

The role of pre-sleep arousal and frontoparietal circuitry in ADHD - a dimensional Approach



By

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Abstract

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder currently estimated to be diagnosed globally in around 3.1% in adults and 8% in children and adolescents (Ayano, Demelash, et al., 2023; Ayano, Tsegay, et al., 2023). The primary diagnostic trait of ADHD is impaired executive functioning, and symptoms negatively impact across multiple facets of day-to-day life including familially, socially, educationally and vocationally (Luo et al., 2019). One executive function which is impaired in ADHD is response inhibition (Penadés et al., 2007; Pievsky & McGrath, 2018; Willcutt et al., 2005; Wright et al., 2014). Response inhibition relies on recruitment of the left intraparietal sulcus (IPS), and its recruitment in ADHD is dictated on a specific frontoparietal functional circuitry between the inferior frontal gyrus (IFG) and the IPS (Kolodny et al., 2017, 2020). Chapter 2 investigates the role of white matter structure underpinning this frontoparietal circuitry in ADHD and its role in impaired response inhibition, finding that individual differences in the structural properties of the IPS-IFG circuit, including tract volume and diffusivity, were linked to IPS activation and even predicted response inhibition performance outside the scanner. These findings highlight the structural-functional coupling of the IFG-IPS circuit in response inhibition in ADHD and suggest a structural basis for maladaptive functional top-down control in deficient inhibition in ADHD. Building upon these findings, chapter 3 investigated the impact of IIPS inhibition via continuous theta-burst transcranial magnetic stimulation (cTBS) on response inhibition. I report that the disruption to response inhibition by IIPS inhibition is increased in individuals with greater ADHD traits, which may reflect individuals with greater ADHD traits may having reduced compensatory mechanisms or the complex relationship between TMS and activation state in the targeted region may also explain our these findings, such as ADHD-related differences in ongoing IIPS activity or increased cognitive load in the disorder.

As well as response inhibition, sleep impairments are reported in 70-90% of the ADHD population, with the difficulties with sleep-initiation being among the most commonly reported sleep impairments in the disorder (Kooij et al., 2001; Mindell et al., 2009; Park et al., 2011). Sleep impairments in ADHD are of particular importance because impaired sleep can both cause and exacerbate ADHD symptoms in both ADHD and neurotypical cohorts, such as by impairing sustained attention and response inhibition performance (Chuah et al., 2006; Drummond et al., 2006; Goel et al., 2009; Imeraj et al., 2012; Lowe et al., 2017). In chapter 4 I highlight the mediating role of cognitive pre-sleep arousal in the relationship between ADHD traits and insomnia symptoms, and report a particular significance for two components of cognitive pre-sleep arousal: thoughts about “your personal life” and “being mentally alert/active”. Taking this further, in chapter 5 I investigate task-to-rest switching, a state switch which can be likened to sleep initiation. I highlight a role for the rRSC, a node of the DMN which is activated by spontaneous autobiographical thoughts during resting state scans (Andrews-Hanna et al., 2010), whilst also being implicated in sleep initiation via a de-coupling to the wider DMN (Sämann et al., 2011; Vogt & Laureys, 2005) and in ADHD through having reduced volume in the disorder (Overmeyer et al., 2001). I report that rRSC activation is modulated by task-to-rest switching, and that this modulation was significantly influenced by cognitive pre-sleep arousal. Thus, I suggest that the rRSC is involved in task-to-rest switching, and that individuals with greater cognitive pre-sleep arousal may experience difficulties with the rRSC’s ability to engage during task-to-rest transitioning, perhaps contributing to challenges faced during wake-to-rest transitions in those with greater cognitive pre-sleep arousal.

Due to COVID-19, the trajectory of this thesis was adapted to allow the analysis of existing datasets (*chapter 2*) and the subsequent expanding upon this analysis (*chapter 3*) whilst awaiting the resumption of in-person testing (*chapters 4 and 5*).

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Key abbreviations

AD	Axial Diffusivity
ADHD	Attention Deficit Hyperactivity Disorder
ASRS	Adult ADHD Self-Report Scale
BET	Brain Extraction Tool
BOLD	Blood Oxygen Level-Dependent
cTBS	continuous Theta Burst Stimulation
DMN	Default Mode Network
dMRI	diffusion Magnetic Resonance Imaging
DSM	Diagnostic Statistics Manual
FA	Fractional Anisotropy
fMRI	functional Magnetic Resonance Imaging
FPN	Frontoparietal Network
FSL	FMRI Software Library
GCTI	Glasgow Content of Thoughts Inventory
GLM	Generalised Linear Model
IFG	Inferior Frontal Gyrus
IPS	Intraparietal Sulcus
ISI	Insomnia Severity Index
MD	Mean Diffusivity
PSAS	Pre-sleep Arousal Scale
AI	Anterior Insula
RD	Radial Diffusivity
RI	Response Inhibition
ROI	Region Of Interest

RSC	Retrosplenial Cortex
SLF	Superior Longitudinal Fasciculus
SN	Salience Network
TMS	Transcranial Magnetic Stimulation
TPJ	Temporal Parietal Junction
WM	White Matter

Chapter 1

General Introduction

Chapter 1

This chapter will provide the background which underpins both the reasoning and intentions of the empirical research included in my thesis. I will first focus on the three overarching focuses of my thesis: attention deficit hyperactivity disorder (ADHD), sleep, and response inhibition. These sections will focus on their history, their underlying neural mechanisms, how they are researched and how issues arising can be treated. Next, the neuroscientific methodologies used in my thesis will be discussed, namely magnetic resonance imaging, diffusion weighted imaging and transcranial magnetic stimulation. Here I will focus on the physical concepts underlying how these methodologies work and how they have been previously used in the study of ADHD, sleep and response inhibition.

1.1 ADHD

ADHD is a neurodevelopmental disorder whose primary diagnostic trait is impeded executive functioning. Executive functions include a range of high-order cognitive elements, such as sustained attention, organisation and working memory (Diamond, 2013). One of the core executive functions which is impeded in ADHD is response inhibition (Diamond, 2013); an executive function which is a major focus of this thesis and is discussed in more detail in section 1.3. Recent meta-analyses suggests that global diagnosis rates of ADHD sit at around 3.1% in adults and 8% in children and adolescents (Ayano, Demelash, et al., 2023; Ayano, Tsegay, et al., 2023). The symptoms of ADHD negatively impact across multiple facets of day-to-day life including familally, socially, educationally and vocationally (Luo et al., 2019). For example, those with ADHD often have difficulty remembering commitments they have made to their partner which often results in increased stresses in their relationship. Similarly, those with ADHD often struggle with organisation and time management which then results

in increased stressed in their job. ADHD is classed as a disability in the United Kingdom. As such, understanding what underpins ADHD and its symptoms is necessary in order to better target treatments and thus improve the lives of those with the condition. While ADHD as a condition involving a wide range of symptoms across multiple domains, the role of impaired response inhibition may specifically impact quality of life through its contribution to increased risk of school suspension and exclusion (Rohde et al., 1999), reduced job stability (Gordon & Fabiano, 2019), increased risk of injury and increased risk of substance abuse (Wilens et al., 2011) and thus is a worthy focus of the current thesis. Response inhibition will be discussed in more detail in *section 1.3*.

1.1.1 The history of ADHD

ADHD is often believed to have been first recognised in 1845 when a collection of nursery rhymes was published by German physician Heinrich Hoffman in which a character named Fidgety Philip displayed behaviours symptomatic of a modern-day ADHD diagnosis (Thome & Jacobs, 2004). In 1902 came the first clinical observations of ADHD, when George Still described hyperactive children who could not control their behaviour as other children could despite no impairment to their intelligence (Still, 1902). However, hyperactivity was first described by Scottish physician Alexander Crichton as ‘mental restlessness’ in 1798 (Crichton, 1798).

The first definition of ‘hyperkinetic reaction of childhood’ was included in DSM-II in 1968, which was renamed ‘ADD with or without hyperactivity’ in the DSM-III in 1980, before being renamed again, this time to ADHD, in DSM-III-R in 1986 (M. Smith, 2012; P. T. Wilson & Spitzer, 1968). Up until this point ADHD was believed to be a childhood condition which affected mainly young boys. However, with the publication of the DSM-V, it has been acknowledged that ADHD is a condition which affects both males and females,

persists into adulthood, and has three presentations (M. Smith, 2012; Thompson & Miller, 2013): primarily inattentive (ADH-PI), primarily hyperactive (ADHD-PH) and combined (ADHD-C).

For a childhood diagnosis of ADHD in the UK, children must present with six or more symptoms of inattention and/or hyperactivity outlined in DSM-V (*see Table 1.1*). In adults, five or more symptoms are often sufficient for a diagnosis. Additionally, in adulthood, symptoms must have a moderate effect across multiple areas of their life, such as dangerous driving, underachieving at work and difficulties in maintaining social relationships. Symptoms must have been present since before the age of 12, must be present across at least two settings, must reduce quality of life and should not be better explained by another mental disorder (National Health Service, n.d).

It is worth noting at this point that, although the view that ADHD is a male condition is now outdated, females are still to this day underdiagnosed when compared to their male peers. (da Silva et al., 2020). The reasons for this historical view of ADHD being a male condition and the modern problem of underdiagnosis in females may in part stem from ADHD-like behaviour being seen as masculine (Holthe, 2013). As such, modern girls are more likely to be criticised for displaying ADHD symptoms (Holthe, 2013) and as a result are likely to mask their symptoms to a greater extent than boys (Waite, 2010). Another possible explanation is that girls are more likely to present as ADHD-PI (Nussbaum, 2012) and boys as ADHD-PH or ADHD-C. Children with ADHD-PI tend to be less disruptive than those with ADHD-PH or ADHD-C and are therefore less likely to be noticed by their teachers and are referred for an ADHD assessment (Waite, 2010).

Table 1.1. The symptoms of ADHD according to DSM-V

Domain	Symptoms
Symptoms of inattention	Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or with other activities. Often has trouble holding attention on tasks or play activities. Often does not seem to listen when spoken to directly. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., loses focus, side-tracked). Often has trouble organizing tasks and activities. Often avoids, dislikes, or is reluctant to do tasks that require mental effort over a long period of time (such as schoolwork or homework). Often loses things necessary for tasks and activities (e.g. school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones). Is often easily distracted. Is often forgetful in daily activities.
Symptoms of Hyperactivity/Impulsivity	Often fidgets with or taps hands or feet, or squirms in seat. Often leaves seat in situations when remaining seated is expected.

Often runs about or climbs in situations where it is not appropriate (adolescents or adults may be limited to feeling restless).

Often unable to play or take part in leisure activities quietly.

Is often “on the go” acting as if “driven by a motor.”

Often talks excessively.

Often blurts out an answer before a question has been completed.

Often has trouble waiting their turn.

Often interrupts or intrudes on others (e.g., butts into conversations or games).

1.1.2 The presentations of ADHD

The most common presentation of ADHD is ADHD-PI. In children, ADHD-PI has a global prevalence rate of around 3%, with levels being maintained into adulthood unlike ADHD-PH and ADHD-C (Ayano, Demelash, et al., 2023; Ayano, Tsegay, et al., 2023; Willcutt, 2012). Those with ADHD-PI primarily struggle with symptoms of inattention, such as often making careless mistakes, difficulty with sustaining attention, difficulty with organisation, forgetfulness, being easily distracted and frequently losing things (American Psychiatric Association, 2013). Additionally, those with ADHD-PI have been found to have more sluggish cognitive tempo (Capdevila-Brophy et al., 2014; McBurnett et al., 2001, 2014; Willcutt et al., 2012, 2014), worse working memory (Simone et al., 2016) and slower processing speed (Hunt et al., 2012; Nigg, 2005) than those with other presentations of ADHD and neurotypicals.

The next most common presentation of ADHD is ADHD-PH which has a global prevalence rate of around 2.95% in adulthood (Ayano, Demelash, et al., 2023; Ayano, Tsegay, et al., 2023). Individuals with this presentation of ADHD suffer primarily with symptoms of hyperactivity and impulsivity, such as fidgeting, feeling restless, excessive talking, feeling as if being ‘driven by a motor’, difficulties with turn waiting and interrupting (American Psychiatric Association, 2013).

The least common presentation of ADHD is ADHD-C, which has a global prevalence rate of around 2.44% in adults (Ayano, Demelash, et al., 2023; Ayano, Tsegay, et al., 2023). This presentation is characterised by both the inattention and hyperactivity/impulsivity diagnostic domains being met by an individual (American Psychiatric Association, 2013).

1.1.3 ADHD across the lifespan

ADHD is a lifetime condition, but how it presents itself often differs between childhood and adulthood, with childhood ADHD more commonly presenting hyperactive and impulsive symptoms, versus more inattentive presentations in adulthood (Stahl, 2021). Interestingly, the prevalence of ADHD diagnosis diminishes with age, despite the condition persisting throughout the lifespan (Ayano, Demelash, et al., 2023; Ayano, Tsegay, et al., 2023). This is likely due to a myriad of reasons. For example, we currently understand more about ADHD than ever before, meaning that diagnoses in children are increasing and adult rates are yet to catch up. Also, as with age those with ADHD learn better how to mask and manage their symptoms, adults are less likely to receive a diagnosis.

In childhood, hyperactivity often presents itself outwardly, such as constant climbing, squirming in their chair, constant fidgeting and running. In adulthood, hyperactivity is often felt more internally as a general restlessness and getting bored easily, although ADHD adults may still find sitting still difficult, as well as talking excessively (Hagan, 2019). Impulsivity in children is often seen at school with behaviours such as skipping queues due to a difficulty with turn-waiting, blurting out answers, interrupting others and intruding on personal space. ADHD adults' impulsivity will often present itself in their spending habits and engaging in risky behaviours, such as substance use, as well as struggling with interrupting others and turn waiting (Hagan, 2019). Finally, symptoms of inattention in ADHD children are most easily noticed in their school work, as well as in losing things, having problems listening and sustaining attention. ADHD adults also often struggle with losing things and make careless mistakes due to lapses in sustained attention. They too struggle with listening to others but their difficulties with organisation become more apparent than in childhood (Hagan, 2019). Additionally, by adulthood people with ADHD will have often learnt, either consciously or subconsciously, ways to both manage and mask their symptoms. As a result, ADHD is often

less apparent in adults than when they were children. However, due to the more serious nature of everyday life in adulthood, ADHD can become more apparent in adulthood due to its more serious effect on well-being and work, such as reduced job stability (C. T. Gordon & Fabiano, 2019), increased risk of injury and increased risk of substance abuse (Wilens et al., 2011). Despite the seriousness of adulthood ADHD's impact on life, the condition is still often seen primarily as a childhood condition and as such research often focuses on the condition in childhood. The empirical chapters in this thesis have attempted to counteract the omission of adulthood ADHD research by focusing on the condition in adulthood.

1.1.4 Biological theories of ADHD

The biological underpinnings of ADHD are still poorly understood. Perhaps the most widely accepted theory of ADHD is the Dopamine Hypothesis. Dopamine is a neurotransmitter which is often referred to as a 'feel good' chemical due to its role in the brain's reward system (Arias-Carrión et al., 2010; Bannon et al., 2020). Dopamine has been implicated in numerous other disorders, such as Parkinson's Disease and Schizophrenia (Iversen & Iversen, 2007). Stimulants, such as methylphenidate, increase dopamine levels by inhibiting dopamine transporters which typically remove released dopamine from synapses, the effect of which has been confirmed by imaging studies (Iversen, 2008; Volkow et al., 2004). As use of these drugs also improves ADHD symptoms, it is thus believed that an underlying hypofunctional dopaminergic state underpins ADHD (Iversen & Iversen, 2007). This theory is further supported by evidence of an association between ADHD and genes which encode for dopamine receptors and transporters (Bobb et al., 2006).

The heritability of ADHD, as suggested by twin studies, is believed to be around 80% (Grimm et al., 2020). Therefore, another theory of ADHD is the genetic theory of ADHD. Two of the most commonly linked genes relating to ADHD are both dopamine-related genes:

the dopamine transporter gene SLC63A and the dopamine receptor gene DRD4 (DiMaio et al., 2003). This fact lends further support to the dopamine hypothesis of ADHD. For example, SLC63A knock out mice display behaviours often seen in ADHD, such as increased spontaneous hyperactivity, and are calmed by stimulant medications used to treat ADHD (Giros et al., 1996). Similarly, the DRD4 gene is associated with attention and inhibition (Noaín et al., 2006) and lower mRNA expression of this gene is found in ADHD (Taurines et al., 2011).

An alternative theory of ADHD which has been proposed is the Default Mode Network (DMN) interference hypothesis (Sonuga-Barke & Castellanos, 2007). Put simply, the DMN is typically more active during rest and introspection and thus disengages during tasks (Fox et al., 2015). The DMN interference hypothesis proposes that reduced DMN suppression during tasks in ADHD results in the disruption of task-positive networks, resulting in lapses of attention and impaired task-performances. Evidence supports this claim. For example, ADHD individuals taking medication have less DMN activity during reward-based decision making tasks than those who are unmedicated (Mowinckel et al., 2017). However, this theory only explains the attention-based difficulties of ADHD, and not elements of the condition which are related to hyperactivity or impulsivity.

1.1.5 ADHD and co-occurring conditions

ADHD rarely occurs alone, often coinciding with at least one other condition. The most common of these is oppositional defiance disorder (ODD); a behavioural disorder in which patients display hostility towards authority figures (Aggarwal & Marwaha, 2024). ODD coincides with ADHD in around of 50-60% of cases (Noordermeer et al., 2017; Serra-Pinheiro et al., 2004) whilst its typical prevalence ranges between 2 and 11% (Aggarwal &

Marwaha, 2024). Similarly, of those with conduct disorder, which occurs in 2-10% of the general population (Mohan et al., 2024), around 16-20% will also have ADHD (Lillig, 2018).

Also commonly co-occurring with ADHD are mood disorders, such as bipolar disorder, which a recent meta-analysis found occurs in 5.66-14.03% people with ADHD (Schiweck et al., 2021), compared to between 1-3% globally (Merikangas et al., 2007, 2011). ADHD is believed to increase the risk of developing a depressive disorder by at least 100% (Jensen et al., 1993; Kessler et al., 2006). However, evidence suggests that stimulant medication can alleviate this risk (Biederman et al., 2009). As well as increasing the risk of depressive disorders, ADHD also increases the risk of substance use disorders. For example, ADHD adults are twice as likely to become addicted to nicotine than their neurotypical peers (Kollins et al., 2005; Wilens et al., 2008) and individuals with ADHD have been found to have more severe and long-lasting substance abuse problems than those without ADHD (Levin, 2001; Wilens et al., 2008, 2008; Wilson & Levin, 2005). As a result, there have been fears that taking stimulant medication into adulthood could increase the risk of substance use disorders in ADHD individuals. However, evidence suggests that this is not the case (Biederman et al., 2008).

Other neurodevelopmental conditions are also commonly co-occurring with ADHD. For example, autism spectrum disorder (ASD) symptoms occur in around 20-50% of those with ADHD (van der Meer et al., 2012). However, ADHD symptoms occur in around 50-70% of those with ASD, suggesting that ADHD symptoms are more likely to be found in ASD than vice versa (Rong et al., 2021). ASD occurs globally at a rate of between 0.02% and 1.16% (Chiarotti & Venerosi, 2020). Dyslexia is also common in ADHD, occurring in between 25-45% of cases (DuPaul et al., 2013), compared to common estimates of between 3% and 7% globally (Wagner et al., 2020). Similarly, tic disorders frequently co-occur with ADHD, with 60-80% of those with Tourette's Syndrome, a disorder affecting around 0.3-1%

of the general population (Szejko et al., 2022), also having ADHD (Swanson et al., 1999), Also, epilepsy, which is estimated to affect around 50 million people worldwide (WHO, 2019), also has a high-occurrence of ADHD, with between 30-40% of patients also suffering from ADHD (Ahmed et al., 2022). Lastly, issues with sleep are common in ADHD, with as many as 70-90% of those with ADHD reporting sleep difficulties (Kooij et al., 2001; Mindell et al., 2009). Sleep, its disturbance and its links with ADHD will be discussed in more detail in *section 1.2*.

1.1.6 Treating ADHD

ADHD is most commonly treated using medication, either stimulant or non-stimulant. Stimulant medication aims to boost levels of dopamine and norepinephrine neurotransmission in the prefrontal cortex (Briars & Todd, 2016; Markowitz et al., 2003; Stahl, 2021). One form of stimulant medication is methylphenidate, which works by inhibiting pre-synaptic dopamine (and to a lesser extent, norepinephrine) transporters of central adrenergic neurons, thereby increasing the levels of neurotransmitters in the synaptic cleft (Markowitz et al., 2003). Meanwhile, amphetamine acts directly on dopamine and norepinephrine transporter binding sites to increase the amount of dopamine and norepinephrine release (Stahl, 2021).

Non-stimulant medications are also used in the treatment of ADHD. For example, atomoxetine is a selective norepinephrine reuptake inhibitor which is used to treat ADHD (Briars & Todd, 2016; Stahl, 2021). Alpha-2-agonists are also used to treat ADHD, although the mechanism underpinning their success in treating ADHD is currently unknown (Brown et al., 2018).

There are also a number of psychosocial alternatives to pharmacological treatments, although these are less commonly employed when treating ADHD. Perhaps the most

common of these is cognitive behavioural therapy , which focuses on developing behavioural strategies to manage symptoms and alter dysfunctional thinking styles (Safren et al., 2004). Dialectical behavioural therapy has also had success in treating ADHD by teaching acceptance of ADHD symptoms as well as the skills required for self-management (Hesslinger et al., 2002). Mindfulness training utilises meditation to treat ADHD symptoms (Zylowska et al., 2008) whilst cognitive training aims to strengthen key brain networks involved in ADHD through regular activities, such as working memory tasks (Vinogradov et al., 2012). Recently, computerised progressive attention training has been shown to improve symptoms in ADHD in adults in the short-term, although improvements had disappeared by a four-month follow up (Stern et al., 2023). Lastly, neurofeedback has also been shown to improve ADHD symptoms through operant conditioning which promotes self-regulation of specific brain activity patterns (Hammond, 2007).

Brain stimulation has also shown some promise in improving ADHD symptoms, including response inhibition, which is discussed in more detail in *section 1.4*. This thesis will build upon this limited research by investigating its ability to mediate neurotypical response inhibition when targeting the left intraparietal sulcus.

1.2 Sleep

Approximately a third of our life is spent sleeping. Sleep is defined as “a state of immobility with greatly reduced responsiveness, which can be distinguished from coma or anaesthesia by its rapid reversibility” (Siegel, 2005). Sleep has been previously implicated in ADHD symptoms, including response inhibition, and thus will be a focus of this thesis.

1.2.1 The stages of sleep

Sleep can be split into two overarching stages: rapid eye movement (REM) and non-rapid eye movement (NREM) sleep. Within NREM sleep there are three individual stages. The first stage (N1) accounts for around 5% of total sleep time and is characterised by slow eye movement, low amplitude mixed frequency EEG activity mainly in the 4-7Hz range, and the presence of vertex sharp waves. The second stage (N2) accounts for around 50% of total sleep time and is characterised by the presence of k-complexes and sleep spindles. The third stage of NREM sleep (N3) accounts for around 20-25% of total sleep time. Also known as Slow Wave Sleep, this stage is characterised by large amplitude slow waves typically in the range of 0.5-2Hz. In healthy sleepers, after passing through the three stages of NREM sleep we enter REM sleep. This stage accounts for around 15-25% of total sleep time, is characterised by rapid eye movements and is often associated with dreaming (Iber, 2007), although dreams do still occur in NREM sleep. Human sleep cycles through the NREM and REM stages throughout the night, with each cycle lasting around 90 minutes (Ogilvie, 2001).

1.2.2 The functions of sleep

When deprived of sleep the body attempts to recoup the sleep it has lost, which demonstrates that sleep is not simply a period of reduced activity but is required for processes vital for the mind and body. A range of functions have been proposed for sleep. For example, wakefulness places a high demand on cells and neurotransmitters, and macromolecules which are vital to life are depleted throughout the day. Sleep is important for the replenishment and maintenance of the cellular environment to counteract the demands of wakefulness (Mignot, 2008). Additionally, sleep has been implicated in neural plasticity, memory consolidation and learning (Walker & Stickgold, 2004). When sleep is prevented or impaired it can lead to a number of negative outcomes. These negative outcomes include hypertension (Grandner et

al., 2018), obesity and type-2 diabetes (Reutrakul & Van Cauter, 2018), impaired immune functioning (Watson et al., 2017) and increased risk of mood disorders (Lyall et al., 2018), to name but a few.

1.2.3 The sleep-wake cycle

Human circadian rhythms (24-hour rhythms) are governed by a ‘biological clock’: the suprachiasmatic nucleus (SCN) in the hypothalamus (Doghramji, 2007). The SCN regulates the timing of melatonin release from the pituitary gland, and in turn melatonin feeds back into the SCN to inhibit its firing (Doghramji, 2007). Melatonin promotes tiredness and is entrained to external elements, such as environmental light intensity, with melatonin secretion being promoted by darkness and inhibited by light (Pace-Schott & Hobson, 2002).

The phase of an individual’s sleep-wake cycle can be categorised into chronotypes. Chronotype refers to the natural preference for the time of day an individual wants to sleep and feels most energetic, which is linked to their circadian rhythm. Those with a morning chronotype (also known as “morning larks”) prefer to be awake in the early part of the morning and sleep in the early part of the night (Zou et al., 2022). Evening chronotypes (also known as “night owls”) prefer to be awake in the later part of the morning and sleep in the later part of the night (Zou et al., 2022) and are more likely to suffer from disrupted sleep and are more likely to be diagnosed with a sleep disorder (Alvaro et al., 2014; Owens et al., 2016). Those with no preference have neutral chronotypes (Zou et al., 2022).

1.2.4 The methodologies used to investigate sleep

Sleep can be measured using a number of methodologies to assess a number of quantifiable sleep domains, such as total sleep time, wake after sleep onset and sleep percentage. Perhaps the gold standard method is polysomnography (PSG). PSG utilises a variety of physiological

measures (electroencephalogram, electro-oculogram and electromyogram) to allow sleep staging and to comprehensively monitor a range of sleep elements, such as sleep discharges, limb movements and respiratory effort (Rundo & Downey, 2019). Alternatively, actigraphy watches are also often used to measure facets of sleep. Actigraphy involves the participant wearing a device on their wrist which records movement. An algorithm is then used on the resulting data, resulting in estimations of sleep parameters (Martin & Hakim, 2011). A review of 15 studies investigating the validity of actigraphy when compared with that of PSG found that actigraphy is useful in estimating total sleep time, wake after sleep onset and sleep percentage, although it is less consistent as a measure of sleep-onset latency (Martin & Hakim, 2011). As well as objective measures, sleep research often employs subjective measures, such as questionnaires like the Pittsburgh sleep quality.

1.2.5 Disordered sleeping

An individual's sleep is not always healthy and there are numerous sleep-related clinical disorders. With symptoms affecting around 30% of the adult population, the most common sleep-disorder is insomnia (Roth, 2007). Insomnia is characterised by patient complaints of a difficulty in initiating or maintaining sleep, associated with daytime functioning impairments (Chokroverty, 2010). Also common is restless leg syndrome (RLS), which involves patients suffering from intense disagreeable feelings in their legs at night which provoke movement of the legs to alleviate discomfort (Chokroverty, 2010). Obstructive sleep apnoea syndrome (OSAS) is another sleep disorder which occurs in around 4% of men and 2% of women aged 30-60 (Chokroverty, 2010). Symptoms of this disorder can be both nocturnal and diurnal. Examples of nocturnal symptoms include loud snoring, sleep choking and unusual motor activities during sleep. Diurnal symptoms include sleep attacks which last between half an hour and two hours (Chokroverty, 2010).

1.2.6 Sleep problems in ADHD

As was touched on briefly previously, issues with sleep are common in ADHD, with as many as 70-90% of those with ADHD reporting sleep difficulties (Kooij et al., 2001; Mindell et al., 2009). These sleep problems manifest in increased prevalence of several clinically diagnosed sleep disorders in ADHD, including insomnia disorders, sleep-wake transition disorders, excessive daytime sleepiness and sleep sweating (van der Heijden et al., 2018). Similar sleep problems in ADHD are self-reported even without a clinical diagnosis of a sleep disorder (De Crescenzo et al., 2016; Díaz-Román et al., 2018; Gruber et al., 2000; Owens et al., 2009; Van Der Heijden et al., 2006). Some of the most frequently reported sleep difficulties in people diagnosed with ADHD are in falling asleep, awaking prematurely and not feeling rested despite sleeping (Park et al., 2011). Those with ADHD are also more likely to have an evening chronotype than their neurotypical peers (Bae et al., 2010; Baird et al., 2012; Bijlenga et al., 2013; Caci et al., 2009; Gruber et al., 2012). Interestingly, as previously mentioned, evening chronotypes (also known as ‘night owls’) are more likely to suffer from disrupted sleep and are more likely to be diagnosed with a sleep disorder (Alvaro et al., 2014; J. A. Owens et al., 2016), and thus the greater proportion of evening chronotypes in ADHD may partly drive the increased prevalence of sleep problems in the condition. As sleep-onset problems are commonly reported in ADHD, these will be the primary sleep-problem focus of this thesis.

1.2.7 The impact of sleep problems on cognition

Poor sleep, irrespective of ADHD, is also associated with cognitive impairments, many of which are also present in ADHD. For instance, performance in sustained attention and response inhibition are both also impaired by poor sleep (Chuah et al., 2006; Drummond et

al., 2006; Goel et al., 2009; Imeraj et al., 2012; Lowe et al., 2017). For example, a recent study of 30 healthy adults found that response inhibition performance was significantly worse following a night of sleep deprivation, with participants making an average of 20.87% commission errors after a night of sleep deprivation versus only 15.86% commission errors following a night of normal sleep, although this effect was found to be counteracted by 30 minutes of aerobic exercise (Liu & Zhang, 2022). Similarly, another recent study assessed sustained attention using a psychomotor vigilance task in 24 adults after a night of normal sleep and a night of five hour sleep deprivation and found that participants had a significantly greater number of attentional lapses after sleep deprivation than a normal night's sleep (Shenfield et al., 2020). Working memory has also been found to be impeded by poor sleep. For example, when individuals working memory is assessed via the Sternberg Item Recollection Paradigm in healthy adults who have had their sleep restricted to four hours for nine days, their working memory performance does not improve with practise, unlike in adults who have not undergone any imposed sleep restriction (Casement et al., 2006).

The symptoms of poor sleep mentioned above, as well as others not discussed presently, mirror those of ADHD to such an extent that it has been suggested that sleep quality should be assessed as a potential cause of ADHD symptoms prior to diagnosing an individual with ADHD (Cortese et al., 2013). Thus, it is not surprising that poor sleep in individuals with ADHD further exacerbates their impairments in sustained attention and response inhibition, and their ADHD severity (Becker et al., 2019; Gruber et al., 2011; Knight & Dimitriou, 2019; Lycett et al., 2014; Mahajan et al., 2010).

1.2.8 Pre-sleep arousal

An often overlooked element of sleep problems is pre-sleep arousal and its effect on sleep-onset. For example, in insomniacs, sleep initiation problems have been attributed to both

cognitive (or mental) and somatic (relating to the body) pre-sleep arousal, although cognitive arousal has been blamed by up to 10x more than somatic arousal (Lichstein & Rosenthal, 1980). Measures of sleep onset latency using actigraphy correlate with pre-sleep cognitive activity in insomniacs (Wicklow & Espie, 2000). The pre-sleep cognitive content of insomniacs has been identified to reflect three fields: active problem solving, present state monitoring and environmental reactivity (Wicklow & Espie, 2000). The relevance of pre-sleep arousal to sleep-onset latency has also been demonstrated in good sleepers where increasing their pre-sleep cognitive arousal led to delayed sleep latency (Gross & Borkovec, 1982).

1.2.9 The treatment of sleep problems

Sleep issues are often treated behaviourally. For example, relaxation techniques can be taught to patients in an attempt to alleviate pre-sleep arousal. Somatic pre-sleep arousal, such as muscle tension, can be targeted by progressive muscle relaxation, autogenic training and biofeedback (Sharma & Andrade, 2012). Meanwhile, cognitive pre-sleep arousal, such as racing thoughts, can be targeted by imagery training and meditation (Edinger & Means, 2005). Sleep hygiene education is also frequently employed when treating sleep problems. Using this technique, patients are educated about healthy sleep habits, such as only using their bed to sleep in and avoiding technology late at night (Kleitman, 1939). Similarly, stimulus control utilises operant conditioning to strengthen sleep-compatible associations and weaken sleep-incompatible associations in order to treat sleep-problems (Bootzin, 1973). Cognitive behavioural therapy is perhaps the most effective form of behavioural intervention used to treat insomnia-like sleep problems with a clinical review of over 50 studies proving the efficacy of cognitive behavioural therapy as an insomnia treatment (Malaffo & Espie, 2007).

Biological treatments of sleep-onset problems often focus on the hormone melatonin. As mentioned previously, human circadian rhythms regulate the timing of melatonin release, a hormone which then feeds back into the SCN to inhibit its firing (Doghramji, 2007). Melatonin promotes tiredness and is entrained to external elements, such as environmental light intensity, with melatonin secretion being promoted by darkness and inhibited by light (Pace-Schott & Hobson, 2002). As such, for those whose circadian rhythm is misaligned, light exposure therapy can re-align their rhythm. For individuals who are phase-delayed, meaning their circadian rhythm is running late and thus their melatonin secretion is running late, early morning light exposure therapy can be effective in re-aligning their circadian rhythms, whilst afternoon or evening exposure can be an effective treatment for those who are phase-advanced (Dodson & Zee, 2010; Lewy et al., 2006). Medications which increase melatonin levels are effective in treating sleep-onset problems (Zhdanova et al., 2001), and this medication is often prescribed for those suffering from jet-lag.

1.3 Response inhibition

Inhibiting responses is a necessity, from holding our tongue to stay out of trouble to not stepping into the road as a car hurtles round the bend. Impaired response inhibition is one of the most prominent and reproducible behavioural dysfunctions in ADHD, (Penadés et al., 2007; Pievsky & McGrath, 2018; Willcutt et al., 2005; Wright et al., 2014). Poor sleep also results in impaired response inhibition (Chuah et al., 2006; Drummond et al., 2006; Lowe et al., 2017). As has been previously discussed, impaired response inhibition may impact quality of life through its contribution to increased risk of school suspension and exclusion (Rohde et al., 1999), reduced job stability (Gordon & Fabiano, 2019), increased risk of injury and increased risk of substance abuse (Wilens et al., 2011).

1.3.1 The neural underpinnings of response inhibition and how it has been studied historically

Response inhibition have primarily been assessed using two tasks: the stop-signal task (Lappin & Eriksen, 1966) and the go/nogo task (Gordon & Caramazza, 1982). The go/nogo task involves participants being presented with either a go or a no-go stimulus, which require a response (usually via a button press) or no response, respectively. This task relies on action withholding – inhibiting the response initiation. In contrast in the stop-signal task a go stimuli (which should elicit a response) may occasionally be quickly followed by a “stop” stimuli, indicating that participants should no longer respond to the initial “go” stimuli. This task relies on action cancellation - inhibiting an already initiated response. The number of erroneous responses recorded when no response should have been given, termed commission errors, is typically used to quantify response inhibition performance.

Using primarily these two tasks, evidence suggests that a large-scale network formed of the dorsolateral prefrontal and posterior parietal cortices, which is termed the frontoparietal network (FPN), underpins response inhibition. A meta-analysis of 225 neuroimaging studies concluded that successful response inhibition was reliant on this network (R. Zhang et al., 2017). Furthermore, in neurotypical adults exercising both domains of response inhibition (action withholding and action cancellation), increased FPN activation is seen (Sebastian et al., 2013).

However, the validity of these tasks, and thus their combined findings, has been brought into question. The stop-signal and the go/nogo tasks rely on separate mechanisms (action cancellation and action withholding, respectively); two mechanisms whose performances bear a limited relationship (Schacter et al., 2007). Indeed, the developmental trajectories and peak latencies of various components of event-related potentials, meaning time-locked neural responses to stimuli, elicited by each task differs as a function of age in

children (Johnstone et al., 2007). Furthermore, both tasks only share an activation of one region of the FPN (the middle PFC) (Zheng et al., 2008). It is therefore questionable whether the two tasks should be considered interchangeably in studying response inhibition and whether the previously reported wide-spread brain activations are specific enough. Additionally, with regards to the go/nogo task, the “go” and “nogo” trials are typically contrasted in neuroimaging studies, meaning the results may be confounded by differences in more than the cognitive element of response inhibition, such as the motor component involved.

1.3.2 A new way to study response inhibition

In an attempt to focus on the cognitive rather than the motor aspect of response withholding, Kolodny and colleagues (2017) proposed the use of a novel go/nogo task in which inhibitory demand was manipulated by controlling the frequency of nogo trials to create a high vs low tendency to respond in different conditions. Using fMRI with neurotypical adults, the study documented much more focused brain activations associated with increased response inhibition demand within the broad frontoparietal network implicated by the previous research outlined above. Specifically, the authors reported increased activity in three parietal regions: the bilateral intraparietal sulcus (IPS) and left temporoparietal junction (TPJ). Crucially, these regions overlap with previous findings, but are more localised regions of the previously implicated FPN.

Subsequently, Kolodny and colleagues (2020) used their novel go/nogo task to investigate response inhibition in 37 ADHD adults. Interestingly, they found that IPS and TPJ modulation during inhibitory demand was itself modulated by ADHD severity (quantified using the Hebrew version of the Adult ADHD Self-Report Scale (ASRS; Kessler et al., 2005;

Zohar & Konfortes, 2010)) such that high symptom severity was associated with reduced modulation of the parietal nodes. In addition, they found that functional connectivity (meaning highly correlated activity temporarily between distinct brain regions) between a frontal FPN node, the inferior frontal gyrus (IFG) and the IPS was also similarly modulated by ADHD severity during inhibitory demand, so that increased symptom severity coincided with reduced functional connectivity between the nodes.

1.4 Transcranial Magnetic Stimulation

The neural underpinnings of ADHD, sleep and response inhibition can be assessed using a number of neuroimaging and neurostimulation techniques, three of which have been employed in this thesis and will be discussed below. The first of these techniques is the brain stimulation technique transcranial magnetic stimulation (TMS) a method which may also be employed to treat ADHD symptoms such as impaired response inhibition. In 1985, in response to limitations regarding pain inflicted upon patients by transcranial electric stimulation (TES), Barker and colleagues (1985) first demonstrated that it was possible to non-invasively stimulate the brain without causing any pain to the patient. This method of brain stimulation is TMS and is still used today both clinically and in research.

1.4.1 The mechanism behind TMS

To stimulate the brain, a high current electric pulse is produced in a magnetic coil which is held to the scalp. This pulse produces a magnetic field perpendicular to the coil which passes through the skull and into the brain. As a result, an electric field is produced perpendicular to the magnetic field. The basic principle of TMS is that this electric field induces neuronal activation by depolarising neurons which results in action potentials (Hallett, 2000, 2007).

1.4.2 The outcome of TMS

The outcome of TMS stimulation varies according to a number of variables. One variable is the shape of the magnetic coil (Hallett, 2000, 2007). Round coils are powerful whilst figure of eight coils are more focal, with the maximum field strength produced at the centre of the figure of eight. Cone-shaped coils, which are figure of eight coils with the two circles of the eight being at an angle, increase the power at the centre of the figure of eight further. Meanwhile, H-coils, so named after their shape, allow for a more gradual decline in intensity of the magnetic field with depth (Zangen et al., 2005).

The type of protocol used also impacts the outcome of TMS. There are three main protocols: single pulse, paired pulse and repetitive TMS (rTMS). In single pulse TMS, one pulse is applied no faster than once every three seconds and is used to measure immediate but short-lasting stimulation effects (Galletta et al., 2011). Paired pulse involves two pulses being applied successively after either a short or long inter-stimulus interval with the goal of inhibiting or exciting neurons within a hemisphere, or to inhibit neurons in one hemisphere whilst exciting neurons in the other (Galletta et al., 2011). When rTMS is used, a 'train' of pulses is applied rapidly at a certain frequency, intensity and time duration to invoke either excitation or inhibition in the targeted cortical region (Galletta et al., 2011). For example, the continuous theta burst stimulation protocol (cTBS) consists of 600 pulses occurring in bursts of three at 30 Hz which are delivered every 200ms to produce an inhibitory effect on the targeted cortical region (Meconi et al., 2021). rTMS, unlike single pulse and paired pulse, is able to alter brain activity for a duration extending the stimulation period, making it the often preferred protocol to investigate how sustained neural alteration impacts cognition (Klompai et al., 2015). The primary protocol used in this thesis is cTBS.

1.4.3 TMS and ADHD

TMS has been used, although to a limited extent, in the treatment of ADHD symptoms through either the longer-term excitation or inhibition of brain regions involved in various ADHD symptoms. For example, an inhibitory low frequency (1 Hz) rTMS to the supplementary motor area (SMA), an area of the brain proposed to be involved in internally generated movement (Roland et al., 1980), of ADHD individuals resulted in a significant improvement to their hyperactivity symptoms over a 4-week period, whilst a sham-stimulation lead to no such improvement (Niederhofer, 2008). Similarly, low frequency rTMS to the SMA in an ADHD individual lead to a 3-week improvement to hyperactivity symptoms (Niederhofer, 2012). Additionally, high frequency rTMS to the right prefrontal cortex on 13 ADHD adults resulted in improved attention 10 minutes post-stimulation whilst no improvements were seen following a sham-stimulation (Bloch et al., 2010). However, no long-term effects were measured in this experiment.

1.4.4 TMS and response inhibition

As with ADHD symptoms, TMS has also been used to improve response inhibition performance, albeit to a similarly limited extent. For example, cTBS over the right inferior frontal gyrus (rIFG) prior to a stop-switching task and single pulse TMS over the pre-SMA during a stop-signal task have both been found to result in significantly worsened action cancellation performance (Obeso et al., 2013). Alternatively, intermittent theta burst stimulation (iTBS) over the pre-SMA has been shown to improve inhibitory control during a stop-signal task (Ji et al., 2019). The same experiment also found that iTBS improved reaction times, although this finding was not reproduced reliably in a second replication experiment by the same authors (Ji et al., 2019). Action cancelation performance during a stop-signal task has also been found to be impaired by cTBS over the right anterior insula

(rAI), whilst action withholding performance on a go/nogo task was impaired by cTBS of the rAI as well as the superior frontal gyrus (Dambacher et al., 2014).

1.4.5 TMS and sleep

TMS has been used to treat sleep problems to a much greater extent than it has been used to improve ADHD symptoms and response inhibition performance. In insomnia, TMS to the dorsal lateral prefrontal cortex (DLPFC) has been suggested by a number of studies to improve sleep. For example, rTMS to the rDLPFC in 120 insomniacs lead to better stage N3 and REM sleep, as assessed by PSG (Jiang et al., 2013). More recently, low frequency rTMS to the lDLPFC in 78 insomniacs saw an improvement to subjective sleep quality scores (as assessed by the PSQI) as well as to total sleep time, sleep onset latency, sleep efficiency and wakefulness after sleep onset, measured subjectively through sleep diaries and objectively through actigraphy (Y. Zhang et al., 2018). Again the DLPFC was implicated when it was found that sequential 1 Hz rTMS to the DLPFC bilaterally in 32 right-handed insomniacs resulted in the reduction of PSQI scores, reduction of MEP amplitudes (which reflect motor cortical excitability) and the increase of serum brain-derived neurotrophic factor (BDNF) and gamma-aminobutyric acid (GABA; Feng et al., 2019). Interestingly, all of these reductions and increases correlated with one another, which cause the authors to suggest the mechanism of the protocols' improvement to insomnia is through increasing BDNF and GABA whilst reducing motor cortical excitability.

As well as for insomnia, TMS has been shown to be effective in treating hypersomnia. For example, 30 daily sessions of 20 minute 10 Hz rTMS to the left DLPFC improved hypersomnia symptoms in 17 patients (Sonmez et al., 2020). The left DLPFC is also a target for TMS treatment of narcolepsy, with 25 sessions of 10 Hz rTMS to this region of the brain resulting in an improvement of narcoleptics' symptoms (Lai et al., 2017). High-frequency

rTMS over the SMA also improves RLS symptoms (Altunrende et al., 2014), whilst 14 sessions of high-frequency rTMS to the leg representation in the primary motor cortex sees improvements to subjective RLS measures which last for two months (Lin et al., 2015). Bruxism, meaning excessive teeth grinding, clenching and gnashing, too can be improved using 5 consecutive daily sessions of 20 minute 1 Hz rTMS to the primary motor cortex through its inhibitory effect on jaw muscle movement during sleep (Zhou et al., 2016). Finally, TMS has also shown promise in reducing obstructive sleep apnoea symptoms by improving airflow when applied over the motor cortex at the beginning of inhalation (Melo-Silva, Borel, et al., 2013; Melo-Silva, Gakwaya, et al., 2013).

1.5 Magnetic Resonance Imaging

As well as stimulating the brain we are also able to image it and its activity. Magnetic Resonance Imaging (MRI) is one of the major imaging techniques used in neuroscience research and is employed throughout this thesis in various ways.

1.5.1 How MRI works

The physics underlying how MRI images the brain and its activity relies primarily on hydrogen nuclei in the brain. Hydrogen nuclei have one proton and are thus positively charged. The hydrogen nucleus has a property called ‘spin’. Spin can be oriented in different ways and has a magnetic field.

The magnet in an MRI machine creates a strong, continuous magnetic field. This magnetic field causes the protons spin to align with it. Most will align in a parallel fashion as this requires the least energy, although some spins will align in an anti-parallel manner if they are at a higher energy. Next, energy in the form of a rapidly changing magnetic field is produced by radiofrequency (RF) coils (RF energy) tuned to the resonant frequency of

protons. The RF energy causes the spins to ‘tip off’ their alignment with the external magnetic field. After a short period, the RF energy is stopped and protons return to their original energy state and alignment, emitting the excess RF energy. When these protons return to their original alignment, they release energy in the form of RF power which is detected by receiver coils and converted into an electrical current signal. Protons in different tissues relax at different rates, meaning we can use MRI to distinguish between and map different tissues.

1.5.2 Functional MRI

As well as anatomically mapping the brain, MRI can be used to infer the activity levels of different brain regions through functional MRI (fMRI). Active brain regions require more oxygen than non-active regions and thus deoxyhaemoglobin is more abundant than oxyhaemoglobin around active brain regions. Deoxyhaemoglobin and oxyhaemoglobin have different magnetic properties and can thus be differentiated using MRI. When a region of the brain becomes active there is an initial increase in deoxyhaemoglobin and then a subsequent overflow of oxyhaemoglobin. This subsequent overflow is recorded by the MRI to infer which areas of the brain are more active during tasks than others. This is known as the blood-oxygen-level-dependant (BOLD) signal. Due to the BOLD signal occurring slower than neuronal activity, fMRI has relatively poor temporal resolution, albeit good spatial resolution.

Functional connectivity between brain regions can also be studied using fMRI, with functional connectivity being defined as “the temporal dependency, or correlated neuronal activity, between separate anatomically defined brain regions” (Friston et al., 1993). The functional connectivity between multiple regions of the brain allows us to determine the organisation of multiple regions of the brain into brain networks, such as the frontoparietal network discussed previously which has been implicated in response inhibition. As well as

functional MRI, diffusion MRI can also be used to investigate the brain by recording information on the structural make up of white matter. This method is employed in this thesis and is discussed in more detail in *section 1.6*.

1.5.3 MRI and ADHD

fMRI is a tool which has been used extensively in the investigation of ADHD. For example, using fMRI to investigate sustained attention in ADHD, it has been found that sustained attention tasks result in reduced activation of frontal and parietal regions in ADHD children when compared to their neurotypical peers (Cao et al., 2008; Epstein et al., 2009; S. Wang et al., 2013) and decreased activation in ADHD adults' fronto-striatal and parietal networks (Cubillo et al., 2012; Schneider et al., 2010). When investigating attentional control performance in ADHD, fMRI has implicated lower activation in the frontoparietal network in ADHD children versus neurotypical children (Godinez et al., 2015) and lower DLPFC activity in ADHD adults versus neurotypical adults (Banich et al., 2009; Burgess et al., 2010; Depue et al., 2010). A meta-analysis of 55 studies using fMRI to investigate differences in brain activity between those with ADHD and neurotypicals suggests that, in ADHD, there is hypoactivation of frontoparietal and ventral attention networks as well as hyperactivation of the DMN, somatomotor network and visual systems (Cortese et al., 2013).

1.5.4 MRI and response inhibition

Likewise, fMRI has been used to a great extent in the investigation of response inhibition, implicating a wide range of brain regions. For example, a meta-analysis of 11 fMRI studies employing to go/nogo task report a role in response inhibition for the Pre-SMA, right frontal regions, left pre-motor regions, left premotor cortex, bilateral inferior parietal regions, bilateral occipital regions, bilateral putamen, bilateral insula and the precuneus (Simmonds et

al., 2008). fMRI findings have implicated numerous regions of the brain which are typically classified as belonging to a large scale fronto-parietal network (Sebastian et al., 2013; R. Zhang et al., 2017). However, due to the limitations of the tasks used to assess response inhibition and their use in conjunction with one another which were previously discussed it has been argued that this large-scale network historically implicated in response inhibition is too broad. In response to these criticisms, by altering the go/nogo task to provide a cleaner measure of the cognitive element of response inhibition, fMRI has narrowed down the relied upon brain regions to the IPS and TPJ (Kolodny et al., 2017).

1.5.5 MRI and sleep

As with ADHD and response inhibition, MRI has been used to study sleep. For example, fMRI was used to investigate the relationship between functional connectivity and cumulative total sleep time (cTST) measured using actigraphy over two weeks in 33 healthy adults, finding that greater cTST was significantly correlated with functional connectivity between the mesial prefrontal cortex of the DMN and the right anterior insula of the salience network (Khalsa et al., 2017). Typically, when fMRI is used to study sleep it is used in conjunction with EEG in order to classify the stages of sleep and their neural activity. An early experiment which combined the modalities of EEG and fMRI to study sleep found that the activation of the brain in response to auditory stimulation is reduced in NREM sleep when compared to wakefulness (Czisch et al., 2004). Specific regions have been shown to have reduced activity levels during slow wave sleep than wakefulness using EEG-fMRI, such as the anterior cingulate cortex, left insula and hippocampal regions (Kaufmann et al., 2006). Additionally, EEG-fMRI found that the DMN becomes more deactivated during REM sleep in 11 healthy adults (Hong et al., 2021).

1.6 Diffusion Weighted Imaging

Diffusion weighted imaging is an MRI technique which assesses water diffusion within tissues and is able to provide information on the microstructure on white matter within the brain.

1.6.1 Grey and white matter

The brain is made up of two types of tissue: grey matter and white matter. Grey matter is made up of neuronal cell bodies and dendrites, which receive signals from other neurons (Mercadante & Tadi, 2023). Extending from the cell bodies are axons, and these transport neural signals to the dendrites of other neurons to allow neural communication. White matter is made up of millions of axonal bundles (Fields, 2010). These tracts are white in colour due to fatty coating on the axons known as the myelin sheath (Fields, 2010). The myelin sheath electrically insulates the axon and is vital for high-speed transmission of electrical impulses along the axon needed for neural communication (Fields, 2010). There are a number of major white matter tracts, such as the superior longitudinal fasciculus (connecting the frontal, occipital, parietal and temporal lobes; (X. Wang et al., 2016), the corpus callosum (connecting the two hemispheres of the brain; (Goldstein et al., 2023) and the inferior longitudinal fasciculus (connecting the temporal-occipital and occipital brain regions to the anterior temporal regions; (Herbet et al., 2018). As well as the many major and named tracts, there are also many unnamed and more minor white matter tracts within the brain.

1.6.2 How DWI works

As well as providing functional information about the activity of the brain's grey matter, MRI can also be used to provide structural information about the brain's white matter. This is called diffusion weighted imaging (DWI). Diffusion is the random Brownian motion of molecules (Baliyan et al., 2016). In extracellular environments, the diffusion of water molecules is relatively free whilst the diffusion of intracellular water molecules is restricted by features of the cell such as the cell membrane, with different cell tissues having different diffusion properties (Baliyan et al., 2016). Anisotropic diffusion is diffusion restricted in all directions, whilst isotropic diffusion is unrestricted diffusion in all directions. DWI provides information about the diffusion of water in the brain to provide information about the tissue the molecules are located in. In white matter, diffusion is anisotropic due to the cell membrane restricting movement in all directions except perpendicular to the cell (Baliyan et al., 2016). The diffusivity data recorded by DWI can be analysed in order provide information on the micro-architecture of white matter and its integrity (Baliyan et al., 2016).

1.6.3 The properties of white matter

Diffusion MRI data analysis typically used in research, and employed in this thesis, is called diffusion tensor imaging (DTI). DTI assesses white matter architecture across five properties: volume, fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD) and mean diffusivity (MD).

White matter FA refers to scalar values ranging from one to zero which describe the extent of diffusional restriction placed on water in a voxel by its surrounding tissue. A value of zero represents isotropic diffusion, whilst a value of one represents anisotropic diffusion. Diffusion magnitudes parallel to fibre tracts and perpendicular to fibre tracts are quantified by

AD and RD, respectively, whilst their average is quantified by MD (Solowij et al., 2017). Typically, white matter health has been linked with increased FA, increased AD and reduced RD (Solowij et al., 2017). However, some argue that the meanings of white matter properties varies, and thus caution should be exercised when interpreting them (Jones et al., 2013). Additionally, the anatomy which underpins both AD and RD is not clear, but reduced AD has been proposed to reflect reduced caliber of, or injury to, axons, or reduced coherence in axon orientation whilst increased RD has been proposed to reflect a loss of myelin, loss of axons, or reduced axonal packing density (Solowij et al., 2017).

1.6.4 DWI and ADHD

DWI has been used to investigate the white matter of those with ADHD, although the research is limited when compared to fMRI and it is primarily focused on children. ADHD children have been found to have atypically low global white matter volume (Castellanos et al., 2002), whilst in ADHD adults it is atypically high (Seidman et al., 2006), suggesting atypical development of global white matter in the condition. As well as global white matter, DWI has been used to examine specific white matter tracts in ADHD. A meta-analysis reported that the most commonly reported white matter difference in ADHD versus neurotypicals is atypical corpus callosum FA (Aoki et al., 2018). However, research on ADHD white matter differences is inconsistent. For example, in a recent meta-analysis of 12 studies researching corpus callosum properties in ADHD children compared to neurotypical children, it was found that eight reported reduced FA in ADHD whilst 4 reported no difference (Connaughton et al., 2022). Similarly, they claim that, in the superior longitudinal fasciculus, there are reports of both increased and decreased FA, increased and decreased MD

and reports of no significant white matter differences in the condition (Connaughton et al., 2022).

1.6.5 DWI and response inhibition

Response inhibition performance in neurotypicals has been linked to white matter metrics in various tracts using DWI. For example, in 92 children aged 7-13 years, a faster inhibition of a prepared response during a stop-signal task was associated with higher FA and lower RD within both the right IFG and the right pre-SMA (Madsen et al., 2010). The authors suggested this may reflect quicker neural conduction in these regions resulting from more densely packed or better myelinated white matter. In adults, albeit in a small sample size of 13, it has been found that good inhibitors on a go/nogo task had greater FA in the right anterior fronto-occipital fasciculus and precuneus (Forstmann et al., 2008). The authors point out that the tracts that they highlight may overlap in part with the uncinate fascicle, the extreme capsule or the superior longitudinal fasciculus III. Regardless of the specific tracts highlighted, these studies evidence the importance of the axonal microstructure underlying neural communication in response inhibition.

1.6.6 DWI and sleep

DWI has also been used to investigate the role of white matter in sleep. For example, a study of 448 older adults (aged 60-82 years, Sexton et al., 2017) which investigated the relationship between global white matter metrics and subjective sleep quality, assessed using the PSQI and the Jenkins Sleep Scale (Jenkins et al., 1988) found that higher global FA and lower

global AD and RD were associated with greater sleep quality. As well as global white matter metrics being link to subjective assessments of sleep, DWI has also been used to link more specific tracts to objective sleep architecture. Fifteen healthy male adults underwent both DWI and overnight high-density EEG (Piantoni et al., 2013). In these 15 participants, higher AD in the forceps minor, the anterior corpus callosum, fascicles in the temporal lobe, and the tracts within and surrounding the thalamus was associated with greater sleep spindle power, whilst a steeper rising slope during N3 sleep was linked to higher AD in the temporal fascicle, forceps minor, anterior corpus callosum (Piantoni et al., 2013). Greater sleep duration has been found to be associated with greater left orbito-frontal and right superior corona radiata FA and lower right orbito-frontal and right inferior longitudinal fasciculus MD, whilst better sleep quality is associated with greater (Khalsa et al., 2017).

1.7 Thesis Aims

Considering all that has been discussed in this chapter it is evident that ADHD is a lifetime condition which impeded a number of executive functions which are necessary for day-to-day life, one of which being impaired response inhibition. Impaired response inhibition has been linked with the activity of, and functional connectivity between, nodes of the frontoparietal network, but, as of yet, the properties of the white matter connecting these regions and its relation to impaired response inhibition in ADHD has not been explored. Additionally, the findings implicating said nodes of the frontoparietal network provide a potential target for brain stimulation as a treatment for response inhibition impairment.

It has also been demonstrated that poor sleep is common in ADHD and that this exacerbates ADHD symptoms, including impaired response inhibition, in both ADHD and

neurotypicals alike, proving a potential route of treatment for said symptoms. A frequent component of sleep impeded in ADHD is sleep-onset. Sleep-onset difficulties in disorders such as insomnia have been demonstrated to be associated with pre-sleep arousal, a facet of sleep-onset which has been overlooked in ADHD-related sleep-onset difficulties. Confirming that pre-sleep arousal plays a role in ADHD-related impaired sleep could provide direction when investigating which regions of the brain underpin such impairments.

This thesis aims to (a) investigate the role of this frontoparietal white matter microstructure in ADHD-related response inhibition impairment (chapter 2), and (b) explore the efficacy of treating impaired response inhibition via TMS to the implicated nodes of the frontoparietal network by investigating the impact on response inhibition in a neurotypical cohort (chapter 3). Whilst one option for ADHD treatment is to focus on a specific symptom, such as by using TMS to treat response inhibition, one could also treat symptoms more generally. As such, the second half of this thesis will investigate the efficacy of focusing treatment of ADHD-impaired sleep – itself a symptom of ADHD which can cause exacerbate a broad range of other ADHD symptoms. As such, this thesis will also (c) explore the relationships between ADHD symptom severity, sleep quality and pre-sleep arousal (chapter 4), and (d) investigate the role of brain regions associated with any components of pre-sleep arousal implicated in chapter 4 in ADHD-related sleep-onset difficulties to provide potential targets for future treatments which would aim to improve sleep difficulties in ADHD and thus their exacerbation of wider ADHD symptoms.

Chapter 2

White matter properties in fronto-parietal tracts predict maladaptive functional activation and deficient response inhibition in ADHD.

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Carmel Mevorach

At the time that this thesis was submitted, the following chapter was under review at Human
Brain Mapping.

Chapter 2

2.1 Abstract

Response inhibition is a key characteristic of adaptive human behaviour. However, in attention deficit hyperactivity disorder (ADHD) it is often impaired. Previous neuroimaging investigations implicate a myriad of brain networks in response inhibition, making it more difficult to understand and overcoming response inhibition difficulties. Recently, it has been suggested that a specific fronto-parietal functional circuitry between the inferior frontal gyrus (IFG) and the intraparietal sulcus (IPS), dictates the recruitment of the IPS during response inhibition in ADHD. To ascertain the critical role of the IFG-IPS functional circuit and its relevance to response inhibition in ADHD, it is crucial to understand the underlying structural architecture of this circuit so that the functional relevance could be interpreted correctly. Here we investigated the white matter pathways connecting the IFG and IPS using seed-based probabilistic tractography on diffusion data in 33 ADHD and 19 neurotypicals, assessing their impact on both IPS recruitment during response inhibition and on response inhibition performance in a Go/No-go task. Our results showed that individual differences in the structural properties of the IPS-IFG circuit, including tract volume and diffusivity, were linked to IPS activation and even predicted response inhibition performance outside the scanner. These findings highlight the structural-functional coupling of the IFG-IPS circuit in response inhibition in ADHD and suggest a structural basis for maladaptive functional top-down control in deficient inhibition in ADHD. Our results also suggest that individual differences in tract-specific functional and structural connectivity could serve as neuromarkers of ADHD.

2.2 Introduction

Inhibiting responses is a survival necessity, from holding our tongue to stay out of trouble to not stepping into the road as a car hurtles round the bend. Nevertheless, impaired response inhibition is one of the most prominent and reproducible behavioural dysfunctions in attention deficit hyperactivity disorder (ADHD, (Penadés et al., 2007; Pievsky & McGrath, 2018; Willcutt et al., 2005; Wright et al., 2014)), and can be linked to various detrimental outcomes in the condition such as increased risk of school suspension (Rohde et al., 1999), reduced job stability (C. T. Gordon & Fabiano, 2019), increased risk of injury and increased risk of substance abuse (Wilens et al., 2011). However, a full mechanistic understanding of the neurobiological mechanisms underlying response inhibition in ADHD is still lacking.

Traditionally, studies have pointed to a large-scale network of frontal, parietal and striatal brain areas, which is recruited during response inhibition tasks (Criaud & Boulinguez, 2013; Swick et al., 2011). However, the recruitment of many of these areas is not specific to inhibition per-se, and can be attributed to other visual, motor and cognitive demands involved in the task. Using a Go/No-go task with a manipulation of target frequency, Kolodny and colleagues (Kolodny et al., 2017) narrowed down these broad frontoparietal activations to specific parietal nodes of the network (bilateral intraparietal sulcus (IPS) and left temporoparietal junction (TPJ)), which were directly modulated by the response inhibition demand (Kolodny et al., 2017). This increased specificity of response inhibition nodes allowed the authors to identify a marked difference in ADHD (Kolodny et al., 2020), where the IPS and TPJ modulation by inhibitory demand was missing. Moreover, individual differences analysis revealed that the parietal nodes recruitment was mediated by ADHD severity (2005; Kessler et al., 2005; Zohar & Konfortes, 2010), and that it was likely associated with a similar scaling of the functional connectivity between the IPS and the inferior frontal gyrus (IFG). Thus, inhibitory load was driving both the recruitment of the

parietal nodes and the connectivity between parietal and frontal nodes, but this modulation dissipated with increased ADHD severity. These findings provide a mechanistic framework for understanding impaired response inhibition in ADHD, whereby communication between frontal and parietal nodes is less effective and results in reduced sensitivity of parietal nodes to inhibitory demand.

However, the underlying cause for the reduced functional connectivity is still obscured. It could represent deficiencies in the functional activation of the specific nodes, a different cognitive strategy, or a genuine structural connectivity deficit. The latter would manifest in changes to the underlying structural substrate of the white matter (WM) pathways that connect the IFG with the IPS and mediate information transfer between them (H. Huang & Ding, 2016; Mollink et al., 2019; van den Heuvel & Sporns, 2019). Previous research has pointed to atypicality in the WM properties in ADHD, which could support the argument for a structural connectivity deficit underlying the functional connectivity differences in ADHD response inhibition, but findings tend to be inconsistent (see (Connaughton et al., 2022) for a recent review). For instance, both in corpus callosum pathways as well as within the superior longitudinal fasciculus (SLF) there have been findings of both increased and decreased WM properties (FA and MD) in ADHD compared with controls (Castellanos et al., 2002). Similarly, studies investigating global WM volume (Castellanos et al., 2002; Seidman et al., 2006) have also reported discrepancy with both low global WM volume in children (Castellanos et al., 2002) and atypically high global WM volume in adults ADHD (Seidman et al., 2006), which may point to atypical development of WM in ADHD. Part of the difficulty in previous studies is related to the focus primarily on childhood ADHD rather than adults, and on whole-brain WM tracts rather than functionally specific ones.

We therefore propose that, in order to better understand the role of fronto-parietal functional connectivity and activation in response inhibition in ADHD, we should assess the

WM properties of the specific underlying structural pathway. Utilizing a multi-modal fMRI-dMRI-behavioural dataset, we use the previous findings of maladaptive frontoparietal functional connectivity during response inhibition in ADHD to guide a targeted analysis of the diffusion-weighted (dMRI) data. We employed seed-based probabilistic tractography delineating WM tracts connecting bilateral IFG and IPS to extract volume and microstructural properties along those specific tracts. We first tested whether any of the structural metrics were atypical in ADHD compared to controls. We next assessed if individual differences in the WM properties of these tracts could predict the individual differences in parietal modulation during inhibitory demand (measured with fMRI). Finally, we also tested if these structural properties could predict performance in a response inhibition task recorded outside the scanner.

2.3 Methods

2.3.1. Participants

The sample consisted of 42 adults with ADHD and 24 neurotypical controls who also participated in our previous studies (*Table A1 in Appendix A*) (Kolodny et al., 2017, 2020, 2022). Participants were recruited via advertisements at college and university campuses. All ADHD participants had a previous diagnosis by a qualified clinician, and underwent full psychiatric evaluation conducted by author ST – a certified psychiatrist. The interview included psychiatric history and mental status examination according to DSM-5 criteria. Participants were excluded if they had any neurological or psychiatric disorders other than ADHD, including major depression, anxiety, OCD or psychosis; if they did not currently meet diagnostic criteria for ADHD; or if they were using any non-psychostimulant psychotropic medication. ADHD current symptom severity was estimated using the total

score on the Hebrew version of the Adult ADHD Self-Report Scale (ASRS), a short scale comprised of 18 items corresponding to the DSM diagnostic criteria (Kessler et al., 2005).

Neurotypical participants had no prior history of neurological or psychiatric disorders and no learning disabilities, and were not taking any psychotropic medications, including psychostimulants. To ensure the absence of attention difficulties, they completed the ASRS, and were included only if they scored within 1 SD of the population's mean (Zohar & Konfortes, 2010).

Fourteen participants (ADHD=9; Control=5) were excluded following dMRI preprocessing due to poor data quality. The final sample consisted of 33 ADHD participants and 19 neurotypical participants (*Table 2.1*). There was no association between group and sex ($\chi^2(1, N=52)=1.942, p=.163$). Of the ADHD participants, 1 was medication-naïve; 5 had used psychostimulant medication in the past; 19 used medication occasionally; and 8 used medication regularly. All participants were required to refrain from using stimulants 24 hours prior to the experiment. There was no significant difference in WM metrics between the different medication groups (*Table A2 in Appendix A*). The study conformed to the Declaration of Helsinki and was approved by the ethics committees of Sheeba Medical Center and of Tel-Aviv University (Israel). All participants provided written informed consent after receiving a complete description of the study.

Table 2.1. Descriptive statistics for demographic and behavioural data

	ADHD	Control	t	df	P	Cohen's d
Sex (M/F)	17/16	6/13				
Age (years)			.171	50	.145	-.049
N	33	19				
Range (y)	19-39	23-37				
Mean (y)	27.5	27.7				
SD (y)	4.4	3.3				
ASRS Total (Max 90)			-7.638	50	<.001**	2.200
N	33	19				
Range	41-85	23-49				
Mean	61.5	32.2				
SD	12.2	6.9				
Response Inhibition Performance ⁺			-1.980	43	.002*	.760
N	30	15				
Range	0-.198	0-.073				
Mean	.067	.033				
SD	.055	.016				

⁺Response Inhibition Performance was quantified as the percentage of commission errors during the rare-No-go condition in the behavioural version of the Go/No-go task.

Note: * $p < .05$, ** $p < .001$

Note: SD = standard deviation, df = degrees of freedom

Note: There is variation in the number of participants for each variable due to missing data.

2.3.2 Materials

2.3.2.1 Response inhibition - Go/No-go Task

Response inhibition performance was assessed using a Go/No-go task with a manipulation of target frequency (*Figure 2.1*) (Kolodny et al., 2017). Briefly, coloured shapes appeared sequentially in the centre of the screen. Participants were instructed to quickly click a button when a red square appeared (Go trial), and withhold response to any other stimuli (No-go trials). The task consisted of two conditions: rare-No-go and prevalent-No-go. The frequent responses in the rare-No-go condition increase the inhibitory demand for No-go trials relative to the prevalent-No-go condition (Kolodny et al., 2017).

The Go/No-go task was used both outside the scanner in a separate behavioural session, and during the fMRI session. Response inhibition performance was assessed during the earlier behavioural session due to possible effects of the scanner environment itself on cognitive processes (Hommel et al., 2012; Kolodny et al., 2022; Koten et al., 2013) and to get an index of performance that reflects trait-like response inhibition. Performance was quantified as the percentage of commission errors made in the rare-No-go condition (i.e., the percentage of failed No-go trials, or false alarms *Table 2.1*). Seven participants (ADHD=3, Controls=4) were missing behavioural data due to technical failure or time constraints during data acquisition.

2.3.2.2 Adult ADHD Self-Report Scale (ASRS)

The ASRS is a widely used questionnaire, which assess the severity with which an adult experiences ADHD symptoms (Kessler et al., 2005). It consists of 18 questions covering two components equally: inattention symptoms and hyperactivity/impulsivity symptoms, each corresponding to one item in the symptoms checklist for ADHD in the DSM. Participants rate

how frequently they experience symptoms using a Likert scale. This provides a severity score ranging from 9-45 for both components, and a combined severity score ranging from 18-90. Higher scores reflect higher symptom severity.

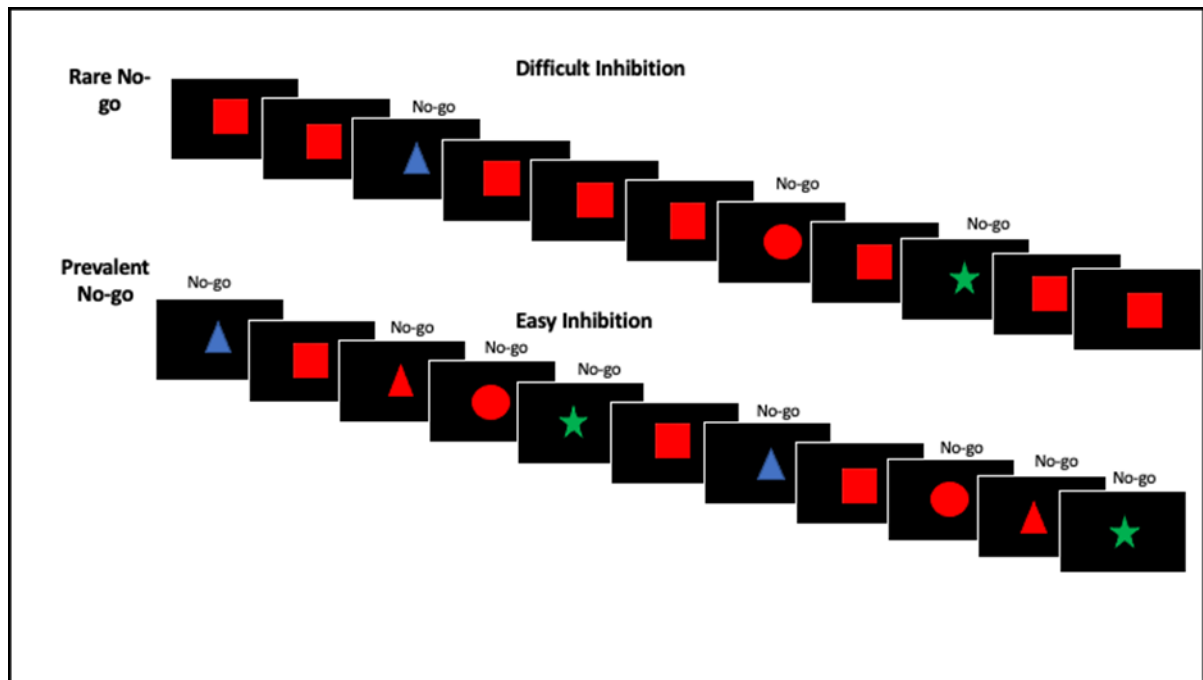


Figure 2.1. The experimental task, used in the behavioral and fMRI sessions. A series of stimuli were displayed in the centre of the screen for 100ms each, with varying inter-stimulus intervals (ISI). Participants were instructed to respond to a Go stimulus (a red square) using a button click and to ignore all other stimuli (No-go stimuli). There were two task conditions presented in separate runs: **(a)** rare No-go (where 25-30% of the trials were No-go trials) and **(b)** prevalent No-go (where 70-75% of trials were No-go trials).

2.3.3 Neuroimaging

Imaging data were collected in a Siemens 3T Prisma MRI scanner at SCAN@TAU centre in Tel-Aviv University, using a 64-channel head coil. All data were collected within a single scanning session.

2.3.3.1 fMRI acquisition- parietal modulation during inhibitory demand

fMRI data used in this study were previously published (Kolodny et al., 2020). Detailed methods including acquisition, task, and processing steps are briefly described as they were previously reported. While participants completed the Go/No-go task, functional images were collected using a gradient-echo sequence (*Supplementary Methods section 1 in Appendix A*).

An ROI analysis was performed to extract parietal modulation during inhibitory demand in right and left IPS and in left TPJ, using masks of inhibition-related activation in neurotypicals (Kolodny et al., 2017) (see *Figure 3, Table 1 and Appendix A* in that paper for ROI details and masks). These regions were chosen as they showed activation changes during inhibitory demand in previous research (Kolodny et al., 2017). In the ADHD group, percent signal change for each condition (rare-No-go and prevalent-No-go) was computed in reference to an implicit baseline and averaged across voxels within each ROI. For each participant and ROI, the difference between conditions served as the fMRI parietal modulation score, and was used as the outcome measure in the regression models described below.

2.3.4 dMRI analysis

2.3.4.1 dMRI acquisition

The dMRI data were acquired using a standard 64-direction protocol using a whole brain echo planar imaging sequence over one phase-encoding direction: phase-encoding direction = A-P, TR = 6900ms, TE = 53ms; 76 slices, slice thickness = 1.7mm, no gap; FOV = 197 x 197 mm, matrix size = 216 x 216, providing a cubic resolution of 1.7 x 1.7 x 1.7 mm. 64 diffusion-weighted volumes ($b = 1000 \text{ sec/mm}^2$ and three reference volumes ($b = 0 \text{ sec/mm}^2$) were acquired using a standard diffusion direction matrix. High-resolution T1-weighted anatomical scans were also collected for each participant to aid co-registration, using a magnetization prepared rapid acquisition gradient echo (MPRAGE) protocol (TR = 1.75 sec, TE = 2.61 msec, T1 = 900 msec, FOV = 220 x 220, matrix = 220 x 220, axial plane, slice thickness = 1 mm, 160 slices, for an isotropic voxel resolution of 1 mm³).

2.3.4.2 dMRI preprocessing and processing

The dMRI preprocessing and processing were performed using the FMRIB Diffusion Toolbox (FDT) in FSL (Jenkinson et al., 2012; S. M. Smith et al., 2004; Woolrich et al., 2009), following FSL's standard dMRI processing pipeline. Unweighted (b_0) scans were extracted from the dMRI data using the FSL utility tool, `fslroi`. Brain extraction was performed on one of these images using BET (fractional intensity = 0.5) (S. M. Smith, 2002). Eddy-current and motion correction were performed using EDDY and outlier slices were replaced with slices generated by the Gaussian prediction (Andersson et al., 2016; Andersson

& Sotiropoulos, 2016) as this is suggested to be the most effective method of reducing motion artefacts (Oldham et al., 2020). The number and orientations of crossing fibres within each voxel were modelled using the FDT tool BEDPOSTx. A ball and stick with single diffusion coefficient model was used (Behrens et al., 2003, 2007)

2.3.4.3 dMRI Quality Assurance

The quality of eddy-current correction was assessed using EDDY QUAD and EDDY SQUAD to flag datasets which potentially contained motion artefacts. Datasets were flagged if their absolute and relative motion metrics were outliers when compared to the control group's distributions of motion metrics, in order to prevent the potential heightened proneness to in-scanner motion in ADHD masking outliers (Aoki et al., 2018). Flagged datasets were then visually inspected for identifiable motion artefacts. Datasets with a volume containing an identifiable motion artefact were dropped from analysis, as has been previously recommended (Bastiani et al., 2019). This resulted in 8 datasets being excluded (ADHD = 6, control = 2). Whole datasets were excluded rather than individually affected volumes as volume removal risks interfering with diffusion metric estimation (Chen et al., 2015). Furthermore, datasets with more than 20% of volumes containing a replaced slice were considered 'poor quality' and also dropped from analysis (ADHD = 3, controls = 3) (Baum et al., 2018). This resulted in a final dMRI sample of 33 ADHD and 19 controls (*Table 2.1*).

2.3.4.4 Probabilistic tractography

ROIs for seed-based tractography were selected at the right IFG, left IFG, right IPS and left IPS, based on the functional connectivity findings in Kolodny (11). Seed ROIs were defined using the FIND Atlas (Shirer et al., 2012) and registered to individual subjects' space

using FLIRT (Greve & Fischl, 2009; Jenkinson et al., 2002; Jenkinson & Smith, 2001). Voxel counts for each of the Seed ROIs were as follows: right IFG = 326, left IFG = 1105, left IPS = 2020, right IPS = 1193. Probabilistic tractography was performed using Probtrackx (Behrens et al., 2003, 2007) to produce a 3D structural connectivity distribution for white matter tracts connecting the four ROIs. FSL's standard settings were used: step length = 0.5mm, samples drawn in each voxel = 5000, subsidiary fibre volume threshold = 0.01, curvature threshold = 0.2. For cross-hemisphere pathways, the corpus callosum was used as a waypoint, defined using the ICBM DTI-81 Atlas (Mori et al., 2008; Oishi et al., 2008).

The end result of tractography was connectivity distributions for four tracts (*Figure 2.2*): 1) IFG-IFG, a tract connecting the right and left IFG; 2) IPS-IPS, a tract connecting the right and left IPS; 3) Right IFG-IPS, a tract connecting the right IFG and the right IPS; 4) Left IFG-IPS, a tract connecting the left IFG and the left IPS.

The IFG-IPS tracts partly overlap with the established Superior Longitudinal Fasciculus (SLF), as determined using the ICBM DTI-81 Atlas. The SLF is a large system of association fibres connecting the frontal and the parietal lobes and prefrontal areas (Barbeau et al., 2020; Janelle et al., 2022; Schurr et al., 2020). The IFG-IFG or IPS-IPS tracts passed through the genu and splenium of the corpus callosum, respectively, but did not clearly overlap with any major WM pathways from the ICBM DTI-81 Atlas.

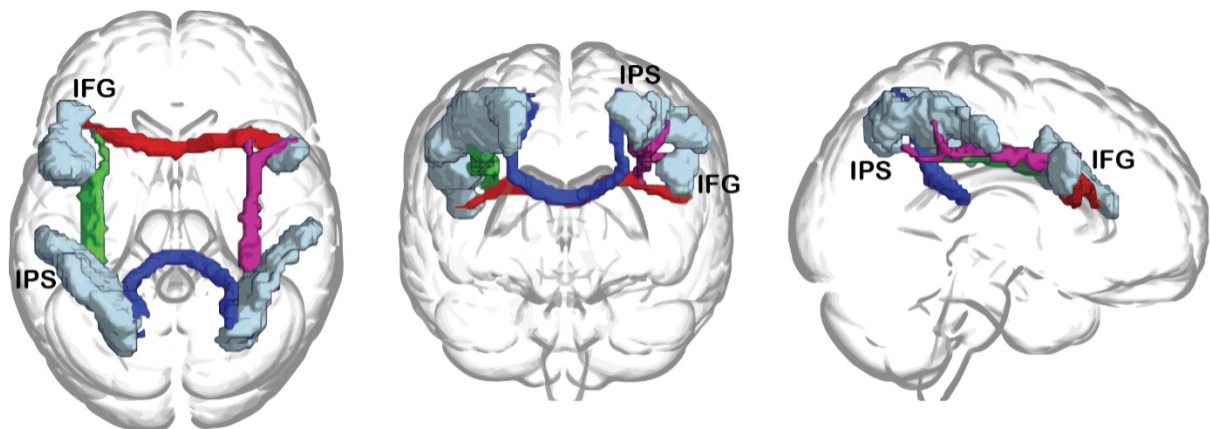


Figure 2.2. Probabilistic tractography outcomes for an example ADHD participant, warped to standard space and presented in superior, posterior and right views. Seed ROIs in the right and left inferior frontal gyrus (IFG) and left and right intraparietal sulcus (IPS) are shown in light blue. Four tracts are depicted, a frontal tract connecting the lIFG and rIFG (red), a parietal tract connecting the lIPS and rIPS (blue), a right frontoparietal tract connecting the rIFG and rIPS (pink), and a left frontoparietal tract connecting the lIFG and lIPS (green).

Illustration created by overlaying Probtrackx output on a standard MNI template, using the glass brain setting in MRICroGL (Rorden & Brett, 2000).

2.3.4.5 White matter property extraction

Diffusion Tensor Fitting was performed at the whole-brain level using DTIFIT to produce FA, AD, RD and MD values in each voxel. Values from voxels contained within the four tracts described above were averaged to produce tract-level metrics.

Tract volumes were obtained using `fslmaths` and `fslstats`. Spurious tract paths were eliminated prior to volume estimation by thresholding tracts at 15% of maximum path count in each individual and binarizing them to create tract masks (Khalsa et al., 2014). To account for the effects of individual brain size differences on tract volume (Morris et al., 2008), for each participant we determined what percentage of that participant's whole brain volume was accounted for by a tract's volume. We then determined what volume this percentage accounted for in MNI standard space. The values produced by DTIFIT from voxels contained within the masks of the four tracts described above were averaged to produce tract-level metrics.

To control for outliers, tracts with within-group volume $z > 3$ were excluded from subsequent analysis for all metrics, on the basis that this likely represents a poor tract reconstruction. FA, AD, RD and MD outliers were excluded individually using the same criterion (i.e., $z > 3$). Following outlier detection, all IPS-IPS metrics for one control participant were removed from analysis due to the tract's volume being an outlier. Individually, one control participant's IFG-IFG MD and AD were also removed from analysis. For the ADHD group, due to tract volume outliers, all metrics for one participant's IFG-IFG tract were removed from analysis and all metrics for another participant's IPS-IPS tract were similarly removed.

2.3.5 Statistical analysis

Parametric tests were carried out in SPSS 26, whilst non-parametric tests were implemented in-house in python. Normality of variables was assessed using the Shapiro-Wilk test of normality (Shapiro & Wilk, 1965), and group differences were tested using t-tests for normally distributed data, and randomisation tests with 100,000 permutations for data with skewed distributions.

To investigate the link between structural connectivity, functional activation and task performance, we used stepwise regression models. The five dMRI metrics (volume, FA, RD, MD & AD) of the four tracts (IPS-IPS, right IPS-IFG, IFG-IFG, left IPS-IFG) were used as potential predictors in these models. Parietal fMRI modulation by inhibitory demand, as well as behavioural response inhibition performance, served as outcome measures. For parietal fMRI modulation, data were available only for the ADHD group, and separate models were used to predict each of the three parietal ROI activations (right IPS, left IPS, left TPJ). To predict behavioural response inhibition task performance, separate models were run for the ADHD and control groups. Thus, five regression models were run in total.

To limit the number of predictors in each regression model and lower the risk of over-fitting, we determined potential predictors to include in the models using Pearson's correlation coefficients: we first calculated partial correlations between dMRI metrics and the outcome measures, controlling for sex and age. Then, the variables which were correlated with the outcome at a relaxed level of significance ($p < 0.10$) were included as potential predictors in the corresponding stepwise regression (Chowdhury & Turin, 2020). In all stepwise regressions, we controlled for age and sex by including them as potential predictors. Collinearity between potential predictors was tested using the variance initiating factor, but no correlation between any predictor variables was severe enough to require attention.

Finally, for all analyses we corrected for multiple comparisons using Benjamini and Hochberg's False Discovery Rate (Benjamini & Hochberg, 1995).

2.4 Results

2.4.1 Group differences in WM properties

We first tested the differences between groups for the five metrics (volume, FA, MD, AD and RD) in each of the four tracts. AD in the IFG-IFG tract was significantly lower in ADHD (n=32, mean= 1.25×10^{-3} s/mm², sd= 3.80×10^{-5}) than in controls (n=18, mean= 1.27×10^{-3} , sd= 3.22×10^{-5} ; randomization test corrected for multiple comparisons p=.005; *Figure 2.3*). Since one particularly low score seemed to be driving the effect, we ran this comparison again without this participant, and IFG-IFG AD was still significantly lower in ADHD (n=31, mean= 1.25×10^{-3} s/mm², sd= 2.90×10^{-5} ; p=.007). No other group differences reached significance (*Table A3 in Appendix A*).

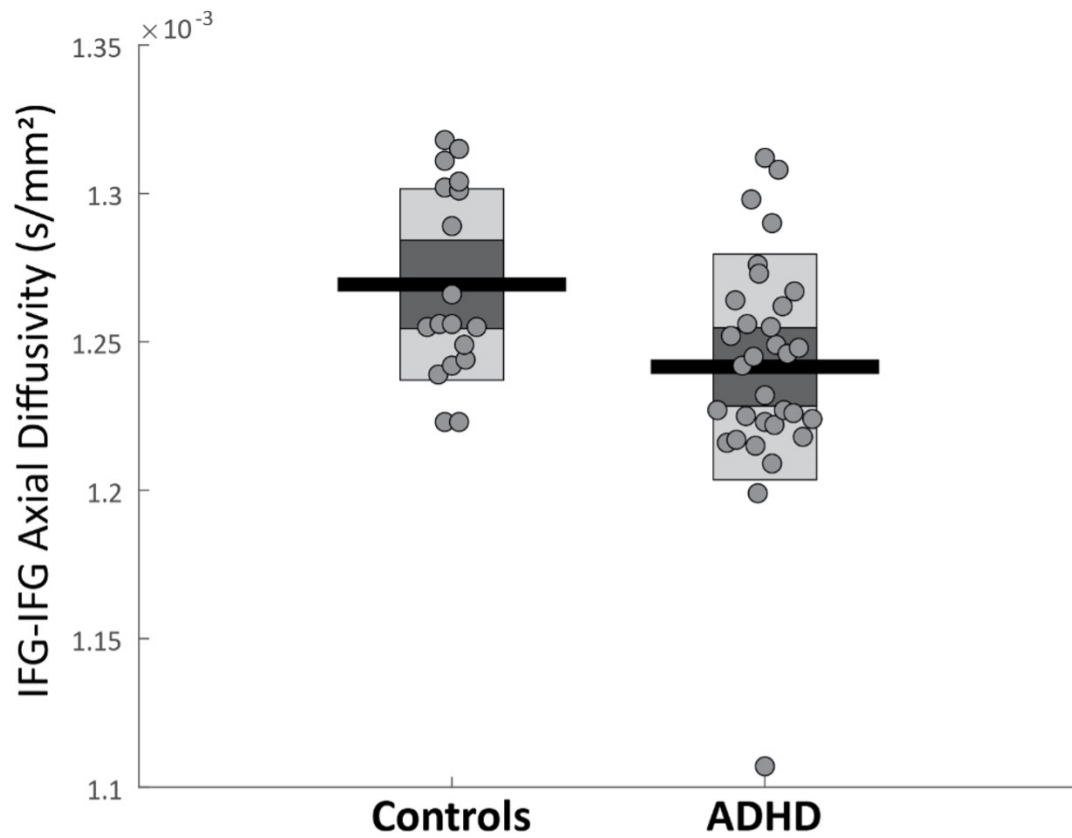


Figure 2.3. Mean axial diffusivity of the white matter tract connecting the right and left IFG for the ADHD and control groups. Horizontal black lines denote group mean, bars denote 95% confidence intervals, and the central dark area of the bar denotes 1 SD around the mean. Circles represent individual participants.

2.4.2 Predicting parietal functional modulation by inhibitory demand in ADHD from WM properties

To assess whether structural properties could underlie functional activation during inhibition in ADHD, we used stepwise regression models. Potential structural predictors were determined using the procedure outlined in *Methods section 2.3.5*, resulting in four predictors consisting of volume and RD from the IFG-IFG and left IFG-IPS tracts. Sex and age were also included in the models. Three separate stepwise regression models were run with activation in the left IPS, left TPJ and right IPS as the outcome measure. Following multiple comparison correction, all three models were significant, indicating that WM metrics of the IFG-IFG and left IFG-IPS tracts predicted parietal functional modulation by inhibitory demand (*Figure 2.4; Table A4 in Appendix A*).

Specifically, left IPS functional modulation was significantly predicted ($F(3,25)=8.750$, $p<.001$, $R^2=.454$), with volumes of the IFG-IFG tract ($\beta=.358$, $p=.017$) and the left IFG-IPS tract ($\beta=.408$, $p=.007$) contributing positively, and the IFG-IFG tract's RD ($r=-.455$, $p=.003$) contributing negatively.

Right IPS functional modulation was also significantly predicted ($F(2,27)=5.775$, $p=.008$, $R^2=.248$). The left IFG-IPS tract volume again positively predicted right IPS modulation ($\beta=.382$, $p=.025$), and the IFG-IFG tract RD again negatively predicted right IPS modulation ($\beta=-.399$, $p=.020$).

Finally, left TPJ functional modulation was also significantly predicted ($F(2,26)=6.264$, $p=.006$, $R^2=.273$). Here too, volumes of the IFG-IFG tract ($\beta=.380$, $p=.026$) and left IFG-IPS tract ($\beta=.429$, $p=.013$) positively predicted left TPJ modulation.

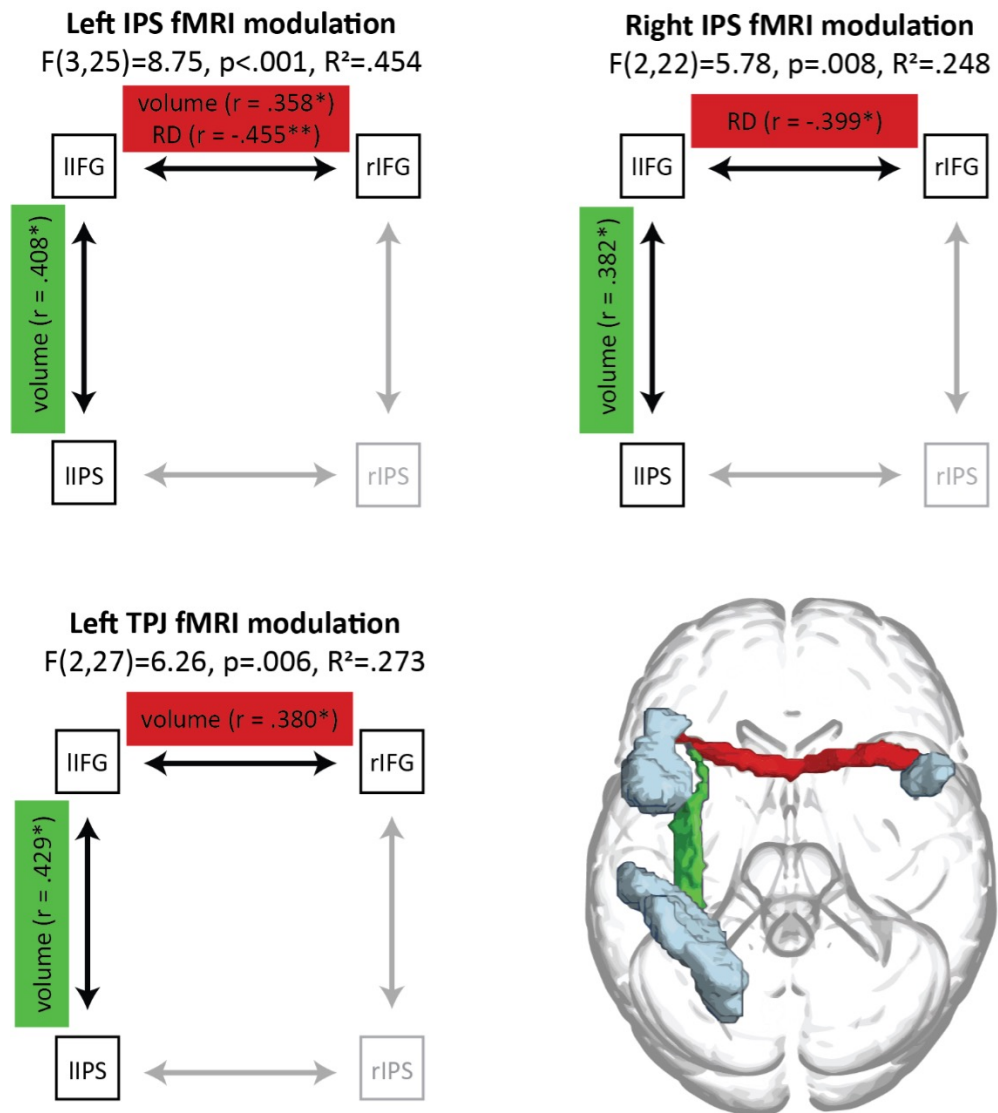


Figure 2.4. Stepwise regression models predicting greater parietal modulations during inhibitory demand in ADHD.

2.4.3 Predicting response inhibition performance in ADHD and controls from WM properties

To investigate the relationship of WM properties to response inhibition performance in the ADHD and control groups, we again used stepwise regressions. Potential predictors were determined using the procedure outlined in *Methods Section 2.3.5*. All of the following results survived multiple comparison correction.

Significant models predicted response inhibition performance in each group, but by different structural properties in different tracts (*Figure 2.5; Table A5 in Appendix A*): In the ADHD group, IFG-IFG tract MD was significantly predictive of response inhibition performance ($F(1,26)=5.380$, $p=.028$, $r^2=.140$), such that higher IFG-IFG tract MD was associated with better response inhibition performance (lower commission errors): $\beta=-.414$, $p=.028$.

In controls, response inhibition performance was significantly predicted by IPS-IPS tract RD: $F(1,14)=6.388$, $p=.024$, $R^2=.264$. The significant contribution made by IPS-IPS tract RD was in a positive direction, with higher IPS-IPS tract RD predicting worse response inhibition performance in controls: $\beta=.560$, $p=.024$.

Since the significant predictors differed between the models for ADHD and controls, we directly compared the strength of predictor-outcome correlations between groups, using Fisher's r to z transformation. We found that the relationship between IPS-IPS tract RD and response inhibition performance was indeed stronger in controls ($r=.544$, $p<.005$) than in ADHD ($r_s(28)=-.252$, $p=.201$; $Z=-2.6$, $p<.005$), but there was no significant group difference in the correlation between IFG-IFG tract MD and response inhibition performance (controls: $r_s(15)=.290$, $p=.294$; ADHD: $r=.125$, $p>.05$; $Z=.52$, $p=0.345$).

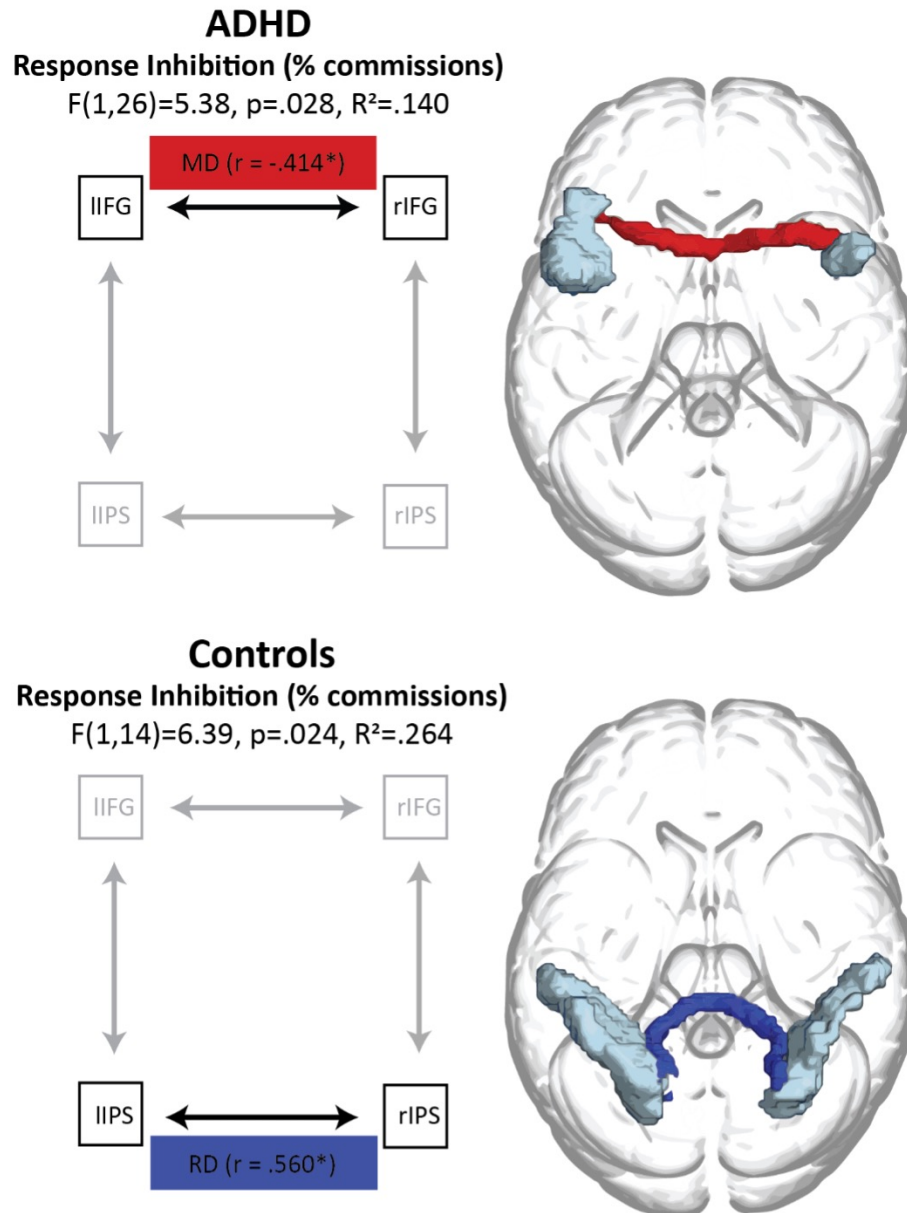


Figure 2.5. Stepwise regression models predicting better response inhibition performance in ADHD and in controls.

2.4.4 Examining potential motion confounds

Although we applied several steps of data cleaning in the dMRI analyses, some residual motion artefacts might still be present and impact the results (Yendiki et al., 2014). As motion is typically higher in ADHD, to ensure structural measures had not been confounded by in-scanner movement we assessed in-scanner absolute and relative motion metrics. There was no significant difference between groups' motion metrics, and neither metric was correlated with any of the dMRI metrics (*Tables A6-A8 in Appendix A*). Thus, it is unlikely that in-scanner motion confounded the current findings.

2.4.5 Examining the potential role of global WM metrics using TBSS

To ascertain the specificity of our findings to the IPS-IFG tracts, we repeated the analysis with global WM metrics. Voxelwise analysis was carried out using TBSS (Tract-Based Spatial Statistics). The skeleton produced by TBSS is created by first aligning each participants FA image into standard space and then averaging these normalised averages to produce a mean FA map. The mean FA map is thinned so that the skeleton represents the centre of all tracts common to the group.

FA and diffusivity metrics were averaged across the skeleton mask, and served as predictors in regression models, with fMRI parietal modulation as the outcome measure, as in the main analyses. However, none of the correlations between global WM metrics and fMRI modulation reached the threshold required to be included as potential predictors (*Table A9 in Appendix A*). Thus, there is no evidence to support the notion that non-specific WM properties underly the observed link between the IFG-IFG and left IFG-left IPS tracts and parietal engagement in response inhibition.

2.5 Discussion

Recent studies from our group pointed to a specific role of functional circuitry between the IFG and the IPS in deficient response inhibition in ADHD (Kolodny et al., 2017, 2020). In the present study we investigated whether this functional connectivity is also reflected in structural connectivity differences. If the functional differences previously reported are coupled with structural ones it can point to a systematic mechanism that underlies deficient response inhibition in ADHD, and is therefore less likely to result from differences in strategy or engagement of top-down processes. Using diffusion-weighted MRI and seed-based probabilistic tractography, we assessed the WM properties of four tracts connecting the IFG and the IPS bilaterally. This identified the importance of transcallosal structural connectivity (volume and diffusivity) between the left and right IFG as well as of a left frontoparietal tract (overlapping with the SLF) in response inhibition in ADHD. On a group level, there were minimal differences between ADHD and control participants in the WM properties (lower AD) of the IFG-IFG tract. However, on an individual differences' level within the ADHD group, WM properties of this tract were significantly associated both the engagement of the parietal regions during task fMRI (volume and RD) and behavioural performance in a response inhibition task (MD).

Some evidence of a role for transcallosal IFG to IFG connectivity in ADHD was provided by lower AD in ADHD compared to controls. Lower AD has been proposed to reflect reduced calibre of, or injury to, axons, or reduced coherence in axon orientation (Solowij et al., 2017). However, the anatomy which underpins AD and thus the implication of lower AD is debated (Jones et al., 2013). Our findings of atypical IFG-IFG AD in ADHD are in line with reports that the IFG is a key node for cognitive and attentional control, whose activity is impaired in ADHD (Cepeda et al., 2000; Cubillo et al., 2012; Dickstein et al., 2006; H. Huang & Ding, 2016). Our results also implicate the IFG-IFG tract's structure

specifically in the context of response inhibition. We found that increased IFG-IFG RD was partly linked with lower left and right IPS modulation during inhibitory demand as measured with fMRI. As with AD, the anatomical underpinnings of RD are debated, but increased RD has been proposed to reflect a loss of myelin, loss of axons, or reduced axonal packing density (Solowij et al., 2017). In addition to the tract's RD, increased IFG-IFG tract volume was significantly associated with greater left IPS and left TPJ fMRI modulation during inhibitory demand (i.e., modulation that is more similar to that observed in control participants). Factors proposed to drive an alteration in WM volume include number of axons, thickness of myelin around axons, number of axons with a myelin sheath, axonal branching and axonal crossing (Fields, 2010).

Importantly, IFG-IFG WM properties were not only linked with functional engagement of parietal nodes for increased inhibitory demand, but also behavioural response inhibition performance in a Go/No-go task among participants with ADHD. Increased IFG-IFG tract MD (the average of AD and RD) was associated with better response inhibition performance. Notably, this was not the case for the control group. Instead, their response inhibition performance was linked with the RD of the parietal tract connecting the left and right IPS. These differential results suggest that response inhibition may be executed differently in individuals with and without ADHD. The IFG is associated with cognitive and attentional control (Hampshire et al., 2010; Shomstein, 2012) and involved in a broad range of other cognitive functions as one of the key domain-general areas in the brain (Fedorenko et al., 2013). The fact that individual differences in the IFG-IFG tract in ADHD are associated with behavioural performance may suggest that difficulties in response inhibition stem from an alteration in a more general cognitive function (e.g. context monitoring), or that during response inhibition a broader and less specialised neural network is recruited.

The IFG-IFG tract in the current study crosses between the hemispheres through the anterior part of the corpus callosum. Our findings are consistent with previous reports highlighting lower corpus callosum volume in children with ADHD, and its association with worse sustained attention and attentional control (Cao et al., 2009; Hutchinson et al., 2008). AD in the corpus callosum has also been implicated in ADHD, with increased AD linked with greater symptom severity, and poorer attention and working memory (Chiang et al., 2020). Thus, the current findings of atypical IFG-IFG connectivity in the more severe ADHD participants may be related to general corpus callosum atypicalities in ADHD and their effect on interhemispheric communication. The fact that the interhemispheric parietal tract was not implicated in ADHD may point to a more specific atypicality in the frontal tract or in the genu of the corpus callosum through which this tract passes. Future research using spatial tract profiling and corpus callosum segmentation is required to further clarify this issue.

The left hemisphere fronto-parietal tract connecting the IFG and the IPS was also related to response inhibition functional modulation in ADHD. Increased left IFG-IPS tract volume was associated with increased activity in the left IPS, right IPS, and left TPJ during inhibitory demand. This supports the notion that IFG-IPS connectivity is important in ADHD for engaging parietal cortices when response inhibition demand increases (Kolodny et al., 2020). Using intracranial EEG and direct electrical stimulation, it has been found that critical time windows for the IPS and the IFG during response inhibition are highly similar, and it has been hypothesized that IFG/IPS processes run separately but in parallel during inhibitory demand (Osada et al., 2019; Swann et al., 2009; Wessel et al., 2013). An alternative hypothesis proposes that the two regions do not behave separately, but that the inferior frontal cortex inhibits down-stream parietal activity during inhibitory demand (Sakai et al., 2009). Our findings lend support to the latter theory that the inferior frontal cortex modulates down-stream parietal activity during inhibitory demand.

The IFG-IPS tract makes up, in part, the ventrolateral subdivision of the superior longitudinal fasciculus (SLF III). Structure-function relationships between the SLF and specific cognitive functions are yet to be fully elucidated, but associations have been suggested with perceptual organization and working memory (Koshiyama et al., 2020), sustained attention (Klarborg et al., 2013), and importantly for the interpretation of current results, response inhibition. Previous research has also implicated WM properties of the SLF in children and in adults with ADHD (Chiang et al., 2015; Hyde et al., 2020; Wolfers et al., 2015). Our findings suggest the left tract, but not the right tract, is important in response inhibition. This may be surprising given the central role of the right IFG, specifically, in previous studies of response inhibition (Aron et al., 2004, 2014). However, since our findings also demonstrate a role for the IFG-IFG tract, they do not detract from the involvement of the right IFG in the inhibition-related circuitry. Furthermore, our findings are consistent with studies highlighting the role of the left IFG in inhibition (Krämer et al., 2013; Serrien & Sovijärvi-Spapé, 2013) and those indicating that its integrity is critical for successful implementation of response inhibition (Swick et al., 2008).

In this discussion, we have implicitly considered that structural metrics underlie functional activation and subsequently cause response inhibition performance variation. However, structure-function relationships are known to be bidirectional, and training has been shown to induce changes in WM properties (Fields, 2010). For example, increased FA in somatosensory and visual cortices followed tactile braille reading training (Molendowska et al., 2021), increased FA in the right IPS followed juggling training (Scholz et al., 2009), and lower MD in the left arcuate fasciculus followed intensive reading intervention (Huber et al., 2018). The findings of the current study suggest that the IFG-IFG and IPS-IFG WM tracts could be used as potential targets to study intervention outcomes. Future research may investigate the plasticity of this neural circuit, perhaps via training. Several training regimes

have been demonstrated to improve executive functioning and inhibitory control, including computerized cognitive training (Kolodny et al., 2017; Zhao et al., 2018), mindfulness practice (Isbel et al., 2020) and neurofeedback (Bluschke et al., 2016), but none of the existing studies tracked induced changes in structural brain properties.

There are a number of limitations to the current study. First, dMRI data was collected using relatively basic acquisition parameters: a single b-value limits the robustness of cross-fibre modelling, relative to current state-of-the-art multi-shell acquisitions. As no opposite phase encoding direction scan was acquired, motion correction could not include an estimation of motion's impact on susceptibility-induced distortions. Whilst this step is not mandatory, it is recommended and could be specifically important when one group of participants is more prone for motion, as is the case for ADHD (Durstun et al., 2003; Epstein et al., 2007; Yu-Feng et al., 2007). We addressed this by strict preprocessing quality control and excluded data flagged for motion. In the retained data, there was no significant group difference in in-scanner motion, and motion parameters did not correlate with any WM metrics. Thus, although distortion correction could have been beneficial, we believe the current findings are not driven by motion artefacts.

The current study demonstrated a role for WM structure in the atypical recruitment of fronto-parietal networks in ADHD during response inhibition. Microstructural properties of the cross-hemispheric IFG-IFG tract and the left fronto-parietal IFG-IPS tract were linked not only fMRI activation but also response inhibition performance in ADHD, as measured behaviourally (outside the scanner). These findings highlight deficient top-down control brought about by maladaptive connectivity as a mechanism of inhibition difficulty in ADHD.

Chapter 3

**The influence of ADHD traits on the effects of IPS
disruption on response inhibition performance: a cTBS
study**

Chapter 3

3.1 Abstract

Response inhibition is an executive function which is impaired in ADHD (Penadés et al., 2007; Pievsky & McGrath, 2018; Willcutt et al., 2005; Wright et al., 2014). The IIPS is typically modulated by inhibitory demand, yet this modulation is less pronounced in individuals with greater ADHD symptom severity (Kolodny et al., 2017, 2020). In the current chapter cTBS targeted participants ($n = 30$) IIPS and a control region (CZ) with inhibitory cTBS prior to them completing a Go/No-go task to investigate the impact of IIPS disruption on response inhibition performance. Our results found that, whilst there was no difference in task performance between stimulation conditions, the effect of IIPS disruption on response inhibition was related to ADHD traits, with IIPS inhibition leading to worse response inhibition performance for individuals with greater ADHD traits. Our findings may be explained by individuals with greater ADHD traits may having reduced compensatory mechanisms through previously discussed atypical connectivity within the IFG-IPS network, resulting in a greater susceptibility to disruption of individual nodes of this network, such as the IIPS in the current study. Alternatively, the complex relationship between TMS and activation state in the targeted region may also explain our these findings, such as ADHD-related differences in ongoing IIPS activity or increased cognitive load in the disorder.

3.2 Introduction

As has been previously discussed (*Chapter 1, section 1.3*), response inhibition is a cognitive process which is underpinned by a broad frontoparietal network (Criaud & Boulinguez, 2013; Swick et al., 2011) and is impaired in ADHD (Penadés et al., 2007; Pievsky & McGrath, 2018; Willcutt et al., 2005; Wright et al., 2014). Previous research employed a modified version of a go/nogo task which contrasted levels of inhibitory demand to implicate specific nodes of the frontoparietal network, namely the bilateral IPS and left TPJ, in neurotypical response inhibition (Kolodny et al., 2017). Following this, the same task was completed by an adult ADHD cohort, suggesting that the modulation of IPS and TPJ activation produced by inhibitory demand was less pronounced in those with more severe ADHD, and that a similar effect of ADHD-severity was present in the functional connectivity between the IPS and IFG during inhibitory demand (Kolodny et al., 2020). In a previous study (*Chapter 2, Smullen et al., in review*), I built upon these findings, demonstrating that structural properties of the white matter underpinning the IFG-IPS circuit predict the modulation of the implicated brain regions during inhibitory demand.

Until now, the research discussed in this thesis has implicated the IPS, both its activation and functional and structural connectivity with the IFG, in response inhibition performance. However, a causal link has yet to be demonstrated. In the current chapter, I aim to demonstrate the causal contribution of IPS activation in response inhibition performance and its association with ADHD tendencies using TMS.

As outlined earlier, a few attempts have been conducted with TMS as an intervention targeting ADHD symptoms (*Chapter 1, section 1.4.3*). For example, an inhibitory 1 Hz TMS to the SMA in ADHD individuals lead to significantly alleviated hyperactivity symptoms over 4 weeks (Niederhofer, 2008), whilst inhibitory low-frequency (1 Hz) repetitive TMS to

the rSMA has also been demonstrated to lead to a 3-week improvement to hyperactivity symptoms in ADHD individuals (Niederhofer, 2012). Inattention symptoms have also been alleviated by TMS, with attention performance 10 minutes after repetitive TMS to the right prefrontal cortex being improved in 13 ADHD adults (Bloch et al., 2010).

More relevant for the current research, TMS has previously been demonstrated to impact response inhibition in neurotypicals such as by inhibitory TMS to the rIFG (Obeso et al., 2013). Single-pulse TMS to the pre-SMA results in impaired action cancellation performance on stop-signal tasks (Obeso et al., 2013), whilst performance is improved by intermittent theta burst stimulation (which is an excitatory TMS protocol) to the same region (Ji et al., 2019). Action withholding has also been demonstrated to be impacted by TMS. For example, it has been reported that following an inhibitory 40s cTBS protocol targeting the rAI and the superior frontal gyrus, both action-cancellation performance on a stop-signal task and action withholding on a go/nogo task were significantly worse when compared to a sham stimulation (Dambacher et al., 2014).

Thus, it remains to be seen whether a similar approach targeting the IPS can demonstrate its causal role in action withholding and especially its scaling with ADHD tendencies. To do that I used continuous theta-burst stimulation (cTBS; Huang et al., 2005), an inhibitory TMS protocol which produces a relatively long-lasting (of up to 1 hour) effect, over the left IPS and a control site (Vertex; Cz) in a neurotypical cohort in which ADHD tendencies were assessed, immediately prior to them completing a modified 10-minute version of the go/nogo task. If the scaling of the IPS modulation during inhibitory demand with ADHD symptoms severity (Kolodny et al., 2020), is causally related to response inhibition performance, I expect the effect of IPS TMS to scale with ADHD trait expression in the current cohort. However, the direction of such scaling is not obvious. One possibility is that participants with greater ADHD trait expression will be more susceptible to the effects of

TMS to the IPS due to their less robust engagement of the IPS during inhibitory demand, compared with participants with low ADHD trait expression. However, given the complex relation between TMS and activation state in the targeted region an opposite direction is also possible whereby the reduced engagement of the IPS in high ADHD trait expression is indicative of less active IPS, and consequently less inhibitory TMS effect (Bradley et al., 2022). Importantly, however, the main question would be whether or not the TMS effect will be scaled with ADHD trait expression in the current cohort, irrespective of its direction.

As a control measure for the specificity of the TMS effect, I also investigated sustained attention performance during the go/nogo task. Similar to response inhibition I tested the TMS effect on sustained attention on the group level, as well as the scaling of the TMS effect with ADHD tendencies. This way, I was able to ensure that any association between inhibitory cTBS to the left IPS and response inhibition performance is indicative of a specific role it plays in this cognitive function.

3.3 Methods

3.3.1 Participants

Participants were Psychology students at the University of Birmingham with no reported history of ADHD diagnosis to ensure that the effects of medication were not present in the data. Participants were recruited via the University of Birmingham's participant pool recruitment website (Sona; <https://birmingham.sona-systems.com>). The initial sample included 32 adult participants aged 18-27 (mean age = 21.42y, sd = 2.78y, male = 8). Following outlier removal (*see section 3.3.5*) there remained 30 adult participants aged 18-27 (mean age = 21.45y, sd = 2.82y, male = 8). The study was approved by the STEM ethics committee at the University of Birmingham. All participants provided informed consent at

the beginning of the study and were informed that they could withdraw their participation and data at any point during or within 5 weeks of the experiment. Participants were compensated for their participation with course credits.

3.3.2 Materials

3.3.2.1 Response inhibition - Go/No-go Task

Response inhibition performance was assessed using a 10-minute adapted version of the Rare No-go condition of the Go/No-go task devised by Kolodny and colleagues (2017, 2020) and outlined previously (*Chapter 2, section 2.3.2.1*). The task was adapted by decreasing the inter-trial interval (ITI) from 1.8-12s to 1-1.8s. This adaptation enabled including more trials (512, relative to 396) within a slightly shorter run (total of 10 minutes, relative to 12 minutes). Importantly, shorter ITIs increase the difficulty of the task and elicit more inhibition errors (false alarms), hence enabling a more sensitive measurement of response inhibition function, suitable for the detection of the typically subtle effects of cTBS (*see Figure 3.1*).

Coloured shapes appeared sequentially in the centre of the screen for 100ms each, with varying inter-stimulus intervals (ISI), ranging between 1 and 1.8s. Shapes were either squares, circles, triangles or stars, and coloured red, blue, green or yellow. Participants were instructed to respond quickly via a button click when a red square appeared (Go trials), and withhold response to any other stimuli (No-go trials). 70% of trials were Go trials. Of the No-go trials, 33% were red non-squares, 33% were non-red squares, and 33% were non-red non-square shapes. Response inhibition performance was quantified as the percentage of commission errors, whilst sustained attention performance was quantified as the standard

deviation of response times for correct responses to Go trials. Participants sat approximately 50cm away from the screen. Stimuli size was set to 9% of total screen size.

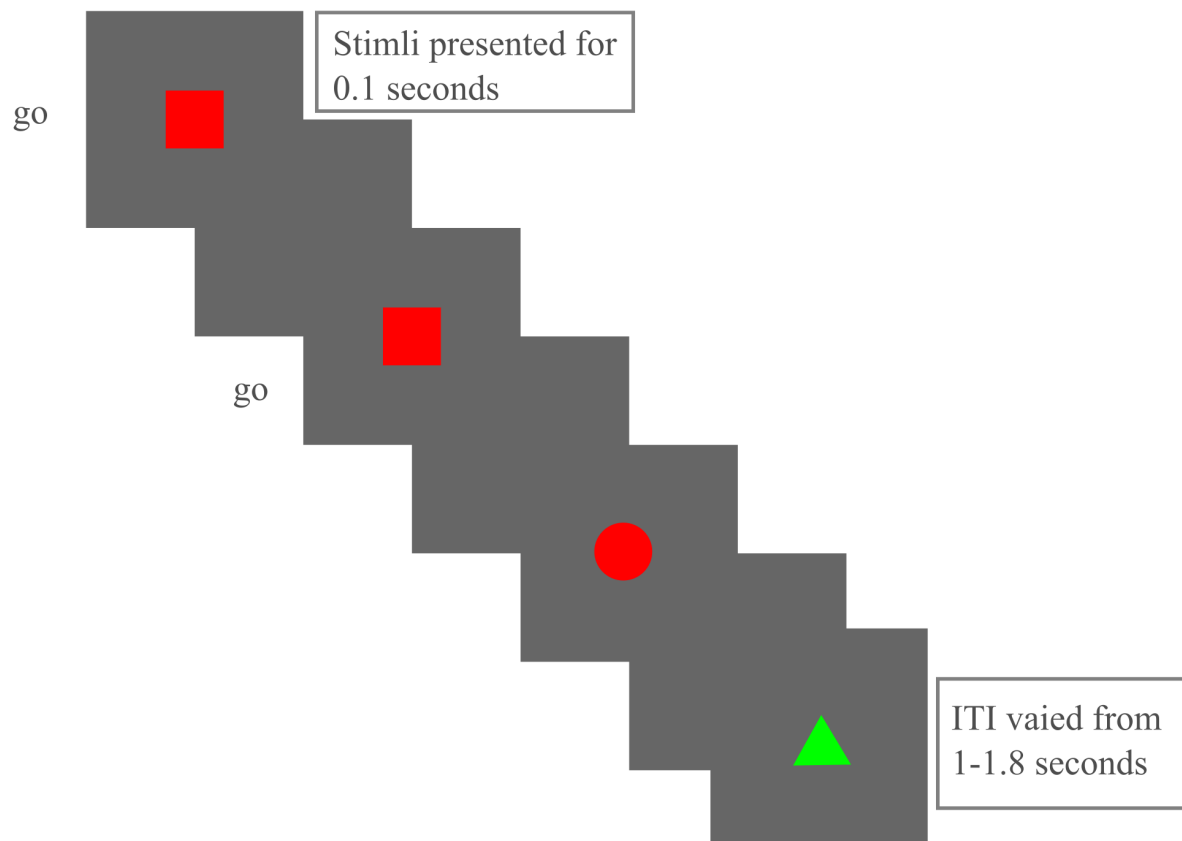


Figure 3.1. Illustration of the Go/No-go task. Participants were shown a series of stimuli and were instructed to respond as fast as possible to go stimuli (a red square) and to withhold responses to all other stimuli. Go trials made up 70% of a total of 512 trials. Participants completed one run of the task.

3.3.2.2 Adult ADHD Self-Report Scale (ASRS)

The ASRS is a widely used questionnaire, which assess the severity with which an adult experiences ADHD symptoms (Kessler et al., 2005). See *Chapter 2, section 2.3.2.2* for more details.

3.3.3 Experimental Procedure

The experiment consisted of 2 sessions (lasting around 40 minutes each) which were conducted roughly a week apart. At the beginning of the first session, participants completed the TMS safety screening form and gave informed consent. Next, participants underwent the TMS protocol during both sessions (outlined in *section 2.4*). Following stimulation the participants completed the Go/No-go task. In the second session, following the Go/No-go task, the participants completed the ASRS. The ASRS was administered at the end of the session in order to avoid priming and influencing the participants behaviour during the task. As the ASRS assesses general symptoms, rather than symptoms at that specific time, responses should not be affected by cTBS

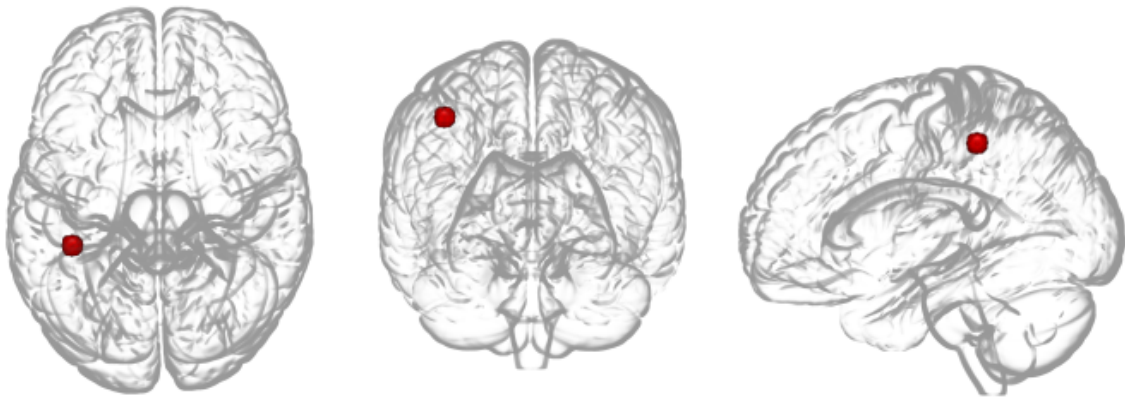


Figure 3.2. A figure depicting the IPS mask used to target cTBS in standard space (MNI -41, -38, 54).

3.3.4 TMS protocol

First, on a day prior to the experiment, participants underwent an anatomical T1 MRI scan on a 3T MRI scanner (Siemens MAGNETOM Prisma) at the Centre for Human Brain Health. The target area was derived from the intersection of ROIs defined in neurotypical subjects (Kolodny et al., 2017) and the clusters where interaction was found between the activation and ASRS scores (Kolodny et al., 2020), and contained 1061 contiguous voxels. From the centre of this cluster a 5mm³ sphere was created and this was used as the target for TMS (MNI = -41, -38, 54; *see figure 3.2*). The target area was translated from MNI space into individual subject space using FLIRT (Greve & Fischl, 2009; Jenkinson et al., 2002; Jenkinson & Smith, 2001).

Using a Magstim Super Rapid 2 Stimulator (MagStim, Whitland, UK) with a 70mm figure of eight (D70 alpha flat coil), participants received offline stimulation to their left anterior IPS (MNI -41, -38, 54) as the target area and to the vertex, identified as Cz, as a control site in two separate experimental sessions. The order of site stimulation was counterbalanced across participants. At the start of the first session stimulation intensity was determined via the participants' individual resting motor threshold (rMT). Each participant's rMT was measured as the lowest intensity able to produce motor evoked potentials (MEPs) in at least 80% of 5 trials, which were recorded from the right first dorsal interosseous muscle using EMG.

Participants received a modified cTBS at 80% of individual rMT for 40 seconds which has an inhibitory effect on the target site. The cTBS protocol consisted of 600 pulses arranged into bursts of three pulses at 30 Hz, which are delivered every 200ms (Hebscher et al., 2020).

The coil position during stimulation of the target area was guided using Brainsight Frameless Stereotaxic software (Rogue Research, Montreal, Quebec, Canada). The position

of the coil and the subject's head were monitored using a Polaris Optical Tracking System (Northern Digital, Waterloo, Ontario, Canada).

3.3.5 Outlier removal and statistical analysis

Statistical analyses were carried out in SPSS 26. Outliers were determined using z-scores relative to the current sample using a ± 3 standard deviations from the mean threshold.

Participants whose percentage of commission errors in either TMS condition were deemed as outliers for that condition were removed from the analysis completely. By removing outliers from both TMS sessions, we ensured that the analysis reflected participants' consistent and reliable performance, thereby confirming that participants took both sessions seriously and adhered to the required protocol. Following this, participants whose difference in commission error percentage between TMS conditions were outliers were also removed from analysis completely ($n = 2$). Outliers for task performance parameters and the ASRS were removed only for individual measures rather than from the whole analysis, resulting in 2 participant's standard deviation of response times being dropped from analysis due to being outliers in at least one of the conditions.

Prior to statistical analysis, normality was assessed using the Shapiro-Wilk test (Shapiro & Wilk, 1965). Differences were tested using Paired Samples T-Tests for parametric data, and Wilcoxon signed-rank tests for non-parametric data. Correlations were tested using Pearson's Product Moment Correlations for parametric data and Spearman's rank correlational coefficients for non-parametric data. Repeated measures ANCOVAs were used to examine the effect of IPS and CZ stimulation on RI performance, with ASRS scores included as a covariate.

When investigating the role of individual differences in task performance, performance was standardised as the difference between commission errors following IPS

stimulation and commission errors after Cz stimulation, divided by commission errors following Cz stimulation. A positive value indicates worse performance following IPS stimulation compared to performance following Cz stimulation. Sustained attention, quantified as the standard deviation of response times, was investigated as a control measure due to its distinction from response inhibition as a cognitive process, as seen in previous research (Kolodny et al., 2017). Since sustained attention also impacts performance on response inhibition tasks, controlling for it ensures that findings regarding task performance are not confounded by variations in sustained attention.

3.4 Results

3.4.1 Interaction Effect of Stimulation Type and ADHD traits on RI Performance

A repeated measures ANCOVA was conducted to examine the effect of IPS and CZ stimulation on RI performance, with ASRS scores included as a covariate. The analysis revealed no significant main effect of stimulation type on RI performance, $F(1, 28) = 3.898$, $p = .058$, indicating that, overall, the type of stimulation did not significantly impact RI performance (*Figure 3.3a*). Importantly however, there was a significant interaction between stimulation type and ASRS scores, $F(1, 28) = 4.901$, $p = .035$, partial $\eta^2 = .149$. This interaction indicates that the effect of TMS on RI performance was dependent on the ASRS scores of each participant.

A repeated measures ANCOVA was conducted to examine the effect of IPS and CZ stimulation on sustained attention performance, with ASRS scores included as a covariate. The analysis revealed no significant main effect of stimulation type on sustained attention performance, $F(1, 25) = 1.12$, $p = .300$ indicating that, overall, the type of stimulation did not significantly impact sustained attention performance (*Figure 3.3b*). Furthermore, there was

no significant interaction between stimulation type and ASRS scores: $F(1, 25) = .032$, $p = .858$, partial $\eta^2 = .001$. This indicates that the effect of TMS on sustained attention performance was not influenced by the ASRS score of each participant.

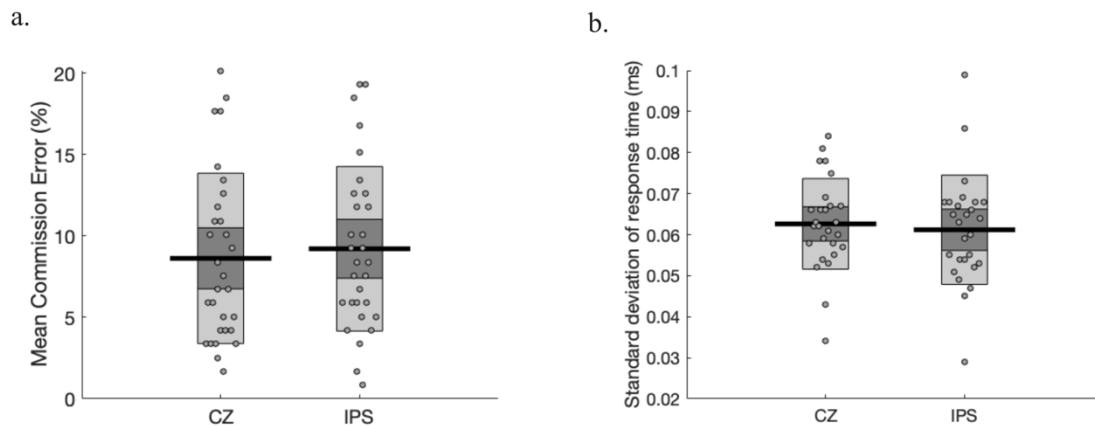


Figure 3.3. Differences in mean (a) response inhibition errors (%) and (b) sustained attention performance (seconds) following IIPS and CZ stimulation. Horizontal black lines denote group mean, bars denote 95% confidence intervals, and the central dark area of the bar denotes 1 SD around the mean. Circles represent individual participants.

3.4.2 The relationship between ADHD trait expression and the effect of inhibitory cTBS to the left IPS on response inhibition performance

To quantify and visualise the association between ADHD trait expression and the TMS's effect on response inhibition performance, we correlated ASRS with the standardised difference in response inhibition (the difference in performance between IPS and Cz). Although no significant interaction in the ANCOVA for between sustained attention performance and ASRS scores was found, we still calculated the correlation to further maintain the specificity of the TMS effect on RI.

A Pearson's product-moment correlation found that there was a significant positive association between ADHD trait expression and the effect of inhibitory cTBS targeting the left IPS on response inhibition performance: $r = 0.466$, $n = 29$, $p = .011$ (*Figure 3.4a*). This finding suggests that left IPS inhibition leads to worse response inhibition performance for individuals with greater ADHD tendencies. In contrast, a Pearson's product-moment correlation found no significant relationship between ADHD traits and the effect of TMS (IPS-Cz) on sustained attention performance: $r = -.01$, $n = 29$, $p = .959$ (*Figure 3.4b*).

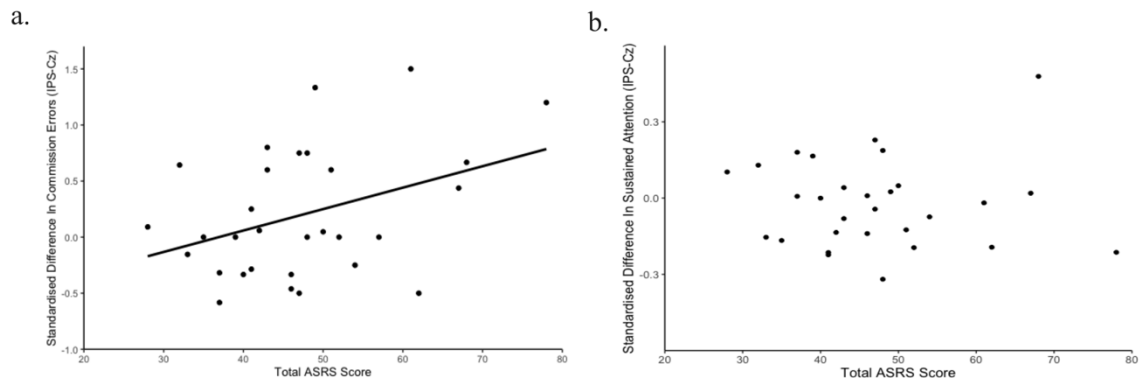


Figure 3.4. Scatterplots depicting the relationship between ADHD traits with standardised differences following cTBS (IPS-Cz) in performance of (a) response inhibition, and (b) sustained attention. A line of best fit is provided for significant relationships only.

3.5 Discussion

In the current study we used TMS to investigate the causal role of IIPS activation during inhibitory demand on response inhibition performance and its association with ADHD tendencies. Previous research has implicated the IIPS in response inhibition in neurotypical adults, whereby the IIPS exhibits increased activation with increasing inhibitory demand (Kolodny et al., 2017). However, our findings in the group analysis did not find a direct impact on inhibitory cTBS stimulation to the IIPS on response inhibition performance. In contrast our individual difference analysis demonstrated that the TMS effect over the IPS depended on the ADHD tendencies of each participant.

Interestingly, our results found that the effect of cTBS to the IIPS on response inhibition was associated with ADHD traits, with the response inhibition performance of those with greater ADHD traits being impaired to a greater extent by cTBS than those with less ADHD traits. Importantly, this relationship was not replicated for sustained attention performance, suggesting that it is specific to response inhibition. Previous research has found that IPS modulation during inhibitory demand is related to ADHD traits, with those with greater ADHD traits having less IPS engagement during inhibitory demand (Kolodny et al., 2020). Thus, the current findings may reflect a greater susceptibility to the effects of cTBS in those with greater ADHD traits due to less robust IPS engagement during inhibitory demand. Similarly, our previous findings have implicated the IFG-IPS network in response inhibition and found a difference in the functional connectivity and underlying structure of this network between an ADHD and controls which relates to response inhibition performance (Kolodny et al., 2017, 2020; *Chapter 2, Smullen et al., in review*). As such, individuals with greater ADHD traits may have reduced compensatory mechanisms through atypical connectivity within the IFG-IPS network, resulting in a greater susceptibility to disruption of individual nodes of this network, such as the IIPS in the current study.

The complex relationship between TMS and activation state in the targeted region may also explain our findings. For example, the ongoing activity of a ROI determines its sensitivity to stimulation (Siebner et al., 2009). As such, as IPS modulation during inhibitory demand is reduced in ADHD (Kolodny et al., 2020), said lower IPS activation may mean that the IPS is more susceptible to the disruptive effects of cTBS in individuals with greater ADHD traits. Alternatively, increased elements of cognitive load heighten the effects of TMS (Albouy et al., 2017; Beynel et al., 2019; Gill et al., 2015; Kundu et al., 2013; Lubner et al., 2008; Van De Ven et al., 2012). Thus, our findings might be partly attributed to those with more severe ADHD traits experiencing greater cognitive load during the go/nogo task due to their general executive function impairments (Diamond, 2013). This increased cognitive load could result in more pronounced disruptive effects of cTBS on the IPS.

While the magnitude of the TMS effect over IPS depended on the ADHD trait expression of the participants, we did not find an overall effect across all participants (irrespective of their ADHD trait expression). Previous findings which implicate IIPS activity in response inhibition also highlight the functional circuitry between the IFG and IPS in response inhibition (Kolodny et al., 2017, 2020), whilst the structural circuitry between these nodes has also been implicated in response inhibition (*Chapter 2, Smullen et al., in review*). In ADHD, we found that parietal modulations during inhibitory demand is predicted by IFG-IPS white matter structure and response inhibition performance is related to IFG-IFG white matter structure (*Chapter 2, Smullen et al., in review*). As the IFG is associated with cognitive and attentional control (Hampshire et al., 2010; Shomstein, 2012) and involved in a broad range of other cognitive functions as one of the key domain-general areas in the brain (Fedorenko et al., 2013), we interpreted these findings as pointing to the top-down engagement of the IPS node by the IFG in ADHD. Thus, the IFG-IPS circuitry, rather than the IPS alone, may be the underlying reason for the IPS previously implicated role in

response inhibition, and so targeting the circuitry with TMS may result with more general effects on RI performance compared to the ones we report here.

A limitation of the current study is that the difficulty of inhibitory demand was not manipulated as it was in the studies which first implicated the IPS in response inhibition (Kolodny et al., 2017, 2020). As such, we were unable to investigate how disrupting IPS recruitment during increasing levels of inhibitory demand affects response inhibition performances. Future research should aim to address this issue by contrasting the difference in performance during easy and difficult response inhibition following both IPS disruption and control stimulation.

A further shortcoming of the current study is that response inhibition was only investigated using a modified go/nogo task which was designed to elucidate the cognitive element of action withholding (Kolodny et al., 2017). Action withholding is one component of response inhibition, which can also include action cancellation, typically investigated using stop-signal tasks (Lappin & Eriksen, 1966). Performance of these components of response inhibition bare a limited relationship (Schachar et al., 2007) and evidence suggests that they share restricted frontoparietal activation (Zheng et al., 2008). Therefore, our findings which implicate the IIPS in ADHD-related response inhibition performance may only be relevant when considering action withholding. Future research should aim to replicate the current investigation to confirm whether our results also apply to action cancellation or are isolated to action withholding.

Another limitation of the current study is that we did not measure IPS activation, meaning that we do not know the exact neural impact of the stimulation, as many elements, such as genetics and skull thickness, can affect the individualised effect of TMS (Cheeran et al., 2008; Opitz et al., 2015). Future research should aim to replicate the current investigation

whilst combining TMS with another neuroimaging technique, perhaps fNIRS, to confirm a significant effect of TMS on IIPS activity.

In conclusion, we found that those with greater ADHD-traits had a greater impairment to response inhibition performance following cTBS to the IIPS than those less ADHD-traits, perhaps reflecting greater susceptibility to the effects of cTBS in those with greater ADHD traits due to less robust IPS engagement during inhibitory demand or due to reduced compensatory mechanisms through atypical connectivity within the IFG-IPS network. Future research should aim to investigate the role of the IFG and its connection with the IPS in inhibitory demand, as well as investigating multiple components of response inhibition. Efforts should also be made to combine TMS with other neuroimaging techniques, especially those that can track both activation and connectivity such as fNIRS, to quantify the efficacy of TMS.

Chapter 4

Pre-sleep arousal as a possible mechanism driving sleep problems in ADHD.

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At the time that this thesis was submitted, the following chapter was under review at
Scientific Reports.

Chapter 4

4.1 Abstract

Attention Deficit Hyperactivity Disorder (ADHD) is inextricably linked with sleep problems. Clinically diagnosed poor sleep is common in ADHD, and subclinical sleep difficulties are frequently reported. However, the mechanisms which underly poor sleep in ADHD are poorly understood. Since one of the most consistently reported sleep difficulties is sleep initiation, it is plausible that pre-sleep arousal plays an important role, but this has not been confirmed. We investigated this by assessing neurotypical adult participants' self-reported perceptions of their sleep difficulties and pre-sleep arousal in relation to their ADHD-like traits. We acquired two independent datasets: an online dataset ($n = 104$) and an in-person replication dataset ($n = 96$). We first assessed the association between ADHD-like traits and sleep quality generally, as well as sleep-onset problems specifically. We then tested the extent to which pre-sleep arousal mediated the association between ADHD traits and sleep initiation problems. There was a clear association in both datasets between ADHD-like traits and their sleep quality – high expression of ADHD-like behaviours coincided with reduced sleep quality. This relationship was largely mediated by the levels of pre-sleep arousal: the link between ADHD-like traits and sleep quality was explained by the relationship between ADHD and (primarily cognitive) pre-sleep arousal. Our findings highlight the role of pre-sleep arousal in the relationship between ADHD-like traits and sleep quality, which could direct future interventions.

4.2 Introduction

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder which affects roughly 2.5% of adults (Faraone et al., 2006; Simon et al., 2009). ADHD often co-occurs with other psychiatric and medical conditions, with one of the most prevalent co-occurring issues being sleep problems. Although these are not typically screened for in a diagnostic setting, studies of sleep in ADHD populations reveal that sleep problems are reported by 70-90% of individuals (Kooij et al., 2001; Mindell et al., 2009). These sleep problems manifest in increased prevalence of several clinically diagnosed sleep disorders in ADHD, including insomnia disorders associated with initiating and maintaining sleep, sleep-wake transition disorders, disorders of excessive somnolence and sleep hyperhidrosis (van der Heijden et al., 2018). Similar sleep problems in ADHD are self-reported even without a clinical diagnosis of a sleep disorder (De Crescenzo et al., 2016; Díaz-Román et al., 2018; Gruber et al., 2000; J. Owens et al., 2009; Van Der Heijden et al., 2006). Those with ADHD are also more likely to have an evening chronotype than their neurotypical peers (Bae et al., 2010; Baird et al., 2012; Bijlenga et al., 2013; Caci et al., 2009; Gruber et al., 2012). Evening chronotypes (also known as ‘night owls’) are more likely to suffer from disrupted sleep and are more likely to be diagnosed with a sleep disorder (Alvaro et al., 2014; J. A. Owens et al., 2016).

One of the most frequently reported sleep difficulties in people diagnosed with ADHD is in falling asleep, or sleep initiation (Park et al., 2011). In people with insomnia, sleep initiation problems have been attributed to both cognitive (related to mental activity) and somatic (related to physiological activity) pre-sleep arousal, although cognitive arousal has been suggested to be up to ten times more frequently experienced than somatic arousal (Lichstein & Rosenthal, 1980). For example, measures of sleep onset latency from actigraphy

correlate with self-reported pre-sleep cognitive activity in people with insomnia (Wicklow & Espie, 2000). The relevance of pre-sleep arousal to sleep-onset latency has also been demonstrated in good sleepers, where increasing pre-sleep cognitive arousal is associated with delayed sleep latency (Gross & Borkovec, 1982; Wuyts et al., 2012). It is therefore plausible that if pre-sleep arousal drives sleep-onset issues in people with insomnia and typical sleepers, it may also drive sleep-onset issues in ADHD. Determining what role pre-sleep arousal plays in ADHD-related sleep issues may guide interventions aimed to improve these sleep problems.

Currently, the underlying mechanisms for impaired sleep in ADHD remain unclear. Understanding these mechanisms, what those with impaired sleep experience and what they attribute their sleep impairment to, could provide new directions for future research into the neurological underpinnings of ADHD-impaired sleep and, importantly, for its treatment. Treating impaired sleep in ADHD may also lead to benefits across other facets of the disorder. This is because, irrespective of ADHD, poor sleep is associated with cognitive impairments often seen in ADHD. For instance, performance in sustained attention and response inhibition are both impaired by poor sleep (Chuah et al., 2006; Drummond et al., 2006; Goel et al., 2009; Imeraj et al., 2012; Lowe et al., 2017). As deficits in these cognitive functions are core characteristics of ADHD (Diamond, 2013; Willcutt et al., 2005; Wright et al., 2014), they might be exacerbated by co-occurring sleep problems, and hence better understanding of sleep issues in ADHD may provide a potential pathway to improve cognitive function in the disorder.

The present study investigated ADHD-traits, pre-sleep arousal, and sleep in a general population of university students, as opposed to a clinically diagnosed ADHD cohort. An advantage of studying ADHD-traits in the general population is that they still exist in varying degrees whilst recruitment difficulty is reduced, allowing for recruitment of a larger sample,

and the impact of medication as a confounder is removed. Investigating ADHD-traits in the general population also addresses the issue that psychopathological symptoms are continuous rather than categorical. This mitigates the limitations of traditional taxonomies of neurodevelopmental disorders surrounding the somewhat arbitrary boundaries between what is classed as disorder and normality when the disorder is itself referred to as a spectrum (Caspi & Moffitt, 2018; Kotov et al., 2017). ADHD symptoms are reported at greater than average rates in university students, with as many as 8% of students reporting clinically significant levels of symptoms (Kavakci et al., 2012). There are a range of possible explanations for these heightened levels, including the effect of academic pressure and lifestyle factors such as alcohol usage (Dougherty et al., 2000; Fernández-Serrano et al., 2010). Whatever the reasons for their over-representation in university student samples, this provides a way of studying the relationships between ADHD traits and sleep without some of the complications that arise from clinical samples.

In the present study we investigated the role of pre-sleep arousal in sleep problems in ADHD by assessing participants' perceptions of their sleep difficulties and pre-sleep arousal at the same time as their ADHD-like symptomatology. We conducted our analysis on two datasets, the first being a dataset collected online, and the second – a replication dataset - collected in-person in the lab. In both cohorts we first assessed the association between ADHD-like traits and sleep quality generally. We then assessed the association between ADHD symptoms, as well as sleep problems, with cognitive and somatic pre-sleep arousal. Finally, we tested the extent to which pre-sleep arousal mediated the association between ADHD and sleep problems. In a further exploratory analysis, we tested which specific elements of pre-sleep arousal best predicted difficulties in falling asleep.

4.3 Methods

4.3.1 Participants

Participants in both the online dataset (collected during the 2021/2022 academic session, during the COVID-19 pandemic) and the replication dataset (collected in-person during the 2022/2023 academic session) were Psychology students at the University of Birmingham, with no overlap between the two samples. The replication dataset was collected for pure replication purposes, as well as to ensure the findings were not driven by the pandemic and its possible effects on mental health, attention and sleep. Participants who reported a previous clinical ADHD or sleep disorder diagnosis were excluded in order to ensure that the effects of medication were not present in our datasets.

The first dataset was collected online and included 110 adults (24 males and 86 females, mean age(SD) = 19.41(1.30)y). Following outlier removal (as described below) there remained 104 participants (18 males and 86 females, mean age(SD) = 19.36(1.29)y). The second replication dataset was collected in-person in the lab one year later, and included 98 adults (19 males and 79 females, mean age(SD) = 19.34(1.05)y). Following outlier removal there remained 96 participants in the replication study (19 males and 77 females, mean age(SD) = 19.35(1.05)y).

The study conformed to the Declaration of Helsinki and was approved by the STEM ethics committee at the University of Birmingham. All participants provided informed consent at the beginning of the study and were informed that they could withdraw their participation and data at any point during or within 5 weeks of the experiment. Participants were compensated for their participation with course credits.

4.3.2 Materials

The study utilised a series of self-report questionnaires to assess ADHD symptomatology on the one hand and sleep problems on the other. The final step of our analysis of the online dataset was a mediation analysis which investigated how pre-sleep arousal mediates the relationship between ADHD symptom severity and sleep quality. Only those measures implicated in the mediation analysis of the online dataset were then used in the replication dataset.

4.3.2.1 Sleep quality measures

Sleep quality has numerous facets which are typically assessed using different questionnaires to ensure they are measured comprehensively. As such, we deployed two commonly used questionnaires which assess various subjective elements of sleep quality and severity of insomnia-related sleep issues.

4.3.2.1.1 Pittsburgh Sleep Quality Index (PSQI)

The PSQI assesses self-reported sleep quality (Buysse et al., 1989). It consists of 20 questions which feed into seven components of sleep quality: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medication and daytime dysfunction. Sleep quality is scored across each component and in a combined overall score. Higher scores suggest reduced sleep quality.

4.3.2.1.2 Insomnia Severity Index (ISI)

The ISI assesses the severity of daytime and night time insomnia symptoms and is often used clinically during the diagnostic process for the disorder (Bastien et al., 2001). It uses seven questions responded to via Likert scales to produce an overall insomnia symptom severity. It

also provides guidance on categorising scores: 0-7 no clinically significant insomnia, 8-14 subthreshold insomnia, 15-21 clinical insomnia (moderate severity), 22-28 clinical insomnia (severe).

4.3.2.2 Pre-sleep arousal measures

Two questionnaires were used to assess pre-sleep arousal. First, the Pre-Sleep Arousal Scale was used, which covers different domains and thus is an effective tool to study overall pre-sleep arousal elements. In addition, the Glasgow Cognitive Intrusions Index was included, specifically for the purpose of assessing individual pre-sleep thought content in a stepwise regression analysis where pre-sleep arousal contents were potential predictors (see below).

4.3.2.2.1 Pre-Sleep Arousal Scale (PSAS)

The PSAS is a 16-item questionnaire assessing the severity of experience of cognitive and physiological arousal when attempting to sleep (Nicassio et al., 1985). The PSAS can be split into two components: somatic and cognitive pre-sleep arousals. Participants respond using Likert scales to report how much they experience arousals such as “shortness of breath, laboured breathing” [somatic] and “worry about falling asleep” [cognitive]. Higher scores reflect more severe experience. Subtypes of the PSAS reflect issues common in ADHD.

4.3.2.2.2 Glasgow Cognitive Intrusions Index (GCTI)

The GCTI was designed to assess the content, character and intrusiveness of cognitions during sleep onset in insomnia patients (Harvey & Espie, 2004). Likert scales are used to assess the frequency with which 25 thoughts, such as “your health”, have kept the participant awake over the previous week. Higher scores indicate higher frequency and hence more severe experience.

4.3.2.3 Adult ADHD Self-Report Scale (ASRS)

The ASRS is a widely used questionnaire, which assess the severity with which an adult experiences ADHD symptoms (Kessler et al., 2005). It consists of 18 questions covering two components equally: inattention symptoms and hyperactivity/impulsivity symptoms, each corresponding to one item in the symptoms checklist for ADHD in the DSM. Participants rate how frequently they experience symptoms using a Likert scale. This provides a severity score ranging from 9-45 for both components, and a combined severity score ranging from 18-90. Higher scores reflect higher symptom severity.

4.3.3 Experimental procedure

For the online dataset, participants were recruited via the University of Birmingham's participant pool recruitment website (Sona; <https://birmingham.sona-systems.com>) and completed the entire experiment using their own PC in their own home. Once recruited, participants were redirected to Qualtrics (<https://www.qualtrics.com>), where they provided informed consent before completing the questionnaires outlined above in the same order (with the exception of GCTI which was completed before the PSAS). Foil questions were also used throughout the survey to ensure proper engagement with the questions. Foil questions appeared at a glance to fit with neighbouring questions but instead asked questions with obvious and objective answers (e.g. "what number comes after 5?") to ensure that participants were reading the questions properly before answering. Any participants who answered the foil questions incorrectly would have been removed, although in practice all were answered correctly. Once the questionnaires were completed, participants completed a Go/No-go task which is not reported in this paper due to poor task engagement. Finally, they

were debriefed and then compensated with course credits. The experiment was conducted completely online and without an experimenter present.

For the replication dataset, participants were again recruited via the University of Birmingham's participant pool recruitment website (Sona), but completed the entire experiment in the lab. Participants were first directed to Qualtrics, where they provided informed consent before completing the questionnaires, in the same order as above, with only a subset of the questionnaires which were implicated in our mediation analysis being included in the analysis of the replication dataset: ASRS, ISI and PSAS. Foil questions were also used throughout the survey to ensure proper engagement with the questions. No participants answered these questions incorrectly. Finally, participants were debriefed and compensated with course credits. The experimenter was present in the lab, but at a distance, throughout the session.

4.3.4 Outlier detection and statistical analysis

Statistical analyses were carried out in SPSS 26. Outliers were determined using z-scores relative to the current sample on each questionnaire separately, using a ± 3 standard deviations threshold. Outliers on questionnaire scores resulted in only that questionnaire being removed from further analysis. From the online dataset four participants were removed from due to not meeting the inclusion criteria, whilst two were removed from the replication dataset. Also, in the online dataset, due to a technical failure resulting in missing datafiles only 83 participants had full PSQI data.

We tested the correlations between sleep quality measures (PSQI and ISI) and ADHD symptom severity; between sleep quality measures (PSQI and ISI) and pre-sleep arousal (PSAS and GCTI); and between ADHD symptom severity and pre-sleep arousal (PSAS and GCTI). Correlations were tested using non-parametric Spearman's rank correlational

coefficients due to non-normal distribution of the data, as assessed using the Shapiro-Wilk test of normality (Shapiro & Wilk, 1965). The strength of difference between correlations was assessed using a Fisher's r to z transformation.

We also used mediation analyses to test whether pre-sleep arousal mediated the relationship between ADHD symptom severity and sleep quality. After first testing the assumptions of mediation analyses, such as normality of residuals, Hayes' PROCESS Macro within SPSS was used to examine the mediation effect of pre-sleep arousal on the relationship between ADHD symptom severity and insomnia symptom severity. The analysis included 5000 bootstrap samples to generate bias-corrected 95% confidence intervals for the indirect effect.

Finally, in order to determine which specific pre-sleep arousal content was most associated with problems in sleep initiation, we performed a stepwise regression analysis in the online dataset, to model which cognitive and somatic pre-sleep arousal components best predicted sleep onset-latency (PSQI component 2). We opted to use this sleep quality component as pre-sleep arousal's impact is most likely to be on the time taken to fall asleep. Potential predictors included in the stepwise regressions were those components (single questions) of the two pre-sleep arousal questionnaires (PSAS & GCTI) whose correlations with PSQI component 2, reached .05 significance. We corrected for multiple comparisons using Benjamini and Hochberg's Step-Up Procedure to control for False Discovery Rate (FDR) (Benjamini & Hochberg, 1995). All significant relationships reported in our results survived multiple comparison correction.

4.4 Results

4.4.1 An overview of the variability of the data and its differences between datasets

Tables 4.1 and 4.2 provide an overview of the questionnaire data from the online and replication datasets, respectively. Figure 4.1 provides an overview of the distributions of total scores for the questionnaires. Figure 4.1 suggests that the two samples are generally comparable across all measures, as also indicated in Tables 4.1 and 4.2. Independent samples t-tests found that there was no significant difference between the online dataset's ISI scores (mean = 8.12, sd = 4.75) and the replications dataset's ISI scores (mean = 7.13, sd = 3.27): $t(178) = 1.717$, $p = .088$ (*Figure 4.1a*). Likewise, there was no significant difference in total PSQI scores for the online (mean = 8.88, sd = 1.26) and replication (mean = 8.28, sd = 2.54) datasets: $t(174) = 1.548$, $p = .123$ (*Figure 4.1b*), or for cognitive PSAS scores (online dataset (mean = 20.53, sd = 7.21), the replication dataset (mean = 19.77, sd = 6.44): $t(196) = .365$, $p = .715$ (*Figure 4.1c*)). However, for somatic PSAS scores there was a significant difference between the online dataset (mean = 13.90, sd = 5.10) and the replication dataset (mean = 11.59, sd = 3.18): $t(171) = 3.849$, $p < .001$ (*Figure 4.1d*). Lastly, there was no significant difference between the total ASRS scores for the online dataset (mean = 48.25, sd = 11.06) and the replication dataset (mean = 47.46, sd = 11.34): $t(196) = .467$, $p = .641$ (*Figure 4.1e*).

Overall, the data demonstrated considerable variability consistent with the idea that studying traits as opposed to diagnoses is reasonable.

Table 4.1. A summary of the questionnaire responses in the online dataset.

	n	possible range	obtained range	mean	std
PSQI	83	0-21	4-16	8.88	1.26
<i>Subjective sleep quality</i>	104	0-3	0-3	1.28	.6
<i>Sleep latency</i>	104	0-3	0-3	2.78	.42
<i>Sleep duration</i>	104	0-3	0-4	1.68	1.17
<i>Sleep efficiency</i>	84	0-3	0-3	.87	.94
<i>Sleep disturbance</i>	103	0-3	0-2	1.19	.44
<i>Use of sleep medication</i>	104	0-3	0-3	.08	.39
<i>Daytime dysfunction</i>	104	0-3	0-3	1.45	.81
ISI	101	0-28	0-21	8.12	4.75
GCTI	103	25-100	25-78	49.63	11.28
PSAS	102	16-80	16-65	34.32	11.01
<i>Cognitive</i>	103	8-40	8-37	20.53	7.21
<i>Somatic</i>	102	8-40	8-30	13.9	5.10
ASRS	102	18-90	18-80	48.25	11.06
<i>Inattention</i>	104	9-45	9-40	26.41	6.87
<i>Imp/Hyp</i>	102	9-45	9-40	21.76	6.6
Note: PSQI = Pittsburgh Sleep Quality Index					
Note: PSAS = Pre-sleep Arousal Scale					
Note: ISI = Insomnia Severity Index					
Note: GCTI = Glasgow Cognitive Thoughts Index					
Note: ASRS = Adult ADHD Self-Report Scale					
Note: Total PSQI data is reduced due to missing data for the sleep efficiency component					

Table 4.2. A summary of the questionnaire responses in the replication dataset.

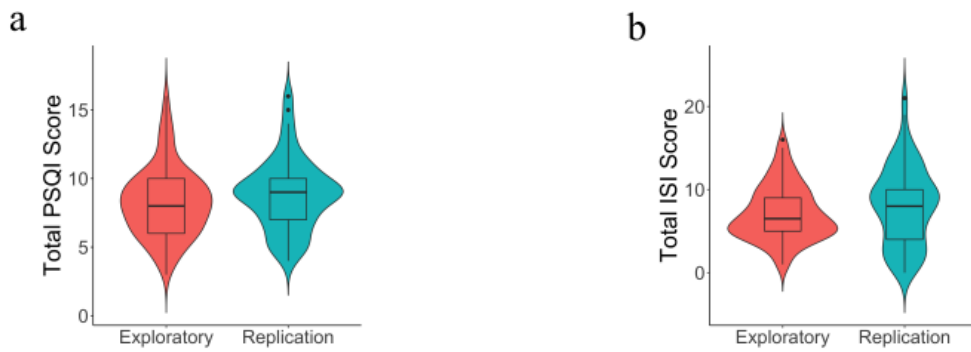
	n	possible range	obtained range	mean	std
PSQI	93	0-21	3-16	8.28	2.54
<i>Subjective sleep quality</i>	94	0-3	0-3	1.16	.61
<i>Sleep latency</i>	94	0-3	2-3	2.61	.49
<i>Sleep duration</i>	94	0-3	0-3	1.36	.93
<i>Sleep efficiency</i>	93	0-3	0-3	0.74	.93
<i>Sleep disturbance</i>	94	0-3	0-2	1.14	.48
<i>Use of sleep medication</i>	94	0-3	0-2	.06	.29
<i>Daytime dysfunction</i>	94	0-3	0-3	1.22	.71
ISI	96	0-28	1-16	7.13	3.27
PSAS	95	16-80	17-53	31.42	8.48
<i>Cognitive</i>	95	8-40	9-35	19.77	6.44
<i>Somatic</i>	95	8-40	8-19	11.59	3.18
ASRS	96	18-90	23-80	47.46	11.34
<i>Inattention</i>	92	9-40	14-43	24.89	6.01
<i>Imp/Hyp</i>	94	9-40	9-39	22.30	6.56
Note: PSQI = Pittsburgh Sleep Quality Index					
Note: PSAS = Pre-sleep Arousal Scale					

Note: ISI = Insomnia Severity Index

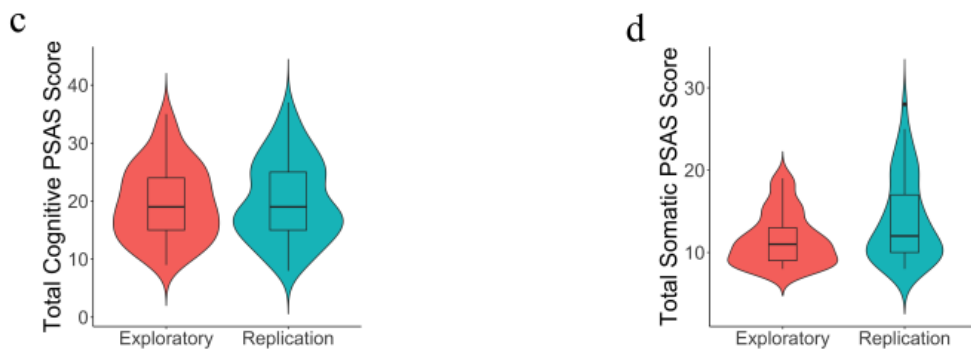
Note: ASRS = Adult ADHD Self-Report Scale

Note: PSQI data is reduced due to missing data for the sleep efficiency component

Sleep quality measures



Pre-sleep arousal measures



ADHD symptom severity measure

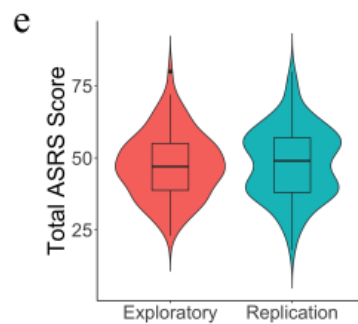


Figure 4.1. Violin plots depicting the differences between the online (red) and replication (blue) datasets for (a) total PSQI score, (b) total ISI score, (c) total cognitive pre-sleep arousal score, (d) total somatic pre-sleep arousal score and (e) total ASRS score

4.4.2 The relationship between ADHD symptom severity and sleep measures

We first assessed the relationship between the two sleep measures (overall sleep quality - PSQI scores, and Insomnia Severity - ISI scores) and ADHD symptom severity (ASRS scores). In the online dataset, we found that ADHD symptom severity (ASRS) significantly and positively correlated with insomnia symptom severity (ISI; $r_s(99) = .330$, $p = .003$; *Figure 4.2a*). However, we did not find a significant relationship between ADHD symptom severity and overall sleep quality as assessed by the PSQI ($r_s(81) = .077$, $p = .496$; *Figure 4.2b*). The same was found in the replication dataset: a significant association between ADHD symptom severity and insomnia symptom severity ($r_s(96) = .278$, $p = .006$; *Figure 4.2a*), but no significant relationship between ADHD symptom severity and overall sleep quality as assessed by the PSQI ($r_s(93) = -.102$, $p = .332$; *Figure 4.2b*). When controlling for the effect of sex, no difference was found in the outcomes of correlation tests (see *Appendix B, Tables B1 and B2*).

4.4.3 The relationship between ADHD symptom severity and cognitive and somatic pre-sleep arousal

Next, we investigated the relationship between ADHD symptom severity (ASRS scores) and cognitive and somatic pre-sleep arousal (PSAS scores) using Spearman's Rank Correlation Coefficients. For the online dataset, we found a statistically significant positive correlation between ADHD symptom severity and cognitive pre-sleep arousal ($r_s(100) = .405$, $p < .001$; *Figure 4.2c*) and ADHD symptom severity and somatic pre-sleep arousal ($r_s(101) = .529$, $p < .001$; *Figure 4.2d*). In the replication dataset, we also found a statistically significant positive correlation between ADHD symptom severity and cognitive pre-sleep arousal ($r_s(95) = .402$, $p < .001$; *Figure 4.2c*) and ADHD symptom severity and somatic pre-sleep arousal: $r_s(95) =$

.417, $p < .001$; *Figure 4.2d*). As previous research in insomnia pointed to a greater prevalence of cognitive pre-sleep arousal relative to somatic pre-sleep arousal (Lichstein & Rosenthal, 1980) we tested for a difference in the strength of the association between ADHD symptoms and somatic vs cognitive arousal using Fisher's r to z transformation. However, there was no significant difference in the online dataset ($p = .379$) or the replication dataset ($p = .452$). When controlling for the effect of sex, no difference was found in the outcomes of correlation tests (see *Appendix B, Tables B1 and B2*).

4.4.4 The relationship between pre-sleep arousal and sleep quality

In order to determine whether both cognitive and somatic pre-sleep arousal were associated with reduced sleep quality in the online dataset, we used Spearman's Rank Correlation Coefficients. In the online dataset, cognitive pre-sleep arousal ($r_s(100) = .665$, $p < .001$; *Figure 4.2e*) and somatic pre-sleep arousal ($r_s(99) = .492$, $p < .001$; *Figure 4.2f*) were significantly positively correlated with ISI scores (again, the strength of the associations did not significantly differ from one another; $p = .102$). For the replication dataset, we also found that cognitive pre-sleep arousal ($r_s(95) = .423$, $p < .001$; *Figure 4.2e*) and somatic pre-sleep arousal ($r_s(95) = .290$, $p = .004$; *Figure 4.2f*) were significantly positively correlated with ISI scores (the strength of the associations did not significantly differ; $p = .298$).

In the online dataset, both cognitive pre-sleep arousal ($r_s(82) = .410$, $p < .001$; *Figure 4.2g*) and somatic pre-sleep arousal ($r_s(82) = .399$, $p < .001$; *Figure 4.2h*) were significantly positively correlated with PSQI scores. Here too we assessed the difference in strength of these correlations using Fisher's r to z transformation but found no significant difference ($p = .942$). However, these results did not replicate in the second dataset, where neither cognitive pre-sleep arousal ($r_s(92) = .087$, $p = .411$; *Figure 4.2f*) nor somatic pre-sleep arousal ($r_s(92) = .108$, $p = .307$; *Figure 4.2h*) were significantly positively correlated with PSQI scores. When

controlling for the effect of sex, no difference was found in the outcomes of correlation tests (see *Appendix B, Tables B1 and B2*).

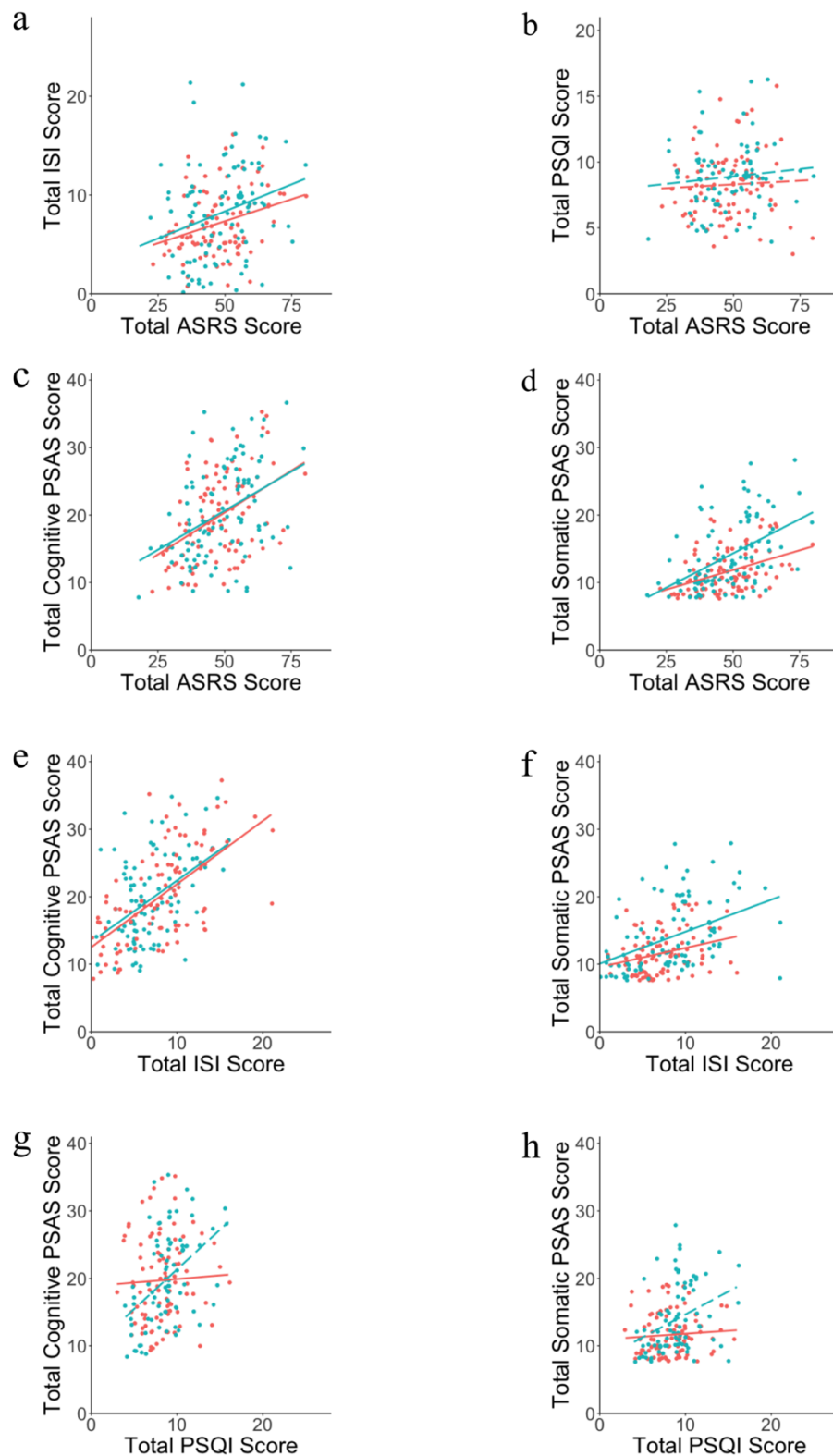


Figure 4.2. Scatterplots depicting the relationships for the online (red) and replication (blue) datasets

4.4.5 Pre-sleep arousal mediates the relationship between ASRS and ISI

After verifying the relationship between ADHD symptoms severity and insomnia symptoms severity, and finding a relationship between both of these and pre-sleep arousal, we turned to investigate the possible role of pre-sleep arousal as a mediator, including the measures that showed correlations with each other: ASRS for ADHD symptom severity, ISI for sleep quality, and PSAS for pre-sleep arousal. Specifically, we investigated whether pre-sleep arousal mediates the relationship between ASRS and ISI scores according to the models (illustrated in *Figure 4.3*), where c' denotes the direct effect of ASRS on ISI whilst the a and b paths elucidate how the relationship between ASRS and ISI is mediated by pre-sleep arousal. These analyses were performed twice, once using pre-sleep cognitive arousal as a mediator and once using pre-sleep somatic arousal.

Analysis 1: Pre-sleep cognitive arousal as a mediator

For the online and replication datasets, the mediation analysis revealed a significant indirect effect of ADHD symptom severity on insomnia symptom severity through cognitive pre-sleep arousal. For both datasets, the total effect of ADHD symptom severity and insomnia symptom severity was significant (online dataset: $b = .123$, $SE = .012$, $t(104) = 3.504$, $p < .001$; replication dataset: $b = .093$, $SE = .028$, $t(93) = 3.288$, $p = .001$). Again, for both datasets, when controlling for cognitive pre-sleep arousal, the direct effect of ADHD symptom severity on insomnia symptom severity was no longer significant (online dataset: $b = .012$, $SE = .034$, $t(103) = .385$, $p = .701$; replication dataset: $b = .043$, $SE = .03$, $t(93) = 1.476$, $p = .143$). For both datasets the indirect effect was significant (online dataset: $b = .099$, $SE = .028$, 95% CI [.05, .03]; replication dataset: $b = .05$, $SE = .029$, 95% CI [.02, .09]). Since the confidence intervals do not include zero, we conclude that the indirect effects are statistically significant. This indicates that cognitive pre-sleep arousal mediates the

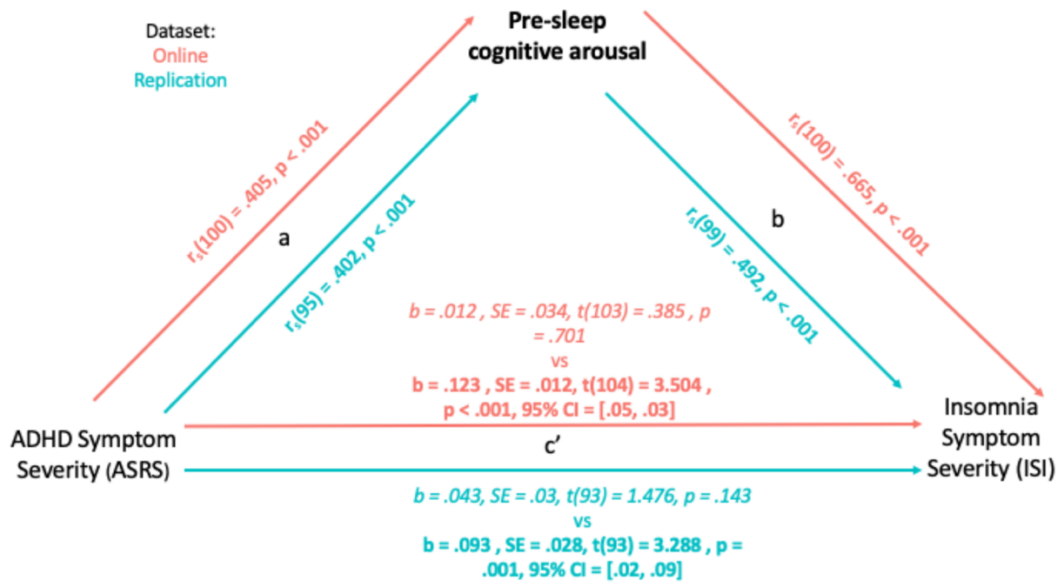
relationship between ADHD symptom severity and insomnia symptom severity for both datasets.

Analysis 2: Pre-sleep somatic arousal as a mediator

For the online dataset the mediation analysis revealed a significant indirect effect of ADHD symptom severity on insomnia symptom severity through somatic pre-sleep arousal.

However, for the replication dataset, it did not. For both datasets the total effect of ADHD symptom severity on insomnia symptom severity was significant (online dataset: $b = .121$, $SE = .037$, $t(103) = 3.508$, $p < .001$; replication dataset: $b = .116$, $SE = .028$, $t(93) = 4.395$, $p < .001$). For the online dataset, when controlling for somatic pre-sleep arousal, the direct effect of ADHD symptom severity on insomnia symptom severity was no longer significant ($b = .048$, $SE = .041$, $t(102) = 1.268$, $p = .207$). However, for the replication dataset, when controlling for the effect of somatic pre-sleep arousal, ADHD symptom severity still significantly predicted insomnia symptom severity ($b = .07$, $SE = .031$, $t(93) = 2.277$, $p = .02$). For the online dataset, the indirect effect was significant ($b = .078$, $SE = .023$), with 95% bootstrap confidence interval of $[.04, .13]$. Since the confidence interval does not include zero, we conclude that the indirect effect is statistically significant. This indicates that somatic pre-sleep arousal mediates the relationship between ADHD symptom severity and insomnia symptom severity. However, for the replication dataset, the indirect effect was not significant ($b = .023$, $SE = .014$), with 95% bootstrap confidence interval of $[-.005, .052]$. This indicates that somatic pre-sleep arousal does not mediate the relationship between ADHD symptom severity and insomnia symptom severity.

a



b

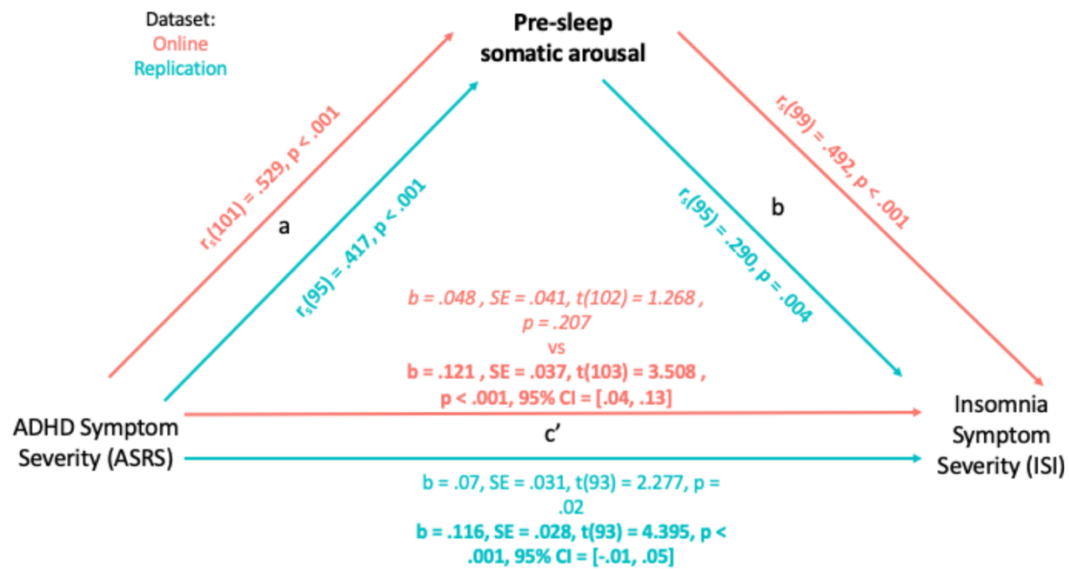


Figure 4.3. Figures depicting the mediation effect of (a) cognitive pre-sleep arousal and (b) somatic pre-sleep arousal on the relationship between ADHD symptom severity and Insomnia symptoms severity for the online (red) and replication (blue) datasets

4.4.6 The link between pre-sleep arousal and sleep onset latency

In order to determine which specific pre-sleep arousal content is most associated with poorer sleep initiation, we ran a stepwise regression analysis in the online dataset, to model which cognitive and somatic pre-sleep arousal components best predicted subjective sleep onset-latency (PSQI component 2). Two pre-sleep arousal questionnaires (PSAS and GCTI) were included to ensure the most comprehensive analysis of pre-sleep arousal components possible. The final model included GCTI question 21 (thoughts about “your personal life”: $r = .290, p = .002$) and PSAS question 13 from the cognitive subscale (“being mentally alert, active”: $r = .316, p < .001$) as significant predictors of sleep onset latency ($F(2, 109) = 7.547, p < .001, R^2 = .106$). As GCTI data was not collected for the replication dataset this analysis was not repeated.

4.4.7 Greater ADHD symptom severity is associated with the pre-sleep predictors of sleep onset latency

Finally, we assessed whether the two specific pre-sleep arousal components implicated in increased sleep-onset latency were also more commonly expressed in those with greater ADHD symptom severity, and whether they could explain increased sleep-onset latency in the condition. Thus, we assessed the relationships between ADHD symptom severity and the two pre-sleep arousal components using Spearman’s Rank Correlational Coefficients. We found that ADHD symptom severity was significantly positively associated with pre-sleep thoughts about “your personal life” ($r_s(104) = .355, p < .001$) and “being mentally alert, active” ($r_s(104) = .341, p < .001$).

4.5 Discussion

In the current study we focused on a possible underlying mechanism – pre-sleep arousal – that may contribute to the high prevalence of sleep initiation problems in ADHD. As predicted, we found that higher ADHD traits were associated with greater insomnia symptom severity (although not with overall sleep quality as measured by PSQI). This association was robust and replicated across both the online and the replication datasets. These findings align with previous investigations demonstrating a relationship between ADHD symptom severity and sleep quality (McGowan et al., 2016; Uygur & Bahar, 2023). Furthermore, we found that pre-sleep arousal mediated the association between ADHD symptoms and insomnia symptoms. While this was evident for both somatic and cognitive pre-sleep arousal in the online dataset, in the replication dataset only cognitive pre-sleep arousal mediated the link between ADHD and insomnia symptomatology. Our inclusion of pre-sleep arousal metrics and the mediation analysis point to the critical role pre-sleep arousal is likely playing in driving sleep quality problems (and symptoms of insomnia more specifically) in ADHD.

Our results also showed that greater pre-sleep arousal (both somatic and cognitive) was associated with greater ADHD symptom severity as well as increased insomnia symptom severity. Unlike what has been found in insomnia patients (Lichstein & Rosenthal, 1980), the differences in associative strength between somatic and cognitive arousal with ADHD symptom severity were not significant. However, regression analyses, implemented as part of the mediation analyses, suggest that the effect of cognitive pre-sleep arousal is more robust than its somatic counter-part. For the online dataset both pre-sleep cognitive and somatic arousal were significantly linked with insomnia symptom severity, but only the link involving pre-sleep cognitive arousal was replicated in the replication dataset. This would be in line with previous findings in insomnia and other sleep problems, which suggest that cognitive

pre-sleep arousal has a stronger effect on sleep difficulties than somatic pre-sleep arousal (Alfano et al., 2010; Gregory et al., 2008; Lichstein & Rosenthal, 1980; Puzino et al., 2019).

As our results implicate a role for pre-sleep arousal in the relationship between ADHD symptom severity and insomnia symptom severity, we investigated which specific pre-sleep arousal contents best predicted increased sleep-onset latency. We chose sleep-onset latency from the PSQI as the variable to be predicted, as it is likely that this is the component of sleep that would be most impacted by pre-sleep arousal. We found that the combination of pre-sleep thoughts about “your personal life” and “being mentally alert/active” was a significant predictor of sleep onset latency. Interestingly, these specific pre-sleep arousal components were also significantly associated with ADHD symptom severity. This provides a shared theme of pre-sleep arousal between increased ADHD symptomatology and increased sleep-onset latency, perhaps providing a mechanism for the two to relate to one another. Future research should aim to confirm this shared relationship, such as using brain stimulation to target regions involved in pre-sleep arousal to determine its effect on ADHD symptoms and sleep onset latency, as well as assessing sleep onset latency more objectively using methods such as polysomnography.

A main limitation of the study is that because of the data we collected, we were not able to determine the directionality of the associations. One possible explanation for the association between ADHD symptoms and sleep issues is that ADHD symptoms cause sleep problems, but it may also be the case that sleep problems are causing, or more likely exacerbating, ADHD symptoms. There is some evidence which suggests that poor sleep can result in ADHD-like symptoms in non-ADHD individuals, for example impeding both sustained attention and response inhibition (Chuah et al., 2006; Drummond et al., 2006; Goel et al., 2009; Imeraj et al., 2012; Lowe et al., 2017). Likely the reality is a mixture of both, with ADHD symptoms exacerbating sleep issues and sleep issues exacerbating ADHD

symptoms. If sleep problems are exacerbating ADHD symptoms, their treatment may provide a way of reducing ADHD symptomatology. For example, sleep hygiene interventions, which have been shown to be effective in alleviating sleep problems in ADHD (Nikles et al., 2020), have led to improvements in cognitive processes which are effected by ADHD, such as planning and attention (Almondes et al., 2017). Similarly, the directionality of pre-sleep arousal is not determined in the current research. Whilst we confirm a mediating role of pre-sleep arousal in the relationship between ADHD symptoms and sleep problems, our research is not able to determine whether pre-sleep arousal is an effect of ADHD symptoms, of impeded sleep or both. Future longitudinal and interventional studies will be needed to resolve this ambiguity.

While the causal relationships between ADHD symptoms, pre-sleep arousal and sleep problems will need to be more fully investigated, the relationships we have identified provide a basis for thinking about future interventions. In the presence of a potentially complex causal web, interventions targeting sleep may provide a non-pharmacological way of perturbing the system. Sleep problems can have both biological and behavioural causes. For instance, an individual's innate circadian rhythm is largely driven by activity in the suprachiasmatic nucleus of the hypothalamus (see van Esseveldt et al., 2000 for review) and is reliant on the light-dark cycle and CLOCK, PER and BMAL genes (Kim et al., 2018; King et al., 1997; Takahashi, 2017). However, it can be externally altered. For example, bright light exposure at night, such as from a phone or television, can delay circadian phase (Kelly et al., 1997) whilst bright light exposure in the morning can advance it (Crowley & Eastman, 2015). Delays to feeding can also alter CLOCK gene expression (Wehrens et al., 2017) and timing of exercise can also impact circadian rhythm (Youngstedt et al., 2019). Thus, as both biological and external factors can impact sleep, treatment for sleep issues can also take a more biological or more behavioural approach.

Due to the relationship between ADHD and sleep and the suggestion of a role for pre-sleep arousal in this relationship, we would argue that targeting pre-sleep arousal provides a potential treatment route for ADHD. Behavioural approaches to sleep improvement have been shown to be effective previously. For example, Cognitive Behavioural Training has been shown to reduce pre-sleep cognitive arousal in people with insomnia (Espie et al., 2014). Sleep hygiene training, which focuses on teaching healthy bedtime habits but does not specifically target pre-sleep arousal, has also been shown to improve sleep problems in children with ADHD (Keshavarzi et al., 2014), who have poorer baseline sleep hygiene than their neurotypical peers (van der Heijden et al., 2018). A recent meta-analysis reported that, out of 16 studies examined, 15 reported sleep hygiene interventions improving sleep problems in ADHD children, with improvements including sleep-onset latency, daytime sleepiness and total sleep duration (Nikles et al., 2020). Implicating pre-sleep arousal as a target for intervention may also suggest a focus on meditation and mindfulness, with this approach already showing promise in relieving sleep issues and specifically reducing pre-sleep cognitive arousal in insomniacs (Cincotta et al., 2011; Huberty et al., 2021; Ong et al., 2008; Rusch et al., 2019).

In terms of biological approaches to treatment, the implication of pre-sleep thoughts surrounding “your personal life” and “being mentally alert/active” provide a framework for understanding which neuronal networks and areas may be involved in heightened pre-sleep arousal in ADHD. These might then be potential targets for treatment, via neurostimulation using methods such as transcranial magnetic stimulation (TMS), rather than the currently more common pharmacological methods (e.g., melatonin tablets). A network which may underpin cognitive pre-sleep arousal is the Default-Mode Network (DMN). The DMN is believed to be the major network which underpins internal mental activity (Andrews-Hanna, 2012). In ADHD, its activity appears dysregulated and its functional connectivity is

sometimes disturbed, leading to hyperactivation which has been hypothesised to cause excessive mind-wandering in the disorder (Bozhilova et al., 2018; Christakou et al., 2013). Within the DMN, a region which may be related to pre-sleep thoughts is the retrosplenial cortex (RSC). The RSC is a node of the medial temporal subsystem of the DMN – a system which is reliably activated by thoughts about one’s past and future (Andrews-Hanna, 2012; Andrews-Hanna et al., 2014; Buckner et al., 2008; Schacter et al., 2007; Yeo et al., 2011). The RSC itself has been demonstrated to be activated by spontaneous autobiographical thoughts during resting state scans (Andrews-Hanna et al., 2010). Interestingly, this region has also been implicated in the regulation of neurotypical sleep; it has been suggested to play a key role in consciousness and it has been found to decrease its overall contribution to DMN activity during the descent to sleep (Sämann et al., 2011; Vogt & Laureys, 2005). In addition, the RSC has been implicated in ADHD as it has been found to have a reduced volume in the disorder when compared to neurotypicals (Overmeyer et al., 2001). By shedding light on the specific pre-sleep thought contents which most affect ADHD-related sleep problems, our findings enable future research into potential treatments for ADHD-related sleep problems to be more finely targeted.

It is worth noting that the current research investigated ADHD symptoms, but not an ADHD population. Although our approach addresses the issue of continuous rather than categorical psychopathological symptoms (Caspi & Moffitt, 2018; Kotov et al., 2017), and a wide range of our participants’ ASRS scores would be screened positively for ADHD, it remains to be seen whether our findings would hold in a clinical sample. It is also important to investigate the effect that ADHD medications may have on our findings, as these treatments typically aim to reduce arousal in patients. This may also reduce pre-sleep arousal and alter its mediating effect on ADHD symptoms and sleep problems, but can also cause sleep difficulties (Kidwell et al., 2015). This highlights the benefits of identifying the

relationships in the absence of medications, in a non-clinical sample, prior to generalizing to diagnosed patients.

In conclusion, our results have highlighted a significant relationship between both cognitive and somatic pre-sleep arousal with ADHD symptom severity and insomnia symptom severity. We argue for a mediating role for these two forms of pre-sleep arousal in the relationship between ADHD and insomnia symptom severity and suggest that the effect of cognitive pre-sleep arousal is more robust than its somatic counterpart. Our findings also highlight a specific role for increased pre-sleep thoughts about “your personal life” and “being mentally alert/active” in sleep-onset latency. This work could help direct future treatments of sleep issues by focusing on the role of pre-sleep arousal in ADHD-related sleep problems.

Chapter 5

The role of the retrosplenial cortex and anterior insular in task-to-rest switching and their relationship with ADHD traits and cognitive pre-sleep arousal

Chapter 5

5.1 Abstract

Attention Deficit Hyperactivity Disorder (ADHD) is inextricably linked with sleep problems. Previously, I demonstrated that cognitive pre-sleep arousal mediates the relationship between ADHD traits and insomnia symptoms and highlighted the role of specific components of cognitive pre-sleep arousal: thoughts about “your personal life” and “being mentally alert/active” (*Chapter 4, Smullen et al., in review*). Sleep initiation can be conceptualised as a form of task-to-rest switching, which is underpinned by nodes of the default mode network (DMN) and salience network (SN), such as the retrosplenial cortex (RSC) and right anterior insular (rAI). The current chapter involved participants ($n = 35$) completing a state-switching task whilst undergoing an fMRI scan to investigate RSC and rAI activity during task-to-rest switches, and how activity is influenced by ADHD traits and cognitive pre-sleep arousal. We found that rRSC activity was significantly and consistently modulated by task-to-rest switch activity, and that this modulation was significantly influenced by cognitive pre-sleep arousal, but not by ADHD traits. We also found that rAI activity was modulated by task-to-rest activity and that this modulation interacted with cognitive pre-sleep arousal. These findings suggests that the rRSC and rAI are involved in task-to-rest switching, and that individuals with greater cognitive pre-sleep arousal may experience difficulties with the rRSC and rAI’s ability to engage during task-to-rest transitioning, perhaps contributing to challenges faced during wake-to-rest transitions in those with greater cognitive pre-sleep arousal, as seen in ADHD.

5.2 Introduction

Impairments to sleep are reported in 70-90% of the ADHD population, with the difficulties with sleep-initiation being among the most commonly reported sleep impairments in the disorder (Kooij et al., 2001; Mindell et al., 2009; Park et al., 2011; *see Chapter 2, Smullen et al., in review for review*). Understanding the underpinnings of sleep-initiation difficulties, and thus allowing for the potential treatments of sleep difficulties, is of particular importance with regards to ADHD because impaired sleep can both cause and exacerbate ADHD symptoms in both ADHD and neurotypical cohorts, such as by impairing sustained attention and response inhibition performance (Chuah et al., 2006; Drummond et al., 2006; Goel et al., 2009; Imeraj et al., 2012; Lowe et al., 2017). By identifying the underlying processes of ADHD-related sleep initiation difficulties, treatments could be targeted which, by improving sleep in the disorder, may also go on to improve a wider range of cognitive difficulties experienced by those with ADHD.

Sleep initiation difficulties in other disorders, such as insomnia, have previously been attributed to increased levels of cognitive and somatic pre-sleep arousal (Lichstein & Rosenthal, 1980; Wicklow & Espie, 2000), two arousal types which are experienced to heightened levels in individuals with greater ADHD traits (*Chapter 2, Smullen et al., in review*). Interestingly, we found that both cognitive and somatic pre-sleep arousal mediates the relationship between ADHD traits and insomnia traits, suggesting a role for pre-sleep arousal in ADHD-related sleep difficulties (*Chapter 2, Smullen et al., in review*). However, only the mediating effect of cognitive pre-sleep arousal was replicated in a follow-up investigation, which aligned with previous findings which suggest cognitive pre-sleep arousal has more of an impact on sleep initiation than somatic pre-sleep arousal (Alfano et al., 2010; Gregory et al., 2008; Lichstein & Rosenthal, 1980; Puzino et al., 2019).

Building further upon these findings, we found two specific components of cognitive pre-sleep arousal which were significantly related to both greater sleep-onset latency and ADHD traits: thoughts about “your personal life” and “being mentally alert/active” (*Chapter 2, Smullen et al., in review*). Due to the implication of these components of cognitive pre-sleep arousal, we propose a role of the DMN in ADHD-related sleep-initiation difficulties. The DMN underpins internal mental activity (Andrews-Hanna, 2012), and in ADHD is found to be dysregulated and atypically functionally connected, resulting in excessive mind-wandering (Bozhilova et al., 2018; Christakou et al., 2013). More specifically, a node within the network called the retrosplenial cortex (RSC) may play a role in ADHD-related sleep difficulties, as it is activated by spontaneous autobiographical thoughts during resting state scans (Andrews-Hanna et al., 2010), whilst also being implicated in sleep initiation via a decoupling to the wider DMN (Sämann et al., 2011; Vogt & Laureys, 2005). Moreover, the RSC has been shown to have reduced volume in ADHD (Overmeyer et al., 2001). Thus, overall DMN activity, as well as specific RSC activity, during the initiation of rest is a potential neural correlate of ADHD-related sleep initiation difficulties which could provide targets for future treatments (e.g., using brain stimulation approaches).

Another way of conceptualising the initiation of sleep in the brain is as a form of state-switching: switching from an active task state to a rest state. Thus, the role of the DMN and the RSC can be seen in a similar way to their role in state switching in awake participants. The DMN has previously been implicated in switches from task to rest, with this switch eliciting DMN up-regulation, whilst the network is disengaged during switches from rest to task states (Sidlauskaite et al., 2016). This engagement and disengagement is in part co-ordinated by activity in the right anterior insula (rAI; Menon & Uddin, 2010; Seeley et al., 2007; Sidlauskaite et al., 2014; Sridharan et al., 2008). The rAI is a node of the salience network (SN), a network consistently activated by state-switching (Sidlauskaite et al., 2016).

Importantly, in individuals with ADHD, who have difficulties in task performance following a state-switch (ref), the rAI activation during switches is reduced (Sidlauskaitė et al., 2016). Therefore, the rAI provides another possible neural underpinning of difficulties in sleep initiation that may occur in ADHD, perhaps via under-engagement when transitioning from a task state to a rest state. Atypical rAI engagement during switches to rest may result in atypical DMN engagement and thus heightened cognitive pre-sleep arousal leading to difficulties in sleep initiation.

The current chapter aimed to investigate the role of DMN activity in sleep-initiation difficulties by investigating whole-network activity, as well as specific RSC and rAI activity, during switches from task to rest in a neurotypical cohort split into two groups either based on ADHD tendencies or pre-sleep arousal tendencies: First, the sample was split into a high ADHD-trait group and a low ADHD-trait group, and then similarly the whole sample was also split based on the pre-sleep cognitive arousal (using the PSAS). The benefits of investigating traits are discussed in chapter 4. Participants completed a task-switching paradigm, which included task-to-task and task-to-rest switch trials, whilst undergoing a fMRI scan. DMN activation was assessed during rest to confirm greater DMN activity during rest vs. task trials and during task-to-rest switches. Similarly, SN activation during switch vs repeat trials was investigated to confirm greater SN activity during switching. Subsequently, I examined the differential engagement of the rAI and RSC during task-to-rest switches in comparison to task-to-task switches. Additionally, I explored the link between these neural activation differences and both ADHD and pre-sleep arousal traits.

Post-hoc, due to the links previously outlined (*see chapter 4*), we also investigated the role of cognitive pre-sleep arousal in an exploratory analysis. The analyses outlined previously were re-ran but investigating low and high cognitive pre-sleep arousal groups

rather than ADHD trait groups. Participants were categorised a posteriori based on the whole-cohort cognitive pre-sleep arousal median.

I predicted that (a) DMN activation will be significantly increased during rest trials compared to task trials. Furthermore, (b) this increase in DMN activation during rest trials will be significantly greater in individuals with high ADHD traits compared to those with low ADHD traits, and similarly greater in individuals with high cognitive pre-sleep arousal compared to those with low cognitive pre-sleep arousal. I also predict that (c) the rAI will show significantly greater activation during task-to-rest switches, but (d) this up-regulation will be significantly less pronounced in individuals with high ADHD traits and in those with high cognitive pre-sleep arousal. Similarly, (e) RSC activation is expected to significantly increase during task-to-rest switches, with (f) this up-regulation being significantly less pronounced in the high ADHD trait group and the high cognitive pre-sleep arousal group.

5.3 Methods

5.3.1 Participants

The sample consisted of 39 participants aged between 18-35 years (male = 6, mean age = 20.89y, sd = 2.54y). Participants were Psychology students at the University of Birmingham and were recruited via the University of Birmingham's participant pool recruitment website (Sona; (Monsell, 2003)). The study conformed to the Declaration of Helsinki and was approved by the STEM ethics committee at the University of Birmingham. All participants provided informed consent at the beginning of the study and were informed that they could withdraw their participation and data at any point during or within 5 weeks of the experiment. Participants were compensated for their participation with course credits. Following outlier removal (*see section 5.3.5*), the final sample consisted of 35 participants aged between 18-35

years (male = 5, mean age = 20.57y, sd = 2.33y). Participants were also grouped into low and high ADHD traits a priori, determined by a threshold score of 54 which has been shown in previous research to indicate a high probability for ADHD diagnosis (Zohar & Konfortes, 2010). The low ADHD traits group consisted of a sample of 19 (male = 3, mean age = 20.37y, sd = .42y) whilst the high ADHD traits group consisted of a sample of 16 (male = 2, mean age = 20.81y, sd = .71y). Post-hoc, the low and high cognitive pre-sleep arousal groups were defined by the whole-cohort cognitive PSAS median (18). The retrospectively defined low cognitive pre-sleep arousal group consisted of a sample of 17 (male = 5, mean age = 20.82y, sd = 2.63y), whilst the high cognitive pre-sleep arousal group consisted of 18 (male = 0, mean age = 20.33y, sd = 2.06y). There was a somewhat uneven overlap between these groups, with 12 participants having low cognitive PSAS and low ASRS scores, 5 participants having low cognitive PSAS and high ASRS scores, 7 participants having high cognitive PSAS and low ASRS scores, and 11 participants having high cognitive PSAS and ASRS scores. More information on how the ASRS and cognitive PSAS groups overlapped can be found in Appendix C, Table C1.

It is important to note that this chapter represents a shift from the dimensional approach used in Chapters 3 and 4 to a categorical approach. The initial plan was to create four groups, each representing a combination of high and low ADHD traits and cognitive pre-sleep arousal, to allow for direct comparisons between these groups. This approach aimed to increase statistical power without requiring a large sample size. However, due to time constraints during the recruitment process, it was not possible to fill all four groups as planned, necessitating a retrospective adjustment to the group definitions.

5.3.2 Materials

5.3.2.1 Pre-Sleep Arousal Scale (PSAS)

The PSAS is outlined in chapter 4, section 4.3.2.2.1.

5.3.2.2 Adult ADHD Self-Report Scale (ASRS)

The ASRS is outlined in chapter 4, section 4.3.2.3.

5.3.2.3 Task-switching task

The task is based on that used by Sidlauskaite and colleagues (2016). It involved participants being presented with a series of trials requiring different action. Parity trials required participants to answer if a number is odd or even; magnitude trials required participants to answer if a number is greater than or less than 5; whilst rest trials required no action from the participant. The trial sequence was designed so that some trials repeat the previously required action, while others involve switching to a new action.

The task began by a fixation dot appearing in the centre of the screen for 500ms. Following this a cue appeared on the screen for 500ms. The cue was either a square (cueing a magnitude trial), a triangle (cueing a parity trial) or a circle (cueing a rest trial). Following the cue, there was a cue-target interval ranging from 200-6800ms for magnitude and parity trials where the screen was blank. Next, for magnitude and parity trials, a number between 0-9 appeared on the screen for 500ms. During magnitude trials, the participant responded via a button click, indicating whether the number on their screen is less than 5 or equal to or greater than 5. In parity trials, the participant responded via a button click to indicate whether the number on their screen is odd or even. The interstimulus interval ranged between 200-

6800ms. For rest trials, following the cue the screen remained blank for 13s before the next trial began, during which time the participants did nothing (*see Figure 5.1*). Trial types alternated in a pseudo-random fashion, so that the switch (task-to-rest, rest-to-task, task-to-task) and repeat (task repeat, rest repeat) trial ratios were kept at 1:3 to ensure a robust switch effect (Sidlauskaitė et al., 2016). There were 3 blocks of 100 trials, with each block lasting 16 minutes. Cue and stimuli size were set to 10% of total screen size.

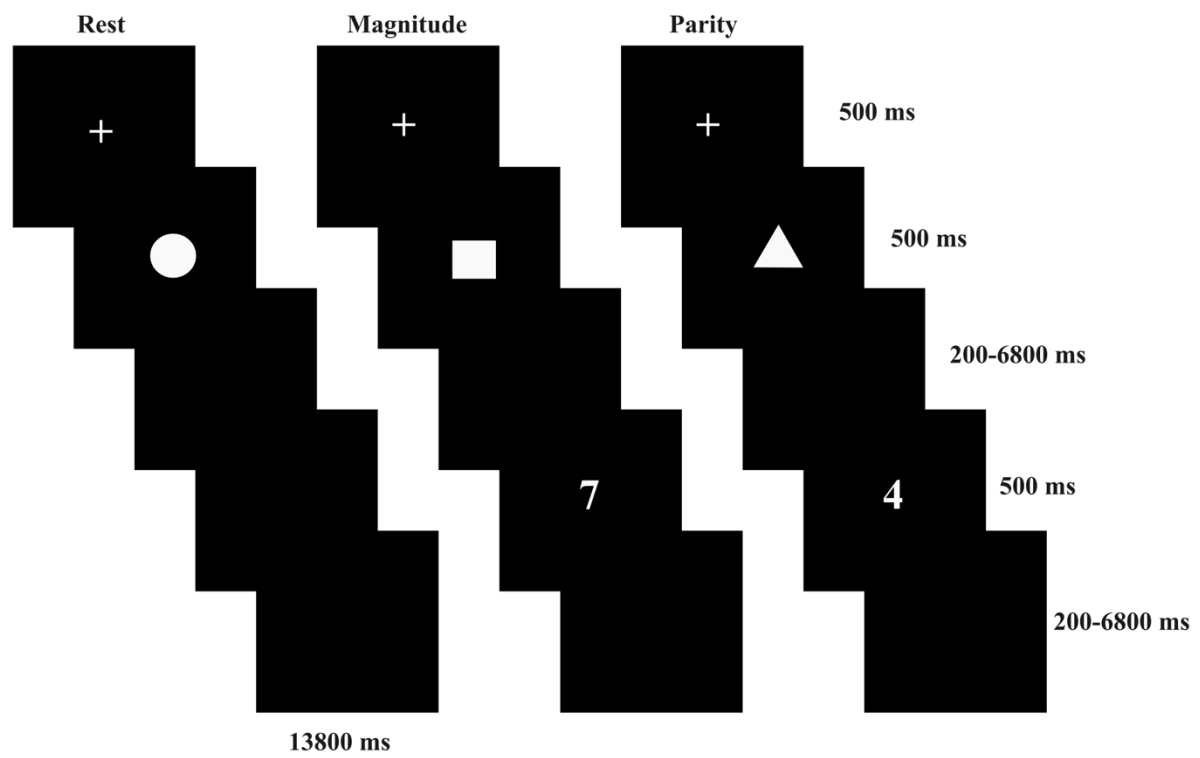


Figure 5.1. An illustration of the task-switching paradigm.

5.3.3. Procedure

Participants first gave informed consent before completing the questionnaires and a 10-minute practise of the task outside of the scanner. Next, participants completed a 5-minute practise of the task in the scanner before undergoing three 16 minute blocks of the task in the scanner. Following this, participants underwent a 10 minute eyes-open resting-state scan (not reported here).

5.3.4 fMRI data acquisition

Data was acquired using a Siemens MAGNETOM Prisma 3T scanner at the Centre for Human Brain Health (CHBH, University of Birmingham) using a 64-channel head coil. Task fMRI data were collected in three runs with an EPI sequence and the following scanning parameters: 650 volumes per run, 57 slices, TR = 1500 ms, TE = 35 ms, voxel size = 2.5x2.5x2.5 mm, flip angle = 71°, matrix size = 84x84x57, field of view = 210x210mm. Each run lasted approximately 16 minutes. A 10-minute eyes-open resting state scan was also collected using the same scanning parameters as the task runs (300 volumes). High resolution (1mm MPRAGE) anatomical T1-weighted images were collected for co-registration purposes using the following parameters: TR = 2400 ms, TE = 2.22 ms, flip angle = 8°, matrix size = 208x300x320, field of view = 256x256, voxel size = 0.8x0.8x0.8 mm, slice timing correction = interleaved.

5.3.5 fMRI pre-processing & outlier removal

Participants who had below 60% accuracy on any of the task conditions were dropped from the analysis due to improper engagement (n = 2; Calzolari et al., 2022). fMRI data were processed and analysed using the FSL tool, FEAT (Woolrich et al., 2001, 2004) following the standard preprocessing pipeline steps: motion correction was performed using MCFLIRT

(Jenkinson et al., 2002). Spatial smoothing used a 5mm^3 Gaussian kernel. A high pass filter was employed with a cutoff of 100s. Transforms to MNI152 were calculated via non-linear alignment (FNIRT and FLIRT; Jenkinson & Smith, 2001). At this stage, any participants who had over 10% of volumes with framewise displacement greater than 0.9mm (Kolodny et al., 2020) were dropped from the analysis ($n = 2$).

5.3.6 Whole brain analysis

The fMRI analysis was based on the five conditions of interest in this design: task-to-rest switches, rest-to-task switches, task-to-task switches (i.e. switches from parity trials to magnitude trials, and vice-versa), task-repeats and rest-repeats. For these analyses we only focused on the time-window encompassing the cue and cue-to-target durations in each trial to isolate the switch period from other cognitive processes involved in the task (Calzolari et al., 2022). For rest trials, where there was no target presented after the cue (and therefore no cue-to-target duration), we used in the GLM an ‘assumed’ cue-to-target duration of 6800 which was added to the cue duration. This value represents the maximum possible duration of cue-to-target intervals in the task trials. A number of nuisance regressors were included in the model. These had the onset of the stimuli onsets (duration of 0.5s) and keyboard response onsets (duration of 0.1s). Additionally, volumes with a framewise displacement of 0.9mm were included in the model as confound EVs (Power et al., 2014). A second level FEAT analysis was conducted to obtain subject-level contrast averages before a group-level FEAT analysis (FLAME1, Z threshold = 3.1, cluster p threshold = 0.05) to obtain group-level contrast averages (Woolrich et al., 2004). Cluster-based multiple comparison correction used the Family-Wise Error method. The contrasts of interest were (1) rest vs task trials, (2) switch vs repeat trials, and (3) task-to-rest vs task to task switches (which is the main contrast of

interest). The whole-brain activation for these contrasts was then narrowed down to activity within the DMN and SN, using masks from the FindLab Atlas (Shirer et al., 2012).

5.3.7 ROI analysis

The rAI ROI was created using fslmaths to create a 10mm³ sphere around the co-ordinates reported previously in the context of state-switching (MNI = 34, 28, 6; Sidlauskaite et al., 2016). The rRSC/PCC (MNI = 14, -54, 14) and the lRSC/PCC (MNI = -12, -58, 16) ROIs were taken from the FindLab Atlas (Shirer et al., 2012). ROI parameter estimates were obtained using fslmeans. These estimates were used as dependent measures in a repeated-measures analysis of variance (rmANOVA) using SPSS v29.0.2.

To investigate ROI attenuation, rmANOVAs for all ROIs included a switch factor with two levels as a within-subjects factor (e.g. task-to-task and task-to-rest switches) to investigate the effect on activity by task-to-rest switching, and a group factor (i.e. low and high ADHD traits, or low and high cognitive pre-sleep arousal) as a between-subjects factor to investigate the effect of ADHD traits and cognitive pre-sleep arousal on task-to-rest switch activation. Normality of variables was assessed using the Shapiro-Wilk test of normality (Shapiro & Wilk, 1965). Multiple comparisons were corrected for using Benjamini and Hochberg's False Discovery Rate (Benjamini & Hochberg, 1995).

5.3.8 Behavioural analysis

Task performance was analysed to confirm expected trends using SPSS v29.0.2. Typically, errors and RTs are found to be significantly greater on switch trials versus repeat trials, demonstrating what is referred to as a 'switch cost', and so we investigated the difference in these task performance measures between switch and repeat trials across the whole group

(Monsell, 2003). Normality of variables was assessed using the Shapiro-Wilk test of normality (Shapiro & Wilk, 1965). Within-group trial-type performance differences were assessed using Mann-Whitney U tests, whilst low vs high ADHD trait and low vs high cognitive pre-sleep arousal differences in performance were assessed using two-way ANOVAs. Task performance measures included % of errors and RT mean. Multiple comparisons were corrected for using Benjamini and Hochberg's False Discovery Rate (Benjamini & Hochberg, 1995).

5.4 Results

5.4.1 The cost of switching on task performance

Switch cost was found in both RT and ACC, as expected, confirming the switch manipulation. There were no group differences in switch cost between high and low ADHD or between high and low PSAS. A full breakdown of the behavioural results can be found in Appendix C: results 1, results 2, and figure C1.

5.4.2 ADHD traits

5.4.2.1 Rest vs task DMN activation

First, I contrasted the whole-brain rest vs task activation for the whole group to confirm DMN activation was greater during rest than task trials. We only focus on activations within the canonical nodes in the DMN according to a standard DMN mask (FindLab Atlas; Shirer et al., 2012). Significant clusters of activation were found across several DMN nodes: PCC/Precuneus, Medial Frontal/ACC/Orbifrontal, Hippocampus, Angular Gyrus/Medial Occipital Gyrus, Middle Occipital Gyrus, Parahippocampal Gyrus, Midcingulate Cortex and Middle Frontal Gyrus (*see Table 5.1*). We then compared these activation between those with

high and low ADHD traits, finding clusters of significantly increased activation in the precuneus and thalamus in the high versus low ADHD traits groups. (see *Table 5.2*).

Table 5.1. Clusters of DMN activation contrasting rest and task trials for the whole group

Brain region	Hemisphere	N voxels	Max Z-stat	x	y	z
PCC / Precuneus	L/R	3584	6.19	0	-44	54
medial frontal / ACC / orbitofrontal	L/R	1226	5.5	0	36	16
Hippocampus	L	444	6.42	-14	-34	0
Angular Gyrus / Medial Occipital Gyrus	R	399	5.4	38	-72	32
Middle Occipital Gyrus	L	331	5	-34	-82	24
Parahippocampal Gyrus	R	203	5.34	24	-36	-18
Midcingulate Cortex	L/R	103	5.35	4	-12	38
Middle Frontal Gyrus	L	87	4.69	-24	2	64

N voxels: number of activated voxels per cluster; Max Z-stat: maximum z-statistic for each clusters; x, y and z are MNI coordinates for the peak of each cluster. R = right, L = left. PCC = posterior cingulate cortex, ACC = anterior cingulate cortex.

Table 5.2. Clusters of DMN activation contrasting rest and task trials for low versus high ADHD traits

Brain region	Hemisphere	N voxels	Max Z-stat	x	y	z
Precuneus	L/R	488	5.61	8	-70	50
Thalamus	L/R	113	4.64	-6	-2	6

N voxels: number of activated voxels per cluster; Max Z-stat: maximum z-statistic for each clusters; x, y and z are MNI coordinates for the peak of each cluster. R = right, L = left.

5.4.2.2 *Switch vs repeat SN activation*

Next, to confirm that SN activation was greater during switch than repeat trials, we contrasted whole-group switch and repeat trials. Whole-brain activations were masked using a standard SN mask to identify activations in nodes of the SN (FindLab Atlas; Shirer et al., 2012). Significant clusters of activation were found across several SN nodes: ACC/Medial Prefrontal/SMA, Middle Frontal Gyrus, Supramarginal/Inferior Parietal Gyrus, Insula, left cerebellar Lobule VI/Crus I and Thalamus (*see Table 5.3*). We then compared these activations between those with high and low ADHD traits, finding no significant differences.

Table 5.3. Clusters of SN activation contrasting switch and repeat trials for the whole group

Brain region	Hemisphere	N voxels	Max Z-stat	x	y	z
ACC / Medial Prefrontal / SMA	L/R	1819	6.79	-4	10	54
Middle Frontal Gyrus	L	360	5.99	-36	54	22
Supramarginal / Inferior Parietal Gyrus	L	326	6	-52	-38	50
Middle Frontal Gyrus	R	298	5.64	30	42	26
Supramarginal / Inferior Parietal Gyrus	R	175	5.39	56	-40	32
Insula	R	155	6.16	38	20	4
Insula	L	151	6.61	-30	24	4
Lobule V1 / Crus I	L	95	5.88	-36	-52	-32
Thalamus	L	48	4.51	-12	-22	10
Thalamus	R	43	4.25	12	-10	12

N voxels: number of activated voxels per cluster; Max Z-stat: maximum z-statistic for each clusters; x, y and z are MNI coordinates for the peak of each cluster. R = right, L = left. cluster. R = right, L = left. ACC = anterior cingulate cortex, SMA = supplementary motor area.

5.4.2.3 ROI analysis - difference in RSC and rAI activity between task-to-rest and task-to-task switches, and the effect of ADHD traits

BOLD activations in the RSC and rAI nodes were analysed using a repeated measure ANOVA with condition (task-to-rest vs. task-to-task) as a within subject factor and group (High vs. Low ADHD) as a between subject factor. For the IRSC node, we found no significant main effect of trial type with comparable activation during task-to-rest switches (mean = -.639, sd = .673) and task-to-task switches (mean = -.836, sd = .475): $F(1, 33) = 3.377$, $p = .075$. Similarly, when investigating the effects of low (mean = -.736, sd = .133) and high ADHD traits (mean = -.708, sd = .147), there was no main effect of group: $F(1, 33) = .112$, $p = .740$ (see figure 5.2a). Additionally, there was no significant interaction between trial type and ASRS group: $F(1, 33) = .659$, $p = .423$, suggesting that IRSC activation for task-to-rest and task-to-task switch trials did not differ for the high-ASRS and low-ASRS groups.

In contrast, rRSC activation was significantly greater during task-to-rest switches (mean = -.534, sd = .635) compared to task-to-task switches (mean = -.862, sd = .497): $F(1, 33) = 8.877$, $p = .005$. However, when investigating the effects of low (mean = -.637, sd = .142) and high ADHD traits (mean = -.700, sd = .140), there was no main effect of group: $F(1, 33) = .607$, $p = .441$ (see figure 5.2b). Furthermore, there was no significant interaction between trial type and ASRS group: $F(1, 33) = .003$, $p = .954$, suggesting that there was no significant difference in rRSC activation between task-to-rest and task-to-task switch trials for the high-ASRS and low-ASRS groups.

Similarly, rAI activation was also significantly greater during task-to-rest switches (mean = .673, sd = .410) compared to task-to-task switches (mean = .273, sd = .479): $F(1, 33) = 19.074$, $p < .001$. However, when investigating the effects of low (mean = .535, sd = .090) and high ADHD traits (mean = .400, sd = .124), there was no main effect of group: $F(1, 33) =$

1.228, $p = .276$ (*see figure 5.2c*). Lastly, there was no significant interaction between trial type and ASRS group: $F(1, 33) = 1.198$, $p = .282$, suggesting that there was no significant difference in rAI activation between task-to-rest and task-to-task switch trials for the high-ASRS and low-ASRS groups.

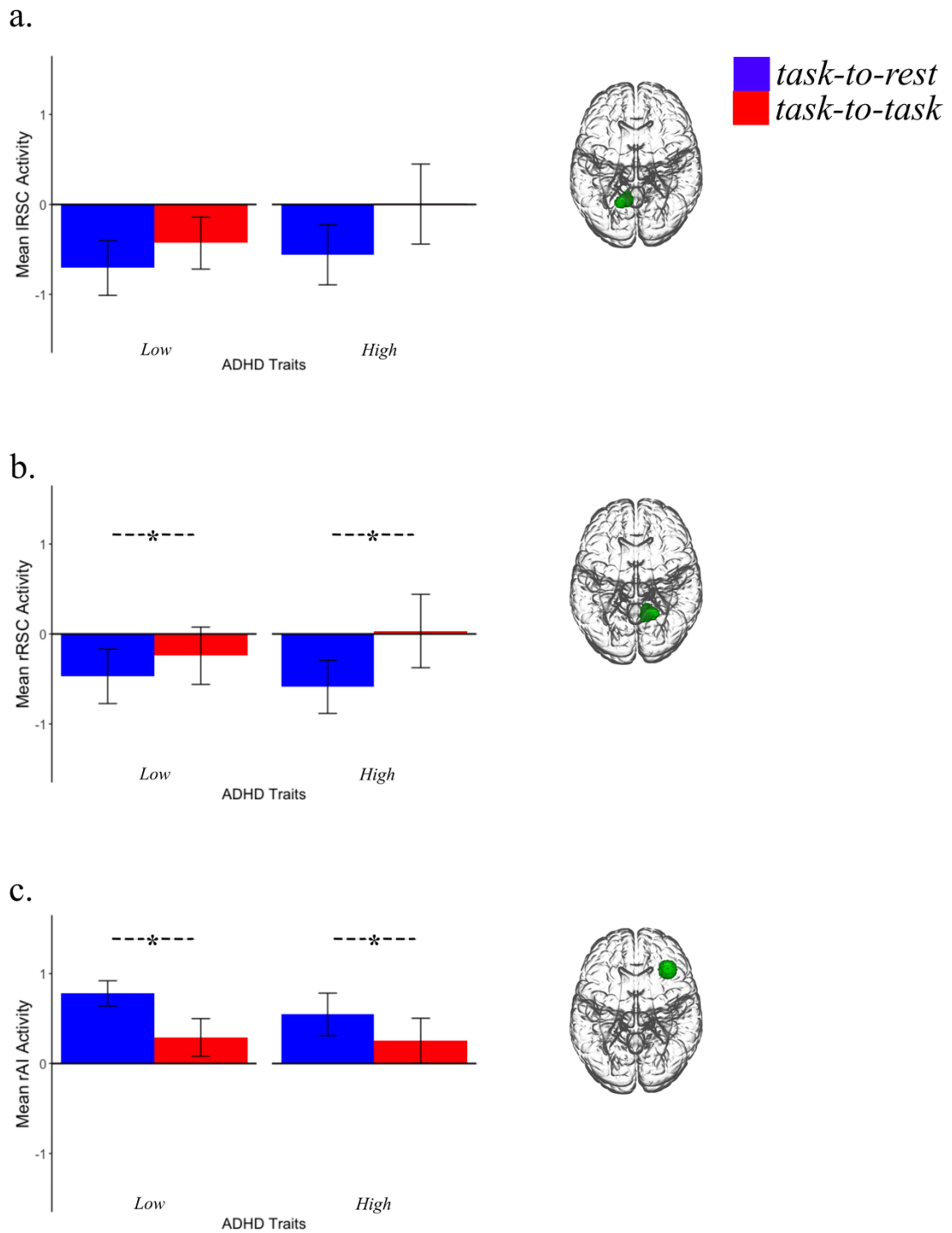


Figure 5.2. Modulation for the (a) IRSC, (b) rRSC and (c) rAI during task-to-rest (blue) and task-to-task (red) switches for those with low and high ADHD traits. Error bars represent 95% CI. Significant differences are illustrated with an asterisk.

5.4.3 Cognitive pre-sleep arousal

Next, we re-ran the ROI analysis. However, this time our participants were grouped into low and high cognitive pre-sleep arousal instead of ADHD traits. These groups were defined by the median of the cognitive pre-sleep arousal score of the entire group (18).

Post-hoc, when the groups were Rest vs task DMN activations and Switch vs Repeat SN activation were defined according to cognitive pre-sleep arousal scores contrasted between the high and low groups, no significant clusters were found.

5.4.3.1 ROI analysis - difference in RSC and rAI activity between task-to-rest and task-to-task switches, and the effect of cognitive pre-sleep arousal

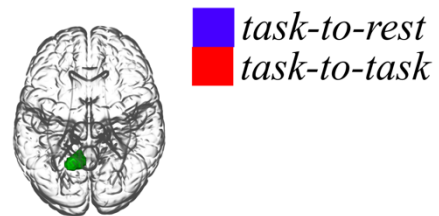
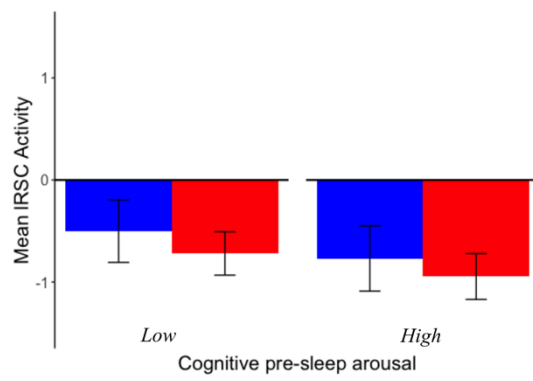
An rmANOVA found that there was no significant difference in IRSC activation during task-to-rest switches (mean = -.639, sd = .673) and task-to-task switches (mean = -.836, sd = .475): $F(1, 33) = 3.107$, $p = .087$. When investigating the effects of low (mean = -.610, sd = .132) and high cognitive pre-sleep arousal (mean = -.862, sd = .139), there was also no effect of group: $F(1, 33) = 2.390$, $p = .132$ (see figure 5.3a). Additionally, there was no significant interaction between trial type and cognitive pre-sleep arousal condition: $F(1, 33) = .035$, $p = .853$, suggesting that there was no significant difference in IRSC activation between task-to-rest and task-to-task switch trials for the low and high cognitive pre-sleep arousal groups.

An rmANOVA found that rRSC activation was significantly greater during task-to-rest switches (mean = -.534, sd = .635) compared to task-to-task switches (mean = -.862, sd = .497): $F(1, 33) = 9.743$, $p = .004$. Furthermore, when investigating the effects of low (mean = -.488, sd = .111) and high cognitive pre-sleep arousal (mean = -.888, sd = .141), there was a significant main effect of group: $F(1, 33) = 7.773$, $p = .009$ (see figure 5.3b). However, there was no significant interaction between trial type and cognitive pre-sleep arousal group: $F(1,$

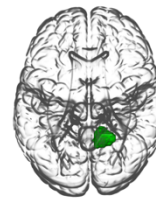
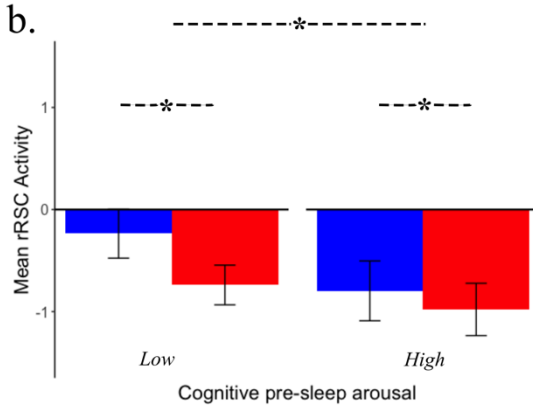
33) = 2.144, $p = .153$, suggesting that there was no significant difference in rRSC activation between task-to-rest and task-to-task switch trials for the low and high cognitive pre-sleep arousal groups.

Lastly, an rmANOVA found that rAI activation was significantly greater during task-to-rest switches (mean = .673, sd = .410) compared to task-to-task switches (mean = .273, sd = .479): $F(1, 33) = 22.512$, $p < .001$. However, when investigating the effects of low (mean = .453, sd = .107) and high cognitive pre-sleep arousal (mean = .492, sd = .105), there was no main effect of group: $F(1, 33) = .100$, $p = .754$ (*see figure 5.3c*). Interestingly, there was a interaction between trial type and cognitive pre-sleep arousal condition: $F(1, 33) = 4.459$, $p = .042$, suggesting that there was a significant difference in rAI activation between task-to-rest and task-to-task switch trials for the low and high cognitive pre-sleep arousal groups. To explore this interaction, we investigated the difference in rAI activation between task-to-rest and task-to-task switches, comparing this difference between the low and high cognitive pre-sleep arousal groups. Post-hoc comparisons utilising a paired-samples t-test found that, for the low cognitive pre-sleep arousal group, rAI activation during task-to-rest switches (mean = .745, sd = .418) was significantly greater than rAI activation during task-to-task switches (mean = .160, sd = .463): $t(16) = 4.295$, $p < .001$. Meanwhile, a paired-samples t-test also found that, for the high cognitive pre-sleep arousal group, rAI activation during task-to-rest switches (mean = .604, sd = .4109) was significantly greater than rAI activation during task-to-task switches (mean = .379, sd = .482): $t(16) = 4.295$, $p < .047$. However, this result did not survive multiple comparison correction, indicating the finding is insignificant after correction.

a.



b.



c.

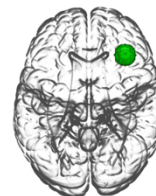
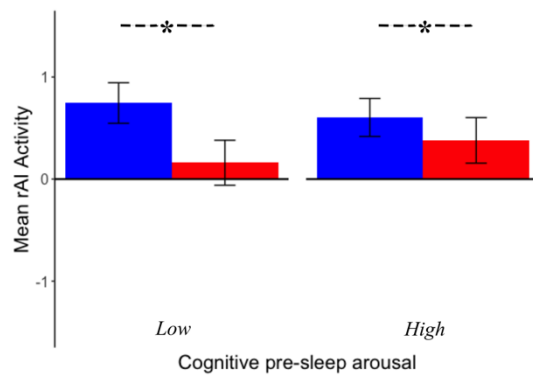


Figure 5.3. A figure depicting modulation for the (a) lRSC, (b) rRSC and (c) rAI during task-to-rest (blue) and task-to-task (red) switches for those with low and high cognitive pre-sleep arousal. Error bars represent 95% CI. Significant differences are illustrated with an asterisk.

5.5 Discussion

Previous research has implicated ADHD-traits and cognitive pre-sleep arousal in difficulties with sleep initiation (*see chapter 4 for review*). In the current study these findings were built upon by investigating the neural underpinnings of task-to-rest switching, as a proxy for wake-to-sleep transitions. After confirming that total error percentage and RT mean were significantly greater for switch vs repeat trials, I tested the prediction that (a) DMN activation would be significantly increased during rest trials compared to task trials, finding this to be the case. Similarly, I found that nodes of the SN were activated during switch trials. I also predicted that (b) these up-regulations would be significantly greater in those with high ADHD traits versus low ADHD traits, and in those with high cognitive pre-sleep arousal versus low cognitive pre-sleep arousal. This prediction was confirmed in cognitive pre-sleep arousal, but not in ADHD traits. Next, I focused on the role of three specific ROIs during task-to-rest switching: lRSC, rRSC and rAI. The RSC was investigated due to its relation to cognitive pre-sleep arousal, whilst the rAI was investigated due to its implication in state-switching. I predicted that (c) the rAI would show significantly greater activation during task-to-rest switches, but (d) this up-regulation would be significantly less pronounced in individuals with high ADHD traits and in those with high cognitive pre-sleep arousal. Similarly, (e) RSC activation was expected to significantly increase during task-to-rest switches, with (f) this up-regulation being significantly less pronounced in the high ADHD trait group and the high cognitive pre-sleep arousal group. We found that RSC and rAI activity was regulated by task-to-rest switching but that this regulation was not significantly affected by ADHD trait severity. However, rRSC up-regulation during task-to-rest switching

was significantly lower in those with greater cognitive pre-sleep arousal. Furthermore, rAI up-regulation during task-to-rest was affected by cognitive pre-sleep arousal group, with this up-regulation only being significant in those with low cognitive pre-sleep arousal.

Previously, this thesis outlined findings implicating specific components of pre-sleep arousal in ADHD-related difficulties with sleep initiation: thoughts about “your personal life” and “being mentally alert/active” (*Chapter 4, Smullen et al., in review*). This finding suggested the focus on the RSC in the current study as this node of the DMN is activated by spontaneous autobiographical thoughts during resting state scans (Andrews-Hanna et al., 2010), and, via de-coupling to the wider DMN, is involved in sleep initiation (Sämann et al., 2011; Vogt & Laureys, 2005). The RSC has also been implicated in ADHD, and has reduced volume in the disorder (Overmeyer et al., 2001). Interestingly, the current research found that rRSC activation was greater during task-to-rest switches than task-to-task switches. These findings suggest that the rRSC is involved in the switch from active to rest states, which is consistent with its proposed role in preparing the brain to enter a more restive state conducive to sleep initiation (Sämann et al., 2011). Importantly, the rRSC’s up-regulation during task-to-rest versus task-to-task switching did not differ between those with low or high ADHD traits, but we found that overall rRSC activity was significantly lower in those with greater cognitive pre-sleep arousal when compared to those with lower cognitive arousal. This suggest that individuals with greater cognitive pre-sleep arousal may experience difficulties with the rRSC’s ability to engage during task-to-rest transitioning, perhaps contributing to challenges faced during wake-to-rest transitions in those with greater cognitive pre-sleep arousal. Future research should focus on the rRSC as a potential target for treatment of sleep-initiation difficulties, perhaps via direct stimulation through methods such as transcranial ultrasound stimulation to improve its engagement during sleep initiation in those with high cognitive pre-sleep arousal to determine whether this improves sleep initiation difficulties.

However no significant difference in lRSC activation was observed when comparing task-to-rest with task-to-task switches. This pattern suggests that RSC involvement in task-to-rest switching may be limited to the right hemisphere. It is worth noting that the main effect was approaching significant ($p = .087$), and thus may reflect an issue with power rather than no difference in reality.

The rAI was found to be up-regulated by task-to-rest transitions compared to task-to-task switching, which aligns with previous implications of this node of the SN in state switching (Menon & Uddin, 2010; Seeley et al., 2007; Sidlauskaite et al., 2014; Sridharan et al., 2008). However, our results did not confirm previous findings that this regulation is less pronounced in those with greater ADHD traits. However, importantly we did find that there was a significant interaction between rAI activation during task-to-rest versus task-to-task switching and cognitive pre-sleep arousal. After multiple comparison correction, our results found rAI activity was significantly greater during task-to-rest versus task-to-task switching for only the low cognitive pre-sleep arousal group. These findings suggest that rAI engagement during task-to-rest switching is less pronounced in those with greater cognitive pre-sleep arousal. This reduced engagement may impair the rAI's ability to effectively facilitate the shift from active to restful states in those experiencing elevated pre-sleep cognitive arousal.

As previously noted, our findings regarding RSC and rAI engagement during state-switching were, somewhat surprisingly, not influenced by ADHD traits in the same way as they were by cognitive pre-sleep arousal. One possible explanation for this discrepancy could be that our low and high ADHD-trait groups were determined based on ASRS scores rather than a clinical diagnosis. Since the ASRS is not a diagnostic tool, its cutoffs are somewhat arbitrary and may not capture sufficiently extreme differences between groups to reveal

neural distinctions. Future research should aim to test this theory by replicating the current research with clinically diagnosed ADHD and control groups.

A limitation of the current research is that it focused on the activation of nodes rather than the communication between them. Consequently, our results primarily discuss the recruitment of the RSC and rAI during different switch types, without providing insight into how switching, ADHD traits, or cognitive pre-sleep arousal affect communication between nodes in the DMN and SN. As a result, the study does not elucidate sensitivities in communication during task-to-rest transitions in individuals with greater ADHD traits or those experiencing greater cognitive pre-sleep arousal. Future research should address this gap by investigating intra-network communication within the DMN and SN during task-to-rest transitions, to determine whether ADHD traits or cognitive pre-sleep arousal influence this communication. For example, future research should aim to build upon the findings by Sämann and colleagues (2011), which implicated RSC-DMN de-coupling in the transition from wake-to-rest by investigating the relationship between this de-coupling behaviour and ADHD traits, and cognitive pre-sleep arousal.

A significant limitation of the current research is the method used to allocate participants into the low and high cognitive pre-sleep arousal groups. These groups were allocated a posteriori based on the group median. This specific cohort had a limited number of participants surpassing the a priori threshold for ‘average’ cognitive pre-sleep arousal based on the median answer being selected for all items of the PSAS. Consequently, whilst half of the cohort were classified as high pre-sleep arousal, many within this classification would fall in the ‘low’ group in a more evenly distributed sample, perhaps skewing our findings regarding cognitive pre-sleep arousal. Also, due to the uneven overlap of pre-sleep arousal and ADHD trait groups, a fully factorial design could not be implemented. Future

research should aim to replicate the current analysis with a greater distribution of pre-sleep arousal scores.

Another limitation of the current study is that ADHD was categorised by low and high traits in a general sample of university students rather than a diagnosed and undiagnosed group. There are benefits to this approach, as discussed previously (*see chapter 4*). However, by categorising participants based on traits rather than diagnosis, we may overlook critical aspects of ADHD which are more evident in a clinically diagnosed population. Future research should aim to replicate the current research but with a clinically diagnosed ADHD group and a non-diagnosed control group, as this approach would provide insights into how neural activity during task-to-rest switching manifests in a clinically diagnosed sample.

In a related fashion, we were not able to utilise a factorial design in the current study to enable us to contrast between ADHD and pre-sleep arousal. Therefore, our findings regarding pre-sleep arousal may still incorporate effects of high and low ADHD tendencies, especially as these tend to correlate (*see chapter 4*). Future research should employ a fully factorial design with even distribution across these combinations of traits to ascertain the contribution of each trait independently of the other. With that being said, it is worth noting that these traits are not distributed evenly in real-world samples, and as such our distributions, whilst not desirable from a methodological standpoint, do reflect the unequal distributions seen in reality.

In conclusion, the current research investigated the relation between ADHD traits and cognitive pre-sleep arousal with RSC and rAI activity during task-to-rest switching. Whilst there was evidence for IRSC, rRSC and rAI involvement in task-to-rest switching, none of these involvements appeared to be mediated by ADHD traits. However, rRSC activity in general was significantly lower in those with greater cognitive pre-sleep arousal, suggesting a

potential role of the rRSC in cognitive pre-sleep arousal, and therefore providing a potential target for treatment of sleep-initiation difficulties in those with high cognitive pre-sleep arousal. importantly, rAI recruitment during task-to-rest switching was mediated by cognitive pre-sleep arousal, which may be linked to the difficulty to facilitate the transition from active to rest states. We propose that future research should also address the question of functional communication between these seemingly critically nodes of the DMN and SN and whether they are similarly mediated by ADHD and/or pre-sleep arousal.

Chapter 6

General Discussion

Chapter 6

6.1 Summary of aims and results

This thesis aimed to investigate the neural underpinnings of ADHD symptoms to guide the focus of future treatments of the disorder. The first part of this thesis focused on a specific symptom of ADHD: response inhibition. Through the use of a novel go/nogo task which manipulated the frequency of go trials to elucidate the cognitive component of response inhibition, previous research has implicated the parietal nodes (TPJ and IPS) in neurotypicals (Kolodny et al., 2017). The same authors later used the novel go/nogo task with an adult ADHD cohort, finding modulation of the TPJ and IPS during inhibitory demand is less pronounced in individuals with greater ADHD symptoms (Kolodny et al., 2020). Furthermore, they found that IFG and IPS functional connectivity during inhibitory demand is also similarly modulated by ADHD severity during inhibitory demand, so that increased symptom severity coincided with reduced functional connectivity between the nodes (Kolodny et al., 2020).

In chapter 2, the thesis first aimed to build upon these findings by investigating the white matter underpinning the IFG-IPS connection by assessing group differences in structural properties in these connections between ADHD and controls and then assessing the contribution of these white matter tracts to recruitment of the parietal nodes during inhibitory demand as well as to response inhibition performance. I found that, on a group level, individuals with ADHD had significantly lower axial diffusivity in the tract connecting the left and right IFG than the control group. Furthermore, I found that, on an individual level, in the ADHD group, a combination of volume and diffusivity metrics of the transcallosal IFG-IFG and left IFG-IPS tracts were linked with parietal modulations during inhibitory demand. Lastly, I found that in ADHD greater IFG-IFG mean diffusivity was linked with better

response inhibition performance, whilst in controls better response inhibition performance was linked with lower IPS-IPS radial diffusivity.

The thesis then aimed to confirm a causal role of the left IPS in response inhibition in and its modulation in ADHD by targeting the region using inhibitory cTBS. While the inhibitory cTBS to the left IPS did not have a general effect across all participants, ADHD traits modulated the TMS effect so that greater ADHD traits expression was linked with greater impairment in response inhibition performance following inhibitory TMS over the left IPS.

Following this, the focus of the thesis shifted from response inhibition to sleep difficulties in ADHD. Studies of sleep in ADHD populations reveal that sleep problems are reported by 70-90% of individuals (Kooij et al., 2001; Mindell et al., 2009), with one of the most reported sleep difficulty in the disorder being problems with sleep initiation (Park et al., 2011). Interestingly, poor sleep is associated with many cognitive impairments which are common in ADHD (Chuah et al., 2006; Drummond et al., 2006; Goel et al., 2009; Imeraj et al., 2012; Lowe et al., 2017). Ergo, understanding the underpinnings of ADHD-related sleep-initiation difficulties may provide a potential treatment route which improves not only sleep problems, but wider ADHD symptoms. An aim of this thesis was to investigate the role of pre-sleep arousal in ADHD and sleep difficulties. In chapter 4, I found that both somatic and cognitive pre-sleep arousal are related to ADHD traits and insomnia traits. What's more, I found that cognitive pre-sleep arousal mediates the relationship between ADHD traits and insomnia traits. On top of that, our results linked two specific components of cognitive pre-sleep arousal with sleep initiation: thoughts about "your personal life" and "being mentally alert, active". Interestingly, these components were also linked with ADHD traits.

Continuing from these findings, the thesis then aimed to establish the neural underpinnings of cognitive pre-sleep arousal's role in ADHD-related difficulties with sleep

initiation by investigating the activation during task-to-rest switching in the DMN, RSC and rAI, and its connection to both ADHD traits and pre-sleep arousal. The DMN was chosen as a focus because this network underpins internal mental activity (Andrews-Hanna, 2012), and is thought to be dysregulated and atypically functionally connected in ADHD, resulting in excessive mind-wandering (Bozhilova et al., 2018; Christakou et al., 2013). The RSC node of the DMN was chosen as a more specific focus because this node is activated by spontaneous autobiographical thoughts during resting state scans (Andrews-Hanna et al., 2010), whilst also being implicated in sleep initiation via a de-coupling to the wider DMN (Sämann et al., 2011; Vogt & Laureys, 2005) and in ADHD through having reduced volume in the disorder (Overmeyer et al., 2001). The rAI was selected as a focus because state-switching elicits DMN regulation, and said regulation is partly coordinated by the rAI (Menon & Uddin, 2010; Seeley et al., 2007; Sidlauskaite et al., 2014; Sridharan et al., 2008), and ADHD-related difficulties with state-switching is linked with lower rAI engagement (Sidlauskaite et al., 2016).

6.2 Interpretation of results

6.2.1 The role of the frontoparietal network in response inhibition

Throughout chapter 2, the IFG was implicated in ADHD-related response inhibition. Specifically, the white matter properties of the tract connecting the IIFG and IIPS were significantly linked with parietal modulations during inhibitory demand in individuals with ADHD. This supports the notion that IFG-IPS functional connectivity differences are associated with ADHD-related response inhibition impairments (Kolodny et al., 2017, 2020). These findings provide possible structural properties underlying the functional connectivity-response inhibition links. Interestingly, the white matter structure between the right IFG

(rIFG) and lIFG was also linked to response inhibition performance in ADHD, whereas the white matter structure between the right IPS (rIPS) and lIPS was linked to response inhibition performance in controls. These differential results suggest that response inhibition may be executed differently in individuals with and without ADHD. The IFG is associated with cognitive and attentional control (Hampshire et al., 2010; Shomstein, 2012). Therefore, my findings might suggest that ADHD-related response inhibition difficulties originate from broader impairments in cognitive control, whereas neurotypical response inhibition performance is more sensitive to specific neural functions related to response inhibition. Previous research reports impaired IFG functionality in ADHD (Cepeda et al., 2000; Cubillo et al., 2012; Dickstein et al., 2006; H. Huang & Ding, 2016). Our results further indicate atypical white matter structure underpinning the rIFG-lIFG connection in ADHD, characterized by lower axial diffusivity. This lower AD may reflect reduced calibre or injury to axons, or reduced coherence in axon orientation (Solowij et al., 2017), although the exact anatomical underpinnings are still under debate (Jones et al., 2013). Regardless of the anatomical specifics, our results highlight that IFG-IFG white matter differs between ADHD adults and controls, which may result in impaired cognitive control. This impaired cognitive control might partly explain the role of IFG-IPS communication in ADHD-related response inhibition performance via atypical top-down engagement of the IPS during inhibitory demand.

6.2.2 The IPS as a potential target for response inhibition treatment

Following the examination of IFG-IPS connectivity in ADHD-related response inhibition impairments, which implicates the IPS in ADHD-related response inhibition, I then explored the causal role of the IPS in response inhibition and its potential as a intervention target.

Despite previous findings which suggest that IPS activation is mediated by inhibitory demand

(Kolodny et al., 2017), chapter 3 found that inhibiting IPS activity during inhibitory demand via cTBS did not result in impaired response inhibition performance. These findings may suggest that there is no causal link between IPS activation and response inhibition, suggesting instead that previous research implicating the IPS may highlight a by-product of another cause, such as a sensitivity to top-down IFG-IPS engagement during inhibitory demand.

Interestingly, chapter 3 did report a relationship between the effect of cTBS to the IPS on response inhibition and ADHD traits, suggesting that individuals with greater ADHD traits experience a greater impairment to response inhibition following IPS inhibition. Modulation of the IPS during inhibitory demand is related to ADHD traits (Kolodny et al., 2020). Ergo, the findings of chapter 3 may reflect a greater susceptibility to IPS disruption in those with greater ADHD traits due to less robust IPS engagement during inhibitory demand.

Furthermore, as the IFG-IPS network's functional connectivity and underlying structure has been implicated in response inhibition and differences have been found between ADHD and control groups, perhaps those with greater ADHD traits possess reduced compensatory mechanisms within the IFG-IPS network to counteract IPS disruption through atypical connectivity within this network.

6.2.3 The role of pre-sleep arousal and the DMN in ADHD-related sleep difficulties

While the first half of my thesis examined response inhibition dysfunction and potential treatment targets, the second half shifted focus to sleep—a critical behavioural component whose dysfunction broadly impacts various cognitive difficulties, including response inhibition. In chapter 4, we confirmed previous findings which report an association between greater ADHD traits and sleep difficulties (McGowan et al., 2016; Uygur & Bahar, 2023). Building upon this known relationship, chapter 4 then reports that pre-sleep arousal mediates the relationship between ADHD traits and insomnia symptoms. This mediating role was

initially found for both cognitive and somatic pre-sleep arousal, although it was only replicated for cognitive pre-sleep arousal. These results point to a critical role that cognitive pre-sleep arousal is likely playing in driving sleep difficulties in ADHD. By elucidating the role of pre-sleep arousal in ADHD-related sleep problems, I provide a potential treatment route to alleviate the effects that sleep impairments can have on wider ADHD symptoms (Chuah et al., 2006; Drummond et al., 2006; Goel et al., 2009; Imeraj et al., 2012; Lowe et al., 2017).

Going further, chapter 4 then implicated specific components of pre-sleep arousal in ADHD traits and insomnia symptoms: thoughts about “your personal life” and “being mentally alert/active”. The implication of these components led to our proposal for a role of the DMN in ADHD-related sleep initiation difficulties as this network underpins internal mental activity (Andrews-Hanna, 2012) and in ADHD is related to excessive mind-wandering due to its atypical functioning in the disorder (Bozhilova et al., 2018; Christakou et al., 2013). Specific nodes of the DMN may underpin increased cognitive pre-sleep arousal in ADHD. For example, the RSC is implicated in sleep-onset difficulties (Sämann et al., 2011; Vogt & Laureys, 2005) as well as with spontaneous autobiographical thoughts during resting state scans (Andrews-Hanna et al., 2010). Thus, chapter 5 investigated the activity of the DMN, as well as specific RSC activity during task-to-rest state switching to shed light on the neural underpinning of pre-sleep arousal’s role in ADHD-related sleep initiation difficulties. Importantly, our findings suggest that the rRSC is upregulated during task-to-rest switching versus task-to-task switches, suggesting an involvement of the rRSC in transitions from active to rest states. Importantly, we found that rRSC up-regulation during task-to-rest switching was significantly less pronounced in individuals with greater cognitive pre-sleep arousal, suggesting that those with greater cognitive pre-sleep arousal may experience difficulties with the rRSC’s ability to engage during these transitions, perhaps contributing to

challenges faced during wake-to-rest transitions in those with greater cognitive pre-sleep arousal. However, as the rRSC activation was not affected by ADHD traits, our results suggest that the rRSC's function in managing state transition is not altered by the presence of ADHD traits.

6.3 Limitations & Future directions

As has been discussed throughout this thesis, limitations occur across all chapters, many of which offer interesting directions for future research. A limitation which required special attention was that the diffusion data discussed in chapter 1 was collected without an opposite phase-encoding direction, preventing estimations of motions effect of susceptibility-induced distortions being included in motion-correction. Whilst this preprocessing step is not mandatory, it is suggested for cohorts likely to experience greater in-scanner motion, such as our ADHD cohort (Durstun et al., 2003; Epstein et al., 2007; Yu-Feng et al., 2007). To account for this, I employed particularly stringent motion-control checks where any datasets flagged for motion were removed. The remaining datasets exhibited no significant difference in motion between the ADHD and control groups and motion did not correlate with any white matter metrics, suggesting our results did not result from motion artifacts.

Another weakness of the thesis is that response inhibition is only investigated through the lens of the novel go/nogo task. Whilst this enabled a cleaner measure of the cognitive component of the action withholding domain of response inhibition (Kolodny et al., 2017), it does not provide a measure of the action cancellation domain of response inhibition. As previously discussed, action withholding and action cancellation are distinct behavioural processes with limited shared frontoparietal activation (Schacter et al., 2007; Zheng et al.,

2008). Therefore, it is likely that our findings regarding action withholding do not translate to action cancellation. Future research should aim to replicate our research into action withholding but using tasks which measure action cancellation, such as the stop-signal task (Lappin & Eriksen, 1966) to confirm that our findings relate only to action withholding, and thus providing a more comprehensive understanding of the neural underpinnings of ADHD-related response inhibition as a whole.

Across Chapters 3, 4, and 5, the majority of participants were female. Given that ADHD is diagnosed far more frequently in males, this represents a clear limitation in the generalisability of the findings to the broader population of individuals with elevated ADHD symptoms (Rucklidge, 2008). Furthermore, as males and females often present ADHD symptoms differently, the predominance of female participants may have influenced the patterns and interpretations of symptomatology observed in this thesis. Additionally, a significant limitation of this thesis lies in the inability to control for the co-occurrence of other conditions commonly associated with ADHD. As discussed in Section 1.1.5, ADHD frequently co-occurs with a wide range of other conditions. This presents a limitation for this thesis, as the relatively small sample size did not allow for controlling the expression of these comorbid conditions. Consequently, the findings related to ADHD trait expression may, in part, reflect influences from traits associated with other disorders, such as depression, anxiety, ODD, OCD, or ASD. Addressing this limitation would require large datasets, such as those provided by the ENIGMA Consortium, to achieve sufficient statistical power to control for these many potential confounds.

Another weakness in this thesis is that chapter 3 relies on the assumption that cTBS is having a significant effect on IPS activity. However, there are a variety of individual differences which can impact the extent to which stimulation inhibits a target region, such as anatomical features like skull thickness (Opitz et al., 2015) and genetic features such as

BDNF polymorphisms (Cheeran et al., 2008). Thus, it is possible individual differences which were not accounted for could have affected the efficacy of cTBS stimulation. Future research should aim to better account for these individual differences, perhaps by combining TMS with another neuroimaging method, such as fNIRS, to confirm a neural impact of TMS and to provide a control measure of the effect of TMS on neural activity.

Chapter 3 focused on stimulating the IPS, yet this is not the only region that we have previously implicated in response inhibition. For example, the IFG is another region which has been implicated (Chapter 2; Smullen et al., in review). As such, future research should aim to target said regions to confirm a causal relationship between their activation during inhibitory demand and task performance, as well as to investigate their potential as a target for treatment of response inhibition difficulties.

In a similar vein, whilst chapter 4 highlighted a relationship between ADHD traits, insomnia symptoms and pre-sleep arousal, we were unable to confirm the direction of said relationships. As discussed previously, ADHD symptoms may cause sleep problems, or possibly sleep problems may be exacerbating ADHD symptoms. In actuality, it is likely a combination of both directions. Likewise, whilst pre-sleep arousal was demonstrated to mediate the relationship between ADHD and insomnia symptoms, we did not confirm whether pre-sleep arousal is resultant from ADHD symptoms, sleep difficulties, or both. Future longitudinal and interventional research should aim to pick these relationship apart further to investigate their directions.

In chapter 5, participants were categorised into low and high cognitive pre-sleep arousal groups. Due to recruitment difficulties, these groups were determined a posteriori, based on the median score of the current cohort. The current cohort had a limited number of participants surpassing the a priori threshold for ‘average’ cognitive pre-sleep arousal based on the median answer being selected for all items of the PSAS, meaning the current cohorts

‘high cognitive pre-sleep arousal’ group may not be truly representative of individuals suffering from high levels of cognitive pre-sleep arousal. Future research should aim to address this limitation by recruiting a sample with more distributed PSAS scores to ensure a more balanced sample.

Similarly, the sample in chapter 5 could not be categorised into all combinations of low and high ADHD traits and cognitive pre-sleep arousal, with differences instead being required to be investigated across dimensions, separately. Future research should aim to replicate the research with a sample which encompasses all combinations of low and high ADHD traits and cognitive pre-sleep arousal. This approach will enable a deeper understanding of how the interaction between ADHD traits and cognitive pre-sleep arousal influences neural activity during task-to-rest transitioning.

A more general limitation of the thesis is that, other than chapter 2, ADHD was focused on individual ADHD-traits rather than contrasting ADHD and control cohorts. There are advantages to this method, such as addressing the fact that symptoms occur in a continuous rather than categorical nature in the general population which mitigates the limitations of traditional taxonomies of neurodevelopmental disorders surrounding the somewhat arbitrary boundaries between what is classed as disorder and normality when the disorder is itself referred to as a spectrum (Caspi & Moffitt, 2018; Kotov et al., 2017). However, in a clinical sense ADHD is treated categorially. Thus, future research would benefit from replicating our research via contrasting cohorts with an ADHD diagnosis and control cohorts.

ADHD symptomatology in this thesis was assessed using overall symptom severity scores derived from ASRS responses. This approach reflects the multifaceted nature of ADHD, a condition whose wide range of symptoms can be significantly influenced by sleep difficulties. Moreover, many individuals with ADHD do not align neatly with specific subtypes (e.g., predominantly inattentive), making an emphasis on overall symptomatology

more appropriate. By focusing on the broader scope of symptoms, this method offers a more comprehensive understanding of ADHD and effectively captures the variability inherent in the disorder. However, ADHD symptoms can also be analysed through specific subtypes, which may offer deeper insights into particular cognitive processes explored in this thesis, such as the relationship between response inhibition and impulsivity symptoms. Future research should aim to replicate the findings of this thesis while focusing on these ADHD subtypes to determine if unique patterns or associations emerge within specific symptom domains.

Finally, by implicating the rRSC in task-to-rest transitioning and highlighting how its activity is influenced by cognitive pre-sleep arousal, this thesis provides a potential target for future treatments of sleep-initiation difficulties. Future research should investigate the efficacy of targeting those nodes of the DMN, perhaps using TUS or TMS, to determine whether enhancing its functioning during task-to-rest transitions improves sleep initiation in those experiencing high levels of cognitive pre-sleep arousal.

6.4 Conclusions

This thesis aimed to investigate the neural underpinnings of both response inhibition and sleep initiation difficulties in ADHD. I provided evidence for a role of frontoparietal white matter structure connecting the IFG and IPS in ADHD-related response inhibition impairments, reporting reduced frontal axial diffusivity in ADHD as well as highlighting a difference in which tract relates to response inhibition performance between groups, with ADHD performance relative to frontal tract structure and control performance relating to parietal tract structure. The thesis also reported a relationship between frontoparietal white matter structure and parietal modulations during inhibitory demand. Additionally, the thesis reported that the effect of cTBS disruption of parietal (lIPS) activity on response inhibition is

influenced by ADHD traits, with those suffering from greater ADHD traits experiencing greater disruption to response inhibition following IIPS inhibition. The focus of the thesis then shifted from response inhibition to sleep impairments in ADHD, finding that cognitive pre-sleep arousal mediates the relationship between ADHD and insomnia traits, highlighting specific components of cognitive pre-sleep arousal as of particular import: thoughts about “your personal life” and “being mentally alert/active”. Building upon this, the rRSC was emphasized as a node involved in task-to-rest transition, which may be mediated by cognitive pre-sleep arousal. This finding provides a potential neural target for treatment of sleep initiation difficulties in groups experiencing high levels of cognitive pre-sleep arousal.

Appendix

Appendix A

Methods

1. fMRI acquisition

Images were acquired on a 3T MRI (Magnetom Prisma, Siemens Medical Inc., Erlangen, Germany) scanner at SCAN@TAU center in Tel-Aviv University, using a 64-channel head coil. While participants completed the Go/No-go task, functional images were collected using a single-shot 2D gradient-echo echo-planar sequence with the following parameters: slice thickness = 3.6 mm, 33 transverse slices in ascending interleaved order, TR = 2 sec, TE = 35 msec, flip angle = 90°, matrix 96 x 96, FOV = 192 mm, for a voxel-wise resolution of 2 x 2 x 3.6 mm. During the fMRI scan, participants performed 4 runs of the task, each of them with 236 volumes: two runs of rare-No-go and two runs of prevalent-No-go, interspersed by an anatomical T1-weighted scan. The order of block types was counterbalanced across participants.

Tables

Table A1. Descriptive statistics for demographic and behavioural data prior to outlier removal

	ADHD	Control	t	df	P	Cohen's d
Sex (M/F)	20/23	8/16				
Age (years)			-.537	65	.595	-.137
N	43	24				
Range (y)	19-39	19-38				
Mean (y)	26.7	27.3				
SD (y)	4.4	4.2				
ASRS Total			9.813	65	.005*	2.500
N	43	24				
Range	41-85	23-49				
Mean	63.0	37.7				
SD	11.6	6.7				
Response Inhibition Performance ⁺			2.744	51	<.001**	.786
N	34	19				
Range	0-.198	0-.073				
Mean	.064	.028				
SD	.053	.016				

⁺Response Inhibition Performance was quantified as the rate of commission errors during the rare-No-go condition in the behavioural version of the Go/No-go task.

Note: * $p < .05$, ** $p < .001$

Note: SD = standard deviation, df = degrees of freedom

Note: There is variation in the number of participants for each variable due to missing data.

Table A2. ANOVA results investigating the difference in white matter metrics between medication usage groups due to medication's known effect on white matter. Whilst tests were limited by uneven group sizes and no medication-naïve group, we nevertheless found that medication had no significant effect on white matter properties.

	n	df	Mean	F	p
IIFG-IIPS Volume		3, 29		.076	.972
Past Medication Use	5		2865.73		
Occasional Medication Use	19		3145.15		
Regular Medication Use	8		3093.07		
rIFG-rIPS Volume		3, 29		.5	.685
Past Medication Use	5		2463.11		
Occasional Medication Use	19		2697.35		
Regular Medication Use	8		2784.12		
IFG-IFG Volume		3, 28		.871	.468
Past Medication Use	5		3600.63		
Occasional Medication Use	18		3666.50		
Regular Medication Use	8		3495.14		
IPS-IPS Volume		3, 28		.966	.422
Past Medication Use	5		3443.78		
Occasional Medication Use	19		4086.29		
Regular Medication Use	7		3747.73		
IIFG-IIPS FA		3, 29		.553	.650
Past Medication Use	5		.484		
Occasional Medication Use	19		.492		
Regular Medication Use	8		.501		
rIFG-rIPS FA		3, 29		.174	.913
Past Medication Use	5		.487		
Occasional Medication Use	19		.488		
Regular Medication Use	8		.489		
IFG-IFG FA		3, 28		.737	.593
Past Medication Use	5		.476		
Occasional Medication Use	18		.494		
Regular Medication Use	8		.481		
IPS-IPS FA		3, 28		.729	.543
Past Medication Use	5		.576		
Occasional Medication Use	19		.568		
Regular Medication Use	7		.582		
IIFG-IIPS MD		3, 29		.364	.779
Past Medication Use	5		.0703 x 10 ⁻³		
Occasional Medication Use	19		.0708 x 10 ⁻³		
Regular Medication Use	8		.0708 x 10 ⁻³		
rIFG-rIPS MD		3, 29		.849	.479
Past Medication Use	5		.0717 x 10 ⁻³		
Occasional Medication Use	19		.0724 x 10 ⁻³		
Regular Medication Use	8		.0718 x 10 ⁻³		
IFG-IFG MD		3, 28		.746	.534
Past Medication Use	5		.0765 x 10 ⁻³		
Occasional Medication Use	18		.0771 x 10 ⁻³		
Regular Medication Use	8		.0773 x 10 ⁻³		
IPS-IPS MD		3, 28		1.342	.281

Past Medication Use	5		$.0765 \times 10^{-3}$		
Occasional Medication Use	19		$.0774 \times 10^{-3}$		
Regular Medication Use	7		$.0765 \times 10^{-3}$		
IIFG-IIPS AD		3, 29		1.871	.157
Past Medication Use	5		1.10×10^{-3}		
Occasional Medication Use	19		1.14×10^{-3}		
Regular Medication Use	8		1.12×10^{-3}		
rIFG-rIPS AD		3, 29		.306	.821
Past Medication Use	15		1.11×10^{-3}		
Occasional Medication Use	19		1.11×10^{-3}		
Regular Medication Use	8		1.11×10^{-3}		
IFG-IFG AD		3, 28		.280	.840
Past Medication Use	4		1.12×10^{-3}		
Occasional Medication Use	19		1.12×10^{-3}		
Regular Medication Use	8		1.12×10^{-3}		
IPS-IPS AD		3, 29		.051	.985
Past Medication Use	5		1.13×10^{-3}		
Occasional Medication Use	19		1.14×10^{-3}		
Regular Medication Use	8		1.13×10^{-3}		
IIFG-IIPS RD		3, 29		.093	.963
Past Medication Use	5		0.504×10^{-3}		
Occasional Medication Use	19		0.501×10^{-3}		
Regular Medication Use	8		0.498×10^{-3}		
rIFG-rIPS RD		3, 29		.838	.484
Past Medication Use	5		0.510×10^{-3}		
Occasional Medication Use	19		0.516×10^{-3}		
Regular Medication Use	8		0.515×10^{-3}		
IFG-IFG RD		3, 29		.448	.720
Past Medication Use	5		0.540×10^{-3}		
Occasional Medication Use	19		0.539×10^{-3}		
Regular Medication Use	8		0.545×10^{-3}		
IPS-IPS RD		3, 29		.2.293	.099
Past Medication Use	5		0.473×10^{-3}		
Occasional Medication Use	19		0.485×10^{-3}		
Regular Medication Use	8		0.467×10^{-3}		

Table A3. A summary of t-tests and randomisation tests assessing the difference in white matter properties between the ADHD and control groups which were either non-significant or did not survive multiple comparison correction

	ADHD	Control	t	df	P
IIFG-IIPS volume			1.243	50	.219
N	33	19			
Mean (mm ³)	3082.34	2679.89			
SD (mm ³)	1180.29	1015.77			
IIFG-IIPS FA			-.361	50	.167
N	33	19			
Mean	4.93×10^{-1}	4.95×10^{-1}			
SD	2.40×10^{-2}	2.30×10^{-2}			
IIFG-IIPS MD			-1.465	50	.237
N	33	19			
Mean	7.08×10^{-4}	7.18×10^{-4}			
SD	1.47×10^{-5}	3.31×10^{-5}			
IIFG-IIPS AD			-1.608	50	.114
N	33	19			
Mean	1.12×10^{-3}	1.14×10^{-3}			
SD	2.90×10^{-5}	4.35×10^{-5}			
IIFG-IIPS RD			-.890	50	.445
N	33	19			
Mean	5.00×10^{-4}	5.07×10^{-4}			
SD	2.00×10^{-5}	3.43×10^{-5}			
rIFG-rIPS volume					.077
N	33	19			
Mean (mm ³)	2748.12	1008.81			
SD (mm ³)	2387.73	531.97			
rIFG-rIPS FA			-1.166	50	.249
N	33	19			
Mean	4.87×10^{-1}	4.95×10^{-1}			
SD	2.23×10^{-2}	2.04×10^{-2}			
rIFG-rIPS MD			-.043	50	.966
N	33	19			
Mean	7.22×10^{-4}	7.22×10^{-4}			
SD	2.14×10^{-5}	2.58×10^{-5}			
rIFG-rIPS AD			-.699	50	.487
N	33	19			
Mean	1.14×10^{-3}	1.14×10^{-3}			
SD	3.28×10^{-5}	4.24×10^{-5}			
rIFG-rIPS RD			.477	50	.635
N	33	19			
Mean	5.15×10^{-4}	5.11×10^{-4}			

SD	2.47×10^{-5}	2.45×10^{-5}			
IIFG-rIFG volume					.086
N	32	19			
Mean (mm ³)	3695.83	3067.17			
SD (mm ³)	1649.05	1480.51			
IIFG-rIFG FA					.083
N	32	19			
Mean	4.87×10^{-1}	5.00×10^{-1}			
SD	3.03×10^{-2}	3.27×10^{-2}			
IIFG-rIFG MD			-.723	48	.473
N	32	18			
Mean	7.72×10^{-4}	7.77×10^{-4}			
SD	2.37×10^{-5}	1.74×10^{-5}			
IIFG-rIFG RD			1.222	49	.228
N	32	19			
Mean	5.42×10^{-4}	5.30×10^{-4}			
SD	3.57×10^{-5}	3.18×10^{-5}			
IIPS-rIPS volume					.021
N	32	18			
Mean (mm ³)	3863.55	1122.91			
SD (mm ³)	4842.95	2109.02			
IIPS-rIPS FA			.260	48	.796
N	32	18			
Mean	5.71×10^{-1}	5.70×10^{-1}			
SD	2.83×10^{-2}	2.75×10^{-2}			
IIPS-rIPS MD			-1.571	47	.123
N	32	17			
Mean	7.72×10^{-4}	7.85×10^{-4}			
SD	2.60×10^{-5}	2.90×10^{-5}			
IIPS-rIPS AD			-.962	48	.341
N	32	18			
Mean	1.35×10^{-3}	1.37×10^{-3}			
SD	6.32×10^{-5}	5.306×10^{-5}			
IIPS-rIPS RD			-1.055	48	.297
N	32	18			
Mean	4.81×10^{-4}	4.90×10^{-4}			
SD	2.96×10^{-5}	3.61×10^{-5}			

Note: All p values are raw

Note: Tests without t values were randomisation tests

Table A4. A summary of the stepwise regression model predicting left IPS, right IPS and left TPJ modulations during inhibitory demand by white matter predictors within the ADHD group.

	r	β	t
lIPS modulation ($R^2 = .454$)			
Age	.288	.147	.956
Sex	.120	-.544	-.954
rIFG-lIFG volume	.382**	.358**	2.555**
rIFG-lIFG RD	-.471***	-.455***	-3.252***
lIFG-lIPS volume	.395***	.408**	2.920**
lIFG-lIPS RD	-.043	--	--
rIPS modulation ($R^2 = .248$)			
Age	.077	-.021	-.122
Sex	.117	-.098	-.543
rIFG-lIFG volume	.324	--	--
rIFG-lIFG RD	-.392**	-.399**	-2.476**
lIFG-lIPS volume	.375**	.382**	2.374**
lIFG-lIPS RD	-.138	--	--
lTPJ modulation ($R^2 = .273$)			
Age	.288	.136	.787
Sex	.257	.091	.497
rIFG-lIFG volume	.375**	.380**	2.360**
rIFG-lIFG RD	-.268	--	--
lIFG-lIPS volume	.425**	.429**	2.666**
lIFG-lIPS RD	-.065	--	--
Note: * $p < .01$, ** $p < .05$, *** $p < .005$			

Table A5. A summary of the stepwise regression model predicting response inhibition performance by white matter potential predictors within the ADHD and control groups.

	r	β	T
ADHD Response Inhibition ($R^2 = .140$)			
Age	-.044	-.136	-.742
Sex	-.271	.165	.916
rIFG-lIFG MD	-.406**	-.414**	-2.319**
rIFG-lIFG RD	-.331**	.190	-.648
lIFG-lIPS FA	.337	.259	1.484
rIFG-rIPS MD	-.383**	-.281	-1.591
rIFG-rIPS RD	-.414**	-.298	-1.692
lIPS-rIPS RD	.125	--	--
Controls Response Inhibition ($R^2 = .264$)			
Age	-.367	-.265	1.189
Sex	.439*	.362	1.726
rIFG-lIFG MD	-.089	--	--
rIFG-lIFG RD	.015	--	--
lIFG-lIPS FA	-.449	--	--
rIFG-rIPS MD	.237	--	--
rIFG-rIPS RD	.107	--	--
lIPS-rIPS RD	.544**	.560**	2.582**
Note: * $p < .01$, ** $p < .05$, *** $p < .005$			

Table A6. Descriptive statistics of absolute and relative motion metrics

	ADHD	Control	t	df	P
Absolute motion			-.537	49.76	.134
Mean	.72 mm	.62 mm			
SD	.31 mm	.16 mm			
Relative motion			.356	50	.724
Mean	.35 mm	.36 mm			
SD	.03 mm	.04 mm			
Note: absolute and relative motion metrics provided by FSL.					
Note: SD = standard deviation, df = degrees of freedom					

Table A7. Correlations for the ADHD group between absolute and relative motion with white matter structural metrics in order to ensure motion did not confound white matter structural metrics as it has been previously shown to do.

	N	Correlation Coefficient	p
IIFG-IIPS Volume			
Relative Motion	33	-.050	.784
Absolute Motion	33	-.214	.232
rIFG-rIPS Volume			
Absolute Motion	33	.136	.449
Relative Motion	33	.267	.134
IFG-IFG Volume			
Relative Motion	32	.075	.682
Absolute Motion	32	.137	.454
IPS-IPS Volume			
Absolute Motion	32	.181	.321
Relative Motion	32	.269	.137
IIFG-IIPS FA			
Absolute Motion	33	.120	.505
Relative Motion	33	-.121	.503
rIFG-rIPS FA			
Absolute Motion	33	-.012	.949
Relative Motion	33	-.335	.057
IFG-IFG FA			
Absolute Motion	32	.090	.625
Relative Motion	32	-.201	.269
IPS-IPS FA			
Absolute Motion	32	.151	.410
Relative Motion	32	.009	.960
IIFG-IIPS MD			
Absolute Motion	33	.005	.979
Relative Motion	33	.185	.303
rIFG-rIPS MD			
Absolute Motion	33	-.028	.876
Relative Motion	33	.166	.355
IFG-IFG MD			
Absolute Motion	32	.335	.061
Relative Motion	32	.298	.098
IPS-IPS MD			
Absolute Motion	32	.232	.201
Relative Motion	32	.278	.124
IIFG-IIPS AD			
Absolute Motion	33	.058	.749
Relative Motion	33	.036	.843
rIFG-rIPS AD			
Absolute Motion	33	-.014	.821
Relative Motion	33	-.198	.269
IFG-IFG AD			
Absolute Motion	32	.317	.077

Relative Motion	32	.039	.831
IPS-IPS AD			
Absolute Motion	32	.150	.404
Relative Motion	32	.152	.399
IIFG-IIPS RD			
Absolute Motion	33	-.023	.898
Relative Motion	33	.181	.312
rIFG-rIPS RD			
Absolute Motion	33	-.010	.956
Relative Motion	33	.348	.047
IFG-IFG RD			
Absolute Motion	32	.075	.678
Relative Motion	32	.272	.126
IPS-IPS RD			
	32	.023	.897
	32	.196	.274

Note: Correlations were tested using Spearman's Rank Correlational Coefficient

Note: No correlations remained statistically significant following multiple comparison correction

Note: There is variation in the number of participants for each variable due to variation in the number of datasets lost for each variable due to outlier removal

Note: The P values reported are raw values, none of which survived multiple comparison correction

Table A8. Correlations for the Controls group between absolute and relative motion with white matter structural metrics in order to ensure motion did not confound white matter structural metrics as it has been previously shown to do.

	N	Correlation Coefficient	P
IIFG-IIPS Volume			
Relative Motion	19	-.190	.436
Absolute Motion	19	-.172	.481
rIFG-rIPS Volume			
Absolute Motion	19	-.240	.323
Relative Motion	19	-.134	.584
IFG-IFG Volume			
Relative Motion	19	.113	.644
Absolute Motion	19	.226	.352
IPS-IPS Volume			
Absolute Motion	18	-.165	.512
Relative Motion	18	-.069	.787
IIFG-IIPS FA			
Absolute Motion	19	-.347	.145
Relative Motion	19	-.026	.917
rIFG-rIPS FA			
Absolute Motion	19	-.067	.786
Relative Motion	19	.158	.581
IFG-IFG FA			
Absolute Motion	19	-.283	.240
Relative Motion	19	-.047	.849
IPS-IPS FA			
Absolute Motion	18	.235	.349
Relative Motion	18	.296	.233
IIFG-IIPS MD			
Absolute Motion	19	.147	.549
Relative Motion	19	-.122	.619
rIFG-rIPS MD			
Absolute Motion	19	.054	.827
Relative Motion	19	.049	.841
IFG-IFG MD			
Absolute Motion	19	.622	.006
Relative Motion	19	.147	.561
IPS-IPS MD			
Absolute Motion	18	.029	.911
Relative Motion	18	-.464	.061
IIFG-IIPS AD			
Absolute Motion	19	-.006	.980
Relative Motion	19	-.225	.354
rIFG-rIPS AD			
Absolute Motion	19	-.224	.357
Relative Motion	19	-.064	.794
IFG-IFG AD			
Absolute Motion	19	-.206	.412

Relative Motion	19	-.338	.170
IPS-IPS AD			
Absolute Motion	18	-.127	.615
Relative Motion	18	-.555	.017
IIFG-IIPS RD			
Absolute Motion	19	.328	.170
Relative Motion	19	.037	.880
rIFG-rIPS RD			
Absolute Motion	19	.168	.492
Relative Motion	19	.006	.980
IFG-IFG RD			
Absolute Motion	19	.583	.009
Relative Motion	19	.255	.292
IPS-IPS RD			
	18	.270	.264
	18	.009	.971

Note: Correlations were tested using Spearman's Rank Correlational Coefficient

Note: No correlations remained statistically significant following multiple comparison correction

Note: There is variation in the number of participants for each variable due to variation in the number of datasets lost for each variable due to outlier removal

Note: The P values reported are raw values, none of which survived multiple comparison correction

Table A9. A summary of the correlations between the white matter metrics of the tbss skeleton and the left IPS, right IPS and left TPJ modulations during inhibitory demand within the ADHD group.

	N	Correlational co-efficient	p
IIPS modulation			
Volume	30	.070	.713
FA	30	.066	.728
MD	29	.146	.451
AD	29	.171	.374
RD	30	.178	.345
rIPS modulation			
Volume	30	.043	.822
FA	30	.135	.476
MD	29	.031	.872
AD	29	.072	.709
RD	30	.038	.842
lTPJ modulation			
Volume	30	.255	.174
FA	30	.058	.760
MD	29	.157	.415
AD	29	.197	.307
RD	30	.157	.408
Note: * $p < .01$, ** $p < .05$, *** $p < .005$			

Appendix B

Tables

Table B1. Partial correlations controlling for sex for the exploratory dataset.

	df	Correlation Coefficient	p
ASRS Total			
PSQI Total	78	.107	.173
ISI Total	96	** .287	.002
PSAS Cognitive	98	*** .409	< .001
PSAS Somatic	97	*** .497	< .001
PSAS Cognitive			
PSQI Total	79	*** .467	< .001
ISI Total	97	*** .656	< .001
PSAS Somatic			
PSQI Total	79	*** .370	< .001
ISI Total	96	*** .463	< .001
Note: * p < .05, ** p < .01, *** p < .001			

Table B2. Partial correlations controlling for sex for the replication dataset.

	df	Correlation Coefficient	p
ASRS Total			
PSQI Total	85	.065	.274
ISI Total	88	** .305	.002
PSAS Cognitive	87	*** .440	< .001
PSAS Somatic	87	*** .423	< .001
PSAS Cognitive			
PSQI Total	85	.043	.347
ISI Total	87	*** .462	< .001
PSAS Somatic			
PSQI Total	85	.064	.278
ISI Total	87	** .298	.002
Note: * p < .05, ** p < .01, *** p < .001			

Appendix C

Results

1. Low vs high ADHD trait task performance

A two-way mixed ANOVA was conducted to investigate the impact of ASRS score and task switch versus task repeat on errors (%). The within-group factor was error percentage, whilst the between-group factor was low or high ADHD traits. There was a significant effect of trial type: $F(1, 32) = 34.026$, $p < .001$, indicating significantly greater error percentage for switch trials compared to repeat trials, confirming a switch cost. However, there was no significant effect of ASRS score $F(1, 32) = .740$, $p = .396$, indicating no difference in error % between high and low ASRS. Lastly, there was no significant interaction between trial type and ASRS condition: $F(1, 32) = 1.009$, $p = .323$, suggesting that there was no significant difference in error % between switch and repeat trials for the high-ASRS and low-ASRS groups (*see figure C1a*).

Similarly, a two-way mixed ANOVA was conducted to investigate the impact of ASRS score and task switch versus task repeat on RT mean. The within-group factor was RT mean (s), whilst the between-group factor was low or high ADHD traits. There was a significant effect of trial type: $F(1, 32) = 104.16$, $p < .001$, indicating a significant difference in RT mean for switch trials compared to repeat trials, suggesting a switch cost. There was no significant effect of ASRS condition: $F(1, 32) = .878$, $p = .356$, indicating no difference in RT mean between high and low ASRS. Lastly, there was no significant interaction between trial type and ASRS condition: $F(1, 32) = 1.353$, $p = .253$, suggesting that there was no significant difference in RT mean between switch and repeat trials for the high-ASRS and low-ASRS groups (*see figure C1b*).

2. Low vs high cognitive pre-sleep arousal task performance

A two-way mixed ANOVA was conducted to investigate the impact of cognitive pre-sleep arousal and task switch versus task repeat on errors (%). The within-group factor was error percentage, whilst the between-group factor was low or high cognitive pre-sleep arousal. There was a significant effect of trial type: $F(1, 32) = 35.091, p < .001$, indicating significantly greater error percentage for switch trials compared to repeat trials, confirming a switch cost. However, there was no significant effect of cognitive pre-sleep arousal $F(1, 32) = .019, p = .891$, indicating no difference in error % between low and high cognitive pre-sleep arousal. Lastly, there was no significant interaction between trial type and cognitive pre-sleep arousal: $F(1, 32) = 1.248, p = .272$, suggesting that there was no significant difference in error % between switch and repeat trials for the low and high cognitive pre-sleep arousal groups (*see figure C1c*).

A two-way mixed ANOVA was conducted to investigate the impact of cognitive pre-sleep arousal and task switch versus task repeat on mean RT (s). The within-group factor was error percentage, whilst the between-group factor was low or high cognitive pre-sleep arousal. There was a significant effect of trial type: $F(1, 32) = 108.521, p < .001$, indicating significantly greater mean RT for switch trials compared to repeat trials, confirming a switch cost. However, there was no significant effect of cognitive pre-sleep arousal $F(1, 32) = .012, p = .915$, indicating no difference in mean RT between low and high cognitive pre-sleep arousal. Lastly, there was no significant interaction between trial type and cognitive pre-sleep arousal: $F(1, 32) = 3.098, p = .088$, suggesting that there was no significant difference in mean RT between switch and repeat trials for the low and high cognitive pre-sleep arousal groups (*see figure C1d*).

Figures

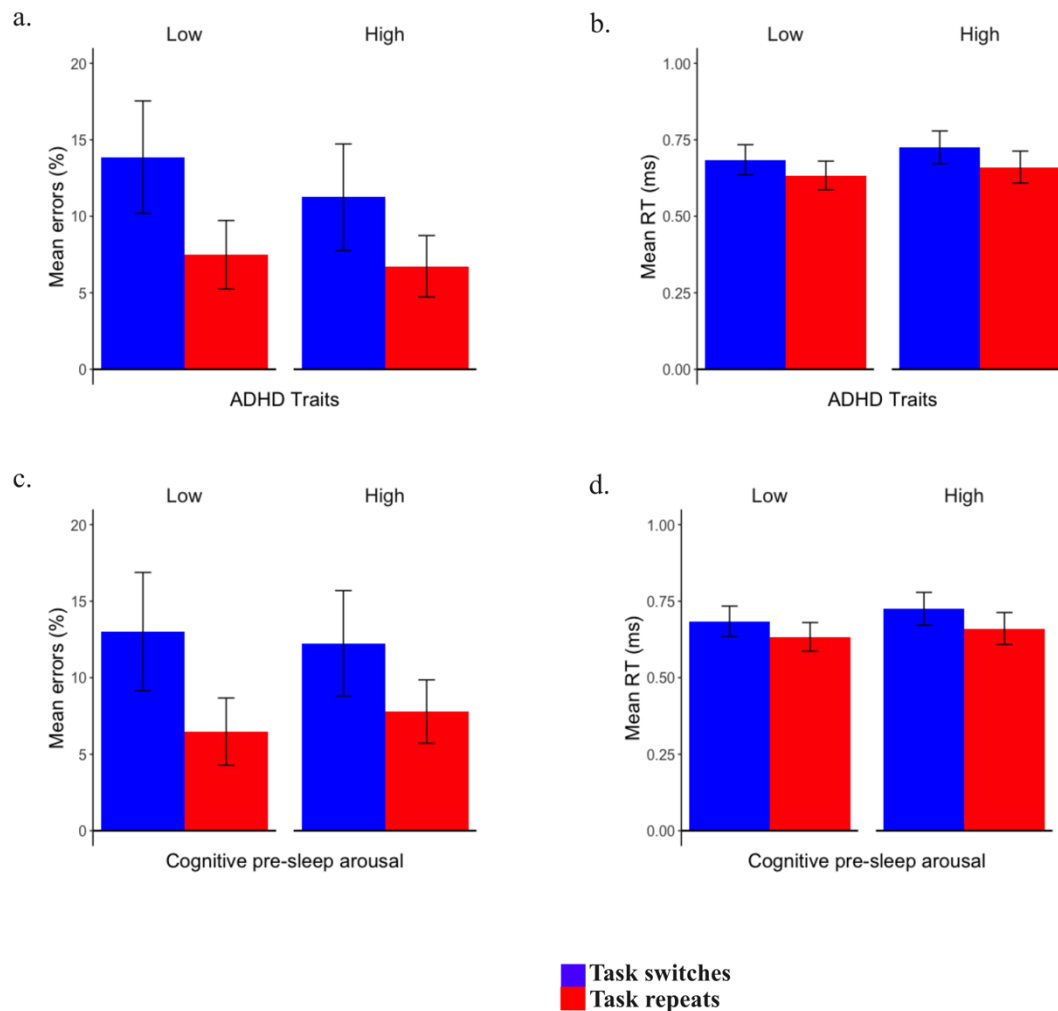


Figure C1. A figure depicting the difference between task switches (blue) and task repeats (red) for the low and high ADHD groups in (a) mean errors (%) and (b) mean RT (s), and for the low and high cognitive pre-sleep arousal groups in (c) mean errors (%) and (d) mean RT (s). Error bars represent 95% CI.

Tables

Table C1. A table depicting descriptive data for combinations of cognitive PSAS and ASRS scores.

Group (Cognitive PSAS – ASRS)	N (male)	Age range (y)	Mean Age (y)	SD of Age (y)
Low-Low	12 (3)	18-25	20.58	2.11
Low-High	5 (2)	18-28	21.40	3.85
High-Low	7 (0)	18-22	20.00	1.29
High-High	11 (0)	18-26	20.55	2.46
Note: PSAS = Pre-Sleep Arousal Scale; ASRS = Adult ADHD Self-Report Scale.				

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