FROM STATE TO STATE: THE MODULATION AND ORGANISATION OF STATE-DEPENDENT BRAIN NETWORKS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

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From state to state: The modulation and organisation of state-dependent brain networks in attention-deficit/hyperactivity disorder

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CHAPTER 1

GENERAL INTRODUCTION

Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a highly prevalent childhood onset neurodevelopmental disorder characterized by developmentally inappropriate levels of inattention and/or hyperactivity/impulsivity, which often persists into adulthood. In this chapter we first provide some general information about the core characteristics of ADHD, discuss the main aetiological risk factors, and introduce the main neuropsychological theories to explain ADHD-related deficits. We then discuss the potential neurobiological underpinnings of ADHD, which are the central focus of the current doctoral dissertation. Finally, we introduce the main goals and provide a brief overview of the empirical chapters.

What is ADHD?

Attention-deficit/hyperactivity disorder (ADHD) is an early onset neurodevelopmental disorder, characterized by age inappropriate levels of inattention and/or hyperactivity, which often persists into adulthood. According to the Diagnostic and Statistical Manual of Mental Disorders - fourth edition, text revision (DSM-IV-TR, American Psychiatric Association (APA), 2000) ADHD can be subdivided into: i) predominantly inattentive type; ii) predominantly hyperactive/impulsive type; and iii) combined type. The symptoms of inattention and/or hyperactivity/impulsivity must emerge before the age of seven years with some impairment in more than one setting, affecting social, academic or occupational functioning. The strength of symptom expression highly depends on the situational factors, such as the presence and intensity of reward, external stimulation, personal interest in the activity, situational novelty, etc. (APA, 2000). Of note, participants with ADHD from the studies included in this dissertation were diagnosed with ADHD based on the DSM-IV-TR criteria, however, meanwhile a new edition of the DSM, i.e., DSM-5 has been released (APA, 2013). The updated DSM-5 ADHD diagnosis criteria remained largely the same as in the previous version, except for the subtype replacement with presentation specifiers that directly map onto the previous subtypes, and the raise of the symptom presentation age from 7 years in DSM-IV-TR to 12 years in DSM-5 (APA, 2013).

ADHD is a highly prevalent disorder affecting 5 - 7% worldwide across the life span (Willcutt, 2012). In ADHD samples from the general population the inattentive type is the most common, while in clinic-based samples the most prevalent type is the combined (Willcutt, 2012). ADHD appears to be more prevalent in males than females with a female-to-male ratio of 1:3 in general population samples and 1:9 in clinic-referred samples (Barkley, 1997; Biederman et al., 2002). Moreover, ADHD is a highly

comorbid condition which commonly co-occurs with learning disabilities and other neuropsychiatric or neurodevelopmental disorders. Those often include oppositional defiant disorder, conduct disorder, mood and anxiety disorders, tic disorders, dyslexia and dyscalculia, depression and autism spectrum disorders (Thapar, Cooper, Jefferies, & Stergiakouli, 2012). Therefore, ADHD is a very complex and heterogeneous disorder posing a high burden on the affected individual, as well as on his/her family and the community.

What Causes ADHD?

Despite the fact that ADHD is currently one of the most studied conditions, the exact cause of ADHD is still to be determined. However, adding to the complexity and heterogeneity of ADHD, there exists a wide-range of different candidate aetiological factors (Tarver, Daley, & Sayal, 2014). These include the general categories of environmental and biological influences, as well as their interplay.

The heritability estimates of ADHD reach approximately 76%, which makes it one of the most heritable neurodevelopmental disorders worldwide (Faraone et al., 2005). Therefore, genetic factors should play a big role in the development and the course of ADHD (Cortese, 2012). The most frequently investigated candidate genes in ADHD relate to dopaminergic, noradrenergic and serotonergic neurotransmission systems due to their relation to stimulant medication effects, attentional or other higher cognitive functions, as well as impulsiveness (Banaschewski, Becker, Scherag, Franke, & Coghill, 2010). The most commonly studied genes in ADHD include those encoding dopamine receptor subtypes (D4 and D5) and the dopamine active transporter 1 (DAT1), noradrenaline transporter (NET1/SLC6A2) and the adrenergic alpha receptors 2A and 2C, serotonin transporter (5HHT) and the synaptosomal-associated protein 25 (SNAP-25) (Banaschewski et al., 2010; Faraone & Mick, 2010). While there exists evidence

that those gene variants may increase the risk for ADHD, meta-analyses and genome-wide association studies show non-significant associations between these risk genes and the disorder (Ashmore, 2013; Neale et al., 2010). This suggests that the effects of individual ADHD risk gene variants are small, and that different or very rare variants may explain the high heritability of the disorder (Banaschewski et al., 2010; Neale et al., 2010). For instance, the inherited copy number variation (CNV) related genes in ADHD were enriched for genes suggested as candidates - A2BP1, AUTS2, CNTNAP2, IMMP2L - in other neuropsychological disorders. Moreover, deletions were reported in the protein tyrosine phosphatase gene, implicated in restless leg syndrome and glutamate receptor gene (Elia et al., 2010).

Evidence shows that different environmental factors may play a predisposing role or increase the risk for developing ADHD. These primarily include prenatal maternal stress and anxiety, maternal prenatal alcohol consumption, nicotine, and illicit drug use (Thapar et al., 2012). Other adverse environmental factors are premature birth and low weight at birth, environmental toxins and poor diet, childhood diseases, and general psychosocial adversity (e.g., adverse social and immediate family environment, low socioeconomic status, lack of effective parent-child relationships, instances of parental psychopathology) (Cortese, 2012; Tarver et al., 2014; Thapar et al., 2012). Despite the number of environmental risk factors associated with ADHD, none of them has yet been evidenced to play a critical causal role for the disorder (Cortese, Faraone, & Sergeant, 2011). On the one hand, some of these environmental risk factors may be altered by genetic influences - via gene x environment interactions, on the other hand, environmental circumstances may modify certain gene functions (Thapar et al., 2012). Moreover, early environmental adversity during development has been shown to have a deteriorating effect on brain development (Mehta et al., 2009).

Neuropsychological Explanatory Models of ADHD

Based on the data from neuropsychological studies, several models of ADHD-related deficits have been developed (Chandler, 2011). The *Executive dysfunction theory of ADHD* (Barkley, 1997), suggests that ADHD represents a fixed executive functioning deficit and that the core disturbance is abnormal inhibitory control, which in turn affects other aspects of executive functioning (Barkley, 1997; Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Although studies have provided evidence for executive dysfunction in ADHD, meta-analyses indicate only moderate effect sizes and a lack of universality (Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005; Willcutt et al., 2005).

Evidence of the dynamic nature of ADHD-related deficits, led to models centred around contextual and state-dependent factors (Sonuga-Barke, Wiersema, van der Meere, & Roeyers, 2010a). The *Delay aversion theory* (Sonuga-Barke, Taylor, Sembi, & Smith, 1992) is one of the most prominent motivational ADHD accounts. Deficits are proposed to be caused by altered reward signalling, so that immediate rewards are preferred to delayed ones, which creates an impulsive drive to choose for immediate rewards as opposed to delayed ones, and predisposes one to less time and effort allocation to long and tedious tasks and increases the tendency to avoid and/or escape delay (Sonuga-barke, Houwer, Ruiter, Ajzenstzen, & Holland, 2004; Sonuga-Barke, et al., 2010a). Although evidence implicates *delay aversion* in ADHD; it also is neither necessary, nor sufficient to cause ADHD (Sonuga-Barke, Sergeant, Nigg, & Willcutt, 2008). *The state regulation deficit* theory (Sergeant, 2005; van der Meere, 2005), based on the cognitive energetic model of Sanders (1983) proposes that task-related processing is influenced by both, processing stages (i.e., encoding, feature extraction, response selection and response execution), and energetic state-dependent factors (i.e., arousal,

activation and effort) (Sanders, 1983; Sergeant, 2000). Individuals with ADHD, according to this theory, have difficulties in regulating their energetic state (arousal, activation) by extra effort allocation when challenged with suboptimal conditions (Sonuga-Barke et al., 2010a). Support for this model comes from studies manipulating the stimulus presentation rate, with ADHD individuals exhibiting performance decrements with fast and slow presentation rates, compared to moderate ones (Brown & Vickers, 2004; Metin, Roeyers, Wiersema, van der Meere, & Sonuga-Barke, 2012; Rubia, Taylor, Taylor, & Sergeant, 1999; Scheres, Oosterlaan, & Sergeant, 2001; Wiersema, van der Meere, Antrop, & Roeyers, 2006a; Wiersema, van der Meere, Roeyers, Van Coster, & Baeyens, 2006b), as well as from psychophysiological response studies using event-related potentials (ERPs) and heart rate indices (Börger & van der Meere, 2000; Wiersema et al., 2006a,b).

Although these neuropsychological accounts provide important explanations of ADHD symptoms, none is completely successful in explaining the full spectrum of ADHD-related deficits. Hence, ADHD is increasingly recognized as a very heterogeneous condition, having multiple developmental causal pathways (Nigg, 2005; Sonuga-Barke, Bitsakou, & Thompson, 2010).

Recent advances in neuroimaging techniques and data analysis methods have facilitated the increasing search for and examination of the neurobiological underpinnings potentially implicated in the pathophysiology of ADHD. To date, neuroimaging studies have indicated that besides apparent behavioural disturbances, there exist widespread neural abnormalities across several brain systems implicated in different cognitive and attentional functions (Bush, 2010; Cao, Shu, Cao, Wang, & He, 2014; Cortese et al., 2012; van Ewijk, Heslenfeld, Zwiers, Buitelaar, & Oosterlaan,

2012). These ADHD-related neurobiological abnormalities are the central focus of the current doctoral dissertation.

ADHD Neurobiology: Moving from the study of single regions to the way brain networks are organised

There exist a number of different neuroimaging methods (e.g., electroencephalography (EEG), magnetoencephalography (MEG)), however, here we focus on findings from the two most frequently employed non-invasive magnetic resonance imaging (MRI) techniques: (i) functional MRI (fMRI) - generally used to study task-related brain activations and functional task-related/task-unrelated connectivity; and (ii) diffusion MRI (dMRI) - typically used to examine structural brain organisation.

fMRI in ADHD

Initial task-based fMRI studies in ADHD revealed several task-specific regional brain activation abnormalities in primarily prefrontal-striatal regions which provided crucial information about the first candidate neural underpinnings of ADHD (Dickstein, Bannon, Castellanos, & Milham, 2006; Matthews, Nigg, & Fair, 2014). Later, with accumulation of data, the focus shifted beyond that, and now ADHD-related regional brain abnormalities are known to be diverse and widespread, encompassing temporal, parietal, occipital, limbic, and cerebellar regions (Castellanos & Proal, 2012; Cortese et al., 2012; Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013). Although the findings of alterations in a number of discrete brain regions tapping different cognitive functions provided important insights, a new paradigm shift in contemporary neuroscience is emerging. This account goes beyond the sole mapping of cognitive functions onto

distinct regions and instead stresses the cooperative functions of brain regions operating in tandem as coordinated large-scale brain networks (Bressler & Menon, 2010). Established regional abnormalities in ADHD relate to several robust brain networks. Disturbances in ventral lateral frontal cortices and posterior parietal regions suggest abnormalities of the twofold attentional control system (Cortese et al., 2012), comprised of dorsal and ventral attention networks (DAN and VAN), which operates as an integrated supramodal top-down and bottom-up attentional gating system (Corbetta & Shulman, 2002; Hopfinger, Buonocore, & Mangun, 2000; Vossel, Geng, & Fink, 2014; Woldorff et al., 2004).

Naturally, traditional accounts have primarily focused on alterations in the attention system as a putative locus for ADHD-related behavioural deficits (Cubillo, Halari, Smith, Taylor, & Rubia, 2012). However, the recent shift of interest in contemporary neuroscience form task-based to task-free or resting brain functional properties has introduced the importance of the task-independent - default mode network (DMN) in attentional processes (Raichle et al., 2001). The DMN is a set of brain regions involving primarily anterior and posterior midline structures (medial prefrontal cortex (mPFC) and posterior cingulate cortex (PCC)/ precuneus), together with lateral parietal and medial temporal lobe regions (Buckner, Andrews-Hanna, & Schacter, 2008). Its activity increases during periods of rest or internally-focused, self-referential processing and is attenuated following the switches to externally-oriented, goal-directed cognitive tasks (Gerlach, Spreng, Gilmore, & Schacter, 2011; Raichle et al., 2001; Singh & Fawcett, 2008; Spreng & Grady, 2010). Importantly, the DMN is also referred to as a ”task-negative” network due to its anti-correlated and to some degree antagonistic relationship with the attention or “task-positive” brain system (Fox et al., 2005). This implies that externally-oriented attentional processes require the

coordinated attenuation of the DMN and upregulation of task-related attention networks (Lawrence, Ross, Hoffmann, Garavan, & Stein, 2003; Sonuga-Barke & Castellanos, 2007), and performance decrements, such as attentional lapses, errors, increases in response times (RT), have been shown to coincide with excess task-related DMN (Bednarski et al., 2011; Fassbender et al., 2009; Li, Yan, Bergquist, & Sinha, 2007; Weissman, Roberts, Visscher, & Woldorff, 2006).

The established involvement of the DMN in attentional processes has led to the formulation of a DMN-based neurocognitive model to explain task-related performance deficits. *The DMN interference hypothesis* postulates that under certain suboptimal circumstances (e.g., in individuals with ADHD) DMN activity may persist into or recur during the periods of externally-oriented task-related processing and interfere with neural activity in task-relevant regions causing performance decrements (e.g., lapses of attention, errors, RT variability) (Sonuga-Barke & Castellanos, 2007). Studies have provided evidence of disturbed ADHD-related task and rest state-dependent DMN functioning, namely, excess task-related activity and disturbed functional connectivity (Castellanos et al., 2008; Fassbender et al., 2009; Liddle et al., 2011; Mccarthy et al., 2013; Tian et al., 2006). Hence, these DMN alterations may represent one of the putative causal pathways linked to ADHD. As a result, this poses a crucial question about the potential role of *DMN interference* in the pathophysiology of ADHD, which requires further examination (Sonuga-Barke & Castellanos, 2007). In the current doctoral dissertation we tackle this question by examining several neural properties (discussed below), which may predispose an individual with ADHD for levels of excess task-related DMN interfering with task-related neural processes and causing performance decrements.

Another important account of state-dependent neural dynamics centres around the salience network (SN), comprised of anterior cingulate cortex (ACC) and bilateral insulae, specifically right anterior insula (rAI) as the core node within the SN (Seeley et al., 2007). This model, introduced by Menon and Uddin (2010), postulates that SN operates as a central switching hub coordinating the upregulation of task-relevant attention networks and attenuation of the DMN, and there is now compelling evidence to support this model (Goulden et al., 2014; Jilka et al., 2014; Rilling, Dagenais, Goldsmith, Glenn, & Pagnoni, 2008; Sridharan, Levitin, & Menon, 2008). In terms of ADHD, activation, functional connectivity and structural abnormalities are reported in regions comprising the SN (Lemiere et al., 2012; Tian et al., 2006; Lopez-Larson, King, Terry, McGlade, & Yurgelun-Todd, 2012). Thus, in keeping with the ADHD-related activity abnormalities in the attention networks and DMN during tasks, as well as disturbances of the SN, controlling switches between rest (supported by the DMN) and task (supported by task-related attention networks) states, ADHD may represent a condition underlined by deficits in state-dependent brain network engagement and disengagement. This becomes particularly relevant when switching between different cognitive states, (i.e., rest and task states), because the anticipatory neural preparation is crucial for an effective initiation of an upcoming state and must occur during a very limited time (Wylie, Javitt, & Foxe, 2006). Moreover, evidence suggest that task-related brain activation disturbances may be sculpted by the alterations of the intrinsic brain network organisation during rest (Bressler & Menon, 2010; Deco & Corbetta, 2011), and that ADHD may represent a condition underlined by deficits in functional brain network organisation (Menon, 2011; Cortese et al., 2012). Specifically, the key ADHD-related dysfunction may lie in the abnormal coordination of the DMN and attention

networks, controlled by the SN (Aboitiz, Ossandón, Zamorano, Palma, & Carrasco, 2014; Supekar & Menon, 2012).

dMRI in ADHD

Although abnormalities in functional organisation of several brain networks implicated in cognitive and attentional control processes are commonly reported in ADHD; the alterations in structural brain network organisation that may underlie functional and behavioural deficits are still poorly understood (Cao et al., 2014; Weyandt, Swentosky, & Gudmundsdottir, 2013). The use of dMRI allows the examination of microstructural properties and connections inside the living brain (Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000; O'Donnell & Pasternak, 2014), and has opened new opportunities to study the pathophysiology of ADHD in terms of structural white matter brain abnormalities (Weyandt et al., 2013). Although dMRI studies in ADHD, especially in adults with ADHD, are yet relatively scarce and the results are not very consistent, the most commonly reported white matter alterations include inferior and superior longitudinal fasciculus, cingulum bundle, anterior corona radiata, internal capsule, forceps minor, cerebellar tracts, thalamic radiation, and isthmus of corpus callosum (Kobel et al., 2010; Konrad & Eickhoff, 2010; Peterson et al., 2011; van Ewijk et al., 2012; Weyandt et al., 2013; Zhang & Li, 2010). In addition, recently graph-theoretic analysis has been applied in two studies to examine the organisation of structural brain networks in children with ADHD (Cao et al., 2013; Ray et al., 2014). While this provided initial evidence for structural brain network organisation abnormalities in ADHD, the investigation of graph metrics and their potential alterations in adult ADHD is lacking. Although dMRI studies offer strong evidence of multiple structural alterations in the ADHD brain, there are still numerous gaps to be filled by future research (Cao et al., 2014). As a first step, adult ADHD-related structural brain

network organisation in terms of graph metrics will be examined in the current dissertation.

Research goals and the overview of the doctoral dissertation

The main goal of the current doctoral dissertation was to investigate the neural properties of state-dependent brain networks implicated in attentional processes in adults with ADHD. We examined the neural modulatory properties of brain network engagement and disengagement during transitions between different cognitive states (i.e., rest and task states), intrinsic functional intra- and inter- state-dependent network organisation, and graph metrics of structural brain networks in adults with ADHD. In doing so, we sought to establish a better understanding of the neural systems implicated in attentional processes and their potential disruptions that may account for the ADHD-related deficits.

This doctoral dissertation is comprised of six chapters. *Chapter1* - general introduction (the current chapter); *Chapter 2* to *Chapter 5* - empirical chapters, where the findings from the studies conducted are presented (overviewed in more detail below); *Chapter 6* - general discussion, which encompasses an integrated perspective on the main findings, theoretical and clinical implications, methodological limitations and future research recommendations.

The empirical chapters

Chapter 2. In this chapter we present and validate a novel experimental paradigm, which we developed to study the neural modulation of brain networks during state-to-state transitions. While steady state outcomes of those transitions are well investigated, little is still known about the actual process of state-to-state switching, namely, task-to-rest and vice versa, described by the anticipatory modulation of DMN and SN which is

proposed to control the DMN modulation during state-to-state transitions (Menon & Uddin, 2010). There were three major goals of the study. First, we needed to establish that our novel paradigm allows DMN modulation anticipating state-to-state switches to be studied in a valid way. Thus, we first investigated whether the DMN, shown previously to be implicated in steady state rest, is responsive to brief cues signalling rest and if so, whether it was attenuated by cues signalling task. Second, we investigated the DMN modulation following the anticipation of state switches of an opposite direction - i.e., whether there was an up-regulation of DMN upon task-to-rest cues. Third, we examined the role of the SN, specifically rAI during the anticipation of different switch types, thus whether - rAI was equally involved in within- and between-state switches.

Chapter 3. Here we applied the previously validated (*Chapter 2*) state-to-state switching paradigm to study the neural modulation of the DMN, rAI (a core node of SN) and task-relevant areas in adults with ADHD. We tested the hypothesis that impaired state-to-state switching in ADHD would be related to altered anticipatory downregulation of DMN and/or upregulation of task-relevant regions during rest-to-task switching. To investigate whether rest-to-task switching impairments may indicate a more general state-to-state switching deficit (e.g., state regulation deficit) we also compared groups for brain activation upon cues of upcoming task-to-rest switches. Furthermore, we examined rAI involvement in this process (Menon & Uddin, 2010; Sridharan et al., 2008).

Chapter 4. Evidence supports the idea that patterns of intrinsic task-free brain organisation sculpt task-related attentional neural processes, and it has been suggested that ADHD may represent a condition caused by underlying deficits in intrinsic brain

organisation (Bressler & Menon, 2010; Cortese et al., 2012; Deco & Corbetta, 2011). Thus, in the current study we examined the intrinsic organisation of brain networks implicated in attentional processes, namely the DMN, VAN, DAN and SN in a group of adults with ADHD by employing a network-based connectivity approach.

Chapter 5. Prior structural dMRI studies provide evidence for the alterations in several white matter fibre tracts and structures encompasing regions of frontal, temporal, parietal and occipital cortices (Weyandt et al., 2013). Graph theory, which is a branch of mathematics focusing on formal characteristics and analysis of graphs (i.e., mathematical structures for modelling pairwise object relationships), is a way of investigating the organisation of brain networks in healthy people and in psychopathology (Bullmore & Sporns, 2009; Griffa, Baumann, Thiran, & Hagmann, 2013; Xia & He, 2011). However, to date only two studies have examined structural brain network organisation in ADHD. These studies provided initial evidence for alterations (Cao et al., 2013; Ray et al., 2014) in children with ADHD. The study presented in *Chapter 5* is the first one examining structural whole-brain network organisation in adults with ADHD, employing a graph theory approach.

It is important to highlight that the empirical chapters comprising the current doctoral dissertation are original research reports, which either have already been published or accepted for publication, or are currently under review or have been submitted for publication. As a result, each empirical chapter is stand-alone and, thus, there can be considerable overlap between the chapters.

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CHAPTER 2

ANTICIPATORY PROCESSES IN BRAIN STATE SWITCHING - EVIDENCE IMPLICATING DEFAULT MODE AND SALIENCE NETWORKS[1]

Abstract

Objective: The default mode network (DMN) is the core brain system supporting internally oriented cognition. The ability to attenuate the DMN when switching to externally oriented processing is a prerequisite for effective performance and adaptive self-regulation. Right anterior insula (rAI), a core hub of the salience network (SN), has been proposed to control the switching from DMN to task-relevant brain networks. Little is currently known about the extent of anticipatory processes subserved by DMN and SN during switching. **Method:** We investigated anticipatory DMN and SN modulation using a novel cued-switching task of between-state (rest-to-task/task-to-rest) and within-state (task-to-task) transitions. Twenty healthy adults performed the task implemented in an event-related functional magnetic resonance imaging (fMRI) design. **Results:** Increases in activity were observed in the DMN regions in response to cues signalling upcoming rest. DMN attenuation was observed for rest-to-task switch cues.

[1]Based on Sidlauskaite, J., Wiersema, J. R., Roeyers, H., Krebs, R. M., Vassena, E., Fias, W., & Sonuga-Barke, E. (2014). Anticipatory processes in brain state switching - Evidence from a novel cued-switching task implicating default mode and salience networks. *NeuroImage*, *98*, 359-365. doi:10.1016/j.neuroimage.2014.05.010

Obversely, DMN was up-regulated by task-to-rest cues. The strongest rAI response was observed to rest-to-task switch cues. Task-to-task switch cues elicited smaller rAI activation, whereas no significant rAI activation occurred for task-to-rest switches. **Conclusions:** Our data provide the first evidence that DMN modulation occurs rapidly and can be elicited by short duration cues signalling rest- and task-related state switches. The role of rAI appears to be limited to certain switch types - those implicating transition from a resting state and to tasks involving active cognitive engagement.

Introduction

The brain at rest is characterized by coherent spontaneous low-frequency fluctuations across multiple discrete brain networks (i.e. resting state networks; RSNs) (Damoiseaux et al., 2006; De Luca, Smith, De Stefano, Federico, & Matthews, 2005). The default mode network (DMN) (Raichle et al., 2001) incorporates frontal and posterior midline regions, including medial prefrontal cortex (mPFC), and posterior cingulate cortex (PCC)/precuneus. This neural circuit controls internally-oriented, self-referential cognition (Buckner, Andrews-Hanna, & Schacter, 2008; Gerlach, Spreng, Gilmore, & Schacter, 2011; Spreng & Grady, 2010). DMN activity increases during wakeful rest, and tasks of self-referential, introspective cognition, but is attenuated following the switch to externally-oriented attention-demanding tasks (Spreng & Grady, 2010; Spreng, Stevens, Chamberlain, Gilmore, & Schacter, 2010). Increase in cognitive load across a range of cognitive tasks, generally those, that do not involve social and/or self-referential processing, leads to enhanced DMN suppression (McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003; Pyka et al., 2009; Singh & Fawcett, 2008). Moreover, processing efficiency during those tasks is correlated with the degree of DMN attenuation (Greicius, Krasnow, Reiss, & Menon, 2003; Greicius & Menon, 2004; Meyer, Spunt, Berkman, Taylor, & Lieberman, 2012). According to the DMN interference hypothesis (Sonuga-Barke & Castellanos, 2007), insufficient DMN suppression during the switch to externally-oriented cognitively-demanding tasks interferes with task performance, producing periodic lapses of attention (Bednarski et al., 2011; Li, Yan, Bergquist, & Sinha, 2007; Weissman, Roberts, Visscher, & Woldorff, 2006), and increased intra-individual behavioural variability (Sandrone & Bacigaluppi, 2012).

Comparatively little is known about the process, in contrast to the outcome, of these switches between resting and task related states. Initial research highlights the importance of preparatory processes occurring just prior to active task engagement controlling DMN attenuation. Sridharan and colleagues (2008) observed increased activation in right fronto-insular cortex (rFIC), (which together with anterior cingulate cortex (ACC) is part of the salience network [SN]), prior to both DMN attenuation and increased activation in neural circuits supporting task-specific processing. This led Menon and Uddin, (2010) to propose the hypothesis that right anterior insula (rAI), is a critical hub initiating switches between DMN and brain networks of goal-directed, task-specific engagement. In addition, Bonnelle and colleagues (2012) have shown that effective DMN modulation depends on the structural integrity of SN.

The classical cognitive control experiments investigating preparatory processes during switching between tasks have shown a robust involvement of the fronto-parietal network in task set initiation (Monsell, 2003) along with anticipatory pre-activation of specific brain areas relevant for the execution of a particular upcoming task (Wylie, Javitt, & Foxe, 2006). Such studies typically employ cued task-switching paradigms, consisting of a series of discrete trials on which participants perform one of a limited number of different tasks, i.e., on some trials they are prompted to repeat the immediately preceding task (non-switch trials), on others they are asked to perform a different task (switch trials) (Kiesel et al., 2010; Wylie et al., 2006). The use of anticipatory cueing in such paradigms enables the investigation of the preparatory cognitive and neural processes occurring before the actual initiation of goal-directed actions (Brass & Cramon, 2002; Meiran, Hsieh, & Dimov, 2010). Although the role of the SN, specifically rAI, has generally not been the central focus of investigation in these studies, robust responses of both ACC and rAI have been commonly reported (Dove, Pollmann, Schubert, Wiggins, & von Cramon,

2000). Thus, the widespread functions of rAI suggest this region to be a general multimodal integration unit, which operates by gathering motivationally salient information, facilitating the appropriate neural reconfiguration and higher-level cognitive processing (Cauda et al., 2012; Chang, Yarkoni, Khaw, & Sanfey, 2013; Downar, Crawley, Mikulis, & Davis, 2000, 2001; Kurth, Zilles, Fox, Laird, & Eickhoff, 2010; Uddin, Kinnison, Pessoa, & Anderson, 2013). In turn, this highly coordinated processing is essential for effective cognitive control during different types of cognitive or mental switches.

Here we investigate the switch-related anticipatory processes with a task that extends the classical cued task-switching paradigm to also study state-to-state switches, i.e. switches from rest-to-task and vice versa. Crucially, this novel design enables the identification and comparison of the neural reconfiguration and associated network activations during the anticipation of both within- (task-to-task) and between-state switches.

The current study addresses three questions. First, from a methodological point of view we need to establish that our newly developed task provides a valid way of studying DMN attenuation during state-to-state switch anticipation. Thus, the first question is - *is the DMN, shown previously to be implicated in steady-state rest, responsive to cues signalling rest?* If so, is this DMN activity attenuated to cues of an upcoming task? Second, previous studies have only focused on DMN suppression following the switch from rest-to-task; here we raise the related question concerning the anticipation of switches in the opposite direction, i.e., *is there an up-regulation of DMN following the presentation of cues signalling an upcoming switch from task-to-rest?* Finally, we

examine the role of rAI during the anticipation of different switch types. Thus, the third question is - *is rAI equally involved in within- and between-state switch anticipation?*

To address these questions we developed a new paradigm and implemented it within an event-related experimental design in which visual cues signalled the nature of the following trial while fMRI was being acquired. We included rest trials and two different types of task trials. With regard to our three research questions we predicted that: (i) DMN will be activated in response to rest cues and that this activity will be attenuated by rest-to-task switch cues; (ii) cues signalling the switch from task-to-rest will elicit anticipatory DMN up-regulation; (iii) in keeping with the model of Menon and Uddin (2010), state-to-state switches requiring DMN disengagement will elicit the highest rAI response.

Method

Participants

Twenty healthy adults with no prior history of neurological or psychiatric disease participated in the study. They all had an IQ in the average and above average range IQ (> 85) measured by the Ward 7-subtest short form of the Wechsler Adult Intelligence Scale-III (Pilgrim et al., 1999), mean IQ = 117.9 (*SD* = 11.2). Study participants were recruited via internet, magazine and internal university advertising. Two subjects had to be excluded from further analysis due to excessive head motion. The primary analysis included 18 subjects (10 female; mean age = 26.6 years; *SD* = 8.9; 3 left-handed) with normal or corrected to normal vision. All participants gave their written consent before entering the experiment and received a monetary reward for participation. The study was approved by the local ethical committee of Ghent University Hospital.

Task

The cued-switching task was programmed using Presentation software package (Neurobehavioral Systems, www.neurobs.com). Visual stimuli were presented in the middle of a black screen viewed by the participants through a mirror attached to a head-coil. The behavioural responses were recorded using two MR-compatible response boxes, one positioned under each hand. Participants responded by pressing a response button with their right or left index finger, depending on task rules.

The cued-switching task was comprised of three types of trials: i) rest, ii) task1 and iii) task2 (Figure 1). Trials alternated in pseudo-random fashion, so that the ratio of 1:3 was kept between switch (i.e., rest-to-task, task-to-rest, task-switch [task1-to-task2, task2-to-task1]) and repeat trials (task-repeat (task1-to-task1, task2-to-task2), rest-repeat [rest-to-rest]). Each trial started with the presentation of a fixation cross (+) for 500 ms in the middle of the screen followed by one of the predefined geometrical shape cues (a circle, a square or a triangle) counterbalanced across participants. The cue was presented for 500 ms and indicated trial type. During rest trials no stimuli followed the cue indicating rest and subjects were instructed to relax and rest with their eyes open until the next cue appeared. The duration of rest trials ranged from 6000 ms to 19200 ms. On task trials, number stimuli (ranging from 1 to 9, excluding 5) followed the cues and were presented in the centre of the screen for 500 ms. Depending upon the preceding cue, participants had to perform either a parity (task1) or a magnitude (task2) judgment task. In the parity judgment task participants had to decide whether the number presented was odd or even and in the magnitude judgment task, they had to decide whether the number presented was higher or lower than five. Parity and magnitude judgment tasks are two of the most commonly used tasks in task-switching experiments since they involve relatively abstract

goal shifts, limited amount of attentional shifting and the same numeric stimulus modality (Kiesel et al., 2010). Subjects were instructed to respond as fast as possible by pressing the correct response button without sacrificing accuracy. The cue-target interval (CTI) was pseudo logarithmically jittered to separate anticipatory cue-related activity from target-related activity (De Baene & Brass, 2011). The jittering interval ranged from 200 ms to 6800 ms; 50% of the trials had a CTI ranging from 200 ms to 2000 ms. On 30% of the trials the CTI ranged from 2600 ms to 4400 ms. The remaining trials had the CTI in a range from 5000 ms to 6800 ms. The response-fixation cross interval was jittered in the same fashion as the CTI.

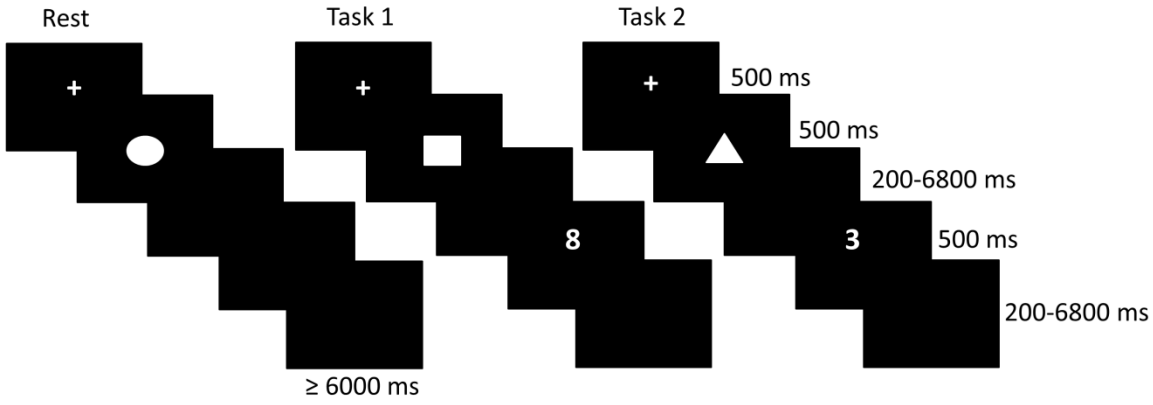

Figure 1. Outline of the cued switching task. Each trial starts with a fixation cross, followed by one of the three cues. The cue indicates the type of the trial: rest, task1 (parity judgment) or task2 (magnitude judgment). On task trials, after a jittered cue-target interval, a target appears on the screen and subjects have to respond by pressing a correct response button. Response-fixation cross interval is jittered in the same manner as cue-target interval. The minimum duration of rest trial is 6000 ms, no stimuli are presented, subjects are asked to relax and rest until the next trial indicating cue is presented.

Before the start of the experiment, subjects underwent a training session which was comprised of four blocks of trials. The first three included sequences of single-cue conditions. During the fourth block the cues were randomly intermixed and subjects had to alternate between performing the two tasks and rest trials. The task performed inside the scanner was comprised of a total of 300 trials, distributed over three runs. Every run started with an instruction screen informing the participants about cue-trial associations.

fMRI data acquisition and analysis

Subjects were positioned supine head first inside the scanner. Images were acquired with a 3T Siemens Magnetom Trio MRI system (Siemens Medical Systems, Erlangen, Germany) using a standard 32-channel head coil. For all participants structural high-resolution 1 mm^3 images were acquired using a T1-weighted 3D MPRAGE sequence. Whole brain functional images were collected with a T2*-weighted EPI sequence, sensitive to BOLD contrast (TR = 2000 ms, TE = 35 ms, acquisition matrix = 64 x 64, FoV = 224 mm, flip angle = 80^0, slice thickness = 3 mm, voxel size 3.5 x 3.5 x 3.5 mm^3, 30 axial slices). The first four EPI images of each run were discarded to reduce T1 relaxation artefacts.

Images were preprocessed and analysed using the Statistical Parametric Mapping software (SPM8; http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Functional images were slice-time corrected and realigned to the first EPI. Next, functional-to-anatomic coregistration was performed. Images were normalized to the Montreal Neurological Institute (MNI) template and smoothed with an isotropic full-width half-maximum (FWHM) Gaussian kernel of 8 mm. Head motion parameters were estimated separately for every run. A high-pass temporal filter with a 128 s cut-off was applied.

Single-subject event-related BOLD response amplitudes were estimated using the general linear model (GLM) implemented in SPM8. Event onset vectors were created based on the experimental conditions. To study cue and switch type-related anticipatory BOLD response, onset-time regressors of interest were computed based on all cue and switch types.

The current design allowed us to isolate cue-related BOLD responses from all other events of the paradigm (targets, responses), which together with error trials, were modelled as regressors of no interest. Onset vectors were convolved with the canonical haemodynamic response function (HRF) (Friston, Glaser, Mechelli, Truner & Price, 2003) and were used to compute the GLM design matrix. In addition, six head motion parameters (3 translational and 3 rotational) were included in the model to account for head movement variance.

Whole-brain analysis

The whole-brain analysis served two main goals. First, to answer the question whether rest cues in this task elicited the same brain DMN as has been shown in studies examining steady state rest. Second, to define the regions of interest (ROI) in an independent manner, thus to avoid "double dipping" (Kriegeskorte, Simmons, Bellgowan, & Baker, 2009).

To establish whether rest cues elicit activation in the DMN, brain activity in response to rest cues was directly compared to activity in response to task cues (rest cue vs. task cue). In order to be sure that activity in the contrast map was related to the DMN, we masked this contrast with a DMN template (ref_default_mode) provided in the GIFT toolbox (http://mialab.mrn.org/software/gift/). To identify the common switch-related

activity, single-subject whole brain activation contrasts were computed independent of any particular switch or repeat condition, i.e. collapsing across all switch conditions irrespective of the nature of the switch (state-to-state switches together with task-to-task switches), and contrasted with all repeat conditions (rest repeat and task repeat trials collapsed). To ensure that the resulting activation map corresponded to the SN, specifically rAI, it was inclusively masked with an SN mask comprised of bilateral insula and ACC computed using WFU Pickatlas automated anatomical labelling atlas (Kullmann et al., 2013; Seeley et al., 2007; Tzourio-Mazoyer et al., 2002).

All whole-brain single-subject contrasts were subjected to a second-level random effects analysis. Group whole-brain activation maps were generated using a one sample *t* test. Activations were reported as significant if they survived a family-wise error (FWE) correction at a cluster level ($p < .05$), based on an auxiliary voxel-wise height threshold ($p < .001$ uncorrected).

ROI analyses

To investigate the specific activation patterns associated with the anticipation of switches from rest-to-task, task-to-rest and task-to-task, ROI analyses were performed. To this end, one set of ROIs was derived from the group activation map directly contrasting rest cues with task cues, inclusively masked with the DMN "ref_default_mode" template (GIFT toolbox, http://mialab.mrn.org/software/gift/) to ensure the overlap of the activations. A second set of ROIs i.e. rAI, was derived from the group activation map comparing the collapsed switch conditions with collapsed repeat conditions. Thus, the definition of both sets of ROIs was independent of any specific comparison conducted in the ROI analysis (Kriegeskorte et al., 2009) and Bonferroni correction for multiple comparisons was applied. The parameter estimates (beta values) for every switch and

repeat condition in each of the ROIs was extracted from a 10-mm sphere centered at the respective local activation maxima.

Results

Participants performed with a very high degree of accuracy (correct responses > 98% (*SD* = 1.28). A GLM repeated measures analysis of variance (ANOVA) revealed a main effect of switch type ($F(2, 34) = 21.78$, $p < .001$, $\eta^2_p = .56$). A task switching (task-to-task) cost was observed with slower response times (RT) on task switch than non-switch trials. The rest-to-task switch cost was smaller but still statistically significant (task-to-task switch: 873 ms, $p < .001$; rest-to-task switch: 809 ms, $p = .007$; task repeat: 738 ms).

Do anticipatory rest cues rapidly activate the DMN and is it attenuated in response to cues signalling switches to a task?

Figure 2 (A) illustrates the brain regions differentially activated by rest cues compared to task cues (for the reverse contrast see the Appendix of the current chapter Table 1, Figure 1). Significant regions included superior medial frontal gyrus (SmFG) and precuneus (the regions that correspond to the frontal and posterior parts of the DMN) together with cuneus and lingual gyrus, regions that have been found co-activated with the DMN under eyes closed conditions, following spontaneous blinks and general change in luminance (Marx et al., 2004; Nakano et al., 2012). Figure 2 (B) displays results of rest cue vs. task cue contrast for the ROIs, i.e., SmFG and precuneus (Bonferroni correction for multiple comparisons $p < .025$). A repeated measures ANOVA of the ROI-based parameter estimates (beta values) revealed a main effect of switch type in both DMN regions (SmFG: $F(4, 68) = 9.88$, $p < .001$, $\eta^2_p = .36$; precuneus: $F(2.24, 38.09) = 13.22$, $p < .001$, $\eta^2_p = .43$). Specific pairwise comparison (rest-to-rest (rest-repeat) vs. rest-to-task

switch) demonstrated significant attenuation in the SmFG (i.e. frontal DMN region) during rest-to-task switch anticipation (Figure 2 (B); $p = .024$). No difference between these conditions was observed in precuneus ($p = .620$).

Do cues signalling an upcoming switch from task-to-rest elicit a preparatory increase in the DMN in contrast to the attenuation that typically follows rest-to-task switches?

Figure 2 (C) depicts differences in DMN activation levels elicited by task-to-rest switch and task repeat cues. As predicted, there was an anticipatory increase in activation in both SmFG ($p < .001$) and precuneus ($p = .001$) associated with task-to-rest switch cues (Bonferroni correction for multiple comparisons $p < .025$).

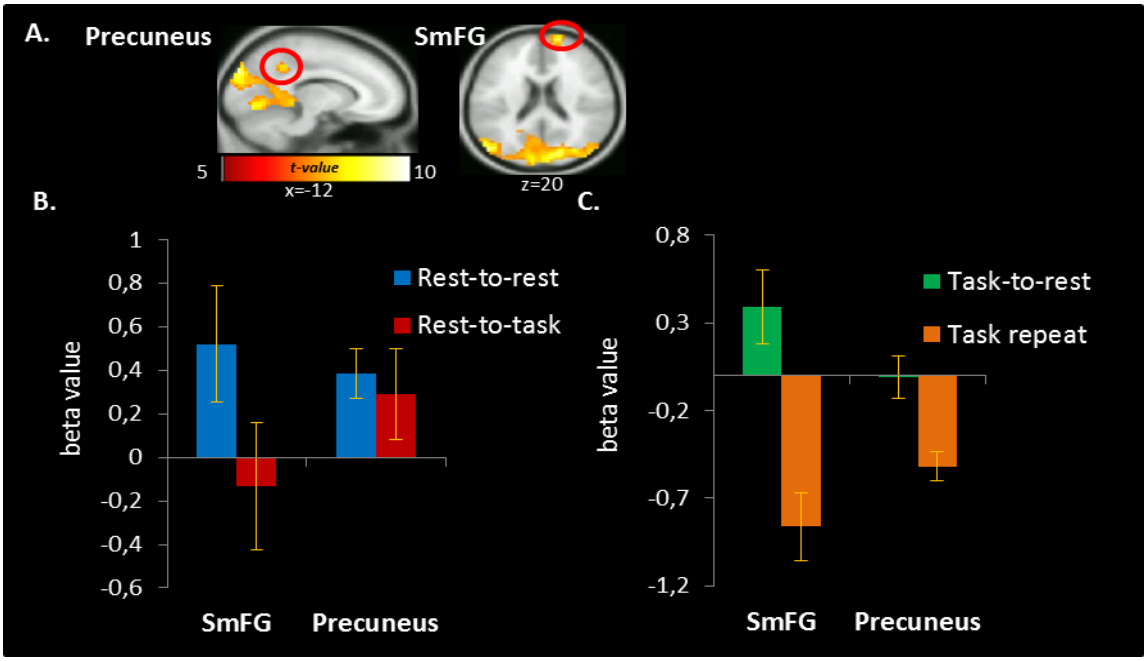

Figure 2. (A) Brain activation map averaged over 18 subjects depicting DMN areas exhibiting activation increases upon rest cues (rest cue vs. task cue), inclusively masked by "ref_default_mode" template (cluster level FWE-corrected $p < .05$). (B) Region of interest analysis on the frontal and posterior DMN regions showing more activation in response to rest cues compared to task cues during rest-to-rest (rest repeat) trials and to cues signalling the switch from rest-to-task anticipation. Average beta values (with *SE*) extracted from 10-mm spheres centered at the peak voxel coordinate for each area. Blue bars represent the activation in superior middle frontal gyrus and precuneus during rest-to-rest trials. Red bars depict the attenuated activation in those areas during rest-to-task switch trials. (C) Region of interest analysis on the frontal and posterior DMN regions showing more activation in response to rest cues compared to task cues during task-to-rest switch and task repeat trial anticipation. Average beta values (with *SE*) extracted from 10-mm spheres centered at the peak voxel coordinate for each area. Green bars represent increased activation in superior middle frontal gyrus and precuneus during task-to-rest switch trials, orange bars depict the attenuated activation in those areas during task repeat trials.

Table 1. The overview of peak activation coordinates for rest cue vs. task cue contrast inclusively masked by "ref_default_mode" template (p < .05, cluster-level FWE-corrected).

Region	Hemisphere	BA	MNI coordinates			Cluster extent	Z-value	FWE-corrected cluster p-value
			x	y	z			
Lingual gyrus	L	18	-18	-74	-12	1567	5.79	.000
Cuneus	L	19	-15	-91	34		5.75	
Middle temporal gyrus	L	-	-50	-80	16		5.68	
Superior medial frontal gyrus	R	10	13	63	20	120	5.34	.000
Superior frontal gyrus	R	9	16	42	44		4.64	
	R	9	20	60	34		4.53	
Precuneus	L	7	-12	-49	41	27	4.57	.005

Is rAI implicated equally in task-to-task and state-to-state switching?

Figure 3 (B) shows the patterns of rAI activation to cues signalling different types of switches based on a ROI analysis (F(1.98, 33.6) = 24, p < .001, η^2_p = .58). Specific pairwise comparisons between switch types revealed that rAI exhibited the strongest activation to rest-to-task switch cues which significantly differed from all other switch types (all p's < .001). rAI activation during task-to-task switches was less pronounced though significantly higher than during task-to-rest switches (p = .030), task repeats (p = .001) and rest-to-rest trials (p = .006). In contrast, task-to-rest switch cues did not yield significant increases in rAI activation as compared to task repeat (p = .706) and rest-to-rest trials (p = .820) (see Figure 3 [B]).

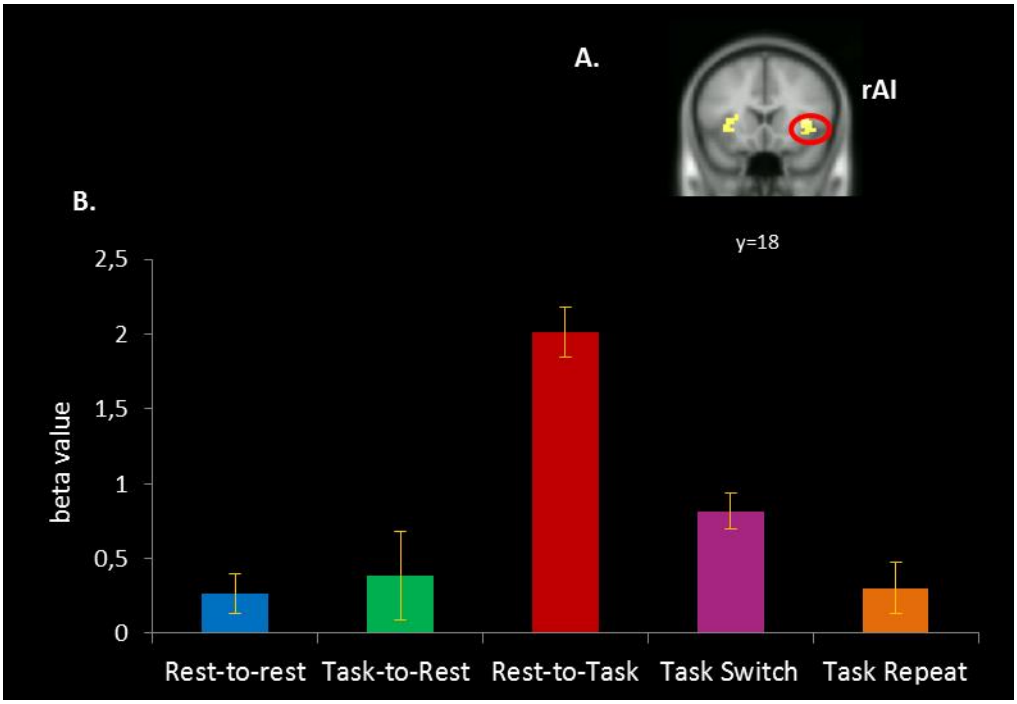

Figure 3. (A) Brain activation map averaged over 18 subjects depicting areas exhibiting higher activation for all switch trials compared to all repeat trials inclusively masked by SN template (cluster level FWE-corrected $p < .05$). (B) Region of interest analysis on rAI during state-to-state and task-to-task switches. Average beta values (with *SE*) extracted from 10-mm spheres centered at the peak voxel coordinate.

Table 2. The overview of peak activation coordinates comparing all switch trials with all repeat trials, inclusively masked by SN template (switch trial vs. repeat trial; $p < .05$, cluster-level FWE-corrected).

Region	Hemisphere	BA	MNI coordinates			Cluster extent	*Z*-value	FWE-corrected cluster *p*-value
			x	y	z			
Anterior cingulate	R	32	6	35	20	46	5.51	.000
	L	-	-4	24	30		5.29	
	L	-	-12	32	24		5.24	
Anterior insula	L	-	-29	24	10	32	5.51	.000
	L	47	-36	18	-4		5.03	
	R	-	34	18	6	40	5.36	.000
	R	-	30	24	-4		5.26	

Discussion

The current study provides the first evidence of the rapid modulation of DMN and SN during state-to-state transitions using a cued-switching task.

Rest cue elicited rapid onset, anticipatory DMN activation and its attenuation during switches to task

Successful implementation of this novel cued-switching task was confirmed. The anticipatory rest cues induced activation in SmFG and precuneus - the regions that belong to frontal and posterior DMN. The expected DMN attenuation to task predicting cues was also observed. Current results provided the first evidence to support the idea that DMN activity, previously reported only during prolonged rest periods, can be elicited by short duration cues signalling upcoming circumscribed rest periods, suggesting that the neural rest-to-task modulations can occur in a relatively abrupt and rapid way early in the

transitional process. It appears that the DMN reconfigures quickly in response to external stimuli signalling forthcoming mental states. The fact that the attenuation of neural activity only occurred in frontal DMN was surprising, given previous findings of posterior and frontal DMN to be among regions showing the highest activity during rest and robust attenuation following goal directed cognitive engagement (Greicius, Srivastava, Reiss, & Menon, 2004; Shulman et al., 1997). However, previous studies suggest the level of the frontal DMN suppression to be specifically related to enhanced performance and increasing cognitive demands (Gusnard, Akbudak, Shulman, & Raichle, 2001; Lawrence, Ross, Hoffmann, Garavan, & Stein, 2003; Shulman et al., 1997), while precuneus has also been shown to be involved in interpretation of and orientation in environment (Gusnard & Raichle, 2001; Hahn, Ross, & Stein, 2007). Thus, the absence of attenuation in the posterior part of the DMN in the current study may represent cue-related attentional reorientation supported by precuneus.

Task-to-rest switch cue elicited DMN up-regulation

Our data also provided the first evidence for DMN up-regulation during switches from task-to-rest - the obverse of attenuation typically seen during rest-to-task switches. This finding fits well with the growing literature on states other than pure rest that can activate the DMN. Specifically, previous studies reported substantial increases in DMN activity during transitions from stimulus-driven to intrinsically oriented cognitive tasks, such as, autobiographic memory (Addis, Wong, & Schacter, 2007), internal mentation (Andrews-Hanna, 2012) and theory of mind (Buckner et al., 2008; Reniers et al., 2012; Spreng & Grady, 2010), as well as representations of self and others (Mars et al., 2012; Tononi & Koch, 2008; Uddin, Iacoboni, Lange, & Keenan, 2007). Moreover, Preminger and colleagues (2011) showed that activity in the DMN can be prompted and differentially

modulated even in the absence of external stimuli, thus solely as a response to stimulus-free thoughts. Importantly, our results demonstrated that cue-related rest trial anticipation induced DMN up-regulation mimicking the sustained DMN response during isolated periods of self-referential engagement.

Anticipatory rAI response was dependent on switch type

rAI activation was triggered to different degrees by different types of switch cues. More specifically, rAI response to cues signalling an upcoming switch from rest-to-task was larger than for all other switch types. Activation levels were next largest for task-to-task switches, while task-to-rest switches did not yield a significant activation of rAI. This finding is in line with the model of Menon and Uddin (2010) and the findings of Sridharan and colleagues (2008) where rAI was suggested to play a central role controlling those large scale shifts in brain network dynamics, involved principally in DMN disengagement and the subsequent activation of task specific brain regions. The fact that we saw greater increase in rAI activity during rest-to-task switches, compared to task-to-task switches, suggests a special role for this region in the modulation of resting brain states. Furthermore, the results indicate that rAI is preferentially involved in a certain type of state-to-state transitions where it is associated with down-regulation and not the augmentation of the DMN. This is a crucial finding because it provides a highly novel insight into DMN functional modulation by rAI. The results are also in line with the findings of Bonnelle and colleagues (2012) where rAI or SN integrity in general has been found to predict the efficacy of the DMN modulation. In addition, lately there has been an emerging number of studies implicating the more dorsal part of the rAI, in higher cognitive operations (Cauda et al., 2012; Chang et al., 2013; Uddin et al., 2013). This is consistent with the extension of activation into this region seen in the current study. Given

that our data provide no evidence for rIA as a generic state switching hub, it is on the face of it, still difficult to distinguish between the notion of rIA as a specialised (rest-to-task) switching hub and the classical notion that its primary role is signalling the salience of upcoming events - provided that cues of an upcoming task when one is in a resting state are more salient than when one is already performing a task (Crottaz-Herbette & Menon, 2006; Dosenbach et al., 2006; Dove et al., 2000; Medford & Critchley, 2010; Seeley et al., 2007). Moreover, rAI has been implicated in regulation of autonomic bodily functions, such as blood pressure, heart and respiratory rate, etc. Thus, during the anticipation of rest-to-task switches, rAI may operate to prepare the body for the greater upcoming challenges than those when switching between tasks or from task-to-rest (Craig, 2009; Ullsperger, Harsay, Wessel, & Ridderinkhof, 2010).

The disturbance of this dynamic balancing between DMN and task-specific brain networks, controlled by rAI, has been implicated in various psychopathological conditions, such as depression, schizophrenia, autism, anxiety and attention deficit hyperactivity disorder (Chen et al., 2013; Menon, 2011). Thus, being validated in a sample of healthy participants, the current cued-switching paradigm is a promising tool to be applied in studies on different psychopathological conditions. Importantly, targeting the anticipatory DMN and SN modulation during state-to-state switching, the current task can aid in revealing and understanding disorder-specific DMN and SN alterations.

Limitations

The inclusion of state-to-state switches in the experimental design was challenging per se, in that it incorporates both task trials and rest periods. One potential constraint in this regard is the limited temporal differentiation between cued anticipatory processes preceding rest trials and the initiation of the rest phase itself. While task anticipation and

initiation were separated by the appearance of a target, rest was not. Thus, rest anticipation and initiation could not be clearly differentiated. However, even taking this into account our finding of cue-related DMN attenuation during rest-to-task switches provides initial support for rapid anticipatory DMN modulation during state-to-state switching.

Conclusions

The present data support the rapid modulation of the DMN regions following short duration anticipatory cues signalling rest-to-task and task-to-rest switches. The findings extend the understanding of rAI during the anticipation of different types of cognitive switches. Only transitions to active cognitive engagement yielded significant levels of rAI activity, with the largest rAI response during switches from rest-to-task.

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Appendix

Table 1. The overview of peak activation coordinates for rest task cue vs. rest cue contrast ($p < .05$, cluster-level FWE-corrected).

Region	Hemisphere	BA	MNI coordinates x	y	z	Cluster extent	Z-value	FWE-corrected cluster *p*-value
Supplementary motor area	L	-	-12	4	55	573	5.60	.000
Precentral gyrus	L	-	-50	7	38		5.00	
Superior frontal gyrus	R	-	29	-10	62		4.59	
Middle occipital gyrus	R	-	27	-94	-4	72	5.25	.015
Inferior parietal lobule	L	-	-36	-42	44	419	5.01	.000
	L	-	-36	-56	52		4.99	
Inferior occipital gyrus	L	-	-29	-98	-8	73	4.89	.014
Thalamus	L	-	-12	-21	13	161	4.20	.000
	L	-	-1	-24	2		4.18	
Midbrain	R	-	6	-24	-12		4.10	
Precentral gyrus	R	6	38	-21	62	144	4.09	.000
Inferior parietal lobule	R	-	38	-46	44		3.83	
	R	-	34	-56	48		3.73	
Lateral globus pallidus	R	-	13	4	-1	59	3.97	.030
Thalamus	R	-	16	-7	-1		3.81	

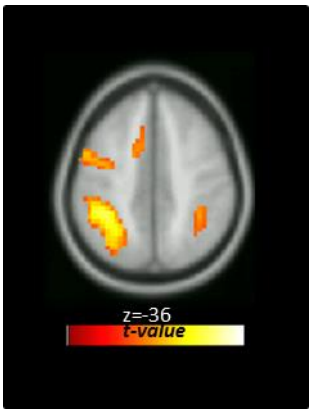

Figure 1. Brain activation map averaged over 18 subjects depicting areas exhibiting activation increases upon task cues (task cue vs. rest cue; cluster level FWE-corrected $p < .05$).

CHAPTER 3

DEFAULT MODE NETWORK ABNORMALITIES DURING STATE SWITCHING IN ADHD[1]

Abstract

Objective: Individuals with ADHD display abnormal activity within brain networks regulating attentional engagement during goal-directed tasks: hyperactivation of default mode network (DMN) and hypoactivation of regions regulating task-related attention (i.e., task-relevant regions). One hypothesis is that this is due to attenuated downregulation of DMN and/or upregulation of task-relevant regions during rest-to-task switching. This may be associated with dysfunction of right anterior insula (rAI) involved in DMN modulation during state-switching. **Method:** These hypotheses were tested in the current study in which 19 adults with ADHD and 21 typically developing controls undertook a novel state-to-state switching paradigm in the scanner. Advance cues signalled upcoming switches between rest and task periods and switch-related anticipatory modulation of DMN, and task-relevant regions was measured. To examine whether rest-to-task switching impairments may be a specific example of a more general state regulation deficit, activity upon rest-to-task and task-to-rest cues was analysed.

[1]Based on Justina Sidlauskaite, Edmund Sonuga-Barke, Herbert Roeyers, Jan R. Wiersema (2014). *Default mode network abnormalities during state switching in attention-deficit/hyperactivity disorder*. Manuscript submitted for publication.

Results: There was a trend towards a significant reduction in task-relevant areas activation upon rest-to-task cues, however, downregulation of DMN was intact in individuals with ADHD. Instead, upregulation of DMN upon task-to-rest cues was attenuated in ADHD, while downregulation of task-relevant areas was intact. rAI activation was reduced to all cues and not specifically implicated in switching. **Conclusions:** Difficulties in state-to-state switching in ADHD are not confined to rest-to-task switching but also comprise task-to-rest switching, and seem to be linked to "switching-on" brain areas required for future states, rather than "switching-off" brain regions related to the current state.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) has a complex pathophysiology related to dysfunctions in multiple brain regions (Coghill, Seth, & Matthews, 2013; Cortese et al., 2012; Sonuga-Barke, Bitsakou, & Thompson, 2010). While these have a degree of task specificity they also typically implicate hypoactivation in task-related but non-specific regions known to mediate effective engagement of attention during goal directed tasks (Aron & Poldrack, 2005; Bush et al., 1999; Ernst, 2003). In recent years, the new focus on the resting brain and the discovery of the default mode network (DMN) has provided a different perspective on deficient attentional engagement during task performance in ADHD (Konrad & Eickhoff, 2010; Paloyelis, Mehta, Kuntsi, & Asherson, 2007; Raichle et al., 2001). The DMN – encompassing anterior and posterior midline brain structures (medial prefrontal cortex (mPFC) and posterior cingulate cortex (PCC)/ precuneus) – is active during rest or when individuals are engaged in internally-oriented self-referential cognitive processes (Buckner, Andrews-Hanna, & Schacter, 2008a; Gerlach, Spreng, Gilmore, & Schacter, 2011; Spreng & Grady, 2010). DMN attenuates following engagement with tasks requiring externally orientated, goal directed attention. The degree of attenuation (i) varies as a function of cognitive load (Fransson, 2006; Greicius, Krasnow, Reiss, & Menon, 2003; Greicius & Menon, 2004; McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003; Pyka et al., 2009; Singh & Fawcett, 2008) and (ii) is predictive of performance deficits linked to residual task-related DMN activity (Li, Yan, Bergquist, & Sinha, 2007; Sonuga-Barke & Castellanos, 2007; Weissman, Roberts, Visscher, & Woldorff, 2006). Consistent with the default mode interference hypothesis (Sonuga-Barke & Castellanos, 2007) there is evidence of DMN hyperactivation during task performance in individuals with ADHD (Fassbender et al., 2009; Helps et al., 2010; Liddle et al., 2011; Peterson et al., 2009). This is postulated to

cause lapses of attention and increased reaction time variability (Karalunas, Geurts, Konrad, Bender, & Nigg, 2014; Weissman et al., 2006).

The exact mechanism limiting either engagement of task-relevant regions or disengagement of DMN in ADHD is currently unknown. One hypothesis is that it is caused by deficient switching from resting to active goal directed task states. More specifically, anticipatory preparation for, and implementation of, rest-to-task state switching may be impaired, reflecting problems either "switching off" the DMN or "switching on" task-relevant areas, or both. In accord with this, event-related potential (ERP) research showed that response execution and inhibition deficits in ADHD are preceded by impaired task or response preparation, as evidenced by a smaller contingent negative variation (CNV) (Albrecht et al., 2014; Banaschewski et al., 2004, 2008) thought to reflect decreased anticipatory engagement of task-relevant regions. However, to date, no study has directly investigated the contribution of DMN and task-relevant brain networks during rest-to-task switching in ADHD.

Consistent with its central role in recent models of between brain network switching, our investigation will also focus on the role of the salience network (SN) specifically its core node - right anterior insula (rAI). rAI a multifunctional region, which gathers and integrates motivationally salient information and fosters effective neural modulation (Dove, Pollmann, Schubert, Wiggins, & Yves von Cramon, 2000; Downar, Crawley, Mikulis, & Davis, 2000, 2001; Downar, Crawley, Mikulis, & Davis, 2013; Kurth, Zilles, Fox, Laird, & Eickhoff, 2010). It has been postulated to play a critical role in state-to-state switching, controlling DMN disengagement and engagement of task-relevant brain networks (Menon & Uddin, 2010a; Seeley et al., 2007; Sidlauskaite et al., 2014; Sridharan, Levitin, & Menon, 2008). Failures of rest-to-task transitioning in ADHD might therefore be expected to implicate rAI. Indeed, although its role in state-to-state

switching in ADHD has not been investigated directly, altered insula structure and function has been demonstrated in the condition (Lemiere et al., 2012; Lopez-Larson, King, Terry, McGlade, & Yurgelun-Todd, 2012; Spinelli et al., 2011; Sripada et al., 2014; Tian et al., 2006; Valera et al., 2010).

To study rest-to-task switching in ADHD, we used a recently developed task modelled on the classical cued task-switching paradigm (Sidlauskaite et al., 2014). This task includes advance cues signalling upcoming switches between rest and task periods. The use of these cues allows the investigation of anticipatory switch-related neural processes (Brass & Cramon, 2002; Meiran, Hsieh, & Dimov, 2010). In healthy adults, Sidlauskaite and colleagues (2014) using this paradigm found that cues signalling upcoming rest-to-task switches downregulated DMN and upregulated task-relevant areas (e.g., supplementary motor area (SMA), inferior parietal lobule (IPL), precentral gyrus [PG]). The obverse occurred upon cues signalling task-to-rest switches (upregulation of DMN and downregulation of task-relevant areas). The core node of the SN – rAI appeared to be implicated when switching to tasks requiring active cognitive engagement.

For the current study, we predicted impaired anticipatory downregulation of DMN and/ or upregulation of task-relevant regions in ADHD accompanied by decreased activation in rAI during rest-to-task switching. To examine whether rest-to-task switching impairments may be a specific example of a more general state-to-state switching deficit (e.g., state regulation deficit) (Metin, Roeyers, Wiersema, van der Meere, & Sonuga-Barke, 2012; Sonuga-Barke, Wiersema, van der Meere, & Roeyers, 2010; Wiersema, van der Meere, Antrop, & Roeyers, 2006), we also compared groups for brain activation to cues signalling upcoming task-to-rest switches.

Method

Participants

The study was approved by Ghent University Hospital ethics committee. Participants gave written informed consent and received a monetary reward for participation. Nineteen individuals with a clinical diagnosis of ADHD (13 combined type; 6 inattentive type) and 21 typically developing controls (TD) participated in the study (the control sample in the current study highly overlaps (4 additional TD participants in the current study) with the subject sample from Sidlauskaite and colleagues (2014)). Both individuals with and without ADHD diagnosis were recruited via advertising in local magazines, social websites, word of mouth or from the pool of individuals who have participated in earlier experiments and have agreed to be contacted for future research. Individuals with ADHD met the life span criteria for the disorder and had both an official clinical diagnosis obtained in a clinical setting and a research diagnosis of ADHD established and confirmed using the DSM-IV-based structured clinical Diagnostic Interview for Adult ADHD (DIVA 2.0; Kooij & Francken, 2010). Moreover, all participants with ADHD scored above cut-offs on self-report measures of ADHD symptoms retrospectively in childhood (Wender Utah Rating Scale (WURS; M = 62.84, SD = 14.27); childhood ADHD criteria is met when the score is higher than 46; Ward et al., 1993) and in adulthood (Self-report questionnaire on problems of inattention and hyperactivity in adulthood and childhood; following the diagnostic guidelines adults with ADHD were required to exhibit at least 4 symptoms in the inattentinve and/or hyperactive/impulsive domain to meet the adulthood ADHD criteria; Kooij & Buitelaar, 1997). None of the TD participants scored above the cut-offs on WURS (M = 26.95, SD = 12.70) and/or Self-report questionnaire on problems of inattention and hyperactivity in

adulthood and childhood and nor met the criteria for childhood or adulthood ADHD. All participants had a full range IQ in the normal or above range (> 80) derived from a seven subtest version of the Wechsler Adult Intelligent Scale (Ryan & Ward, 1999). Groups did not differ on IQ (TD: *M* = 117.95, *SD* = 11.20; ADHD: *M* = 112.05, *SD* = 13.60; *p* = .146), sex ratio (TD: 9 female; ADHD: 10 female) or age (TD: *M* = 26.80 years, *SD* = 8.62 ADHD: *M* = 29.78 years, *SD* = 9.61; *p* = .308). Nine ADHD group participants were taking psychostimulant medication (8 – methylphenidate and 1 – dextroamphetamine) from which they had to refrain for at least 24 h before the experiment. Four individuals with ADHD were also taking antidepressant medication (3 – selective serotonin reuptake inhibitors and 1 – buproprion chloride) which they could continue using. The overall exclusion criteria were neurological or psychiatric disease and history of brain damage. All participants had normal or corrected to normal vision, four were left-handed (1 ADHD).

Task Design

Presentation software package (Neurobehavioural Systems, www.neurobs.com) was used to program the task. It was presented in the scanner and had three trial types consisting of two different task trials, either a magnitude, where participants had to respond to numerical stimuli by deciding whether they were smaller or bigger than 5, or parity judgment, where participants had to respond to numerical stimuli by deciding whether they were odd or even, and rest trials. At the start of each trial a fixation cross appeared on the screen (500 ms) which was followed by a cue (500 ms) signalling the nature of the upcoming trial, (i.e. parity judgment task (task 1), magnitude judgment task (task 2) or rest). All stimuli were presented on a black screen and viewed via a mirror attached to the head-coil. Participants were instructed to respond as fast and accurate as possible. Depending on task rules, participants had to respond by pressing a button with

their right or left index finger. During rest trials (minimum duration 6000 ms), there were no stimuli presented and participants were instructed to relax and rest. Trial types alternated in a pseudo-random fashion, so that the switch (task-to-rest, rest-to-task and task-to-task) and repeat (task repeat, rest repeat) trial ratios were kept at 1:3. The duration of inter-event intervals was pseudo-logarithmically jittered (Figure 1; also see Sidlauskaite and colleagues (2014) for further details). All participants undertook four blocks of training before the experiment. The first three blocks were single-cue condition trials for learning the cue-trial associations. The last block mimicked the real task where the cues were intermixed and participants had to alternate between the two tasks and rest trials. There was a total of 300 trials in the experiment. These were divided into three runs performed inside the scanner. At the beginning of each run instructions were displayed to remind the cue-trial associations.

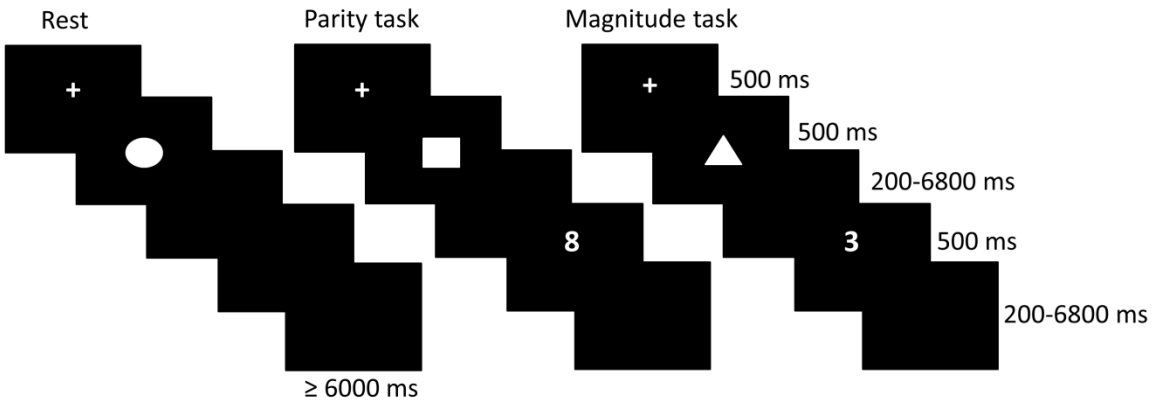

Figure 1. An outline of the cued state-to-state switching task. Each trial starts with a presentation of a fixation cross, followed by one of the three cues. The cue indicates the type of the trial. On task trials, after a jittered cue-target interval, a target appears on the screen and subjects have to respond by pressing a correct response button. The minimum duration of a rest trial is 6000ms; no stimuli are presented and subjects are asked to relax and rest until the next fixation cross and trial indicating cue are presented.

Image Acquisition and Data Analysis

Images were acquired using a 3T Siemens Magnetom Trio MRI system (Siemens Medical Systems, Erlange, Germany) with a standard 32-channel head-coil. High-resolution $1mm^3$ anatomical images were taken with a T1-weighted 3D MPRAGE sequence. Whole-brain functional images were acquired using T2*-weighted EPI sequence, which is sensitive to BOLD contrast (TR = 2000 ms, TE = 35 ms, acquisition matrix = 64 x 64, FoV = 224 mm, flip angle = 80^0, slice thickness = 3 mm, voxel size = 3.5 x 3.5 x 3.5 mm^3, 30 axial slices). To diminish T1 relaxation artefacts, the first four EPI images of every run were removed. Imaging data were pre-processed and further analysed with Statistical Parametric Mapping software (SPM8; http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). During data pre-processing, first,

functional images were slice-time corrected and realigned to the first EPI. Second, functional-to-anatomic coregistration was conducted. Next, images were normalized to the Montreal Neurological Institute (MNI) template and smoothed using isotropic 8 mm full-width half-maximum (FWHM) Gaussian kernel. Six movement parameters were estimated for each run and a high-pass temporal filter with a 128s cut-off was applied. Event-related single-subject BOLD response was estimated using the general linear model (GLM) in SPM8. The experimental conditions were used to compute event onset vectors. To study cue and switch type-related anticipatory BOLD response, onset-time regressors of interest were formed based on all cue and switch categories. This design enabled us to differentiate the cue-related BOLD response from all other events in the experiment (targets, responses, errors) which were modelled as regressors of no interest. Onset vectors formed the GLM matrix and were convolved with the canonical hemodynamic response function (HRF). To account for head movement, 6 motion parameters (3 translational and 3 rotational) were included into the model. Data were excluded if motion parameters exceeded 3 mm translationally and/or 3 degrees rotationally. Two subjects from the initial sample had to be excluded based on this criteria. A two-sample *t-test* analysis of the head motion parameters revealed no significant group differences in neither translational (ADHD: x = .173, *SD* = .090; y = .141, *SD* = .059; z = .429, *SD* = .300; TD: x = .183, *SD* = .100; y = .163, *SD* = .070); z = .382, *SD* = .186); *p's* respectively: .753; .296; .204), nor rotational (ADHD: roll =.0068, *SD* = .0044; pitch = .0039, *SD* = .0019; yaw = .0029, *SD* = .0012; TD: roll = .0054, *SD* = .0029; pitch = .0034, *SD* = .0019; yaw = .0026, *SD* = .0014; *p's* respectively: .237; .414; .560) motion.

Whole-brain analyses

Whole-brain analyses were used to define the regions of interest (ROIs) in an independent and unbiased manner to avoid "double dipping" (Kriegeskorte, Simmons, Bellgowan, & Baker, 2009). First, we needed to establish whether rest cues elicited DMN activity (as was previously shown by Sidlauskaite and colleagues (2014)), thus the neural activity upon rest cues was compared to the activity elicited by task cues (i.e., rest cue vs. task cue contrast). Second, to define the areas elicited by task cues (i.e., task-relevant regions), we conducted the opposite comparison, i.e., we contrasted task cues to rest cues. Third, to identify common switch-related activity, we contrasted all switch cues (irrespective of switch type, thus collapsing across state-to-state and task-to-task switches) with repeat cues (irrespective of repeat type, thus collapsing across rest and task repeat conditions). To confirm that the resulting activation maps from rest vs. task cue comparisons corresponded to the DMN, we masked it using the standard DMN mask, comprised of bilateral superior medial frontal gyrus and posterior cingulate/precuneus (Buckner, Andrews-Hanna, & Schacter, 2008; Franco, Pritchard, Calhoun, & Mayer, 2009). To ensure that the switch-related activation from switch vs. repeat cues corresponded to the SN, specifically rAI, we masked the activation maps using the standard SN mask comprised of bilateral insula and anterior cingulate cortex (ACC) (Kullmann et al., 2013; Seeley et al., 2007). Both DMN and SN masks were generated using the WFU Pickatlas automated anatomical labelling atlas (Tzourio-Mazoyer et al., 2002). All whole-brain single-subject contrasts were subjected to a second-level random effects analysis. For both groups whole-brain activation maps were computed using a one sample *t* test. Activations were deemed significant if they survived a family-wise error (FWE) correction at a cluster level ($p < .05$), based on an auxiliary voxel-wise height threshold ($p < .001$ uncorrected).

ROI analyses

To ensure an unbiased way of sampling the activity of the DMN, rIA and task-relevant areas in the ADHD group, the corresponding ROIs were defined based on the activity peaks in the control group during the relevant comparison (Bonnelle et al., 2012). The DMN ROIs, derived from rest vs. task cue comparisons, included superior medial frontal gyrus (SmFG), MNI coordinates 13, 63, 20 and precuneus, MNI coordinates -12, -49, 41. Task-relevant ROIs corresponding to attention networks were identified by comparing task to rest cues (i.e., task cue vs. rest cue). These included supplementary motor area (SMA), MNI coordinates -12, 4, 55; precentral gyrus (PG), MNI coordinates -43, 4, 34; and inferior parietal lobule (IPL), MNI coordinates -32, -56, 48 (Corbetta & Shulman, 2002; Fox et al., 2005). rAI cluster, MNI coordinates 41, 14, -4, was derived from the switch collapsed vs. repeat collapsed comparison (whole-brain activation maps of control and ADHD groups for the relevant comparisons are provided in the Appendix of the current chapter (Tables 1-6; Figures 1-6). Experimental condition-related parameter estimates (beta values) were extracted from 10-mm radius spheres centred around the respective MNI coordinate for all ROIs. ROI parameter estimates were used as dependent measures in GLM repeated measures analysis of variance (rANOVA) using Statistical Package for Social Sciences (SPSS, v.19), and Bonferroni correction for multiple comparisons was applied (DMN ROI analyses – $p < .025$; task-relevant areas ROI analyses – $p < .016$). The modulation of activity within ROIs during rest-to-task switching was based on the comparison of rest-to-task and rest-to-rest cues. Task-to-rest modulation involved the comparison of task-to-rest and task-to-task (task repeat) cues.

Results

Error rate did not differ by group (controls > 97% correct, *SD* = .92; ADHD > 86%, *SD* = 13.70; *p* = .09). The ADHD group had significantly slower responses in all conditions ($F(1,38) = 9.57$, $p = .004$, $\eta^2_p = .20$ controls: task-switch *M* = 897 ms, *SD* = .20; rest-to-task 826 ms, *SD* = .19; task-repeat *M* = 762 ms, *SD* = .16; ADHD: task-switch *M* = 1096 ms, *SD* = .27; rest-to-task *M* = 1069 ms, *SD* = .25; task-repeat *M* = 942 ms, *SD* = .21. There was a main effect of switch condition ($F(2,76) = 39.29$, $p < .001$, $\eta^2_p = .50$), with slowest responses for task switch trials. The group x condition interaction was not significant ($F(2,76) = 1.91$, $p = .155$, $\eta^2_p = .04$).

Rest-to-task switches: Anterior but not posterior DMN was downregulated (SmFG: $F(1,38) = 5.99$, $p = .019$, $\eta^2_p = .13$; precuneus: $F(1,38) = .74$, $p = .393$, $\eta^2_p = .01$). No main group effect was apparent (SmFG: $F(1,38) = .11$, $p = .734$, $\eta^2_p = .003$; precuneus: $F(1, 38) = .352$, $p = .557$, $\eta^2_p = .009$). The degree of DMN downregulation did also not differ between groups (group x condition interaction; SmFG: $F(1,38) = .005$, $p = .942$, $\eta^2_p = .000$; precuneus: $F(1,38) = .032$, $p = .859$, $\eta^2_p = .001$) (Figure 2). Upregulation of all task-relevant ROIs was observed (SMA: $F(1, 38) = 130.27$, $p < .001$, $\eta^2_p = .77$; PG: $F(1,38) = 72.88$, $p < .001$, $\eta^2_p = .65$; IPL: $F(1,38) = 103.37$, $p < .001$, $\eta^2_p = .73$). A main group effect was found in SMA ($F(1,38) = 5.94$, $p = .020$, $\eta^2_p = .13$), but not in PG ($F(1,38) = 1.67$, $p = .204$, $\eta^2_p = .04$) or IPL ($F(1,38) = 1.79$, $p = .188$, $\eta^2_p = .04$). ADHD was associated with a trend towards reduced anticipatory upregulation of task-relevant areas (PG ($F(1,38) = 3.93$, $p = .055$, $\eta^2_p = .09$; rest-to-task: $t(38) = 1.77$, $p = .083$; rest-to-rest: $t(38) = -.79$, $p = .943$; and the same trend in SMA ($F(1,38) = 3.33$, $p = .076$, $\eta^2_p = .08$; rest-to-task: $t(38) = 2.37$, $p = .023$; rest-to-rest: $t(38) = .69$, $p = .493$)). No group difference was observed for

IPL upregulation (group x condition interaction; $F(1,38) = 2.83$, $p = .131$, $\eta^2_p = .05$) (Figure 3).

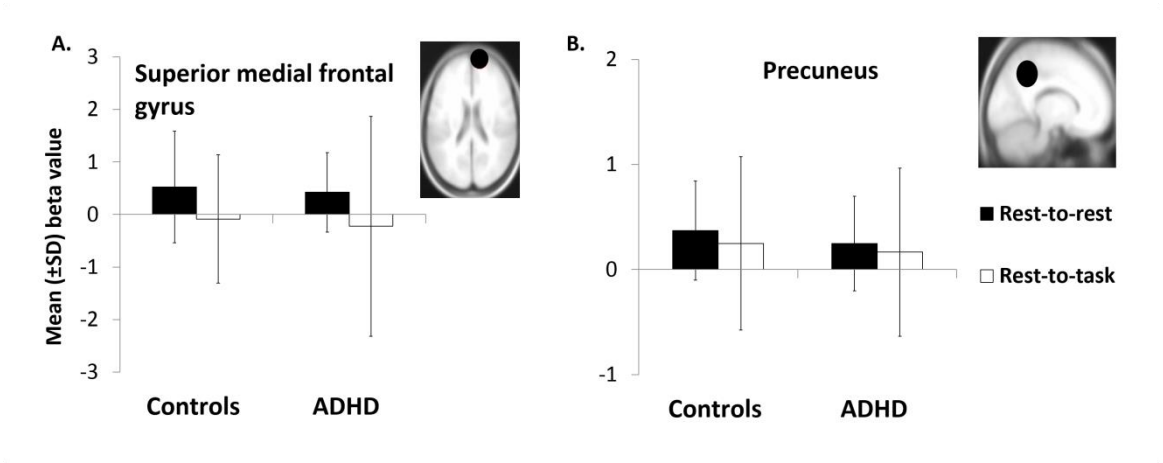

Figure 2. Default mode network modulation anticipating rest-to-rest and rest-to-task switches in adults with ADHD and controls. The average parameter estimates (beta values ±SD) for the ADHD and control group extracted from default mode network (DMN) regions. (A) Region of interest (ROI) analysis of the DMN – superior medial frontal gyrus (SmFG) during rest-to-rest and rest-to-task cues. (B) ROI analysis of the posterior DMN – precuneus during rest-to-rest and rest-to-task cues.

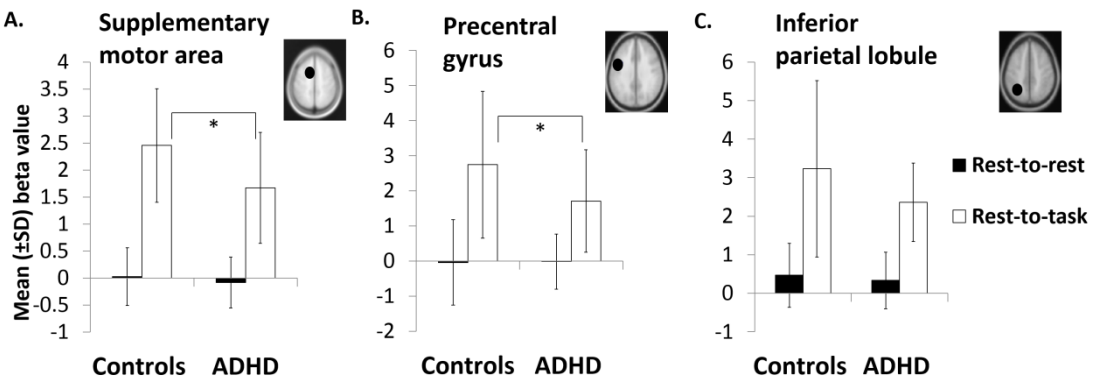

Figure 3. Modulation of task-relevant areas anticipating rest-to-rest and rest-to-task switches in adults with ADHD and controls. The average parameter estimates (beta values ±SD) for the ADHD and control group extracted form task-relevant areas. (A) Region of interest (ROI) analysis of supplementary motor area (SMA) during rest-to-rest and rest-to-task cues. (B) ROI analysis of precentral gyrus (PG) during rest-to-rest and rest-to-task cues. (C) ROI analysis of inferior parietal lobule (IPL) during rest-to-rest and rest-to-task cues. A trends towards significant group x condition interaction is marked by an asterisk (*).

Task-to-rest switches: DMN activity was upregulated to cues signalling task-to-rest switches (SmFG: $F(1,38) = 12.97$, $p = .001$, $\eta^2_p = .25$; precuneus: $F(1,38) = 9.89$, $p = .003$, $\eta^2_p = .20$). A trend toward a group effect was observed in SmFG ($F(1,38) = 4.53$, $p = .040$, $\eta^2_p = .10$) with no group effect in precuneus ($F(1,38) = .88$, $p = .345$, $\eta^2_p = .02$; Bonferroni correction $p < .025$). Upregulation of SmFG was greater in controls than participants with ADHD (group x condition interaction; $F(1,38) = 5.42$, $p = .025$, $\eta^2_p = .12$; task-to-rest: $t(38) = 2.93$, $p = .006$; task-to-task repeat: $t(38) = .025$, $p = .980$), there was no difference between groups in terms of precuneus upregulation (group x condition interaction; $F(1,38) = 2.04$, $p = .161$, $\eta^2_p = .05$) (Figure 4). In addition to DMN upregulation, a downregulation of task-relevant regions was observed (SMA: $F(1,38) =$

58.69, $p < .001$, $\eta^2_p = .60$; IPL: $F(1,38) = 24.89$, $p < .001$, $\eta^2_p = .39$; PG: $F(1,38) = 34.61$, $p < .001$, $\eta^2_p = .47$). A significant main group effect in SMA ($F(1,38) = 13.73$, $p = .001$, $\eta^2_p = .26$), and a trend to significant effect in IPL ($F(1,38) = 3.59$; $p = .066$, $\eta^2_p = .08$) was found for ADHD (less activation in those regions). There was no main group effect in PG observed ($F(1,38) = 1.88$, $p = .178$, $\eta^2_p = .04$) and the group x condition interactions were not significant (SMA: $F(1,38) = .56$, $p = .458$, $\eta^2_p = .01$; IPL: $F(1,38) = 1.35$, $p = .251$, $\eta^2_p = .03$; PG: $F(1,38) = .001$, $p = .972$, $\eta^2_p = .000$) (Figure 5).

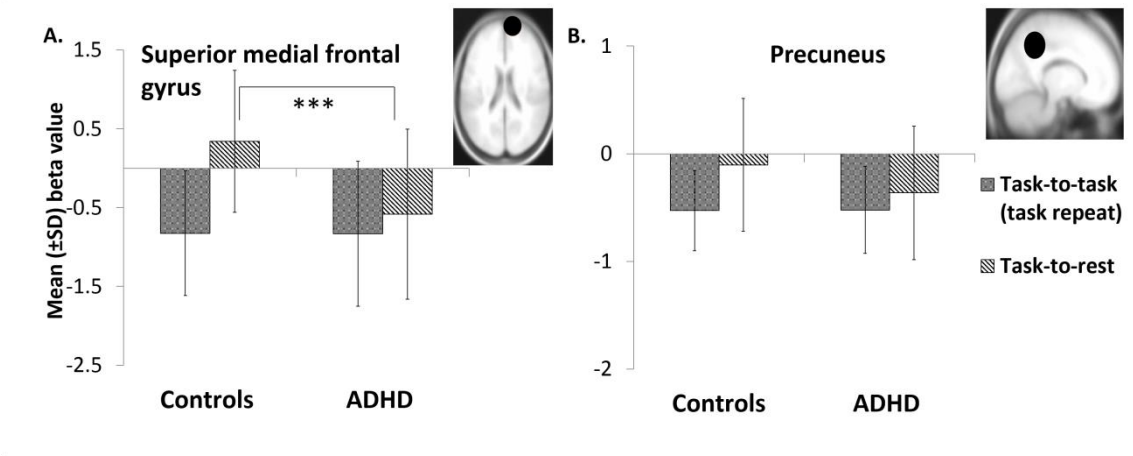

Figure 4. Default mode network modulation anticipating task-to-task (task repeat) and task-to-rest and switches in adults with ADHD and controls. The average parameter estimates (beta values ±SD) for the ADHD and control group extracted from default mode network (DMN) regions. (A) Region of interest (ROI) analysis of the DMN – superior medial frontal gyrus (SmFG) during task-to-task (task repeat) and task-to-rest cues. (B) ROI analysis of the posterior DMN – precuneus during task-to-task (task repeat) and task-to-rest cues. A significant group x condition interaction is marked by 3 asterisks (***).

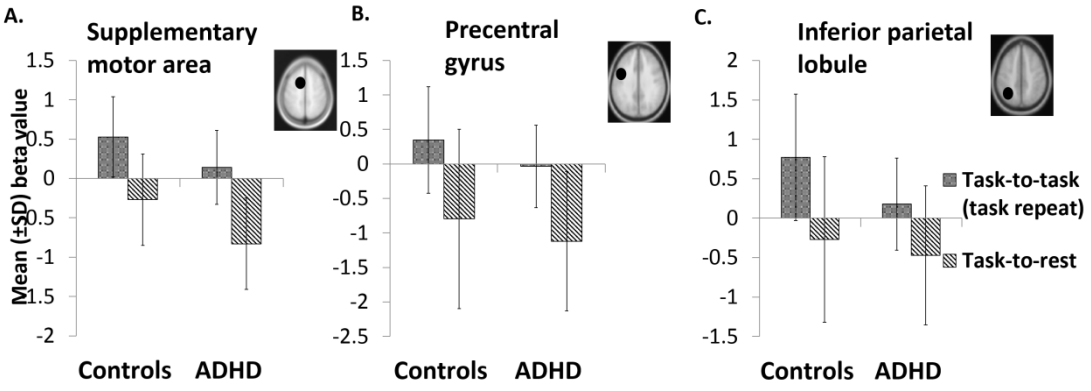

Figure 5. Modulation of task-relevant areas anticipating task-to-task (task repeat) and task-to-rest switches in adults with ADHD and controls. The average parameter estimates (beta values ±SD) for the ADHD and control group extracted form task-relevant areas. (A) Region of interest (ROI) analysis of supplementary motor area (SMA) during task-to-task (task repeat) and task-to-rest cues. (B) ROI analysis of precentral gyrus (PG) during task-to-task (task repeat) and task-to-rest cues. (C) ROI analysis of inferior parietal lobule (IPL) during task-to-task (task repeat) and task-to-rest cues.

rAI: Switch type modulated rAI activation ($F(2.98,113.26) = 31.63$, $p < .001$, $\eta^2_p = .45$), with the strongest rAI response to rest-to-task cues. Groups did not differ with respect to this effect as indicated by the absence of a significant condition x group interaction ($F(2.98, 113.26) = 2.14$, $p = .099$, $\eta^2_p = .05$). Instead, the ADHD group showed consistently less rAI activation irrespective of switch type ($F(1,38) = 6.02$, $p = .019$, $\eta^2_p = .13$) (Figure 6).

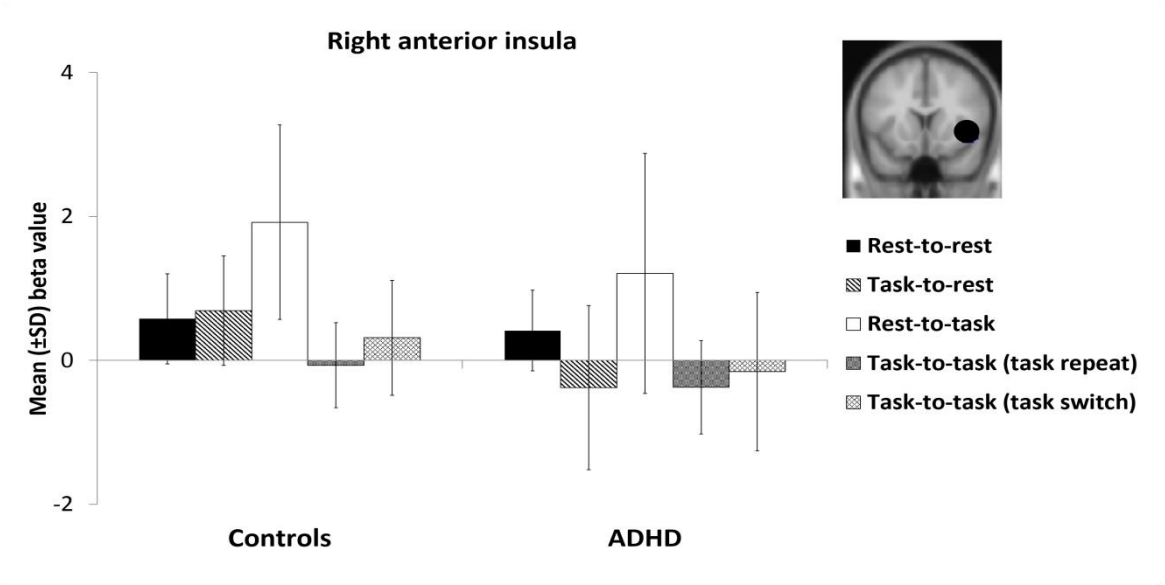

Figure 6. Modulation of rAI during different types of switches in adults with ADHD and controls. The average parameter estimates (beta values ±SD) for the ADHD and control group extracted form rAI per switch/repeat condition.

Discussion

The present study tested the hypothesis that anticipatory rest-to-task switching is impaired in ADHD. It provides the first evidence for ADHD-related difficulties in DMN upregulation when switching from task-to-rest although rest-to-task DMN attenuation appears intact. In addition, the current study suggests that adults with ADHD have difficulties upregulating task-relevant areas when switching from rest-to-task, which together with reduced task-to-rest DMN upregulation, may indicate a putative deficit in anticipatory preparation for a future state.

We did not find support for our prediction that excessive DMN activity previously observed during goal directed tasks in ADHD may be due to impaired attenuation of DMN activity during rest-to-task switching. Adults with ADHD downregulated anterior DMN to the same degree as controls. Posterior DMN – precuneus was not attenuated in

controls or participants with ADHD. The heterogeneity of the DMN with regard to state switching replicates the findings of Sidlauskaite and colleagues (2014) and is in line with the literature implicating precuneus also in visuospatial processing, orientation within and interpretation of surroundings (Gusnard & Raichle, 2001; Hahn, Ross, & Stein, 2007). If DMN downregulation during rest-to-task switching is intact in individuals with ADHD, what might then explain DMN hyperactivation during tasks indicated by previous research (Fassbender et al., 2009; Liddle et al., 2011)? One possibility is that after a successful switch, individuals with ADHD may have difficulties maintaining the required level of effort or motivation to sustain suppression of DMN activity overtime, leading to DMN re-emergence during prolonged task intervals (Sonuga-Barke & Castellanos, 2007). This increase in DMN activity over time spent on task has been previously shown in patients with traumatic brain injury (Bonnelle et al., 2011). However, this hypothesis still requires further investigation in ADHD with tasks incorporating longer trial blocks designed to test for sustained DMN suppression.

While the process of switching off the DMN appeared intact, the results provide some evidence that adults with ADHD may have a problem switching on task-relevant regions, required for attentional allocation to goal-directed tasks. The relevance of efficient anticipatory processing has been highlighted by numerous cognitive control experiments showing that efficient pre-activation of task-relevant areas is crucial for successful task execution (Gruber, Karch, Schlueter, Falkai, & Goschke, 2006; Karayanidis et al., 2010; Wylie, Javitt, & Foxe, 2006). Our findings are in accord with previous neuroimaging studies, demonstrating hypoactivation of neural activity in task-relevant areas in ADHD compared to healthy controls during cued response time tasks (e.g., thalamus, ACC, striatum, IPL, SMA) (Clerkin et al., 2013; Cubillo, Halari, Smith, Taylor, & Rubia, 2012). In addition, electrophysiological studies implicate the CNV,

originating in mid ACC and SMA in preparatory and anticipatory attention processes (Brunia & van Boxtel, 2001; Nagai et al., 2004), which has previously been found reduced in ADHD and suggests decreased readiness to respond (Kenemans et al., 2005; Linssen, Sambeth, Riedel, & Vuurman, 2013).

Interestingly, for task-to-rest switches we found an attenuated anticipatory upregulation of the anterior DMN in ADHD (i.e., problems switching the DMN back on again when moving back to rest). This novel finding of reduced DMN upregulation has several implications. The present study extends the understanding of anticipatory preparation to encompass not solely transitions to cognitive processing (King, Colla, Brass, Heuser, & von Cramon, 2007; Perchet, Revol, Fourneret, Mauguière, & Garcia-Larrea, 2001), but also to rest states and indicates that a state switching deficit in ADHD may not be confined to rest-to-task switching, but comprises task-to-rest switching as well, which adds to the existing evidence of a state regulation deficit in ADHD (Metin et al., 2012; Sergeant, 2004; Sonuga-Barke et al., 2010; van der Meere, Shalev, Borger, & Wiersema, 2009; Wiersema, van der Meere, Roeyers, Van Coster, & Baeyens, 2006).

Second, the fact that our data show diminished upregulation of DMN and trends towards diminished upregulation of task-relevant areas, together with fully intact downregulation of DMN and task-relevant areas, tentatively suggests a general difficulty "switching on" brain areas required for future states, rather than "switching off" brain regions related to the current state in ADHD. Hence, further research is required to elucidate the properties of anticipatory preparation for future states in terms of state-dependent neural modulation.

rAI was differentially modulated by the anticipation of different switch types but both groups were affected in the same way with the strongest rAI response during rest-to-task cues. This finding is in line with the model of rAI as a between large-scale brain

network switching hub, controlling transitions disengaging the DMN and employing task-relevant brain regions (Menon & Uddin, 2010; Sidlauskaite et al., 2014; Sridharan et al., 2008). rAI activation was found to be reduced in ADHD, however irrespective of switch type. rAI dysfunction is in accord with existing literature on insula function and activity alterations in ADHD, as well as evidence of structural volumetric abnormalities of this region in ADHD (Lemiere et al., 2012; Lopez-Larson, King, Terry, McGlade, & Yurgelun-Todd, 2012b; Spinelli et al., 2011; Sripada et al., 2014; Valera et al., 2010). Since rAI is functionally multifaceted and sophisticated, one cannot strictly dissociate its specialized role in switching from DMN to task states, general saliency processing, and regulation of autonomic bodily functions (Medford & Critchley, 2010; Seeley et al., 2007). Because rAI activation to cues appeared unrelated to abnormal switching patterns in ADHD, it may indicate general reduced saliency of cues in ADHD.

Limitations

The current experimental task included rest trials to investigate the state-to-state transitions. However, on these trials the cued anticipatory phase could not be completely temporally separated from the actual rest period. While task anticipation and initiation were separated by the appearance of a target, rest was not. Nevertheless, our findings provide clear evidence of impaired early cue-related upregulation of DMN in ADHD. The temporal resolution of fMRI is inherently limited due to the BOLD hemodynamic response. Combining fMRI with electroencephalography (EEG) with its excellent temporal resolution in future studies, may increase our understanding about the timing of the processes involved in impaired anticipatory state switching in ADHD.

Conclusions

Anticipatory rest-to-task switching, in terms of cue-related DMN attenuation, seems to be intact in ADHD. In contrast, a deficit in anticipatory DMN upregulation during task-to-rest switching was observed. Reduced anticipatory engagement of the DMN together with trends towards diminished anticipatory engagement of task-relevant areas during rest-to-task switching, tentatively suggest a putative deficit in "switching on" rather than "switching off" state relevant brain areas when anticipating a transition. This represents a potential target for cognitive anticipation training approaches; however, further research is needed to comprehensively examine the properties of anticipatory preparation for future states in terms of state-dependent neural modulation in ADHD.

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Appendix

Whole-brain analyses results for the control group

Table 1. Overview of peak activation coordinates of DMN areas for the rest cue vs. task cue contrast inclusively masked by the standard DMN mask.

		MNI coordinates					
Region	Hemisphere	x	y	z	Cluster extent	*Z*-value	FWE-corrected cluster *p*-value
Superior medial frontal gyrus	R	13	63	20	724	5.31	.000
Superior frontal gyrus	R	20	38	44		5.06	
		20	56	38		4.82	
Precuneus	L	-12	-49	41	429	5.07	.000
	R	10	-42	52		4.67	
	R	13	-42	6		4.64	

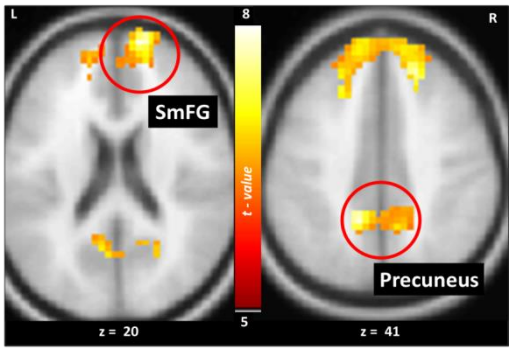

Figure 1. Brain activation map averaged over 21 control subjects depicting DMN areas exhibiting activation increases upon rest cues (rest cue vs. task cue), inclusively masked by standard DMN mask (FWE-cluster level corrected $p < .05$).

Table 2. Overview of peak activation coordinates of task-relevant areas for the task cue vs. rest cue contrast.

		MNI coordinates					
Region	Hemisphere	x	y	z	Cluster extent	*Z*-value	FWE-corrected cluster *p*-value
Inferior parietal lobule	L	-32	-56	48	291	4.75	.000
	L	-43	-42	41		4.43	
Precentral gyrus	L	-43	4	34	268	4.74	.000
	L	-36	-10	62		4.03	
		-29	-7	58		4.02	
Supplementary motor area	L	-12	4	55	169	5.63	.000
Superior occipital gyrus	L	-26	-98	-8	74	4.82	.000
	R	27	-94	-4	72	5.15	.000

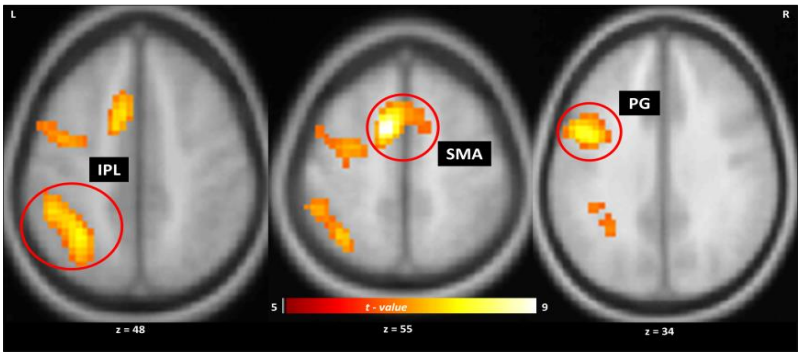

Figure 2. Brain activation map averaged over 21 control subjects depicting task-relevant areas exhibiting activation increases upon task cues (task cue vs. rest cue) (FWE-cluster level corrected $p < .05$).

Table 3. Overview of peak activation coordinates of SN areas for the switch cue vs. repeat cue contrast, inclusively masked by the standard SN mask.

		MNI coordinates					
Region	Hemisphere	x	y	z	Cluster extent	*Z*-value	FWE-corrected cluster *p*-value
Anterior cingulate cortex	L	-8	18	27	359	5.12	.000
	R	2	32	24		4.83	
	R	10	35	2		4.27	
Anterior insula	R	41	14	-4	262	5.31	.000
	R	38	4	13		4.76	
	R	38	-18	2		4.49	
	L	-40	-10	-4	228	5.06	.000
	L	-40	10	-4		4.99	
	L	-32	-4	13		4.75	

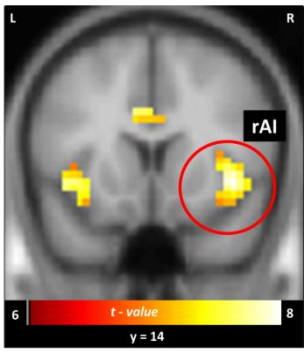

Figure 3. Brain activation map averaged over 21 control subjects depicting SN areas, specifically rAI, exhibiting activation increases upon switch cues (switch cue vs. repeat cue) (FWE-cluster level corrected $p < .05$).

Whole-brain analyses results for the ADHD group

Table 4. Overview of peak activation coordinates of DMN areas for the rest cue vs. task cue contrast inclusively masked by the standard DMN mask.

		MNI coordinates					
Region	Hemisphere	x	y	z	Cluster extent	*Z*-value	FWE-corrected cluster *p*-value
Superior frontal gyrus	L	-18	60	16	625	4.91	.000
Superior medial frontal gyrus	L	-4	52	34		4.44	
	R	6	32	62		4.41	
Precuneus	R	2	-52	55	480	4.96	.000
	R	10	-56	13		4.69	
	R	24	-63	20		4.42	

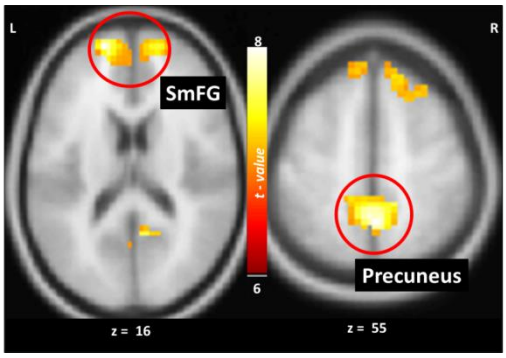

Figure 4. Brain activation map averaged over 19 subjects with ADHD depicting DMN areas exhibiting activation increases upon rest cues (rest cue vs. task cue), inclusively masked by standard DMN mask (FWE-cluster level corrected $p < .05$).

Table 5. Overview of peak activation coordinates of task-relevant areas for the task cue vs. rest cue contrast.

		MNI coordinates					
Region	Hemisphere	x	y	z	Cluster extent	Z-value	FWE-corrected cluster *p*-value
Supplementary motor area	L	-8	10	55	208	5.58	.000
Middle cingulate gyrus	R	13	14	41		3.76	
Inferior parietal lobule	L	-43	-46	44	192	4.65	.000
	L	-26	-66	44		3.94	
Precentral gyrus	L	-43	4	38	126	4.16	.001
	L	-36	-4	58		3.92	

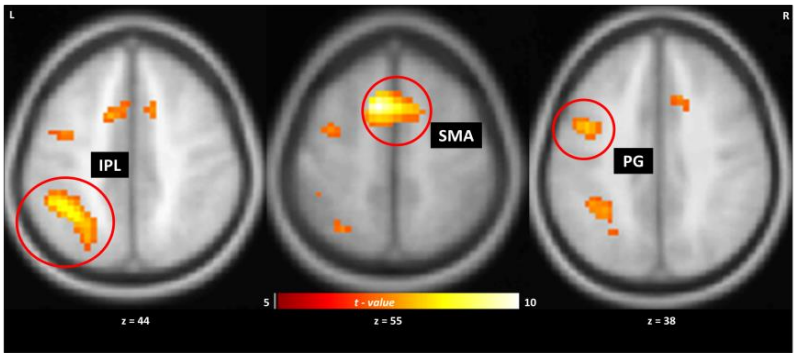

Figure 5. Brain activation map averaged over 19 subjects with ADHD depicting task-relevant areas exhibiting activation increases upon task cues (task cue vs. rest cue) (FWE-cluster level corrected $p < .05$).

Table 6. Overview of peak activation coordinates of SN areas for the switch cue vs. repeat cue contrast, inclusively masked by the standard SN mask.

		MNI coordinates					
Region	Hemisphere	x	y	z	Cluster extent	*Z*-value	FWE-corrected cluster *p*-value
Anterior insula	L	-29	28	-1	14	3.62	.583
	R	30	28	6	6	3.53	.789

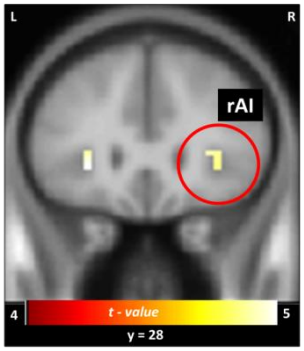

Figure 6. Brain activation map averaged over 19 subjects with ADHD depicting SN areas, specifically rAI, exhibiting activation increases upon switch cues (switch cue vs. repeat cue).

CHAPTER 4

ALTERED INTRINSIC ORGANISATION OF BRAIN NETWORKS CO-ORDINATING ATTENTIONAL ENGAGEMENT IN ADHD[1]

Abstract

Objective: Deficits in task-related attentional engagement in attention-deficit/hyperactivity disorder (ADHD) have been hypothesized to be due to altered interrelationships between attention, default mode and salience networks. We examined the intrinsic connectivity during rest within and between these networks. **Method:** Six minutes resting state scans were obtained. Using a network-based approach, connectivity within and between the dorsal and ventral attention, the default mode and the salience networks was compared between the ADHD and control group. **Results:** The ADHD group displayed hyperconnectivity within and between the two attention networks and within the default mode network. The salience network was hyperconnected to the ventral but hypoconnected to the dorsal attention network. Connectivity within and between other networks was unrelated to ADHD. **Conclusions:** Our findings highlight the altered connectivity within and between attention networks, and between them and the salience network in ADHD.

[1]Based on Justina Sidlauskaite, Edmund Sonuga-Barke, Herbert Roeyers, Jan R. Wiersema (2014) *Altered intrinsic organisation of brain networks co-ordinating attentional engagement in adult attention-deficit/hyperactivity disorder: A resting state study of attention, default mode and salience network connectivity*. Manuscript submitted for publication.

One hypothesis to be tested in future studies is that individuals with ADHD are affected by an imbalance between ventral and dorsal attention systems with the former playing a dominant role during task engagement making individuals with ADHD highly susceptible to distraction by salient task-irrelevant stimuli.

Introduction

Efficient allocation of attention is a pre-requisite for effective information processing during task performance. This requires a control system that is responsive to the dynamic nature of task demands in terms of the need for focusing, switching and dividing attention and the ability to resist distraction (Tortella-Feliu et al., 2014; Ziaei, Peira, & Persson, 2014). Functional magnetic neuroimaging (fMRI) studies have identified the core brain regions implicated in attentional control. These include dorsal and ventral lateral frontal cortices, together with posterior parietal areas (Corbetta & Shulman, 2002; Hopfinger, Buonocore, & Mangun, 2000; Woldorff et al., 2004). These regions form a twofold attentional control system comprised of dorsal and ventral attention networks (DAN and VAN), operating as an integrated supramodal top-down and bottom-up attentional gating system (Corbetta & Shulman, 2002; Vossel, Geng, & Fink, 2014). While traditional accounts of attentional function and dysfunction have focused on task-dependent neural activity within these networks, recent formulations have stressed the importance of a task-independent network as well (Buckner, Andrews-Hanna, & Schacter, 2008). This network, termed the default mode network (DMN), comprises frontal and posterior midline structures (medial prefrontal cortex, posterior cingulate cortex (PCC) with adjacent precuneus) and lateral parietal and medial temporal lobe regions (Buckner et al., 2008; Raichle et al., 2001). The DMN is active during periods of rest and is attenuated following the onset of tasks (Raichle et al., 2001). The DMN is also referred to as the task-negative network, because of its anti-correlated, and to some extent antagonistic relationship to activity in attention networks (also termed the task-positive network; Fox et al., 2005). This means that effective attentional engagement requires both - the "switching on" of the task-positive attention networks and the "switching off" of the DMN (Lawrence, Ross, Hoffmann, Garavan, & Stein, 2003; Sonuga-Barke &

Castellanos, 2007; Weissman, Roberts, Visscher, & Woldorff, 2006). Indeed, there is compelling evidence that performance suffers when excess (residual) DMN activity is observed during attention demanding tasks (Bednarski et al., 2011; Fassbender et al., 2009; Weissman et al., 2006). Recently, Menon and Uddin (2010) postulated that the salience network (SN), comprising bilateral insula and anterior cingulate cortex (ACC), provides the neural substrate of a switching hub controlling the up-regulation of attention networks and the down-regulation of the DMN. Support for this view comes from a range of recent studies (Goulden et al., 2014; Jilka et al., 2014; Rilling, Dagenais, Goldsmith, Glenn, & Pagnoni, 2008; Sidlauskaite et al., 2014; Sridharan, Levitin, & Menon, 2008).

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental condition characterised in part by symptoms of distractibility and an inability to ignore irrelevant stimuli - characteristics related to deficits in attentional control (Cubillo, Halari, Smith, Taylor, & Rubia, 2012). While in the past explanatory models have focused on localized deficits in brain regions, such as dorsal lateral prefrontal, posterior parietal, anterior cingulate cortices, within attention systems (Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013), more recent studies have examined the alternative possibility that attentional failures in ADHD during task performance may relate to interference by residual DMN activity (Sonuga-Barke & Castellanos, 2007). Indeed, there is now compelling evidence from fMRI and electroencephalographic (EEG) studies that individuals with ADHD show excess DMN activity during tasks and that this has an adverse effect on their performance (Fassbender et al., 2009; Helps et al., 2010; Liddle et al., 2011; Peterson et al., 2009). While the reason for this higher DMN activity during tasks remains to be determined, one possibility is that it is due to failures of the between-network switching mechanism governed by the SN (Menon, 2011; Sidlauskaite et al., 2014). Currently there is no direct evidence to support this hypothesis; however, it is interesting that in more general terms

SN task-related activation abnormalities have been reported in ADHD (Cortese et al., 2012; Dibbets, Evers, Hurks, Bakker, & Jolles, 2010; Dickstein, Bannon, Castellanos, & Milham, 2006; Lemiere et al., 2012). Furthermore a number of studies also point to ADHD-related structural and volumetric abnormalities of SN regions (Lopez-Larson, King, Terry, McGlade, & Yurgelun-Todd, 2012).

Building on recent evidence that patterns of intrinsic task-free brain organization sculpt task-related neural processes (Bressler & Menon, 2010; Deco & Corbetta, 2011), it has been suggested that ADHD is a condition caused by underlying deficits in brain organisation (Cortese et al., 2012). Moreover, it has been proposed that the key locus of dysfunction in ADHD may lie in the abnormal coordination of the DMN and attention networks, controlled by the SN (Menon, 2011; Supekar & Menon, 2012). In the current paper we provide the first test of this hypothesis by exploring the intrinsic organization of DMN, DAN, VAN and SN and their interactions in adults with ADHD by evaluating patterns of BOLD signal correlations measured during rest (Bressler & Menon, 2010; Damoiseaux et al., 2006; De Luca, Beckmann, De Stefano, Matthews, & Smith, 2006). Prior resting state studies have found reduced connectivity in ADHD between DMN regions (Castellanos et al., 2008; Fair et al., 2010; Konrad & Eickhoff, 2010; for opposite findings see McCarthy et al., 2013; Tian et al., 2006), as well as altered organisation of DAN and VAN (Cubillo et al., 2012; McCarthy et al., 2013; Zhu et al., 2008). However, no study has directly explored connectivity within and between the DMN, DAN, VAN and SN in ADHD.

We employed a hypothesis driven anatomical, network-based, parcellation approach, which differs from more traditional seed-based voxel-wise connectivity or independent component analysis accounts. This method builds on the graph theoretical analysis approach (Bullmore & Sporns, 2009) in that it uses an anatomical atlas based on

an *a priori* parcellation scheme to identify the networks of interest and is not limited to a single predefined seed region (Uddin et al., 2008; Wang et al., 2009). The use of several key regions instead of one seed to describe brain networks, enables a more comprehensive and reliable examination of the intrinsic intra- and inter-network organization (Schultz et al., 2014). Thus, this allows the direct comparison of the within- and between- brain network organisation in two different groups. In addition, this method ensures the reproducibility and comparability of the results across studies employing the same parcellation scheme, and enables the comparison of small and unequal sized samples (Schultz et al., 2014).Our predictions were as follows: i) based on the majority of previous findings we predicted hypo-connectivity within the DMN, DAN, and VAN in adults with ADHD; ii) based on the assumption that ADHD-related deficits in attentional control result from dysfunctional SN-DMN and/or SN-DAN/VAN coordination we predicted reduced connectivity between SN and DMN, as well as between SN and attention networks in ADHD.

Materials and Methods

Participants

The study was approved by the medical ethics committee of Ghent University Hospital. Participants gave their written informed consent before participation and received a monetary reward after participation. A total of 19 adults with an official diagnosis of ADHD obtained in a clinical setting (13 combined; 6 inattentive type) and 23 typically developing (TD) controls participated. Both groups of participants were recruited through the means of local advertising, social websites, word of mouth or from the pool of individuals who had participated in previous experiments. Participants with ADHD met the lifespan criteria for the disorder and had both - an official clinical

diagnosis and research diagnosis of ADHD, confirmed by the DSM-IV-based semi-structured clinical Diagnostic Interview for Adult ADHD (DIVA; Kooij & Francken, 2010). In addition, all participants with ADHD scored above cut-offs on self-report measures of childhood and adult ADHD symptoms (Wender Utah Rating Scale (WURS); Ward, 1993; Self-report questionnaire on problems of inattention and hyperactivity in adulthood and childhood; Kooij & Buitelaar, 1997). All TD participants scored below the cut-offs on these questionnaires. All participants in both groups had a full scale IQ in the normal or above average range (>80) as measured by a seven subtests version of the Wechsler Adult Intelligent Scale (Ryan & Ward, 1999). Groups did not differ on IQ (TD: M = 117.26; SD = 10.99; ADHD: M = 112.05; SD = 13.60; p = .187), sex ratio (TD: 10 female; ADHD: 10 female), or age (TD: M = 27.17 years; SD = 8.65; ADHD: M = 29.78 years; SD = 9.61; p = .365). Nine participants with ADHD were taking stimulant medication (8 - methylphenidate and 1- dextroamphetamine) and were asked to refrain from taking these for at least 24h prior to the experiment. Four ADHD participants were also taking antidepressant medication which they were allowed to continue (3 - selective serotonin reuptake inhibitors and 1 - buproprion chloride). All participants had normal or corrected to normal vision, five were left-handed (1 ADHD). The general exclusion criteria were history of brain damage, a neurologic or psychiatric condition, or IQ < 80.

fMRI data acquisition

Functional and structural images were obtained with a Siemens Magnetom Trio MRI system (Siemens Medical Systems, Erlangen, Germany) operating at 3T, using a standard 32-channel head-coil. Study participants were positioned supine head first inside the scanner and instructed to relax and rest with their eyes closed. Structural high-resolution 1 mm^3 images were collected using a T1-weighted 3D MPRAGE sequence.

Functional whole-brain images were collected in a single run of 180 whole-brain volumes lasting 6 min, using gradient echoplanar imaging (EPI) T2*-weighted sequence sensitive to BOLD contrast (TR = 2000 ms, TE = 29 ms, acquisition matrix = 64 x 64, FoV = 224 mm, flip angle = 90^0, slice thickness = 3 mm, voxel size 3.5 x 3.5 x 3.5 mm^3, 40 axial slices). The first four EPI images of each run were discarded to reduce T1 relaxation artefacts.

fMRI data preprocessing

Data preprocessing was conducted using Statistical Parametric Mapping software (SPM8; Welcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Functional images were slice-time corrected and realigned to the first EPI. Rigid body transformation correction for within-run head motion was applied and six head motion parameters were estimated. Data were to be excluded if motion parameters exceeded 3 mm and/or 3 degrees in any direction during the scan; however, none of study participants met this exclusion criteria. A two-sample *t-test* analysis of the six motion parameters generated revealed no significant group differences in neither translational (ADHD: x = .07 mm, *SD* = .04; y = .09 mm, *SD* = .07; z = .23, SD = .28; TD: x = 0.08, *SD* = .06; y = .10, *SD* = .08; z = .17, *SD* = .14; *p's* respectively: .722; .606; .377), nor rotational (ADHD: roll = .0038, *SD* = .0050; pitch = .0021, *SD* = .0015; yaw = .0014, *SD* = .0009; TD: roll = .0034, *SD* = .0031; pitch = .0019, *SD* = .0014; yaw = .0016, *SD* = .0013; *p's* respectively: .732; .579; .702) motion.

Next, functional-to-anatomic coregistration was performed. Spatial normalization to the standard (3 x 3 x 3 mm) Montreal Neurological Institute (MNI) template was applied to functional and structural images. Functional data were spatially smoothed with an isotropic full-width half-maximum (FWHM) Gaussian kernel of 8 mm. Structural images

were segmented into individual white matter (WM), grey matter and cerebrospinal fluid (CSF) masks. Data was band-pass filtered (.01 Hz < *f* < .1 Hz) further processed and corrected using CONN-fMRI Functional Connectivity toolbox (www.nitrc.org/projects/conn/) (Whitfield-Gabrieli & Nieto-Castanon, 2012). Sources of spurious variance such as, signal from WM, CSF (five dimensions) and movement parameters, extracted from the realignment process, were removed by linear regression. Importantly, CONN toolbox employs anatomical component-based noise correction method (aCompCor) (Behzadi, Restom, Liau, & Liu, 2007) which has been shown to effectively reduce the physiological and other sources of noise in BOLD signal, and thus has proved particularly useful in increasing the sensitivity and validity of fMRI analysis (Whitfield-Gabrieli & Nieto-Castanon, 2012).

Functional resting-state connectivity analysis

Anatomically landmarked regions of interest (ROIs) corresponding to DMN, DAN, VAN and SN (Buckner et al., 2008; Fox et al., 2005; Seeley et al., 2007) (Table 1; Figure 1) were derived from the Automatic Anatomic Labelling (AAL) atlas implemented in the WFU Pickatlas (Eichele et al., 2008; Maldjian, Laurienti, Kraft, & Burdette, 2003; Tzourio-Mazoyer et al., 2002). Averaging over the relevant voxels, mean signal time series were extracted from each ROI and were used to create individual ROI-to-ROI, within- and between-network connectivity matrices. Fisher's r to z transformation was applied. The network forming scheme corresponded to the ones widely used in graph theoretical analysis where the brain networks are defined by several key regions (Hosseini, Hoeft, & Kesler, 2012). False-positive control was implemented using false discovery rate (FDR)-corrected p-values ($p < .05$). Average within- and between-network

connectivity (mean connectivity data of all pair-wise comparisons between ROIs comprising a network) were compared between groups.

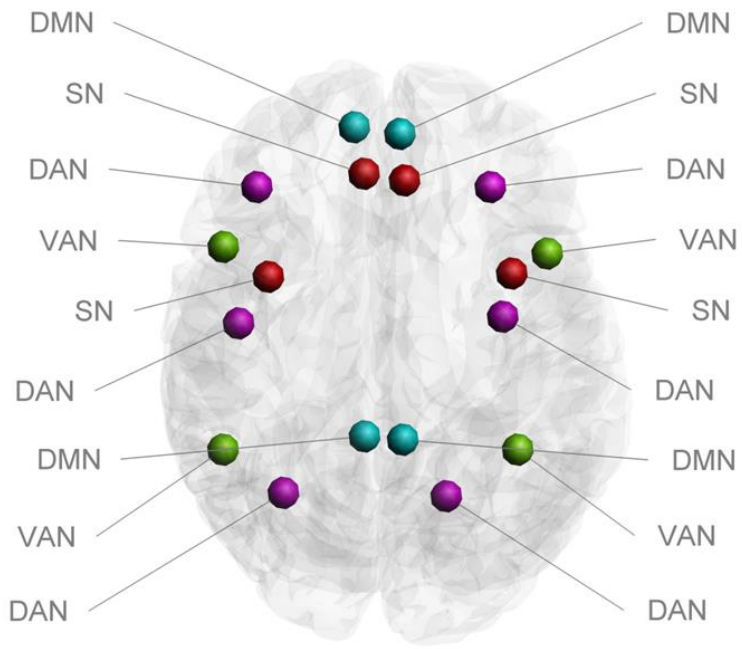

Figure 1. The schematic outline of the AAL regions corresponding to the DMN, DAN, VAN and SN used in the network connectivity analyses.

Table 1. Regions selected from the AAL atlas corresponding to the DMN, DAN, VAN, and SN and their centre of mass coordinates.

	Network							
	DMN		DAN		VAN		SN	
Region	Superior medial frontal gyrus	(R) [-5 49 30]	Middle frontal gyrus	(R) [35 33 34]	Inferior frontal gyrus	(R) [49 14 21]	Insula	(R) [38 6 2]
		(L) [8 50 30]		(L) [-34 32 35]		(L) [-49 12 19]		(L) [-36 6 3]
	Posterior cingulate gyrus	(R) [6 -41 21]	Precentral gyrus	(R) [40 -8 52]	Inferior parietal gyrus	(R) [45 -46 49]	Anterior cingulate gyrus	(R) [7 37 15]
		(L) [-5 -42 24]		(L) [-39 5 50]		(L) [-43 -45 46]		(L) [-5 35 13]
			Superior parietal gyrus	(R) [25 -59 62]				
				(L) [-24 59 58]				

Results

Within network connectivity: Both groups showed strong functional connectivity within the DMN (TD: $t(22) = 12.27$, $p < .001$; ADHD: $t(18) = 10.02$, $p < .001$), DAN (TD: $t(22) = 6.90$, $p < .001$; ADHD: $t(18) = 9.50$, $p < .001$), VAN (TD: $t(22) = 6.58$, $p < .001$; ADHD: $t(18) = 10.41$, $p < .001$) and SN (TD: $t(22) = 18.58$, $p < .001$; ADHD: $t(18) = 11.10$, $p < .001$). Against our prediction, network functional connectivity was stronger for both the DMN and VAN in the ADHD group (DMN: $t(40) = 3.02$, $p = .002$; VAN: $t(40) = 2.68$, $p = .005$) and the same trend was observed for the DAN ($t(40) = 1.53$, $p = .066$). ADHD and control groups did not differ in terms of within SN connectivity ($t(40) = .93$, $p = .179$).

Between network connectivity: Consistent with prior studies, activity within the DAN and VAN was correlated (TD: $t(22) = 8.50$, $p < .001$; ADHD: $t(18) = 11.22$, $p <$

.001), and both attention networks were anti-correlated with the DMN (DAN - TD: $t(22) = -3.88$, $p < .001$; ADHD: $t(18) = -2.87$, $p = .005$; VAN - TD: $t(22) = -1.85$, $p = .030$; ADHD: $t(18) = -2.43$, $p = .010$). The DMN and SN were positively correlated (TD: $t(22) = 4.92$, $p < .001$; ADHD: $t(18) = 3.43$, $p < .001$). There was no group difference in the strength of anti-correlations between the DMN and attention networks (DMN and DAN: $t(40) = .40$, $p = .343$; DMN and VAN: $t(40) = 1.18$, $p = .122$) or the DMN and SN correlation ($t(40) = .61$, $p = .271$). However, the DAN and VAN were more strongly correlated in the ADHD group ($t(40) = 2.15$, $p = .018$). The DAN and SN were significantly anti-correlated only in the TD group (TD: $t(22) = -2.06$, $p = .025$; ADHD: $t(18) = .96$, $p = .174$) producing a significant group difference ($t(40) = -2.00$, $p = .025$). The VAN-SN connectivity was significant only in the ADHD group (ADHD: $t(22) = 2.85$, $p = .005$; TD: $t(18) = .66$, $p = .25$), with a trend towards a group difference ($t(40) = 1.56$, $p = .06$) (Figure 2).

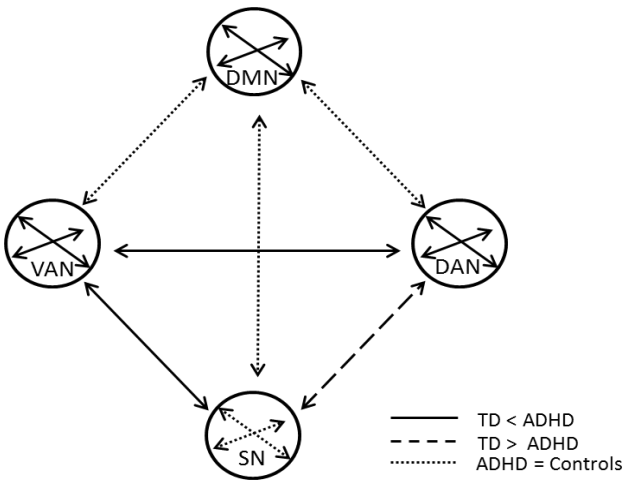

Figure 2. The schematic representation of the main intra- and inter- DMN, DAN, VAN and SN connectivity findings and differences between groups. "TD < ADHD" represents stronger connectivity in the ADHD group; "TD > ADHD" weaker connectivity in the ADHD group; "ADHD = Controls" represents the absence of group differences in connectivity strength.

Discussion

In the current study, using resting state connectivity analyses, we tested the hypothesis that abnormalities in the intrinsic organisation of brain networks implicated in attentional control - the DMN, attention networks and the SN - may lie at the heart of the pathophysiology of ADHD (Menon, 2011; Supekar & Menon, 2012). Our network-based approach to study connectivity patterns allowed us to look directly at both - connectivity between the key regions within networks and between these specific networks as a whole (Schultz et al., 2014; Shenton, Kubicki, & Makris, 2014). There were a number of findings of note that provide further evidence of connectivity abnormalities within networks implicated in attentional control in ADHD (Menon, 2011).

First, we found altered connectivity in ADHD with regard to the attention networks - DAN and VAN. Two aspects of ADHD-related intrinsic organisation of these networks were particularly striking. (i) The attention networks were hyperconnected, both within and between. Moreover, (ii) the VAN and DAN displayed differential connectivity patterns with SN-VAN being hyperconnected and SN-DAN hypoconnected. The potential significance of these findings for models of ADHD pathophysiology becomes apparent once one considers the respective roles of those brain networks during the control of goal-directed and stimulus driven attention, as well as the importance of their effective coordination (Corbetta, Patel, & Shulman, 2008; Corbetta & Shulman, 2002). In healthy individuals the DAN and VAN systems display strong differentiation based on their specific functions to facilitate processes in attentional control (Fox, Corbetta, Snyder, Vincent, & Raichle, 2006; Vossel et al., 2014). The DAN is involved in top-down voluntary allocation of goal-driven attention, whereas the VAN is involved in the detection of unexpected task-relevant stimuli to trigger attentional shifts, thus in stimulus-

driven attention. Although they have specialised roles they continuously interact to control "where" and "what" one attends to (Corbetta et al., 2008; Vossel et al., 2014). Our data suggest that the DAN and VAN are less segregated functionally in ADHD. This may create altered interactions between the attention networks in ADHD, where task-relevant inputs from the DAN filter stimulus-driven signals originating in the VAN, and where task-relevant stimuli trigger the VAN to interrupt and reorient the DAN to relevant stimuli. More specifically, decreased intrinsic segregation of the attention networks may alter the information exchange threshold between the two systems with VAN signals interrupting goal-directed task-relevant DAN activity. This is consistent with recent findings that increasingly point to VAN as the locus of attentional dyscontrol and enhanced distractibility in ADHD (Cortese et al., 2012; Helenius, Laasonen, Hokkanen, Paetau, & Niemivirta, 2011; Sripada et al., 2014). For instance, López et al. (2008) observed that in the ADHD group, but not in controls, unattended task-irrelevant distractors elicited increased VAN-related P300 activity. Our finding of increased within connectivity in the two attention networks in ADHD further suggests the possibility of reduced flexibly and capacity to alternate between goal-driven and relevant stimulus-driven attentional processing in ADHD.

Our finding of an imbalance between SN-DAN and SN-VAN connectivity in ADHD underscores the specificity of DAN and VAN roles in attentional control. This would be consistent with the idea that increased SN-VAN coupling produces an altered saliency attribution mechanism, where the discrimination between environmental distractors and task-relevant stimuli is muted. Therefore, in the context of ADHD this might be hypothesized to relate to symptoms of distractibility and inability to ignore irrelevant stimuli. It is however difficult to directly compare our results with previous studies as a differentiation between the VAN and SN is often not made (Sripada et al.,

2014). For instance, Sripada et al. (2014) did not differentiate between the VAN and SN and included insula as part of the VAN. We based our analyses on the model of the SN as a between-network switching hub, as proposed by Menon and Uddin (2010), which is differentiated from the attentional networks. Hence, we separated the SN, comprised of bilateral insula and anterior cingulate cortex (ACC), from the VAN-DAN system (Aboitiz, Ossandón, Zamorano, Palma, & Carrasco, 2014; Seeley et al., 2007). The finding of a stronger SN-DAN anti-correlation in the control group, as well as SN-VAN hyperconnectivity in the ADHD group, suggests a decreased brain network functional differentiation and adds to the frameworks where deficits in between brain networks balance are proposed to underlie ADHD. Crucially, the trend to SN-VAN hyper-connectivity in ADHD extends the recent findings suggesting ADHD-related attentional control deficits to be related to VAN alterations (Helenius et al., 2011; Sripada et al., 2014).

Second, we reported stronger intra-DMN coupling in ADHD. The field has produced inconsistent results in this regard. While most studies have reported reduced DMN connectivity (Castellanos et al., 2008; Fair et al., 2010; Sripada et al., 2014; Uddin et al., 2008), hyperconnectivity has also been observed (McCarthy et al., 2013; Tian et al., 2006) and one study found hyperconnectivity for some regions and hypoconnectivity for others within the DMN (Franzen et al., 2013). These inconsistencies may be due to differences between studies in analysis techniques used or sample characteristics. For instance, Castellanos et al. (2008) used a seed-based approach and found decreased connectivity between two DMN regions - PCC and medial prefrontal cortex in an adult ADHD group. In the same sample of participants, Uddin et al. (2008) applied a network homogeneity approach and showed ADHD-related reductions in only the posterior DMN, i.e., PCC. The method employed in the current study, however, was based on a network

perspective where the DMN and other networks were formed of several key regions comprising that specific neural circuit. This was done in order to be able to estimate overall network connectivity using a comprehensive approach, which is different from previous seed-based connectivity or network homogeneity studies. Moreover, the current sample included adults, while other studies with a comparable network approach that reported disconnection between DMN regions were conducted in adolescent samples (Fair et al., 2010; Sripada et al., 2014). The finding of intra-DMN hyperconnectivity in our ADHD sample appears to be consistent with the concept of resting state affinity proposed as a potential mechanism behind problems in state-to-state switching (Sonuga-Barke & Castellanos, 2007), with hyper-connectivity within resting networks increasing affinity for that state and reducing the potential for switching to active goal directed states. The above evidence of similar patterns of hyperconnectivity within attention networks may also be consistent with this.

Third, connectivity between DMN and attention networks, as well as connectivity between DMN and SN was unaffected in ADHD. In recent literature there has been a strong focus on the DMN as a core feature of attentional dyscontrol in ADHD. Task-based studies have provided evidence for elevated DMN levels in ADHD during task processing (Fassbender et al., 2009; Liddle et al., 2011) which has been related to attentional deficits (Bednarski et al., 2011; Sonuga-Barke & Castellanos, 2007; Weissman et al., 2006). In terms of intrinsic network organization, studies have suggested diminished antagonistic relationship between DMN and attention networks which may lead to excess task-related DMN (Cao et al., 2009; Castellanos et al., 2008; Sripada et al., 2014; Sun et al., 2012). However, more recent models have introduced the crucial role of the SN to control the state-dependent switching between DMN and task-related attention networks (Menon & Uddin, 2010). Specifically, studies found support for a central role of

the SN in attenuating the DMN and upregulating attention networks when switching from rest-to-task (Sidlauskaite et al., 2014; Sridharan et al., 2008). Interestingly, our results imply an intact between DMN and SN connectivity in ADHD, and indicate another locus of functional disorganisation that may relate to attention deficits, namely, the imbalance between SN and attention networks.

Limitations

Our study has some limitations that are important to address. First, our network-based connectivity method highly relies on the *a priori* choice of brain regions to form the brain networks of interest. Hence, the results strongly depend on the brain parcellation scheme used and this in turn indicates the supreme relevance of the advances in the development of representative and reliable brain network templates. Second, history and duration of stimulant medication use, which may exert differential effects on the functional brain organisation, was not taken into account in the current study.

Conclusions

The current findings add to the growing evidence of altered intrinsic brain organization in ADHD. Crucially, our results highlight the connectivity disturbances in attention networks and between them and SN as a putative locus for ADHD-related deficits in task engagement. An important target of investigation in future studies is the hypothesis that individuals with ADHD may suffer from imbalanced ventral and dorsal attention systems with the former playing a principal role during task engagement introducing increased susceptibility to salient but task-irrelevant stimuli.

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CHAPTER 5

WHOLE-BRAIN STRUCTURAL TOPOGRAPHY IN ADULT ADHD: PRESERVED GLOBAL – DISTURBED LOCAL NETWORK ORGANISATION[1]

Abstract

Objective: Prior studies demonstrate altered organisation of functional brain networks in attention-deficit/hyperactivity disorder (ADHD). However, the structural underpinnings of these functional disturbances are poorly understood. **Method:** We applied graph theory to whole-brain diffusion magnetic resonance imaging data to investigate the organisation of structural brain networks in adults with ADHD and unaffected controls using deterministic fibre tractography. **Results:** Groups did not differ in terms of global network metrics - *small-worldness, global efficiency and clustering coefficient*. In contrast, there were widespread ADHD-related effects at the nodal level in relation to *local efficiency* and *clustering*. The affected nodes included superior occipital, supramarginal, superior temporal, inferior parietal, angular and inferior frontal gyri, as well as putamen, thalamus and posterior cerebellum. **Conclusions:** Overall, the findings indicate preserved global but altered local network organisation in adult ADHD implicating the regions underpinning putative ADHD-related neuropsychological deficits.

[1]Based on Justina Sidlauskaite, Karen Caeyenberghs, Edmund Sonuga-Barke, Herbert Roeyers, Jan R. Wiersema (2014). *Whole-brain structural topography in adult attention-deficit/hyperactivity disorder: preserved global – disturbed local network organisation.* Manuscript submitted for publication.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is associated with widespread but often subtle alterations in multiple brain regions affecting brain function (Cortese et al., 2012). From a systems neuroscience perspective ADHD is increasingly seen as the product of disturbances in intrinsic organisation of brain networks comprised of these regions (Aboitiz, Ossandón, Zamorano, Palma, & Carrasco, 2014; Konrad & Eickhoff, 2010; Menon, 2011; Ray et al., 2014). Studies using functional magnetic resonance imaging (fMRI) report altered intrinsic connectivity within and between networks including the dorsal and ventral attention, salience (Mccarthy et al., 2013; Sripada et al., 2014), and default mode networks (Castellanos et al., 2008; Fair et al., 2010; Franzen et al., 2013; Mccarthy et al., 2013; Sripada et al., 2014; Uddin et al., 2008). Structural connectivity studies are less common and the extent to which these functional alterations are underpinned by deep-seated structural effects remains to be determined (Cao, Shu, Cao, Wang, & He, 2014).

Diffusion MRI (dMRI) is a powerful neuroimaging technique used to examine microstructural brain properties and connections (Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000; O'Donnell & Pasternak, 2014; Weyandt, Swentosky, & Gudmundsdottir, 2013). In ADHD there is evidence for alterations of white matter fibre tracts and structures encompassing inferior and superior longitudinal fasciculus, cingulum bundle, anterior corona radiata, internal capsule, forceps minor, cerebellar tracts, thalamic radiation and isthmus of corpus callosum (Kobel et al., 2010; Konrad et al., 2010; Makris, Biederman, Monuteaux, & Seidman, 2009; Pavuluri et al., 2009; Peterson et al., 2011; Silk, Vance, Rinehart, Bradshaw, & Cunnington, 2009; Weyandt et al., 2013; Zhang & Li, 2010), however, results lack consistency (for reviews, see Cao et al., 2014; van Ewijk,

Heslenfeld, Zwiers, Buitelaar, & Oosterlaan, 2012; Weyandt et al., 2013). Region of interest (ROI) studies typically report lower fractional anisotropy (FA; a measure of white matter integrity) in ADHD, while whole-brain studies find the opposite result (Ashtari et al., 2005; Davenport, Karatekin, White, & Lim, 2010; A. Konrad et al., 2010; Nagel et al., 2011; Zhang & Li, 2010); perhaps because they include a larger set of brain regions containing so-called "crossing fibres".

Graph theory, which is a branch of mathematics focusing on the formal characterisation and analysis of *graphs* (i.e., mathematical structures for modelling pairwise object relationships), has been recognized as an informative approach to investigate brain networks (Bullmore & Sporns, 2009; Griffa, Baumann, Thiran, & Hagmann, 2013; Xia & He, 2011). It represents the brain as a formal *graph* comprised of a selection of nodes (vertices) and inter-nodal links (edges). Nodes represent anatomical brain regions, while edges describe the properties of the connections (e.g., functional, effective or structural). Structural connections between brain areas (nodes) parallel white matter tracts and are effectively reconstructed using dMRI (Hagmann et al., 2008; Rubinov & Sporns, 2010; van den Heuvel & Sporns, 2011). Graph theoretic analysis suggests compromised brain network organisation in several conditions (e.g., Alzheimer's disease (Lo et al., 2010); schizophrenia (van den Heuvel, Mandl, Stam, Kahn, & Hulshoff Pol, 2010) and autism spectrum disorder (Rudie et al., 2012)). With regard to ADHD, Cao and colleagues (2013) found reductions in both global (lower *global efficiency* and higher *shortest path length*) and *local efficiency* (in left parietal, left frontal and left occipital cortices) in a sample of drug-naive boys (8 – 14 years) with ADHD. Ray and colleagues (2014) found that children with ADHD (7 – 13 years) had lower internal, but higher external *rich-club* connectivity (i.e., highly connected regions that are also very highly connected between them).

The current study is the first to extend the graph theory approach to the study of structural brain network organisation in adult ADHD. Based on the findings from studies with children, we predicted that adults with ADHD would exhibit both global (e.g., *clustering coefficient, characteristic path length*) and local network disruptions (specifically in frontal, parietal and occipital cortices).

Method

Participants

Eighteen adults with ADHD (12 combined and 6 inattentive type) and 21 healthy controls participated. The study was approved by the medical ethics committee of Ghent University hospital. Participants gave informed consent before participation and received a monetary reward afterwards. All participants with ADHD had an official clinical diagnosis of ADHD, as well as a research diagnosis of ADHD confirmed by the DSM-IV-based structured Diagnostic Interview for Adult ADHD (DIVA; Kooij & Francken, 2010). They also scored above the cut-offs on three ADHD self-report questionnaires; The Wender Utah Rating Scale (WURS; Ward, 1993); a DSM-based self-report questionnaire on problems of inattention and hyperactivity in adulthood and childhood (Kooij & Buitelaar, 1997); and the Adult Self-Report (ASR; Achenbach & Rescorla, 2003). None of the controls scored above the cut-off scores for ADHD on any of these questionnaires. All participants had a normal or above normal full scale IQ (>80) derived from a seven subtests version of the Wechsler Adult Intelligent Scale (Ryan & Ward, 1999). Nine participants with ADHD taking stimulant medication (8 - methylphenidate and 1- dextroamphetamine) refrained from use for at least 24h prior to testing. Three ADHD participants were taking antidepressant medication which they were allowed to continue (2 - selective serotonin reuptake inhibitors and 1 - buproprion chloride).

Participants were excluded if they had a neurological or psychiatric condition or a history of brain damage. All participants had normal or corrected to normal vision. Four were left-handed (1 ADHD).

Data acquisition

MRI data were acquired with a Siemens Magnetom Trio MRI system (Siemens Medical Systems, Erlangen, Germany) operating at 3T, using a standard 32-channel head-coil. The participants were positioned supine head first inside the scanner. Structural high resolution 1-mm^3 T1-weighted images were obtained using a magnetization prepared rapid gradient echo sequence (MPRAGE; repetition time (TR)=2300 ms; echo time (TE)=3.03 ms; inversion time=1100 ms; flip angle=8º; field of view (FoV)=256. dMRI data were acquired using diffusion-weighted spin-echo echoplanar imaging (TR=7000 ms; TE=85 ms; flip angle=90º; matrix size=128x128; slice thickness=2 mm; voxel size=2x2x2 mm^3; 60 diffusion directions with b=1000 s/mm^2; and additional 2 images without diffusion weighting [i.e., b=0 s/mm^2]) covering the whole brain, with a total acquisition time of 13 min.

dMRI data preprocessing

dMRI data were preprocessed using ExploreDTI *version 4.8.3* (Leemans et al., 2009) employing: 1) correction for geometrical distortion, caused by eddy currents and subject motion; 2) diffusion tensor calculations; 3) performance of dMRI data coregistration to the MNI space.

Whole-brain tractography and connectivity matrix construction

Deterministic streamline whole-brain tractography algorithm was applied on our dMRI data. Fibre seeds were placed on a uniform grid throughout the data at a 2 mm isotropic resolution. Fibre trajectory (‘streamline’) reconstruction was initiated by

following the primary eigenvector which defined the main diffusion direction. When the fibre touched a voxel with an FA (ranging from 0 to 1) value < 0.2 or it made a high angular turn (angle > 30º) compared to the neighbouring eigenvectors the tractography was terminated. The step size was set at 1 mm and only tracts with a minimum length of 50 mm were considered. Anatomical labelling atlas (AAL; Tzourio-Mazoyer et al., 2002), comprising 116 cortical and subcortical regions (58 for each hemisphere), was employed to parcellate whole-brain fibre tracts. The number of streamlines connecting each pair of the AAL atlas regions was used to create a 116 x 116 connectivity matrix. Two regions were assumed connected if a fibre originated from either of the two areas and terminated in the other area. Furthermore, all non-zero weights (i.e., all connections) were set to one and to zero otherwise (van den Heuvel et al., 2010). The end result of this procedure was an unweighted binary network. Thus, for each participant, there were two different kinds of white matter networks ('streamline count' and binary), each of which was represented by a symmetric 116 x 116 matrix.

Graph-theoretical analysis

The graph-theoretical analysis toolbox (GAT) (Hosseini, Hoeft, & Kesler, 2012) was employed. Global network metrics of interest included *small-worldness*, *normalized clustering coefficient*, *normalized path length* and *global network efficiency*. *Small-worldness* represents the properties of simultaneous segregation and integration (Bassett & Bullmore, 2006). Segregation represents local, and integration global processing capability (Hosseini et al., 2013). A *small-world* network represents an ideal combination of local and global information processing. *Small-world* networks can be distinguished from other classes of networks (e.g., random or regular) in terms of *clustering coefficient* (*C*) and the *characteristic path length* (*L*) (He & Evans, 2010). The *clustering coefficient* measures the existing number of connections between the node and its nearest neighbours

as a ratio of all the possible connections (Bullmore & Sporns, 2009). The network *clustering coefficient* is the average of *clustering coefficients* across network nodes and characterizes network segregation. Hence, the *clustering coefficient* represents the network's specialization in information processing (Hosseini et al., 2013). The *characteristic path length* is a measure of network integration and reflects the shortest path length between all network node pairs. Thus, the *characteristic path length reflects* the network's ability to distributed information processing (Rubinov & Sporns, 2010). Metrics are compared to random graph mean values in order to evaluate the organisation of a brain network. *Small-world* networks are characterized by a *clustering coefficient* higher than one of a random network, whereas the *characteristic path length* is comparable to that from a random network. Thus, the *small-worldness* (*S*) of a network is formally expressed as follows: $S=(C/C_{rand})/(L/L_{rand})$ with a value > 1. The *global efficiency* (E_{global}), which is inversely related to path length, is also a measure of network integration (Rubinov & Sporns, 2010).

Second, we examined the regional network measures, including the nodal *clustering coefficient* and *local efficiency*. The former is the ratio of the sum of the weights across all complete triangles around the node and the number of edges connecting the node. Furthermore, *local efficiency* is equivalent to the *global efficiency* computed for each node (Sporns & Zwi, 2004). Finally, we also calculated *betweenness centrality* as a nodal metric, which is defined as the fraction of all shortest paths in the network that pass through a given node. This measures the importance of nodes to an overall network integrity. The nodes with the largest *betweenness centrality* were considered pivotal network nodes (i.e., hubs). Specifically, we considered a node a hub if its nodal *betweenness centrality* was at least two standard deviations (SD) higher than the mean network *betweenness centrality*.

Statistical Analysis

Between-group differences in structural network connectivity (i.e. between global and regional graph metrics, extracted using GAT toolbox, AUC-correction applied) were examined using two-sample *t*-tests.

Results

Demographic data

The ADHD and control group did not differ on IQ (controls: M = 116.90, SD = 11.24); ADHD: M = 112.05, SD = 13.99, p = .238), age (controls: M = 26.95 years; SD = 8.52); ADHD: M = 30.11 years, SD = 9.78, p = .288), or male to female ratio (controls: 9 females; ADHD: 9 females).

Global network metrics

Both groups showed *small-worldness* of brain organization and did not differ in the three relevant metrics (normalized *clustering coefficient* – $\gamma > 1$; normalized *path length* – $\lambda \sim 1$; *small-worldness* – $\sigma > 1$; γ – $t(37) = .84$, $p = .405$; λ –$t(37) = .62$, $p = .539$; σ – $t(37) = .80$, $p = .425$) or in terms of *global efficiency* ($t(37) = .60$, $p = .550$) or *clustering coefficient* ($t(37) = -.35$, $p = .728$; Figure 1).

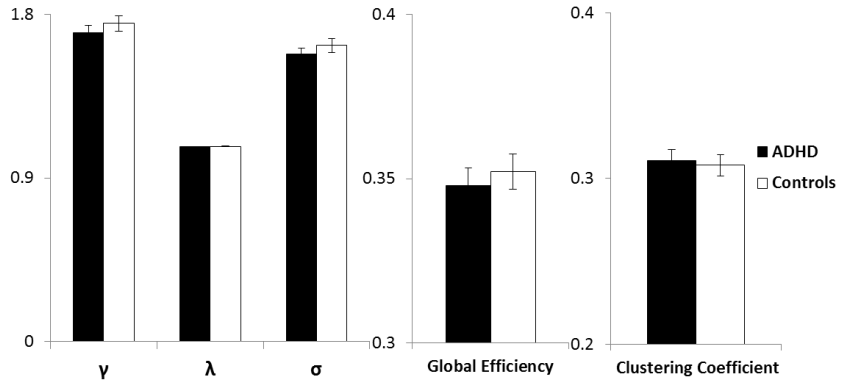

Figure 1. A graphical representation of global graph metrics. *Small-worldness* parameters (*γ, λ* and *σ* ±*SE*), *gobal efficiency* and *clustering* (±SE) in the ADHD and control group. No differences between groups in either *γ, λ, σ* or *global efficiency* and *clustering*.

Local network metrics

N***odal efficiency:*** The ADHD group displayed left lateralized, significantly lower *local efficiency* in superior occipital gyrus, supramarginal gyrus, superior temporal gyrus and posterior cerebellum (lobule VI) (see Table 1). Nodal *efficiency* was significantly greater right lateralized, in superior occipital gyrus and inferior parietal gyrus in ADHD (see Table 1, Figure 2).

Table 1. Regions showing ADHD-related significant changes in *local efficiency*

Region	Hemisphere	*t* value	*p* value
ADHD-related lower nodal *efficiency*			
Superior occipital gyrus	L	2.21	.040
Supramarginal gyrus	L	2.47	.018
Superior temporal gyrus	L	2.13	.040
Cerebellum VI	L	2.46	.019
ADHD-related higher nodal *efficiency*			
Superior occipital gyrus	R	-2.91	.006
Inferior parietal gyrus	R	-3.06	.004

t – statistical value indicating a difference between groups ($p < .05$). Positive *t* value denotes ADHD-related lower nodal *efficiency*, while the negative *t* value indicates ADHD-related significant higher nodal *efficiency*. R – right; L – left.

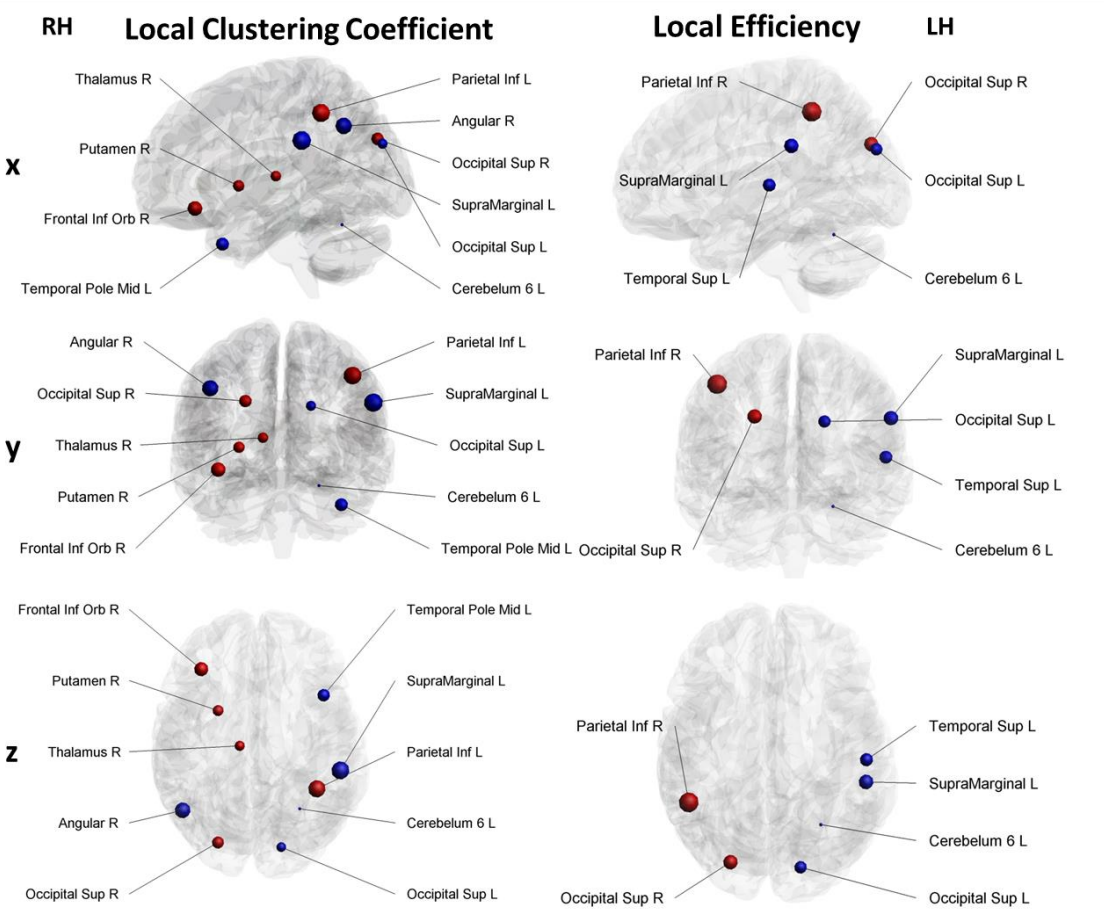

Figure 2. Nodes exhibiting significant group differences in *local efficiency* and *local clustering*. The sizes of the spheres are based on *local efficiency* and *local clustering* estimates in the ADHD group, blue colour represents significantly lower *local efficiency* and *local clustering* in the ADHD group, red colour represents significantly higher *local efficiency* and *local clustering* in the ADHD group. RH – right hemisphere; LH – left hemisphere; x, y, z – anatomical planes.

Nodal clustering: Significantly lower values for nodal *clustering* were observed in the ADHD group left lateralized in superior occipital gyrus, supramarginal gyrus, superior temporal gyrus, posterior cerebellum (lobule VI) and right angular gyrus. (see Table 2). ADHD-related significantly higher nodal *clustering* was observed in the right lateralised

areas of inferior frontal gyrus, superior occipital gyrus, putamen, thalamus and in left inferior parietal gyrus (see Table 2, Figure 2).

Table 2. Regions showing ADHD-related significant changes in *local clustering*

Region	Hemisphere	*t* value	*p* value
ADHD-related lower *local clustering*			
Superior occipital gyrus	L	2.39	.022
Supramarginal gyrus	L	2.35	.024
Angular gyrus	R	2.08	.044
Temporal pole: superior temporal gyrus	L	2.10	.042
Cerebellum IV	L	2.59	.013
ADHD-related higher *local clustering*			
Inferior frontal gyrus, orbital part	R	-2.58	.014
Superior occipital gyrus	R	-2.25	.030
Inferior parietal gyrus	L	-2.97	.005
Putamen	R	-2.09	.043
Thalamus	R	-2.49	.017

t – statistical value indicating a difference between groups (p <.05). Positive *t* value denotes ADHD-related lower *local clustering*, while the negative *t* value indicates ADHD-related significant higher *local clustering*. R – right; L – left

Hub analysis: right superior frontal gyrus, bilateral precuneus, and left thalamus were hubs in both groups. Of note, right putamen was also identified as hub in the control group, but not in the ADHD group, while the opposite was seen for right thalamus.

Discussion

The current study provides the first evidence of alterations in white matter brain network organisation in adults with ADHD using deterministic tractography and graph theoretical analysis. The analyses did not identify deficits in global network properties, but rather suggest localized nodal disturbances in adult ADHD.

Global network metrics

In both groups structural brain networks exhibited small-world properties and groups did not differ in global network metrics. This suggests that global structural brain network organisation is preserved in adult ADHD. It also adds to the evidence that *small-worldness* can survive in psychopathological and neurodevelopmental conditions (Griffa et al., 2013). Although the finding of preserved *small-worldness* in ADHD is in line with Cao and colleagues (2013), the absence of ADHD-related alterations in other global metrics is not. Cao and colleagues (2013) found lower *global efficiency* and greater *path length* in ADHD, while our results did not indicate group differences in those metrics. Moreover, our results contrast with the findings from other graph analyses of brain *function* in ADHD. These indicate that functional brain networks in ADHD are characterized by increases in local and decreases in *global efficiency* (Ahmadlou, Adeli, & Adeli, 2012; Fair et al., 2012; Wang et al., 2009). It is, however, of importance to note that all these studies included children or adolescents with ADHD. In the only equivalent graph analytic study on adult ADHD but using fMRI data Cocchi and colleagues (2012) found that adults with ADHD did not differ from controls in terms of global network

metrics. Taken together with our findings, this suggests more localised and subtle disturbances in adults compared to children. Studies suggest that the maturation of normal brain involves local to distributed trajectory, which is consistent with the idea of delayed network maturation in individuals with ADHD (Dosenbach et al., 2010; Fair et al., 2009). Longitudinal studies are required to examine the potential developmental delay in ADHD.

Local network metrics

We identified widespread ADHD-related differences in *local efficiency* and *clustering*. This is in line with current models where individual mental disorders are increasingly associated with deficits in multiple brain networks (Cao et al., 2013; Cocchi et al., 2012; Cortese et al., 2012; Rubinov & Bassett, 2011; Xia & He, 2011). We observed ADHD-related lower *local efficiency* and *local clustering* in left superior temporal, supramarginal, superior occipital gyri and posterior cerebellum (lobule VI) (Table 1 and Table 2) – areas implicated in attention reorientation and allocation to rare stimuli, motor coordination (Aboitiz et al., 2014; Rubia, Smith, Brammer, & Taylor, 2007; Vaidya, 2012). Additionally, a lower *local clustering* was also identified in right angular gyrus. Our results also indicated greater *local efficiency* and *clustering* in adults with ADHD. These areas included right inferior parietal and superior occipital gyri. Additionally, greater *local clustering* was observed in right inferior frontal gyrus, putamen and thalamus (Table 1 and Table 2), and left inferior parietal gyrus. Generally these areas of disturbed *local efficiency* and/or *local clustering* are commonly found to exhibit functional and structural alterations in ADHD and (e.g., inferior parietal gyrus, angular gyrus, inferior frontal gyrus) relate to neuropsychological impairments (Bush, 2010; van Ewijk et al., 2012). Moreover, previous studies have also shown ADHD-related lower cortical thickness in temporal and parietal areas, and volumetric reductions of posterior cerebellum (Krain & Castellanos, 2006; Proal, Reiss, Klein, Mannuzza, &

Gotimer, 2011). In addition, diffuse white matter alterations in frontal, temporal and parietal areas, involving regions implicated in higher order cognitive and attentional processing, are reported (Cortese et al., 2013; Konrad & Eickhoff, 2010; van Ewijk et al., 2012). Furthermore, functional disturbances of these regions identified by a wide range of task-based (Cortese et al., 2012), and task-free resting state studies (Posner, Park, & Wang, 2014) have been observed in ADHD. In addition Ray and colleagues (2014), suggested that ADHD-related abnormalities involve *rich-club* nodes, encompassing (pre)frontal, anterior (posterior) cingulate, temporal, parietal regions.

Our results point to a tendency for adults with ADHD to exhibit less nodal *efficiency* and *clustering* in the left hemisphere, and greater *efficiency* and *clustering* was predominantly observed in the right hemisphere. This tendency to show less left lateralised nodal *efficiency* has been previously reported by Cao and colleagues (2013) in children with ADHD. Moreover, Wang and colleagues (2009) observed higher *local efficiency* of right inferior frontal gyrus while in the current study we found greater local *clustering* of the same region. In addition, some functional activation studies also provide evidence for a right hemisphere dominance in ADHD (Hale, Zaidel, McGough, Phillips, & McCracken, 2006), while others indicate weaker task-related left-lateralised activation (Kobel et al., 2009; Valera, Faraone, Biederman, Poldrack, & Seidman, 2005). Hence, these findings highlight the potential importance of laterality effects, and are in line with the existing evidence of atypical cerebral asymmetry in ADHD and may indicate abnormal brain development (Giedd, Blumenthal, Molloy, & Castellanos, 2006).

In addition to parietal and occipital areas, greater local network metrics in ADHD also included several subcortical regions such as thalamus and putamen (*local clustering*). Thalamus and putamen (part of striatum) have previously been implicated in ADHD in terms of weaker connections with cortical regions and activation abnormalities (Clerkin et

al., 2013; Kasparek, Theiner, & Filova, 2013; Mills et al., 2012). Those disturbances have been suggested to relate to higher cognitive processes, such as cognitive flexibility, working memory and attentional processes (Kimura, Minamimoto, Matsumoto, & Hori, 2004; van Schouwenburg et al., 2014). Thus, the current findings add to the existing literature by indicating a greater segregation of thalamus and putamen in adults with ADHD.

Limitations

In the current study a deterministic tractography approach was applied to construct structural brain networks (Basser et al., 2000; Mori & van Zijl, 2002). Although, this method is widely used, it has a limited capacity of fibre tracking in the brain regions that comprise so-called "crossing fibres" (Jeurissen, Leemans, Jones, Tournier, & Sijbers, 2011; Tournier, Mori, & Leemans, 2011). This may result in the loss of the existing fibres constituting a network (Gong et al., 2009). Hence, more advanced acquisition methods such as, diffusion spectrum magnetic resonance imaging (DSI) (Wedeen et al., 2008) or high angular resolution diffusion imaging (HARDI) (Hess, Mukherjee, Han, Xu, & Vigneron, 2006; Jeurissen et al., 2011), that allow for the reconstruction of multiple fibre orientations could be considered. However, these methods generally increase the acquisition time significantly and time needed to lie still in the scanner during the acquisition is a crucial limiting factor in clinical populations such as ADHD (Hong et al., 2014). Another limiting factor of deterministic fibre tractography is the uncertainty about the reliability of the reconstructed trajectory, especially in brain areas in close proximity to grey matter (Mukherjee, Berman, Chung, Hess, & Henry, 2008; Prckovska et al., 2013). Thus the probabilistic tractography algorithm, which takes direction-uncertainty into account by producing a distribution of possible directions from a starting point, could be considered in the future (Jones, 2008). Moreover, we did not take into account the

history and duration of stimulant medication use, which may have an effect on brain's microstructural organisation of the ADHD group (Shaw et al., 2009).

Conclusions

Despite these limitations, our results indicate, for the first time, that brain networks in adult ADHD display widespread localised disturbances in regions implicated in cognitive and attentional control but are normal in terms of their global organisation. This contrasts to the global disturbances seen in children with ADHD.

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CHAPTER 6

GENERAL DISCUSSION

Abstract

The main objective of this doctoral dissertation was to examine the neural properties of state-dependent brain networks implicated in attentional processes in order to gain a more in-depth understanding of their potential disruptions which may help to identify cognitive mediators of attention-deficit/hyperactivity disorder (ADHD). In this chapter we provide and integrated overview of the empirical chapters. Then we discuss the potential methodological and clinical implications of the main findings, address the limitations, suggest future research directions, and end with final conclusions.

General Discussion

The general goal of this doctoral dissertation was to broaden our understanding of the potential neural underpinnings of ADHD. The main focus was specifically on brain networks known to regulate/control task-related attentional processes, in terms of early anticipatory neural modulation, intrinsic functional organisation and structural topology. In the current thesis four empirical studies are presented in which we tested the general hypothesis of disturbed anticipatory state-to-state switch-related neural modulation of areas belonging to brain networks implicated in attentional processes, the intrinsic architecture of intra- and inter-functional connectivity of these networks, as well as the organisation of structural whole-brain network in adults with ADHD.

General overview of the results

In *Chapter 2* we developed and validated an experimental task to address a gap in the existing literature to study anticipatory state-to-state switching-related neural activity. With this novel state-switching paradigm we reliably elicited default mode network (DMN) activity in response to rest cues and examined its switch-related modulation. Based on a model of right anterior insula (rAI; a core node of salience network (SN)) as a key hub regulating DMN attenuation and upregulation of task-relevant regions, we also examined the role of rAI during different types of switches. The expected pattern of rest-to-task cue-related DMN attenuation was observed. For the first time it was shown that task-to-rest switches elicit significant upregulation of the DMN. rAI was most responsive to switches from rest-to-task, followed by task-to-task switches while task-to-rest switches did not yield significant rAI activation. Hence, the findings of *Chapter 2* indicated that DMN activity, previously related to prolonged periods of rest, can be elicited by short duration cues that signal rest and is differentially modulated by rest-to-

task and task-to-rest switch anticipation. This suggested that the DMN can reconfigure rapidly in response to external cues signalling new upcoming cognitive states. The findings extend the understanding of the role of rAI in the anticipation of different switch types by implicating it specifically in transitions to active cognitive engagement.

During goal-directed tasks, individuals with ADHD display disruption in brain networks supporting attentional engagement: hyperactivation of the DMN - *DMN interference hypothesis* (Sonuga-Barke & Castellanos, 2007), and hypoactivation of regions controlling task-related attention - task-relevant regions. This can be caused by deficient switching from rest to active goal-directed states i.e., attenuated DMN downregulation and/or upregulation of task-relevant regions, and may relate to dysfunction of rAI (Menon & Uddin, 2010; Sidlauskaite et al., 2014; Sridharan, Levitin, & Menon, 2008). Thus, in *Chapter 3* we tested the hypothesis of impaired rest-to-task switching in adults with ADHD by employing the novel state-switching paradigm (*Chapter 2*). To examine whether rest-to-task switching impairments may be a specific example of a more general state regulation deficit (Metin, Roeyers, Wiersema, van der Meere, & Sonuga-Barke, 2012; Sonuga-Barke, Wiersema, van der Meere, & Roeyers, 2010; Wiersema, van der Meere, Antrop, & Roeyers, 2006), task-to-rest switch-related brain activation was also analysed. The results provided initial evidence for deficient DMN upregulation during task-to-rest switching, while rest-to-task switching in terms of DMN attenuation seemed to be intact in ADHD. The findings also suggested diminished upregulation of task-relevant areas switching from rest-to-task. Thus, diminished task-to-rest DMN upregulation combined with attenuated rest-to-task upregulation of task-relevant regions indicated a putative deficit in anticipatory "switching on" rather than "switching off" of the brain areas required for future states. rAI function, although generally reduced, appeared not to be related to the switching impairments.

It has been proposed that the intrinsic task-free brain organisation sculpts task-related neural processes (Bressler & Menon, 2010), and that ADHD may represent a disorder caused by underlying alterations in brain organisation (Cortese et al., 2012; Menon, 2011). Therefore, in *Chapter 4* we examined the hypothesis that abnormalities in the intrinsic organization of brain networks implicated in attentional processes - the DMN, attention networks and the SN - may be central to the pathophysiology of ADHD. We employed resting state network-based functional connectivity approaches that allowed us to study both - connectivity within and between the specific brain networks (Schultz et al., 2014; Shenton, Kubicki, & Makris, 2014). Individuals with ADHD exhibited hyperconnectivity within and between attention networks and within the DMN. The SN was hyperconnected to the ventral attention network (VAN), but hypoconnected to the dorsal attention network (DAN). The results provided additional evidence of disturbed intrinsic brain organisation in ADHD. Crucially, they highlighted the imbalance within the attention system in individuals with ADHD revealed by altered connectivity within attention networks and between them and the SN.

In *Chapter 5,* we further investigated the organisation of brain networks in adults with ADHD using dMRI data. Employing a deterministic tractography and theoretical graph analysis approach we examined the structural brain network organisation. Our findings provide the first evidence of structural brain network organisation alterations in adults with ADHD. In contrast to the existing graph-theoretical analysis studies in children with ADHD, we did not find alterations of global graph metrics. Our results suggested more subtle and localized nodal disturbances related to adult ADHD rather than general structural brain network dysconnectivity, possibly reflecting a developmental delay.

Integration of the findings

DMN interference hypothesis

According to the *DMN interference hypothesis*, one possible explanation of excess task-related DMN is an abnormal rest-to-task switch-related neural modulation. In this way, the inefficiently attenuated DMN activity persists into task-related processing and interferes with neural activity of task-relevant networks causing performance deficits (e.g., lapses of attention, errors, response time variability) (Sonuga-Barke & Castellanos, 2007). Contrary to our predictions, the findings of *Chapter* 3 did not indicate an attenuated DMN downregualtion during rest-to-task switching in individuals with ADHD. It appears that the DMN in people with ADHD is as responsive to rest-to-task switches as it is in healthy controls, and can be rapidly attenuated when a change in cognitive state is anticipated. Thus, the excess task-related DMN activity, reported by previous studies (Fassbender et al., 2009; Helps et al., 2010; Liddle et al., 2011; Peterson et al., 2009), appears unrelated to DMN modulation during switching from rest to task states, and it seems that individuals with ADHD are able to successfully disengage from rest by attenuating the DMN upon rest-to-task switches. However, it could be that, despite the successful initial DMN downregulation when switching from rest-to-task, individuals with ADHD are more vulnerable to the emergence of DMN later during tasks. This would suggest that individuals with ADHD are less able to maintain the levels of initial DMN attenuation, which may be a result of the combination of situational factors (e.g., long and boring tasks, fatigue, diminished motivation) and specific individual characteristics (e.g., disturbed intrinsic functional and/or structural brain organisation, deficient state regulation) (Sonuga-Barke & Castellanos, 2007). The increase in DMN activity with time spent on task and resultant failures in efficient cognitive and attentional control have

already been shown in individuals with traumatic brain injury (Bonnelle et al., 2011). However, the effects of task duration on the levels of DMN re-emergence have not yet been investigated in ADHD, and thus this aspect needs to be addressed in future research.

A potential deficit in "switching-on" future state-dependent brain regions

Although we did not observe ADHD-related disturbances in DMN attenuation to cues indicating future rest-to-task switches, interestingly, the findings of *Chapter 3* indicated a tendency for individuals with ADHD to upregulate task-relevant regions to a lower degree than controls to such cues. Previous cognitive control studies have established the importance of anticipatory neural preparation, in terms of pre-activation of task-relevant areas, to efficient task performance (Gruber, Karch, Schlueter, Falkai, & Goschke, 2006; Wylie, Javitt, & Foxe, 2006). In addition, our results are not only in line with the existing literature indicating ADHD-related attenuated activation in task-relevant areas during cued tasks (Clerkin et al., 2013; Cubillo, Halari, Smith, Taylor, & Rubia, 2012), they also highlight potential anticipatory and preparatory attention deficits in ADHD. Previous research has provided evidence for weaker ADHD-related preparatory engagement of future task-relevant brain regions. Moreover, potential links between deficient task preparation, rather than response execution, and performance decrements have been suggested (Brunia & van Boxtel, 2001; Hakvoort Schwerdtfeger et al., 2012; Johnstone & Clarke, 2009; Kenemans et al., 2005; King, Colla, Brass, Heuser, & von Cramon, 2007; Nagai et al., 2004). Moreover, the results of *Chapter 3* not only add to those suggesting deficient anticipatory task preparation in ADHD, but crucially, they indicate reduced neural preparation also for rest in terms of lower DMN upregulation upon task-to-rest switches. Importantly, this broadens the scope of anticipatory preparation, traditionally centred around switches to task-related processing (King et al., 2007; Perchet, Revol, Fourneret, Mauguière, & Garcia-Larrea, 2001), to involve

transitions to a rest state. In terms of ADHD, this suggests abnormalities encompassing both directions of state switches (i.e., rest-to-task and task-to-rest) and adds to the evidence of state regulation deficits in ADHD (Metin et al., 2012; Sonuga-Barke et al., 2010; van der Meere, Shalev, Börger, & Wiersema, 2009; Wiersema et al., 2006). Moreover, the unaffected downregulation of the DMN and task-relevant regions, but attenuated upregulation of the DMN and the same tendencies in task-relevant areas upon relevant state switches, suggest a difficulty in individuals with ADHD to "switch-on" future state-dependent brain networks. This implies that individuals with ADHD may exhibit deficits in future state engagement, rather than in the disengagement from the current state.

Intrinsic functional brain organisation

The human brain previously seen as a system operating on the basis of the classic feed-forward information processing principle, is now understood as actively enabling the emergence of specific context-dependent elements of cognition and behaviour (Deco & Corbetta, 2011; Varela, Lachaux, Rodriguez, & Martinerie, 2001). It is now known that ongoing spontaneous local activity fluctuations and the intrinsic functional organisation of neural networks affect information processing in the brain (Bressler & Menon, 2010). Thus, *Chapter 4* was based on the hypothesis, that abnormalities of the intrinsic organisation of brain networks implicated in attentional control processes, may be central in ADHD pathophysiology (Menon, 2011). Recently the DMN has been strongly linked to attentional control processes. Moreover, the model of the SN, as a between state-dependent network switching hub, has primarily implicated DMN attenuation and upregulation of task-relevant attention networks (Menon & Uddin, 2010). However, the findings of *Chapter 4* did not indicate the expected abnormalities in SN-DMN connectivity in ADHD. Instead, a new potential locus of inter-network connectivity

alteration was observed - an ADHD-related imbalance of the SN and attention networks. The attention system, comprised of the VAN and DAN, exhibits strong functional differentiation between its components, but coordinated interplay of them is needed for coherent attentional processes (Fox, Corbetta, Snyder, Vincent, & Raichle, 2006). Hence, the increased inter DAN-VAN connectivity suggests that the two attentional system components are less functionally distinct in ADHD, which may have important implications. The DAN controls voluntary top-down allocation of goal-directed attention, while the VAN governs stimulus-driven attention by detecting unexpected but task-related stimuli (Corbetta, Patel, & Shulman, 2008; Corbetta & Shulman, 2002). Thus, a hyperconnected DAN-VAN system may alter the threshold of information transfer, so that VAN activity more frequently interrupts goal-driven DAN processing. This is in line with the emerging literature implicating the VAN in ADHD as a source of deficits in effective modulation of behaviour when switching attention to salient environmental stimuli, which results in increased distractibility (Aboitiz, Ossandón, Zamorano, Palma, & Carrasco, 2014; Cortese et al., 2012; Helenius, Laasonen, Hokkanen, Paetau, & Niemivirta, 2011; Sripada et al., 2014). Moreover, the finding of an imbalance between the attention networks and the SN highlights the functional specificity of the DAN and VAN, and adds to the evidence relating VAN alterations to distractibility. Namely, the tendency towards VAN-SN hyperconnectivity suggests that the saliency threshold may be altered in ADHD. In this way, the VAN becomes easily triggered by external stimuli blurring the relevance attribution and thus interrupting the DAN as suggested by the hyperconnection between the DAN and VAN. Importantly, the intrinsic functional brain architecture is believed to confine task-related neural activations (Deco & Corbetta, 2011; Greicius & Menon, 2004; Sadaghiani, Hesselmann, Friston, & Kleinschmidt, 2010; Seeley et al., 2007). Thus, although direct parallels cannot be drawn between the findings of *Chapter 3* and *4*,

nevertheless, they suggest that the alterations of intrinsic functional brain organisation in ADHD may bias task-related information processing and associated neural modulation. Importantly, the tendencies towards attenuated anticipatory engagement of future state-dependent brain regions in *Chapter 3* could relate to intrinsic coupling alterations of SN and attention networks (*Chapter 4*). For instance, one could speculate that, altered saliency processing and the oversensitivity of the VAN may result in an increased frequency of signals that interrupt the DAN, but decrease the task-relevant signal intensity, so that when the actual behavioural change needs to occur (e.g., engagement of state-dependent brain regions) the VAN circuit braking function is attenuated. Hence, intrinsic brain connectivity may represent a basis for neural modulation during different cognitive states, combining different neural circuits to adequately co-ordinate behaviour (Deco & Corbetta, 2011).

Structural brain network organisation

Both task-related neural responses and the intrinsic functional brain organisation necessarily involve anatomical connections between brain regions, and evidence suggest, that to a large extent, functional dynamics can be traced back to structural brain properties (Damoiseaux & Greicius, 2009; Deco & Corbetta, 2011; Honey, Thivierge, & Sporns, 2010). In *Chapter 5*, we adopted a network perspective to investigate the structural brain organisation employing deterministic tractography and graph theory. To the best of our knowledge, this was the first study examining structural brain topography in adults with ADHD. Building on the few existing graph analytic studies in children with ADHD (Ahmadlou, Adeli, & Adeli, 2012; Cao et al., 2013; Fair et al., 2010; Ray et al., 2014; Wang et al., 2009) and previous evidence of functional and structural brain alterations (Cao, Shu, Cao, Wang, & He, 2014; Konrad & Eickhoff, 2010; van Ewijk, Heslenfeld, Zwiers, Buitelaar, & Oosterlaan, 2012; Weyandt, Swentosky, & Gudmundsdottir, 2013),

we expected the brain network organisation in adults with ADHD to be altered at a global and local level. In fact, our data revealed widespread ADHD-related *local clustering* and *efficiency* disturbances in regions implicated in cognitive and attentional control, which adds to the existing evidence that these areas are disturbed in ADHD (Bush, 2010; Castellanos & Proal, 2012; Cortese et al., 2012, 2013; Posner, Park, & Wang, 2014). Crucially, in contrast to our prediction, we did not observe adult ADHD-related global structural graph metric abnormalities (Cao et al., 2013). Interestingly, in the only existing graph analysis study on adults with ADHD, but using fMRI data, Cocchi and colleagues (2012) did not observe group differences in global network metrics either. This combined with our findings of *Chapter 5* suggests that adult ADHD relates to more subtle nodal-level structural network disturbances, as opposed to both local and global network organisation abnormalities in children with ADHD. Typical human brain maturation follows a local-to-distributed development of organisation for both functional and structural brain networks (Dosenbach et al., 2010; Fair et al., 2009; Hagmann et al., 2010; Huang et al., 2013). Thus, the findings of global network organisation disturbances in children, combined with our adult ADHD findings of *Chapter 5*, are consistent with an idea of a delayed brain network organisation development in ADHD (Fair et al., 2010). However, further longitudinal studies are necessary to provide support for this notion.

Synthesis of the main findings

The prime objective of this doctoral dissertation was to establish a better understanding of neural systems implicated in attentional processes and their potential ADHD-related abnormalities (see Table 1 for the summary of main findings). We started with employing a novel state-to-state switching task (*Chapter 2*) to examine the rest-to-task switching-related DMN modulation as a potential basis for DMN persistence into and interference during tasks in individuals with ADHD (*DMN interference hypothesis*;

Sonuga-Barke & Castellanos, 2007). However, we neither found lower rest-to-task related DMN attenuation (*Chapter 3*), nor an intrinsic DMN-SN connectivity disturbance (*Chapter 4*), which based on the SN model as between network switching hub (Menon and Uddin, 2010), could suggest difficulties in DMN modulation when switching to cognitive engagement (*Chapter 2*). Hence, the current findings do not support the idea of ADHD as a "DMN disorder" and add to the evidence emphasizing the situational context of neural disturbances. For instance, it could be that despite the successful attenuation upon rest-to-task switches, DMN activity re-emerges during prolonged periods of tasks due to a combination of the effects of situational and neural factors (Sonuga-Barke & Castellanos, 2007). Some putative suggestions of potential failures to maintain an adequate cognitive state through effortful control during suboptimal task states (e.g., slow, long, boring) comes from *Chapter 5*. We observed increased local clustering of the right thalamus in individuals with ADHD. Interestingly, the thalamus has been implicated in the regulation of cognitive states by previous research (Kimura, Minamimoto, Matsumoto, & Hori, 2004; Llinás & Steriade, 2006; van Schouwenburg et al., 2014) and found to be disturbed in ADHD, which may be related to deficient state-dependent neural coordination (Clerkin et al., 2013; Kasparek, Theiner, & Filova, 2013; Kooistra et al., 2010). Moreover, a tendency for an attenuated upregulation of task-relevant regions and DMN upon switches to task and rest respectively, observed in *Chapter 3*, suggested a potential anticipatory difficulty in "switching-on" rather than "switching-off" future state-dependent brain networks in ADHD. Crucially, this may relate to the intrinsic functional brain organisation alteration observed in *Chapter 4*. Namely, the imbalance of SN and attention networks may predispose individuals with ADHD for a higher susceptibility to distraction by salient, but task-irrelevant stimuli, which could potentially be reflected in difficulties of neural anticipatory engagement seen in *Chapter 3*. Despite the fact that the

findings from the empirical chapters in the current dissertation cannot be directly compared, it can be speculated that the specific local structural abnormalities observed in *Chapter 5* (e.g., thalamus) may relate to the functional brain network coordination abnormalities described in *Chapter 3* and *4*, and this is a crucial question to be addressed in future studies.

Methodological and Clinical Implications

Traditionally, the DMN has been investigated during sustained periods of rest or task, hence, as an end result of a state-to-state transition (Buckner, Andrews-Hanna, & Schacter, 2008). However, the understanding of the neural processes during these transitions has been lacking. In *Chapter 2* we developed and validated a novel experimental task, suitable for reliable examination of neural modulation in terms of DMN, task-relevant regions and SN, during state-to-state transitions. Importantly, this paradigm extends the classical task-switching paradigm by inclusion of rest trials and, hence, enables the investigation of state anticipatory neural processes (i.e. task- and rest-related). In *Chapter 3* we applied this task to individuals with ADHD and found a potential deficit in future state-dependent brain network engagement, which added to the existing evidence of state regulation deficits in ADHD (Metin et al., 2012; Sonuga-Barke et al., 2010). Moreover, the finding of difficulty in "switching-on" future state-dependent brain networks suggest an extension of existing anticipatory training schemes, based on slow cortical potentials (e.g., anticipation-related contingent negative variation), to include not only tasks requiring cognitive engagement, but also rest anticipation (Heinrich et al., 2014; Mayer, Wyckoff, & Strehl, 2013). In addition, the state-switching paradigm, targeting the anticipatory neural modulation during state-to-state switching, can help reveal the neural underpinnings of other psychopathological conditions as well. The

findings of *Chapter 4* and *Chapter 5* have several important implications. First, they bring forward the importance of connectomics approaches in the study of psychopathological conditions in general and specifically ADHD. This approach focuses on the notion that even the smallest and simplest of tasks involves the coordination of multiple brain regions from different brain networks (Griffa, Baumann, Thiran, & Hagmann, 2013; Shenton et al., 2014; Smith et al., 2013). Second, they point to the relevance of studying the relationship between structural and functional brain connectivity, which may not be straightforward, but will help to evaluate the causality between structural white matter alterations and functional disturbances, as well as their effects on developmental trajectory (Damoiseaux & Greicius, 2009; Hagmann et al., 2010; Huang et al., 2013; Konrad & Eickhoff, 2010). Furthermore, the potential imbalance between SN and attention networks observed in *Chapter 4,* may introduce a novel target for the existing psychological intervention strategies.

Limitations

There are several limitations of the current doctoral dissertation that need to be recognised. First, in *Chapter 2* and *Chapter 3* we used a state-switching task to study anticipatory neural modulation of state-dependent brain networks. While this task provided important inferences and extended the classical task-switching paradigm, the inclusion of rest trials to the cued task-switching experimental design was challenging. The major constraint regarding rest trials was the temporal differentiation between the anticipatory period-related neural response, and the actual initiation of rest phase and the related brain activation. In task trials the anticipatory phase and actual task initiation was separated with the appearance of a target, however, rest trials were lacking that. Thus, we cannot be sure that rest anticipatory period did not involve any of the neural activity

related to rest initiation, and future research should attempt to more reliably single out the anticipatory phase for a state with no direct state initiation indication.

Second, it is known that fMRI suffers for an inherently low temporal resolution as opposed to its high spatial resolution. Generally the switch anticipatory phase is very time-constrained. As a result, the related neural processes have to occur very rapidly, and fMRI might not capture all the temporal aspects of anticipatory neural modulation. Therefore, combining fMRI and electroencephalography (EEG), which has an excellent temporal resolution, should be considered in order to increase our understanding of these time scale sensitive neural events.

Third, the connectivity results of both *Chapter 4* and *Chapter 5* are highly dependent on the brain parcellation scheme used to define the brain network nodes. Despite the fact that the atlas employed for node definition in both chapters is widely used across other brain connectivity studies (Bassett & Bullmore, 2009; Griffa et al., 2013; Smith et al., 2013), this brings forward the importance of investigating and developing reliable and representative brain parcellation templates (Schultz et al., 2014).

Fourth, the deterministic tractography algorithm, applied in *Chapter 5*, suffers from a limited capacity to account for the fibre directionality, which may result in the loss of the existing fibres constituting a network (Gong et al., 2009; Tournier, Mori, & Leemans, 2011). Therefore, more advanced acquisition methods such as, diffusion spectrum magnetic resonance imaging (DSI) (Wedeen et al., 2008) or high angular resolution diffusion imaging (HARDI) (Hess, Mukherjee, Han, Xu, & Vigneron, 2006), that enable the reconstruction of multiple fibre orientations should be considered. However, the drawback of these methods is that they increase the acquisition time, which is a crucial limiting factor in clinical populations like ADHD (Hong et al., 2014).

Fifth, the history and duration of stimulant and other psychoactive medication use, across all studies, was not taken into account. However, there exists evidence that psychoactive medication use may exert differential effects on both functional and structural brain organisation, which may have influenced our results (Shaw et al., 2009; Spencer et al., 2013).

Sixth, our ADHD group represents a community-based, well-functioning sample, which is known to be related to less severe symptom expression and impairment as compared to clinic-based ADHD groups (Brassett-Harknett & Butler, 2007), and which could have mediated our results. Moreover, the considerable overlap among the participant samples across all studies may limit the generalizability of the findings.

Future Research

The empirical chapters presented in the current dissertation led to important results, which raised several relevant questions and opened new potential avenues for future research.

In contrast to our prediction, DMN attenuation during rest-to-task switching appeared to be intact (*Chapter 3*), and thus, what can explain the excess levels of DMN activity during tasks in ADHD remains to be established. One possibility is that after a successful switch-related DMN attenuation, individuals with ADHD are more susceptible to the failures of keeping DMN suppressed during the periods of prolonged tasks, and DMN activity re-emerges over time interfering with performance. Hence, it is important that future studies investigate this hypothesis by employing experimental designs involving longer task blocks enabling the examination of DMN suppression over time. The crucial finding in *Chapter 3* was the potential difficulty for individuals with ADHD to "switch-on" rather than "switch-off" future state-dependent brain networks. Due to the

fact that some of the effects were only trend-like statistically, future research is required to elucidate the neural processes involved in the anticipatory engagement of future state-dependent brain networks. This could be done by employing a refined version of state-switching task. Such a task should include only state-to-state switches, excluding task-switches, which would increase the power to study state switch-dependent neural modulation. Another important question to be answered by future research is about the generalizability of ADHD-related deficit in anticipatory neural response. More specifically, we observed tendencies for diminished upregulation of the anticipated state related brain networks. However, what is unclear is whether this deficit is state specific, or could indicate broader, more general abnormalities in overall anticipatory processing in ADHD. Furthermore, in *Chapter 4*, from the intrinsic functional brain network organisation perspective, we observed a new potential deficit in ADHD - an imbalance between SN and attention networks. The hypothesis, which could be tested in future studies is that individuals with ADHD may be affected by this imbalance resulting in inattentiveness and distractibility. Moreover, a potential delayed developmental effect for structural brain network organisation, suggested in *Chapter 5*, requires further longitudinal studies. Finally, probably the most important and challenging implication for future research is the development of reliable methods to combine the study of task-related cognitive processes, intrinsic functional brain network organisation, as well as structural brain architecture in a way that direct parallels could be drawn between different results. This would promise an invaluable tool for in-depth understanding of the development and course not only of ADHD, but also other disorders, in terms of their neural underpinnings.

Conclusion

The main goal of the current doctoral dissertation was to study the neural properties of state-dependent brain networks implicated in attention processes and gain a better understanding of their potential disruptions that may help explain ADHD-related deficits. We investigated the neural properties of brain network engagement and disengagement when individuals were switching between rest and task states, the intrinsic functional organisation of within and between state-dependent networks, and structural brain network architecture based on graph metrics. Our results did not indicate a deficit in DMN attenuation upon rest-to-task switches and instead the findings revealed a potential ADHD-related deficit in the anticipatory engagement of future state-dependent brain networks. The study of intrinsic functional brain network organisation revealed an imbalance between SN and attention networks - a new potential locus for ADHD-related deficits of inattention and distractibility. Furthermore, the structural brain network organisation was found to be affected on the widespread nodal level, but not in terms of global network metrics. The absence of a global network disturbance in adults with ADHD contrasts the findings from child ADHD studies and suggests a potential delay in structural brain network organisation development. In summary, in the current dissertation we provided important additional evidence for different functional and structural neural disturbances in ADHD applying task- and rest-based fMRI, as well as dMRI. Our findings not only provide relevant implications for ADHD pathophysiology, but also offer new and promising future research avenues.

Table 1. The summary of the main findings.

Study	Study type	Objective	Main findings
Brain state switching (*Chapter2*)	fMRI, task-based activation, ROI	Validation of the state-to-state switching task; anticipatory DMN and SN modulation during state-to-state switching	DMN is responsive to brief rest cues and is differentially modulated by rest-to-task (attenuated) and task-to-rest (upregulated) switch anticipation; rAI (core node of SN) is the most responsive to switches to cognitive engagement, primarily rest-to-task
Brain state switching in ADHD (*Chapter 3*)	fMRI, task-based activation, ROI	DMN persistence into tasks due to faulty rest-to-task switching; DMN, task-relevant regions and SN modulation during state-to-state switching	DMN attenuation is intact upon rest-to-task switches in ADHD, but deficient upregulation of task-relevant regions. Task-relevant regions' attenuation is intact upon task-to-rest cues, but reduced DMN upregulation; rAI seems unrelated to switching deficits in ADHD.
Functional brain network organisation in ADHD (*Chapter 4*)	fMRI, resting state functional connectivity, network approach, ROI	Intrinsic organisation of DMN, SN and attention networks (DAN, VAN)	Hyper- DMN, DAN and VAN intra connectivity in ADHD; Hyper- VAN-SN, DAN-VAN connectivity and hypo- DAN-SN; intact DMN-DAN, DMN-VAN, DMN-SN and within SN connectivity
Structural whole-brain network organisation in ADHD (*Chapter 5*)	dMRI, deterministic tractography, graph-theoretic analysis	Structural global and local brain network organisation	Local disturbances of network metrics in regions underpinning ADHD-related neuropsychological deficits; No global adult ADHD-related network metric disturbance

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NEDERLANDSTALIGE SAMENVATTING

"Attention-deficit/hyperactivity disorder" (ADHD), in het Nederlands "aandachtsdeficiëntie-/hyperactiviteitsstoornis", is een veel voorkomende aandoening met aanvang in de kindertijd, die gekenmerkt wordt door leeftijdsinadequate niveaus van aandachtstekort en/of hyperactiviteit, en die vaak aanhoudt tot in de volwassenheid en een ernstige invloed heeft op werkprestaties en –vaardigheden, en sociaal functioneren (Diagnostic and Statistical Manual of Mental Disorders (DSM-5), American Psychiatric Association (APA), 2013). De erfelijkheidsramingen van ADHD zijn ongeveer 76%, waardoor het één van de meest erfelijke neurobiologische aandoeningen wereldwijd is (Faraone et al., 2005). Bijgevolg blijken genetische factoren een belangrijke rol te spelen in de ontwikkeling en het verloop van ADHD (Cortese et al., 2012). Bovendien kunnen verschillende omgevingsfactoren, zoals prenatale maternale stress en angst, en prenataal gebruik van alcohol, nicotine en/of illegale drugs door de moeder ook het risico op het ontwikkelen van ADHD verhogen. Andere negatieve factoren zijn vroeggeboorte, een laag geboortegewicht, milieu-toxines, slechte voeding, kinderziekten, en algemene psychosociale tegenspoed (Cortese et al., 2012; Thapar, Cooper, Jefferies & Stergiakouli, 2012).

Er bestaan verschillende neuropsychologische verklaringsmodellen van ADHD. De Executieve disfunctie theorie van ADHD (Barkley, 1997), suggereert dat er bij ADHD sprake is van een tekort in executief functioneren, dat gekenmerkt wordt door abnormale controle van inhibitie. Volgens de *Delay aversion theory*, zijn ADHD-gerelateerde tekorten veroorzaakt door een afkeer voor wachten, voortkomend uit een verstoord signaleren van beloningen (Sonuga-Barke, Taylor, Sembi, & Smith, 1992). De voorkeur voor onmiddellijke beloningen boven uitgestelde komt sterker tot uiting bij

ADHD, wat een impulsieve drang creëert om te kiezen voor onmiddellijke beloningen in tegenstelling tot uitgestelde. Dit maakt personen met ADHD vatbaar om minder tijd en moeite toe te wijzen aan lange en vervelende taken en verhoogt de neiging om uitstel te vermijden of te ontvluchten (Sonuga-Barke, Wiersema, van der Meere, & Roeyers, 2010).

De *state regulation deficit theory* (Sergeant, 2005; van der Meere, 2005), gebaseerd op het cognitief-energetisch model van Sanders (1983), stelt dat mensen met ADHD moeite hebben met het reguleren van hun energetische toestand door het toewijzen van extra effort in het geval van een suboptimale toestand. Alhoewel deze neuropsychologische verklaringsmodellen belangrijke inzichten verschaffen, is geen enkel model volledig succesvol in het verklaren van het volledige spectrum van ADHD-gerelateerde tekorten. Vandaar wordt ADHD tegenwoordig beschouwd als een aandoening met meerdere causale ontwikkelingspaden (Sonuga-Barke, Bitsakou, & Thompson, 2010).

Recent is er een toename in het onderzoek naar de neurobiologische basis van ADHD (Bush, 2010; Cortese et al., 2012; Van Ewijk, Heslenfeld, Zwiers, Buitelaar, & Oosterlaan, 2012) en dit is de centrale focus van het huidige proefschrift.

ADHD Neurobiologie: van enkele gebieden tot hoe hersennetwerken zijn georganiseerd

Taak-gebaseerde fMRI studies bij ADHD onthulden afwijkingen in verscheidene taak-specifieke regionale hersenactiviteit. Onlangs heeft een paradigmaverschuiving in de neurowetenschappen het concept geïntroduceerd van hersennetwerken. Dit concept beklemtoont de coöperatieve functies van hersengebieden, die in tandem actief zijn als gecoördineerde grootschalige neurale circuits (Bressler & Menon, 2010). Regionale

afwijkingen in ADHD maken onderdeel uit van verschillende robuuste hersennetwerken (Bush, 2010; Cortese et al., 2012). Niet verwonderlijk, hebben traditionele verklaringsmodellen zich vooral gefocust op veranderingen in het aandachtssysteem (Cubillo, Halari, Smith, Taylor, & Rubia, 2012). De recente belangstelling in functionele eigenschappen tijdens een taakvrije toestand of toestand in rust heeft het belang van het taak-onafhankelijke default mode network (DMN) in aandachtsprocessen geïntroduceerd (Raichle et al., 2001). Het DMN bestaat onder andere uit de mediale prefrontale en posterieur cingulate cortex (mPFC; PCC)/precuneus (Buckner, Andrews-Hanna, & Schacter, 2008). De activiteit van deze gebieden neemt toe tijdens periodes van rust of tijdens intern-gerichte, zelf-referentiële verwerking en wordt verzwakt ten gevolge van de omschakeling naar extern gerichte, doelgerichte cognitieve taken (Gerlach, Spreng, Gilmore, & Schacter, 2011; Singh & Fawcett, 2008; Spreng & Grady, 2010). Extern georiënteerde aandachtsprocessen vereisen de gecoördineerde demping van het DMN en opwaartse regulatie van taakgerelateerde aandachtsnetwerken (Lawrence, Ross, Hoffmann, Garavan, & Stein, 2003; Sonuga-Barke & Castellanos, 2007), en verminderde taakprestaties hangen samen met overtollig taakgerelateerde DMN activiteit (Fassbender et al., 2009; Li Yan, Bergquist, & Sinha, 2007; Weissman, Roberts, Visscher, & Woldorff, 2006).

De DMN-interferentie-hypothese stelt dat onder bepaalde suboptimale omstandigheden (bijvoorbeeld bij personen met ADHD), DMN-activiteit kan aanhouden of opnieuw opleven tijdens periodes van extern georiënteerde taakgerelateerde verwerking en interfereren met neurale activiteit in taakrelevante regio's waardoor de prestaties afnemen (Sonuga-Barke & Castellanos, 2007). Daarom zouden veranderingen in DMN één van de vermeende causale paden kunnen vertegenwoordigen die verbonden zijn met ADHD, wat een cruciale vraag oproept over de mogelijke rol van DMN-

inmenging in de pathofysiologie van ADHD (Sonuga-Barke & Castellanos, 2007). Deze vraag proberen we te beantwoorden in dit proefschrift.

Menon en Uddin (2010) stellen dat het saillantie-netwerk (SN), bestaande uit de anterior cingulate cortex (ACC) en insula (specifiek rechts anterior insula (rAI)), werkt als een centrale schakelhub die de opwaartse regulatie van taakrelevante aandachtsnetwerken en demping van het DMN coördineert. Bijgevolg zou ADHD een aandoening kunnen vertegenwoordigen die gekenmerkt wordt door problemen in het koppelen en ontkoppelen van toestand-afhankelijke hersennetwerken, wat vooral van belang is bij het omschakelen tussen verschillende cognitieve toestanden, (d.w.z., rust- en taaktoestanden). Derhalve zou het kunnen dat storingen in de functionele organisatie van hersennetwerkern onderliggend is aan de ADHD-problematiek (Menon, 2011; Cortese et al., 2012), waarbij de belangrijkste verstoring zich bevindt in de abnormale coördinatie van het DMN en de aandachtsnetwerken, gecontroleerd door het SN (Aboitiz, Ossandón, Zamorano, Palma & Carrasco, 2014).

Diffusie-MRI (dMRI), dat het onderzoek van microstructurele eigenschappen en verbindingen binnen het levende brein mogelijk maakt (Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000; O'Donnell & Pasternak, 2014), heeft bewijs gevonden voor structurele afwijkingen in het ADHD-brein, die betrekking kunnen hebben op functionele tekorten (Van Ewijk et al., 2012; Weyandt, Swentosky, & Gudmundsdottir, 2013). Onlangs is gebruik gemaakt van de grafentheorie-analyse om onderzoek te doen naar de organisatie van structurele hersennetwerken bij kinderen met ADHD (Cao et al., 2013; Ray et al., 2014.). In dit proefschrift onderzoeken we de structurele hersennetwerkmetrieken bij volwassenen met ADHD.

Het doel van het proefschrift en de samenvatting van de bevindingen

Het doel van het huidige proefschrift was om de neurale eigenschappen van toestands-afhankelijke hersennetwerken die betrokken zijn bij aandachtsprocessen bij volwassenen met ADHD te onderzoeken. Wij onderzochten de neurale modulerende eigenschappen van de koppeling en ontkoppeling van hersennetwerken tijdens de transities tussen verschillende cognitieve toestanden, de intrinsieke functionele intra- en inter-toestands-afhankelijke netwerkorganisatie, en de grafenmetriek van structurele hersennetwerken bij volwassenen met ADHD.

In hoofdstuk 2 hebben wij een experimentele taak ontwikkeld en gevalideerd om een hiaat in de bestaande literatuur aan te pakken om de aan anticiperende toestand-tot-toestand omschakeling gerelateerde neurale activiteit te bestuderen. Met dit nieuwe toestandsomschakeling-paradigma hebben wij op een betrouwbare wijze DMN activiteit uitgelokt in reactie op rustsignalen en onderzochten we de schakel-gerelateerde modulatie van DMN activiteit Gebaseerd op een model van de rAI (een centraal knooppunt van het SN) als een belangrijk knooppunt dat DMN-demping en opwaartse regulatie van taakrelevante gebieden regelt, hebben wij ook de rol van de rAI onderzocht gedurende verschillende soorten omschakelingen. Rust-naar-taak cue-gerelateerde DMN-demping werd waargenomen. Voor het eerst werd aangetoond dat taak-naar-rust omschakelingen het DMN opwaarts reguleren. rAI was het meest responsief bij omschakelingen van rust naar taak. De bevindingen gaven aan dat DMN-activiteit kan worden uitgelokt door rustsignalen van korte duur en differentieel gemoduleerd wordt door rust-naar-taak en taak-naar-rust anticipatie van omschakeling. Daarom kan het DMN snel herconfigureren als reactie op externe signalen die nieuwe opkomende cognitieve toestanden signaleren. Bovendien werd het begrip van de rol van de rAI in het anticiperen van verschillende types van omschakeling uitgebreid door de

betrokkenheid van de rAI specifiek in de omschakeling naar actieve cognitieve betrokkenheid.

In hoofdstuk 3 hebben we de hypothese getoetst van verstoorde rust-naar-taak omschakeling, als een mogelijke oorzaak van DMN-persistentie in en interferentie met de taakuitvoering, in ADHD door het gebruik van het toestandsomschakelingsparadigma. Om te onderzoeken of verstoringen in het omschakelen van rust naar taak een specifiek voorbeeld is van een meer algemeen tekort in toestandsregulering (Metin, Roeyers, Wiersema, van der Meere & Sonuga-Barke, 2012; Sonuga-Barke et al., 2010; Wiersema, van der Meere, Antrop, & Roeyers, 2006), werd ook omschakelings-gerelateerde hersenactiviteit ten gevolge van taak-naar-rust geanalyseerd. We vonden evidentie voor gebrekkige opwaartse regulatie van het DMN tijdens de omschakeling van taak-naar-rust, terwijl de omschakeling van rust-naar-taak qua DMN-demping intact was bij ADHD. Bovendien werd een neiging tot verminderde opwaartse regulatie van taakrelevante gebieden bij het omschakelen van rust-naar-taak gesuggereerd. Dus, verminderde taak-naar-rust opwaartse regulatie van het DMN, gecombineerd met verminderde rust-naar-taak opwaartse regulatie van taakrelevante gebieden geven een mogelijk tekort aan in het anticiperend "inschakelen" in plaats van "uitschakelen" van hersengebieden die nodig zijn voor toekomstige toestanden. De problemen met omschakelen bij volwassenen met ADHD konden niet gerelateerd worden aan een verstoorde rAI-functie, de rAI activatie was in het algemeen verminderd.

In hoofdstuk 4 toetsten we de hypothese dat afwijkingen in de intrinsieke organisatie van hersennetwerken, die betrokken zijn bij aandachtsprocessen, centraal betrokken zijn in de pathofysiologie van ADHD. Resting state netwerk-gebaseerde functionele-connectiviteitbenaderingen werden toegepast (Schultz et al., 2014; Shenton,

Kubicki, & Makris, 2014). Personen met ADHD vertoonden hyperconnectiviteit binnen en tussen aandachtsnetwerken en binnen de DMN. Bij volwassenen met ADHD was het SN sterker verbonden met het ventrale aandachtsnetwerk (VAN), maar minder sterk met het dorsale aandachtsnetwerk (DAN) dan bij typisch ontwikkelde volwassenen. De resultaten gaven aanvullende evidentie voor verstoorde intrinsieke hersenorganisatie bij ADHD. Bovendien benadrukten de resultaten een disbalans binnen het aandachtssysteem bij personen met ADHD, gekenmerkt door veranderde connectiviteit binnen aandachtsnetwerken zelf en tussen de aandachtsnetwerken en het SN.

In hoofdstuk 5 hebben we verder onderzoek gedaan naar de organisatie van hersennetwerken bij volwassenen met ADHD met behulp van dMRI data. Gebruikmakend van een deterministische tractografie en theoretische grafenanalyse-aanpak, onderzochten we de structurele hersennetwerkorganisatie. We vonden evidentie voor wijzigingen in de structurele hersennetwerkorganisatie bij volwassenen met ADHD. In tegenstelling tot de bestaande grafen-theoretische analysestudies bij kinderen met ADHD, stelden we geen veranderingen vast in de globale grafenmetrieken. Onze resultaten laten subtiele en gelokaliseerde nodale afwijkingen zien in plaats van een globale structurele hersennetwerkdisconnectiviteit bij volwassenen met ADHD, mogelijks verklaard door een vertraging in de ontwikkeling.

Conclusie

De resultaten wijzen niet op een tekort in DMN-demping bij rust-naar-taak omschakelingen, in plaats daarvan onthulden de bevindingen een potentieel ADHD-gerelateerd tekort in de anticiperende betrokkenheid van de toekomstige toestandsafhankelijke hersennetwerken. De studie van de intrinsieke functionele hersennetwerkorganisatie onthulde een onevenwicht tussen SN en aandachtsnetwerken - een nieuwe potentiële locus voor ADHD-gerelateerde tekorten van onoplettendheid en

verstrooidheid. Bovendien vonden we een verstoring van de structurele hersennetwerkorganisatie op wijd verspreid nodaal niveau, maar intacte globale netwerkmetrieken. De afwezigheid van een globale netwerkverstoring bij volwassenen met ADHD contrasteert met de bevindingen van ADHD-studies bij kinderen en suggereert een mogelijke vertraging in de ontwikkeling van de structurele hersennetwerkorganisatie. In het huidige proefschrift, gaven we belangrijke aanvullende evidentie voor verschillende functionele en structurele neurale afwijkingen bij ADHD met behulp van toegepaste taak- en rust-gebaseerde fMRI, evenals dMRI. Onze bevindingen helpen niet alleen bij het beter begrijpen van de ADHD-pathofysiologie, maar geven ook vorm aan nieuwe veelbelovende toekomstige onderzoekslijnen.

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