situations, to such a degree that symptoms severely interfere with the individual's daily life functioning (American Psychiatric Association, 2000, 2013). Prevalence rates are estimated around 6-7% for childhood ADHD and 5% for young adults (e.g. Willcutt, 2012). However, these rates vary dramatically between studies, and concerns have arisen that ADHD may be overdiagnosed. This may be due to the fact that some of the most important diagnostic criteria, including impairment, pervasiveness, and differential diagnostics, are easily and often overlooked in the diagnostic process, in research as well as in the clinical field. Consensus guidelines emphasize the importance of strictly adhering to standard diagnostic criteria for the diagnosis of ADHD, such as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM), and preferably include a full clinical interview in the diagnostic process (Kendall, Taylor, Perez, & Taylor, 2008; Pliszka, 2007; Seixas, 2013; Wolraich et al., 2011).

Throughout history, ADHD was first described as a hyperkinetic disorder, followed by the inclusion of, and focus on, inattentive symptoms in the DSM-III (1980). The DSM-IV again redefined the diagnosis in 1994, distinguishing the predominantly inattentive (ADHD-I) and predominantly hyperactive-impulsive (ADHD-H) subtypes, as well as the combined subtype (ADHD-C) for children showing both inattentive and hyperactive-impulsive symptoms. The current version of The DSM (DSM-5; American Psychiatric Association, 2013) retains these subtypes (now called *presentations*). However, debate is ongoing regarding the validity of the distinction between different subtypes (e.g. Coghill & Seth, 2011), and many researchers prefer speaking in terms of two symptom dimensions (inattentive versus hyperactive/impulsive), rather than three subtypes.

Throughout the past few decades, scientific interest in ADHD and knowledge about the disorder have grown exponentially. While a large body of research is available on the aetiology, treatment and neurobiological and neurocognitive features associated with ADHD, the number of unanswered questions is still substantial. ADHD appears to be a clinically and aetiologically heterogeneous disorder, and literature is often inconsistent, possibly due to the heterogeneous character of the study samples.

COMORBID PROBLEMS

The majority of children and adolescents with ADHD experience a wide variety of comorbid problems and disorders (Gillberg et al., 2004; Spencer, Biederman, & Mick, 2007). Common comorbid disorders include, but are not limited to, oppositional defiant disorder (ODD) and conduct disorder (CD), with estimates around 60% for ODD and 40% for CD (Connor, Steeber, & McBurnett, 2010). In adolescence and young adulthood, ADHD is associated with heavier and an earlier start of cigarette smoking (Lee et al., 2011; McClernon & Kollins, 2008), and increased risk for misuse of alcohol and other substances (Biederman et al., 2006). Adult ADHD is also associated with a high occurrence of antisocial behaviours (such as theft, assault, vandalism or disorderly conduct) and high rates of arrests, convictions and incarceration (Biederman et al., 2006; Küpper et al., 2012). On top of the adverse outcomes, ADHD patients are frequently experienced as a burden on their families (Coghill et al., 2008; Pardini & Fite, 2010), and the disorder has been shown to have a substantial negative economic impact, mostly due to loss of productivity and income in adults, and extra costs in health care and education in children with ADHD (Doshi et al., 2012). While the prevalence of comorbid problems in ADHD is high, research studies often neglect to take these into account in their design or interpretation of results. Consequently, it is largely unknown to what extent these comorbid problems may have influenced results in the current literature.

AETIOLOGY

ADHD is best described as a multifactorial disorder in which a variety of risk factors, and combinations of these factors, contribute to the overall risk of developing the disorder. From twin and adoption studies it has become clear that heritability estimates are high in ADHD (~76%; Biederman & Faraone, 2005), implicating a major role of genetic influences. In spite of the high heritability, only few risk genes with small effect sizes have been identified so far (Gizer, Ficks, & Waldman, 2009; Thapar, Cooper, Eyre, & Langley, 2013). The difficulty in identifying ADHD risk genes may partly be due to the complex nature of genetic influences, including epigenetic effects and interactions between risk genes and environmental risk factors. Another factor that appears to play a role is the large heterogeneity in the behavioural presentation of the disorder. During the past decade, researchers have suggested to move forward towards identifying 'endophenotypes' (e.g. Castellanos et al., 2002), which are heritable traits that are more closely linked to the genetic underpinnings of a

disorder than to the (more heterogeneous) behavioural manifestation (Gottesman & Gould, 2003; Kendler & Neale, 2010; Rommelse, 2008), such as neurocognitive deficits or specific neurobiological abnormalities that are characteristic for ADHD. Endophenotypes have the potential to overcome the heterogeneity that is present in the behavioural presentation of the disorder, and may thus provide useful directions for the search for specific candidate risk genes. Unaffected siblings are uniquely valuable in endophenotype research, since they share on average 50% of their genes with their affected siblings, yet they do not qualify for the disorder at the clinical level. Consequently, if unaffected siblings were found to suffer from a neurocognitive deficit or brain abnormality that is characteristic of ADHD, this would indicate that these deficits are not a result of ADHD symptoms (as unaffected siblings do not display these symptoms), but are more likely to be a neurocognitive impairment or brain abnormality underlying the risk of developing the disorder, or may be caused by the same risk genes that play a role in the development of ADHD. This way, endophenotypes may also improve our understanding of the causality of cognitive and neurobiological dysfunctions in ADHD.

NEUROBIOLOGICAL AND NEUROCOGNITIVE FEATURES

Given its high heritability rates, ADHD is believed to have an important neurobiological basis. It is likely that ADHD risk genes exert influence on early brain development, and alter maturational processes in the developing brain. Abnormalities in brain anatomy and activity could, in turn, cause neurocognitive dysfunctions such as poor working memory and inhibition, which may in turn play a role in the behavioural symptoms of the disorder. With advancing research techniques, considerable progress has been made in unravelling the neurobiological and neurocognitive correlates of ADHD. Specifically, neuroimaging techniques such as Magnetic Resonance Imaging (MRI) have proven to be useful tools to detect abnormalities in brain structure and functioning in ADHD.

Brain structure in ADHD

Brain volumes in ADHD, as measured by structural MRI, have been studied for decades. ADHD patients often show a reduced overall brain volume in comparison to healthy controls, as well as regional volume decreases in subcortical structures (including the striatum), prefrontal cortex, corpus callosum, anterior cingulate cortex, amygdala, and cerebellum (Frodal & Skokauskas, 2012; Nakao, Radua, Rubia, & Mataix-Cols, 2011; Valera, Faraone, Murray, &

Seidman, 2007). With advancing imaging techniques and knowledge about healthy and disturbed brain functioning, however, the focus of neuroimaging research in ADHD has shifted from studying local abnormalities to investigating structural and functional brain networks (K. Konrad & Eickhoff, 2010). White matter (WM) tracts, or axonal bundles, play a critical role in brain networks, by connecting distant brain regions and facilitating communication between these regions. Thereby, structural connectivity (i.e. the structure and organisation of WM tracts) also forms an important basis for functional brain connectivity. Diffusion Tensor Imaging (DTI) is a relatively new MRI technique that allows us to characterise structural connectivity, by measuring the microstructural properties of brain WM (Alexander, Lee, Lazar, & Field, 2007; Basser, Mattiello, & LeBihan, 1994). Most commonly used measures include fractional anisotropy (FA) and mean diffusivity (MD), representing the directionality and magnitude of water diffusion, respectively.

DTI studies are just beginning to emerge in ADHD research, and interpretation is still limited by methodological issues. Studies investigating specific regions of interest (ROIs) have identified abnormalities in WM microstructure in ADHD in a wide variety of WM tracts and regions, including the inferior and superior longitudinal fasciculus, anterior corona radiata, corticospinal tract (including the internal capsule), cingulum, corpus callosum, caudate nucleus, and cerebellum (e.g. see Bechtel et al., 2009; Hamilton et al., 2008; Peterson et al., 2011; Silk et al., 2009). Studies adopting a whole-brain approach have replicated some of these findings, but also reported findings in several other regions (e.g. Davenport, Karatekin, White, & Lim, 2010; A. Konrad et al., 2010; Qiu et al., 2010). Together, these findings implicate disturbances in white matter microstructure in ADHD, which could possibly - at least partly - underlie functional brain abnormalities, cognitive impairment, and behavioural problems associated with the disorder.

However, overlap between findings is limited, impeding the formation of a clear image regarding the location and direction of WM abnormalities in ADHD. For example, while most studies report lower FA and higher MD in ADHD compared with controls, some studies report higher FA and lower MD. Inconsistencies in the current DTI literature in ADHD are likely due to variations in sample selection (such as small sample sizes, differences in diagnostic methods, or inclusion of comorbid disorders), scanning procedures, and analysis methods (including motion correction or multiple comparison corrections). Future larger studies with more stringent diagnostics and methodology can hopefully provide us with a more consistent image of

WM pathology in ADHD. Given the important role of the microstructure and organization of WM tracts in structural and functional brain connectivity, more consistent knowledge on WM abnormalities in ADHD would be highly valuable to advance our understanding of the neurobiological underpinnings of the disorder.

Brain function in ADHD

NEUROCOGNITIVE DEFICITS

ADHD is associated with a wide range of neurocognitive deficits. Early studies primarily focused on neurocognitive indices of inattention, motor restlessness and impulsivity, aiming to provide more objective measures of ADHD symptoms (Corkum & Siegel, 1993; Kuehne, Kehle, & McMahon, 1987; Porrino et al., 1983). While deficits have consistently been found on these measures (Alderson, Rapport, & Kofler, 2007; Huang-Pollock, Karalunas, Tam, & Moore, 2012; Huizenga et al., 2009; Losier, McGrath, & Klein, 1996; Rapport et al., 2009), effect sizes are generally small, findings remain inconsistent, and neurocognitive measures have not proven to be useful aids in the diagnosis of ADHD. More recent neurocognitive studies adopted a broader perspective and investigated a large variety of neurocognitive functions in children and adults with ADHD, aiming to obtain a more comprehensive understanding of the neurocognitive correlates of the disorder. Evidence suggests that deficits in working memory are one of the key deficits in ADHD (Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005; Willcutt et al., 2005), with the strongest impairments reported for the spatial domain of working memory, as opposed to the verbal or phonological domain (Martinussen et al., 2005). Working memory impairment has also been put forward as one of the most promising endophenotypes for the disorder (Castellanos & Tannock, 2002), yet little research is available that has explicitly tested this hypothesis.

ALTERED BRAIN ACTIVATION

Using functional MRI (fMRI), brain activation patterns can be investigated during performance of cognitive tasks. In general, fMRI studies show that ADHD patients often fail to recruit sufficient brain activation during a wide range of cognitive tasks (Cortese et al., 2012; Dickstein, Bannon, Castellanos, & Milham, 2006; Hart et al., 2013), and that even during rest, the ADHD brain shows altered activation patterns (K. Konrad & Eickhoff, 2010). Studies investigating brain activation during working memory tasks frequently report reduced activation in frontal and temporal

brain regions in ADHD, most consistently in the left inferior frontal gyrus, left anterior insula, and right middle frontal gyrus (Cortese et al., 2012). However, while neurocognitive impairments in ADHD are strongest for spatial working memory, all available fMRI studies have adopted non-spatial paradigms (Cortese et al., 2012) or poorly validated spatial tasks (Bédard et al., 2014; Ko et al., 2013), limiting comparability between results from behavioural and imaging studies. Consequently, it is currently unknown if, and how, visuospatial working memory (VSWM) impairments in ADHD may be underpinned by altered brain activation patterns.

The role of age and gender

It is important to view both brain structure and function in ADHD in the light of possible age- and gender effects. In healthy controls, important differences have been reported in brain structure, function, and chemistry between males and females, including white matter microstructure, working memory performance, and working memory-related brain activation patterns (Bell et al., 2006; Goldstein et al., 2005; Gong, He, & Evans, 2011; Hsu et al., 2008; Speck et al., 2000). Such differences underline the importance of taking gender into account in studying brain structure and functioning in health and disease, specifically when dealing with psychiatric disorders that are more common in either males or females. Prevalence rates of ADHD are 2 to 3 times higher for males than for females (Ramtekkar, Reiersen, Todorov, & Todd, 2010; Willcutt, 2012), however, no studies up to date have investigated gender effects on WM microstructure in ADHD or VSWM performance. One study investigated whether abnormalities in VSWM-related brain activation in ADHD interacted with gender, and found that brain activation abnormalities were only present in males with ADHD (Valera et al., 2010). However, these results were obtained using a non-spatial task in a sample of adults with ADHD. Taken together, it is currently unknown if gender effects play a role in WM abnormalities or in VSWM impairment and its associated brain activation patterns in children, adolescents and young adults with ADHD.

Age effects on neurocognitive and neurobiological correlates of ADHD are another relatively unexplored topic. Some theories state that abnormalities in brain structure in ADHD may represent a maturational delay, where brain development of children with ADHD is lagging behind that of their typically developing peers (Rubia, 2007; Shaw et al., 2006). This developmental delay is hypothesized to be nonprogressive and persistent. On the other hand, evidence exists that at least some of the structural brain abnormalities in ADHD may catch up during adolescence (Castellanos et al., 2002). Only one study specifically investigated

the developmental trajectory of WM abnormalities in ADHD, and reported a catch-up of abnormal FA values in the caudate nucleus during mid- to late adolescence (Silk et al., 2009). However, the scope of that study was restricted to subcortical regions of the basal ganglia, and no whole-brain studies investigating this issue are currently available. At the behavioural level, it has been proposed that neurocognitive dysfunctions in ADHD are relatively pervasive into adulthood, although improvement of neurocognitive functions may be seen in patients with remitting symptoms (Halperin & Schulz, 2006). However, up to date, no studies have specifically investigated the developmental trajectory of VSWM impairment in ADHD or its neural correlates. Taken together, it is currently unknown whether WM abnormalities and VSWM dysfunctioning in ADHD are persistent into adulthood, or may catch up during adolescence.

AIMS OF THIS THESIS

The overall aim of the current thesis was to explore two critical, but relatively under investigated neurocognitive and neurobiological correlates of ADHD. The thesis is divided into two parts to address two specific aims: Part I describes the microstructure and organization of WM tracts in ADHD (chapter 2-5); part II describes VSWM and its neural correlates in ADHD (chapter 6-7).

Across both parts, children with ADHD will be compared to healthy controls, but also to unaffected siblings of ADHD patients, to explore whether white matter microstructure and VSWM may be useful endophenotypes for ADHD. Furthermore, we will try to capture part of the complexity of ADHD by taking important factors into account such as age- and gender effects and comorbid problems in ADHD.

STUDY DESIGN

Participants of the studies in this thesis originally took part in the International Multicenter ADHD Genetics (IMAGE) study, performed between 2003-2006 (Müller et al., 2011a, 2011b; Rommelse et al., 2008). Between 2009-2012, all Dutch families from the IMAGE cohort were re-invited for participation in a follow-up study (NeuroIMAGE), with a mean follow-up period of 6 years. NeuroIMAGE is a multi-site prospective cohort study designed to investigate the course of ADHD, its genetic and environmental determinants, its neurocognitive and neurobiological correlates, and its consequences in adolescence and adulthood. Inclusion criteria for the studies included in this thesis were: age between 8-30 years, of European Caucasian descent,

IQ \geq 70, and no known neurological or genetic disorder. Comorbid psychiatric disorders reported by parents were also excluded, except for ODD, CD and pervasive developmental disorder not otherwise specified (PDD-NOS), given their high co-occurrence in ADHD. Including a number of newly recruited families to balance out differences in gender and age, the total NeuroIMAGE cohort consisted of 323 ADHD families and 153 control families. Data collection during NeuroIMAGE consisted of a broad assessment battery, including a full clinical diagnostic interview for ADHD and comorbid disorders, behavioural questionnaires, neurocognitive measures, structural and functional neuroimaging, and genome-wide genetic information. Families were invited for a full testing day at either the VU University Amsterdam/VU University Medical Centre in Amsterdam, or the Radboud University Medical Centre in Nijmegen. A full description of the study design is published elsewhere (Von Rhein et al., 2014).

THESIS OUTLINE

Part I of this thesis explores the relatively new field of WM microstructure abnormalities in the ADHD brain, as measured by DTI. In **chapter 2**, an extensive and critical systematic literature review and meta-analysis is provided, discussing the currently available DTI literature in ADHD. Results are discussed in light of (in)consistencies and limitations of the current literature, and future directions are provided. In **chapter 3**, WM microstructure is compared between subjects with ADHD, their unaffected siblings, and healthy controls from the NeuroIMAGE cohort, and the association between ADHD symptom count and WM microstructure is investigated. Stringent diagnostic criteria and technical and statistical methods are adopted in the largest sample to date, to help move the field of DTI research in ADHD forward towards a more consistent image of WM pathology in the disorder. **Chapters 4 and 5** elaborate on WM microstructure in ADHD by exploring whether highly comorbid problems in ADHD are associated with additive, or differential, abnormalities in WM microstructure. **Chapter 4** focuses on comorbid ODD/CD in ADHD. WM microstructure is compared between ADHD patients with and without ODD/CD, to determine whether comorbid ODD/CD is associated with different WM abnormalities compared with ADHD-only, and whether the current DTI literature in ADHD may have been confounded by samples including ADHD patients comorbid for ODD/CD. **Chapter 5** investigates the effect of smoking on WM microstructure in adolescents with ADHD and healthy controls. Given that adolescents with ADHD are at increased risk for developing nicotine dependence, and that both ADHD and smoking are associated with

alterations in WM microstructure, it is possible that both factors share underlying mechanisms, which could in turn explain the increased risk for nicotine dependence in ADHD. Furthermore, it is possible that smoking may have a different or stronger effect on the already vulnerable WM microstructure in ADHD compared with controls.

Part II of this thesis focuses on visuospatial working memory. In **chapter 6**, VSWM performance is compared between individuals with ADHD and healthy controls, and unaffected siblings are included to examine whether VSWM may be a useful endophenotype for ADHD. Furthermore, the trajectory of VSWM development from childhood to young adulthood is examined in all groups to investigate whether VSWM deficits in ADHD may catch up during adolescence or young adulthood. **Chapter 7** maps the neural correlates of VSWM deficits in ADHD using fMRI and a well-validated spatial span task. Brain activation patterns are compared between individuals with ADHD and healthy controls. Furthermore, age- and gender effects are examined in both groups in order to investigate whether abnormal activation patterns in ADHD are present in both males and females, and whether these abnormalities may catch up during adolescence.

The thesis concludes with a general discussion in **chapter 8**, which summarizes the main findings from each of these chapters. Results will be discussed in light of strengths and limitations of each of the studies, and avenues for future research are suggested. Insights from the different chapters will be combined to help to move towards a better understanding of the neurobiological correlates of ADHD as well as possible factors contributing to the complexity of the disorder.

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