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## Brain Structure and Function in ADHD:

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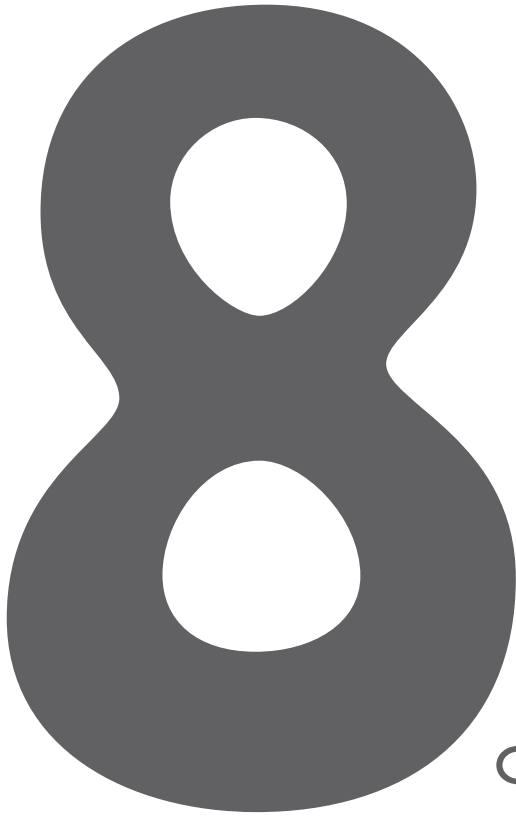
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General Discussion

The aim of the current thesis was to shed more light on the neurocognitive and neurobiological correlates of Attention-Deficit/Hyperactivity Disorder (ADHD), while capturing part of the complexity of the disorder by including unaffected siblings and studying age- and gender effects as well as comorbid problems in ADHD. First, the microstructure and organisation of white matter (WM) tracts, as measured by Diffusion Tensor Imaging (DTI), was explored from different angles to investigate possible abnormalities in structural brain connectivity in ADHD. Second, visuospatial working memory (VSWM), a key neurocognitive deficit in ADHD, was investigated from both the behavioural and the brain perspective.

Below, the main results from each chapter of this thesis are summarized. Subsequently, findings are discussed in a broader context, and linked to the current knowledge and challenges of the ADHD literature. Finally, strengths and limitations are discussed and recommendations are made for future research.

## **SUMMARY OF MAIN FINDINGS**

### **PART I - WHITE MATTER MICROSTRUCTURE IN ADHD**

#### **Chapter 2 - DTI in ADHD: review and meta-analysis**

This chapter provides an extensive overview of the current knowledge on WM microstructure in ADHD, as measured by DTI. All studies published before June 2011 were subjected to a systematic literature review and additionally, all whole-brain studies were included in a quantitative meta-analysis. The reviewed literature provided clear evidence of alterations in WM microstructure in the ADHD brain, in children as well as adults. The meta-analysis identified five regions in which altered fractional anisotropy (FA) had most consistently been reported, located in the right anterior corona radiata, right forceps minor, bilateral internal capsule, and left cerebellum. However, included studies differed greatly in terms of sample characteristics, analysis techniques and statistical procedures, hampering the formation of a consistent and robust image of WM abnormalities in ADHD. Furthermore, validity of results was often impeded by methodological limitations, such as inadequate diagnostics and the absence of corrections for head motion during scanning or statistical multiple comparison corrections. Despite the limitations of the current literature, DTI appears to be a valuable and promising technique in unravelling the neurobiological correlates of ADHD, by being able

to detect abnormalities in the microstructure and organization of brain WM tracts that are undetectable using conventional imaging techniques.

### Chapter 3 - Different mechanisms of WM abnormalities in ADHD

Following the review and meta-analysis in chapter 2, we set out to investigate WM microstructure in ADHD in a large and extensively phenotyped sample of individuals with ADHD, their unaffected siblings, and healthy controls. Results confirmed widespread alterations in WM microstructure in ADHD compared with controls, represented by lower FA in most of the major WM tracts in the frontal, temporal and parietal lobes, and lower mean diffusivity (MD) in the right temporal lobe. Furthermore, strong and widespread associations throughout the whole brain were observed between higher ADHD symptom count and WM abnormalities represented by higher FA and lower MD. This association was present for both symptom dimensions, indicating that both inattentive and hyperactive/impulsive symptoms are related to WM abnormalities in ADHD. Findings did not interact with age, gender or IQ, implicating that WM abnormalities in ADHD are present at all ages, in both males and females, and at all levels of cognitive functioning. Moreover, results were not confounded by comorbid disorders, a history of medication treatment, or socio-economic status. Unaffected siblings showed decreased FA similar to individuals with ADHD, but had MD values similar to those of controls. Taken together, these findings indicate that WM abnormalities in ADHD appear to be driven by two different mechanisms. First, decreased FA in ADHD may be due to a familial vulnerability to the disorder (i.e. shared genetic or environmental factors), causing decreased FA in children who are at genetic risk to develop the disorder. For example, ADHD risk genes could cause reduced myelination of several WM tracts in children with ADHD and their unaffected siblings. A second mechanism may drive the association between ADHD symptom count and WM alterations (represented by higher FA and lower MD), which appears to be linked to the presence of the symptoms of the disorder, and is therefore not present in unaffected siblings. For example, the presence of ADHD symptoms could cause decreased neurite outgrowth in the developing brain of children with ADHD.

### Chapter 4 - WM abnormalities associated with comorbid ODD/CD

In this chapter, we investigated the influence of highly common comorbid disorders on WM abnormalities in ADHD. We zoomed in on individuals with ADHD, and compared ADHD

patients with and without comorbid oppositional defiant disorder or conduct disorder (ODD/CD). Findings showed group differences in WM microstructure in frontotemporal WM tracts and subcortical structures. More specifically, the comorbid group (ADHD+ODD/CD) had lower FA compared with the ADHD-only group in the left corticospinal tract, uncinata fasciculus, inferior fronto-occipital fasciculus, corpus callosum (genu and splenium), and subcortical structures in and around the basal ganglia (thalamus, putamen, pallidum and internal capsule). Furthermore, we found an interaction between these categorical group differences and a dimensional measure of antisocial behaviour in several of these regions. This interaction showed that lower FA was mainly present in individuals with comorbid ODD/CD *in combination with* high rates of antisocial behaviour. Comorbid ODD/CD with low rates of antisocial behaviour, and high rates of antisocial behaviour without an ODD/CD diagnosis, did not appear to be associated with lower FA. Given that our comorbid group mostly consisted of individuals with ODD (only a minority had CD), and our dimensional measure mostly represented CD-like behaviours, it is possible that this interaction in fact represents an interaction between ODD and CD at the neurobiological level.

## Chapter 5 - Smoking and WM microstructure

ADHD is associated with an increased risk for developing nicotine dependence, and DTI studies have shown that smoking is associated with altered WM microstructure in adulthood, though literature on adolescence is scarce. In this chapter, we investigated the effects of regular smoking on WM microstructure in adolescents and young adults, and examined whether this was different in the already vulnerable ADHD brain. Results showed higher FA and lower MD to be associated with regular smoking, compared with irregular smokers and non-smokers, mainly in the corpus callosum and bilateral WM tracts located in and around the basal ganglia. It is possible that smoking causes alterations in WM microstructure of the maturing brain or, conversely, that pre-existing WM microstructure differences reflect a risk factor for developing a smoking addiction. ADHD was associated with lower FA in several WM tracts and regions, consistent with our findings in chapter 3. While effects of ADHD and smoking were located in partly overlapping areas, both factors did not interact, and effects of ADHD and smoking were in opposite directions (i.e. lower versus higher FA). This suggests that ADHD and smoking may interact with WM microstructure through different neurobiological mechanisms. For example, ADHD could be associated with decreased myelination (indicated by lower FA), while smoking may be associated with a higher cell density (represented by higher FA).

### Chapter 6 - VSWM: behavioural performance

Chapter 6 describes performance on a VSWM task for individuals with ADHD, their unaffected siblings, and healthy controls in a broad age range. Age effects were studied in all groups to investigate whether VSWM deficits in ADHD may catch up during adolescence or represent a more persistent neurocognitive impairment. Results showed impaired performance for ADHD patients compared with controls, which was similar for both the high and the low memory load (i.e. no group-by-memory load interaction). These results are consistent with a more general processing or executive deficit, rather than a storage deficit (which is further discussed below). Unaffected siblings performed better than their affected siblings, and similar to controls. Across all groups, the developmental trajectory of VSWM performance followed an inverse quadratic trajectory, indicating that VSWM abilities improve throughout childhood and adolescence, but that this development gradually decelerates as children grow older, reaching maturity during mid to late adolescence. We found similar age effects for all groups, indicating that VSWM impairment in ADHD, as well as the absence of VSWM impairment in unaffected siblings, is stable and persistent into young adulthood.

### Chapter 7 - VSWM: brain activation

In this chapter, brain activation patterns associated with VSWM were investigated using functional magnetic resonance imaging (fMRI) to gain more insight into the neural correlates of VSWM in ADHD and controls. Furthermore, effects of age and gender were examined to shed more light on the persistence of abnormal VSWM-related brain activation in ADHD into young adulthood, and to investigate whether these abnormalities were present in males as well as females. Our whole-brain analyses showed higher activation for ADHD compared with controls in left inferior frontal regions during memory load increase (i.e. high versus low load), more specifically in the left inferior frontal gyrus (IFG), pars opercularis and triangularis, and the lateral frontal pole. Follow-up analyses revealed that in the IFG pars opercularis, this difference was due to higher activation in ADHD compared with controls on the high memory load, with similar activation on low memory load. Conversely, in the IFG pars triangularis, we found lower activation in ADHD compared with controls during low memory load, and similar activation during high memory load. In several regions, effects of age and gender were found on VSWM-related brain activation. These effects did not interact with group, indicating that

the effects of age and gender were similar for ADHD and controls, and that abnormalities in brain activation in ADHD were present in both males and females, and at all ages, thus persistent into young adulthood.

## GENERAL DISCUSSION

### White matter microstructure

Structural brain connectivity, represented by WM tracts or axonal bundles, plays a vital role in the communication between brain regions. During the past decade, DTI research in ADHD has quickly gained scientific interest. Meta-analytic evidence (chapter 2) as well as results based on our own data (chapter 3) confirm the presence of abnormalities in WM microstructure and organisation in ADHD. While previous studies hypothesized that WM abnormalities in ADHD could be local, or predominantly present in frontostriatal circuitries (e.g. De Zeeuw et al., 2012; Silk et al., 2009), more recent studies as well as our own findings suggest that alterations in WM may be much more widespread than previously thought (Chapter 3, also see Cortese et al., 2013). By addressing several of the limitations observed in previous research (as discussed in Chapter 2), our results provide a clear image of WM abnormalities in ADHD, which was robust for a wide variety of possible confounders. Our findings implicate (at least) two different mechanisms underlying WM abnormalities in ADHD, one being linked to a familial vulnerability, the other more closely linked to the clinical state (i.e. the presence of symptoms). For example, it is possible that ADHD risk genes might cause poor myelination (decreased FA) in individuals with ADHD and their family members (first mechanism), while environmental risk factors for ADHD (such as pre- or perinatal difficulties), or the symptoms themselves, could cause decreased axonal density or reduced neurite outgrowth (increased FA and decreased MD) in individuals with ADHD (second mechanism). Such different mechanisms are a typical example of the complexity of ADHD, as will further be discussed below ("*Heterogeneity in ADHD*").

In addition to these different mechanisms, our findings demonstrate an important role of comorbid problems in ADHD in characterising WM abnormalities associated with the disorder. First, we showed that ADHD patients with and without comorbid ODD/CD differ in the microstructure of frontotemporal WM tracts, represented by decreased FA for ADHD+ODD/CD compared with ADHD-only (Chapter 4). Decreased FA in frontotemporal tracts has also

been demonstrated in 'pure' ODD/CD (without comorbid ADHD) (Haney-Caron, Caprihan, & Stevens, 2014; Passamonti et al., 2012; Sarkar et al., 2013), and in our sample, FA did not interact with ADHD symptoms. This suggests that our finding of decreased FA for ADHD+ODD/CD compared with ADHD-only was most likely due to the presence of ODD/CD in itself, and independent of ADHD symptoms. WM abnormalities were located in tracts that underlie cognitive and behavioural functions that are implicated in ODD/CD as well as antisocial behaviour, such as reward processing, motivation, and language functioning (Blair, 2004; Duffau et al., 2005; Fryer et al., 2008; Hogan, 1999; Kim et al., 2006; Vigneau et al., 2006; Von Der Heide, Skipper, Klobusicky, & Olson, 2013). It is likely that altered development of these tracts plays a role in the development of ODD/CD and aggressive behaviour, both in individuals with and without ADHD.

Second, we showed that regular smoking in adolescence was associated with altered WM microstructure, mainly in striatal regions and the corpus callosum (Chapter 5). Of note, the effects of ODD/CD and smoking did not interact with ADHD (symptom count), and thus appeared to be independent of ADHD-related WM abnormalities, yet they were (partly) located in the same regions as the effects of ADHD. This could indicate that ADHD and comorbid problems such as ODD/CD or smoking may have additive effects on WM microstructure in these regions, and that comorbidities may lead to additional brain abnormalities in the already vulnerable ADHD brain. Such an accumulation of WM abnormalities may lead to a higher vulnerability for associated cognitive and behavioural problems in comorbid individuals, and could also underlie the poorer long-term functional outcome reported in ADHD+ODD/CD compared with pure ADHD (Connor, Steeber, & McBurnett, 2010; Loeber et al., 2000). These inferences cannot be drawn with certainty from the current work given the cross-sectional design of our MRI data and the lack of a pure ODD/CD group, but deserve attention in future research.

In conclusion, Chapters 2-5 add to the current DTI literature in ADHD by revealing that WM abnormalities in ADHD may be much more widespread and complex than previously thought, and that comorbid problems such as ODD/CD and smoking may play an important role in the specific type, location and severity of WM abnormalities found in ADHD.

## Visuospatial working memory

Both children and adults with ADHD are known to suffer from neurocognitive deficits, in particular impairments in VSWM (Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005; Willcutt et al.,



2005), which are thought to be underpinned by abnormal brain activation (Bédard et al., 2014; Ko et al., 2013). However, the exact mechanisms underlying VSWM deficits in ADHD are still unclear, and fMRI studies generally use poorly validated tasks that do not clearly correspond to the paradigms used for behavioural research. Using a well-validated spatial span task, our results confirm the presence of VSWM deficits in ADHD at the behavioural level, and show that these deficits are present in males as well as females and across the whole age range investigated (8-30 years), persisting into young adulthood (Chapter 6). Impairment was similar at both memory loads, indicating that the number of items to be remembered did not play a role in the impairment, but that impaired performance is more likely to result from a more general processing or executive deficit. In terms of Baddeley's model of working memory (Baddeley, 2007), this would be most consistent with dysfunctioning of the central executive (CE), which is in line with previous meta-analytic findings that indicated that CE demand was one of the strongest moderators of the observed VSWM deficits in ADHD (Kasper, Alderson, & Hudec, 2012). Given the nature of the CE (i.e. attentional and executive control), this finding points towards a relatively general processing deficit underlying impaired VSWM performance in ADHD, rather than limitations in storage capacity.

Consistent with performance deficits, we found abnormal brain activation in ADHD during the spatial span task (Chapter 7). Results showed different activation patterns between ADHD and controls during memory load increase. This was further explained by underactivation in ADHD compared with controls during low memory load (but similar activation during high load) in the left IFG pars triangularis, which could indicate that ADHD patients failed to recruit this region due to a lack of arousal or attention, which improved when the task became more complex. Conversely, in the IFG pars opercularis, we found similar levels of activation during low load, but higher activation in ADHD compared with controls on the high load. However, this did not transfer to better behavioural performance on the high load compared with the low load, pointing towards inefficient recruitment of this brain region during VSWM in ADHD (consistent with Bédard et al., 2014). These findings were again similar for males and females, and stable across the whole age range, thus persistent into young adulthood.

In sum, Chapters 6-7 provide a robust image of persistent VSWM deficits in individuals with ADHD, but not their unaffected siblings, which are most likely due to a general processing or executive deficit. Furthermore, we add to the literature by adopting a well-validated paradigm to study brain activation patterns underlying VSWM, and showing that individuals

with ADHD have difficulty recruiting brain resources sufficiently and efficiently to facilitate adequate performance at the behavioural level.

## Risk or result? Causality and endophenotypes

One prominent question that remains is the issue of causality: Do the neurocognitive and neurobiological abnormalities that we observe in ADHD represent a risk factor for the disorder, or are they a *result* of the presence of the symptoms?

One possibility is that neurocognitive and neurobiological correlates of ADHD are caused by risk genes that play a role in the development of the disorder. For example, ADHD risk genes may influence early brain development, thereby causing alterations in brain structure and functioning, which may ultimately underlie the behavioural symptoms of the disorder. Alternatively, it is possible that certain ADHD risk genes have an effect on the development of the disorder, but at the same time have an independent effect on neurocognitive or neurobiological abnormalities associated with the disorder. Both these models are consistent with the existence of neurocognitive and neurobiological endophenotypes, that should also be present - to a certain extent - in unaffected siblings of ADHD patients (Kendler & Neale, 2010). A second possibility is that neurocognitive and neurobiological correlates of ADHD are a result of the presence of the disorder. It is possible that at birth, the ADHD brain is similar to that of typically developing children, but factors associated with the disorder alter brain structure and functioning during (early) childhood. The brain displays a remarkable plasticity during childhood, and WM microstructure can be altered by environmental experiences or (visuo)motor training (e.g. Fields, 2008; Scholz, Klein, Behrens, & Johansen-Berg, 2009). Following this reasoning, ADHD-related factors (such as negative parent and peer interactions or medication treatment) could disrupt the development of the young ADHD brain.

Understanding the causal relationship between neurocognitive and neurobiological impairments and ADHD symptoms might help us clarify whether these impairments reflect a familial (genetic or shared environmental) risk for developing the disorder, are better understood as epiphenomena, or may rather be a result of the behavioural manifestation of ADHD. The current thesis aimed to shed more light on this issue, by including unaffected siblings. Preliminary evidence for decreased FA in unaffected siblings (chapter 3; also see Lawrence et al., 2013) suggests that FA may prove to be a useful endophenotype for ADHD, and that WM abnormalities - as represented by lower FA - are most likely to be an epiphenomenon or

a risk factor for developing the disorder, rather than a result of the behavioural symptoms. For example, it is possible that ADHD risk genes cause altered development of specific WM tracts, creating a neurobiological vulnerability for the disorder that could - in combination with other risk factors - ultimately lead to the behavioural symptoms in children who develop the full disorder. Importantly, we found a second pattern of WM abnormalities that was only present in individuals with ADHD, not their unaffected siblings. On the one hand, it is possible that this second pattern also reflects a pre-existing risk for the disorder, and only children who show *both* patterns of WM abnormalities go on to develop ADHD. On the other hand, it is possible that the second pattern is a *result* of the disorder and associated features, for example being induced by pharmacological treatment or adverse psychosocial circumstances. Clearly, this issue deserves further attention in future research using longitudinal MRI designs.

We did not find any evidence for VSWM as an endophenotype for ADHD, as unaffected siblings performed similar to controls (Chapter 6) across the whole age range. This finding indicates that VSWM deficits in ADHD are more closely related to the presence of the symptoms, rather than a familial vulnerability or risk factor. This notion is further supported by a recent review that showed that working memory skills were not predictive of ADHD persistence (Van Lieshout et al., 2013). This suggests that working memory and ADHD symptoms may not share the same aetiology and that VSWM deficits may instead merely be a 'by-product' of ADHD. Although working memory has previously been put forward as a promising endophenotype for ADHD (Castellanos & Tannock, 2002; Gau & Shang, 2010), this proposition was based on relatively weak evidence. Available studies that included unaffected siblings generally did not control for (subclinical levels of) ADHD symptoms in these siblings (Bidwell, Willcutt, Defries, & Pennington, 2007; Gau & Shang, 2010). Consequently, in these studies, VSWM impairment in siblings may have been the result of (subclinical) ADHD symptoms in unaffected siblings, rather than representing a familial vulnerability. Considering our large and diagnostically well-defined sample, our results question the usefulness of VSWM as an endophenotype, consistent with other critical discussions of the neurocognitive endophenotype construct in ADHD (Coghill et al., 2005; Nigg, Blaskey, Stawicki, & Sachek, 2004). Of note, one previous study using a similar task and partly overlapping sample did show impaired VSWM performance in truly unaffected siblings (i.e. without subclinical ADHD symptoms; Rommelse et al., 2008). Children in that study were tested on average 6 years before the current study (at mean age 12), raising the possible interpretation that VSWM deficits are present in unaffected siblings at a younger age, but subside as they grow older. This could indicate that VSWM may be a useful

endophenotype for ADHD in young children, but that this familial vulnerability diminishes in unaffected siblings as their brain maturation catches up to controls towards adolescence (also see Nikolas & Nigg, 2014; Thissen et al., 2014). However, our results showed parallel developmental trajectories for all groups between the ages of 8-30 years (Chapter 6), which contradicts the interpretation of a developmental catch-up in unaffected siblings.

The question remains whether VSWM impairment is a *result* of the presence of ADHD symptoms, or a neurocognitive deficit *underlying* these symptoms. Given the nature of the symptoms of ADHD, it is likely that ADHD patients have trouble staying focused on the task during neurocognitive assessments, and that they may respond impulsively. Consequently, it is plausible that the presence of ADHD symptoms may have a negative impact on performance on cognitive tasks, especially when taking into account that ADHD patients are often tested off medication. This is further supported by evidence showing that attentional distraction during a VSWM task leads to a decline in spatial working memory performance in healthy controls (Awh & Jonides, 2001). However, the opposite hypothesis, that VSWM or CE deficits may *underlie* the behavioural symptoms of ADHD, is just as plausible. In healthy controls, it has been shown that increasing the memory load on a working memory task resulted in more distractibility from the main task as well as more task-irrelevant brain activation (de Fockert, Rees, Frith, & Lavie, 2001). These results suggest that poor working memory skills could result in more difficulty to filter out task-irrelevant information and thus increase distractibility during cognitive tasks. Based on this evidence, it is possible that VSWM impairment could (partly) underlie distractibility in ADHD, as also suggested by two previous studies (Kofler et al., 2010; M. D. Rapport et al., 2009).

Unfortunately, the causality of the association between VSWM impairment and ADHD symptoms cannot be determined based on the currently available data, and warrants further research. For example, intervention studies that target the training of working memory skills might provide more insight into this issue. If VSWM deficits underlie the symptoms of ADHD, working memory training should also have a positive effect on ADHD symptoms. Indeed, some studies report a positive long-term effect of working memory training, not only on working memory skills as such, but also on inattentive symptoms in ADHD (Shinaver III, Entwistle, & Söderqvist, 2014). However, the majority of randomized controlled trials and meta-analyses failed to find such long-term effects, or transfer effects to the behavioural symptoms of ADHD (Dongen-Boomsma, Vollebregt, Buitelaar, & Slaats-Willems, 2014; Melby-Lervåg & Hulme,

2013; Mark D Rapport, Orban, Kofler, & Friedman, 2013), suggesting that VSWM deficits may not play a direct causal role in the behavioural symptoms of the disorder.

## Heterogeneity in ADHD

ADHD is generally known as a complex disorder, reflected by a large heterogeneity in the aetiology, phenotypical presentation, neurocognitive and neurobiological deficits, and comorbid problems. For example, heterogeneity in the aetiology is reflected by a large number of risk genes (Gizer, Ficks, & Waldman, 2009) and environmental factors (Banerjee, Middleton, & Faraone, 2007; Bhutta et al., 2002; Biederman & Faraone, 2005; Linnet et al., 2003) being involved in the risk for developing ADHD. Neurocognitive heterogeneity is illustrated by the fact that different groups of patients show different types or combinations of neurocognitive deficits, and another group shows no deficits at all (Nigg, 2005; Sonuga-Barke, Bitsakou, & Thompson, 2010). A multiple pathway model could underlie this heterogeneity, where different (combinations of) risk factors could trigger different causal pathways to ADHD, represented by different patterns of symptoms and associated deficits (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005).

The heterogeneous nature of ADHD causes difficulties in the formation of a consistent image of the disorder, and will keep causing mixed results in the literature as long as ADHD is being treated as one homogeneous group, as is done in most studies that compare groups of ADHD patients and healthy controls. Identifying the specific sources of heterogeneity can help us create more homogeneous subgroups of ADHD, which will ultimately bring us closer to unravelling the complex aetiology of the disorder. Disentangling mixed results in the literature and identifying factors that differ between these studies may provide important clues regarding sources of heterogeneity. For example, differences between male and female samples of ADHD are often reported, such as abnormal brain functioning in males, but not females with ADHD (Valera et al., 2010). Such discrepancies may indicate that male and female ADHD have different neurobiological correlates and may reflect (partly) different causal pathways (Davies, 2014).

We here present several possible sources of inconsistencies in the DTI literature in ADHD that may be indicators of heterogeneity associated with the disorder. First, our finding of 2 different mechanisms of WM abnormalities indicates that different patterns of disturbances can be found, depending on the genetic profile, the number of symptoms of the ADHD patients,

which brain regions are investigated, and whether ADHD is investigated as a categorical or dimensional concept. For example, it is possible that ADHD patients with a strong familial risk (e.g. multiple risk genes combined) may mainly show decreased FA, while patients who only have a mild familial risk but are more impaired at the clinical level may predominantly show increased FA and decreased MD. This is a typical example of heterogeneity in ADHD and underlines the importance of considering ADHD in light of its heterogeneity and look at different patterns of abnormalities that may be linked to different aetiological pathways.

Second, it is possible that comorbidities in ADHD may point towards specific 'subtypes' of the disorder. For example, we here show that ADHD+ODD/CD is associated with different or additional WM abnormalities than ADHD-only. Consequently, it is possible that ADHD+ODD/CD may be a specific neurobiological 'subtype' of the disorder (as also previously suggested; e.g. Jensen et al., 2001), with a (partly) different aetiological pathway than ADHD-only, which could in turn underlie the differences in functional outcome between the groups (Connor et al., 2010; Loeber et al., 2000).

While it is often suggested that the three ADHD subtypes may have distinct neurobiological correlates (Willcutt et al., 2012), we did not find evidence for such a distinction, as both symptom dimensions were significantly associated with the WM alterations we found (Chapter 3). We also did not find evidence for specific effects of age and gender on WM abnormalities or VSWM deficits in ADHD, suggesting that these factors are less likely to be the cause of mixed results in current literature, and may not play a large role in the heterogeneity of ADHD, at least not in terms of WM microstructure and VSWM.

## **STRENGTHS AND LIMITATIONS**

An important strength of the sample used in this thesis is the large sample size. Given the complexity and heterogeneity of ADHD, large sample sizes are needed to overcome the risk of false positives or negatives associated with small, heterogeneous samples. Due to our large number of participants, we had sufficient power to provide robust estimates of WM and VSWM deficits in individuals with ADHD and their unaffected siblings. Moreover, our sample size provided the opportunity to address the heterogeneity of ADHD by taking a broad range of factors into account and study the effects of age (in a broad age range), gender, and different comorbid problems.

A second strength of the current thesis is the rigorous diagnostic procedure applied to all participants. While ADHD diagnostics are best performed using a combination of instruments and informants (Charach, Chen, Hogg-Johnson, & Schachar, 2009; Müller et al., 2011; Valo & Tannock, 2010), many studies base their diagnosis solely on questionnaires, only use one informant, or rely on previously established diagnoses. The current thesis adopted an extensive diagnostic algorithm, which was based on different instruments (a clinical interview supplemented with questionnaires), and combined information from multiple informants (the ADHD patients themselves, their parent(s), and - if available - a teacher report). Information from these different sources was evaluated by trained experts, combined with the assessing expert's own clinical impression of the child and family, and all information was considered in a broader perspective (e.g. taking differential diagnostics into account) before determining a final diagnostic category. Furthermore, relatively 'pure' groups of controls and unaffected siblings were established by not simply defining them as 'not having ADHD', but also requiring them to only show a minimal number of symptoms, to ensure they did not experience elevated or subclinical levels of ADHD, which could confound results.

A particular strength of the DTI studies reported in this thesis is that these studies addressed several important methodological limitations that were observed in previous literature. For example, the studies reviewed in Chapter 2 generally did not correct for multiple comparisons, and only half of the studies had corrected for head motion during scanning. Such factors are likely to result in false positive findings. Our data was pre-processed using a combination of well-established and high quality (pre)processing techniques, and strict statistical methods were applied in order to reduce the chance of false positives and negatives.

Concerning part II of this thesis, an important strength is the use of a well-validated working memory paradigm (Klingberg, Forssberg, & Westerberg, 2002; Westerberg, Hirvikoski, Forssberg, & Klingberg, 2004). Many previous studies (in particular fMRI studies) used visuospatial N-back tasks, of which the construct validity has not conclusively been established (Kane, Conway, Miura, & Colflesh, 2007; Redick & Lindsey, 2013). By using a spatial span paradigm when studying VSWM performance and its underlying neural correlates, a first attempt could be made to compare VSWM impairments in ADHD on both the behavioural and the neural level.

The results presented in this thesis should also be viewed in light of some limitations. First, we used a cross-sectional sample to investigate age effects in order to shed light on the developmental trajectories of WM microstructure and VSWM deficits in ADHD. Studying

developmental trajectories should ideally be undertaken by following a large sample longitudinally, from childhood into adulthood, and collecting measures at different time points. Nevertheless, our large sample size and broad age range did allow us to provide exploratory insights into the development of WM microstructure and VSWM.

A second limitation is the relatively 'pure' control group in the IMAGE cohort. Control participants were excluded if they showed any neurological or psychiatric disorders, such as autism spectrum disorders or ODD/CD. Consequently, the controls used in the current thesis are a relatively pure and problem-free sample and may not be fully representative of the general population. In addition, due to these exclusion criteria, our results on WM microstructure in ODD/CD (Chapter 4) could not be generalized ODD/CD itself, only to *comorbid* ODD/CD in ADHD, due to the lack of a 'pure ODD/CD' group.

Third, the ADHD and control groups differed in gender and were not equally balanced across the scan sites in Amsterdam and Nijmegen. Such confounding factors can cause biased results. For example, the majority of ADHD subjects were males, and the majority of controls were females, which could have confounded our group effects with gender differences. To avoid such confounding effects, we controlled for gender and scan site in all analyses. Furthermore, given our large overall sample size, the number of male and female participants was sufficient to be able to test for possible group-by-gender interactions. The absence of such interactions shows that the WM and VSWM deficits were similar for males and females, which makes it unlikely that the imbalance in gender would have influenced our results.

A general problem with DTI research in psychiatric disorders, including our own work, is the limited interpretation of altered DTI parameters in terms of underlying neurobiological mechanisms. For a large part, this is inherent to the nature of DTI, which measures the magnitude and direction of water diffusion, and thereby provides an *indirect* measure of WM microstructure and organisation. Since water is more likely to diffuse parallel to axon bundles instead of perpendicular to them, DTI gives us a sensitive approximation of WM microstructure and organization. However, while DTI parameters are overall sensitive to a wide range of tissue properties (such as myelination, cell density or fibre orientation), neither one is sensitive to one specific property (Jones, Knosche, & Turner, 2013). Consequently, while we can conclude that the microstructure and/or organisation of WM tracts is altered in ADHD, we cannot tell which specific tissue property (such as myelination, axonal density, or fibre orientation) is damaged or different. More (preliminary) insight can be obtained from the use of additional measures



or parameters (such as the mode of anisotropy or magnetization transfer imaging; also see Chapter 2), and the in-depth analysis of specific mathematical and geometrical properties of DTI parameters (Wheeler-Kingshott & Cercignani, 2009). Unfortunately, we did not have such measures available for the studies described in the current thesis.

## **FUTURE RESEARCH**

The current thesis adds to the literature by providing robust images of structural and functional brain deficits in ADHD, and discussing these in a broader perspective including familiarity, age, gender and comorbid problems. However, several important issues and questions remain, and new topics have emerged from the current results that deserve further attention in future research.

First, the heterogeneity of ADHD should be recognized and modelled in future ADHD research, specifically when addressing issues of causality (also see Coghill et al., 2005). While we made a first attempt by investigating the effects of age, gender, familiarity and comorbidities, many more factors can, and should, be investigated. Possible sources of heterogeneity and inconsistencies that were not elaborated upon in this thesis include, but are not limited to, the effects of medication treatment, differences between the three subtypes or presentations of ADHD, or differences between persisters and remitters, and the association with well-established ADHD risk genes.

Second, abnormalities in WM microstructure should be linked to functional implications, such as neurocognitive and behavioural correlates. Although first attempts have been made to link WM microstructure of specific tracts to neurocognitive functions in healthy controls (Böhr et al., 2007; Glasser & Rilling, 2008; Schmithorst, Wilke, Dardzinski, & Holland, 2005; Tuch et al., 2005), the exact functional correlates of many WM tracts remain poorly understood. Furthermore, in psychiatric research, it is important to gain more insight into the association between the presence of WM abnormalities and the neurocognitive or behavioural problems associated with the disorder. Such information could, for example, help to determine whether WM abnormalities in ADHD may underlie the behavioural symptoms, or may just be a by-product that is independent of the phenotypical presentation of the disorder. While our work (Chapters 3-4) and other studies (e.g. Haney-Caron et al., 2014; Li et al., 2010; Nagel et al., 2011; Peterson et al., 2011; Sarkar et al., 2013) have provided first evidence for such associations, this

body of literature is scarce, inconsistent (negative reports also exist; e.g. Nagel et al., 2011), and analyses are usually limited to the specific regions of interest defined in a study, limiting the formation of a clear whole-brain picture. Interestingly, one study combined DTI with fMRI measures of VSWM in healthy controls, and found that WM development in several cortical and subcortical regions was associated with increases in VSWM-related brain activation as well as VSWM capacity (Olesen, Nagy, Westerberg, & Klingberg, 2003). This study is an interesting example of linking (the maturation of) brain structure and functioning at different levels, and would be interesting to replicate in ADHD, to test whether WM and VSWM abnormalities in ADHD may also be also linked at a neurobiological level.

Third, it will be interesting to take a step back from treating ADHD as a categorical construct (i.e. comparing groups of individuals with and without ADHD), and move towards investigating the dimensional construct, where ADHD symptoms lie on a continuum from normal to abnormal behaviour, with ADHD as a clinical disorder on the extreme end (Lubke et al., 2009). Consistent with this view, it should be expected that ADHD-related neurocognitive and 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 neurocognitive and neurobiological correlates of categorical distinctions (Morris & Cuthbert, 2012). Indeed, we demonstrated the fruitfulness of this approach in our own data, which showed a much more widespread association between ADHD symptoms and WM abnormalities in our dimensional analysis as compared with the categorical analysis (Chapter 3). However, this analysis was only conducted within ADHD patients, and thus restricted to individuals at the high end of the continuum. Ideally, future research would be population-based and consider the whole range from healthy controls to ADHD, including subclinical cases, to shed more light on the entire continuum.

## IN CONCLUSION

The main conclusions that can be drawn from this thesis are:

- DTI is a promising technique in ADHD research, which could – if applied correctly – provide new insight into alterations in the structure and organisation of WM tracts in ADHD.
- The ADHD brain shows widespread alterations in the organisation and microstructure of WM tracts that are not confined to frontostriatal circuits.
- Different neurobiological and aetiological mechanisms underlie WM abnormalities in ADHD: On the one hand, a familial vulnerability to the disorder is associated with decreased FA in several WM tracts in individuals with ADHD as well as their unaffected siblings. On the other hand, widespread WM abnormalities that are represented by higher FA and lower MD appear to be more closely linked to the clinical state (i.e. the presence of symptoms), and are only present in individuals with the full diagnosis.
- WM abnormalities as represented by decreased FA in several WM tracts could prove to be a useful neurobiological endophenotype for ADHD.
- Comorbid ODD/CD is associated with additional or different WM abnormalities compared with ADHD-only, and may represent a specific and important subgroup of ADHD.
- ADHD and smoking have different, independent effects on WM microstructure, which may implicate an additive effect of smoking on the already vulnerable ADHD brain.
- VSWM is impaired in ADHD but not unaffected siblings, questioning the usefulness of VSWM as a neurocognitive endophenotype for ADHD.
- ADHD is associated with abnormal VSWM-related brain activation in left inferior frontal regions, implicating inefficient recruitment of these regions when the task becomes more complex.
- A dimensional approach may be more powerful in studying the neurobiological correlates of ADHD than a categorical approach, though a combination of both will be most valuable.

- Both VSWM impairment and WM abnormalities are present in both males and females.
- Impaired VSWM and WM abnormalities are stable throughout development into young adulthood. This indicates that these neurocognitive and neurobiological impairments do not worsen over time, but also do not catch up during adolescence, but are persistent into young adulthood.

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