

Neural Measures of Visual Attention and Suppression as Biomarkers for ADHD- associated Inattention

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August 2019

Abstract

Whilst there is a wealth of literature examining neural differences in those with ADHD, few have investigated visual-associated regions. Given extensive evidence demonstrating visual-attention deficits in ADHD, it is possible that inattention problems may be associated with functional abnormalities within the visual system. By measuring neural responses across the visual system during visual-attentional tasks, we aim to explore the relationship between visual processing and ADHD-associated Inattention in the typically developed population.

We first explored whether differences in neural responses occurred within the superior colliculus (SC); an area linked to distractibility and attention. Here we found that Inattention traits positively correlated with SC activity, but only when distractors were presented in the right visual field (RVF) and not the left visual field (LVF).

Our later work followed up on these findings to investigate separate responses towards task-relevant targets and irrelevant, peripheral distractors. Findings showed that those with High Inattention exhibited increased responses towards distractors compared to targets, while those with Low Inattention showed the opposite effect. Hemifield differences were also observed where those with High Inattention showed increased RVF distractor-related signals compared to those with Low Inattention. No differences were observed for the LVF.

Finally, we examined attention and suppression-related neural responses. Our results indicated that, while attentional responses were similar between Inattention groups, those with High Inattention showed weaker suppression responses towards the unattended RVF. No differences were found when suppressing the LVF.

Findings across all studies suggest that differences in neural responses between those with High and Low levels of Inattention exist within the visual system. Such differences appear to relate to suppression of task-irrelevant distractors rather than attention towards task-relevant targets, suggesting such mechanisms are differentially affected in those with frequent Inattention problems. We also show a clear relationship between Inattention traits and visual suppression of the RVF.

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Abbreviations

Abbreviations

| | |
|---------|--|
| ADHD | Attention-deficit Hyperactivity disorder |
| ADHD-C | Combined ADHD presentation |
| ADHD-H | Hyperactive/Impulsive ADHD presentation |
| ADHD-I | Inattention ADHD presentation |
| ADHD-OS | Other specified ADHD |
| ADHD-U | Unspecified ADHD |
| ASRS | <i>Adult self-report scale</i> |
| BOLD | Blood Oxygen Level Dependence |
| CAARS | <i>Conners Adult ADHD rating scale</i> |
| CCPT | <i>Conners' Continuous performance task</i> |
| CPT | Continuous performance task |
| COVAT | Covert Orienting of Visuospatial Attention Task |
| DSM | <i>Diagnostic and Statistical manual of Mental Disorders</i> |
| EEG | Electroencephalography |
| fMRI | Functional Magnetic Resonance Imaging |
| FA | Fractional anisotropy |
| GNG | Go No-go |
| GM | Grey Matter |
| LGN | Lateral geniculate nucleus |
| LVF | Left Visual Field |
| RT | Reaction time |
| RTvar | Reaction time variability |
| RVF | Right Visual Field |
| SRT | Stimulus response time |
| SC | Superior Colliculus |
| SOA | Stimulus onset asynchrony |
| SSVEP | Steady-state visual evoked potential |
| VBM | Voxel-Based Morphometry |
| VS | Visual search |
| V1 | Primary visual cortex |
| WM | White matter |

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Acknowledgements

Acknowledgements

First and foremost, I would like to express my sincere thanks and gratitude to my supervisor Prof. Antony Morland for his continuous support throughout my PhD study and for his patience, motivation, and immense knowledge. Without his guidance and advice this PhD would not have been achievable.

I would also like to thank the members of my thesis advisory panel; Dr. Dan Baker, Prof. Alex Wade and Dr. Silke Goebel. Their advice, insightful comments and encouragement certainly helped me think about my research in new and exciting ways. I would also like to add further thanks to Dan for his help and guidance on all things EEG when working on Chapter 4. I am also hugely appreciative to Dr. André Gouws for his advice and expertise in MRI analysis and coding.

My thanks also go to those at the University of Leeds and University of Sheffield, particularly Prof. Paul Overton, Dr. Tom Stafford, Dr Jac Billington and Dr. Maria Panagioti for their ideas and collaborative work on Chapter 3.

I would finally like to thank my family and friends for their support throughout the last four years, especially my Mum, Nanna and Brother who have experienced the joys and stresses of my PhD journey with me. Particular thanks also go to my long-suffering husband-to-be Luke, for being the guinea-pig for many of my experiments, reading multiple drafts of this thesis and providing constant encouragement.

Declaration

Declaration

I declare that this thesis is a presentation of original work, carried out under the supervision of Professor Antony B. Morland, and I am the sole author. This work has not previously been presented for an award at this, or any other, University. All sources are acknowledged as references.

Data reported in **Chapter 3** were presented at both the Yorkshire Vision Network conference (2016), York, UK and at the 6th World Congress on ADHD (2017) Vancouver, Canada as:

Kitching, Rebecca Elizabeth, Overton, Paul, Panagiotidi, Maria, Billington, Jac, Morland, Antony and Stafford, Tom (2017) Evidence for hyperactivity in the superior colliculus in Attention-Deficit/Hyperactivity Disorder.

Chapter One: Introduction

A review of the visual system and visual attention within Attention Deficit Hyperactivity Disorder

1.1 Overview

Whilst previous research has tended to focus on frontal and parietal regions as a biomarker for Attention Deficit Hyperactivity Disorder (ADHD), few studies have explored whether such loci can occur within low-level, sensory regions. The primary aim of this thesis is to understand whether neurological differences exist within the visual system in relation to ADHD-associated Inattention traits within the typically developed population. The three empirical chapters being presented here will each explore whether distinct areas of the visual system, including the Primary Visual Cortex (V1), Lateral Geniculate Nucleus (LGN) and Superior Colliculus (SC), exhibit different neural responses in those with low and high levels of Inattention during sustained and selective attention tasks. More specifically, this thesis will also examine the influence of task attentional-load and both distractor location and type on such responses.

Due to the limited research exploring the general relationship between Inattention traits and the visual system, this chapter will focus on the current theories and research surrounding the association between the visual system and ADHD to provide a background and framework for the following three empirical chapters. These will be discussed in three core areas. The first will provide a brief overview of ADHD and its associated symptoms, diagnosis tools and prevalence. The second area will then introduce literature exploring visual attention within ADHD. The third and final area will then explore current ideas and findings regarding the relationship between ADHD and the visual system.

1.2 Attention Deficit Hyperactivity Disorder

1.2.1 ADHD Symptoms and Diagnosis criteria

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder defined by frequent characteristics of attentional difficulties and/or

hyperactive-impulsive tendencies. There are currently two definitions used in the diagnoses of ADHD: the American-preferred *Diagnostic and Statistical manual of Mental Disorders* (DSM) and the European-preferred *International Classification of Mental and Behavioural Disorders* (ICD).

Within the recent classification of the *DSM, 5th edition* (DSM-V), there are three presentation subtypes proposed; Predominantly Inattentive presentation (ADHD-I), Predominantly Hyperactive-impulsive presentation (ADHD-H) and a Combined presentation (ADHD-C) (American Psychiatric Association., 2014). Each is diagnosed dependent upon which and how many of the 18 symptoms (9 Inattention and 9 Hyperactive-impulsive) are observed as discussed below.

ADHD-I: Extensive attentional problems but few impulsive and hyperactive tendencies. Possible attentional characteristics can include failure to pay close attention to details, difficulties sustaining attention, easily distracted by unrelated stimuli, does not follow instructions and fails to finish a task, problems organizing activities, avoid and dislike of tasks requiring sustained mental effort and appears to not listen when being directly spoken to.

ADHD-H: Extensive impulsive and hyperactive tendencies but relatively few attentional problems. Such hyperactive tendencies can include frequent fidgeting with hand or feet, failure to remain seated within situations where it is expected (e.g. within meetings or the classroom), excessively running or climbing behaviours in inappropriate situations, excessive talking and problems engaging in activities in a quiet manner. Impulsive symptoms can also include frequent interruptions within conversations, problems awaiting their turn and often blurting out answers to questions before completion.

ADHD-C: Extensive characteristics of both attentional problems and hyperactive-impulsive tendencies.

In each of these cases, at least six of the nine associated symptoms from either or both behavioural types (Inattention and Hyperactive-impulsive), persisting for at least six months, must be present for a diagnosis. Some problems should also have been

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observed, at the time or retrospectively, before the age of 12 years, as well as being apparent in at least two distinct settings (e.g. within a school/work environment and at home). This is in direct contrast to the *DSM, 4th edition* (DSM-IV), which states symptoms should be observed before 7 years and should cause some impairment, rather than just being present, within in two settings.

Differing from the previous editions, the DSM-V now also creates a more relaxed symptom threshold for those over the age of 17, to reflect the tendency for symptoms to reduce with age (Faraone, Biederman, & Mick, 2005), whereby a minimum of five symptoms are required to meet the ADHD criteria. There must also be evidence that the associated symptoms interfere with the individual's social, academic or occupational life. Clinicians are also able to use the criteria to designate a severity level from mild to severe.

Previous DSM manuals (DSM-IV) also classify a fourth subtype; ADHD not otherwise specified (ADHD-NOS). This subtype is often characterised by those who show prominent symptoms of inattention or hyperactivity-impulsivity but fail to meet the full criteria for one of the other ADHD subtypes, often due to late-onset (after 7 years of age) or failure to meet the minimum symptoms threshold. Similarly, DSM-V also specifies similar subtypes known as *Other Specified ADHD* (ADHD-OS) and *Unspecified ADHD* (ADHD-U). The former being when the full criteria are not met and a specific reason is given (e.g. Other Specified ADHD with insufficient hyperactive symptoms) and the latter, again when the full criteria are not met but with no given reason.

Similarly, the recently released World Health Organization's ICD, *11th edition* (ICD-11) (World Health Organization, 2018), also stipulated similar diagnoses conditions for ADHD as the DSM-V. However, the patient must exhibit a combination of both inattentive and hyperactive symptoms to be diagnosed, similar to the DSM-V's ADHD-C presentation. This edition is the first to classify ADHD in line with the DSM, where previous versions of the ICD, including the recently replaced ICD-10, classified ADHD-associated symptoms as a Hyperkinetic Disorder. Under this classification system, individuals are 3-4 times less likely to be diagnosed as having ADHD compared to the DSM-V (Rohde et al., 2005; Santosh et al., 2005) likely due to the emphasis on having both behavioural characteristics and the fact that the ICD does not allow

comorbidity with other psychiatric disorders (excluding Conduct disorder) unlike the DSM-V.

1.2.2 Diagnostic Tools

Whilst both the DSM and ICD diagnostic criteria provide full accounts of the symptoms associated with ADHD, they do not provide guidance concerning how clinicians should obtain the information required to make a diagnosis. Many clinicians therefore choose to opt for a multi-tool approach including self-report questionnaire, observational questionnaires and clinical interviews, which can all be used to diagnose both child and adult patients.

Within the adult population there are currently many types of questionnaire used, of which, the two most common are the *Connors Adult ADHD rating scale* (CAARS) (Connors, Erhardt, & Sparrow, 2002) and the World Health Organization's *Adult self-report scale* (ASRS) (Kessler et al., 1999). The CAARS questionnaire uses a set of statements relating to ADHD-associated behaviours and beliefs for each of the three symptom types (inattention, impulsivity and hyperactivity) as well as assessing self-esteem. For each, patients report using a Likert-scale how much they agree with the statements (Table 1.1). This therefore has the advantage that it can separately assess and provide a score for each of the three main symptoms in addition to creating a combined overall ADHD measure. Once scored, the clinician can then examine where the individual lies on the population distribution for each behavioural type individually or as a combined ADHD score. Critically, the raw scores for each measure first have to be standardized to take into account the patients age and gender, whereby younger adults and males have to exhibit a higher number of symptoms than older adults and females to be given the same ADHD score, allowing members of different populations to be accurately assessed and compared. Guidance indicates that those with a standardized score 1 standard deviation away from the mean are thought to exhibiting ADHD-associated traits however there is no exact score which indicates a clinical ADHD diagnosis should be given. The distance away from the mean can also give an indication of the severity of the condition.

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Within a clinical setting, such self-reports can also be accompanied with an observational questionnaire often completed by a parent, friend or spouse to verify the patients report. The questionnaire can also come in both long and short versions depending on the time restraints of the clinician. This scale also comes in a similar form for children, aged 6 -17 (*Connors Rating Scale, third edition*, Connors, 2008), although this primarily relies more on the parent and teacher observations rather than self-report which is only used in older aged samples.

Table 1.1: The 4 main components tested using the Connors Adult ADHD rating scale (CAARS) and examples of associated items (Connors et al., 2002).

| ADHD symptoms | Example Item |
|----------------------|---|
| Inattention | I don't finish things I start I have trouble keeping my attention focused when working |
| Hyperactivity | I like doing active things I leave my seat when I am not supposed to |
| Impulsivity | I blurt things out I have a short fuse/hot temper |
| Self-esteem | I get down on myself I'm not sure of myself |

The ASRS questionnaire also uses a self-report methodology with 18-item Likert-scale which, similar the CAARS, can independently assess inattention and hyperactivity-impulsive traits as well as an overall ADHD outcome (Kessler et al., 1999). However, in this case no distinction is made between hyperactive and impulsive traits. Once scored, these can also be compared to a population distribution to assess the presence of ADHD traits. Research has shown that both the CAARS and ASRS tend to show similar patterns of diagnosis and scores obtained using both measures are highly correlated (Hines, King, & Curry, 2012; Kim, Lee, & Joung, 2013; Takeda, Tsuji, & Kurita, 2017).

Whilst self-report methodology can have the advantage of directly assessing the individual, it can fall down on accuracy and participants reporting their symptoms inconsistently. Indeed, previous literature has examined the rate of 'faked' or

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malingering ADHD within the adult population whereby estimates indicate that approximately 20% of those clinically referred for ADHD exaggerate their symptoms (Harrison, 2006). To take account of these factors, recent self-report questionnaires, including the CAARS, have added an inconsistency scale where the individual's rating for similar items are compared and differences in reporting are summed. For example, on the CAARS, a patient reporting 'agree' (numerically ranked 4) to the 'I'm disorganized' item and 'disagree' (numerically ranked 2) to the 'I'm absent-minded in daily activities' item would have an inconsistency of 2. This is then done for 8 pairs of items deemed to be assessing similar components and behavioural where the overall inconsistencies are summed. If a patient receives an inconsistency score of 8 or more, their results are considered potentially unreliable and should be interpreted with caution and combined with other measures. The CAARS questionnaire will be discussed in more detail in Chapter 2.

1.2.3 Prevalence

ADHD is now considered to be the most prevalent neurodevelopmental disorder across the globe (Faraone, Sergeant, Gillberg, & Biederman, 2003) with an estimated 0.85% – 17.8% prevalence worldwide in childhood (Ford, Goodman, & Meltzer, 2003; Froehlich et al., 2007; Huss, Hölling, Kurth, & Schlack, 2009; Polanczyk, de Lima, & Horta, 2007; Rothman, Petroff, Behar, & Mattson, 1993; Skounti, Philalithis, & Galanakis, 2006), with some finding an increased prevalence in western cultures (Ford et al., 2003; Polanczyk, Willcutt, Salum, Kieling, & Rohde, 2014). While it is possible that there are some differences in prevalence across populations, it is largely believed such variance is driven by differences between the study methodologies including diagnostic criteria and method of assessment (Polanczyk et al., 2007). Direct cross-cultural comparisons have also deemed difficult due to the differing interpretations of what is classed as 'normal behaviour' within each culture. Due to this, it is therefore largely assumed that prevalence across populations are similar.

From children with ADHD, it is thought than approximately two thirds continue to show debilitating ADHD symptoms into adulthood (Faraone, Biederman, & Mick, 2005), whereby inattention symptoms are more likely than hyperactive traits to persist in this manner (Hart, Lahey, Loeber, Applegate, & Frick, 1995; Millstein, Wilens, &

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Biederman, 1997; Wilens et al., 2009). This reduction in symptoms with age reflects the differences in the DSM-V criteria for adults and children discussed previously (See ADHD Symptoms and Diagnosis criteria, p13). Adult ADHD is therefore thought to have a prevalence of 0.5%- 4.4% (Faraone et al., 2005; Fayyad et al., 2007; Ford et al., 2003; Kessler, 2006).

1.3 Visual Attention in ADHD

It is now well known that attention is not a unitary concept and is comprised of multiple sub-components including selective, sustained, divided and executive attention. Previous research has shown that each attentional component can involve distinct brain regions and may be differentially affected in other neurological conditions (Lincoln, Lai, & Jones, 2002; Plaisted, Swettenham, & Rees, 1999). It may therefore be necessary to examine each of these components separately in relation to ADHD to understand the exact nature of the condition and its associated attentional symptoms. Throughout the main three empirical chapters, we used three separate tasks designed to assess and engage sustained attention to ensure participants remain focused on a particular area within the visual field. This section will discuss the relationship between sustained attention and ADHD within the visual domain. It will also provide some insight into how variations within the visual field of stimuli presentation and the attentional load of a task can influence attention in general in those with ADHD.

1.3.1 Sustained attention

Sustained Attention is often described as the ability to maintain attention on a specific task. This type of attention can also be thought of in two separate components whereby, deficits can either occur at the vigilance level or vigilance reductions over time. At the vigilance level, deficits may result in momentary lapses of concentration, causing brief increases in reaction time or omission errors (Robertson, Manly, Andrade, Baddeley, & Yiend, 1997). Reductions in vigilance over time, however, often involves the gradual decrease in sustained attention over prolonged periods of time, which is accompanied again by increases in response time (RT) and error rates over time. Sustained Attention is often assessed using tasks requiring participants to attend and respond to infrequent targets in a stream of non-targets whereby both the reaction time,

successful detection and error rates can be calculated. Of these tasks, the two most common include the Continuous Performance Task (CPT) and a variant of the CPT, known as the Go No-Go (GNG) task.

Continuous Performance Task

The Continuous Performance Task (CPT) was originally introduced by Rosvold, Mirsky, Sarason, Bransome Jr and Beck (1956) to measure sustained attention within brain damaged patients. To this day, the CPT remains one of the most popular methods to research attention and have been extensively used to measure sustained attention in those with ADHD, particularly in children. The CPT involved a continuous stream of sequentially presented stimuli, shown over the course of 10-30 minutes, whereby the participant is required to respond only when a pre-defined target is seen. The most common variant of this task is the X-version, where an infrequent 'X' character is the response target within a continuous letter stream while all other characters must be ignored (Figure 1.1). Using a CPT paradigm, attentional and inhibition mechanisms are assessed using a variety of behavioural measures including number of errors and both mean reaction time (RT) and variability (RTvar). Errors are often further broken down into omission errors (failing to respond to a target) and commission (responding to a non-target).

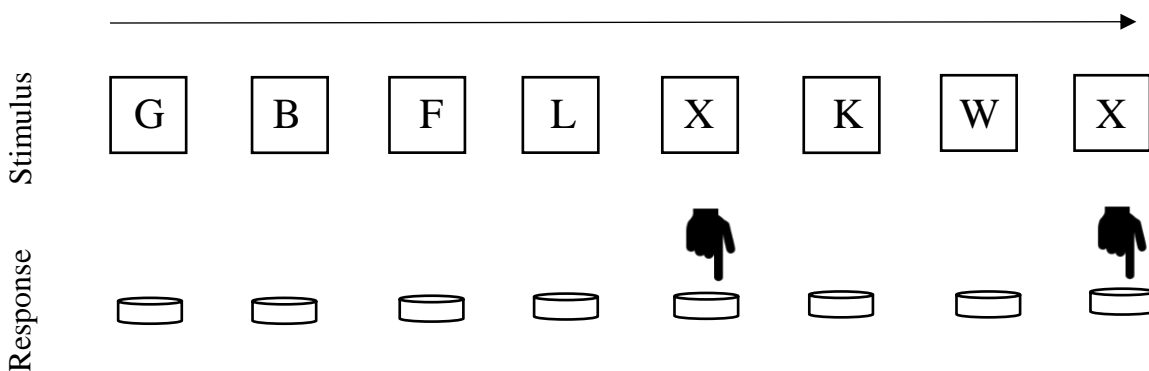


Figure 1.1: Continuous Performance Task (CPT) to measure sustained attention. Participants are required to respond with a button press to only when the infrequent pre-defined X targets are displayed.

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Within the current ADHD literature, whilst the idea of a general deficit in sustained attention remains controversial, a large number of studies have found clear deficits in behavioural performance within the CPT task. When measuring accuracy and the number of errors made, research has largely found that those with ADHD tend to exhibit an increased number of commission errors (*Children and adolescence*: August & Garfinkel, 1989; Cerullo et al., 2009; Chee, Logan, Schachar, Lindsay, & Wachsmuth, 1989; Epstein et al., 2003; Hinshaw, Carte, Sami, Treuting, & Zupan, 2002. *Adults*: Epstein et al., 2003; Loo et al., 2009) in addition to increased omission errors (*Children*: August & Garfinkel, 1989; Barkley, Grodzinsky, & DuPaul, 1992; Börger et al., 1999; Breen, 1989; Carter, Krener, Chaderjian, & Northcutt, 1995; Chee et al., 1989; Epstein et al., 2003; Fallgatter et al., 2004; Hinshaw et al., 2002; Hooks, Milich, & Puzles Lorch, 1994. *Adults*: Advokat, Martino, Hill, & Gouvier, 2007; Epstein, Conners, Sitarenios, & Erhardt, 1998). Results have also shown deficits within RT which are slower and more variable for those with ADHD compared to controls (*Children*: Börger et al., 1999; Carter et al., 1995; Epstein et al., 2003; Fallgatter et al., 2004; Stins et al., 2007; Wood, Maruff, Levy, Farrow, & Hay, 1999. *Adults*: Advokat et al., 2007). Similar results have also been found exploring CPT within virtual classroom environments, where children with ADHD continue to perform worse and are influenced more by distractors compared to controls, demonstrating that such deficits remain in a real-world environment (Adams, Finn, Moes, Flannery, & Rizzo, 2009; Parsons, Bowerly, Buckwalter, & Rizzo, 2007). However, there remain some studies that find no significant difference in CPT errors or RT (Loo et al., 2009; Wood et al., 1999).

Over the last few decades, there have been multiple systematic reviews and meta-analysis conducted to try and summarize the wealth of research coming from the CPT paradigm within ADHD. Indeed, a recent meta-analysis examining 47 studies using the CPT on children with ADHD, showed the largest effect size for both mean RT and RT variability as well as for omission and commission errors, with those with ADHD showing slower, more varied responses and more errors compared to controls (Huang-Pollock, Karalunas, Tam, & Moore, 2012). Nevertheless, the authors note a moderate publication bias for CPT and ADHD, including the four major CPT performance measures discussed above. When such effect sizes were corrected for such bias to provide a better estimate of the population-level, they were heavily reduced with

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sampling error accounting for between 32% (mean RT) to 90% (omission errors) of the variance. However, some variance was yet to be explained and therefore, could reflect real differences within ADHD and controls for the CPT task. Similar meta-analyses exploring 26, 44, 47 studies respectively have also found comparable results where clear deficits in CPT performance are observed within ADHD (Klein, Wendling, Huettner, Ruder, & Peper, 2006; Losier, McGrath, & Klein, 1996; Mowinckel, Pedersen, Eilertsen, & Biele, 2015), with children with ADHD making on average twice as many commission and omission errors as control children (Losier et al., 1996). Overall, such results indicate that those with ADHD have a clear deficit in maintaining attention where lapses in attention result in both increased RT and increased omission errors towards target stimuli. The increases seen for commission errors can also suggest that participants with ADHD also have problems with impulsivity where they are more likely to respond to non-targets.

Similar results have also been obtained using a rewarded-version of the CPT task, following suggesting that those with ADHD also exhibit motivational and reward-value deficits. During these tasks, participants perform the same CPT paradigm but can also receive rewards (whether monetary or socially) for correct responses. Rubia and colleagues studying children and adults with ADHD often showed clear deficits within task performance with those with ADHD showing increased omission errors (Rubia, Halari, et al., 2009; Rubia, Smith, et al., 2009; Rubia, Smith, & Taylor, 2007), commission errors (Cerullo et al., 2009; Rubia, Halari, et al., 2009; Rubia et al., 2007) and RT (Cubillo, Halari, Smith, Taylor, & Rubia, 2012). Additional research however has shown that reward-based incentives can improve CPT performance in those with ADHD, although this remains controversial, with some studies showing improved errors (Marx, Höpcke, Berger, Wandschneider, & Herpertz, 2013; Rubia, Smith, et al., 2009) and RT (Rubia et al., 2007), while others show no effect of reward (Cubillo et al., 2012; Rubia, Halari, et al., 2009). However, any improvement in performance may suggest that those with ADHD can employ strategies to prevent error and remained focused on the task being performed.

One area of the CPT performance not fully explored however concerns whether such deficits seen in ADHD also interact with time on task, demonstrating reduced vigilance over time, where performance continues to decline the longer the task lasts.

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Indeed, a study by Hooks et al. (1994) showed that children with ADHD increased in omission errors over time at a higher rate than control children. Other studies however have shown that reduced CPT performance over time occurs at the same rate in ADHD participants and controls (Stins et al., 2007), while others group differences depend on CPT measure used (Börger et al., 1999). Collings (2003) however showed that the effect of vigilance may depend on ADHD subtype, where only children with ADHD-C showed decreased performance over time on task while those with ADHD-I did not. Additional research is clearly needed to explore the effect within ADHD in more detail.

A final area of research exploring the connection between ADHD and the CPT centres around the effect of psychostimulants, particularly Methylphenidate, often used to treat ADHD (for review see Storebø et al., 2015). Given that such medication heavily reduces the associated ADHD-symptoms, it is also expected that any sustained attention and behavioural deficit will also improve under treatment. Whilst there is some discussion concerning which specific CPT behavioural measures change, most research appears to demonstrate improved performance while on medication (Konrad, Günther, Hanisch, & Herpertz-Dahlmann, 2004; Rubia, Halari, et al., 2009; Solanto, Wender, & Bartell, 1997; Sykes, Douglas, & Morgenstern, 1972), while some show a trend improvement (Handen et al., 1992). Meta-analyses again have explored the impact of psychostimulants on CPT performance in ADHD and have demonstrated significant reduction in errors (Losier et al., 1996).

Go No-go task

A Go No-go (GNG) often comprises a continuous sequential stream of visual stimuli (letters, shapes or numbers) in which the participant is required to perform a binary decision on each stimulus dependent on pre-defined targets; 'Go' stimuli or 'No-go' stimuli. During a 'Go' trial, participants are instructed to make a motor response such as button press when the 'Go' stimuli appears. During the 'No-go' trials however, this "Go" response needs to be inhibited and the button should not be pressed. For example, in a stream of green and red squares, participants may be told to respond to all green squares ('Go') and to inhibit the response to red squares ('No-go') (Figure 1.2). It is usually the case that the majority of stimuli presented are classified as 'Go' trials in order to ensure the participant is expecting to respond on most trials and

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therefore, makes the inhibition of infrequent 'No-go' trials more difficult. This can therefore often be seen as the opposite of the CPT task whereby, instead of responding only to infrequent stimulus, responses are inhibited to infrequent stimuli instead. Due to this difference, it is thought that the GNG task and its variants place greater demands on sustained attention where withholding a frequent response required greater attention than initiating an infrequent response. However, such task also places higher demands on inhibition compared to the standard CPT, so is often considered an inhibition response paradigm in addition to assessing sustained attention. During the task, both RT and error rates (omission: inhibition of responses to go trials and commission: responding to no-go trials) are often measured for both trial types.

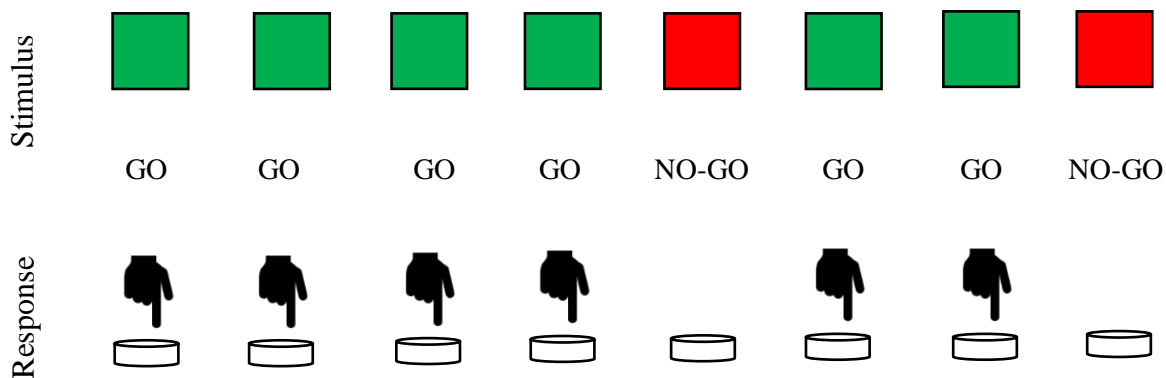


Figure 1.2: Go No-Go task to measure sustained attention. Participants are required to respond with a button press to all green 'Go' trials but to inhibit this response when a red 'No-Go' stimulus is presented.

In an early study by Durston et al. (2003) children with ADHD were presented with a cartoon characters GNG task, where they were required to respond with a button press for Go trials and inhibit this response to infrequent No-go trials. Results showed that children with ADHD made significantly more commission errors (responding to no-go trials) compared to control children while no difference was found for either omission errors (inhibition of response to go trials) or mean RT. The fact that differences are not found for omission errors indicates that children with ADHD are able to make motor responses in response to stimuli but find it more problematic to inhibit these responses. Similar results have also been replicated in children and adolescents with ADHD showing they make more commission errors than controls but did not differ in RT or omission errors (Rubia et al., 2007; Schulz et al., 2004; Vaidya et al., 1998). A meta-analysis by Oosterlaan, Logan and Sergeant (1998) examined the eight previous studies on ADHD and the Stop task, a variant on the GNG where a stop

cue is given before a go-response, and showed robust deficits in sustained attention and inhibition where children with ADHD were less successful at inhibiting the go-response during stop-trials (commission error). Nevertheless, some continue to find opposing results, with some showing increased mean RT and variability (Rubia et al., 2001) and an increase in omission errors (Klein et al., 2006; Rubia et al., 2001; Yong-Liang et al., 2000) - although Klein did note that the increases seen in omission errors for ADHD became non-significant once IQ was controlled for.

Some more recent studies on adults with ADHD have also produced some differing results, with some finding an increase in both omission errors (Dibbets, Evers, Hurks, Marchetta, & Jolles, 2009) and commission errors (Dibbets et al., 2009; Tamm et al., 2013) as well as slower or more variable RT for those with ADHD. In a more recent study by Newman et al. (2016), adults with ADHD were studied using a longitudinal design whereby both typically-developing and children with ADHD were tested throughout childhood and into early adulthood. They showed that adults with persistent ADHD made significantly more commission errors than both controls and those with childhood ADHD. Interestingly, those with childhood ADHD continued to show significantly more commission errors compared to controls despite their reduction in ADHD symptoms, suggesting the ADHD-associated deficits are somewhat long-lasting into adulthood. Nevertheless, there are some studies that continue to show no group difference in GNG error rates (Dillo et al., 2010; Kooistra et al., 2010).

Such differences, however, may be accounted for by methodological disparities in studies, which often differ in the frequency of no-go trials (from 0.05-25%), inter-stimulus interval (ISI) (from 200ms to 3000ms) and stimulus presentation (500ms to 800ms). By altering such parameters, this may have caused the task difficulty to change whereby no-go trials that occur more frequently are likely easier to inhibit than those occurring less frequently. Whilst Kooistra et al. (2010) showed no interaction between ADHD diagnosis and ISI speed (*Fast ISI*; average 1500ms. *Slow ISI*: average 7000ms), a more recent meta-analysis by Metin, Roeyers, Wiersema, van der Meere and Sonuga-Barke (2012) examining 30 GNG studies on those with ADHD did show some influence of ISI. They showed the effect size for the increased commission errors for those with ADHD was greater for fast ISI trials while the effect of slowed RT was

larger within slow ISI trials, suggesting the underlying mechanisms behind both RT and error are differentially affected within ADHD.

Further differences between studies can also be accounted for by variation in the target stimuli complexity whereby some use simple targets, unique to each condition (X for go and Y for no-go) while others use more complex targets where the go-target varied, and participants had to keep track of the previous go targets. Dibbets et al. (2009) for example, defined go-trials as alternating presentations of X and Y characters while no-go trials occurred to repetitions of X or Y. Such variations within target complexity are likely to have a large influence on cognitive demands of the task and may therefore lead to different patterns of task performance. In a more complex block design study, Booth et al. (2005) examined the combination of visual search and the GNG task, whereby observers had to search for the presence of a pre-defined GNG target in a set size of 9 stimuli (Figure 1.3). On 'Go' blocks, participants responded on all trials regardless of target presence while on 'No-Go' block, participants withheld their response if the target was present. Behaviourally, it was also shown that those with ADHD made significantly more commission and omission errors than controls, as well as a slower RT to both trial types. This again suggests that such differences in the literature may be due to the difficulty of the task whereby more demanding tasks are

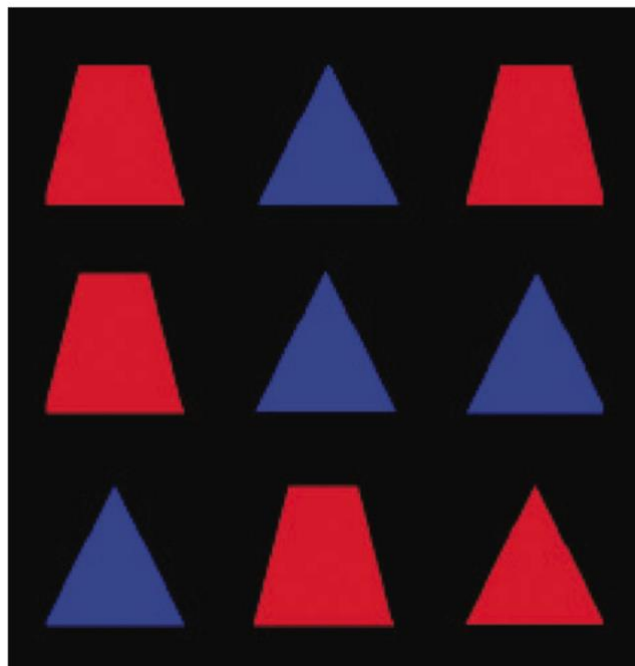


Figure 1.3: An example of the 9-item visual research GNG task used by Booth et al. (2005). During 'Go' trials, participants always responded regardless of whether the target (red triangle) was present. During 'No-Go' trials, participants withheld his response if the target was present.

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more likely to reveal ADHD deficits. Further research is therefore recommended in order to systematically examine the effect of task difficulty, and attentional load on GNG performance. The effect of cognitive demands and task attentional load will be discussed in more detail later in this chapter (See, 1.3.3 Attentional Load, p32).

Additional research has also examined a variation of the GNG whereby, rather than a motor response, an oculomotor saccade is made instead. In such a study by Hanisch, Radach, Holtkamp, Herpertz-Dahlmann and Konrad (2005) children were required to make a saccade to peripheral stimuli based upon the colour of the central target, whereby a green colour indicated a 'Go' trial and a red indicated a 'No-Go' trial. They showed that children with ADHD made significantly more commission errors (saccades on no-go trials) than controls and that, interestingly, this also significantly interacted with the hemifield the peripheral target was presented in, with ADHD participants being significantly more impaired in inhibiting responses when the stimuli were in the right visual field (See 1.3.2 Visual field differences in Attention, p28). Using a similar oculomotor paradigm, Mahone, Mostofsky, Lasker, Zee and Denckla (2009) also showed that children with ADHD, regardless of gender, again made more commission errors. Similar to research within the CPT, other lines of research have also examined the effect of psychostimulants, particularly Methylphenidate, within the GNG task. Both Trommer, Hoepfner and Zecker (1991), and later Vaidya et al. (1998), showed the prescription of Methylphenidate reduced the number of commission errors in those with ADHD. Such reduction in inattention-related errors following treatment suggest a clear link between ADHD and visual attention.

Overview

Examining both the GNG and CPT paradigms, there appear to be some overall differences within sustained attention. For the GNG task, differences between ADHD and controls have been reported within multiple behavioural measures including increases in commission errors, omission errors, mean RT and RT variability. Similar differences have also been found for the CPT paradigm where ADHD again show increased commission errors and omission errors as well as slower and more variable RT. Research also showed improvements in sustained attention within ADHD when methylphenidate medication was administered.

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Indeed a recent meta-analysis by Wright, Lipszyc, Dupuis, Thayapararajah and Schachar (2014) examined the overall differences in ADHD for both CPT and GNG as well as the Sustained Attention Reaction Task (SART). It was shown that those with ADHD showed significantly more commission errors (based on 78 studies), more omission errors (based on 69 studies) and a slower mean RT (based on 94 studies) compared to controls.

Due to this research into sustained attention, a version of the CPT has been specially designed to be used with ADHD patients and now forms part of the clinical diagnostic tool used to assess ADHD (*Conners' continuous performance test*, CCPT, Conners et al., 2000). It has also been shown that such a behavioural test is particularly immune to malingering ADHD whereby it is hard to successfully fake symptoms (Booksh, Pella, Singh, & Drew Gouvier, 2010; Quinn, 2003) although more recent research has questioned this (See review: Musso and Gouvier, 2012).

1.3.2 Visual field differences in Attention

Research into those with ADHD has often demonstrated significant attentional difficulties characterised by increased distractibility, slower target detection and more response errors due to attentional lapses. Some research however has suggested that such attentional deficits within ADHD may depend on which spatial location attention is being directed towards and which location stimuli and distractors are presented in. It has long been theorized that attention mechanisms within the left parietal cortex control spatial attention directed towards the right side of space while the right parietal cortex controls attention towards both left and right sides of space (De Schotten et al., 2011; Heilman & Valenstein, 1979; Heilman & Van Den Abell, 1980; Kinsbourne, 1987). Due to such right hemisphere dominance for spatial attention, damage to the right parietal cortex is more likely to result in attentional deficits, particularly towards the left side of space, compared to the left hemisphere. Indeed, attentional deficits following right hemisphere parietal damage have been extensively researched and often manifest as unilateral neglect; a condition where left space is often ignored despite attention to the right being intact. Several studies have also suggested that ADHD Inattention may result from a right hemisphere deficit within such parietal regions (for review see Hale et al., 2009; Stefanatos & Wasserstein, 2001), which may manifest in differences in

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attention between both sides of space. Given the clear hemispheric nature of the visual system, where stimuli presented in the left visual field (LVF) are processed by the right hemisphere while the right visual field (RVF) is processed by the left hemisphere, differences in attention towards both VFs may be more readily examined in the visual domain. Whilst the above discussion focuses on sustained attention within ADHD, due to the limited number of studies specifically exploring visual field differences within ADHD, studies from selective-attention paradigms will also be discussed. Such studies include the GNG, CPT, Covert Visual Attention Task (COVAT), Flanker and Line-bisection task.

One of the most common paradigms used to explore hemifield differences in attention is the COVAT (also known as the Posner Cueing Task) (Posner, 1980). During these tasks, a central target is presented before a second target appears in the periphery within the LVF or RVF. Critically, just before the second target presentation, a cue is used to direct attention to the location of the upcoming stimuli. In some cases, this cue will accurately predict where the target will appear (Valid cue) while at other times it will direct participants to an incorrect location (Invalid cue). During such trials, participants are required to respond when the second target has been detected and the reaction time recorded. Using this paradigm, healthy participants often exhibit a benefit (reduced reaction time) when a valid cue is used compared to the no cue conditions, while the presence of an invalid cue causes a cost, or increase, in reaction time. Examining responses initially to un-cued responses, children with ADHD demonstrated increased errors and slower RT to targets presented in the LVF compared to the RVF (Bellgrove, Chambers, et al., 2007; Nigg, Swanson, & Hinshaw, 1997). Similar RVF-biases were also found in those with ADHD when examining the cost of invaliding cues which direct attention away from the target location. Here, those with ADHD showed slower RT to LVF targets following an invalid cue directing attention to the RVF compared to responses made to the RVF following invalid LVF cues (Epstein, Conners, Erhardt, March, & Swanson, 1997; Geeraerts, Lafosse, Vaes, Vandebussche, & Verfaillie, 2008; ter Huurne et al., 2013). Taken together, these appear to show that ADHD is associated with RVF hemifield-bias where attention is more readily directed towards the RVF compared to the left and there is increased ability to ignore the LVF. One study however has shown the opposite effect whereby there is a slower RT to RVF targets following invalid LVF cues (Swanson et al., 1991).

Nevertheless, research has shown that there may be a more complex relationship between ADHD and hemifield-bias. Carter, Krener, Chaderjian and Northcutt (1995b) used a COVAT to examine the effect of cue type (*Endogenous*; central fixation cue which symbolically indicates probable target location. vs. *Exogenous*; cue occurs at the proposed target location). They showed that under endogenous cueing, those with ADHD showed an increased cost (slower RT) following invalid LVF cues compared to RVF cues. However, under exogenous cueing, the opposite effect was observed with an increased cost now following invalid RVF cues. Previous research has suggested that both cue types assess different mechanisms of attention, assessing automatic, ‘bottom up’ attention (exogenous) and controlled, ‘top-down’ attention (endogenous). Such differences may therefore indicate attentional differences within ADHD can occur at both stages of attention.

Hanisch et al. (2005) also used the GNG task to explore differences in VF where the stimuli were presented to peripheral LVF or RVF locations compared to being presented centrally as in the traditional GNG paradigm. Here they found a significant interaction between group (ADHD vs control) and hemifield of target presentation where children with ADHD were significantly more impaired in inhibiting stop responses to RVF stimuli compared to controls. No group differences were found for the LVF. Others using variants of the CPT similarly showed slower RT and more errors to RVF stimuli in those with ADHD compared to controls (Bellgrove, Eramudugolla, Newman, Vance, & Mattingley, 2013; Silk, Newman, Eramudugolla, Vance, & Bellgrove, 2014) whilst line-bisection tasks also show more errors within the LVF in relation to ADHD traits (Bellgrove, Barry, et al., 2007; Sandson, Bachna, & Morin, 2000). Similar to the COVAT, this may suggest that those with ADHD more readily attend to the RVF compared to controls so have problems inhibiting this response.

Hemifield biases were also discovered by Chan et al. (2009) who used a modified flanker task to examine sustained attention in children with ADHD under both high and low perceptual load (many vs a single distractor). Under low-load conditions, those with ADHD demonstrated an increased interference from incongruent flankers when the target stimulus was presented in the RVF compared to the LVF. Interestingly, control children showed the opposite effect of increased interference from

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incongruent flankers for LVF targets compared to RVF. Huang-Pollock, Nigg and Carr (2005) (reanalysed by Chan et al., 2009) using a near-identical paradigm, similarly showed a significant interaction between ADHD diagnosis and the visual field of distractor presentation, where children with ADHD again showed increased interference when attending to the RVF.

Whilst the majority of research has focused on exploring hemifield bias in attention with those clinically diagnosed with ADHD, other have also examined the effect of ADHD characteristics in the typically developed population. Manly, Cornish, Grant, Dobler and Hollis (2005) showed that the number of ADHD-associated traits observed in children showed a positive relationship with LVF inattention during line bisection tasks. Similarly, Poynter, Ingram and Minor (2010) using the attentional network task (ANT; a task similar to the COVAT) showed that adults with higher inattention traits experienced increased problems and were less efficient at orientating attention to the LVF. When orientating to the RVF however, they were shown to be at least as effective as, if not more effective, than adults with fewer traits. From such research, it is apparent that such hemifield differences in attention within ADHD may not relate specifically to those with a clinical diagnosis and can be observed in the typically developed.

Overall such research, while few in number, appears to suggest differences in attentional deficits depending on which visual field the focus or suppression of is directed towards. Interestingly, such literature often fits with those on neglect syndrome which presents as the visual neglect of stimuli within the LVF following damage to the parietal lobe (George, Dobler, Nicholls, & Manly, 2005). In the case of ADHD it appears that stimuli in the LVF are less distracting and take longer to react to compared to the quicker response to stimuli in the RVF. Indeed a study by Geeraerts et al. (2008) compared both ADHD and neglect patients to controls using a visual orientation-discrimination task where participant's just-noticeable difference thresholds were calculated within each hemifield with and without the presence of distractors contralateral. It was shown that both clinical groups exhibited similar patterns whereby, both showed significant interference (reduced sensitivity) from RVF distractors but no interference from a LVF distractor. However, whether such differences are due to an added "pull" of attention from the RVF or a neglect of the LVF is still to be

investigated. Additional research has also demonstrated that such hemifield differences in attention in those with ADHD can be normalized through psychostimulants, typically Methylphenidate. This was shown to occur across multiple attentional-paradigms in both children and adults with ADHD (Nigg et al., 1997; Sheppard, Bradshaw, Mattingley, & Lee, 1999; Silk et al., 2014; Tucha et al., 2006), again suggesting a link between ADHD, neural processing and hemifield bias.

1.3.3 Attentional Load

Another line of research within the field of ADHD and attention has started to examine whether visual attention deficits are dependent upon the attentional load and complexity of the task. According to the Load theory of attention proposed by Lavie and colleagues (Lavie, 1995; Lavie, Hirst, de Fockert, & Viding, 2004) the critical component that determines our success in focusing attention concerns the level of perceptual load, defined as ‘the quantity of stimuli requiring perceptual processing, or the complexity of perceptual judgments’ (Forster, Robertson, Jennings, Asherson, & Lavie, 2014). Tasks with a low perceptual load (few distractors which are distinctive from the target; Figure 1.4, *left*) often require some allocation of attentional resources to successfully complete, however some capacity remains and is used by the automatic processing of the distractors. In order to ignore the distractors therefore, late-attentional mechanisms are required to suppress the stimuli. Tasks with high perceptual load (many distractors which may be similar to the target; Figure 1.4, *right*) on the other hand, are thought to require more attentional allocation and result in limited or no processing capacity left to attend to the distractors. This facilitation of avoiding the distractors is therefore thought to be processed by early selective mechanisms. This is, it appears that distraction by task-irrelevant stimuli can be prevented, providing the attentional load of the task is high enough. Again, due to the limited number of studies exploring attentional load within ADHD, studies from both sustained and selective-attention paradigms will be discussed.

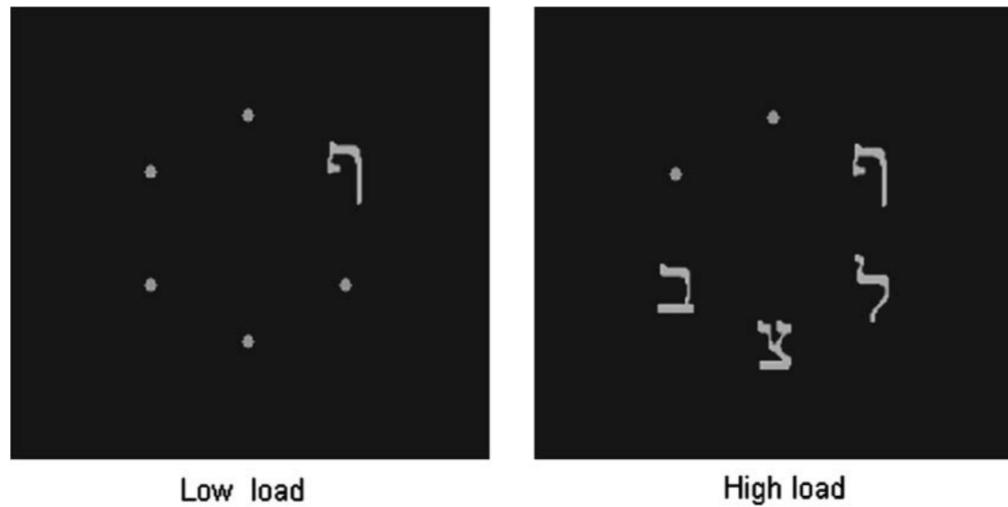


Figure 1.4: Low and High perceptual load. Examples of stimuli used by (Forster & Lavie, 2009) to examine the effect of perceptual load with both Low-load (left) and High-load (right) images. The Low-load image shows the distinctiveness of the target symbol from its surround task-irrelevant distractors while the High-load shows the similarity of distractors from the target

Using a visual task similar to those above with letters, Forster et al. (2014) examined the effect of perceptual load in children with ADHD by varying the set size of the distractors stimuli while also introducing additional salient infrequent distractors (pictures of cartoon characters) within the periphery during individual trials. When examining the cost of the distractor (distractor – no distractor RT), it was shown that those with ADHD exhibited a higher cost, almost doubled to that of the controls under both low and high-load conditions and that this cost strongly correlated with ADHD inattention scores across both groups. The reduced distractor cost when increasing perceptual load was significant for both groups. When error rate was measured however, those with ADHD were shown to make significantly more errors than controls, particularly when under high load conditions. This may therefore suggest that the proposed perceptual load theory can go some way into explaining visual search behavioural patterns in those with ADHD as well as controls, as an increased perceptual load decreased the distractor costs, indicating the distracting stimuli was processed less frequently. The authors comment that such effect of load seen in ADHD likely indicates that the early selective mechanisms (those involved in high-level tasks) are intact, while the late selection mechanisms suppressing distractors in the low-level task are disrupted.

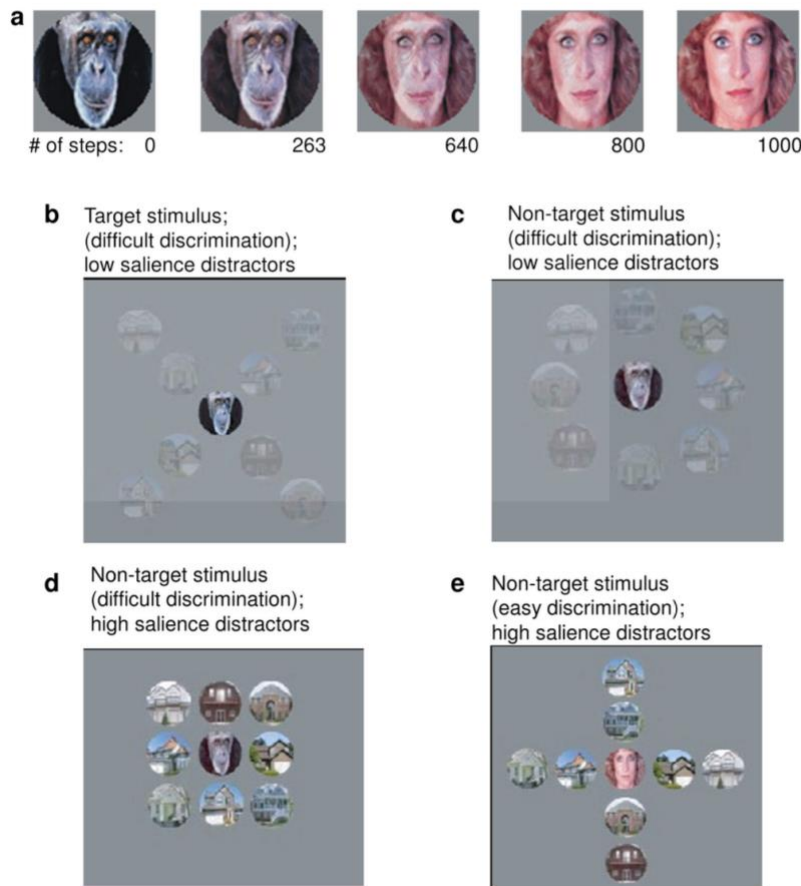


Figure 1.5: Friedman-Hill et al., 2010 Attentional morphed face-identification task. Non-morphed ape and human faces as well as human-ape morphs were presented centrally. The central discrimination task (original ape vs not original ape) consisted of either easy discrimination

In a unique study by Friedman-Hill et al. (2010), both children with ADHD and controls completed a central face-identification task, where they decided whether a central face was the pre-defined target (an ape) or a non-ape (possibly a full human face or an ape-human morph) (Figure 1.5). While they were doing this central task, distracting visual stimuli were presented in the surround and were varied in salience, manipulated by contrast, to change the perceptual demands of the task. Results showed that when the filtering cost of the high salience stimuli (RT high salience – RT low salience) was examined, children with ADHD showed a significant negative reduced cost compared to positive cost for both control adults and children, indicating that those with ADHD made faster responses when flanked by high salient stimuli relative to the low salient stimuli. Interestingly however, this difference was only found in an easy discrimination task while there was no difference in the difficult discrimination,

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suggesting that ADHD attentional deficits are more likely when both perceptual load and distractor salience are low.

Similar results were also seen in studies using CPT-variant and flanker paradigms, where ADHD deficits in attention were primarily seen under easy, low-load conditions (Bellgrove et al., 2013; Chan et al., 2009; Huang-Pollock et al., 2005). Indeed, both Chan et al. (2009) and Huang-Pollock et al. (2005) showed that visual field differences in attention discussed previously (See 1.3.2 Visual field differences in Attention, p28) were only apparent during low-load conditions.

Given these results, whilst few in number, the relationship between ADHD and visual attentional appears to depend on the perceptual or attentional-load of the task being performed where those with ADHD experience greater attentional problems under easy, low-load conditions. Based on Lavie's Load Theory, this would therefore suggest that ADHD is associated with a deficit in the controlled, 'top-down' attentional system, where the allocation of excess attentional capacity towards distractors must be suppressed.

1.4 The Visual System and ADHD

While most research within the ADHD literature has largely focused on differences within the prefrontal regions, there is clear evidence to suggest that visual attention deficits are a core symptom of ADHD. Considering the occipital cortex interacts with the attention network in order to maintain attention (Shulman et al., 2009) and suppress irrelevant distractors (Capotosto, Babiloni, Romani, & Corbetta, 2009; Gouws et al., 2014; Schwartz et al., 2005), it is therefore possible that such deficits may be associated with abnormalities within the visual system. Indeed, a review by Cortese and Castellanos discussing structural and functional differences within ADHD suggested that the visual-system and occipital cortex have been largely ignored within the field and represent a 'fruitful' area of investigation. The following section will firstly explore whether structural and functional differences can be observed in those with ADHD within visually-associated cortical and sub-cortical regions. It will then present an initial background into one theory linking ADHD and the visual system, which focuses on the Superior Colliculus and proposed hyperactivity responses within

those with ADHD.

1.4.1 Functional Differences

A meta-analysis by Cortese et al. (2012) examined functional differences in ADHD in relation to seven reference neuronal systems as defined by Yeo et al. (2011) (Frontoparietal, Dorsal attentional, Ventral attentional, Somatomotor, Visual, Limbic and Default mode networks) by examining 55 studies, including 741 ADHD participants and 801 controls. Comparing 39 studies on children with ADHD, it was shown that 4% of the ADHD > control findings were within the visual system while there were no differences for control > ADHD findings (Figure 1.6). The 16 studies on adults with ADHD however, showed 41% of ADHD > control findings were in the visual system and accounted for the greatest number of findings followed by dorsal attention and default mode networks. Again, no differences were found for controls > adults in the visual system. Two additional meta-analyses focusing on the functional differences specifically during sustained attentional tasks also showed similar results, with adults with ADHD often exhibiting hyperactivity within the occipital cortex (Cubillo et al., 2012; Hart, Radua, Mataix, & Rubia, 2013).

Examining each attentional task separately, both GNG and CPT sustained attention tasks have been the two most popular tasks used when exploring functional differences in ADHD. For the GNG task, Dillo et al. (2010) and Durston et al. (2003) found increased BOLD activity within regions of the middle and inferior occipital cortex for children and adults with ADHD. However reduced activity within similar regions have also been observed within ADHD. Booth et al. (2005) and Schulz et al. (2004) both showed reduced BOLD activity with early occipital regions (Brodmann area 18 and 19) within children and adolescence with ADHD compared to controls during inhibition no-go trials compared to go-trials. Spinelli et al. (2011) too showed reduced activity within the superior occipital gyrus for those with ADHD during inhibition errors compared to controls, although this failed to reach significance.

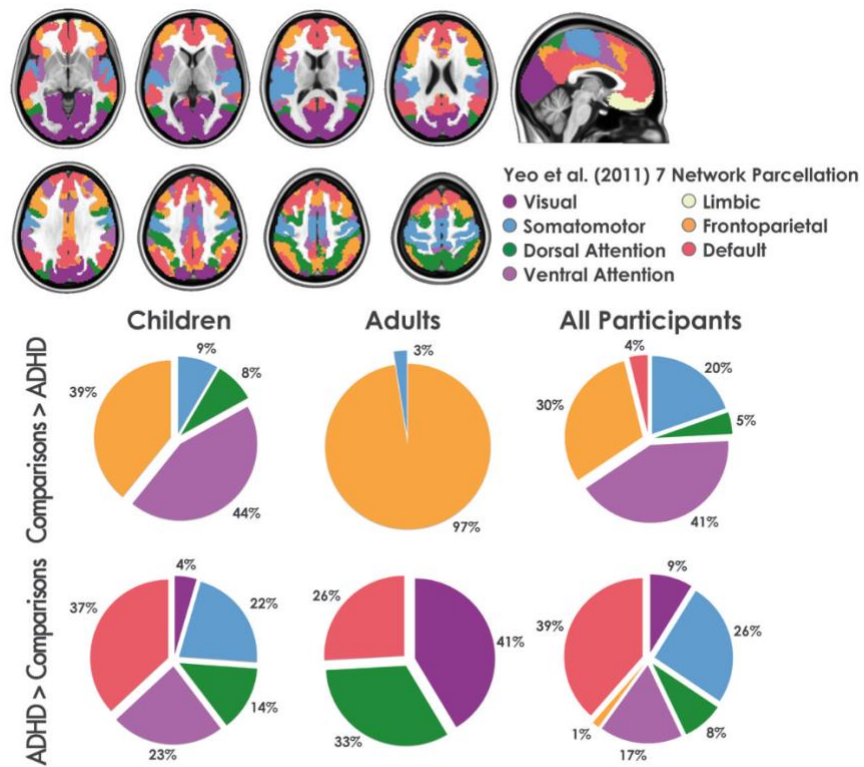


Figure 1.6: Regions of ADHD hyperactivity and hypoactivity findings compared to controls based on 55 MRI studies from Cortese et al. (2012). These are classified according to Yeo's et al. (2011) seven reference networks. This has been done separately for both adults and children with ADHD.

Differences in functional activity during GNG have been observed between ADHD subtypes. Solanto, Schulz, Fan, Tang and Newcorn (2009) found that children with ADHD-Combined subtype showed increased activity within bilateral regions of the medial occipital lobe compared to those with ADHD-Inattentive subtype, potentially indicating that hyperactive and impulsive traits play some role in the hyperactivity observed within such regions. Schulz, Newcorn, Fan, Tang and Halperin (2005) similarly explored the GNG paradigm within adults with remitted childhood ADHD and persisting ADHD. They found that while control and adults with remitted-ADHD exhibited significant activity within the occipital cortex, no such activity was observed for those with persisting ADHD.

Kooistra et al. (2010) however showed that, with respect to GNG task, differences in occipital lobe activity between those with ADHD and controls may depend on the inter-stimulus interval (ISI). Comparing trials with slow (average 7000

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ms) and fast ISI (average 1500 ms) during go trials, those with ADHD showed greater activity during slow in relation fast trials within areas of the lingual gyrus (Brodmann area 18) compared to control participants. Controls on the other hand showed greater activity within the lateral occipital cortex (LOC, Brodmann area 19) compared to those with ADHD. Similar to findings showing the influence of ISI for behavioural measures of the GNG for ADHD (See Go No-go task, p23), this suggests that the relationship between ADHD and sustained attention is more complex than a general attentional deficit whereby timing and response preparation appear to influence inhibitory responses. Indeed, the above GNG task research do use different ISI, ranging from 200ms (Dillo et al., 2010) to 3500 ms (Durstun et al., 2003) and could account for some discrepancies between studies.

Mixed results however have been observed within the CPT sustained attention task. Schneider et al. (2010) showed increased activity within the left fusiform gyrus and bilateral regions of the lingual gyrus for those with ADHD, although only the left fusiform gyrus remained significant after correcting for IQ. They went on to show that Inattention scores correlated positively with activity in the left middle occipital gyrus (Brodmann area 18). Rubia, Halari et al. (2009) also showed increased activity within right occipital regions within adolescents with ADHD. Interestingly however, they found such increases only occurred when ADHD participants were taking methylphenidate medication and that such increased activity correlated negatively with omission errors. This suggests that methylphenidate medication may be establishing a compensatory effect within visually-associated regions, leading to improved task performance. Indeed, a recent meta-analysis examining the effect of stimulant medication, such as methylphenidate, on brain function in ADHD reported an increase in occipital lobe activity within other attentional tasks (Rubia, Alegría, & Brinson, 2014).

Sustained attention has also been examined during a rewarded-CPT, a variation on the standard CPT involving social or monetary incentives for each correct response (See Continuous Performance Task, p20). Similar to the standard CPT task, Rubia, Smith et al. (2009) and Cubillo et al. (2012) showed increased BOLD responses within bilateral regions of the occipital lobe, including the primary visual cortex (V1: Brodmann area 17), for children and adults with ADHD. However, in another CPT

study the same year, Rubia, Halari et al. (2009) showed no difference in occipital lobe activity between children with ADHD and controls under the rewarded CPT, regardless of ADHD medication status.

Other attentional tasks have likewise been examined using fMRI in those with ADHD, who show increased inferior occipital gyrus activity during the Stroop task (Banich et al., 2009) but reduced visual cortex and parietal-occipital activity during mental rotation (Silk et al., 2005; Vance et al., 2007). Cubillo et al. (2010) similarly showed a negative correlation between inattention traits and activity within the occipital cortex during unsuccessful inhibition trials. Tasks on working memory, such as digit span, have also revealed functional differences in for those with ADHD whereby PET scans revealed an increase in occipital lobe blood flow relative to controls (Schweitzer et al., 2000). Hale, Bookheimer, McGough, Phillips and McCracken (2007) showed however that such functional differences between attentional tasks may depend on the level of task difficulty. In a working memory task, easy tasks revealed increased left occipital lobe activity in those with ADHD compared to controls. However hard tasks revealed the opposite effect, whereby those with ADHD now showed reduced left occipital lobe activity compared to controls. Indeed, previous research has shown an effect of task perceptual load on the behavioural performance of ADHD patients (See 1.3.3 Attentional Load, p31), so remains possible that attentional load and differences in task difficulty may influence associated functional activity.

Resting-state studies have further explored differences in regional connectivity and interactions, typically using fMRI, within ADHD. Whilst many studies often focus on the default mode network, a region where the suppression of neural responses has been linked to reduced distractibility and fewer lapses in attention and reduced task errors (for review see Posner, Park, & Wang, 2014), a few have explored such differences within the occipital lobe. Cao et al. (2006) found children with ADHD showed increased homogeneity within the occipital cortex, indicating an increased similarity and synchronization in the activity of voxels and their neighbours. Similar increases were found in adults with ADHD (Wang, Zhu, Li, Chen, & Jiang, 2013). Abnormal regional connections and increased activity within the occipital cortex have also been found in children and adults with ADHD (Cao et al., 2009; Cocchi et al., 2012; Tian et al., 2008; Wang et al., 2009). Sokunbi et al. (2013) recently showed adults

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with ADHD exhibited reduced entropy, indicating an increased “randomness” within activity patterns, within bilateral regions of the occipital cortex compared to controls. Resting-state scans with SPECT (single photon emission computed tomography) have too revealed similar findings where adults with ADHD exhibit increased blood-flow to the occipital gyrus compared to controls (Kim, Lee, Shin, Cho, & Lee, 2002). Such research provides further support to the suggesting that those with ADHD exhibit underlying differences in how the visual-system functions and interacts with other networks.

1.4.2 Structural Differences

In addition to the possible functional differences in the visual system, research has started to explore whether those with ADHD exhibit structural changes to visually-associated regions compared to control participants. Examining differences in cortical structure using MRI and voxel-based morphometry, Ahrendts et al. (2011) found that adults with ADHD displayed reduced grey matter (GM) volumes in bilateral areas of the early visual cortex (V1 and V2) compared to controls. Interestingly, the amount of GM in these areas showed a significant correlation with ADHD symptoms in childhood, whereby those with greater childhood symptoms demonstrated a larger reduction in visual cortex GM. Previous smaller scale studies have shown similar volumetric reductions within the occipital lobe for adults with ADHD, although some only reached trend significance. Structural abnormalities in adults with ADHD have similarly been shown in studies measuring cortical thickness, where those with ADHD show reduced thickness within the occipital lobe (Makris et al., 2007; Proal et al., 2011). One such large-scale study by Proal et al. (2011) additionally compared cortical thickness in adults with persistent and remittent childhood ADHD where those with persistent ADHD exhibited reduced thickness within the left occipital gyrus (BA 19).

Similar occipital cortex deficits have similarly been observed in children with ADHD. A review by Ahrendts et al. (2011) examining differences in children with ADHD showed that eight out of twelve studies found significant reductions in GM volume or cortical thickness within the occipital lobe (Brieber et al., 2007; Castellanos & Proal, 2012; Durston et al., 2003; Filipek et al., 1997; McAlonan et al., 2007; Shaw et al., 2006; Wolosin, Richardson, Hennessey, Denckla, & Mostofsky, 2009) while an additional study showed non-significant reductions (Mostofsky, Cooper, Kates,

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Denckla, & Kaufmann, 2002). Nevertheless, Ahrendts reports some of these studies failed to take into consideration the total brain volume of the subjects making the comparability of these findings difficult.

Whilst the majority of studies show a clear decrease in grey matter and cortical thickness within the occipital lobe, a few continue to show increased structure measures for those with ADHD. Indeed, only one out of the twelve studies focusing on visual cortex structure in children reviewed by Ahrendts et al. (2011) showed an increase in occipital GM for children with ADHD (Sowell et al., 2003). More recent studies have too found the same effect in adults with ADHD who exhibited increased thickness and GM volume within occipital lobe regions, including the lateral occipital cortex, lingual gyrus and pericalcarine cortex (Almeida Montes et al., 2012; Pironti et al., 2014). Nevertheless, a study by Seidman et al. (2011), also exploring structural differences in adults with ADHD, showed that increases and decreases within the occipital lobe for ADHD may simultaneously occur. They found that within the occipital lobe, some parts exhibited an increased GM volume in those with ADHD while other regions showed reduced volumes. Such findings therefore show that examining the visual system for ADHD needs to be explored in more detailed manner, where potential structural differences may be overlooked when only examining large-scale regions of interest, such as the entire occipital lobe. Indeed, the lack of consistency in defining such regions of interest between studies also makes direct comparison difficult. Further large-scale research or meta-analysis are needed to reliably assess such occipital lobe differences within ADHD.

White Matter (WM) volumes have been explored in a similar way to those discussed above with GM using MRI voxel-based morphometry (VBM); a technique used to measure differences in the concentration of neural tissue. Although fewer in number, they too show a tendency for ADHD patients to exhibit reduced WM volume within the occipital lobe and along the Inferior Longitudinal Fasciculus (ILF; a WM tract connecting the occipital lobe to temporal regions) (McAlonan et al., 2007).

Recent advances in MRI protocols and analyses tools have now also allowed WM tracts to be examined in more detail though the use of Diffusion tensor imaging (DTI). Using this technique, researchers can assess the structure of WM tracts, often measuring fractional anisotropy (FA; the degree that diffusion within WM tracts are

coherence and one-directional) and mean diffusion (MD; the degree of overall diffusion, independent of direction). Reduced FA values often indicate the presence of axonal disruption and reduced structural integrity (Basser, Mattiello, & LeBihan, 1994) while increased MD indicates increased water or CSF within intra and extra-cellular space (Clark et al., 2011). Such a technique has recently been utilised in those exploring structural differences in ADHD.

Cortese et al. (2013) conducted a large-scale longitudinal design whereby adults with ADHD were tracked from childhood into adulthood, allowing them to explore potential differences between adults with persisting and remitted ADHD. DTI measures taken in adulthood showed that those with childhood ADHD, regardless of current diagnosis, showed reduced FA within the left Posterior Thalamic Radiation (pTR, including the optic radiation); a tract that carries visual information from the Lateral Geniculate Nucleus (LGN) to V1. Other reductions were found in the left hemisphere within the Inferior Fronto-occipital Fasciculus (IFOF; connecting the occipital lobe with frontal areas) and ILF while the right hemisphere showed reductions in the Superior Longitudinal Fasciculus (SLF; connecting the occipital lobe with frontal, temporal and parietal areas). As adults, those that had persisting ADHD continued to show reduced FA in the right IFOF and ILF compared to controls, however there were no regions where FA differed significantly between those with persisting ADHD and those with remitted ADHD. Comparable results were also found a few years earlier by Konrad et al. (2010) in another large-scale study, where adults with ADHD showed reduced FA within the IFOF and anterior Thalamic Radiation (aTR) in addition to increased MD within the SLF, FOF and aTR. Such results further showed a clear correlation between ADHD-associated traits and DTI measures within the SLF, later replicated by Witt and Stevens (2015), and aTR.

Similar WM abnormalities have similarly been observed in children with reduced FA within the left occipital-parietal regions (Ashtari et al., 2005) and increased MD within both SF and ILF tracts (Pavuluri et al., 2009) (For review see van Ewijk, Heslenfeld, Zwiers, Buitelaar and Oosterlaan, 2012). Similarly, Hamilton et al. (2008) showed abnormalities in WM structures within the SLF for those with ADHD although found no difference in the FOF. Interestingly, they also showed a small reduction in FA within the optic radiation for those with ADHD, although this failed to reach

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significance. Nevertheless, there remains some conflicting results regarding these WM differences where both Silk, Vance, Rinehart, Bradshaw and Cunnington (2009) and Chou, Chou, Chiu and Gao (2007) showed increased FA within areas of the occipital-parietal cortex, including pTR, aTR and SLF, for children and adolescence with ADHD.

Structural abnormalities in both GM and WM and their relation to ADHD have not only been examined in those with the condition but are increasingly being examined in unaffected siblings of those with ADHD as well. Durston et al. (2004) examined such differences using MRI and reported that both children with ADHD and their siblings exhibited reduced GM and WM volumes within the left occipital lobe. Lawrence et al. (2013) also explored WM tract differences in children and adolescences with ADHD and their unaffected siblings, who both showed increased MD within the SLF compared to controls. Such results therefore suggesting that some aspect of the structural differences observed within ADHD have a familial component and could act as a biological marker of ADHD.

1.4.3 Superior Colliculus

Superior Colliculus and Distractibility

One specific visual brain structure that has often been linked to distractibility and attention is the Superior Colliculus (SC); a small laminar sub-cortical structure located in the midbrain. The SC is a structure which primarily acts as part of the visual system with the superficial layers receiving a direct input from the retina and showing clear retinotopic organization (Katyal, Zughni, Greene, & Ress, 2010; Schneider & Kastner, 2005). These neurons often exhibit responses to a large variety of visual stimuli (Humphrey, 1968; Marrocco & Li, 1977; Schiller & Koerner, 1971; Schiller & Stryker, 1972), particularly those showing a motion component (Cynader & Berman, 1972; Marrocco & Li, 1977; Schiller & Stryker, 1972; Schneider & Kastner, 2005). Deeper layers of the SC however are less exclusive to vision and appear to play a role in multimodal sensory integration, with neurons containing receptive field within multiple modalities (Stein, 1998). These sensory maps are then spatially registered to the other modalities and, similar to the retinotopic visual map, tend to represent contralateral space (Wallace, Wilkinson, & Stein, 1996). Research showing heightened responses to multi-modality stimuli (combined across space or time) compared to single-modality

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within these deeper layers supports this suggestion (Dean, Redgrave, & Westby, 1989; Meredith, Wallace, & Stein, 1992). These neurons also exhibit stronger responses to visual motion stimuli compared to static and flashing stimuli (Cynader & Berman, 1972; Marrocco & Li, 1977). This structure has been found to be highly conserved across multiple species (Stein, 1998) and has been extensively studied in mammalian species over the last few decades.

Research has widely acknowledged that there is a connection between colliculus activity and both head and saccadic orientating movements, which aid in changing the focus of overt attention. Indeed, direct stimulation of the SC has previously been shown to evoke saccadic movements. Adamük, who first demonstrated this in the 19th century (as cited by Robinson, 1972), showed that direct SC stimulation resulted in saccades towards the contralateral visual field. Research by Robinson (1972) also showed the general agreement between the visual sensory map, previously shown in the SC, and a motor map of saccade targets shown through direct stimulation. It would therefore appear that when a target in the visual field causes activation within the retinotopically associated area of the SC, this also relates to the motor map, which can direct saccades to the target's location. Similar results showing the effect of SC stimulation on saccade behaviour have been replicated by others (Schiller & Stryker, 1972).

Current proposals behind the SC involvement in such movement, indicate the SC may act as a command centre, creating 'bids' to try and initiate a motor expression. Increased activity within the SC therefore acts as a stronger 'bid' made to the central motor selection device, proposed to be the Basal Ganglia (Redgrave, Prescott, & Gurney, 1999). This idea has been further supported by single-unit recording showing that neurons within the deeper colliculus layers tending to discharge approximately 50-200ms prior to a saccadic movement (Everling, Dorris, Klein, & Munoz, 1999; Mohler & Wurtz, 1976; Robinson & Wurtz, 1976; Schiller, True, & Conway, 1980; Sparks, 1999).

Moreover, additional research has demonstrated that, while the SC is clearly involved in overt-attentional-shifts, it is likely to also be involved in covert attentional-shifts. Ignashchenkova, Dicke, Haarmeier and Thier (2003) showed that the monkey SC, particularly the intermediary layers, exhibited increased activity during covert

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attentional-shifts (without saccades) when measure by single-unit recording. Furthermore, such behavioural benefit gained from valid cues using a Posner-task paradigm was found to correlated positively with SC activity. Using fMRI, Katyal et al. (2010) similarly showed that both superficial and intermediary SC layers within humans, can be activated by visual stimulation and by covert attention.

Other lines of research have also examined the effect of direct SC lesioning or damage to its connections on attention. It has consistently been found across multiple species that direct surgical lesioning of the SC results in changes in distractibility with many often showing a reduced level of distraction to peripheral stimuli when performing a central fixation task (*Rat*: Goodale, Foreman, & Milner, 1978. *Cat*: Sprague, 1966. *Monkey*: Albano, Mishkin, & Westbrook, 1982; Milner et al., 1978). Research by Schiller and colleagues has too show that SC lesioning in monkeys causes deficits in oculomotor movements with reductions in fixation accuracy, number of saccades and saccade velocity (Schiller et al., 1980). In keeping with the clear retinotopic nature of the SC, it has been shown that unilateral SC lesioning eliminated express-saccades (See Express saccades, p53) and increases the reaction time of saccades made towards the contralateral visual field (Schiller, Sandell, & Maunsell, 1987). In a more recent study by Gaymard, François, Ploner, Condy and Rivaud Péchoux (2003), it was shown that a similar effect exists in humans whereby disconnection of the SC from the control of the prefrontal cortex resulted in increased distractibility. This suggested that the SC function and its relation to distractibility is preserved in a very similar way in humans.

ADHD and the Superior Colliculus

As shown above, the SC appears to be heavily involved within attention and the overt behaviours involved within attentional shifts. Distractibility and problems with such attentional-shift however, are often a core symptom of ADHD in both children and adults (See ADHD Symptoms and Diagnosis criteria, p13 and Visual Attention in ADHD, p19). A recent theory by Overton and colleagues (Overton, 2008; Overton & Clements, 2009) therefore proposed that the dysfunction, specifically hyperactivity, of the SC towards sensory stimuli may account for the increase in distractibility seen in those with ADHD. Following the explanation of the SC mechanisms above, the proposed hyperactivity within the SC in those with ADHD may result in an increased

tendency (or stronger ‘bids’ being made) to direct attention towards external stimuli through saccade or head movements. This would likely manifest behaviourally as the typical increase in distractibility often observed in ADHD. Various tasks have been used to assess the collicular functioning within those with ADHD, including various saccade tasks. Further evidence to link ADHD and the SC has also come from research studying the effect of ADHD psychostimulant treatments on the SC and associated behaviours. Each of these will be discussed here in turn.

Saccades

As previously seen, there appears to be a clear link between SC activity and the tendency to make saccades. Research demonstrating any potential abnormalities or deficits in saccadic movements for those with ADHD could therefore provide useful support of the SC-hyperactivity hypotheses. Saccades, however, do not appear just in one form with multiple distinct types often being associated with activity of the SC; Pro-saccades, Anti-saccades and Express saccades.

Pro-saccades

Two of the main tasks used to assess saccadic movements in those with ADHD are pro-saccades, eye movements directed towards a visual target, and anti-saccade tasks, eye movements directed away from a visual target. The pro-saccade task usually assesses the ability to make reflexive orientation towards targets. Typically, the anti-saccade task is often considered to be the opposite of pro-saccades movements, particularly as identical stimuli are often used for both paradigms with varying instructions. However, the processes involved are thought to be more complex with two distinct stages compared to the reflexive single stage used during pro-saccade. The two stages typically involve the initial inhibition of a response towards the target (inhibition of a pro-saccade) before a correct movement in the opposite direction (execution of an anti-saccade). It can therefore be seen that the anti-saccades require an internally generated saccade compared to the external stimulus-driven pro-saccade.

Trials for both tasks typically involve a central fixation target where, after a varied amount of time, a second peripheral target appears (usually to the left or right).

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Depending on the condition, the observers are instructed to either look towards the peripheral target (pro-saccade) or to look away from the target to its mirror position within the opposite visual field (anti-saccade). Such paradigms, particularly the pro-saccade task, can often be likened to the no-cueing conditions within the COVAT or Posner attentional task, with a saccadic response being used as the detection response (See 1.3.2 Visual field differences in Attention, p28 for discussion on COVAT).

In terms of Pro-saccades, research has typically shown that both adults and children with ADHD often exhibit a deficit or abnormalities depending on the specific saccade measure. A large-scale study by Munoz (2003) examined ocular motor differences between 114 ADHD patients and 180 controls, with ages ranging from 9 to 59 years, using a standard pro-saccade paradigm under two conditions. In the first condition, there was a 200-ms delay between the offset of the fixation target and the onset of the peripheral stimuli (gap condition) while the second condition involved the central fixation target continuing to remain on screen after the appearance of the peripheral target (overlap condition). The comparison is done with the idea that the removal of the fixation point in the gap condition allows the release of the fixation mechanism ready for the saccade (which has previously been shown to involve the SC, Dorris, Klein, Everling, & Munoz, 2002) while the overlap condition maintains the mechanism, hence allowing researchers to more specifically examine the deficits in ADHD (Leigh, 2003). For both gap and overlap conditions, ADHD patients were shown to have significantly slower saccadic reaction times (SRT) and an increase in inter-subject response variability compared to controls. Similar results were also found by Klein, Raschke and Brandenbusch (2003) on a smaller sample of children with ADHD and aged-matched controls, with those with ADHD showing longer stimulus response times (SRT) compared to controls as well as an increase in premature saccades (saccades made before the target appeared).

In a study by Hanisch et al. (2005) however using a similar but more child-friendly pro-saccade task, it was found that there was no group difference between the SRT, SRT variability or saccade accuracy in either gap or overlap conditions. The absence of SRT and accuracy differences are too supported by previous studies by Ross and colleagues (Ross, Harris, Olincy, & Radant, 2000; Ross, Hommer, Breiger, Varley, & Radant, 1994). Nevertheless, it is noted that there was a trend-level non-significant

($p=.09$) group difference in the gap effect (SRT overlap – SRT gap conditions) with children with ADHD showing a smaller effect compared to controls.

One possible explanation for these results concerns the idea of varying the time interval between the fixation target appearing and the peripheral target appearing (regardless of gap or overlap conditions). This is often done to avoid observers paying attention to the time component to prepare for the saccade rather than responding directly to the target. This may mean control participants in both Klein et al. (2003) and Munoz (2003) studies may have been more successful than their ADHD counterparts in using the fixed time component to prepare for saccadic responses and hence, are likely to show faster SRT.

Nevertheless, a similar study by Feifel, Farber, Clementz, Perry and Anllo-Vento, (2004) who used varied fixation-target intervals, in addition to a standard and gap conditions, still continued to show pro-saccade abnormalities in ADHD. While there was no difference in saccade amplitude, those with ADHD showed significantly more premature saccades and fewer correct responses in the gap condition and had a tendency, although not significantly, to show longer saccade durations (the time between a saccade velocity increase above $10^\circ/\text{sec}$ and a subsequent velocity decrease below $10^\circ/\text{sec}$) on the standard pro-saccade conditions. Unlike previous studies however, Feifel et al. (2004) tested to see whether group differences in saccades are dependent on the eccentricity of the peripheral targets. While more central targets (5° eccentricity) showed no difference between those with ADHD and controls for SRT, when the target was at more peripheral eccentricities (35°) there was a non-significant trend for those with ADHD to show shorter SRT than controls. This effect of target eccentricity is thought to also reflect group differences in the SC, with previous research showing an increase in SC activity for more peripheral stimuli (Sylvester, Josephs, Driver, & Rees, 2006). It is interesting however that, while the SRT are quicker in ADHD, their saccade durations are longer. The authors suggest this may be due to a tendency for those with ADHD to make slower motor movements.

Additional pro-saccade studies have further examined difference in visually-guided (the standard paradigm) and memory-guided saccades whereby a saccade response is made towards a target after it has disappeared. Ross and colleagues (Ross et

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al., 2000, 1994) found that, for both visually and memory guided saccade types, there was no difference in the SRT between adults with ADHD and controls. However, similar to Feifel et al. (2004) and Klein et al. (2003) they showed more pre-saccadic errors in the ADHD group. In a similar study in children, Goto et al. (2010) compared both young (6-8 years) and older children with ADHD (9-11 years) to 50 controls. Results showed that young children with ADHD has reduced accuracy on both visually and memory guided tasks as well as longer SRT on memory guided tasks only. Older children however showed no difference from controls on either accuracy or latency within either task type. Both ADHD groups did show an increase in anticipatory errors on both tasks. Interestingly, Goto et al. (2010) also conducted the same saccadic tests on 4 individuals with frontal lobe damage, who were shown to exhibit similar response profile to those with ADHD.

Such differences in studies may be explained by the low sample rates however, making them subject to individual difference, with the above studies using 10 and 19 ADHD participants respectively. In a larger scale study by Mahone et al. (2009), 60 children with ADHD were compared to 60 controls using both visually-guided and memory-guided pro-saccade tasks. For visually-guided tasks, those with ADHD had longer SRT and increased variability compared to controls. When these differences were separated into gender comparisons, it was only females with ADHD that differed from both control and ADHD males. Memory-guided tasks however showed no difference in saccade accuracy between groups. Upon investigating the gender ADHD effect further, it was shown that ADHD females scored higher on ADHD traits compared to ADHD males however, even when this difference was controlled for, females with ADHD still exhibited greater pro-saccade deficits.

Deficits in pro-saccade responses have also been examined within each ADHD presentation type, with Mahone et al. (2009) in the experiment discussed above, showing no significant difference in ocular motor profiles between ADHD-I and ADHD-C subtypes. Similarly O'Driscoll, Dépatie and Holahan (2005) examined a small sample of ADHD-I and ADHD-C children as well as aged-matched controls using a visually-guided paradigm. No differences were found between either ADHD group and controls or between both ADHD groups in either SRT, amplitude or peak velocity. This is also supported by Karatekin (2006) who similarly showed no difference in

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saccade accuracy or SRT between ADHD-C presentations and controls in visually-guide saccades. These studies appear to show clear contradictions from the large scale study by Munoz (2003) discussed above, who did show clear increases in SRT, SRT variability and a decreased peak velocity for those with ADHD. Such difference however are likely due to methodological differences in the treatment of extreme outliers within the data, with Munoz (2003) choosing to include outliers while O'Driscoll et al. (2005) excluded them. This shows the importance of deciding on a clear methodology standard within the field and the effect that such analyses decisions can have on the overall outcome and conclusions of a study. There has been no research conducted comparing ADHD-H presentations to either ADHD-I or ADHD-C presentations.

While all the above research has largely focused on the standard left and right saccadic paradigm, a study by Van Der Stigchel et al. (2007) used a more complex task with the peripheral target appearing at 6 possible target locations around the clock face. Additionally, unlike previous studies, for 50% of the trials a distractor target of a different colour appeared simultaneously in the location directly opposite the target. Results showed children with ADHD had significantly slower SRT in both the distractor absent and present conditions while there were no group differences in saccade accuracy towards the target or error saccades to the distractors. Nevertheless, those with ADHD did show significantly more intrusive saccades, defined as those that were directed at neither the target nor distractors, than controls. The increase in such saccades can again represent the higher overall level of distractibility in ADHD, possible from underlying sustained attentional problems as discussed previously (See 1.3.1 Sustained attention, p19). Overall, this shows that those with ADHD are not disproportionately impaired in suppressing the distracting stimuli.

Anti-saccades

Within the typically developed population, anti-saccades are usually shown to suffer from longer response times and frequency errors, whereby a response is often erroneously made towards a target instead, compared to pro-saccade tasks. On the other hand, research into those with ADHD have often shown that they exhibit significantly more of these response deficits than controls.

Klein et al. (2003) used a small sample of children with ADHD and age-matched controls typically made more directional errors (making saccades towards the target) as well as corrected fewer of these errors (e.g. making the correct anti-saccade after an initial error) compared to controls. They also showed that, while control children showed a strong decrease in anti-saccade SRT with age, those with ADHD showed a substantially slower reduction. Similarly Goto et al. (2010) using the standard anti-saccade paradigm with no overlap or gap manipulations, found that both young (6-8 years) and older (9-11 years) both showed more directional errors than age-matched controls. However, only the younger children with ADHD showed longer SRT to correct responses than controls.

In a large-scale study on both adults and children with ADHD, Munoz (2003) showed that both ADHD groups had increased SRT and SRT variability for correct anti-saccades in addition to making more directional errors compared to controls. Similar to the pro-saccade, these differences were found for both the overlap and gap tasks. A smaller scale study by Feifel et al. (2004) on adults with ADHD also showed they exhibited fewer correct responses than control adults regardless of whether the peripheral target (requiring a response in the opposite direction) was at more central or peripheral eccentricities. They however showed no difference in SRT between groups for either gap or overlap anti-saccade tasks and for either target eccentricity.

A study by Hanisch et al. (2005) however, showed that while children with ADHD tended to make more erroneous saccades than control children, this difference was not significant. The possible difference in findings stems from the use of stimuli; the above researchers often used identical stimuli for both pro-saccade and anti-saccade with differing block-wise instructions (Klein et al., 2003) which may have made the tasks more difficult between groups. This is different to Hanisch et al. (2005) who separated both pro and anti-saccades to avoid this influence. Similarly, this may account for the conflicting accounts of Hanisch et al. (2005) to other studies within the pro-saccade literature (See Pro-saccades, p46).

Karatekin (2006) also examined the effect of task manipulation on anti-saccade tasks to understand what, if any, variables improved ADHD performance. Using the

standard anti-saccade paradigm, they showed ADHD adolescents had significantly longer SRT and reduced saccade accuracy compared to age-matched controls and adult control, although not child controls. Training and practice with the task improved all groups performance, however the ADHD group improved disproportionately whereby, after training, they did not differ from age-matched controls in SRT. Regardless of training however, it was still shown that the ADHD group continued to make more saccade errors and premature saccades compared to adolescent and adult controls. This suggests that at least some component of ADHD oculomotor deficits can be explained by attentional factors and shows the importance of testing ADHD participants across multiple task administrations if possible, to explore the effects of practice. The fact that adolescents with ADHD often differed in these tasks from their aged-matched counterparts but not from younger controls, seems to indicate that developmental processes involved in anti-saccades may be either delayed or deviant compared to ‘typical-for-age’ levels.

Another task manipulation examined whether a valid auditory cue, orientating the observer to the target location prior to its appearance, could aid those with ADHD in anti-saccade motions. While the presence of a cue significantly increased saccade accuracy and decreased SRT for those with ADHD, they still made significantly more errors than both adolescent and adult controls. This shows that, even when those with ADHD knew the location of the target in advance, they continued to make more errors. This seems to therefore indicate that a simple deficit in orientating visual-spatial attention cannot be the sole explanation for the deficit in anti-saccade movements. This is at odds however with the visual-orientation paradigms previously discussed (See 1.3 Visual Attention in ADHD), which showed no difference between ADHD and controls in the benefit from valid cues.

Like those studies of pro-saccades, research has similarly examined whether there are gender and ADHD subtype effects for ADHD in anti-saccade tasks. O’Driscoll et al. (2005) comparing a sample of ADHD-I and ADHD-C adolescents to controls, showed only those with ADHD-C showed an increase in directional errors compared to controls, while the ADHD-I group did not differ from either control or ADHD-C. However, similar to Klein et al. (2003), it was shown that both ADHD groups did not exhibit a significant decrease in errors with age unlike the control group who did. Mahone et al. (2009) however, showed that both ADHD-I and ADHD-C participants

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showed more directional errors than controls and did not differ from each other. They further found that, unlike the pro-saccades, there was no difference between male and females with ADHD.

Express saccades

A third type of saccade that are often linked to SC activity are Express saccades; eye movements with a very short latency (80-100ms) that are often made in response to visual stimuli (Munoz & Wurtz, 1992; Sparks, Rohrer, & Zhang, 2000). These are often assessed at the same time as pro-saccades using either the standard, gap or overlap task variations although gap paradigms have been shown to significantly increase the number of express saccades (Edelman & Keller, 1993; Schiller et al., 1987). Previous research has often considered express saccades to be a release from both fixation and suppress of voluntary saccades and visual attention (Breitmeyer, 1993; Fischer & Weber, 1993).

Although there has been substantially less research on express saccades in ADHD compared to pro and anti-saccades, some studies have investigated the potential group differences. Munoz (2003) compared 114 children and adults with ADHD to aged-matched controls using both overlap and gap pro-saccade tasks. They show unusually that, while those with ADHD made more express saccades than the corresponding controls, this difference was not significant. Feifel et al. (2004) also showed those with ADHD exhibit more express saccades during both pro-saccade and anti-saccade gap paradigms. On the other hand, using a similar paradigm, Klein et al. (2003) showed that ADHD patients tended to make fewer express saccades than controls, but only under the gap condition and not the overlap condition.

Saccade Overview

On the whole, ADHD participants appear to have clear deficits in oculomotor control, as measured through pro-saccade, anti-saccade and express saccade studies. For pro-saccades, the deficit in ADHD remains fairly controversial with some studies showing slower SRT (Goto et al., 2010; Klein et al., 2003; Mahone et al., 2009; Munoz, 2003; Van Der Stigchel et al., 2007), more variable SRT (Munoz, 2003) and fewer

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correct responses (Feifel et al., 2004; Goto et al., 2010) in ADHD participants compared to controls. However, some show no difference between ADHD groups and controls in the same measures; SRT (Feifel et al., 2004; Hanisch et al., 2005; Karatekin & Asarnow, 1998; O'Driscoll et al., 2005; Ross et al., 2000, 1994), SRT variability (Hanisch et al., 2005), correct responses (Karatekin, 2006) and saccade amplitude (Feifel et al., 2004; O'Driscoll et al., 2005). Others have also shown that group difference in pro-saccades depend on both the age and gender of the groups studies (Goto et al., 2010; Mahone et al., 2009). There is no evidence to show that those with ADHD have superior performance in pro-saccades to controls.

For anti-saccade movements (saccades away from a target) however, there appears to be a clearer picture of deficits. Here, the majority of literature show that those with ADHD exhibit longer SRT (Karatekin, 2006), increased SRT variability (Munoz, 2003), more directional errors (Feifel et al., 2004; Goto et al., 2010; Hanisch et al., 2005; Karatekin, 2006; Klein et al., 2003; Mahone et al., 2009; O'Driscoll et al., 2005) and fewer corrected errors (Klein et al., 2003) compared to controls. While others have occasionally found no differences between those with ADHD and controls, these studies are fewer in number, with most showing group difference only under certain conditions depending on participant age (Goto et al., 2010), ADHD presentation type (O'Driscoll et al., 2005), and whether task practice was given (Karatekin, 2006). Similar to pro-saccades, there is no known literature showing an ADHD advantage in anti-saccades to controls.

While there has been limited research into the effect ADHD has upon express saccades, research has shown that deficits, although often differing in direction, are observed with some studies finding an increase in the number of express saccades in those with ADHD (Feifel et al., 2004; Munoz, 2003) while others show an decrease (Klein et al., 2003).

Saccade research shows that both anti-saccade and express saccades are likely the most affected by ADHD with research often consistently exhibiting abnormalities in the reaction speed, number, accuracy and variability of these saccade. As both of these saccadic types have been heavily implicated in SC functioning (Edelman & Keller, 1993; Everling et al., 1999; Munoz & Wurtz, 1992; Schiller et al., 1980; Sparks et al.,

2000), this supports the notion that those with ADHD may have hyperactivity of the SC which subsequently affects the ability to initiate correct and accurate saccades and inhibit inappropriate ones. While there do indeed appear to also be some level of deficit within pro-saccade shifts of attention, the research is largely too conflicted at the time to draw any definitive conclusions.

Psychostimulants and the Superior Colliculus in ADHD

Over the last few decades, ADHD has begun to be increasingly treated and controlled by psychostimulant medication with the two most common treatments being amphetamines and methylphenidate. It therefore reasons that, if the SC is a hyperactive locus within ADHD, then medication used to treat the condition should influence both the measurable activity of the structure as well as its associated behaviours.

Studies examining differences in saccade initiation and suppression, as previously discussed (See Saccades, p45), have too examined the effect of psychostimulant medication on ADHD oculomotor responses. A study by Klein, Fischer, Fischer and Hartnegg (2002) compared two groups of children with ADHD on both pro and anti-saccade tasks under two testing orders (on medication then off medication and vice versa). The counterbalanced nature of the experiment further allowed for the effect of practice to be controlled for, which has previously been shown to effect ADHD anti-saccade abilities (Karatekin, 2006) (See Anti-saccades, p49). They showed that Methylphenidate reduced both pro and anti-saccade correct trial SRT and anti-saccade corrected trials SRT (a response made towards the target before being corrected) while increasing the number of express saccades.

Interestingly however, they also found a significant group by medication interaction for the increase SRT, corrected-SRT and reduced directional errors showing some effect of practice. This effect was only observed in the initially unmedicated ADHD group, where the improvement in oculomotor control may have been heightened by the combination of both practice and medication in the second test session. The practice effects within the initially medicated group however may have been masked by the removal of the psychostimulant resulting in a reduced difference between testing sessions. Similarly O'Driscoll et al. (2005) showed that, when on methylphenidate, both

ADHD-C and ADHD-I presentation groups showed a significant decrease in pro and anti-saccade SRT as well as a reduction in anti-saccade directional errors. The similarity of results for both the ADHD groups is consistent with previous research showing that both presentation types respond in a similar way to methylphenidate (Barkley, DuPaul, & McMurray, 1991; Milich, Balentine, & Lynam, 2006; Stein et al., 2003).

However, Mostofsky, Lasker, Cutting, Denckla and Zee (2001) showed that all children with ADHD, regardless of whether they were taking psychostimulants or not, still showed more directional errors in anti-saccade task compared to controls. Un-medicated children however did show a greater variability in SRT compared to controls while the medicated ADHD group did not differ.

Other fields of research have also undertaken a more direct way of assessing the effects of ADHD-associated pharmacological treatments on the SC through the use of animal studies. Such studies involve non-human animals receiving the associated treatments whereby both the associated behaviours, as discussed above, and direct SC activity can be examined. In a study by Gowan and colleagues, the effect of d-amphetamine on visual responses in superficial layers of the SC was investigated in rats through single-unit recording (Gowan, Coizet, Devonshire, & Overton, 2008). Results showed a dose-dependent decrease in SC responsiveness to visual stimuli. This is further supported by the pharmacological suggestion that norepinephrine and serotonin, which are known mechanisms of amphetamine action, both inhibit the superficial layers of the SC in response to visual stimulation (Kawai & Yamamoto, 1969; Tan, Mooney, & Rhoades, 1999).

Studies have too examined the effect of medication on general distractibility whereby Ågmo, Belzung and Rodriguez (1997) again showed a dose-dependent reduction in distractibility for rats following amphetamine injections. In a similar study on human using an easy and hard stimulus-detection task, it was found that d-amphetamine decreased processing speed for hard tasks and a decreased distractibility time for easy tasks (Halliday, Gregory, Naylor, Callaway, & Yano, 1990).

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1.5 Concluding Remarks

The majority of literature exploring behavioural deficits and neurological differences within Attention Deficit Hyperactivity Disorder (ADHD) has largely, sometimes exclusively, focused on the involvement of high-level executive functioning and frontal-lobe involvement. This has come at the expense of other low-level sensory deficits observed within those with ADHD, which are often overlooked. Indeed, a recent meta-analysis examining structural and functional differences in ADHD suggested that the visual-system and occipital cortex represent ‘fruitful’ areas of investigation in order to gain a more complete understanding of the disorder (Cortese & Castellanos, 2012). Throughout this chapter, we have discussed evidence that provides general support for this notion, implicating a visually associated deficit within ADHD. Such research has demonstrated using multiple attentional paradigms that both children and adults with ADHD typically demonstrate a deficit in visual-attention showing slow, variable reaction times and increased errors compared to controls. Neuroimaging literature has also provided evidence showing changes in both the white and grey matter structure in addition to cortical function of the visual system, including areas of the primary visual cortex (V1), within those with ADHD.

Given such literature, we believe that there are still several lines of research that need to be conducted to further explore the relationship between the visual system and ADHD. Throughout this thesis, our research will examine such relationship specifically relating to ADHD-associated Inattention traits rather than ADHD traits as a whole. This was done under the premise that any individual differences in attention-related neural responses are more likely to be associated with Inattention traits rather than Hyperactivity traits. Furthermore, it remains possible that individuals with predominantly Inattention problems may show the same overall ADHD score on diagnostic-screening tests as those with predominantly Hyperactive problems. In that sense, any Inattention-specific results may be masked by comparing those with low and high overall ADHD scores. Following on from this, our research will also focus on individual differences in Inattention traits within the typically developed population rather than specifically focusing on comparisons between those with clinically diagnosed with ADHD-I and controls. Indeed research has shown that ADHD psychopathology can be viewed dimensionally, with Inattentive and Hyperactive-Impulsive symptoms distributed continuously in the general population (Lubke,

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Hudziak, Derks, van Bijsterveldt, & Boomsma, 2009; Polderman et al., 2007). Evidence at the level of molecular genetics also provides support for the hypothesis that ADHD represents the extreme end of traits present in the general population (Larsson, Anckarsater, Råstam, Chang, & Lichtenstein, 2012; Levy, Hay, McStephen, Wood, & Waldman, 1997; Martin, Hamshere, Stergiakouli, O'Donovan, & Thapar, 2014). The approach of using the general population has been very popular in studies on other developmental disorders such as autism spectrum disorder (ASD) (Dickinson, Jones, & Milne, 2014) and has been recently employed by researchers investigating ADHD (Biehl et al., 2013; Polner, Aichert, Macare, Costa, & Ettinger, 2015). Hence, through our research, we selected adult participants from the typically developed population with a range of ADHD-associated Inattention traits rather than those with clinically diagnosed ADHD. Chapter Two provides an overview of the recruitment process used throughout this thesis and its associated ethical and methodological problems, in addition to exploring the overall distribution of ADHD-associated traits in the typically developed population.

The three empirical chapters covered in this thesis will aim to address some of these issues, examining whether individual differences in ADHD-associated Inattention relate to functional differences within visual-attention or suppression mechanisms in the visual system.

Chapter Three will specifically explore whether increased Inattention traits are related to increased neural responses within the Superior Colliculus (SC); a region often linked to visual attention and distractibility (Ignashchenkova et al., 2003; Katyal et al., 2010; Rizzolatti, Riggio, Dascola, & Umiltá, 1987). Indeed, previous literature has often observed increased SC activity in animal models of ADHD (Clements, Devonshire, Reynolds, & Overton, 2014; Brace et al., 2015), while psychostimulant medication given to treat those with clinical ADHD appears to reduce SC activity (Gowan et al., 2008; Hetzler, Meckel, & Stickle, 2014) and distractibility (Ågmo et al., 1997; Halliday et al., 1990). Given such research, Overton and colleagues proposed that ADHD may relate to hyperactivity of the SC (Overton, 2008; Overton & Clements, 2009; Panagiotidi, Overton, & Stafford, 2016). Here, we therefore predict a positive correlation between Inattention traits and SC activity during visually-attention tasks,

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where those with increased Inattention traits are more likely to show hyperactive neural responses.

Chapter Four aims to examine separate neural responses to central targets and peripheral distractors during visual attention tasks. Previous literature has often demonstrated that those with ADHD experience increased interference from peripheral, task-irrelevant distractors during sustained attention tasks (Bellgrove et al., 2013, 2009; Chan et al., 2009; Forster et al., 2014; Geeraerts et al., 2008; Hanisch et al., 2005; Huang-Pollock et al., 2005). It is therefore useful to be able to separately assess responses to both task-related and task-irrelevant stimuli. Here it is hypothesised that those with High Inattention traits will show increased neural responses towards distractors than those with Low Inattention. Furthermore, given research showing that such distractor interference is more likely to occur during easy tasks, where excess attentional resources are allocated to process the distractors, compared to hard tasks where attentional resources are already taken up by the main task (Lavie, 1995, 2005, 2010; Lavie & Tsal, 1994), we will also explore how such differences in distractor and target processing effects of attentional-load. We predict that increases in attentional load will increase responses towards task-related targets while reducing responses towards the distractors.

Our final study in Chapter Five aimed to investigate whether those with low and high levels of ADHD-associated Inattention exhibit differences in attentional modulation within regions of the Lateral geniculate nucleus (LGN) and Primary Visual cortex (V1), specifically related to suppression responses. Research has often shown that spatial attention can modulate neural responses towards visual stimuli; increasing responses towards attended locations (Gandhi, Heeger, & Boynton, 1999; Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999; Luck, Chelazzi, & Hillyard, 1997; Martínez et al., 1999; McAdams & Maunsell, 1999; Moran & Desimone, 1985; Motter, 1993; O'Connor, Fukui, Pinsk, & Kastner, 2002; Reynolds, Chelazzi, & Desimone, 1999; Roelfsema, Lamme, & Spekreijse, 1998; Somers, Dale, Seiffert, & Tootell, 1999; Thiele, Pooresmaeili, Delicato, Herrero, & Roelfsema, 2009; Tootell, Hadjikhani, et al., 1998) while decreasing responses to unattended locations (Gouws et al., 2014; Shmuel et al., 2002; Slotnick et al., 2003; Smith et al., 2000, 2004; Tootell, Hadjikhani, et al., 1998; Tootell, Mendola, et al., 1998; Vanduffel, 2000). From this, we hypothesis that

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Inattention problems may related to an absent or weakened suppression-mechanism where irrelevant stimuli and locations are not suppressed and continue to be processed.

Furthermore, each chapter will also aim to examine how such relationship between Inattention traits and neural activity may change depending on the visual field of stimulus presentation. Following on from limited amount of behavioural research previously mentioned, we predict that differences between those with Low and High levels of Inattention will be strongest when visual stimuli are presented to the right visual field.

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Throughout the course of this research; we aimed to explore the relationship between individual differences in Inattention traits within the typically developed adult population and neural signals within the visual system. In order to achieve this, we pre-screened potential participants using both ASRS and CAARS to measure Inattention, Hyperactivity and Distractibility behaviours before inviting some back to complete the main neuroimaging experiments. This chapter aims to provide an overview of this pre-screening process and participant recruitment in addition to discussing some of the ethical issues associated with studying and measuring ADHD-associated traits. Finally, we will also examine our pre-screened participant pool in more detail to understand the distribution and relationship between ADHD-associated traits in the typically developed adult population.

2.1 Participant Recruitment

During each of our three neuroimaging studies, participants were recruited from a larger sample of pre-screened individuals, who were recruited through online campus adverts on the Department of Psychology website. During this initial recruitment, participants completed a computerized version of either the ASRS or CAARS questionnaires, each measuring Inattention, Hyperactivity and Distractibility traits associated with ADHD. Such diagnostic questionnaires subsequently allowed us to pre-screen individuals in order to ensure that only those who met required Inattention trait levels were invited back to the main neuroimaging phase of each experiment. Within Chapter Three, the ASRS was used to measure ADHD-associated behaviours in 313 individuals where, due to the correlation design of the study, we needed to ensure participants were recruited across the whole range of Inattention scores from individuals with no problems to those with frequent problems. Chapters Four and Five on the other hand collected similar data from 382 individuals using the CAARS, employing a group design where those with very few Inattention problems were compared to those with many problems. Here, participants were only recruited if they displayed an Inattention trait score one standard deviation above or below the population mean (as defined in Conners et al., 2002) - these groups were known as 'Low' and 'High' Inattention

groups. Within all three studies, participants were also only recruited if they were right-handed, had normal or corrected-to-normal vision, had no history of any clinical diagnosis, including ADHD, and were suitable for either EEG or MRI scans. Further details regarding the demographics of these three participant samples can be found within the methods section for each individual chapter.

As noted above, ADHD-associated traits were initially measured using the ASRS questionnaire, as used within Chapter Three, however the decision was made to swap to the CAARS for the remaining studies. This decision was taken due to a number of reasons. Firstly, CAARS questionnaire is able to provide a separate measure for both Hyperactivity and Impulsivity traits while the ASRS measures them on a combined scale. Whilst we are primarily focused on Inattention-traits within this thesis, being able to separate both traits out into separate dimensions allows for a clearer understanding of participants behaviour. Secondly, within the six trait-specific dimensions of the CAARS, two were based on items specifically relating to the DSM-IV diagnosis for ADHD (Table 2.1; Dimensions E and F) which enables us to more closely measure Inattention traits specifically related to clinical ADHD criteria, rather than Inattention traits in general. Finally, the CAARS also enables participant's responses to be assessed for inconsistency whereby large differences in responses to similar questions may indicate a less reliable assessment. As a result, such participants could be detected in the pre-screening and only those with reliable, consistent assessments were invited back to complete the main experiments. Overall, using the CAARS therefore allowed us to more accurately assess ADHD-associated traits and to ensure only participants with reliable responses were recruited.

2.2 Ethics of measuring ADHD

Whilst there are always ethical issues to consider when undertaking any type of research, through the course of this thesis we can across a few ethical issues regarding the assessment of ADHD trait which are worthy of note. Firstly, we had a few participants contact us following the completion of the ASRS and CAARS questionnaire to request their scores and whether or not they had a diagnosis of ADHD. Such requests posed ethical considerations as, whilst some individuals did show high levels of Inattention and Hyperactivity indicative of a potential ADHD diagnosis, such scores could not be conveyed to participants. This is particularly important considering

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that, while such tests are used by diagnosticians to aid ADHD diagnosis, they are only a tool and cannot confirm a diagnosis alone. Furthermore, neither myself nor anyone involved in this research were qualified to make such a diagnosis. As such, revealing any ADHD assessment score to participants may lead to misconceptions about the test and potentially lead some individuals to believe they have been given a clinical diagnosis. It was therefore made clear to participants, both verbally and in the participants information sheets for both pre-screening and main neuroimaging experiments, that no questionnaire scores could be revealed. If any participants inquired further as to their score or anything regarding an ADHD diagnosis, they were encouraged to contact their medical provider if they were concerned about ADHD or any aspect of their health.

Another ethical issue we faced also drove our decision to focus this thesis on individuals within the typically developed population rather than those with a clinical diagnosis of ADHD. During pre-screening, we did obtain a small number of individuals who were clinically diagnosed with ADHD of which, all were receiving medical treatment for the condition. Such participants however pose a number of ethical and methodological issues if invited back to complete the main neuroimaging experiments. Firstly, as discussed in Chapter One, medication used to treat those with ADHD has been shown to have a significant impact not only on the behavioural traits observed in those with ADHD (Karatekin, 2006 ; Mostofsky, Lasker, Cutting, Denckla and Zee 2001), but also on their neural responses, which become more similar to those recorded in control participants compared to individuals with un-medicated ADHD (Rubia, Halari et al. 2009). Given such research, the inclusion of participants receiving ADHD-related medication within our sample may confound any findings, where differences in neural responses may be caused by effects of the medication rather than the individual differences in Inattention traits themselves. As a result, we decided that participants identified as having ADHD and receiving medication would not be eligible for the main neuroimaging experiments. However, this also brought about additional ethical issues whereby such individuals may feel inclined to not declare their medication status or stop their medication in order to become eligible for the study. It was therefore decided to focus this research on examining Inattention traits in the typically developed adult population rather than those with clinically diagnosed ADHD.

2.3 Measuring ADHD traits using the CAARS

Whilst undertaking this thesis, ADHD-associated traits were measured from 313 individuals using the ASRS questionnaire and 382 individuals using the CAARS questionnaire during participant recruitment. Such large-scale questionnaire measures however also allow us to examine the typically developed adult population in more detail by exploring the distribution and relationship between ADHD-associated traits. Considering the more in-depth assessment undertaken using the CAARS and the larger sample collected, this analysis will focus on the population measured by this questionnaire.

The CAARS questionnaire as previously discussed (See 1.2.2 Diagnostic Tools, p16), uses 66-items to assess ADHD characteristics where individuals self-report their level of agreement with how accurate each statement described them. Each of the items is related to a specific trait often associated with ADHD; Inattention, Hyperactivity, Impulsivity and problems with self-concept. Once completed, each individual will have eight separate measures of ADHD, including six trait-specific scores and two overall ADHD scores (Table 2.1). Some questions relate to multiple dimensions. From these dimensions, there are similarities between scales in that two dimensions measure Inattention, two measure Hyperactivity and two measure Impulsiveness. In these cases, one measures a more general view of associated traits while the other measures DSM-specified traits.

Critically, the raw ADHD score are converted into T-scores in order to control for differences in both Age and Gender where males and younger adults typically show increased inattention and hyperactivity traits compared to females and older adults. This means that, to show the same T-score, males need to demonstrate an increased number of traits than females. Correcting for such differences can therefore allow more accurate comparison across age and gender groups. From our sample of 382 individuals, 23.8% were male and users were aged between 18 to 32 years (average 20.04 years). Unusually for our sample however, we see very few differences between the distribution of raw scores between males and females. Figure 2.1 and Figure 2.2 show the distribution of raw scores for each of the eight CAARS dimensions separately for both males and female participants. For the three primary ADHD traits; Inattention (Figure 2.1A and Figure 2.2E), Hyperactivity (Figure 2.1B and Figure 2.2F) and

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Impulsivity (Figure 2.1C and Figure 2.2E) we can see no difference between either the average raw score or the distribution of scores between males and females.

Table 2.1: Connors Adult ADHD Self-report questionnaire (CAARS) questionnaire dimensions and relating statements.

| | ADHD Dimension | Statement Examples |
|----------|--|---|
| A | Inattention/Memory Problems | <ul style="list-style-type: none"> - I depend on others to keep my life in order and attend to details. - I misjudge how long it takes to do something or go somewhere. |
| B | Hyperactivity/ Restlessness | <ul style="list-style-type: none"> - It takes a great deal of effort for me to sit still - I tend to squirm and fidget. |
| C | Impulsivity / Emotional Lability | <ul style="list-style-type: none"> - I blurt things out. - I say things without thinking |
| D | Problems with Self-concept | <ul style="list-style-type: none"> - I get down on myself. - I avoid new challenges because I lack faith in my abilities. |
| E | DSM-IV Inattention Symptoms | <ul style="list-style-type: none"> - I lose things necessary for tasks or activities. - I have trouble keeping my attention focused when working. |
| F | DSM-IV Hyperactive-Impulsive Symptoms | <ul style="list-style-type: none"> - I talk too much. - I leave my seat when I am not supposed to. |
| G | DSM-IV ADHD Symptoms | <ul style="list-style-type: none"> - <i>Sum of both E and F dimensions.</i> |
| H | ADHD Index | <ul style="list-style-type: none"> - I am an underachiever - I can't get things done unless there's an absolute deadline. |

A similar pattern was also observed in the two general ADHD dimensions (Figure 2.2G and Figure 2.2H). Previous research however has suggested that gender differences in ADHD traits within university and college students may not be a consistent finding with some observing similar levels of self-reported inattention and hyperactivity traits between males and females (DuPaul et al., 2001; Weyandt & DuPaul, 2006; Weyandt, Linterman, & Rice, 1995) similar to our own findings. Whilst some continue to find differences between males and females (Lee, Oakland, Jackson, & Glutting, 2008), such research indicates that gender differences in ADHD traits may not be consistently seen and may depend on additional factors such as age and education.

Once raw scores are converted into age and gender-corrected T-scores, the CAARS can then be used to assess how each individual varies on the eight dimensions relative to other adults. Here a T-score of 50 indicates the population average while every 10-unit change in T-scores indicates a 1 standard deviation change. For example, a participant with a raw score 2.6 standard deviations above the population mean would be assigned a T-score of 76. The accompanying CAARS manual does not specify an exact T-score threshold where an ADHD diagnosis is likely, however it recommends that scores over 65 may indicate significant clinical problems while T-scores over 70 on the *ADHD Index* are likely to meet the diagnostic criteria for ADHD (Harrison, Edwards, & Parker, 2007). Figure 2.3 shows the distribution of T-scores for all participants across the eight CAARS dimensions where vertical lines represent the sample mean (red) and population mean (black). Such results were only shown for participants with an Inconsistency Score below 8 (See below for more details). Here we can see that our sample appears to show a similar normal distribution of T-scores across the majority of dimensions, centring around the population mean of 50. This is particularly true for the three dimensions measuring Hyperactivity and Impulsivity which show means of 48.90 (*B: Hyperactivity/ Restlessness*), 50.48 (*C: Impulsivity/ Emotional Lability*) and 49.37 (*F: DSM-IV Hyperactive-Impulsive Symptoms*). Our sample however demonstrated differences within Inattention traits where both *A: Inattention/Memory Problems* and *E: DSM-IV Inattention Symptoms* dimensions show increased T-scores compared to the population mean (Figure 2.3A and E). As a result of *G: DSM-IV ADHD Symptoms* being the sum of both E and F dimensions, such increased T-score were also seen in this dimension (Figure 2.3G). Figure 2.3D similarly

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shows slight increases in *D: Problems with Self-concept*. Indeed, previous research has shown that university and college students often demonstrate increased inattention problems (Harrison, 2004; Weyandt et al., 1995), thought to be brought about by changes in interpersonal relationships and academic pressures as well as learning to live independently (Harrison, 2004). Given such stresses, it is reasonable to assume that university students may show increased problems with self-concept as observed here. However, an alternative possibility is that, due to the voluntary sample used for participants recruitment, our sample may have been slightly bias to include those who have an interest in attention or those who recognize they may experience inattention problems.

Using the CAARS, we were also able to assess the consistency of participant responses and find those who were responding in an invalid manner. The Inconsistency Score, outlined in 1.2.2 Diagnostic Tools p16, involves examining responses to eight pairs of questions assessing similar behaviours, where large differences in responses are thought to indicate conflicting responses. Throughout the course of this thesis, participants were only recruited if they demonstrated an Inconsistency score less than 8, where a score of 8 or more may indicate a potentially inconsistent responder (Conners et al., 2002). Within our questionnaire sample, 14.92% of users were deemed to show responses that could be considered inconsistent. No difference in Inconsistency Score was found between males and females (*independent t test*: $t(380)=0.55$, $p=.580$). However, we found significant positive correlations between Inconsistency Scores and both the raw and T-scores for each of the eight dimensions (all $p<.001$, ranging from $r=.19$ for the *B :Hyperactivity/Restlessness* dimension to $r=.36$ for the *H: ADHD Index* dimension, *Spearman's rank correlations*) where greater inconsistency was observed in those with increased ADHD traits. Figure 2.4 shows the distribution of ADHD Index T-scores for those showing Low (less than 8) and High Inconsistency scores (8 or more) alongside the average score from the sample (blue line) and the proposed population mean following age and gender correction. Here we can see that the sample mean within the High Inconsistency group is greater than the population mean while there is little difference within the Low Inconsistency group. However, such results are unsurprising considering the method used to assess inconsistency, where agreeing with more statements (scored as 2 or 3's) is more likely to result in response differences in the eight statement pairs compared to those mostly responding as disagree (scored as 0).

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Therefore, such results do not necessarily indicate that those with greater ADHD traits are more inconsistent in their responses. Nevertheless, such relationship between Inconsistency Score and ADHD traits may have methodological implications where proportionally, more participants may need to be screened in order to recruit adults with higher numbers of ADHD-associated traits compared to those with fewer traits.

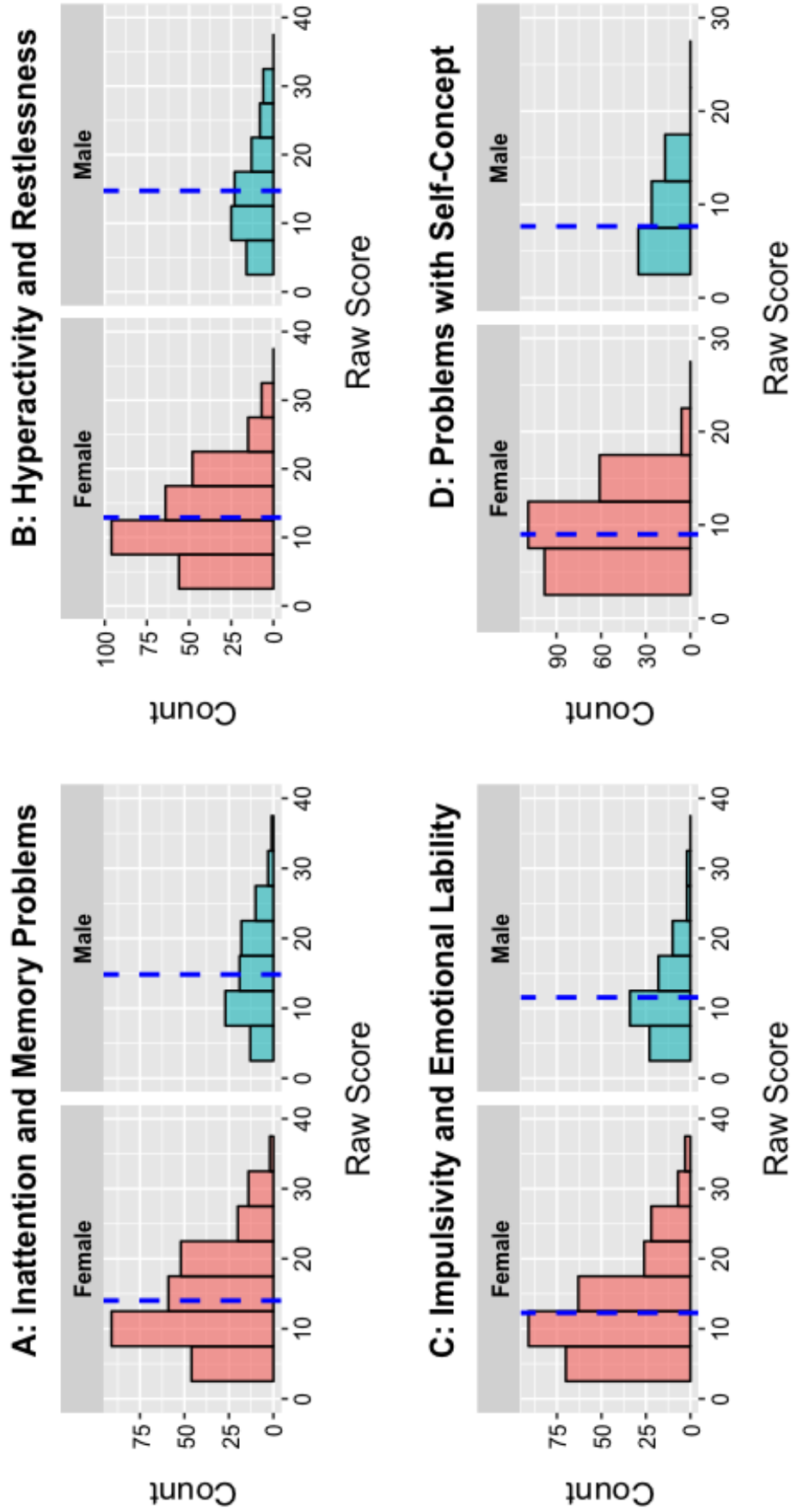


Figure 2.1: Distribution of Raw CAARS Scores (Dimensions A – D). Plots show distribution of Raw scores (uncorrected for age and gender) for both Male and Female participants for four of the main dimensions of the CAARS questionnaire. Blue dashed lines represent the mean of each gender groups.

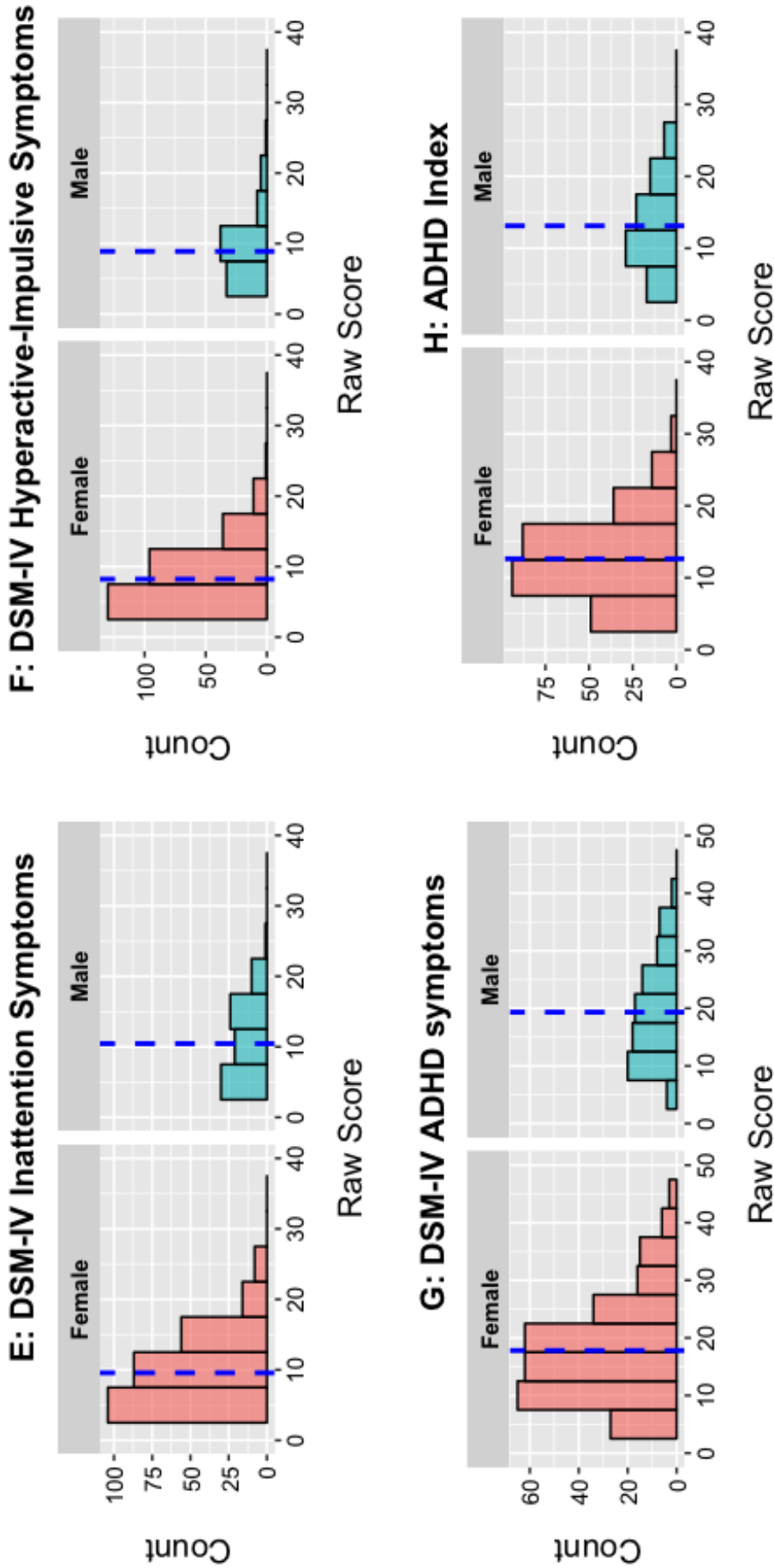


Figure 2.2: Distribution of Raw CAARS Scores (Dimensions E – H). Plots show distribution of Raw scores (uncorrected for age and gender) for both Male and Female participants for four remaining dimensions of the CAARS questionnaire. Blue dashed lines represent the mean of each gender groups.

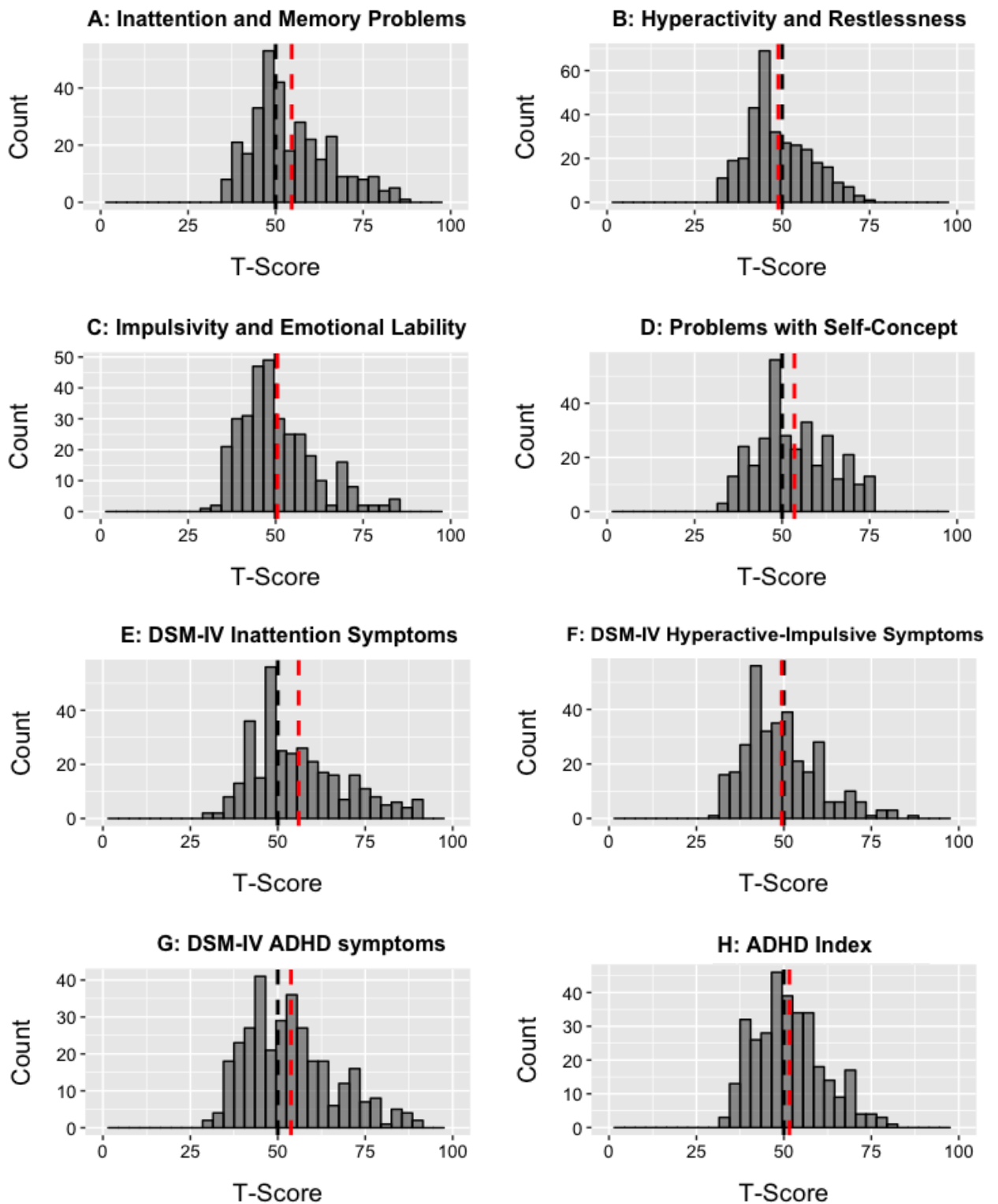


Figure 2.3 : Questionnaire sample distribution of CAARS T-scores. Histogram of T-scores for the eight CAARS dimensions, assessing Inattention, Hyperactivity, Impulsiveness and Self-concept. Black dotted line indicates the population mean (50) while the red line indicates our sample mean. All participants shown had an Inconsistency Score below 8.

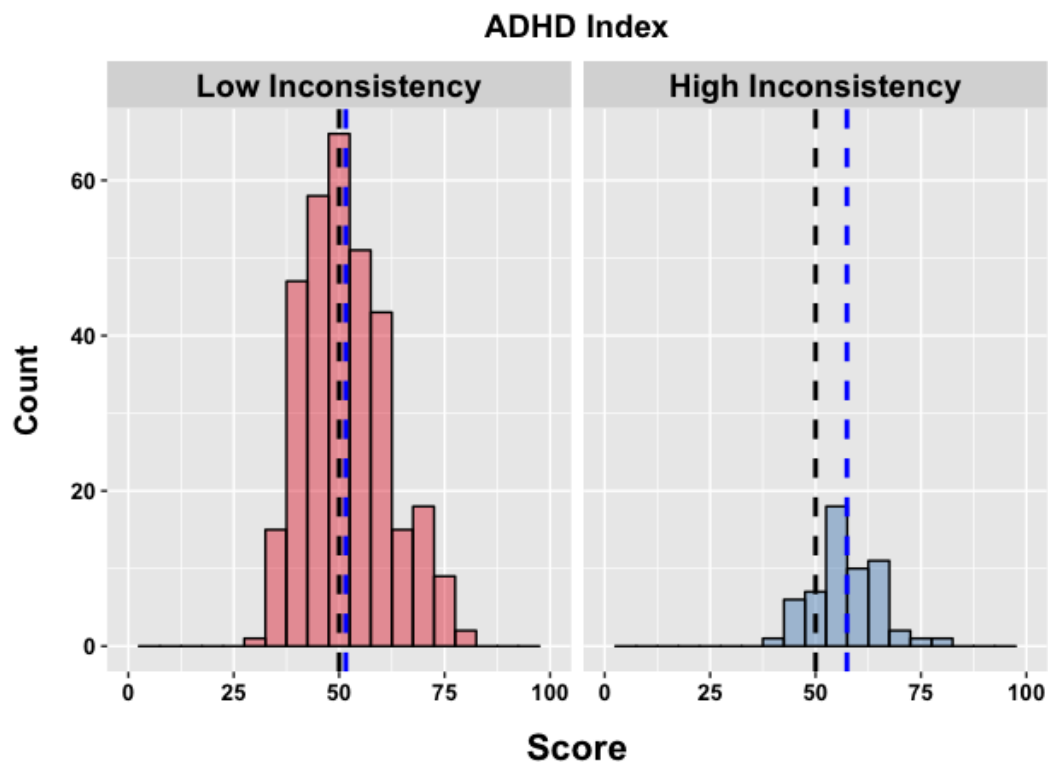


Figure 2.4 : CAARS ADHD Index T-scores for Low and High Inconsistency ratings. Distribution of ADHD Index T-scores, corrected for age and gender, for those showing low level (Inconsistency score below 8) and high levels (Inconsistency score of 8 and above) of inconsistency. Black dashed line indicates population mean (T-score of 50) as defined by the CAARS (Conners et. al 2002)1. Blue dashed line indicates sample mean.

Finally, we examined the relationship between the six trait-specific dimensions measuring Inattention, Hyperactivity, Impulsiveness and Self-concept. Figure 2.5 show a scatter matrix to visualize the relationship between these dimensions along with the accompanying correlations. Spearman’s Rank correlations, used due to the high number of participants showing the same trait scores, revealed significant correlations between all six dimensions whereby participants who demonstrate high T-score on one dimension are likely to also show high scores on the other five dimensions. Interestingly, such correlations appear to occur across dimensions measuring different traits. Whilst it is clear that there are individuals who can show clinically significant problems in one area of ADHD and not others (characterized within the ADHD-I and ADHD-H subtypes), such correlations suggesting that ADHD-associated traits tend to co-occur. Indeed, previous literature has often demonstrated that such traits tend to co-occur (Conners et al., 1999; Conners, Sitarenios, Parker, & Epstein, 1998; McGee, Williams, & Silva, 1985) and even share overlapping genetic markers (Greven, Rijdsdijk, & Plomin, 2011; McLoughlin, Ronald, Kuntsi, Asherson, & Plomin, 2007). This again

may have implications for researching ADHD whereby it becomes difficult to isolate how each behavioral characteristic contributes to task performance or neural differences. Throughout the course of this thesis, we have based our participant selection on ADHD questionnaire scores measuring Inattention-specific traits. However, as suggested by Figure 2.5, such participants are also likely to vary on Hyperactivity, Impulsivity and Self-concept.

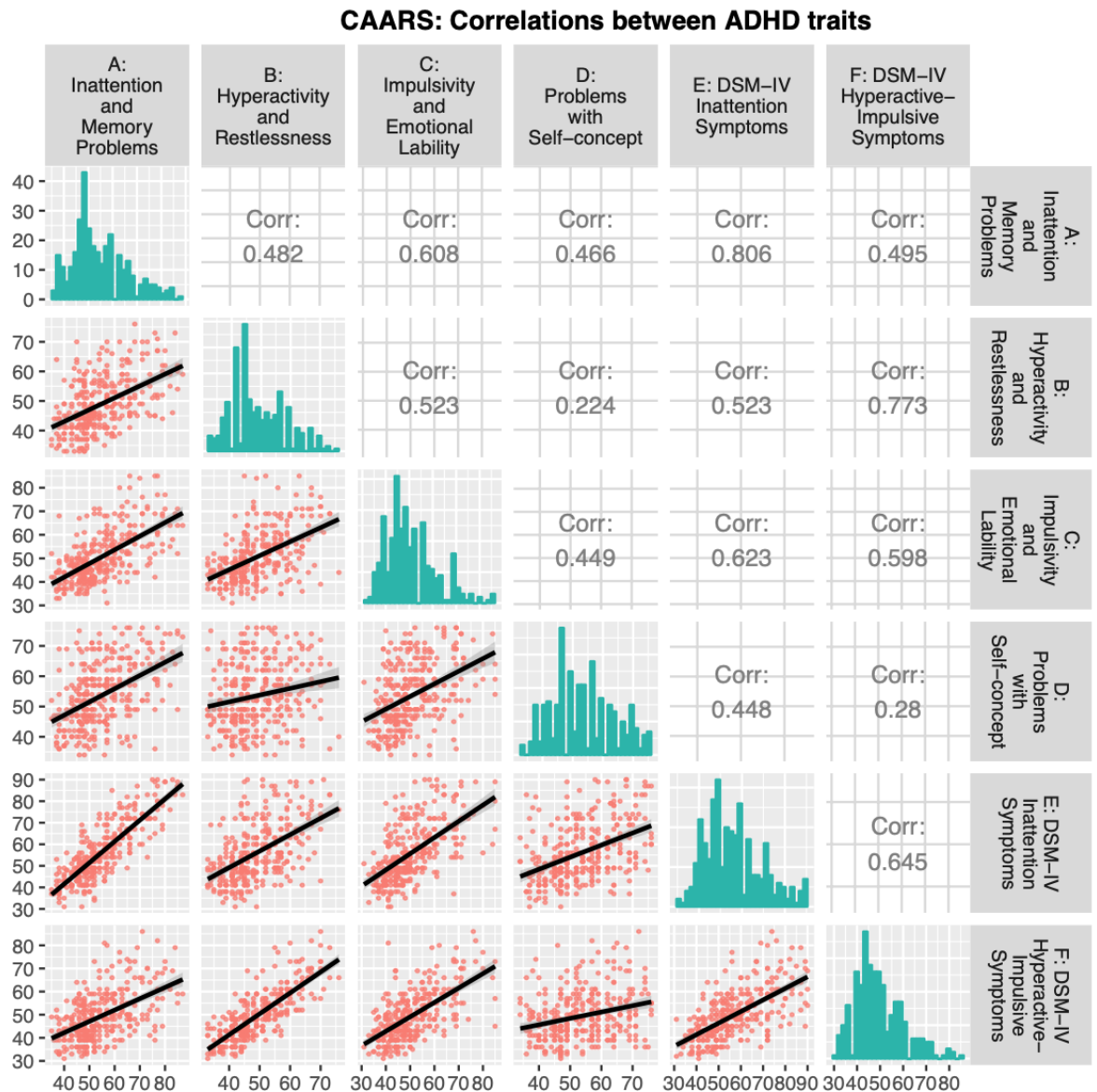


Figure 2.5 : Correlations between CAARS ADHD traits. Lower panel: Scatterplots show the relationship between T-scores from each of the six trait-specific CAARS dimensions measuring Inattention, Hyperactivity, Impulsivity and Self-concept. Diagonal panel: Black lines on the scatter plots show a linear regression between variables. Blue histograms show the distribution of each dimension. Upper panel: Spearman's correlations between each dimension variable shown as r-values; all were significant to $p < .001$ level. All participants included showed Inconsistency Scores below 8 demonstrating valid responses.

Chapter Two: Assessing ADHD in the typical population

Overall, we have shown that our sample of university students follows a similar pattern of ADHD-associated traits as those measured by Conners et al. (2002) using the CAARS questionnaire, whereby behavioural scores for each of the eight dimensions show a typically normal distribution and centre around the population mean. One exception to this was seen on dimensions measuring Inattention traits (*A: Inattention/Memory Problems* and *E: DSM-IV Inattention Symptoms*), where our sample showed a higher number of traits than the population average suggesting university students may experience increased inattention traits compared to their age and gender-matched peers. However, this may result from a bias in our sample, where those who experience inattention may be more likely to volunteer for our study. Correlations also revealed significant positive relationships between each of the trait-specific dimensions where those showing increased traits in one area of ADHD tend to demonstrate increased traits in the other area. This can create problems for research into ADHD and its associated traits whereby exploring the separate effects of Inattention, Hyperactivity and Impulsivity becomes challenging. Finally, we showed a significant relationship between measures of inconsistency and ADHD-traits where higher inconsistency scores are more likely to be seen in those with higher ADHD scores. Whilst likely to be due to the scoring structure of the inconsistency measure rather than a true difference in participants ability to report reliably, this brings about methodological challenges where increased sampling is likely needed to recruit participants with a high number of ADHD-associated traits.

Chapter Three: Evidence for hyperactivity in the superior colliculus in ADHD

3.1 Abstract

The superior colliculus (SC) is a sub-cortical midbrain structure involved in attentional shifts. As attention is often atypical within ADHD, it is possible SC functionality in ADHD is also atypical. Preclinical and experimental work in humans suggests that the SC is hyper-responsive to sensory stimuli in ADHD. This experiment aimed to test this possibility directly using functional magnetic resonance imaging (fMRI). A non-clinical group of 17 adults, ranged along the continuum of ADHD inattention-traits (measured using the Adult ADHD Self-Report Scale, ASRS), were shown radial motion and static dot stimuli presented unilaterally in the left or right hemifield, while they performed a central rapid colour-counting task. Antisaccade performance was also assessed in same subjects, who were found to exhibit error rates that correlated with their ADHD inattention scores, indicative of a functional collicular deficit. BOLD responses in the left and right SC to motion versus static stimuli presented in the right hemifield, showed significant positive correlations with ADHD inattention-traits, with those exhibiting higher levels of inattention-traits showing larger BOLD responses to motion versus static stimuli. However, when the same stimuli were presented in the left hemifield, there was no significant correlation between left or right SC responses to motion versus static stimuli and ADHD inattention-traits. The results provide direct support for the hypothesis that hyperactivity within the SC is related to ADHD-associated Inattention traits, and by extension SC dysfunction may underlie some ADHD distractibility. The fact that the result was confined to the right hemifield may reflect the hemifield differences in spatial attention previously observed within ADHD.

3.2 Introduction

Attention-Deficit Hyperactivity Disorder (ADHD) is the most common neurodevelopmental disorder, characterised by attentional difficulties as well as hyperactive and impulsive tendencies. Current estimates propose the prevalence in childhood ranges from 0.85 to 17.8% depending on country of study (Ford et al., 2003; Froehlich et al., 2007; Huss et al., 2009; Polanczyk et al., 2014; Seixas, Weiss, & Müller, 2012; Skounti et al., 2006) while adulthood prevalence is lower at 0.5 to 4.4% (Faraone, 2005; Fayyad et al., 2007; Ford et al., 2003; Kessler, 2006). Distractibility is one of the primary core symptoms within ADHD, specifically within ADHD-I and ADHD-C presentations (American Psychiatric Association., 2014), with patients often showing problems with attentional shifting (see review: Alvarez & Freides, 2004), saccadic and head movements (Feifel et al., 2004; Karatekin, 2006; Munoz, 2003) and sustained attention (see review: Wright et al., 2014).

The superior colliculus (SC), a sub-cortical mid-brain structure, is one brain region that is often associated with such attention and distractibility traits. The SC is primarily part of the visual system, containing a retinotopic mapping of the contralateral visual field (Katyal et al., 2010; Schneider & Kastner, 2005). Research has shown a link between collicular activity and both head and eye (saccadic) orientating movements (Everling et al., 1999; Grantyn, Moschovakis, & Kitama, 2004; Sparks, 1999), particularly when directed towards peripheral stimuli (Goldberg & Wurtz, 1972), as well as covert orientation of attention (Ignashchenkova et al., 2003; Katyal et al., 2010; Rizzolatti et al., 1987). Previously, lesioning of the SC has been shown to result in changes in distractibility across a variety of species (Albano et al., 1982; Goodale et al., 1978; Milner et al., 1978; Sprague, 1966). Gaymard et al. (2003) too showed a similar effect in humans, whereby disconnection of the SC from the control of the prefrontal cortex resulted in increased distractibility.

Given the links between the SC and distractibility, Overton and colleagues have proposed that the distractibility observed within ADHD could be attributed to dysfunction, specifically sensory hyper-responsiveness, of the SC (Overton, 2008; Overton & Clements, 2009). This is supported by indirect evidence showing that those with ADHD often find it particularly difficult to inhibit saccadic movements (Klein et al., 2003; O'Driscoll et al., 2005). Three specific saccade types, all associated with SC

activity, have been shown to be abnormal within ADHD, with slower and more errors seen in anti-saccades tasks (when saccades are made in the opposite direction to a stimulus) and more microsaccades (involuntary, small jerk-like saccades that are observed while fixating) (Fried et al., 2014; Panagiotidi, Overton, & Stafford, 2017). Additionally, typically developed adults with high levels of ADHD-associated traits have abnormalities in multisensory integration (Panagiotidi et al., 2016, 2017) and show significant problems with covert attention (Alvarez & Freides, 2004; Nigg et al., 1997; Pearson, Yaffee, Loveland, & Norton, 1995; Swanson et al., 1991; Wood et al., 1999), both of which are linked with SC function.

More recent studies have also found more direct evidence of a link between the SC and ADHD. Collicular visual responsiveness has been shown to be enhanced in two animal models of ADHD (Brace et al., 2015; Clements, Devonshire, Reynolds, & Overton, 2014). Furthermore, d-amphetamine and methylphenidate, both effective psychostimulant treatments in ADHD, reduce SC visual responsiveness (Gowan et al., 2008; Hetzler et al., 2014). Both drugs have been shown to result in decreases anti-saccade errors rates and latencies (Allman et al., 2010; O'Driscoll et al., 2005) and to reduce distractibility in rats (Ågmo et al., 1997) as well as humans (Halliday et al., 1990).

However, in spite of an expanding base of preclinical and indirect evidence from humans, abnormalities in the sensory processing properties of the human SC in the context of ADHD have yet to be directly investigated. The present study aims to close this gap in our knowledge by examining visual evoked responses in the SC, measured using functional magnetic resonance imaging (fMRI), in relation to ADHD Inattention-behaviours whilst performing a visual sustained-attention task. Critically, this will be achieved by examining typically developed adults who vary in Inattention traits. We also assessed anti-saccadic performance in the same subjects. Based on such previous work by Overton and colleagues (Overton, 2008; Overton & Clements, 2009; Panagiotidi et al., 2016), we hypothesise that those with increased Inattention traits are likely to exhibit increased fMRI activity within the SC compared with those with fewer traits. Furthermore, we predict that those with increased Inattention traits will also experience increased antisaccade errors and slower reaction times.

3.3 Methodology

3.3.1 Participants

Participants were recruited through online university campus advertisement, which directed participants to initially complete a computerised version of the World Health Organization Adult ADHD Self-Report Scale questionnaire (ASRS: Kessler et al., 1999) in order to assess ADHD-associated traits. This formed a participant pool from which some participants were further contacted to complete the main fMRI experiment (See Chapter 2 for more detail). This was done in order to ensure that we obtained a final participant sample that varied along the whole of the Inattention continuum, which may not have been achieved through an opportunity sample. The ASRS consists of an 18-item scale, whereby participants rate the frequency of ADHD associated symptoms e.g. ‘How often do you feel restless or fidgety?’ (0 = never, 1 = rarely, 2 = sometimes, 3 = often, 4 = very often). These scores could then be summed to obtain a separate measure of both Inattention and Hyperactivity traits in addition to a global ADHD measure. Due to the nature of the SC and its association with attentional components, we specifically focused on the Inattention sub-scale of the ASRS as the trait most likely to be associated with SC functionality.

From this participant pool, twenty-one participants were invited back to complete the main fMRI neuroimaging session. These participants were selected in order to ensure that our total fMRI sample exhibited a range of scores across the Inattention dimension, in addition to being declared safe for fMRI scanning, having normal or corrected-to-normal vision and being right-handed. Participants were not selected if they reported having a previous diagnosis of any clinical disorder, including ASD and dyslexia that are frequently co-morbid with ADHD (Antshel, Zhang-James, & Faraone, 2013; Antshel, Zhang-James, Wagner, Ledesma, & Faraone, 2016; Banaschewski, Poustka, & Holtmann, 2011; Reiersen & Todd, 2008; Sokolova et al., 2017). Such exclusion also included those with clinically diagnosed ADHD whereby, the present study aims to address how functional differences are related to Inattention, specifically within the non-clinical population. Hence, in the present study, we selected healthy adult participants with a range of ADHD-associated Inattention traits, as measured by the ASRS (Kessler et al., 1999), rather than those with clinically diagnosed ADHD.

During the fMRI scanning sessions, four participants withdrew from the study and the full data sets were not collected, hence their data was excluded from the study. The remaining 17 participants (7 females and 10 males; aged between 18 and 25 years with an average age of 20) had scores which ranged from 8 to 27 on the ASRS Inattention-subscale (out of a maximum of 36). Due to the established relationship between Inattention and Hyperactivity (See Chapter 2, p61), we also saw a range of Hyperactivity scores (from 7 to 24) which was shown to significantly correlate with Inattention scores (*Pearson's correlation, $r=.079$, $p<.001$, one-tailed*). Here those with greater Hyperactivity scores were more likely to be observed in those with higher Inattention scores.

All participants received payment of £10 for participating in the fMRI experiment, regardless of whether they withdrew. Critically, participants were never informed of their ASRS scores and were encouraged to seek medical advice if ADHD was something they were concerned about. Participants gave written informed consent to participate in the study, which was approved by York Neuroimaging Centre Ethics Committee and adhered to the Declaration of Helsinki.

3.3.2 Saccade tasks

Although deficits in antisaccade performance have been widely reported in children and adults with a clinical diagnosis of ADHD; no studies, with the exception of Lee et al. (2001), have examined the connection between ADHD-associated traits and antisaccades in a non-clinical adult population. As a consequence, to assess whether our subjects exhibited a deficit in this collicular-dependent saccadic type that matched their level of Inattention problems (indicative of a functional collicular deficit), participants performed a single block anti-saccade task whilst in the MRI scanner (no image acquisition was undertaken at this stage). Stimuli were projected onto a screen at the end of the scanner bore via a projector. Participants viewed the screen while lying in the bore of the scanner via an angled mirror positioned approximately 5 cm from their eyes, which created a total viewing distance of 57cm. The screen refresh rate was 120 Hz with a resolution of 1920 x 1080 pixels. The horizontal and vertical extent of the screen was 40cm and 23cm, respectively. This was the same for the following functional runs discussed below.

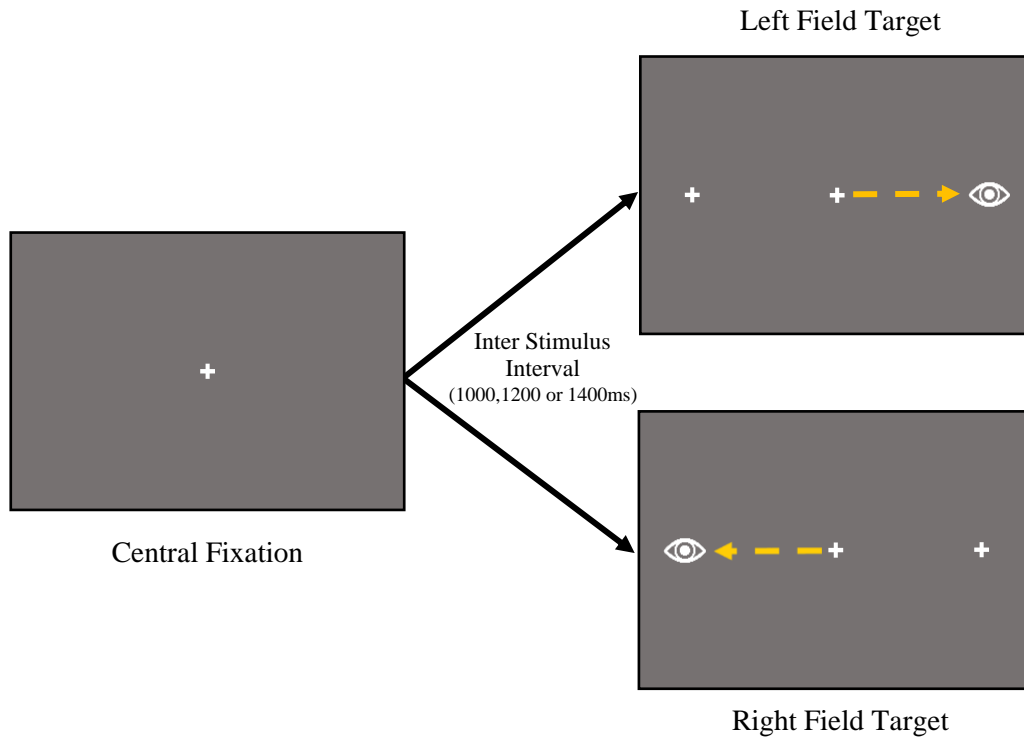


Figure 3.1: Anti-saccade task stimulus. Participants fixated centrally at the white cross. After a variable length of time (1,000, 1,200 or 1,400 ms), a second cross appeared in the left or right visual field. Participants responded by making a saccade (Yellow arrow) towards the mirror position in the opposite visual field from the target.

A white fixation cross (0.2° radius) was shown centrally and after a variable amount of time (1,000, 1,200 or 1,400 ms), an additional white cross target (0.2° radius) appeared at 9.7° either left or right of the central cross on the horizontal midline (Figure 3.1). The inter stimulus interval between the central fixation and peripheral target appearing was randomly varied between the three set durations to ensure participants did not make anticipatory saccades towards the target. All stimuli remained on the screen for 2000 ms before a blank period of 1000 ms. The whole block lasted 4.5 minutes with 33 left visual field and 33 right visual field target trials which were randomised at the beginning of the block. Participants were instructed to initially look at the central cross and, when the target appeared, to look away from the target and towards its mirror position in the opposite hemifield. An example trial was shown to participants before the experiment to ensure full understanding. The stimuli were generated and presented using Psychtoolbox 3.0 (www.psychtoolbox.com) in Matlab v7.14 (MathWorks, Natick, MA).

Whilst performing the task, eye movements were recorded monocularly from the participant's right eye using a custom-written software. This was calibrated before the task to track pupil glint in relation to their gaze direction and the X and Y coordinates, in relation to the central fixation cross, were recorded at a rate of 30 Hz. These were later analysed offline on a trial-by-trial basis where the number of overall errors and reaction time for correct responses were produced for each of the 66 individual trials.

3.3.3 Functional imaging: Stimuli and Task

To investigate the differences in SC activity, both motion (flow from moving dots) and static (matched stationary dots) stimuli were presented unilaterally to both visual fields. Work by Schneider and Kastner (2005) showed radial motion stimuli, contrasted with similar static stimuli, can produce significant activation within the SC. This also follows on from previous fMRI and single-unit recording studies which have shown the preference of the SC for motion stimuli (Cynader & Berman, 1972; Katyal et al., 2010; Marrocco & Li, 1977; Schiller & Stryker, 1972). Previous research has shown that the SC can be difficult to image using fMRI due to its small structure (Cohen, DuBois, & Zeineh, 2000). However, several studies have successfully found SC activation in response to intentionally demanding visual cues (Billington, Wilkie, Field, & Wann, 2010) and eye movements (Furlan, Smith, & Walker, 2015, 2016) using standard scanning protocols.

Stimuli consisted of black background on which 1200 small white dots (0.2° radius) were presented inside a unilateral wedge annulus, 90° in size and beginning 4° from the centre with a width of 10° (Figure 3.2). A moving version of the same stimuli was also created, which consisted of identical wedges with the dots moving radially at $6^\circ/s$ and alternating in direction between inward and outward movement every 40 frames. If a dot passed the boundaries of the annulus, it was removed and reappeared at another random location within the wedge. Both stimulus types (moving and static) were presented unilaterally in both left and right hemifields along with a blank condition with no stimuli. In total, there were therefore five conditions presented; blanks, left visual field (LVF) motion, LVF static, right visual field (RVF) motion and RVF static, with all static and blank conditions lasting 10 s and motion conditions lasting 15 s. Each condition was presented 5 times within each run. The presentation order of each condition was defined by an n-back algorithm to ensure that the same

stimulus condition did not follow on from each other and were equally spaced out throughout the run.

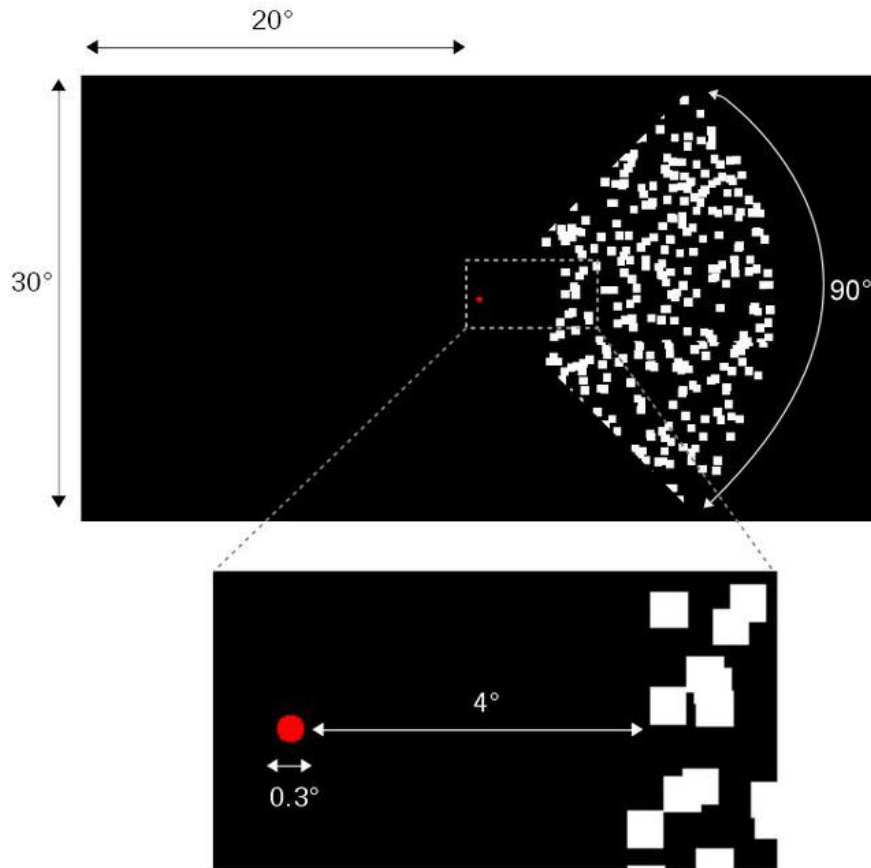


Figure 3.2: Stimulus configuration for the functional MRI scans. The stimulus comprised of two components in all experiments: a large lateralized wedge annulus of small white squares and a small dynamic fixation circle. The white squares differed in terms of which visual field they were presented in (left or right) and also whether they were static or showed radial motion (6°/s).

Throughout the functional runs, a small fixation circle (0.15° radius) was presented at the centre of the screen and changed in colour every 45 frames (375 ms) with 16 colour possibilities in total. During these runs, participants performed a concurrent foveal sustained attention task on this central circle to ensure stable fixation and central allocation of attention. The task required participants to monitor the colour of the central target and, starting at the number 50, add 1 for every green dot and minus 1 for every red dot seen. Participants verbally reported the tally at the end of each of the scans. The task was demonstrated to participants before entering the scanner to ensure full understanding. Although eye-tracking data was not recorded during the functional

runs, the participant's eye was viewed online by the experimenter during the sessions to ensure central fixation.

3.3.4 MRI acquisition

All neuroimaging was conducted at York Neuroimaging centre (YNiC) using a GE Healthcare 3 Tesla HDx Excite MRI scanner with an eight-channel phased-array head coil to ensure appropriate imaging of the SC and midbrain structures. For structural images, a single T1-weighted anatomical image was acquired to aid co-registration alignment with the functional data (TR, 7.8 ms; TE, 3 ms; flip angle, 20°; FOV, 290 mm; matrix size, 256 256; 176 slices, slice thickness, 1 mm; voxel size, 1.13x1.13x1 mm³). Proton density scans (TR, 2520 ms; TE, 35 ms; flip angle, 90°; FOV, 192 mm; matrix size, 512 512; slice thickness, 2mm; voxel size, 0.5 0.5 2 mm³) were also collected in the same functional space to aid in highlighting subcortical structures. Both structural images were acquired at the beginning of each scanning session.

For functional imaging, five functional T2* scans with 5 min stimuli presentation were recorded for each participant (TR, 2500 ms; FOV, 256 mm; flip angle 20°; matrix size, 128 128; 32 slices; slice thickness, 2 mm; voxel size, 2 2 2 mm³). Slices were acquired using an interleaved slice timing.

3.3.5 Analyses of MRI data

Image pre-processing. For each participant, both the T-1 weighted MR image and the axial proton density images were previously skull-stripped using the Brain Extraction Tool (BET) (Jenkinson, Pechaud, & Smith, 2005; S. M. Smith, 2002) in the FMRIB Software Library (FSL, version 5.0, <http://www.fmrib.ox.ac.uk/fsl>) to allow an improved alignment with the functional data acquired.

General Linear Modelling. Analyses of the fMRI data was performed using the FMRI Expert Analysis Tool (FEAT) within FSL. This was used to perform initial processing (first-level analyses) on each run separately. In each of the five functional runs, the first 4 volumes (10 s) were removed in order to reduce the effects of magnetic saturation and an interleaved slice-correction was applied. Motion correction was

applied to each run individually using MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002), as well as both temporal (60 s high pass) and spatial filtering (Gaussian, 4 mm). Functional data were first co-registered to the participants axial proton density images, then the T-1 weighted MR image before finally being registered onto the standard Montreal Neurological Institute (MNI) 152 standard 1mm brain (Evans et al., 2004). If needed, some images were also manually aligned using FSL's NUDGE tool.

Within the model, two separate contrasts were generated for each run to allow the comparison of motion > static visual stimulation in each visual field separately. All statistical images were cluster-corrected to a significance level of $p < 0.05$ with a nominal t-value of 2.3 using standard cluster correction. Individual participant's runs were then combined using a higher-level fixed effect analyses, again using FEAT, to produce an average response for each contrast across all 5 runs.

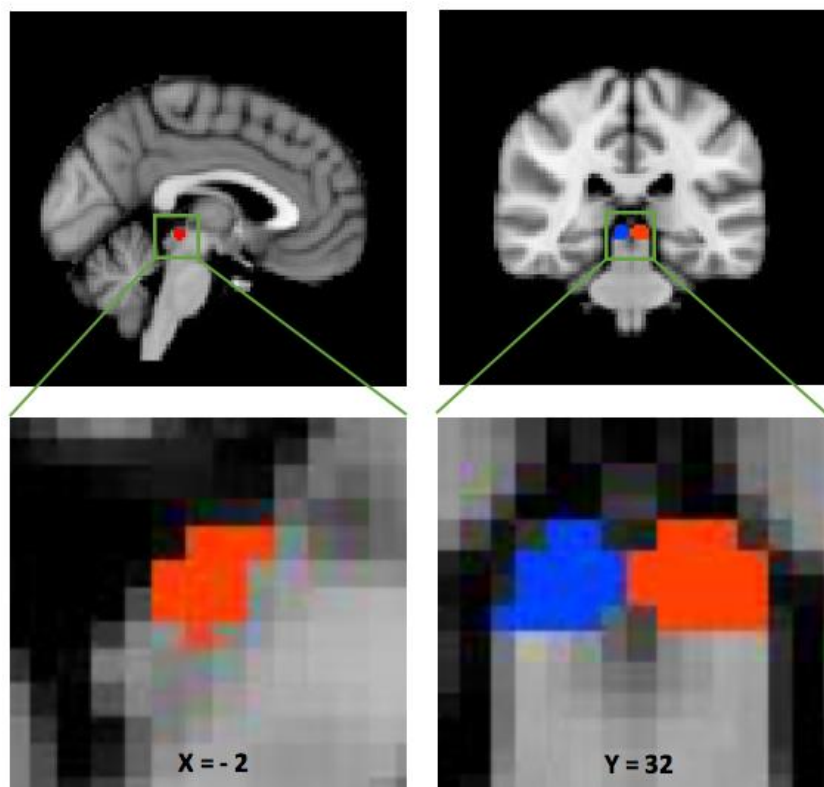


Figure 3.3: Superior Colliculus region of interest. The location of the SC as defined by anatomical boundaries on a standard 2mm T1-weighted MNI brain, seen through coronal and sagittal planes. Red and Blue colouring indicate the area of the SC within both hemifields.

Region of Interest. For the region of interest (ROI) analyses, both the left and right hemisphere SC were identified anatomically using the T1-weighted structural images following Limbrick-Oldfield's et al. (2012) technique and masks were hand drawn separately for each participant to include only the voxels from these regions (Figure 3.3). These were then converted into standard space and used as masks within FEAT Query on the average statistical maps for each participant, whereby the percentage signal change for motion stimuli was compared to static stimuli. This was done for each of the ROIs (left hemisphere SC/ right hemisphere SC) and each visual field stimulation (left hemifield / right hemifield).

3.4 Results

3.4.1 Saccade task

Our first aim was to examine how SC deficits may be observed behaviourally within abnormal antisaccade responses and how this can be linked to Inattention traits. From the saccade task, saccade reaction times (RT) for correct saccades (time between peripheral target appearing and a completed saccade away from the target) and number of errors (saccades made towards the target) were extracted. One participant's eye tracking response to the saccade tasks was not recorded due to a technical fault, and a further participant was also excluded due to problems understanding the task, bringing the total to 15 participants. Pearson's correlations showed that Inattention scores significantly positive correlated with the number of total errors ($r = .63, p = .005$, two-tailed) where those with higher Inattention scores exhibited a greater number of errors than those with fewer Inattention traits. However, there was no correlation between Inattention scores and RT ($r = -.09, p = .74$, *two-tailed*), indicating that all participants are responding at similar speeds during correct responses regardless differences in Inattention traits.

3.4.2 fMRI: Sustained Attention Task and Inattention Traits

We initially examined whether the behavioural accuracy for the central task correlated with ADHD-associated Inattention traits, to exclude the possibility that the attentional demands of the task were differentially affected by the level of traits and that we needed to take this potential confound into account in the imaging. Participant's overall accuracy was calculated and averaged across each of the 5 runs. Initial check on

the data showed it to be normally distributed with no outliers. A two-tailed Person's correlation showed no statistically significant relationship between Inattention scores and average accuracy on the colour-counting rapid visual response task ($r = .057$, $p = .83$). The average accuracy rating for all participants was 85.51%, showing the task required centrally focused attention and was not at ceiling performance. This further showed that any potential differences in fMRI activity within the SC are unlikely due to differences in behavioural responses and task engagement.

3.4.3 fMRI: Superior colliculus and Inattention

The main aim of our study was to examine whether hyperactivity within the SC is associated with ADHD-associated Inattention scores observed in the typically developed adult population, as proposed by Overton and colleagues (Overton, 2008; Overton & Clements, 2009; Panagiotidi et al., 2016). Here, we tested the relationship between Inattention scores and the percentage increase in the BOLD signal for unilateral moving stimuli in comparison to static stimuli. Due to the retinotopic nature of the SC where visual stimuli are processed by the SC in the contralateral hemisphere, this analysis was done separately for both the LVF and RVF as well as both left and right hemisphere SC.

Figure 3.4 (A and C) and Figure 3.5 (A and C) show the relationships between Inattention scores and percentage change in BOLD activity recorded from left (A) and right hemisphere SC (C). Both figures also show the percentage change in BOLD activity averaged across all participants, again done for left (B) and right hemisphere SC (D). Such results are presented separately for activity during presentation of LVF (Figure 3.4) and RVF stimuli (Figure 3.5). For LVF presentation, we can see no apparent relationship between Inattention scores and fMRI BOLD responses with large variance in the fMRI BOLD response occurring across the range of Inattention score. This can be seen in both the left and right hemisphere SC. For RVF presentation however, we can observe a notable increase in BOLD activity in those with higher number of Inattention traits compared to those with fewer traits. Whilst this is seen bilaterally across left and right hemisphere SC, it appears stronger for the left hemisphere. From both figures, we can also see that, in keeping with the retinotopic nature of the SC, increase BOLD activity is observed primarily within the SC contralateral to the visual stimuli while reduced BOLD is observed in the ipsilateral SC.

Unexpectedly, such increased contralateral BOLD activity appears to be stronger within the left hemisphere (responding to RVF visual presentation) compared to the right hemisphere (responding to LVF visual presentations).

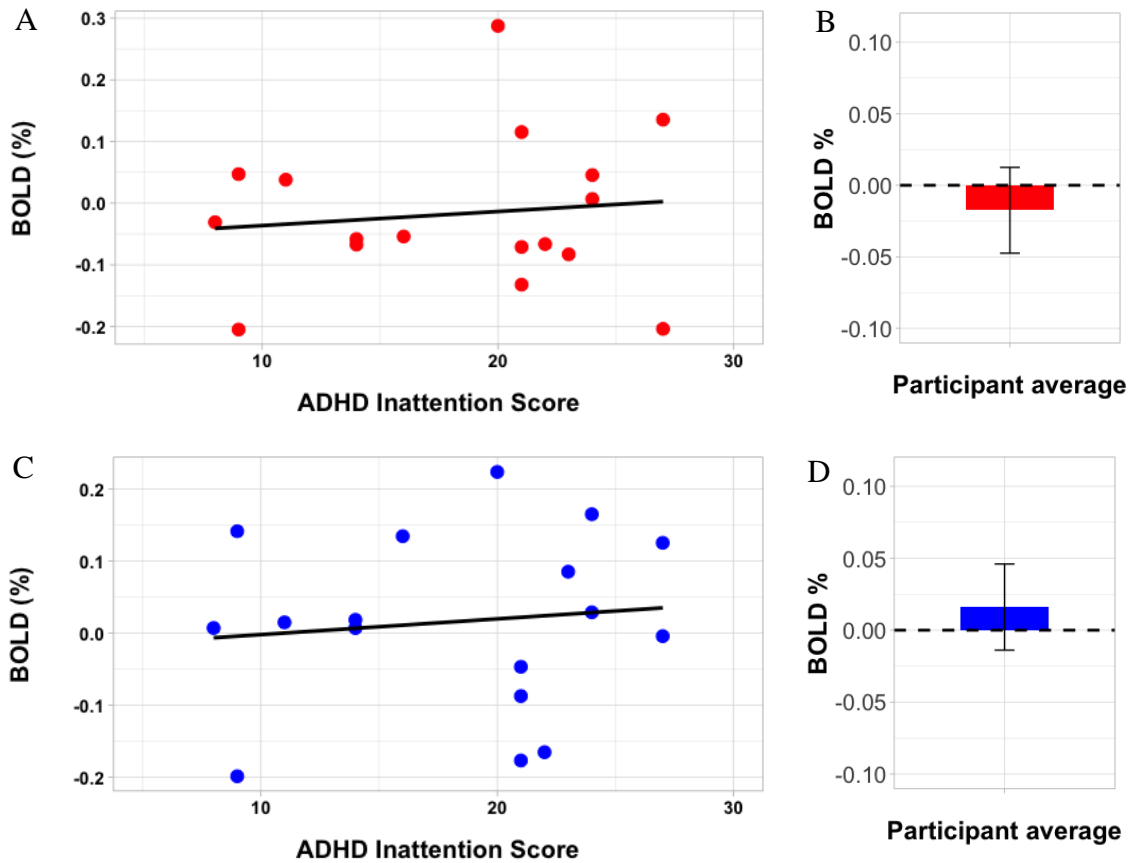


Figure 3.4: Left Visual Field; Correlations between Inattention and SC activity. The relationship between ADHD Inattention scores and the fMRI response to left visual field stimulation in both the left and right superior colliculi (SC). Both left scatter plots show the percentage signal changes for LVF motion in comparison to LVF static stimuli for each participant in relation to their ADHD inattention score. This is done separately for the left (A) and right (C) SC. Both right panels show the main percentage BOLD signal change averaged across all participant, again for LVF stimulation, in the left SC (B) and right SC (D). Error bars represent ± 1 standard error.

To explore such relationships, we conducted four one-tailed Pearson's correlations between Inattention scores and fMRI BOLD activity for each hemisphere and visual field combination. Again, data were initially checked to determine the presence of outliers and data distribution. This showed all variables were normally distributed (Shapiro-Wilk test >0.05) and no outliers were present. Firstly, correlations examining visual stimulation in the RVF showed a significant positive relationship

between Inattention score and percentage change in BOLD signal within both left $r = .63$, $p = .003$, Bonferroni corrected) and right SC regions ($r = .58$, $p = .008$) as shown in Figure 3.5A and C. When the correlations were corrected for multiple comparisons using a Bonferroni correction to an alpha level of .013, both the RVF correlations still remained significant. In contrast, correlations examining visual stimulation in the LVF showed no statistically significant relationship between Inattention scores and percentage change in BOLD signal in either the left ($r = .12$, $p = .326$) or right hemisphere SC ($r = .11$, $p = .333$).

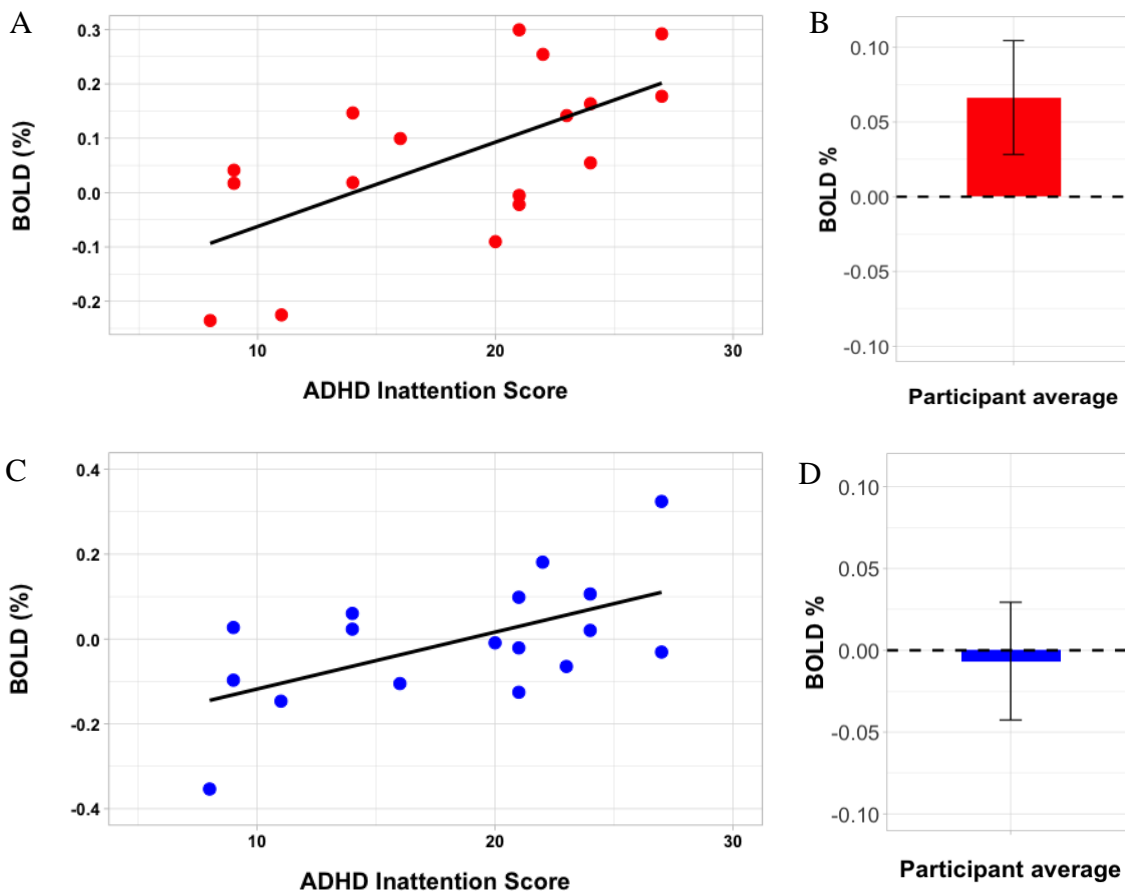


Figure 3.5: Right Visual Field; Correlations between Inattention and SC activity. The relationship between ADHD inattention scores and the fMRI response to right visual field (RVF) stimulation in both the left and right superior colliculi (SC). Both left scatter plots show the percentage signal changes for LVF motion in comparison to RVF static stimuli for each participant in relation to their ADHD inattention score. This is done separately for the left (A) and right (C) SC. Both right panels show the main percentage BOLD signal change averaged across all participant, again for RVF stimulation, in the left SC (B) and right SC (D). Error bars represent ± 1 standard error.

3.5 Discussion

Previous literature has long established a link between visual attention and activity within the superior colliculus (SC) (Ignashchenkova et al., 2003; Katyal et al., 2010; Rizzolatti et al., 1987), with some showing indirect evidence that abnormalities in functioning can lead to extensive inattention problems (Albano et al., 1982; Gaymard et al., 2003; Goodale et al., 1978; Milner et al., 1978; Sprague, 1966). Overton and colleagues recently also proposed that inattention traits observed within ADHD could result from functional differences within the SC (Overton, 2008; Overton & Clements, 2009; Panagiotidi, 2016). Using fMRI during a visual sustained attention task, the current study investigates for the first time whether there is a direct relationship between ADHD-associated Inattention traits in the typically developed population and activity within the SC. To achieve this, task-irrelevant visual stimuli, previously shown to elicit SC responses (Schneider & Kastner, 2005), were presented in the periphery to both left and right visual fields. Behavioural measures were also assessed for both the central, sustained-attention task and anti-saccade task, the latter as a further indicator of collicular functioning.

Firstly, examining behavioural measures of SC functioning through the anti-saccade task, we observed a significant relationship between Inattention traits observed in the non-clinical population and anti-saccade performance. Specifically, it was found that those with a higher number of Inattention traits make more errors (saccades towards the target) than those with fewer Inattention traits. This does appear to match previous literature who demonstrated such increases in error rates for children and adults with a clinical diagnosis of ADHD (Feifel et al., 2004; Goto et al., 2010; Karatekin, 2006; Klein et al., 2003; Munoz, 2003). Such results can therefore provide behavioural support to strengthen the proposed link between Inattention and the SC, whereby abnormalities in SC functioning may manifest as increased errors in directing saccade responses. Nevertheless, such results could be due to problems with response inhibition, whereby those with ADHD and increased Inattention problems also exhibit frequent problems inhibiting automatic and frequent responses (Booth et al., 2005; Durston et al., 2003; Feifel et al., 2004; Goto et al., 2010; Hanisch et al., 2005; Karatekin, 2006; Klein et al., 2003; Mahone et al., 2009; O'Driscoll et al., 2005; Oosterlaan et al., 1998; Rubia et al., 2007; Schulz et al., 2004; Wright et al., 2014). To explore this further, both pro-

saccades and anti-saccades should be examined in relation to ADHD-associated Inattention traits.

As the primary aim of this study, we also examined fMRI responses measured by changes in BOLD signals from the SC during a sustained attention task to explore the direct link between Inattention and SC activity. Firstly, we found no significant relationship between performance on the central fixation-task and Inattention traits, suggesting that any differences in SC responses related to Inattention traits are unlikely to be due to differing task-demands or task engagement. Exploring the BOLD responses recorded from the SC, we observed significant positive correlations between ADHD-associated Inattention traits and SC responses to moving visual stimuli compared to static stimuli, whereby increased activity was observed in those with a greater number of traits. This suggests that the SC may indeed be hyper-responsive to sensory stimuli within those with increased Inattention problems as previously proposed (Overton, 2008; Overton & Clements, 2009; Panagiotidi, 2016), whereby such hyperactivity could result in changes in attentional processing and allocation leading to Inattention problems, such as those frequently observed within ADHD. Although, whether such effect also related to those with clinically diagnosed ADHD, rather than just those with increased Inattention traits in the typically developed population as studies here, requires further examination. Interestingly however, such effect was only found when visual stimulation occurred in the RVF and not when in the LVF, regardless of SC hemisphere. Previous research examining visual attention has indeed found evidence for potential differences between hemifield processing and attentional allocation within those with ADHD. Here it is often found that those with ADHD show faster responses in detecting stimuli and problems inhibiting responses towards stimuli presented in the RVF (Bellgrove et al., 2013, 2009; Hanisch et al., 2005; Nigg et al., 1997). Research has also shown that those with ADHD tend to experience more interference from distractors within the RVF (Chan et al., 2009; Geeraerts et al., 2008; Huang-Pollock et al., 2005). From our data, it may therefore be suggested that those with higher levels of ADHD-associated Inattention traits are more likely to be distracted by visual distractors presented within the RVF, shown through the increase in SC response, compared to those with fewer Inattention traits.

The potential neurological mechanisms behind such differences are currently less clear, however, as the RVF correlations were found in both the left and right hemisphere SC despite its clear topographical nature. This may indicate a modulation by cross hemisphere, top-down mechanisms, in addition to some stimulus-driven input. This is particularly likely given the fact that a stronger correlation and a greater average percentage signal change was observed in the SC contralateral to the RVF stimulation, potentially receiving both bottom-up visual input and top-down information, compared to the ipsilateral SC which may just receive top-down signals. Such a mechanism may be mediated by the parietal or frontal cortex which have direct connections to the SC (Boehnke & Munoz, 2008) and have previously been implicated in distractibility within ADHD (Schneider et al., 2010; Silk et al., 2005; Vance et al., 2007). Such differences, however, could be taken with caution as the present experiment used participants from the non-clinical population who may show reduced symptom severity compared to the clinical population. Future studies may benefit from comparing those with low Inattention traits in the healthy population to those with a clinical ADHD-I presentation, which may be more sensitive to reveal differences for LVF stimulation. Similarly, it may be that differences in SC activity during LVF stimulation are only observed in childhood and reduces over time becoming more normalised, following a similar pattern to previous behaviour and functional differences in ADHD. Although why such a reduction in hyperactivity only occurs to LVF and not RVF stimulation is unclear.

The suggestion that the SC is involved in Inattention and distractibility may have significant implications within the clinical setting if such SC hyperactivity also underlies Inattention in those with clinically diagnose ADHD. Currently, the primary treatment for ADHD, methylphenidate and amphetamines, are associated with abuse problems (Kollins, MacDonald, & Rush, 2001; Morton & Stockton, 2000) and often require frequent doses due to the short-term effects (Punja, Zorzela, Hartling, Urichuk, & Vohra, 2013; Stein et al., 1996; Van der Oord, Prins, Oosterlaan, & Emmelkamp, 2008), creating an added demand for a new improved medication. Identifying specific loci involved in ADHD, such as the SC, may therefore allow for more targeted pharmacological interventions and hopefully allow for a more successful control of ADHD-associated behaviours with fewer side effects. Furthermore, differences across hemifields associated with higher Inattention traits may have implications for both

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teaching and behavioural intervention programs whereby it may be more beneficial to train attention within the RVF and to avoid distracting stimuli appearing in the RVF.

In conclusion, this study shows for the first time that there is an association between ADHD-associated Inattention traits and SC activity within the typically developed adult population, whereby those with higher Inattention levels exhibit increased collicular sensory responsiveness, supporting the 'SC-hypotheses' of ADHD. Interestingly, however, such associations were only found when the stimuli are presented in the RVF, possibly representing some differences in attentional-allocation and distractibility between hemifields.

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4.1 Abstract

Previous research has often shown that those with ADHD can experience increased interference from peripheral distractors during sustained visual attention tasks, particularly during easy, low attentional load tasks. Our own research suggests that those with high levels of Inattention appear to be less successful at suppressing distractors presented within the right-visual field. Here we investigate how those with Low and High levels of Inattention process task-related central targets and peripheral task-irrelevant distractors and whether such visual processing is influenced by attentional-load and distractor location.

Using Electroencephalography (EEG) to record Steady State Visual Evoked Potential (SSVEP), we measured responses to centrally presented task-relevant targets while participants performed both easy (low-load) and hard (high-load) sustained visual-attention tasks. During each task, we also simultaneously measured responses to peripheral task-irrelevant distractors, presented to either the left visual field (LVF), right visual field (RVF) or bilaterally.

Here we show that the Low Inattention group exhibit larger responses towards the task-related stimuli than towards the unrelated distractors, regardless of attentional task, while the High Inattention group show the opposite effect, responding to the irrelevant distractors more than the task-related stimuli. Presentation hemifield and Distractor type were further found to influence distractor processing, where those with High Inattention exhibited an increased response towards RVF distractors compared to those with Low Inattention while no such differences were found for LVF distractors. Those with High Inattention also showed similar responses to distractors under unilateral and bilateral conditions, suggesting abnormal sensory competition. Such results demonstrate clear differences in visual processing of task-related and unrelated stimuli between those with Low and High levels of ADHD-associated Inattention traits and may provide a potential explanation for the enhanced distractibility observed in those with ADHD.

4.2 Introduction

In the previous chapter, we showed that those with higher levels of Inattention displayed significant hyperactivity within regions of the Superior Colliculus when moving visual distractors were presented in the right visual field. Our provisional interpretation of these data was that such stimuli are likely to be suppressed while participants engage in a central task and that those showing high levels of inattention are less successful at achieving this, particularly for peripheral target locations in the right hemifield. In this chapter we explore further the responses to central and peripheral targets, while participants perform sustained attention tasks on the central target. The Steady State Visual Evoked Potential (SSVEP) approach we use also allowed us to investigate additional, theoretically motivated questions concerning attentional load and sensory competition. The background leading up to the questions we ask in this chapter are reviewed first, followed by a description of the approach we will use to answer them.

4.2.1 Perceptual Load

Perceptual load of a task has been shown to heavily influence both our behavioural and neural responses towards attended and unattended stimuli. Originally proposed by Lavie and colleagues (Lavie, 1995, 2005, 2010; Lavie & Tsai, 1994), the Load Theory suggests that distractor processing can be reduced or eliminated if the level of task perceptual load is great enough to exhaust perceptual capacity. During tasks with high perceptual load (e.g. many items or complex judgements), perceptual capacity is largely exhausted by the attention task, resulting in no remaining capacity to process task-irrelevant stimuli. In this case, any additional distractors will likely be ignored. During tasks with low perceptual load (e.g. fewer items or simple judgements) however, there is remaining perceptual capacity which is automatically used to process the task-irrelevant stimuli, leading to distraction. In that sense, perceptual processing only becomes selective once a certain threshold is reached. Indeed, previous literature has already established that increasing load can reduce distractor interference on behaviour (Lavie & Cox, 1997), regardless of distractor salience (Forster & Lavie, 2008) and eccentricity (Beck & Lavie, 2005; Lavie & de Fockert, 2003), and reduced

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neural responses towards distracting stimuli within the LGN (O'Connor et al., 2002), early visual cortex (Bahrami, Lavie, & Rees, 2007; O'Connor et al., 2002; Rees, Frith, & Lavie, 1997; Schwartz et al., 2005) and higher-order visual regions (Rees et al., 1997; Yi, Woodman, Widders, Marois, & Chun, 2004).

Given this, it may be reasonable to assume that for individuals with ADHD, exhibiting significant inattention problems and increased distractibility, the relationship between perceptual load, perceptual capacity and distractor processing may be different. Recent research has shown however that this may not be the case where an increase in perceptual load produces the same reduction in distraction in those with ADHD as it does for controls. Indeed, Forster et al. (2014) found infrequent salient distractors caused greater behavioral interference to visual search reaction times for adults with ADHD compared to controls, yet increasing perceptual load reduced interference in both groups. Similar results have been found for children with ADHD and non-clinical healthy adults; both showing that those with higher levels of individual distractibility, while always showing more distractor interference under low-load conditions compared to their low distractibility peers, still benefited from increased perceptual load (Chan et al., 2009; Forster & Lavie, 2007; Friedman-Hill et al., 2010). However, Huang-Pollock et al. (2005) revealed that such results may depend on hemifield of presentation. In their study, children with ADHD exhibited increased distractibility under low-load conditions compared to high-load only when the distractor was in the right visual field, whereas control children showed the same effect but for left visual field distractors. Interestingly, this appears to fit with our previous MRI research presented in Chapter 3, which showed a positive correlation between ADHD Inattention score and visually evoked BOLD responses in the Superior Colliculus, but only when stimuli were presented in the right visual field. Nevertheless, up until now the relationship between ADHD and perceptual load has only been examined using behavioural measures of distractibility, with no research specifically examining neural responses towards both the task-related stimuli and distractors. Such research exploring the influence of perceptual load on neural responses within ADHD is therefore warranted.

4.2.2 Sensory Competition

A recent line of research has also examined whether neural responses towards stimuli differ between bilateral and unilateral presentations. Bilateral displays presented across left and right visual fields are thought to promote bottom-up perceptual interference, or ‘sensory competition’, between stimuli whereby limited neural and attentional resources are split between competing displays resulting in a reduced neural representation (Desimone & Duncan, 1995; Moran & Desimone, 1985; Reynolds et al., 1999). This has been found to particularly occur when both stimuli are presented across hemifields (Fink, Driver, Rorden, Baldeweg, & Dolan, 2000; Kinsbourne, 1977) and during high attentional-load tasks (Vuilleumier & Rafal, 2000). Using fMRI, Schwartz et al. (2005) assessed neural activity towards irrelevant unilateral and bilateral distractors while performing visually-identical low and high perceptual load tasks. They found reduced neural responses within areas of the parietal cortex towards bilateral distractors compared to unilateral distractors and that, within certain areas, only occurred during high-load tasks. Such sensory competition is also thought to contribute to visual extinction seen in those with unilateral neglect (see Driver & Vuilleumier, 2001), where detectable unilateral targets presented in the left visual field become undetected after a second ‘competing’ target is added to the right visual field. Given those with ADHD often display comparable, although less pronounced, spatial-asymmetries in attention to unilateral neglect patients (Geeraerts et al., 2008) proposed to both share a common neuropsychological mechanism in a right-hemisphere deficit to the attentional-network), we may expect to observe similar asymmetrical sensory competition between bilateral distractors components. We therefore thought it would be valuable to examine the effect of distractor type (unilateral vs bilateral) in relation to ADHD Inattention traits.

4.2.3 Asymmetrical Spatial Attention

As mentioned above, much of the previous research into ADHD has highlighted potential differences in distractibility and attentional allocation between both hemifields. Both Chan et al. (2009) and Huang-Pollock et al. (2005) found, during low-load tasks, children with ADHD are more distracted by right visual field distractors while control children were more distracted by those in the left visual field. Geeraerts et

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al. (2008) and Epstein et al. (1997) similarly showed that adults with ADHD exhibited significant interference from distractors within the right hemifield. Moreover, our previous fMRI work has also highlighted the effects of Inattention scores on responses in the superior colliculus are dependent on the hemifield in which a distractor stimulus is presented (See Chapter 3). Taken together, such studies suggest that further examination of the hemifield location of the distractors and the responses towards them is warranted.

The current study first aims to measure responses to centrally presented task-relevant targets while participants performed both easy (low-load) and hard (high-load) sustained visual-attention tasks. We also aimed to examine whether such central target responses could be modulated by the presence of task-irrelevant, peripheral distractors presented to the left visual field, right visual field or bilaterally. As a result, this allows us to gain an understanding of the interactions between task and distractors on the responses to these task-relevant targets. During each task, we aimed to measure responses to the peripheral distractors themselves in order to explore how they too are influenced by the task being performed on the central target. Finally, we aim to explore how such measures differ between those with low and high levels of ADHD-associated Inattention traits. In order to make such measurements, a technique that can capture responses from different visual field locations simultaneously is required. Below, a brief outline of such technique, steady state visual evoked potentials, and how it can be applied in the context of the aims of this study is given.

4.2.4 The Steady State Visual Evoked Potential and its application to research on attention

Frequency tagging is an Electroencephalography (EEG) method based on the notion that steady state visual evoked potentials (SSVEPs) produced in response to a temporally varying visual stimulus, will have the greatest amplitude at frequency of the temporal modulation of the stimulus. In that sense, it is possible to extract individual SSVEPs in response to different visual stimuli (modulated at different frequencies), even if presented simultaneously or in overlapping areas of visual space, essentially ‘tagging’ each stimulus.

Previous literature has shown that SSVEPs can vary with attention; responses to attended stimuli are enhanced compared to those made towards unattended stimuli

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(Hillyard, Vogel, & Luck, 1998; Toffanin, de Jong, Johnson, & Martens, 2009). Similar attentional-modulations have also been discovered using single-unit recording and other neuroimaging techniques within visually-associated regions and is thought to provide a mechanism by which we can focus on behaviourally-relevant stimuli and ignore potential distractors (for reviews see Beck & Kastner, 2009; Carrasco, 2011; Desimone & Duncan, 1995; Reynolds & Chelazzi, 2004; Yantis & Serences, 2003). The SSVEP approach can therefore allow us to simultaneously measure responses to stimuli that are task relevant – in our case a centrally presented target – and task irrelevant – in our case distractors presented peripherally in each hemifield alone (unilaterally) or together (bilaterally).

Here we use such technique to explore the influences of *i*) task attentional load (Easy and Difficult), *ii*) distractor location (None, Left visual field (LVF), Right visual field (RVF), Bilateral) and *iii*) ADHD-associated inattention traits (Low and High) on the SSVEP responses to both task-relevant targets and irrelevant distractors. In the current study, we used a similar design to that previously used by Schwartz et al. (2005) with fMRI, whereby participants performed a sustained attention task at the central target, which varied in orientation and spatial frequency, while checkerboard distractors were presented in the periphery. Using EEG frequency tagging, we present the central target and hemifield peripheral distractors at different temporal frequencies. This enabled us to separate the SSVEP response produced by each individual stimulus and allowed us to explore whether potential differences in stimulus processing, and hence attentional allocation, exist between each component. Similar to Schwartz et al. (2005), we used four distractor conditions where the peripheral distractor could be absent or presented to either LVF, RVF or bilaterally. This firstly allowed us to investigate potential hemifield differences in distractor processing and whether such distractors differentially impacted the processing of the central target. Additionally, given that LVF and RVF distractors were presented at differing frequencies, this allowed us to present bilateral distractors while extracting signals for each hemifield component separately. By comparing these responses to those where a distractor was presented in isolation (unilateral condition), we can explore the effect of sensory competition between hemifields. Finally, task attentional load was manipulated by having participants performing either an easy, single feature detection task (orientation only) or a difficult conjunction detection task (spatial frequency and orientation). Critically, the central

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visual stream remained identical between both easy and difficult tasks where only the task instructions differed. This ensured that the attentional load manipulation isolated a purely top-down effect and was not influenced by bottom-up mechanisms. Finally, we examine for the first time whether such SSVEP responses towards both task-relevant and irrelevant stimulus differ depending on ADHD-associated Inattention traits by comparing participants with no/few Inattention traits (Low Inattention group) and those with a high level of Inattention traits (High Inattention group) recruited from the typically developed adult population.

4.2.5 Hypotheses and predictions

Based on Lavie's Load Theory, we firstly expect that increasing task attentional load will increase the SSVEP response towards the central target but reduce the response towards the peripheral distractors. As the central task gets more attentionally demanding, perceptual capacity should be taken up processing the central task leaving fewer resources to process the distractors. Related to this, we also expect that the presence of a distractor will only influence central target processing and task performance during easy tasks, where there are excess attentional resources remaining. The interference from and processing of peripheral distractors are thought to be greater for the High Inattention group, who have previously shown greater distractibility from distractors (Forster et al., 2014). Examining the SSVEP response to the distractor stimuli, we further expect that responses towards individual distractor components will be significantly reduced if presented under bilateral conditions, initiating sensory competition, compared to unilateral conditions and that this will likely differ between Inattention groups. Finally, based on our own previous fMRI findings (Chapter 3) in conjunction with previous ADHD research (Chan et al., 2009; Geeraerts et al., 2008; Huang-Pollock et al., 2005), we expect that responses to RVF distractors will differ significantly between Inattention group, while those towards LVF distractors will not.

4.3 Methods

4.3.1 Participants

Three hundred and eighty-two participants completed a computerised self-report ADHD symptom checklist that consisted of sixty-four questions from the English

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Version of the Conners Adult ADHD Rating Scale (CAARS) long self-report form (Conners et al., 2002). This initial participant pool is described in detail in Chapter 2. From these, thirty-six participants were invited to participate in the main EEG experiment. Similar to Chapter 3, this method of initially screening participants was done to assess ADHD-associated traits and to ensure that participants were suitable for EEG before inviting them to participate. Sixteen participants showed an ADHD DSM-Inattention score (Dimension E) at least one standard deviation below their population mean and formed the 'Low Inattention' Group, while a further twenty participants scored at least one standard deviation above their population mean and formed the 'High Inattention' Group. Mean population levels were defined by Conners et al. (2002) and are based on prevalence of associated ADHD symptoms for varying ages and genders. In that sense, correcting for both gender and age allows for an accurate Inattention score. As discussed in Chapter 1, guidance for the CAARS typically suggests that those who show standardised scores at least one standard deviation from the mean, as was the case for all our High Inattention participants, are seen to show ADHD-associated symptoms potentially indicative of an ADHD clinical diagnosis. Whilst no participant declared a previous clinical diagnosis for ADHD, it is possible that such group could be taken as a proxy for a clinical ADHD group although further research should be conducted to explore this.

As a result, Table 4.1 shows that both Low and High Inattention groups significantly differed in ADHD DSM Inattention scores. We can see however that such groups also differed in ADHD DSM Hyperactivity scores and ADHD DSM Combined scores (the sum of Inattention and Hyperactivity scores), which is largely due to the strong positive correlation often observed between both Inattention and Hyperactive components (Conners et al., 2002). Additional characteristics of the participants can be found in Table 4.1. All participants chosen to take part in the EEG section showed an Inconsistency score below the recommended limit of 8 indicating the responses could be considered reliable. Although a significant difference was found between these inconsistency scores between both groups, this is likely due to the type of groups being studied with those in the Low Inattention group largely scoring 0's on each question whereas the High Inattention group tended to score more variably, and hence were more likely to have scoring differences between certain questions. Further details on how this inconsistency score was calculated can be found in Chapter 1 and 2. All thirty-six

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participants were also right-handed, showed normal or corrected-to-normal vision, had at least a partial-degree level of education from the University of York and showed an IQ score of 95 and above using the Wechsler Adult Intelligence Scale II Two subtest (Vocabulary and Matrix reasoning) (Wechsler, 2011). There was no difference in IQ score between both Inattention group. Participants further confirmed no history of psychological or developmental disorders and had no history of epilepsy. All gave informed consent in accordance with the Declaration of Helsinki. The study was approved by the ethics committee of the Department of Psychology, University of York.

*Table 4.1: Characteristics of both Low and High Inattention group. Values represent both means and standard deviations. P-values come from independent-sample t-tests between both inattention groups where * signifies significance.*

| Characteristics | Low Inattention | High Inattention | P Value |
|------------------------|----------------------|-----------------------|---------|
| Gender M/F | 4/12 | 3/17 | .451 |
| Age (years) | 19.63 (\pm 1.41) | 19.60 (\pm 1.27) | .956 |
| Handedness L/R | 0/16 | 0/20 | |
| ADHD-DSM Inattention | 30.94 (\pm 14.40) | 68.35 (\pm 18.53) | <.001* |
| ADHD DSM Hyperactivity | 33.25 (\pm 15.14) | 56.55 (\pm 20.27) | <.001* |
| ADHD DSM Combined | 31.81 (\pm 12.91) | 67.70 (\pm 16.42) | <.001* |
| Inconsistency Score | 3.44 (\pm 1.82) | 5.00 (\pm 1.49) | .008* |
| WASI-II FSIQ-2 score | 119.38 (\pm 9.26) | 123.30 (\pm 15.84) | .387 |

4.3.2 EEG Apparatus

EEG activity was recorded using a 64-electrode cap system (Waveguard64 cap, ANT Neuro, Netherlands). The ground electrode was positioned in the centro-frontal region superior to the forehead (electrode AFZ). During EEG monitoring, all the electrodes were referenced to the whole head average and the impedances (excluding the mastoid electrodes: M1 and M2) were kept below 10k Ω . The EEG signals were digitalised at 1000Hz using an ASA 64-channel amplifier and ASA software (ANT Neuro, Netherlands). Stimulus onset and conditions were recorded on the EEG trace using a low-latency digital trigger.

4.3.3 Stimuli and experimental procedure

Stimuli were displayed using a computer controlled ViewPixx monitor (VPixx Technologies, Canada: *resolution*, 1920x1080) running at 60Hz. The display had a mean luminance of 180cd/m² and was calibrated with a photometer to allow for gamma correction. Participants were positioned 57cm from the screen using a chin rest, so that each degree of visual angle subtended 36 pixels on the display.

Stimuli consisted of two components; the central fixation target and the peripheral distractors (Figure 4.1). The central fixation was present throughout each of the runs and was either presented alone or with a peripheral distractor either unilaterally, within the LVF or RVF, or bilaterally. All stimuli were presented on an equiluminant uniform grey background. The central fixation component included a single sinusoidal grating which was presented within a 1° diameter circular window with a raised cosine soft edge profile (width; 1°). Throughout the run, the central grating changed in spatial frequency and orientation every 1000 ms, where spatial frequency was set to either 2 or 4 cycles per degree (cpd) while orientation differed between 0 and 180 degrees in 15° increments (0°, 15°, 30°, 45°, 60°, 75°, 90°, 105°, 120°, 135°, 150°, 165°) where 0° represents a horizontal grating. Presentation order was pseudorandomised to ensure that central gratings with identical spatial frequency and orientation configurations were not presented sequentially, so at least one component of the grating changed every time. We also ensured that each of the 24 unique combination of spatial-frequency and orientation occurred with equal likelihood and were each

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presented 3 times within a single run. Critically, each of the pre-defined central grating presentation orders were presented during both easy and difficult attentional-load tasks (Figure 4.1B). Figure 4.2 shows an example of the central task visual stream during a single run. This meant that the visual components presented to participants, and their presentation order, were identical within both attentional-load tasks. This allows us to ensure that the only difference between task conditions were the participants instructions and hence the attentional-manipulation.

In addition to the central grating component, some blocks also displayed a peripheral distractor comprising of a 90-degree contrast-reversing checkerboard annulus (inner radius: 2° ; outer radius: 10° , Contrast 24 dB) which was presented equally, divided by the horizontal meridian. These distractors were always irrelevant to the task being performed and participants were instructed to ignore them. Figure 4.1A shows the four Distractor conditions where peripheral gratings were either displayed to the LVF, RVF, Bilaterally or not presented at all. In order to extract the responses for the central target and both LVF and RVF distractor components separately, the contrast of each component was modulated at a different temporal frequency (Central target; 4.00 Hz. LVF distractor; 6.67 Hz. RVF distractor; 7.50 Hz). These frequencies were carefully selected so that each of the three fundamental frequencies remained outside the alpha band (8.0 – 12.5 Hz). Previous literature has demonstrated that alpha oscillations are often observed within visual-associated regions during the suppression of distractors in sustained visual-attention tasks (Händel, Haarmeier, & Jensen, 2011; Kelly, 2006; Rihs, Michel, & Thut, 2007; Thut, 2006; van Gerven & Jensen, 2009; Worden, Foxe, Wang, & Simpson, 2000). We therefore wanted to avoid such attentional manipulation confounding our EEG responses at the three component frequencies.

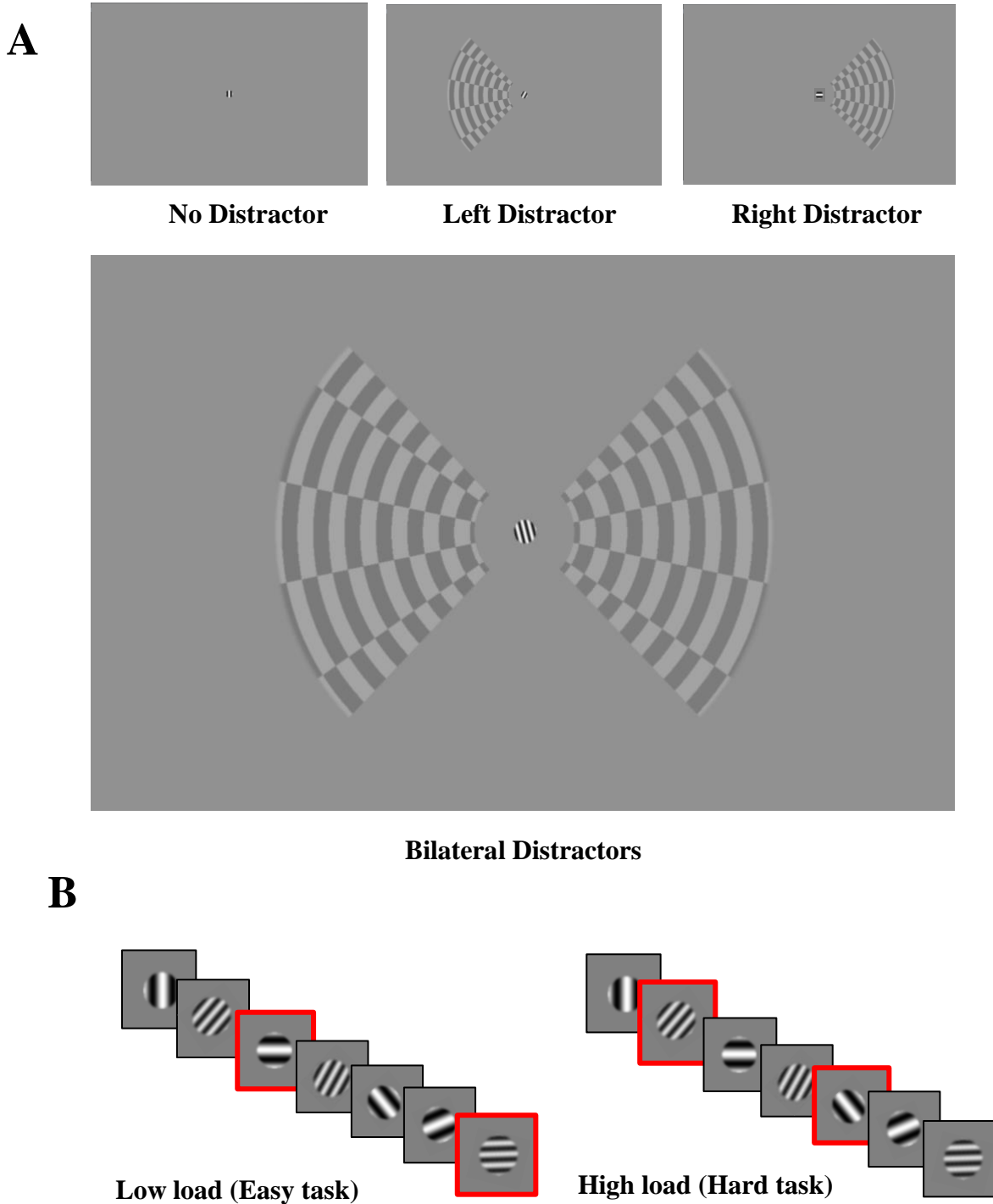


Figure 4.1: Illustrations of the stimuli used within the main EEG experiment. Distractors were presented as lateralized flickering checkerboards to either the left visual field, right visual field, bilaterally or not presented at all (A). A rapid stream of circular gratings appeared at the centre of the screen where the grating changed in either orientation, spatial frequency or both every 1000ms (B). This central stream remained identical within both low and high attentional-load tasks to ensure that visual-input remained constant while only the participants instructions changed. Pre-defined targets in both attentional-load conditions are represented by a red box. During low attentional-load conditions, participants responded to any grating that showed a horizontal orientation regardless of spatial frequency. During high attentional-load tasks however, participants responded to specific combinations of spatial frequency and orientation (gratings with ‘larger bars’ at 2 cycles per degree and a 45-degree orientation and gratings with ‘small bars’ at 4 cycles per degree and a 135-degree orientation).

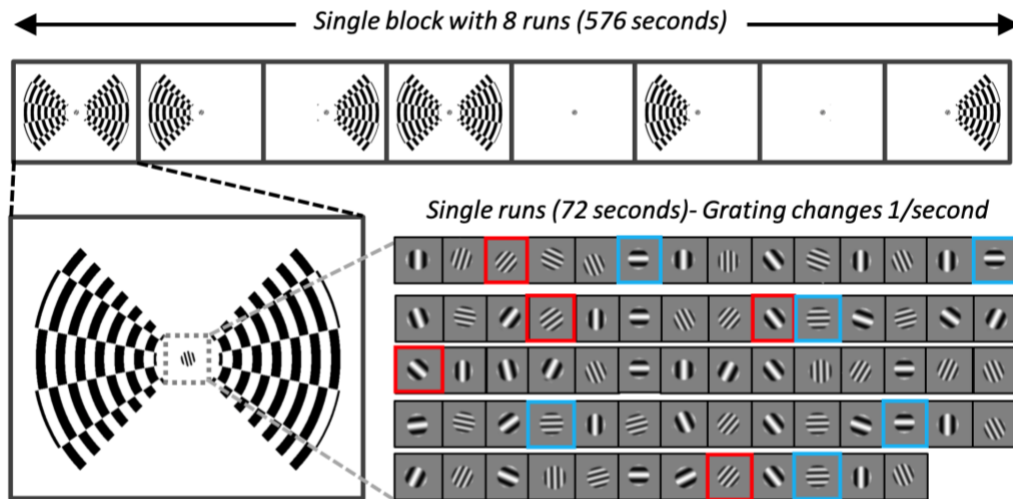


Figure 4.2: EEG Experimental design. Participants performed four blocks during the experiment where two involved the easy task and two involved the difficult task. In a single block, there were eight runs where two runs were presented for each of the distractor types (Left, Right, Bilateral and None). During a single run, the central grating changed in spatial frequency, orientation or both every 1000ms. Targets for both easy and difficult attentional-task loads appeared infrequently at the same rate (8.33%). Red squares signify response targets for the difficult task while blue squares indicate response targets for the easy task. During each task, no two response targets were presented sequentially, and no target was presented in the first 2000ms. Identical central grating streams were presented during both easy and difficult tasks in order to control for visual input where only the task instructions differed.

During each experimental run, participants were instructed to maintain fixation on the central grating and to perform one of two sustained attention tasks. Following a similar procedure to Schwartz et al. (2005), attentional-load was manipulated by asking participants to respond to pre-defined targets, whereby low attentional-load tasks (easy task) involved a single-feature detection while high-load (difficult task) involved conjunction-feature detection, known to increase attentional-load (Lavie, 1995). Research has long established that humans show a greater sensitivity in detecting orientations at the cardinal orientations (horizontal and vertical) compared to more oblique orientations (45 and 135 degrees) (Furmanski & Engel, 2000). With that in mind, detecting horizontal orientation is likely to require lower levels of attentional-load and ‘pop out’ from the non-targets, while detecting oblique orientations will require high levels of attentional-load. During easy tasks, targets were defined as gratings showing horizontal bars (0° orientation) regardless of spatial frequency. In contrast, targets within the difficult tasks were defined as gratings showing a 45° orientation with a spatial frequency of 2 CPD or gratings showing a 135° orientation with a spatial frequency of 4 CPD. Figure 4.1B and Figure 4.2 give examples of these two tasks and

their corresponding targets. Target occurrence was controlled between both attentional-load tasks, forming 8.33% of the central grating presentations, and the pre-defined presentation order ensured that no two targets occurred sequentially. Targets were also never presented within the first 2000ms of each block to give participants time to fixate on the central task. Figure 4.2 further shows an example central task stream during a single run which was used for both easy and difficult tasks. The infrequency of the target stimuli and rapid succession of the stimuli ensured participants remained engaged and fixating centrally. Participants were given examples of the relevant targets before the start of each run to remind them of the configurations and proceeded through the trials at their own pace. Participants received two practice blocks, one for each attentional-load task, at the start of the experiment. All participants' responses were recorded through each block and later analysed offline to examine task accuracy and detection speed.

In total, each participant undertook four experimental blocks, two performing an easy, low attentional-load task and two performing a difficult, high attentional-load task. The order of task performance was completed in either an ABBA or a BAAB sequence which was counter balanced between both Inattention-groups. For each of these blocks, there were eight 72 second runs, where two runs were conducted for each of the distractor conditions (No distractors, a Left distractor, a Right distractor and Bilateral distractors). The order of these distractor conditions was randomised for each experimental block. An illustration of this design can be seen in Figure 4.2.

4.3.4 Eye tracking apparatus and analysis

Throughout each experimental block, eye tracking was used in order to monitor participants' fixation. Pupil position was recorded from the participant's right eye using an EyeLink® 1000 at a rate of 1000 Hz with an elliptical model fit. Eye tracker calibration was made by presenting sequential dots in a 3x3 grid around the edges of the screen and central fixation point which participants tracked around the screen. This was then validated using a similar process where participants again tracked dots around the screen and the calibration error (maximum and average error across all nine grid points) was determined. Here calibration was only accepted if it was rated as 'good' (described as situations where 'Errors are acceptable' within *EyeLink® 1000 User Manual* (2009), p77). Such calibration and validation procedures were conducted before the first and

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fifth block in each of the four runs to reduce the effect of participant position or movement. Two independent t-tests showed that there was no significant difference in either the average or maximum tracking error between both Low and High Inattention groups (*average error*: $t=-1.43$, $p=.161$. *maximum error*: $t=-1.37$, $p=.179$). Overall, the average error rate across all trials and participants was 0.59 visual degrees while the average maximum error rate was 1.25 visual degrees.

Target fixation was analysed offline using the Edf2Mat Matlab Toolbox, designed and developed by Adrian Etter at the University of Zurich, to obtain fixation coordinates. To account for the possible error in eye tracking described above, a sample was considered to be centrally-focused only if the fixation coordinates remained within 1 degree of the central target boundary (1.5 degrees from the screen centre). If coordinates deviated outside this range, the sample was considered unfocused and indicates participants were not fixating centrally. For each participant, we calculated the proportion of time during each trial in which fixation was focused. This was then averaged across both easy and hard attentional load runs separately.

4.3.5 EEG Analysis

Data were epoched according to block onset where the first second of each block was excluded to remove onset transient responses, leaving 71 seconds of data for each block. A Fast Fourier transform (FFT) was conducted on the response obtained from each electrode site for each individual block using MATLAB allowing the steady-state average amplitude response at each of the three stimulus frequencies (4 Hz Central grating, 6.67 Hz LVF distractor and 7.50 Hz RVF distractor) to be obtained. These amplitude responses were then converted into average signal-to-noise ratios (SNR) by dividing them by the average amplitude signal for the frequencies in the surrounding 10 bins (± 0.5 Hz) representing a measure of 'noise'. The SNR signals were initially averaged to create a mean SNR head plot for each distractor condition at each attentional task. This was done separately for each of the three stimulus frequencies. Figure 4.3 shows the average SNR head plots for these eight conditions across each frequency.

We next wanted to define a region of interest (ROI) cluster within our electrode network so that a single SNR value could be extracted for each of the three frequencies. To do this, an average SNR was taken across all conditions where each of the three stimuli were present and averaged across all participants regardless of Inattention group. For the central task grating, SNR was averaged across all eight conditions (4 distractor conditions for each task) as the central task was presented throughout regardless of distractor or task (Figure 4.3, solid black boxes). For both distractors however, the SNR was averaged across the relevant four conditions when each of the distractor stimuli were present (Figure 4.3, LVF distractor frequency: dashed black boxes. RVF distractor frequency: dotted black boxes). This process therefore resulted in three ROI clusters that were independent of task and Inattention group as to compare across both factors equally. Figure 4.4 shows the resulting average SNR head plot for each of the three stimuli. Although there may be differences in the topographical location of the EEG signals between attentional-load task and between inattention-group, these were not the focus of this report so have been controlled for here.

As seen from Figure 4.4, steady-state EEG signals at our three visual stimuli frequencies were evident largely on posterior regions of the scalp, which overlie the visual cortex. The central task grating, as a stimulus at the point of fixation, elicited responses from both left and right hemispheres. Paradoxically however, both left and right visual field distractor frequencies elicited the strongest response to areas of the scalp over the ipsilateral visual cortex, appearing to differ from the known retinotopic nature of the visual system (Holmes, 1918; Horton & Hoyt, 1991). Such response patterns, known as ‘Paradoxical Lateralization’, are thought to be driven by visually-evoked responses on medial surface of the contralateral visual cortex which correspond to the stimulus representation (Barrett, Blumhardt, Halliday, Halliday, & Kriss, 1976). Here corresponding neurons are transversely orientated and are more successfully recorded by electrodes in the ipsilateral hemisphere compared to electrodes directly above the neurons in the contralateral hemisphere. From these SNR head plots, three ROI clusters were manually selected to include electrodes exhibiting high SNR values and hence responding to the related stimuli component. These are shown as green dots within Figure 4.4.

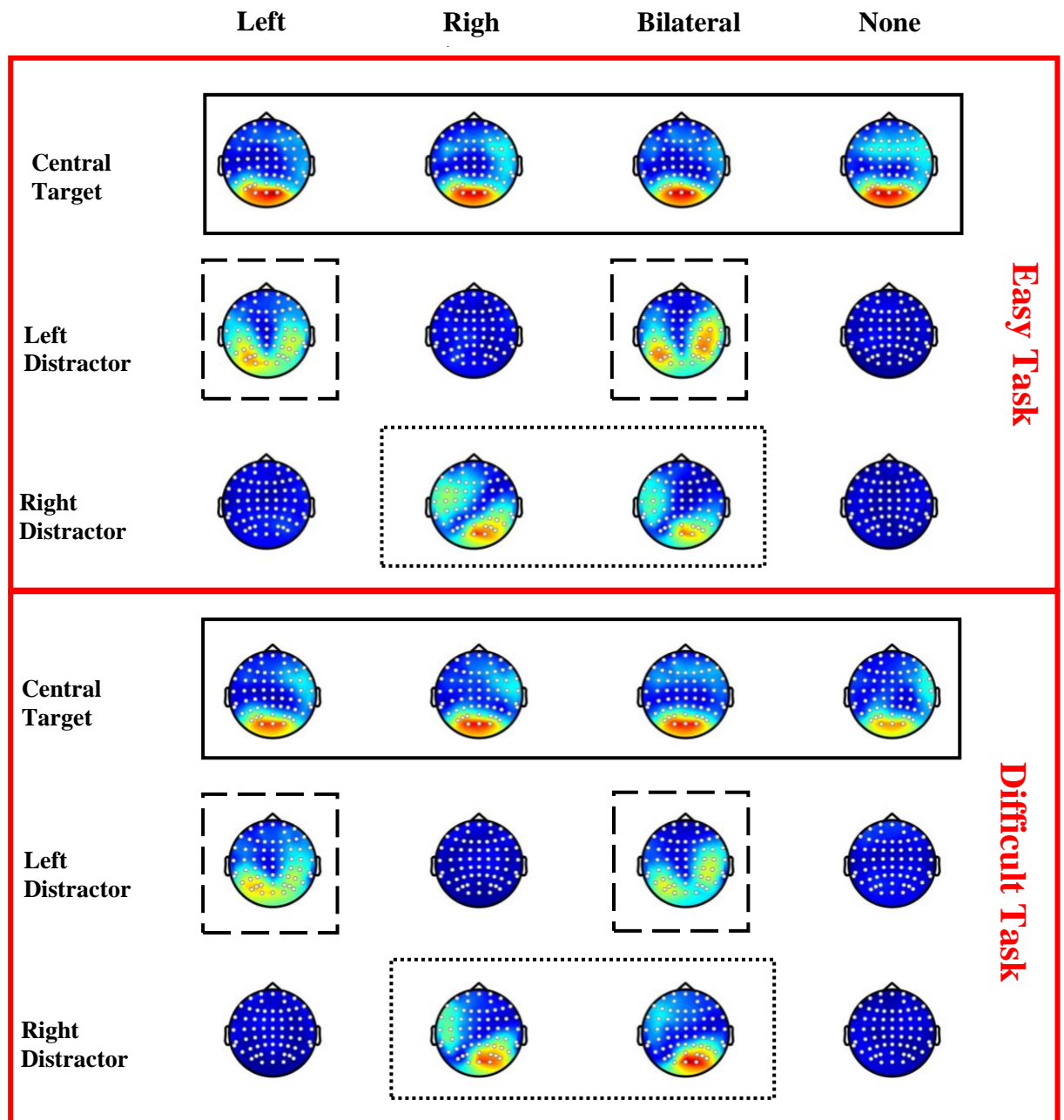


Figure 4.3 : Example EEG activity for a single participant across all conditions. Example head plots for a single participant showing the SNR for each of the three stimuli component frequency (rows); the central task grating (4Hz), the LVF peripheral distractor (6.67Hz) and the RVF peripheral distractor (7.50Hz). There are further presented by attentional-load task (Easy or Difficult) and by Distractor condition (LVF distractor, RVF distractor, Bilateral distractors and No distractors) in columns. Dark blue areas indicate a low SNR response at the specified frequency while dark red areas indicate a high SNR response. White dots indicate an electrode location. Boxes show the conditions that were averaged across to generate ROI clusters. Solid boxes represent the 8 conditions averaged at the central target frequency, Dashed boxes represent the 4 conditions averages across at the LVF distractor frequency and Dotted boxes represent the 4 conditions averages across at the RVF distractor frequency. Resultant averages are shown below in Figure 4.4.

With these ROI clusters, the same FFT process was conducted again from the original trial data. For each participant, the SSVEP time series was averaged across the electrodes within each ROI before applying the FFT to produce a single SNR value at each associated frequency. This was done separately for each of the eight conditions (2 Task conditions and 4 Distractors conditions). These formed the dependent variables used for the rest of the EEG analysis.

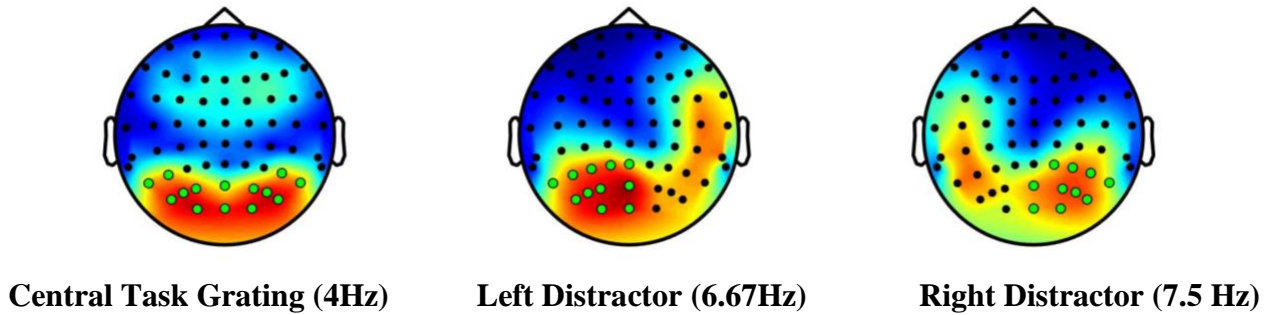


Figure 4.4 : Stimulus average SNR head plots. Head plots showing the average SNR for each of the three stimuli component frequency: the central task grating (4Hz), the LVF peripheral distractor (6.67Hz) and the RVF peripheral distractor (7.50Hz), which have been averaged across each attentional task, inattention-group and distractor type. Dark blue areas indicate a low amplitude response at the specified frequency while dark red areas indicate a high amplitude response. Dots indicate an electrode location where those filled in green were identified as forming the Region of interest (ROI) cluster for each frequency

4.4 Results

4.4.1 Central target Fixation

Eye tracking data were firstly analysed to check that participants remained fixated on the central task and refrained from making saccadic movements towards the distractors. We also wanted to check whether fixation differed between Inattention groups and Task which, if found, could influence both behavioural task accuracy and the EEG SSVEP responses recorded. A 2x2 ANOVA examined the effect of both Inattention group (Low Inattention vs High Inattention) and attentional-load task (Easy vs Difficult) on the average fixation time on the central target. Results showed that there was no main effect of either Group ($F(1,34)=1.00$, $p=.323$) or Task ($F(1,34)=0.37$, $p=.548$) in addition to no interaction between the two factors ($F(1,34)=0.00$, $p=.987$). Here the Low Inattention group spent 99.12% (SD = 1.38) and 99.20% (SD=1.40) of the time fixating centrally during easy and difficult tasks, while the High Inattention group spent 98.58% (SD= 1.91) and 98.66% (SD=1.72) fixating centrally for both tasks respectively. These results indicate that any potential differences within either

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behavioural task accuracy or EEG data are unlikely due to differences in central fixation.

4.4.2 Behavioural Task

Our initial aim here was to investigate whether the effect of attentional load task or distractor type could be observed at the behavioural level in how successful participants were at the central detection tasks. To do this, we extracted the time of all the behavioural responses made during each block. This was then converted into a reaction time (0-1000ms) relative to the onset of the central target displayed when the response was made. These were then coded as correct or incorrect responses, again depending on the central grating displayed during the response. Responses were removed from the analysis if they fell within 300ms of the target onset where these were taken as slow responses to the previous central target or accidental responses. Furthermore, responses made towards a correct target made after the 1000ms stimulus interval, when a new central grating was displayed, were also taken as an incorrect response.

Initially, we examined the average reaction time for correct responses (Hits) for all attentional-tasks and distractor conditions separately for each group. As shown in Figure 4.5A, quicker reaction times were observed during easy tasks compared to difficult tasks while there appears to be little difference in reaction time between the four distractor types. Interestingly, there are appears to be little differences in reaction time between both Low and High Inattention groups. These reaction times were entered into a 2x2x4 ANOVA examining the effect of Inattention group, Attentional-task and Distractor condition. As observed previously (Figure 4.5A), attentional task was shown to have a significant effect on reaction times whereby responses were faster within Easy tasks compared to those in Hard tasks ($F(1,34)=61.60$, $p<.001$, $\eta^2=.64$). There was also no significant main effect of either Distractor ($p=.119$) or Inattention group ($p=.361$). This suggests that the type of distractor does not interfere with the task enough to slow reaction times and that both Low and High Inattention groups exhibit similar reaction speeds. There was no significant interaction effects between any of the three variables.

In addition to the above measures, we further calculated the d' scores as a measure of sensitivity, taking into account both successful responses and false-alarms.

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This was again done for both attentional-tasks and distractor conditions separately. D' scores were calculated using both hit-rates (successful response) and false-alarms (response to a non-target) as shown below (Equation 1).

Equation 1: d' equation as a measure of task sensitivity

$$d' : z(\text{Total Hits} / \text{Number of targets}) - z(\text{Total False Alarms} / \text{Number of non-targets})$$

In cases where participants achieved a False-alarm rate of 0 and a Hit-rate of 1, these were replaced following the standard $1/(2n)$ and $1-1/(2n)$ procedure so that both became 0.02 and 0.98 respectively. Larger d' scores therefore represent increased behavioural sensitivity characterised by a larger number of successful responses in comparison to a reduced number of incorrect responses. As seen in Figure 4.5B, easy tasks appear to exhibit higher d' scores compared to hard tasks. Similar to the above reaction times measure however, there appears to be no difference between Inattention-groups or Distractor type, although the d' for distractor absent conditions seems slightly lower than distractor present conditions. D' scores were also analysed using a 2 x 2 x 4 ANOVA to again examine the effect of Inattention group, Attentional-task and Distractor condition. Mauchley's test of Sphericity was found to be significant for both the main effect of Distractor and interaction between Task and Distractor. Any effects involving these have therefore been corrected using the Huynh-Feldt correction factor.

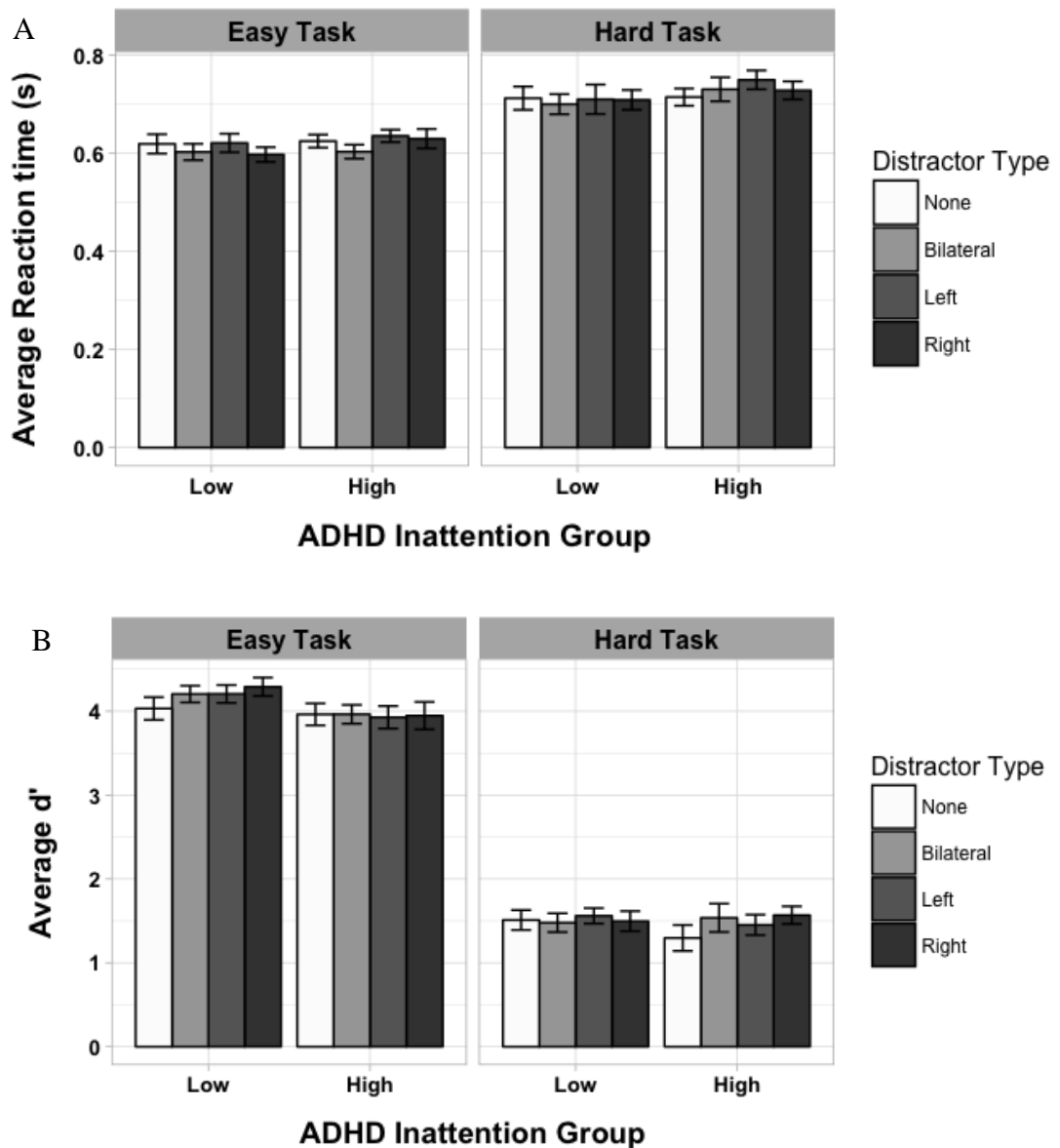


Figure 4.5: Behavioural results for Easy and Difficult attentional tasks. A) Average reaction time (s) for both Low and High attentional load tasks for each ADHD Inattention Group (Low and High) and each Distractor type condition (No distractor, Bilateral distractor, Left distractor and Right distractor). B) D' scores for both Low and High attentional load tasks for each ADHD Inattention Group (Low and High) and each Distractor type condition (No distractor, Bilateral distractor, Left distractor and Right distractor). All error bars represent ± 1 Standard Error.

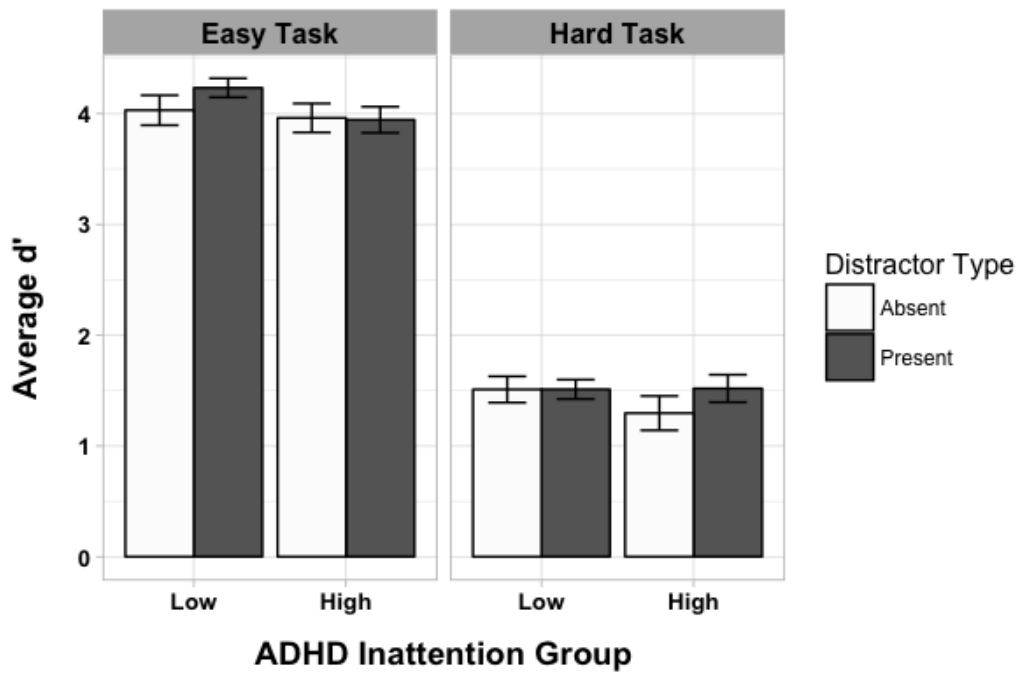


Figure 4.6: D' scores for distractor absent and present conditions for both ADHD Groups.. D' scores for both distractors absent and distractors present (Unilateral left distractor, Unilateral right distractor and bilateral distractors combined) conditions dependent on Attentional-load task (Easy and Hard) and ADHD Inattention Group (Low and High). Here all conditions involving the presence of a distractor (Bilateral distractor, LVF distractor and RVF distractor) have been combined into single condition. Error bars show ± 1 Standard Error.

Results showed that, similar to hit response reaction times, a significant main effect of Attentional-task was found on d' scores ($F(1,34)=666.36, p<.001, \eta^2=.95$) where d' was indeed reduced for Hard compared to Easy tasks, supporting the successful manipulation of attentional-load. There was no significant main effect of Distractor ($p=.132$) or Group ($p=.247$). A significant three-way interaction was found however between Attentional-task, Distractor condition and Inattention group ($F(1,91.88)=2.99, p=.040, \eta^2=.95$; *Huynh-Feldt correction*). Helmert post-hoc tests were used to explore this three-way interaction and showed this result was primarily driven by difference between the distractor absent condition and combined distractor present conditions ($p=.005$; No Distractor vs. Bilateral, Left and Right distractors combined). Figure 4.6 shows such results where during easy tasks, the presence of a distractor increased d' scores for the Low Inattention group but did not influence the High Inattention group. On the other hand, during hard tasks, the presence of a distractor increased the d' score for the High Inattention Group but had no effect on the Low Inattention group. There was no significant three-way interaction when comparing

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bilateral and unilateral conditions ($p=.981$; Bilateral vs. Left and Right combined) and when comparing left and right distractors ($p=.101$; LVF vs RVF). Such results suggest that the presence of any distractor, regardless of presentation hemifield or whether presented unilaterally or bilaterally, influence the task sensitivity of both Inattention groups differently depending on task difficulty.

4.4.3 SSVEP EEG responses

We now turn to examine the SSVEP responses recorded from the EEG while participants undertook the behavioural task. Here we will be examining such responses in three separate areas; Central target processing, Distractor processing and Relationship between Central and Distractor processing. The first two will investigate how our three variables of interest (Inattention Group, Task attentional load and Distractor type) influence the SSVEP EEG response towards the central target and distractors separately. The final section will then examine how such variables influence the interaction between both central and distractor components.

Central Task processing

Our first aim was to examine whether there were any differences in central task processing between both Low and High Inattention groups and whether those differences interact with task (differing levels of attentional load) as well as the presence and location of a peripheral distractor. This will specifically allow us to explore our first three hypotheses where we expect to observe increased responses to the central target during difficult, high-load tasks. Furthermore, we expect the presence of a distractors to reduce central target responses, particularly during easy low-load tasks, and that distractors will have a larger influence within the High Inattention group. Figure 4.7 shows the average SNR responses recorded at the central target frequency. Here, the Low Inattention group appears to show an increased response compared to the High Inattention group, while increased responses are also observed during the Hard compared to Easy tasks. We can further see slight reductions in SNR response under bilateral distractor conditions.

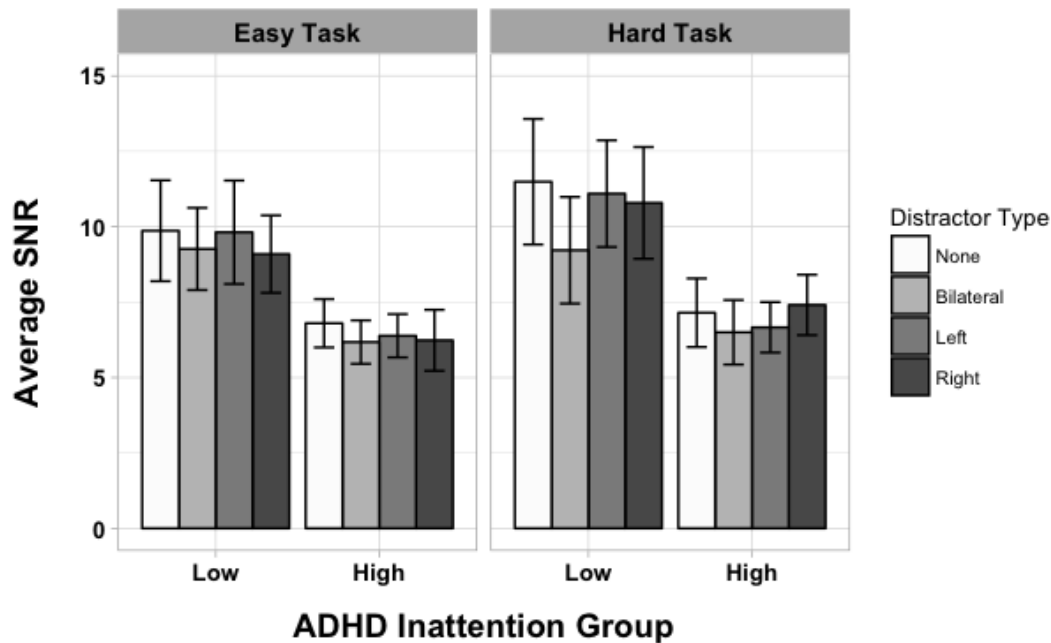


Figure 4.7: Central Target SNR response. Average SNR recorded at the central target frequency (4Hz) for both easy and hard attentional-load tasks, split further by ADHD Inattention group (Low and High) and Distractor type (No distractor, Left, Right or Bilateral). Error bars represent ± 1 Standard Error.

We conducted a single 2 (Inattention group) x 2 (Attentional task) x 4 (Distractor location) mixed measures ANOVA where the average SNR recorded at the central target frequency acted as the dependent variable. As we hypothesised, there was a significant effect of Attentional-load task on central task processing, whereby hard tasks elicited an increased SNR response compared to easy tasks ($F(1,34)=5.70$, $p=.023$, $\eta^2=.14$). This shows that despite identical visual input within both tasks, the hard task with increased attentional load demands more resource to be directed towards the central stimulus, resulting in a raised SSVEP signal. We also see a trend effect for Inattention group, where the reduced signals seen within the High Inattention group compared to the Low group just fail to reach significance ($F(1,34)=4.04$, $p=.053$). Furthermore, there was a significant main effect of Distractor condition on the response to the central target ($F(2.88,96.80)=2.78$, $p=.048$, $\eta^2=.08$; *Huynh-Feldt correction*). Further Helmert post-hoc tests showed this to be primarily driven by differences between the Bilateral and Unilateral conditions ($p=.019$: *Bilateral vs. LVF and RVF Unilateral*) and between the Bilateral and No distractor conditions ($p=.018$) where SNR signals are reduced during Bilateral distractors presentations. There was no significant

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difference between no distractor and unilateral distractors or between unilateral LVF and RVF distractors. This suggests that while bilateral distractors are able to direct attention away from the central task, and hence reducing responses to the central target, unilateral distractors are less successful in achieving this. Unexpectedly, this effect did not interact significantly with Attentional task as predicted, where it was thought that distractors would only influence central task processing under the easy task where there were sufficient 'attentional resources' to process the distractors. As shown in Figure 4.7, this reduction in SNR signal under bilateral distractor conditions can be seen in both easy and hard tasks. Similarly, the effect of distractor condition also did not interact with Inattention group as hypothesised, showing responses to the central task-relevant stimuli in Low and High groups were similarly influenced by the peripheral distractors.

Distractor Processing

Our next aim was to examine whether both Inattention group and Distractor properties (presentation hemifield and distractor type) influence the processing of the peripheral distractors. Here we are only interested in conditions where at least one distractor is present, so this section will focus on the two unilateral (LVF and RVF) and bilateral conditions. This will allow us to explore our original hypothesis that responses to individual distractors will firstly be reduced if presented under bilateral conditions compared to unilateral conditions and secondly, that this relationship may differ between Inattention groups. We also proposed that responses to RVF distractors will differ significantly between Low and High Inattention group, while those towards LVF distractors will not.

Figure 4.8 shows the average SNR signals recorded in response to LVF and RVF distractors separately, under both Unilateral or Bilateral conditions and across both Attentional tasks and Inattention groups. Here we can firstly see that SNR signals appear to be reduced towards RVF distractors compared to LVF distractors in addition to showing reduced SNR signals under bilateral compared to unilateral conditions. We can also see an increase in SNR signals for the High Inattention group, particularly towards RVF distractors. Finally, there appears to be little difference between easy and hard tasks.

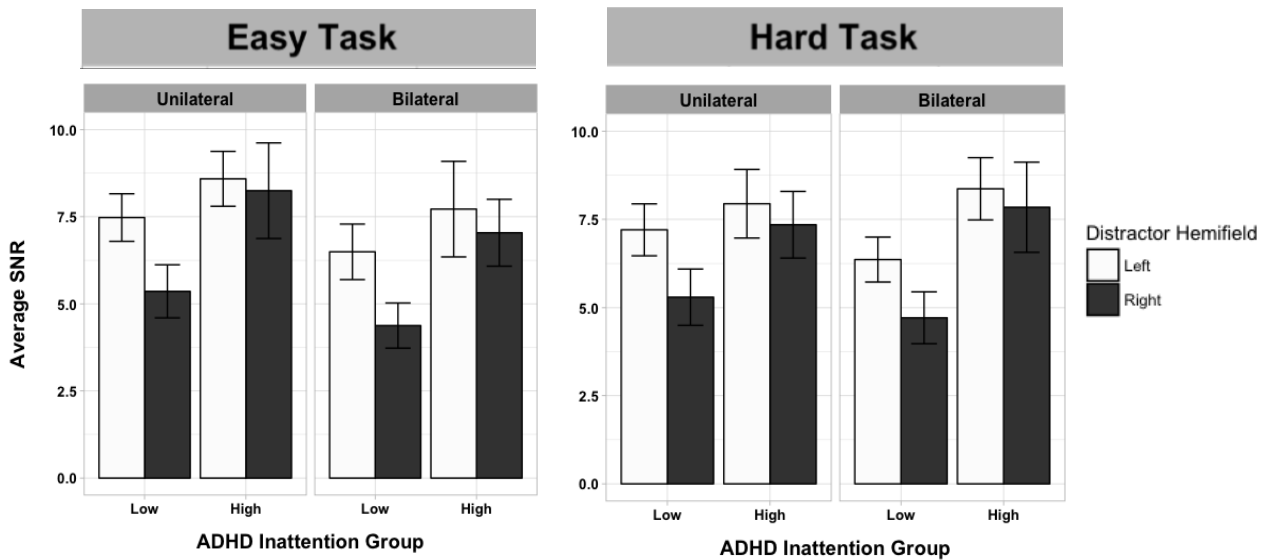
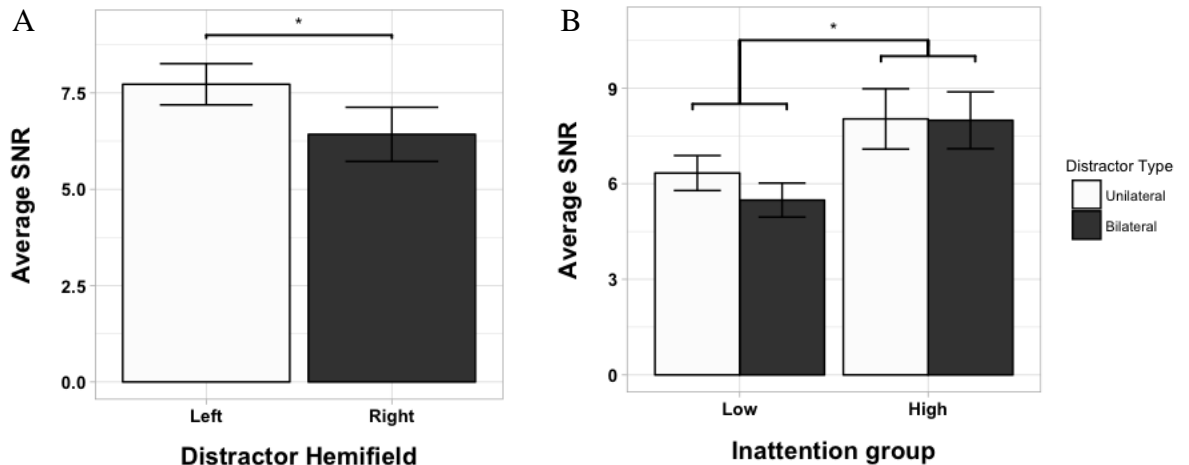


Figure 4.8: Peripheral distractors SNR response. Average SNR signal recorded at both LVF and RVF distractor frequencies under both unilateral or bilateral conditions within both Inattention groups (Low and High) and Attentional tasks (Easy and Hard). Error bars represent ± 1 Standard Error.

To explore this in more detail, we conducted a single 2 (Inattention group) x 2 (Distractor hemifield; LVF vs RVF) x 2 (Distractor type; unilateral vs bilateral) x 2 (Attentional-load Task; Easy vs Hard) mixed measures ANOVA, separating the previous single distractor variable into two separate variables to examine the distinct effect of hemifield and type on the SNR response towards each distractor. Firstly, the effect of Inattention group trended towards significant ($p=.071$), which is primarily driven by the pattern previously noted above in Figure 4.8, where the High Inattention group appear to show greater responses towards the peripheral distractors compared to the Low group. The effect of task (Attentional load) however shows no significant main effect on distractor SNR signals ($p=.467$).

Analysis also revealed a significant main effect of Distractor hemifield ($F(1,34)=8.62$, $p=.006$, $\eta^2=.20$), where distractors in the LVF showed increased SNR responses compared to those in the RVF. Figure 4.9A shows this main effect collapsed across the remaining three variables. However, while such effect could indicate a differing level of distractibility between hemifields, such an effect could be driven by differential sensitivity to the differing frequencies used to encoding both LVF and RVF distractors.

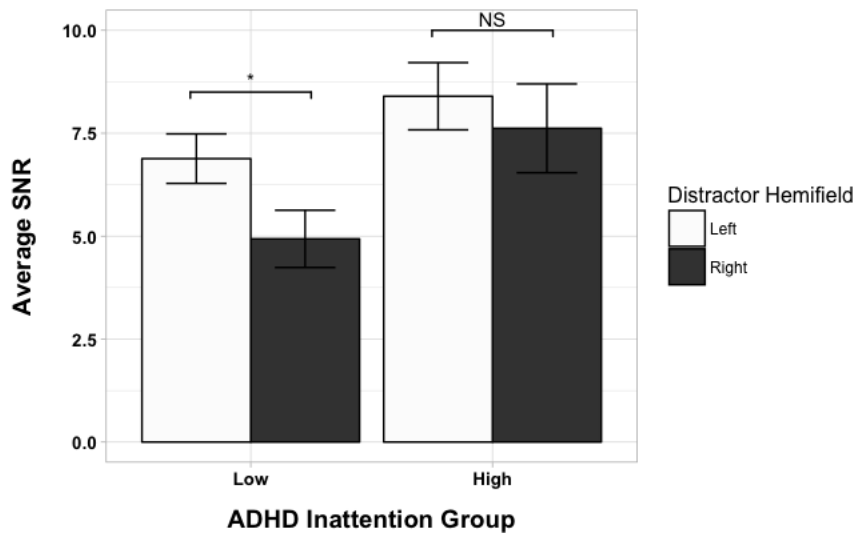


*Figure 4.9: Average Signal to Noise ratio (SNR) response for peripheral distractors. A) Average SNR for both left and right visual field distractors showing the main effect of Distractor hemifield. B) Average SNR for both unilateral and bilateral distractors conditions recorded from both Inattention groups, demonstrating the significant interaction effect between Distractor type and Inattention group. Error bars represent ± 1 standard error. * notes a significant difference between conditions.*

Furthermore, we can observe a significant effect of Distractor type ($F(1,34)=8.27$, $p=.007$, $\eta^2=.20$) and a significant interaction between Distractor type and Inattention group ($F(1,34)=6.75$, $p=.014$, $\eta^2=.17$). Whilst the main effect of Distractor type shows that unilateral distractors exhibit an increased SNR compared to the same component under bilateral distractor conditions, the interaction suggests this relationship differs between group. Figure 4.9B shows this interaction whereby the Low Inattention group display a smaller response to bilateral compared to unilateral stimuli, while the High Inattention group shows little difference in such responses. This pattern appears to suggest that those with Low Inattention are having to split attentional resources across both distractors, resulting in reduced individual distractor processing when presented with a competing distractor (bilateral condition) compared to when presented alone (unilateral condition). Such pattern however is not evident in those with High Inattention, whose responses appear similar regardless of the number of distractors present.

We finally wanted to examine whether each Inattention group exhibit differing responses towards LVF and RVF distractors, as suggested by our own previous research. Here we averaged across both Task and Distractor type to generate an average SNR for both LVF and RVF distractors. Figure 4.10 shows these averaged SNR responses, where we can see that the Low Inattention group exhibit a large reduction in

the response to distractors in the RVF compared to those in the LVF. On the other hand, while the High Inattention group demonstrate a similar pattern with a reduced signal towards the RVF distractor compared to the LVF, this difference is a lot smaller. Two paired-sample t-tests showed that, when applying Bonferroni correction for multiple comparisons (corrected p value = original p value * n tests), the Low Inattention group indeed exhibited a significant reduction in the SNR response towards the RVF distractor compared to the LVF ($t(15)=2.58$, $p= .042$). The High Inattention group however, showed no significant difference between SNR responses to distractors in the LVF and RVF ($t(19)=1.36$, $p=.189$). Further independent sample t-tests also indicated that while the response towards the RVF distractor was significantly lower in the Low Inattention group compared to the High ($t(34)=2.18$, $p=.036$), there was no significant group difference in the LVF response ($t(34)=1.94$ $p=.060$). Such pattern of results may therefore imply that those with low levels of Inattention are more successful at suppressing irrelevant RVF distractors compared to those in the LVF, while those with higher levels of Inattention have a similar ability to suppress distracting stimuli in both hemifields.



*Figure 4.10: Average Signal to Noise ratio (SNR) response for peripheral distractors by Inattention group and Distractor Hemifield.. Average Signal to Noise ratio (SNR) response to distractors presented within the LVF and RVF for both Low and High Inattention-groups. These have been averaged across Task and Distractor type (Unilateral and Bilateral). Error bars represent ± 1 standard error. * notes a significant difference between conditions while a NS notes no significant difference.*

Relationship between Central task and Distractor processing

Our final aim was to explore the direct relationship between the processing of the central target and the peripheral distractors for both Inattention groups, and to examine whether this relationship differs with Task and Distractor hemifield. Here we will just be examining the distractor responses under unilateral conditions as we are interested only in conditions where at least one distractor and the central task were presented. Similarly, bilateral conditions also cannot be used as the response towards the central target during this condition would have to be duplicated to be used to compare to both left and right distractor responses under bilateral conditions, hence this analysis will focus only on unilateral distractor conditions.

Figure 4.11A and B show the responses towards the central target and peripheral distractor (stimulus components) for each Inattention group, Task and Hemifield. Here we can see that the Low Inattention group displays increased SNR response towards the central component relative to the peripheral distractor. This pattern however appears to be the opposite for the High Inattention group who display an increased SNR response instead towards the peripheral distractor compared to the central target. Such pattern appears to hold for both easy and hard tasks and for both LVF and RVF distractor conditions.

Here we use a 2 (Inattention group; Low vs. High) x 2 (Distractor Hemifield; LVF vs. RVF) x 2 (Stimuli component; Central target vs Distractor) x 2 (Attentional task; Easy vs. Hard) mixed ANOVA to explore the responses to both visual components. Critically, we are not interested in any main effects or interaction that do not involve the stimulus component (Central target or Distractor) as our primary aim was to observe the change in their respective relationship and averaging over both components would remove this. These effects will therefore not be reported here.

Analysis revealed a significant interaction effect between stimulus component and Inattention group ($F(1,34)=5.73$, $p=.022$, $\eta^2=.14$). As previously observed, those the Low Inattention group exhibited increased central target SNR responses relative to the distractor response, while those in the High Inattention group exhibited a decreased central target SNR response relative to the distractor response. Figure 4.11C shows this effect where the SNR response has been collapsed across Task and Distractor hemifield. Stimulus component was also found to significantly interact with Attentional Task

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($F(1,34)=14.61, p=.001, \eta^2=.30$) where increasing the attentional load of the task increased the SNR response towards the central target while reducing the SNR response for the distractors (Figure 4.11D). The main effect of stimulus component was not statistically significant ($p=.259$).

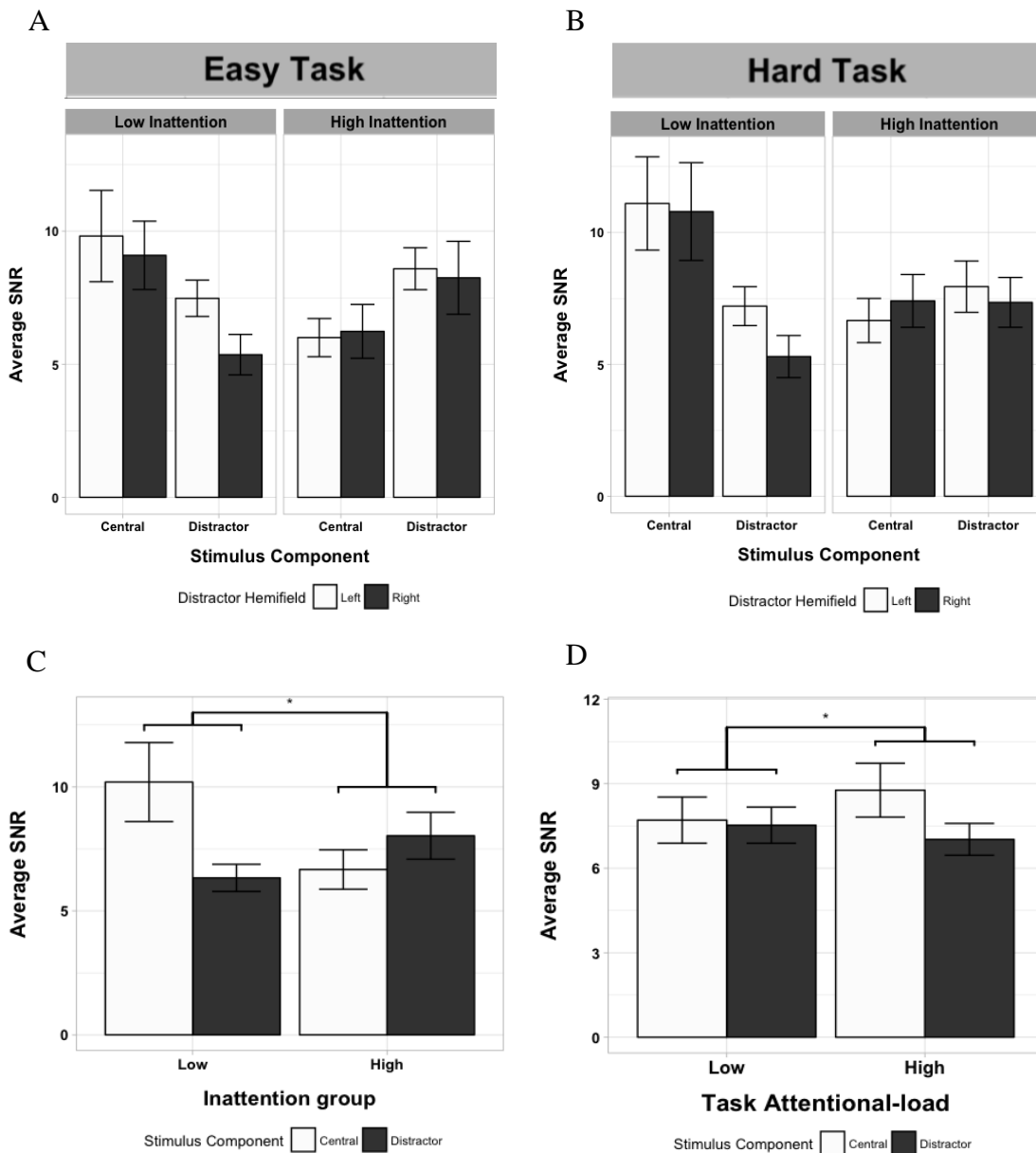


Figure 4.11: Average SNR for both Central targets and Peripheral distractors. Graphs A and B display the average SNR values recorded at either the central task frequency or the distractor frequency for easy (A) and hard tasks (B) respectively and for both Inattention groups and Distractor hemifield (Unilateral LVF and Unilateral RVF). Graph C displays the same information as A and B, showing central target and distractor SNR averaged across attentional task and distractor hemifield. Graph D again shows the same information as A and B, with the central target and distractor SNR values averaged across Inattention group and distractor hemifield.

4.5 Discussion

Despite the high prevalence of ADHD (Faraone et al., 2003; Froehlich et al., 2007; Polanczyk et al., 2007), relatively little is understood about how those with ADHD process the visual world. Using a sustained attentional paradigm with irrelevant peripheral distractors, the current study has investigated how those typically developed adults with low and high levels of ADHD-associated Inattention traits process visual stimuli and allocate attentional resources. This was achieved by measuring neural SSVEP responses elicited by both the task-relevant central target and peripheral, task-irrelevant distractors. We also explore how such responses interact with both task attentional-load and the location of the peripheral distractor.

4.5.1 Increasing Attentional Load

Our first aim was to explore the influence of attentional-load on the processing of both task-related and task-irrelevant stimuli. As anticipated, behavioural results from the central detection task show that all participants found the hard, high perceptual-load task more difficult than the easy, low-load task: showing increased reaction times for correct responses and a reduced d' score, suggesting fewer correct responses and more false alarms, regardless of distractor presence. Such results therefore replicate those seen previously (Lavie, 1995; Schwartz et al., 2005) and demonstrates that perceptual load manipulation was successful in both Inattention groups.

Examining central target responses, we found a clear relationship between central target processing and attentional-task, where neural responses towards the central target increased during hard, high-load tasks compared to easy, low-load tasks. Unexpectedly however, there was no significant effect of attentional load when examining the distractor responses where the SSVEP signals were similar during both easy and hard tasks. Directly comparing responses to both stimulus components during easy and hard tasks further supported this differential relationship whereby neural responses towards the central target were increased relative to the distractor only in hard, high-load tasks while easy, low-load tasks displayed little difference between central and distractor responses. This supports our original hypothesis that increasing attentional-load will increase neural responses towards central task-related targets although our hypothesis that increasing attentional-load would also reduce distractor responses, while there is a small non-significant decrease in the response to peripheral

task-irrelevant distractors, was not supported. This appears to provide some support for the influence of task attentional-load on visual processing and adds further support to the Load Theory whereby, as the central task becomes more attentionally demanding, additional attentional resources are required to complete the task resulting in an increased response towards the central target (Beck & Lavie, 2005; Forster & Lavie, 2008, 2011; Lavie, 2005; Lavie & Cox, 1997; Lavie & de Fockert, 2003; Lavie et al., 2004). Here, the SSVEP results relating to the central target were recorded mainly from a ROI overlapping the occipital lobe, including the visual cortex, suggesting that attentional-load reduces neural signals within the visual system, supporting patterns previously observed using MRI (Bahrami et al., 2007; O'Connor et al., 2002; Rees et al., 1997; Schwartz et al., 2005). In addition, while the absolute level of neural responses towards the peripheral distractors did not decrease significantly during hard, high-load tasks, decreased interference from the distractors may still be experienced due to the large increase in processing for the central target. Here such relative differences between the two stimulus components may be as important as the absolute changes in SSVEP signals in determining the influence of perceptual load on attentional allocation. Further research may be required to understand the importance of such difference.

In addition to examining the influence of attentional-load alone, we also aimed to explore how the relationship between attentional-load and stimulus-related signals may differ depending on ADHD-associated Inattention traits. Here we showed that both the Low and High Inattention groups demonstrated a similar influence of attentional-load: increasing attentional-load increased central target responses while having a limited effect on the distractor responses. This supports previous research who have shown that perceptual load results in heightened focus on the task-related stimuli while reducing distraction in both individual with ADHD and those without (Chan et al., 2009; Forster & Lavie, 2007; Forster et al., 2014; Friedman-Hill et al., 2010; Huang-Pollock et al., 2005). Unexpectedly however, we see a clear difference in the neural signals both Inattention groups display for the central target and distractors, regardless of attentional task. Here, those with no or few inattention traits show greater SSVEP signals towards the central target and weaker responses towards the peripheral distractors. Those with high levels of Inattention however show the opposite pattern, where signals are instead stronger for the peripheral distractor compared to the central target. This therefore indicates that those with high levels of Inattention may have a

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different pattern of attention allocation compared to those with few traits, where distractors are processed and attended to more readily than the central target, despite being irrelevant to the task – possibly accounting for some of the increased inattention experienced in daily life. Such group differences however appear to be largely driven by the responses towards the central target, where larger signals are observed in the Low Inattention group compared to the High group, rather than towards the distractors as expected which shows smaller group differences. Indeed, extensive previous literature has often established evidence for a deficit in sustained attention in individuals with ADHD (Booth et al., 2005; Cubillo et al., 2012; Dibbets et al., 2009; Durston et al., 2003; Hanisch et al., 2005; Huang-Pollock et al., 2005; Kooistra et al., 2010; Mahone et al., 2009; Newman et al., 2016; Rubia, Halari, et al., 2009; Rubia, Smith, et al., 2009; Rubia et al., 2007; Schwartz et al., 2005; Tamm et al., 2013; Vaidya et al., 1998; Wood et al., 1999; Wright et al., 2014). This suggests that Inattention differences between our groups may stem from the ability to process and remain focused on task-related stimuli, where those with many Inattention traits are less successful at sustaining attention on the central target.

4.5.2 Influence of Distractors

Our second aim was to investigate how task-irrelevant peripheral distractors influence task performance, both in terms of the responses to the central target and behavioural performance. Following on from the Load theory discussed above, we hypothesised that distractors will only interfere with the attentional task during easy, low-load conditions when there is excess attentional capacity to process the distractors. Examining the central target SSVEP responses, we observed a significant effect of distractor presence where bilateral distractors decreased the response towards the central target compared to distractor free conditions. This suggests that bilateral distractors provide significant interference and draw attention away from the central target, resulting in a reduced neural response. Unexpectedly however, this was found to occur across both easy and difficult attentional tasks rather than being confined to the easy task as previous research has established (Forster & Lavie, 2008, 2011; Lavie, 1995, 2005, 2010; Lavie et al., 2004). However, one notable difference between both the present study and those previously demonstrating such low-load only effect, arises from the type of distractors used. Previous research has tended to use infrequent, highly salient distractors (e.g. cartoon characters or letters) presented for short durations.

During the current study however, distractor stimuli were presented continuously throughout their associated run, to allow a distractor-associated SSVEP response to be recorded and were presented in 75% of runs. Such stimuli are less likely to be “attention grabbing” compared to those previously used and may therefore interfere with the central task in a different manner. As discussed previously, our results indicated that attentional load did not significantly reduce responses towards the distractor, suggesting that both Inattention groups continued to process the peripheral distractors during both tasks. This may therefore explain why the distractor continues to interfere with central task processing during hard, high-load tasks. Furthermore, it was also found that distractor presence only influenced central target responses under bilateral but not unilateral conditions. This could indicate that bilateral distractors are more distracting and greatly impede the attentional task being performed compared to unilateral targets.

Such reductions in central task processing were found to occur across both Inattention groups suggesting that all participants showed a reduced central focus during the presentation of bilateral distractors. This fails to support our hypothesis that those with high levels of inattention would show an increased interference from the peripheral distractors. Nevertheless, this may again stem from the frequent, continuous distractors used as mentioned above, which could result in similar central focus interference for both Inattention groups. This could suggest that the increased distractor interference often seen in those with ADHD (Forster et al., 2014) may depend on the type of stimulus used whereby, while there was a trend for the distractor to be processed more in those with High Inattention traits, the distractor influenced both groups similarly.

Indeed, behavioral task performance also suggests a more unusual relationship between distractor presence and central target focus. Here we unexpectedly find no significant main effect of Distractor type on behavioural task performance, where both hit reaction time and d' score did not significantly differ with distractor type or presence. Unusually however, we see a three-way interaction emerge between task attentional-load, distractor presence and Inattention-group for d' scores. The presence of a distractor within an easy task, regardless of distractor type and hemifield, increases d' performance for the Low Inattention group while having no effect on the High Inattention-group. Conversely, distractors presented in the hard task, again regardless of distractor type and hemifield, increases d' performance for the High Inattention-group

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while having no effect on the Low Inattention-group. It is currently unclear as to why the presence of task-irrelevant stimuli increases task performance in this way rather than decreasing it, particularly given our results showing a reduced response to the central target during bilateral distractor presentation. There have been some cases of distractor-related increases in behavioural performance however, which have largely been attributed to the distractors acting as ‘alerting mechanisms’ (Thomas & Nicholls, 2018) or increasing arousal (Day, Shyi, & Wang, 2006; Sanders & Baron, 1975), particularly during easy, low-load tasks. Whilst this may account for the increased performance in those with low Inattention, where the peripheral stimuli orientated attention towards the central task resulting in greater focus and increased behavioural performance, this struggles to explain the increases seen during hard tasks for those with High Inattention levels.

4.5.3 Sensory Competition

As part of the present study, we also set to expand on the previous chapter by exploring potential differences between the processing of both unilateral and bilateral peripheral distractors and whether this was influenced by Inattention group and Attentional load. Previous research has often established that bilateral presentations across both LVF and RVF often stimulate ‘sensory competition’, where attentional and processing resources are split across hemifields (Fink et al., 2000; Kinsbourne, 1977; Schwartz et al., 2005; Vuilleumier & Rafal, 2000). Similar to previous findings, we found a significant effect of distractor type where the SSVEP response to a single distractor component was reduced when presented as part of a bilateral pair (bilateral distractor) compared to presented alone (unilateral distractor). This therefore suggests that sensory competition has occurred where both components of the bilateral presentation are competing for resources and neural activity towards each component is reduced (Desimone & Duncan, 1995; Moran & Desimone, 1985; Reynolds et al., 1999). Interestingly, such results were shown to significantly interact with Inattention group where the reduction in distractor SSVEP signal during bilateral presentation was only observed in those with few Inattention traits while those with high inattention traits showed no difference in distractor processing during bilateral and unilateral presentations. Such results therefore support our original hypothesis that both Low and High Inattention groups would likely show differing levels of sensory competition, where it appears that those with high levels of inattention show a significantly reduced

or absent competition response between bilateral distractor components. Whilst there is little previous literature directly assessing neural differences in sensory competition within those with ADHD, research has explored the idea that sensory competition abnormalities can account for visual extinction in those with unilateral neglect (Driver & Vuilleumier, 2001); a condition often compared to ADHD due to the comparable, although more pronounced, spatial-asymmetries in attention and proposed right-hemisphere deficit within the attentional-network (Carter et al., 1995b; Epstein et al., 1997; Geeraerts et al., 2008; Heilman & Van Den Abell, 1980; Sandson et al., 2000; Vance et al., 2007; Waldie & Hausmann, 2010; Weintraub & Mesulam, 1987). Here neglect patients typically show an asymmetrical sensory competition effect where stimuli in the LVF become undetected after a second ‘competing’ target is added to the RVF. Our research however points to those with increased Inattention traits showing little or no effect of sensory competition, where the addition of a competing stimuli, resulting in attention and processing resources being split across the visual fields, has no influence on the processing of each distractor component. Such results therefore suggest that increased sensory competition is not an underlying cause of increased distractibility in those with Inattention problems and may indicate differences in top-down attentional control and resources (Friedman-Hill et al., 2010). Here it is possible that those with high Inattention levels can show sensory competition although this may require more salient distractors or a task with even greater attentional load to elicit such effect where the demand on attentional resources is greater.

4.5.4 Hemifield

Our final aim was to explore whether peripheral distractors would result in increased interference depending on whether they were presented in the LVF or RVF and whether such differences depend on Inattention group. Here we find clear differences in the distractor-associated SSVEP response between Inattention groups whereby the Low Inattention group show significantly stronger responses towards unilateral LVF compared to an identical distractor in the RVF. Those in the High Inattention group however show no significant difference between LVF and RVF distractor responses. This indicates that those with no or few inattention traits are processing the LVF distractors more than those on the RVF, suggesting that RVF stimuli are less distracting and are more easily ignored. Unusually however, we show no other significant difference between LVF and RVF distractors for their influence on

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central target responses or on behavioural task performance. This may therefore suggest that, while the neural representation for both hemifield distractors is different for the Low Inattention group, this fails to impact the sustained attention directed towards the central target. Such findings appear to fit with our original hypothesis where we predicted that both Inattention groups will show a differing response towards the RVF distractors but not towards the LVF distractors. Furthermore, this also adds to our previous finding which showed correlations between ADHD-associated Inattention traits and SC activity only during RVF stimulus presentation (Chapter 3). Previous research however has tended to find clear interactive effects where by those with ADHD are typically more distracted by RVF distractors (Chan et al., 2009; Epstein et al., 1997; Geeraerts et al., 2008; Huang-Pollock et al., 2005) while control participants are more distracted by those in the LVF (Geeraerts et al., 2008; Huang-Pollock et al., 2005). Whilst we can observe that those with low inattention are more likely to process irrelevant stimuli in the LVF, those with high inattention do not show an increased processing of RVF stimuli over LVF. However, our results have previously demonstrated that SSVEP responses towards distractors in the LVF were significantly stronger than those to the RVF distractors. Whilst this may be a general tendency for participants to process the LVF more, it is also likely that such results are due to the differences in the presentation frequency for each component. Future research may wish to explore this idea by counterbalancing the frequency of LVF and RVF distractors or examining both distractors only under unilateral conditions where both can be presented at an identical frequency. It is possible that such differences are masking any hemifield differences seen in those with high Inattention levels.

4.5.5 Final Conclusion

In conclusion, the present study has shown clear difference in visual processing of task-related and unrelated stimuli between those with low and high levels of ADHD-associated Inattention traits. Individuals with low Inattention levels process the task-related stimuli more than the unrelated distractors while those with high Inattention levels showed the opposite effect, processing the irrelevant distractors more than the task-related stimuli. Attentional-load was further shown to significantly influence central target processing in both Inattention groups where neural responses towards task-related components increased with attentional-load. Those with no or few

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inattention traits were also shown to process distractors less than those with high Inattention, but only when presented in the RVF.

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5.1 Abstract

Previous research has shown strong evidence that spatial attention can modulate neural responses to visual stimuli; increasing responses towards attended locations while decreasing responses towards unattended locations. Using fMRI, we set out to explore whether such modulations can differ depending on an individual's Inattention traits, often associated with ADHD. Here we investigated the effect of Inattention level (Low vs High) and Stimulus presentation hemifield (Left - LVF vs Right - RVF) on neural responses within both ipsilateral and contralateral regions of Lateral geniculate nucleus (LGN) and Primary Visual cortex (V1). Participants counted stimulus changes to ensure they attended to the hemifield in which the stimulus was presented. In keeping with previous literature, we show extensive stimulus driven positive BOLD signals within contralateral LGN and V1 regions where there were no significant group differences. Ipsilateral regions of V1 however showed significantly stronger negative BOLD signals for the Low Inattention group compared to the High group when participants attended to stimuli in the LVF. Such group differences were not found in ipsilateral V1 when stimuli were presented to the RVF or for either visual field in the LGN. It appears therefore that low Inattention group shows greater evidence of suppression than high Inattention group when ignoring the RVF. Whole-brain analysis revealed significant group differences in BOLD responses within anterior regions of the Superior Parietal lobe, where the High Inattention group showed positive BOLD right hemisphere activity (LVF stimulus presentation) and bilateral activity (RVF stimulus presentation) while the Low Inattention group who showed negative BOLD responses in the same regions. Such results demonstrate clear differences in suppression mechanisms for those with few and many ADHD-associated Inattention traits whereby those with High inattention levels demonstrate a weak or absent suppression response, particularly in representations of the RVF.

5.2 Introduction

Spatial attention acts as the ability to selectively direct attention to a region of space while being able to ignore distracting and irrelevant information elsewhere. Research has long established the link between such attention and visual processing, where areas of directed-attention show an enhanced level of processing, leading to a heightened perception of visual stimuli at that location. Such mechanisms however do come at a cost, in that surrounding unattended regions of space exhibit a reduced level of perception and visual processing, refuting the idea that perceptual processing has an unlimited capacity (see review: Desimone & Duncan, 1995). Indeed, such cost has been behaviourally shown through Posner Cuing tasks, where invalid cueing away from a target increases stimulus detection time compared to valid cueing (Posner, 1980; Posner, Nissen, & Ogden, 1978).

Single-cell recording has previously demonstrated such neural attentional mechanisms exist within the visual system, with some finding an attentional enhancement of activity within V1 (McAdams & Maunsell, 1999; Motter, 1993; Roelfsema et al., 1998; Thiele et al., 2009) and both V2 and V4 (Luck et al., 1997; McAdams & Maunsell, 1999; Moran & Desimone, 1985; Motter, 1993; Reynolds et al., 1999) in macaques. More recent research has also focused on neuroimaging techniques in humans, whereby fMRI has shown areas of the Lateral Geniculate Nucleus (LGN) (O'Connor et al., 2002) and V1 (Gandhi et al., 1999; Kastner et al., 1999; Martínez et al., 1999; O'Connor et al., 2002; Somers et al., 1999; Tootell, Hadjikhani, et al., 1998), corresponding to attended regions of contralateral visual space, show an increased MR signal regardless of whether a stimulus was present or not. Similar results have been found for V2 and V4 (Kastner et al., 1999; Martínez et al., 1999; Somers et al., 1999; Tootell, Hadjikhani, et al., 1998) which has led to the view that such attentional-modulation increases higher up the visual system.

Nevertheless, while there is strong evidence for an attentional enhancement in early visual areas, there is less evidence to support the idea of attention-modulated suppression within visual areas that correspond to unattended locations. Macaque single-cell recording has revealed some evidence of suppression within both the LGN and V1 (Vanduffel, 2000). Human imaging studies have also provided some evidence

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for this suppression by recording negative BOLD responses, where signals are suppressed below baseline levels, within both striate and extrastriate regions (Shmuel et al., 2002; Slotnick, Schwarzbach, & Yantis, 2003; Smith, Singh, & Greenlee, 2000; Smith, Williams, & Singh, 2004; Tootell, Hadjikhani, et al., 1998; Tootell, Mendola, Hadjikhani, Liu, & Dale, 1998). A recent study by Gouws et al. (2014) further studied visually suppression mechanisms within these areas using fMRI. Using a lateralized visual stimulus, participants performed one of three tasks in order to alter the direction of spatial allocation; stimulus-related tasks directed attention towards to the lateralized stimulus, central tasks saw participants direct their attention to the central fixation point and passive tasks involved no specific attentional-allocation. Critically, in all of these tasks the sensory visual input was identical with only the participants task changing. Results showed that, as expected, contralateral regions of both LGN and V1 show an increased MR signal to process the visual stimulus regardless of attentional task. However ipsilateral regions of both the LGN and V1, processing the unattended visual field, exhibited a reduced MR BOLD signal representing the visual suppression of the unattended location. This was also shown to depend on the task and location of attentional allocation, whereby the suppression was greater during stimulus-related task where attention was spatially directed towards one specific hemifield.

Given the existence of such suppression-mechanisms, it may be logical to assume differences in the strength of this mechanism can influence an individual's ability to inhibit and ignore irrelevant stimuli. Extensive research has already demonstrated that those with ADHD often struggle to suppress behavioural responses and irrelevant information within executive functioning tasks compared to controls (Fassbender et al., 2009; Konrad, Neufang, Hanisch, Fink, & Herpertz-Dahlmann, 2006; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Research, although mixed, has too demonstrated some problems suppressing responses within both spatial-attention tasks including the Posner cueing task, where children with ADHD can show greater cue interference (Wood et al., 1999) and make more unreliable responses (Pearson et al., 1995), and anti-saccade ocular motor tasks; showing longer (Karatekin, 2006) and more variable response times (Munoz, 2003), more directional errors (Feifel et al., 2004; Goto et al., 2010; Hanisch et al., 2005; Karatekin, 2006; Klein et al., 2003; Mahone et al., 2009; O'Driscoll et al., 2005) and fewer corrected errors (Klein et al., 2003) compared to controls. Neuroimaging studies have also explored differences in

neural suppression where those with ADHD often exhibit a reduced ability to suppress neural responses within the default mode network (Fassbender et al., 2009; Konrad et al., 2006): a region where the suppression of neural responses has been linked to reduced distractibility and fewer lapses in attention and reduced task errors (Daselaar, Prince, & Cabeza, 2004; Eichele et al., 2008; Hahn, Ross, & Stein, 2006; Hester et al., 2004; Weissman, Roberts, Visscher, & Woldorff, 2006).

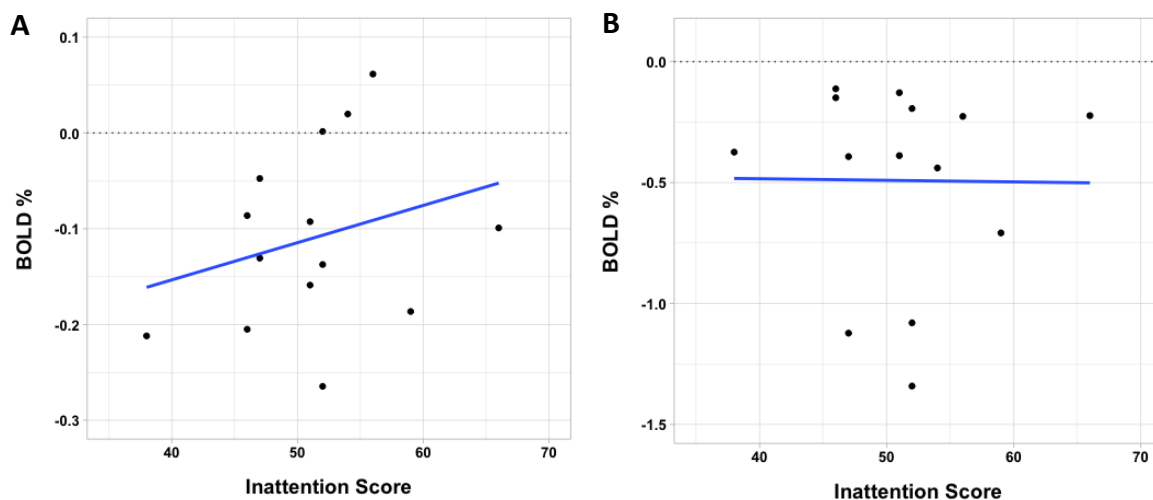


Figure 5.1: Relationship between Inattention score and response in ipsilateral LGN and V1. The relationship between ADHD Inattention scores (higher scores indicate increased Inattention problems) and BOLD responses recorded from ipsilateral regions of the LGN (A) and V1 (B) during a stimulus-related task from Gouws et al. (2014).

Given the fact that those with ADHD already demonstrate abnormal reduced suppression within areas of the default mode network and the extensive attentional problems seen within the visual-domain, it may be plausible that distractibility problems are related to a lack of the attentional-suppression within early visual areas demonstrated by Gouws et al. (2014). In order to investigate this, we re-contacted the participants originally used within the Gouws study and measured their level of Inattention, using the Conners Adult ADHD Rating Scale (CAARS) (Conners et al., 2002) (See Chapter 1 and 2). This was then correlated with the negative BOLD suppression response within ipsilateral areas of both the LGN and V1 for the stimulus-related task and 100% contrast conditions, where the suppression response was at its strongest. From the fourteen participants data were obtained for, there did appear to be a

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positive relationship between the number of Inattention traits and the response within the LGN (whereby those with more inattention traits exhibited a reduced suppression response), although this failed to reach significance (Pearson's correlation: $r=0.27$, $p=.172$) (Figure 5.1A). When examining responses within V1 however, there appeared to be no relationship with Inattention traits (Kendall's Tau: $r= -0.17$, $p=.203$) (Figure 5.1B).

Nevertheless, this analysis was conducted with both LGN and V1 responses being combined for stimulus presentation across both left and right visual fields, because participants were counterbalanced across hemifield conditions. Whilst Gouws et al. (2014) showed no effect of hemifield, our previously presented study on activity of the Superior Colliculus (SC), a sub-cortical visually-associated area, and its interaction with ADHD-associated Inattention were shown to depend on the hemifield of stimulus presentation (Chapter 3). In this case, visually-evoked responses within the SC, measured using fMRI BOLD responses, only correlated with Inattention scores when the distracting visual stimuli was presented in the right visual field and not when in the left. Similarly, we also found that those with High levels Inattention shows an increased SSVEP response towards right visual field distractors compared to those with Low Inattention while no difference was found for the left visual field (Chapter 4). This was interpreted to indicate that those with higher levels of inattention are less able to suppress the distracting stimuli, and hence show an increased visual-evoked response towards it, when presented in the right visual field compared to the left. Unusually this effect appeared to not follow the standard contralateral/ipsilateral pattern expected given the retinotopic nature of the SC, as this right visual field effect was found for both the contralateral (processing the distracting right visual field stimuli) and ipsilateral SC region (processing the unstimulated left visual). This may therefore suggest that possible hemifield differences are driven by cross-hemisphere top-down attentional mechanisms.

Following this retrospective pilot, it was thought worthwhile to investigate whether those with differing levels of ADHD-associated Inattention also differ in this visual-suppression mechanism largely because the participants in the Gouws et al. (2014) study had only a relatively small range of Inattention scores and the study was also likely underpowered to examine the question addressed here. Negative BOLD

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signals were therefore examined using functional MRI while participants performed a stimulus-related task, as conducted in Gouws et al. (2014). This was directly compared across two groups; those showing very low levels and those showing very high levels of Inattention traits similar to the design in Chapter 4. Due to the reasons stated above, this will be examined separately for stimuli presentation in both the left (LVF) and right visual-field (RVF) to investigate the effect of hemifield. Positive BOLD signals within visual areas contralateral to the stimulus presentation and attentional allocation will also be examined. We hypothesise that those showing higher levels of Inattention traits will show a reduced negative BOLD response, in both LGN and V1 regions, compared to those showing lower levels of Inattention traits. Given Gouws and colleagues showed that attention has no effect on the positive BOLD response elicited by the lateralized stimuli, we hypothesise no significant difference in stimulus-related positive BOLD signals within contralateral areas of the LGN and V1 between either Low or High Inattention groups.

5.3 Method

5.3.1 Participants

Three hundred and eighty two participants completed a self-report ADHD behaviour checklist using a computerized version of the English version of the Conners Adult ADHD Rating Scale (CAARS) long self-report form (Conners et al., 2002). As outlined in Chapter 2, this formed part of a two-step recruitment process where all individuals were first assessed for ADHD-associated traits before inviting some individuals back to complete the main neuroimaging experiment. This was employed in order to ensure that only those with specific ADHD-associated Inattention scores were recruited. For the main fMRI experiment, eighteen participants were selected from this cohort. Nine participants showed an ADHD DSM-Inattention Score at least one standard deviation below the population mean, defined by age and gender measured by Conners, and formed the ‘Low Inattention’ group. Similarly, nine showed an ADHD DSM-Inattention Score at least one standard deviation above the population mean and formed the ‘High Inattention’ group. Figure 5.2 shows the distribution of Inattention scores for these eighteen participants relative to the questionnaire distribution. In this case, all participants recruited under the High Inattention group displayed Inattention scores significantly higher than the one standard deviation criteria whereby such group,

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while having no clinical diagnosis of ADHD, may be considered a proxy for those with ADHD-I although further research is required to explore this further. Additional characteristics of both ADHD-Inattention groups can be found in Table 5.1 and shows that both Low and High Inattention groups significantly differed in ADHD DSM Inattention scores as well as DSM Hyperactivity scores and ADHD DSM Combined scores (sum of Inattention and Hyperactivity scores). As mentioned previously in Chapter 2, such differences are due to the strong positive correlation between both Inattention and Hyperactive components (Conners et al., 2002) where it is more unusual to find participants exhibiting proportionally high numbers of Inattention-traits with relatively low levels of Hyperactive traits. Therefore, we note that any potential groups differences observed between both Low and High Inattention groups could be the result of either the inattentive or hyperactive differences or a combination of the two.

Table 5.1: Characteristics of both Low and High Inattention groups. Bracketed numbers represent 1 standard deviation.

| Characteristics | Low Inattention (N=9) | High Inattention (N=9) |
|----------------------------|-----------------------|------------------------|
| Gender M/F | 1/8 | 2/7 |
| Age | 19.78 (2.54) | 19.44 (1.42) |
| Handedness L/R | 0/9 | 0/9 |
| ADHD-DSM Inattention (E) | 37.33 (3.28) | 78.78 (6.59) |
| ADHD DSM Hyperactivity (F) | 39.44 (5.34) | 65.78 (15.57) |
| ADHD DSM Combined (G) | 38.22 (3.42) | 76.00 (11.82) |
| Inconsistency score | 4.11 (1.27) | 5.00 (1.22) |

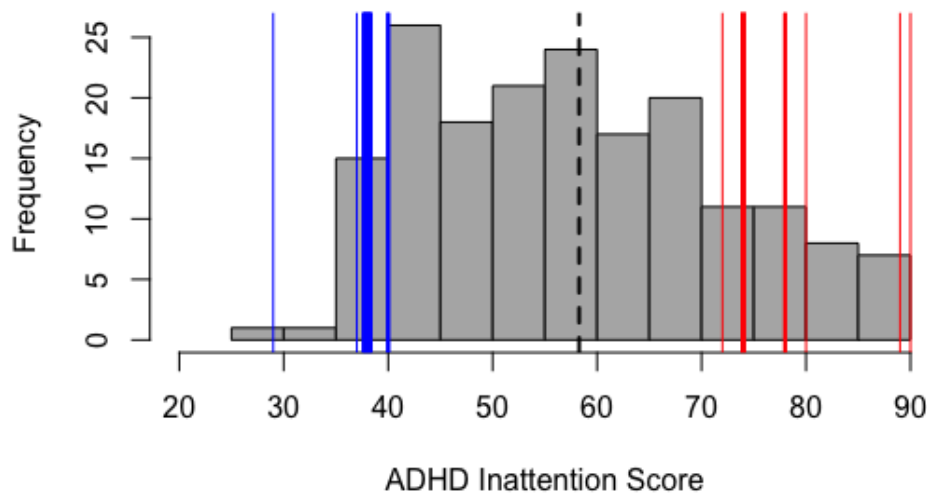


Figure 5.2: Inattention scores from 382 questionnaire responses. Participants recruited for the main fMRI study are shown as separate lines where red lines signify High Inattention group participants and blue signify Low Inattention participants. Although there were nine participants in each group, some exhibited the same Inattention score which is noted here by the line thickness. The black dashed line indicates the mean score for the questionnaire sample.

All participants showed a questionnaire Inconsistency score below the recommended limit of 8, suggesting clear understanding of the questions and reliable responses. All eighteen participants were also right-handed, showed normal or corrected-to-normal vision and had at least a partial undergraduate-degree level of education. Participants confirmed no history of psychological or developmental disorders.

The study was approved by the York Neuroimaging Centre Research Governance Committee (Department of Psychology, University of York) and all participants gave informed consent in accordance with the Declaration of Helsinki.

5.3.2 Visual Stimuli

Stimuli were generated using Psychopy (Peirce, 2009) and were rear-projected (Dukane Image Pro 8942 LCD projector) onto an acrylic screen at the end of the scanner bore via a projector. Participants viewed the screen while lying in the bore of the scanner via an angled mirror positioned 5 cm away from their eyes, which created a

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total viewing distance of 57cm. The screen refresh rate was 120 Hz and the resolution were 1920 x 1080 pixels while the horizontal and vertical extent of the screen was 40cm and 23cm, respectively. Similar to the procedure used by Gouws and colleagues (Gouws et al., 2014), we presented lateralized high-contrast visual stimuli in order to elicit both a positive BOLD response in the LGN and visual cortex contralateral to the stimuli and a negative BOLD response within the respective ipsilateral regions. The stimulus comprised a lateralized 120-degree annulus section (inner radius: 4°; outer radius: 11°) which was symmetrical about the horizontal meridian (Figure 5.3). Both upper and lower sections displayed a drifting sinusoidal grating (contrast: 100%; frequency: 6 Hz; spatial frequency: 0.08 cycles per degree of polar angle) which always drifted in opposing directions (towards or away from the horizontal meridian). Each stimulus presentation lasted for 18 seconds ('on' period) during which the stimulus motion direction changed at random.

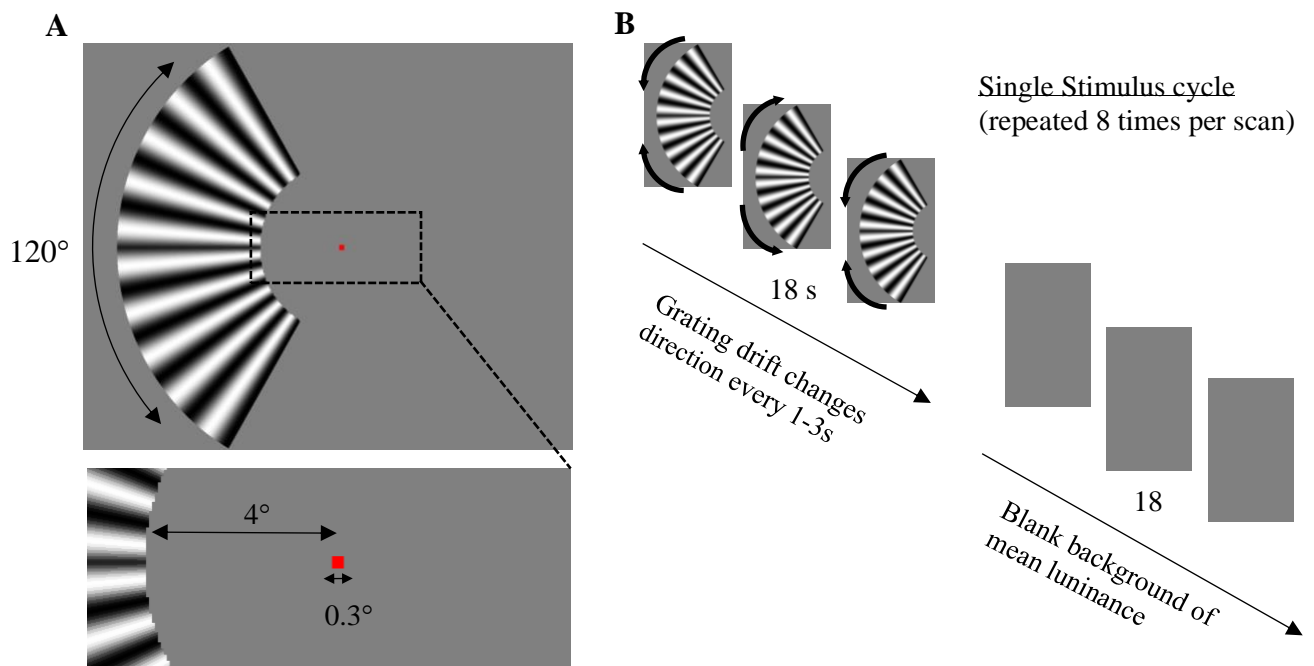


Figure 5.3: Stimulus configurations and timings. A) A large unilateral checkerboard was presented to either left or right visual fields with three runs for the left and three runs for the right. A small red square was positioned centrally and acted as a fixation point which was presented throughout the run. B) The unilateral grating was presented for 18 seconds, where the grating drift reversed direction every 1 to 3 seconds, before being replaced by a blank, mean luminance background for a further 18 seconds. This 36-second stimulus cycle was repeated 8 times within each of the 6 blocks. Participants were required to count the cumulative number of grating direction reversals, while fixating centrally, which was reported verbally at the end of each run.

This was then followed by a blank period of 18 seconds where the annulus stimulus was not presented ('off' period). During both 'on' and 'off' periods, the background was filled with a uniform-grey background, equiluminant to the mean grating luminance (42 cdm^2), and a red fixation point (0.4° visual angle) in the middle of the screen.

As Gouws showed the negative BOLD response was strongest during stimulus-related task conditions, compared to central and passive viewing, participants undertook only the stimulus-related task. During this task, participants counted the total number of motion-direction changes within each run, which occurred at random intervals between 1 and 3s, while maintaining a central fixation. Participants verbally reported this count at the end of each scan.

Each participant undertook six fMRI runs, which were collected in a single session. In order to investigate the potential differences in negative BOLD with visual field presentation; three runs presented the annulus stimuli in the left visual field (LVF) while the other three runs showed the annulus in the right visual field (RVF). The order of these runs was alternated and counterbalanced between groups.

During the same session, participants also undertook a single scan of retinotopic mapping, where a standard rotating wedge was used to map polar angle (Baseler et al., 2011; Engel, Glover, & Wandell, 1997). Stimuli were generated using MATLAB (Mathworks) and presented in the same way as the experimental runs above; participants viewed the rear-projected stimuli using a mirror. The stimulus consisted of unmasked portions of a radial, flickering checkerboard made with 8 rings and 24 radial sections (contrast: 100%; contrast reversal rate: 6 Hz). The radial size of the stimulus has an outer edge at 11 degrees of visual angle in order to match that of the above experimental stimuli. At any time, 90-degree of the stimuli were un-masked and rotated anti-clockwise around the centre of the screen. The cycle period lasted 36 seconds with eight full cycles throughout the scan. At the centre of the screen, a red cross was used in order to ensure central fixation throughout. This was again presented on an equiluminant mean grey background.

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5.3.3 MRI acquisition

Structural data

All data were acquired using a 3 tesla MRI scanner (Siemens) using a 64-channel phased-array head coil at York Neuroimaging Centre (YNiC). At the beginning of the session, an axial proton density image was acquired in order to highlight subcortical structures. A T1-weighted sagittal image was also acquired (TR, 7.8 ms; TE, 3 ms; flip angle, 20°; FOV, 290 mm; matrix size, 256 256; 176 slices, slice thickness, 1 mm; voxel size, 1.13 1.13 1 mm³) to allow a high-quality alignment to both the functional data and other structural images.

Functional data

For functional imaging, six functional T2* scans with 297 seconds (8 on-off cycles) of stimulus presentation were recorded for each participant (TR, 3000 ms; TE, 30 ms; FOV, 256 mm; flip angle, 90°; 128 128 matrix; 44 contiguous slices with 2.5 mm slice thickness; voxel size, 2.0 2.0 2.5 mm³) and covered occipital and LGN regions. A larger voxel size was chosen compared to that of Gouws et al. to increase slice coverage in order to explore neural activity within parietal regions. Slices were acquired using an interleaved slice timing. The first three volumes (9 seconds) of each scan were removed in order to reduce the effect of magnetic saturation. A further functional scan was conducted for retinotopic mapping which maintained the same MRI parameters as the above functional imaging.

5.3.4 Defining Regions of Interest

Region of Interest (ROI) analysis was used to identify the boundaries of both the Primary Visual Cortex (V1) and the Lateral Geniculate Nucleus (LGN) using both functional and anatomical methods respectively.

V1 was assessed using standard fMRI retinotopic mapping procedures from a single rotating wedge stimulus as mentioned above and defined based on associated fMRI BOLD signals. T1-weighted images were segmented into both white and grey matter using mrGray (VistaSoft toolbox; <http://white.stanford.edu/software/>) which, once the ROI was transformed into anatomical space, allowed the V1 ROI to be

restricted to grey matter regions. In this case, each V1 ROI was identified across the whole eccentricity map (0 to 11 degrees) in each hemisphere. This therefore meant that each ROI contralateral to the stimulus contains retinotopic regions that correspond to both the stimulus representation and the central flanking regions (central 4 degrees). As discussed by Gouws (Gouws et al., 2014) this will result in some negative BOLD signal being captured within these contralateral ROIs, driven by the suppression of the areas flanking the stimulus-representation. Nevertheless, since this was consistent for all participants across both Inattention groups, this effect should not influence any pattern of results seen although may have a small influence on the absolute strength of the attentional positive BOLD signal within contralateral V1 regions.

The LGN in each participant was identified using the axial proton density structural images, following criteria previously laid out in Fujita et al. (2001). There was no significant difference in LGN ROI volume between Inattention groups for either left ($p=.593$) or right hemisphere ($p=.809$).

5.3.5 Behavioural Analysis

Task accuracy was also analysed to ensure task engagement and to investigate any behavioural differences in attentional between groups. The mean percentage error score was calculated for each participant for each of the six experimental runs. This was done by calculating the absolute difference between the participants reported total of direction changes and the actual count which was then converted into a percentage error rate. This value was then averaged across each of the runs, again done separately for both left and right visual field stimulus presentations. This was then assessed using a mixed ANOVA to explore the effects of both Inattention group and hemifield presentation.

5.3.6 Blink analysis

During on-off visual-stimulation cycles, it has been previously been established that periods where visual-stimulation is off, often elicit a higher number of blinks from participants compared to periods of visual stimulation. Given research showing the potential influence of blinks on MRI signal primary visual cortex (Tsubota, Kwong, Lee, Nakamura, & Cheng, 1999), we thought it necessary to measure blinks. Indeed,

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Gouws et al showed a selective pattern of blinking that explained a significant proportion of MRI signal variance within ipsilateral areas of the LGN and V1, particularly during stimulus-related tasks (Gouws et al., 2014). It was therefore decided to follow the same procedure to that of Gouws by using blink-events as an additional explanatory variable within the analysis.

Whilst performing the stimulus-related task, video data (30Hz) was recorded monocular from the participant's right eye using a long-range infrared camera (Eyetrack 6000 LR006, Applied Science Laboratories). These video files were then analysed offline in order to detect blink events. This was achieved by correlating each video frame with its predecessor whereby a blink was identified when the pairs correlation dropped below 0.9. Previously reported by Gouws this method of automatic detection had an error of 2% so was used alone to identify blinks. If a correlation below 0.9 fell within 10 frames (333ms) of a previous blink event, this was taken to relate to the same blink event. For four participants, frame correlations failed to drop below 0.9 during blink events so these were assessed manually, and an individual correlation threshold determined. These events were then used to generate a timing file to identify blinks for each of the six scans for each participant, which was later used as an explanatory variable event file within the general linear modelling (GLM) to account for blinks acting as potential confounds to the BOLD responses observed.

5.3.7 MRI analysis

General Linear Modelling

Initial analyses of the fMRI data were performed using FMRIB Software Library (FSL, version 5.0, <http://www.fmrib.ox.ac.uk/fsl>). For each participant, both the T1-weighted sagittal image and the axial proton density image were skull-stripped using the Brain Extraction Tool (BET) in FSL (Jenkinson et al., 2005; S. M. Smith, 2002) to allow an improved alignment with the functional data acquired. Functional data was co-registered to the participants skull-stripped axial proton density images, then to the skull-stripped T1-weighted image before finally being registered onto the standard Montreal Neurological Institute (MNI) 152 standard 1mm brain.

FMRI Expert Analysis Tool (FEAT) was used to perform initial pre-processing (first-level analyses) on each of the six-functional run separately. Within-scan motion

correction was also applied to each run individually using MCFLIRT (Jenkinson et al., 2002) as well as both temporal (36s high pass) and spatial filtering (Gaussian, 4mm). A mean time series was generated for each individual voxel within the brain, across each of the six runs and converted to a percentage signal change. These time series were further restricted to provide a mean for each ROI, achieved by averaging the time series across all voxels within the pre-defined ROI area. These were then averaged across the three scans acquired for both left and right hemifield presentations.

A GLM was applied to each of these ROI mean time series using Matlab's (v7.8.1, MathWorks) regression statistics function (regstats). SPM's (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>) double-gamma hemodynamic response function (spm_hrf) was combined with both the stimulus-related and blink-related event files, containing information on timings and duration, to create predictor time series. The GLM was also fitted with temporal derivatives of both predictors, as well as a constant term. The dependent variable shows the percentage signal change value, indicating either positive or negative BOLD signals, for the combined stimulus and blink predictors. GLMs were run independently for both left and right visual field presentation and for each ROI specified.

Whole Brain Analysis

Whole-brain analysis was also conducted in order to investigate whether group differences in functional responses exist within other sub-cortical and cortical areas. First-level GLM analysis was again conducted using FSL with the same pre-processing parameters as mentioned above. FEAT was then used to construct a GLM to evaluate the effects of both stimulus-related activity and blink regressors on each of the six functional scans. Each individual run was then combined using a second-level, fixed-effects analyses to generate a mean whole-brain time series for each participant. This was done separately for both left and right visual field presentation runs. A final, third-level FLAME 1+2 mixed-effects analyses then combined these to establish the mean group response for both visual field presentations. Thresholding of statistical images was achieved through clustering with a Z-score > 2.3 and a corrected cluster significant threshold of $p = 0.05$.

5.4 Results

5.4.1 Behavioural Accuracy

We firstly wanted to determine whether there were any differences in sustained-attention task accuracy between both Low and High Inattention groups. Group differences in task accuracy could indicate discrepancies in task understanding and engagement, which may subsequently drive differences in neural activity. Figure 5.4 shows the average number of errors (%) from the sustained-attention task for both Low and High Inattention groups when the stimulus was presented in either left or right visual fields. Here we can see that the High Inattention group tended to make slightly more errors compared to the Low Inattention group. There also appears to be small group differences in errors depending on stimulus hemifield whereby those in the Low group made more errors during RVF presentation while the High group made more during LVF presentation.

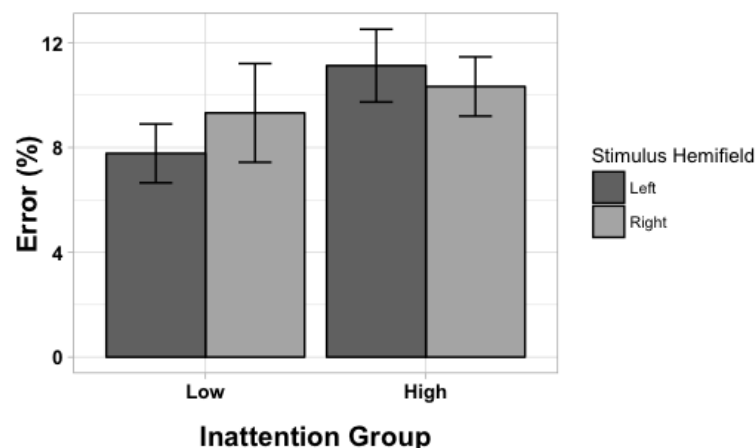


Figure 5.4: Behavioural error rate on the motion-direction task. Percentage counting error for the sustained attention task for both Inattention groups (Low and High) and Stimulus presentation hemifields (Left and Right). Error bars represent ± 1 standard error.

To examine task accuracy further, we used a single 2 (Inattention-group) x 2 (Stimulus Hemifield) Mixed ANOVA to examine the differences on error rates. Results showed there was no significant main effect of Inattention group on error rate ($F(1,16)=1.66, p=.216$) suggesting that both Low and High groups made a similar number of counting errors during the task. Similarly, we showed no significant main effect of Hemifield ($F(1,16)=0.12, p=.732$). Despite the visual differences in the

accuracy for both visual fields between groups seen in Figure 5.4, the Group by Hemifield interaction too failed to reach statistical significance ($F(1,16)=1.20, p=.290$). Similar behavioural error rates across both Inattention groups clearly show that each had a good understanding of the task and that the task did not suffer from a ceiling effect, where the task was difficult enough to ensure participants remained engaged. Such similarities across Inattention groups indicate that any potential differences in fMRI BOLD responses are unlikely to be the result of problems with task misunderstandings or task engagement.

5.4.2 Blink events

Previous research has shown that it can be vital to monitor and measure blink-related signals as a possible source of noise for fMRI when recording from the visual cortex (Hupé, Bordier, & Dojat, 2012). Gouws et al. (2014) previously showed that participants tended to blink more during stimulus-off periods, particularly at times directly following stimulus offset, where no task is being performed compared to stimulus-on periods with an attentional task. Given that blink events are able to produce both retinal and cortical signals, such systematic variation within the blink patterns needs to be evaluated as a potential confound. This is particularly true when measuring negative BOLD from visual regions which tend to follow a similar pattern, with lower signals recorded during stimulus-on periods which then increase at the point of stimulus offset. Such events were therefore controlled for during fMRI analysis as mentioned above. Furthermore, controlling for blink events may be even more critical within the present study as previous research has show that blink rates and patterns can differ between those with ADHD and controls (Armstrong & Munoz, 2003; Caplan, Guthrie, & Komo, 1996; Fried et al., 2014; Tantillo, Kesick, Hynd, & Dishman, 2002).

Here we therefore wanted to examine possible difference in blink rate between both Low and High Inattention groups. Given that the practice of measuring blinks during fMRI sessions is often overlooked within the ADHD literature, any potential group difference observed in blink behaviour may result in unreliable measures of neural activity if not factored into the analysis. Figure 5.5 shows the blink events for both Low and High Inattention groups, averaged for each on-off period across each of the six eight-cycle runs. Firstly, we again see the same pattern previously observed by

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Gouws et al. (2014) where increased number of blinks are made during stimulus-off period compared to stimulus-on periods. Whilst this pattern is seen in both groups, it appears that the Low Inattention group generally blink more, particularly during stimulus-off periods, compared to the High Inattention group. Figure 5.6 also shows this difference where blinks have been averaged for all stimulus-on and off periods for each group. This may therefore suggest that blink rates are different between both Low and High Inattention groups and may subsequently influence the fMRI BOLD signals we record from the visual cortex.

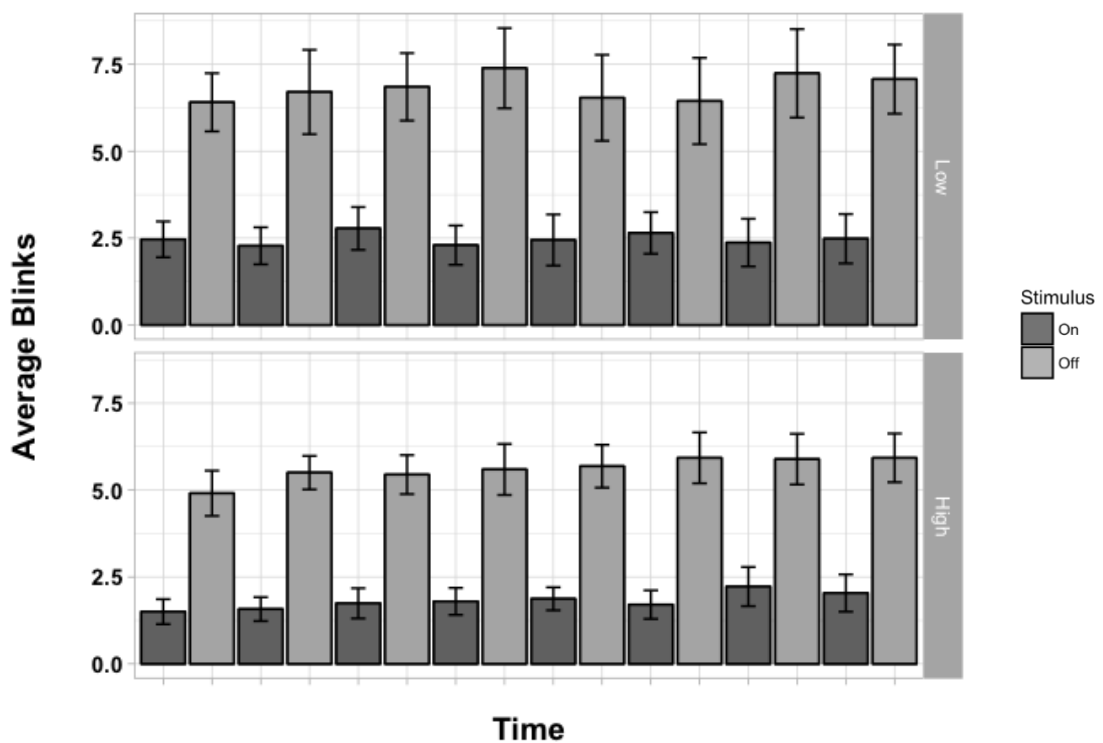


Figure 5.5: Average Blink events by Inattention group per Stimulus Cycle. Total blink events averaged for each Inattention group across each on-off period, over the course of an 8-cycle experimental block. A dark bar indicates stimulus presentation while participants engaged in the lateralized counting task, while a light bar indicate periods with no stimuli or task. Error bars represent ± 1 standard error.

To explore this potential difference further, a mixed 2x2 ANOVA examined the effect of Inattention Group (Low vs. High) and Stimulus-period (On vs Off) on the average number of blinks. This firstly supported the above observation that significantly more blinks occurred during stimulus-off periods compared to stimulus-on periods ($F(1,16)=84.90, p<.001$).

Whilst both Figure 5.5 and Figure 5.6 show the Low Inattention group appear to exhibit an slight increased blink rate compared to the High Inattention group, these differences were found to be non-significant ($F(1,16)=8.37, p=.301$). The Group and Stimulus-period interaction also failed to reach significance ($F(1,16)=0.65, p=.551$). Nevertheless, while there may be no significant differences in blink events between Inattention groups, even small differences may lead to possible differences within blink-related neural activity and therefore still need to be controlled for in analysis of BOLD signals.

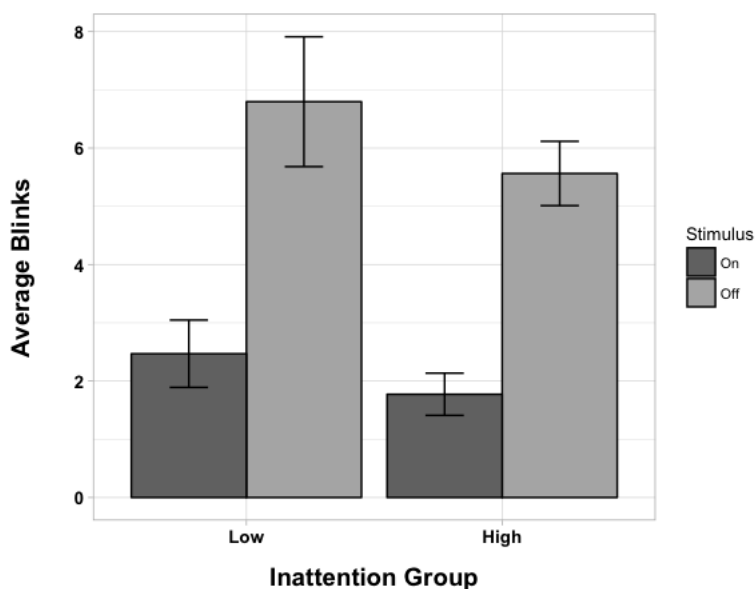


Figure 5.6: Average Blink events by Inattention group. Average blink events for each Inattention group averaged across each on and off period across the six 8-cycle scans. A dark bar indicates stimulus presentation while participants engaged in the lateralized counting task, while a light bar indicate periods with no stimuli or task. Error bars represent ± 1 standard error.

5.4.3 MRI BOLD Response

Lateral Geniculate Nucleus (LGN)

This study aimed to determine whether Inattention traits, often associated with ADHD, are related to differences in attentionally-modulated visual responses within the visual system, specifically within areas of the Lateral Geniculate Nucleus (LGN) and Primary Visual Cortex (V1). Our first aim was to determine whether those with High Inattention levels displayed reduced visual suppression compared to those with Low Inattention levels. To do this we measured BOLD responses from the anatomically

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defined LGN, ipsilateral to the large lateralized grating and therefore processing the unattended and unstimulated visual field.

Figure 5.7 shows the average time series for ipsilateral regions of the LGN separately for LVF and RVF visual stimulation where Inattention group activity have been overlaid. In keeping with previous literature, we can see from the time series that while participants were attending to the contralateral checkerboard stimulus during the first 18 seconds, ipsilateral regions of the LGN exhibited a negative BOLD response. During the following 18 seconds blank period, we observe the signal returned to normal and show the characteristic overshoot past baseline, shown by Gouws et.al (2014), which was thought to be due to increased blinking following the offset of the visual stimulus. Such negative BOLD response also appears to be similar in Low and High Inattention groups. However, negative BOLD appears to be weaker for the High Inattention groups. However, negative BOLD appears to be weaker for the High Inattention group within the right LGN, where an early increase in positive BOLD signal is observed before the end of the attentional task Figure 5.7B.

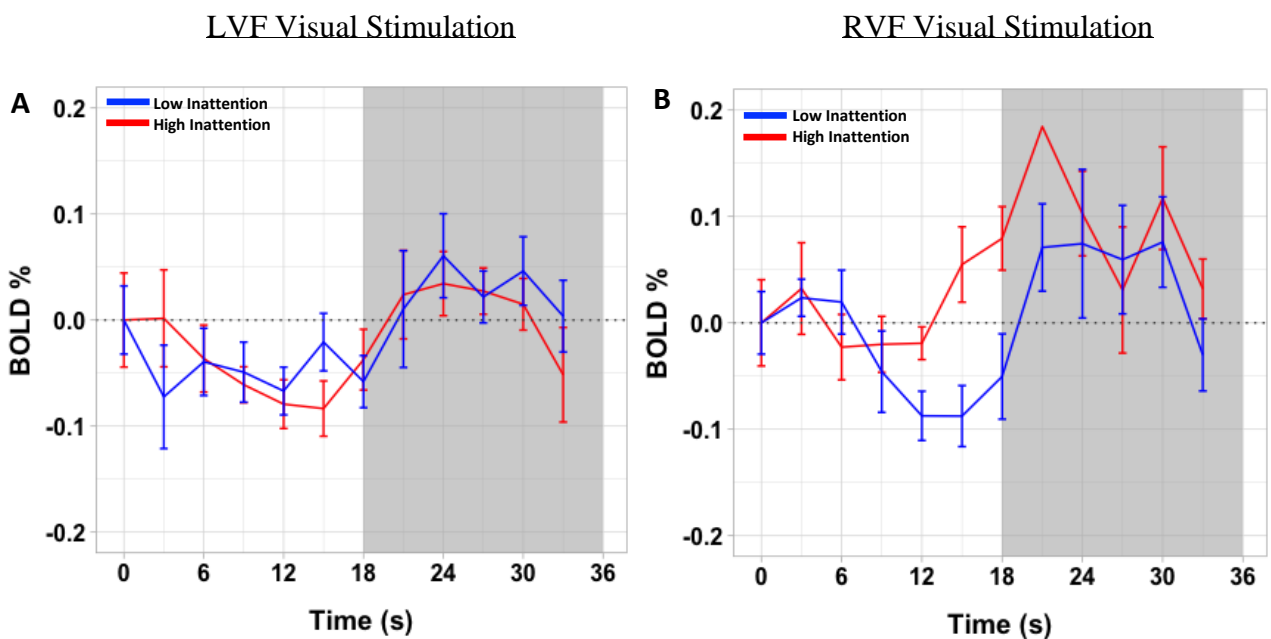


Figure 5.7: Average Inattention groups time series fMRI response for ipsilateral LGN regions. Average time series data for a single on-off stimulus cycle, extracted from both LGN regions ipsilateral to the checkerboard stimuli, which process the unattended visual field, for both High and Low Inattention groups. The first 18 seconds (white background) indicate stimulus presentation while participants engaged in the lateralized counting task, while the final 18 seconds (grey background) indicate periods with no stimuli or task. **A**, the responses obtained from the left hemisphere LGN region ipsilateral to the left visual field stimuli. **B**, the responses obtained from the right hemisphere LGN region ipsilateral to the right visual field stimuli. Blue lines indicate the Low Inattention group while Red lines indicate the High Inattention group. All error bars show ± 1 standard error.

Figure 5.8A shows the average BOLD response from ipsilateral LGN regions for both Inattention groups and Hemifield presentations where the Low Inattention group appear to show consistent negative BOLD while the High Inattention group appear to only show negative BOLD during LVF stimulation. To further explore potential group difference and directly compare across each condition, we conducted a 2x2 mixed AVOVA to explore the effect of both Inattention group (Low vs. High) and Stimulus Hemifield presentation (LVF vs. RVF) on the BOLD response extracted from ipsilateral LGN regions. Despite the quantitative differences evident in Figure 5.8A, the main effects of both Group ($F(1,16)=0.24, p=.629$) and Hemifield ($F(1,16)=2.24, p=.154$) failed to reach significance. There was also no significant interaction between Inattention group and Hemifield ($F(1,16)=2.22, p=.156$). Such results therefore suggest that, at a sub-cortical level, there is no significant difference in the extent to which both Inattention groups suppress the task-irrelevant unstimulated visual fields.

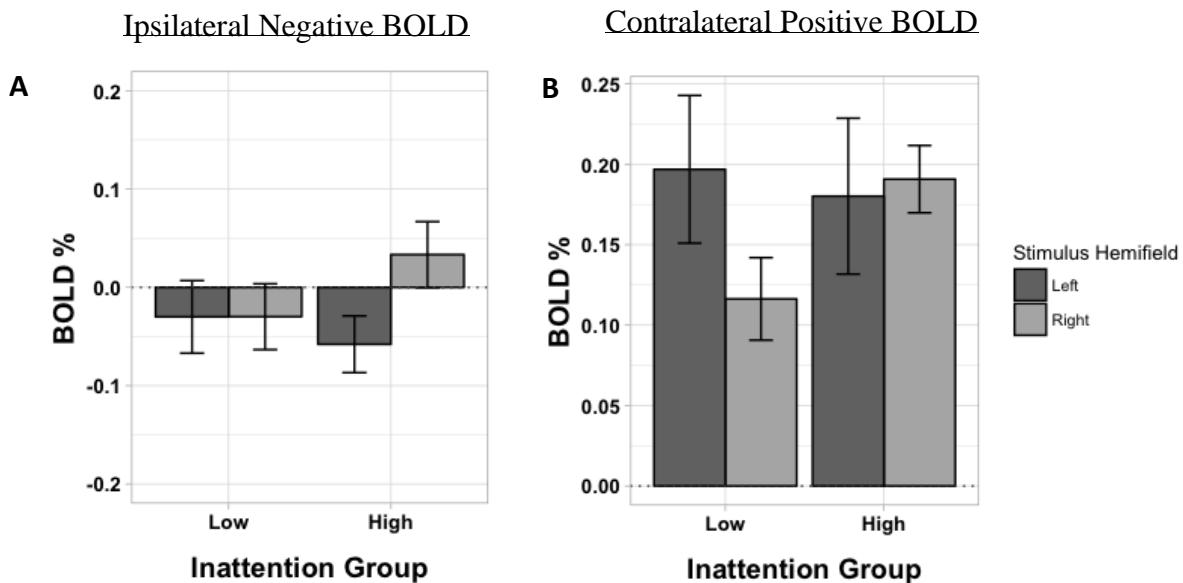


Figure 5.8: Average Inattention group BOLD response from LGN regions. Average LGN fMRI BOLD response extracted from a GLM analysis (Stimulus-related and Blink-related regressors). **A**, Average response extracted from LGN regions ipsilateral to the checkerboard stimuli for both Inattention groups and for both LVF and RVF stimuli presentations. **B**, Average response extracted from LGN regions contralateral to the checkerboard stimuli for both Inattention groups and for both LVF and RVF stimuli presentations. All error bars show ± 1 standard error.

A second aim was to also examine any possible group and hemifield differences in the positive BOLD response showed by areas of the LGN contralateral to the lateralized stimulus. Figure 5.9 shows the averaged single-cycle time series extracted from such contralateral LGN regions for each Inattention group during both LVF

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(Figure 5.9A) and RVF stimuli presentations (Figure 5.9B). Within both left and right contralateral LGN regions, we can see that both Inattention groups exhibit an increase in BOLD response corresponding to the stimulus onset and a decrease in BOLD following stimulus offset.

We again conducted a similar 2x2 Mixed ANOVA to explore the effects of both Inattention Group (Low vs. High) and Stimulus hemifield (LVF vs RVF) on the average positive BOLD responses recorded from contralateral LGN regions. Figure 5.8B shows the average BOLD response from this region where we can see reduced positive BOLD signal within in Low Inattention group during RVF stimulation, mirroring the lower time series line observed within Figure 5.9B. Nevertheless, the ANOVA revealed that both the main effect of Group ($F(1,16)=0.50, p=.489$) and interaction between Group and Hemifield ($F(1,16)=1.87, p=.191$) failed to reach significance. The main effect of Hemifield was also shown to not significantly influence the level of positive BOLD in these regions ($F(1,16)=1.10, p=.310$). Such results indicate that, similar to the negative BOLD observed within ipsilateral LGN regions, both Inattention groups exhibit similar positive BOLD signals to process the lateralized visual stimulus.

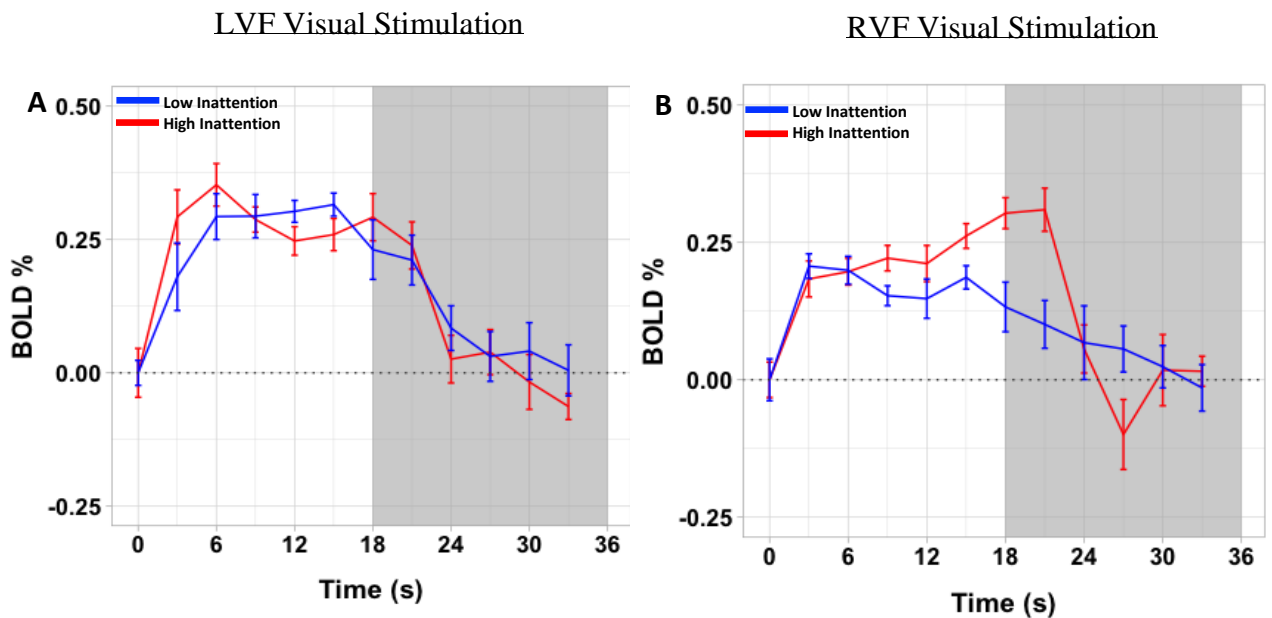
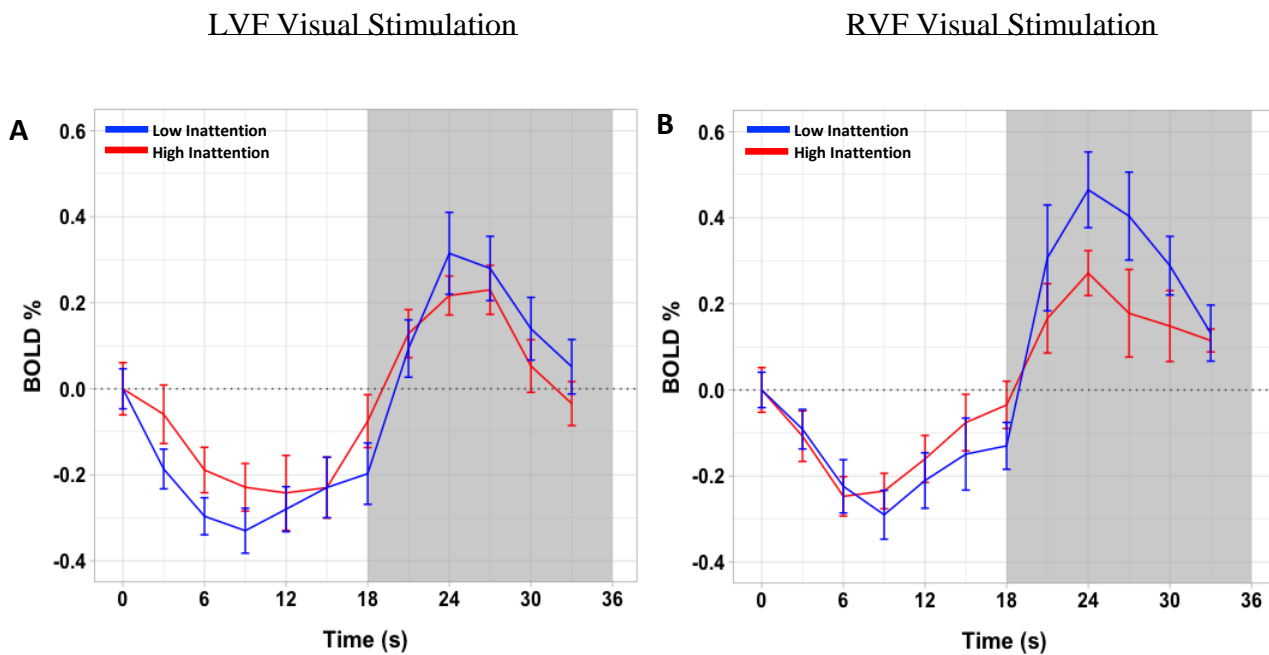


Figure 5.9: Average Inattention groups fMRI response for contralateral LGN regions Average time series data for a single on-off stimulus cycle, extracted from both LGN regions contralateral to the checkerboard stimulus, for both High and Low Inattention groups. The first 18 seconds (white background) indicate stimulus presentation while participants engaged in the lateralized counting task, while the final 18 seconds (grey background) indicate periods with no stimuli or task. **A**, the responses obtained from the right hemisphere LGN region contralateral to the left visual field stimuli. **B**, the responses obtained from the left hemisphere LGN region contralateral to the right visual field stimuli. Blue lines indicate the Low Inattention group while Red lines indicate the High Inattention group. All error bars show ± 1 standard error.

Primary Visual Cortex (V1)

After examining visual-signals within the LGN, our next aim was to also explore how both negative and positive BOLD responses within areas of Primary Visual Cortex (V1) may differ between Inattention group for both LVF and RVF stimulus presentations and whether they show similar results to those previously found within the LGN. Firstly, we want to determine whether those with High Inattention levels displayed reduced visual suppression compared to those with Low Inattention levels as hypothesised. To do this we measured BOLD responses from retinotopically-defined V1 regions, ipsilateral to the large lateralized grating and therefore processing the unattended and unstimulated visual field.



*Figure 5.10: Average Inattention groups time series fMRI response for ipsilateral V1 regions. Average time series data for a single on-off stimulus cycle, extracted from both V1 regions ipsilateral to the checkerboard stimuli, which process the unattended visual field, for both High and Low Inattention groups. The first 18 seconds (white background) indicate stimulus presentation while participants engaged in the lateralized counting task, while the final 18 seconds (grey background) indicate periods with no stimuli or task. **A**, the responses obtained from the left hemisphere V1 region ipsilateral to the left visual field stimuli. **B**, the responses obtained from the right hemisphere V1 region ipsilateral to the right visual field stimuli. Blue lines indicate the Low Inattention group while Red lines indicate the High Inattention group. All error bars show ± 1 standard error.*

Figure 5.10 shows the average time series for a single stimulus cycle generated using a stimulus only GLM for both Inattention groups and visual fields. Similar to responses recorded from the LGN, regions of V1 exhibited negative BOLD signal below baseline whilst attending to the stimulus in the contralateral field. During the

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stimulus-off period, this signal then returned back to baseline after an initial overshoot at stimulus-offset. Such negative BOLD response also appears to be exhibited by both Low and High Inattention groups, regardless of which visual hemifield was being attended to. However, Figure 5.10B shows that amplitude of the response is larger for the Low Inattention group (Blue) compared to the High Inattention group (Red) suggesting some potential group differences in negative BOLD within ipsilateral V1 regions as hypothesised.

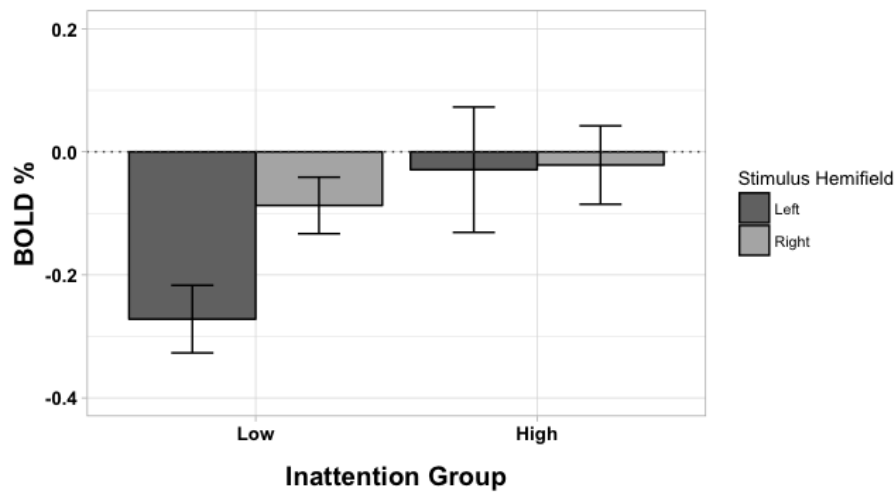


Figure 5.11: Average Inattention group ipsilateral V1 fMRI response. Average fMRI BOLD response extracted from V1 regions ipsilateral to the checkerboard stimuli for both Inattention groups and for both left and right stimuli presentations. Here the left hemisphere V1 will be ipsilateral during conditions where stimuli were presented in the left hemifield and therefore process the unattended right hemifield. Similarly, the right hemisphere V1 will be ipsilateral during conditions where stimuli were presented in the right hemifield. All error bars show ± 1 standard error.

To further examine this difference and directly compare across each condition, we conducted a 2x2 mixed AVOVA to explore the effect of both Inattention group (Low vs. High) and Stimulus Hemifield presentation (LVF vs. RVF) on the average BOLD response extracted from ipsilateral V1 regions. Figure 5.11 shows such averaged BOLD signals where we can again see the reduced BOLD signals exhibited by the High Inattention group. The results showed no overall significant main effect of Inattention group ($F(1,16)=2.75, p=.116$) however there was a significant interaction between Inattention group and Hemifield ($F(1,16)=6.86, p=.019, \eta^2=.30$). The interaction showed that whilst Hemifield appeared to influence the level of negative BOLD response in the Low Inattention group, Hemifield appeared to have little effect within the High Inattention group. Alternatively, we can also say there are significant group differences in V1 negative BOLD when suppressing the RVF (LVF stimulation) but not

when suppressing the LVF (RVF stimulation). Here the Low Inattention group appear to exhibit significantly greater negative BOLD to suppress the RVF compared to the High Inattention group. This therefore suggests that differences in the visual-suppression responses between Low and High Inattention groups are dependent on which hemifield is being suppressed. The results therefore support, at least to some extent, our original hypothesis that those with an increased number of Inattention traits will display a reduced negative BOLD. In this case however, the difference may be driven by the Low Inattention group rather than the High group who appear to be particularly good at suppressing the RVF.

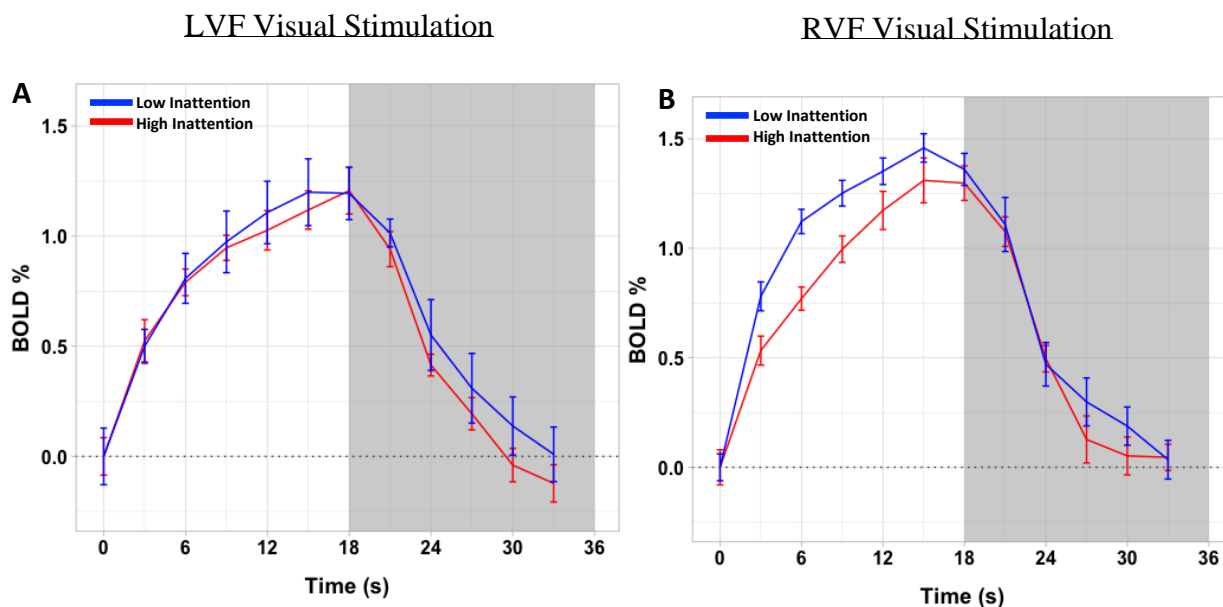


Figure 5.12: Average Inattention groups fMRI response for contralateral V1 regions. Average time series data for a single on-off stimulus cycle, extracted from both V1 regions contralateral to the checkerboard stimulus, for both High and Low Inattention groups. The first 18 seconds (white background) indicate stimulus presentation while participants engaged in the lateralized counting task, while the final 18 seconds (grey background) indicate periods with no stimuli or task. A, the responses obtained from the right hemisphere V1 region contralateral to the left visual field stimuli. B, the responses obtained from the left hemisphere V1 region contralateral to the right visual field stimuli. Blue lines indicate the Low Inattention group while Red lines indicate the High Inattention group. All error bars show ± 1 standard error.

Our second aim was to examine any possible Inattention Group and Hemifield differences in the positive BOLD response showed by areas of V1 contralateral to the lateralized stimulus. Figure 5.12 shows the averaged single-cycle time series extracted from such contralateral V1 regions for each Inattention group during both LVF and RVF stimuli presentations. Within both left and right contralateral V1 regions, we can see that both groups exhibit a large increase in BOLD response corresponding to the

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stimulus onset and a decrease in BOLD following stimulus offset. There also do not appear to be any large differences between Inattention groups although the Low Group appear to show a slight increase in BOLD signal under RVF stimulation. Similarly, the Low Group appears to show a slightly larger response towards the RVF compared to the LVF whilst signals appear similar for the High Inattention group.

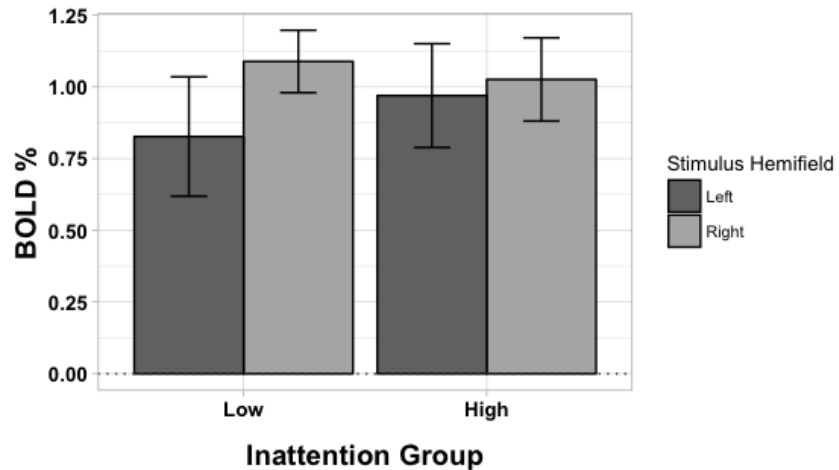


Figure 5.13: Average Inattention group contralateral V1 fMRI response. Average fMRI BOLD response extracted from V1 regions contralateral to the checkerboard stimuli for both Inattention groups and for both left and right stimuli presentations. Here the left hemisphere V1 will be contralateral during conditions where stimuli were presented in the right hemifield. Similarly, the right hemisphere V1 will be contralateral during conditions where stimuli were presented in the left hemifield. All error bars show ± 1 standard error.

We again conducted the same 2x2 mixed AVOVA as above to explore the effects of Inattention group and Stimulus Hemifield presentation, but instead on the average BOLD responses extracted from contralateral V1 regions. Figure 5.13 shows the average BOLD response. Here we found no significant main effect of Inattention group ($F(1,16)=0.04$, $p=.841$) or Stimulus Hemifield ($F(1,16)=1.61$, $p=.223$). There was also no significant interaction between the Group and Hemifield ($F(1,16)=0.67$, $p=.425$). This therefore suggests, as our original hypothesis predicted, that there is no difference between the stimulus-evoked positive BOLD response within contralateral V1 between those with Low and High Inattention traits. Interestingly, and unlike the negative BOLD response seen in ipsilateral V1 regions mentioned above, there was no difference in this response when processing stimuli presented on either LVF or RVF.

Whole Brain Analysis

Our final aim was to examine whether any other regions outside of the LGN and V1 displayed stimulus-driven neural activity, whether positive or negative, and indeed whether such activity differed with Inattention group and the presentation hemifield of the stimulus. Here we conducted a whole-brain analysis, again with both stimulus and blink-related regressors, for both LVF and RVF presentations.

Figure 5.14 shows the average stimulus-related positive BOLD (red) and negative BOLD (blue) activity for all participants for both LVF and RVF presentations. As expected, we can see extensive positive BOLD signals within large portions of the occipital cortex (V1-V4) contralateral to the stimulus presentation, in addition some activity within LGN regions although this appears to be confined to the LVF stimulation. Negative BOLD signals were also found in ipsilateral regions of both the LGN and occipital cortex. This is in keeping with the idea that, while contralateral positive BOLD in the visual system represents the sensory processing of the unilateral stimuli, decreases in BOLD responses within ipsilateral visual regions represents the suppression of the unattended visual locations. We can see some evidence of negative BOLD in contralateral regions of the occipital lobe which likely relate to the areas to unstimulated areas contralateral visual space surrounding the unilateral wedge (Smith et al., 2004). Bilateral increases in activation were further seen in area V5, which exhibits larger, cross-hemifield receptive fields compared to other visual regions (Allman & Kaas, 1971; Amano, Wandell, & Dumoulin, 2009; Zeki, 1969), relating to the motion of the stimuli presented. Significant activity can be observed outside the visual cortex with increased activity in regions of the Superior Colliculus, Pulvinar, Superior Parietal lobe (SPL), Inferior Parietal lobe (IPL), Lateral occipital cortex (LOC), Premotor cortex and Broca's area. The latter of which is thought to relate to internal speech undertaken by participants during the sustained counting task. Similarly, negative BOLD was also found in other areas including the LOC, SPL, IPL, Premotor cortex and Frontal pole. Interestingly, we observe significant stimulus-related negative BOLD within areas of the auditory cortex for both hemifield presentations. This likely relates to the idea that selective attention to visual input, while activating the visual cortex, will concurrently deactivate areas associated with irrelevant sensory processing (Haxby et al., 1994; Shulman, 1997).

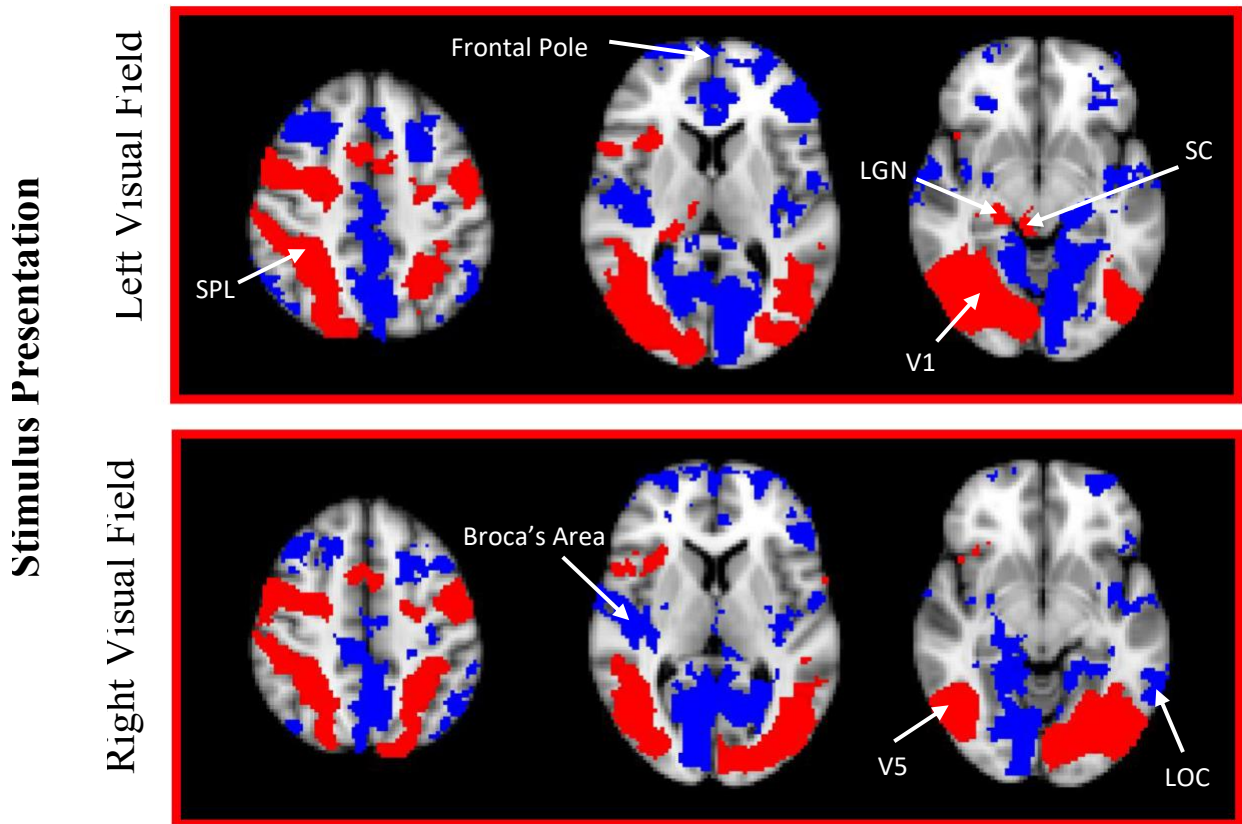


Figure 5.14: Whole brain analysis for Left and Right Visual Field stimuli. Whole brain analysis during stimulus presentation in the left (top) and right (bottom) visual field. Average functional activity for all participants, where red clusters indicate regions of enhanced positive BOLD responses and blue region indicate suppressed negative BOLD responses. All brain images are left-right flipped where left hemisphere appears on the right side and the right hemisphere on the left. LOC: Lateral occipital cortex. SC: Superior Colliculus. LGN: Lateral Geniculate Nucleus. SPL: Superior Parietal Lobe.

To examine the effect of Inattention group on such activity, we examined whole-brain responses for both the Low and High Inattention group separately where Figure 5.15 and Figure 5.16 show the average Inattention group response for LVF and RVF stimulus presentation respectively. For LVF presentation (Figure 5.15), activity patterns seen in both Low and High appears to be similar to the combined average pattern above (Figure 5.14), although perhaps the negative BOLD response seen in visual regions is less wide-spread within the High Inattention group. There also appear to be the tendency for the High Inattention group to show bilateral activation in some areas, particularly within the SPL and Premotor cortex, while the Low Inattention group typically showed unilateral right hemisphere activity. Such activity was directly compared to explore whether any regions differed significantly between groups (Figure

5.15C and D). Here we can see significant Group differences in neural activity within regions of the right hemisphere superior parietal lobe, where the High Inattention group display positive BOLD signals while the Low Inattention group display negative BOLD responses.

Looking at RVF presentations (Figure 5.16), we can see a similar story, with both groups again demonstrating a similar pattern to the combined averages response seen in Figure 5.14. In keeping with the LVF activity, the negative BOLD response seen in visual regions appears to be less widespread within the High Inattention group. Similar results were found when examining group differences in activity, where differences were seen the same region of the SPL although now observed bilaterally compared to just in the right hemisphere. Here the Low Inattention group display significant negative BOLD while the High Inattention group show positive BOLD (Figure 5.16C and D).

Given the pattern of such activity largely occurs in superior parietal regions, an area often associated with attentional-related responses, such group differences in neural activity may represent differences in attentional responses to the task being performed. Such activity also appears to fit in with our original hypotheses that the High Inattention group will display a reduced suppression response, indicated by negative BOLD, compared to the Low Inattention group. Within this region, that indeed appears to be the case where the High Inattention group continue to show increases positive activation compared to the negative signals seen in the Low group.

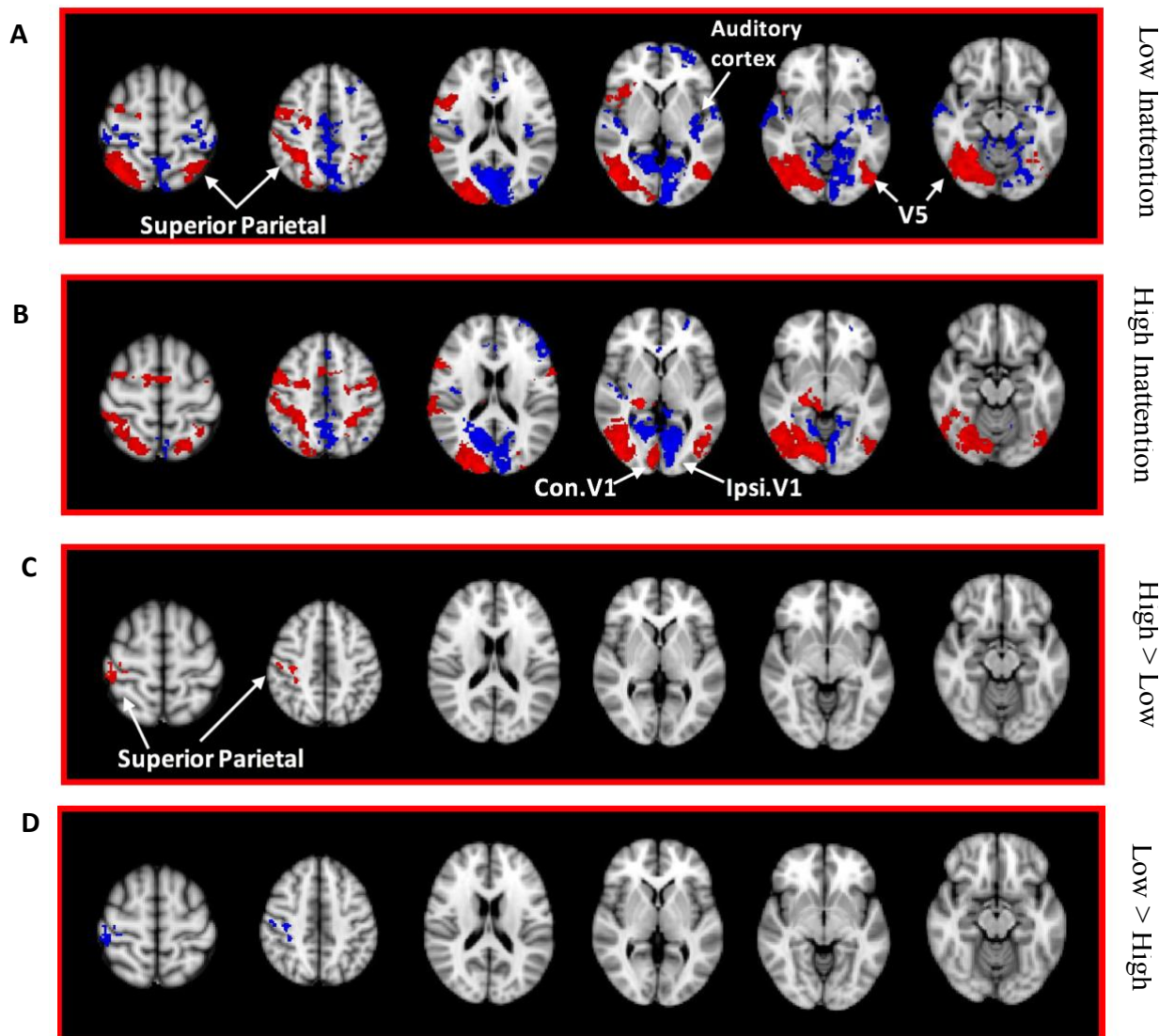


Figure 5.15: Whole brain group BOLD analysis for Left Visual Field stimuli. Whole brain analysis during stimulus presentation in the left visual field. A and B; Functional activity for the Low Inattention and High Inattention groups respectively where red clusters indicate regions of enhanced positive BOLD responses and blue region indicate suppressed negative BOLD responses. C; Clusters showing greater activity within the High Inattention group compared to the Low Inattention group. D; Clusters showing greater activity within the Low Inattention group compared to the High Inattention group. All brain images are left-right flipped where left hemisphere appears on the right side and the right hemisphere on the left.

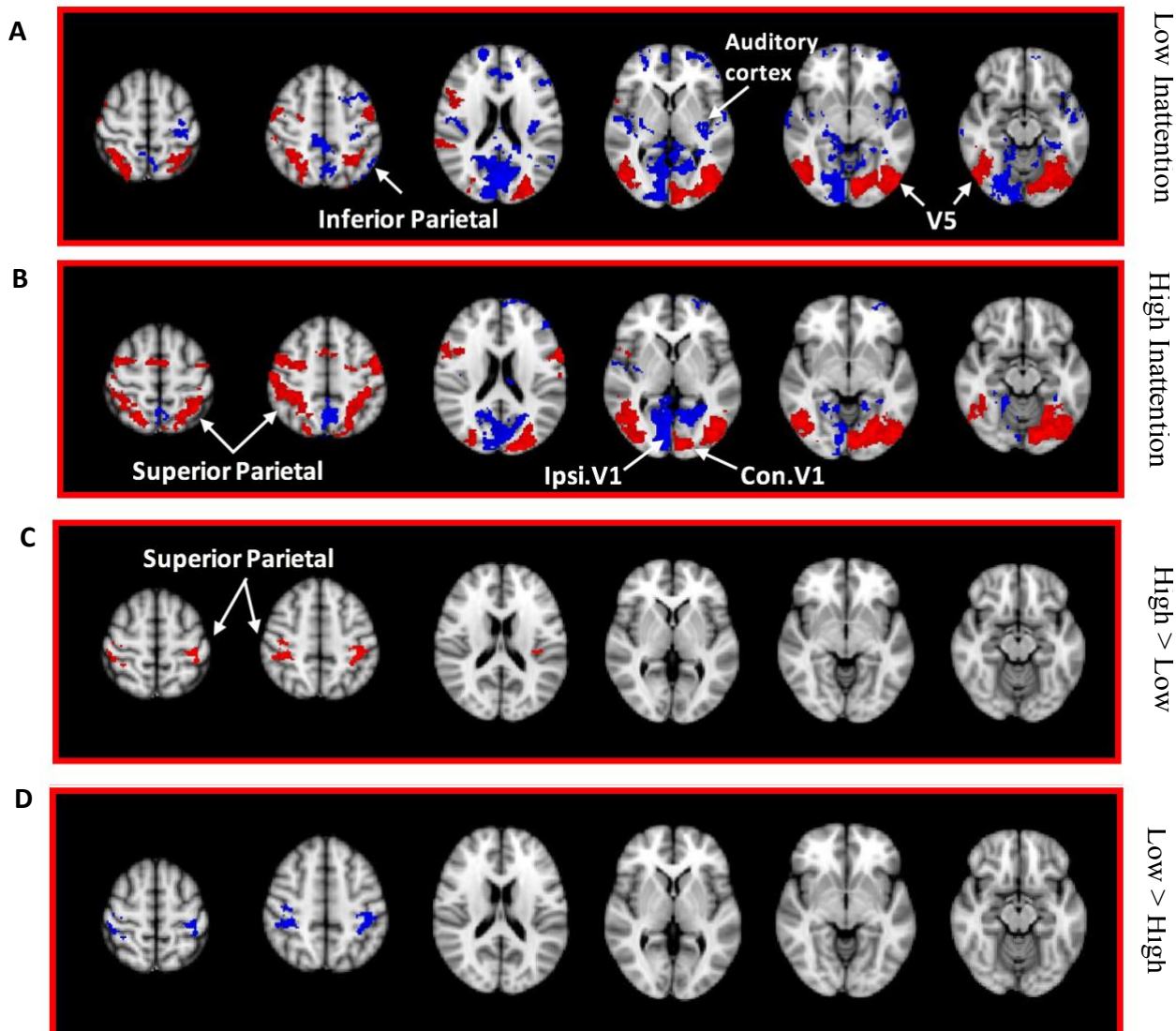


Figure 5.16: Whole brain group BOLD analysis for Right Visual Field stimuli. Whole brain analysis during stimulus presentation in the right visual field. A and B; Functional activity for the Low Inattention and High Inattention groups respectively where red clusters indicate regions of enhanced positive BOLD responses and blue region indicate suppressed negative BOLD responses. C; Clusters showing greater activity within the High Inattention group compared to the Low Inattention group. D; Clusters showing greater activity within the Low Inattention group compared to the High Inattention group. All brain images are left-right flipped where left hemisphere appears on the right side and the right hemisphere on the left.

5.5 Discussion

The current study aimed to explore how ADHD-associated Inattention traits and stimulus visual field presentation influenced the neural signals within both LGN and V1 regions during a sustained visual attention task. We also examined whether such differences occurred on a more global whole-brain level within areas outside the early visual system. When examining responses within regions of the visual system ipsilateral to the presented stimulus, we showed that the Low Inattention group displayed significantly greater negative BOLD responses within V1 during LVF presentation compared to the High Inattention group. Such group differences however were not found in V1 during RVF presentation and were not seen during either LVF or RVF stimulus presentation within the LGN. Responses from contralateral regions of the LGN and V1 showed similar positive BOLD signals for both Low and High Inattention groups regardless of visual field. Finally, we showed Inattention group differences in neural signals recorded within areas of the superior parietal lobe where, in overlapping regions, the High Inattention group displayed clear positive BOLD while the Low Inattention group showed negative BOLD. Both results therefore appear to suggest that those with a high number of Inattention traits show some level of reduced or absent suppression response within areas of the visual and attentional system.

Previous literature has long established attentional-modulation of responses within the visual system under directed sustained-attention tasks (Gouws et al., 2014; Shulman, 1997; Slotnick et al., 2003; Smith et al., 2000, 2004; Tootell, Hadjikhani, et al., 1998; Tootell, Mendola, et al., 1998). Such modulations are often characterised as an enhanced neural signal within visual regions contralateral to the attended stimulus while a suppressed signal, below baseline, is recorded in ipsilateral regions, which correspond to unattended visual space. The present study provides evidence for the latter; regions in the ipsilateral hemisphere, corresponding to the unattended visual field, exhibit response below baseline - negative BOLD responses.

Examining responses from ipsilateral visual regions, corresponding to the unattended visual field, we also found a clear significant interaction effect between Inattention group and Stimulus hemifield on negative BOLD responses within V1. When stimulating the LVF, those showing few Inattention traits showed significantly

greater negative BOLD responses (more negative) to suppress the unattended RVF compared to those showing a high number of traits. When stimulating the RVF on the other hand, there was no group difference within negative BOLD response towards the unattended LVF. Such findings within ipsilateral V1 suggest that the Low Inattention group are significantly better at suppressing the RVF compared to those in the High Inattention group, while no difference is seen when suppressing the LVF. This supports our original hypothesis stating that those displaying an increase number of Inattention traits, will be worse at suppressing irrelevant areas and stimuli shown though a reduced and weaker negative BOLD signal. Interestingly, the group differences in negative BOLD suppression only occur when suppressing the RVF and follow on from our original suggestion that differences between Inattention groups may be more likely in the RVF.

Furthermore, it was evident that such RVF effect is largely driven by the Low Inattention group rather than the High group: A large increase in negative BOLD (more negative signal), relative to both their own response to the LVF and responses of the High Inattention group, suggesting that those with no or few Inattention traits are extremely successful at suppressing the unattended RVF. Such suppression a mechanism may therefore enhance their ability to successfully focus and attend to relevant information while not getting distracted by surrounding irrelevant stimuli, particularly in the RVF.

Examining responses from ipsilateral regions of the LGN however are less clear, where we show no significant difference in negative BOLD responses between Inattention groups or Stimulus Hemifield. However, this is not entirely surprising considering the very small fluctuations in signal recorded which were often less than 0.1%.

In additional to examining responses within visual regions ipsilateral to the stimulus, we also examined those responses in contralateral regions representing the unilateral checkerboard stimulus. Here we showed that, whilst significant positive BOLD signals were recorded in both contralateral LGN and V1 regions, there was no significant difference between signals recorded from Low and High Inattention groups regardless of stimulus visual field. This supports our original hypotheses that Inattention

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traits will not influence the level of positive BOLD in processing the attended stimuli. Gouws et al. (2014) previously noted that there was no significant influence of attentional manipulation upon positive BOLD signals from either the LGN or V1 regions. The finding that individual differences in inattention do not affect such positive BOLD signals therefore follows on from this and indicates that, those showing higher levels of Inattention traits continue to process attended visual stimuli in a similar manner as those showing few traits.

In addition to exploring pre-defined regions of interest, we also examined the whole-brain response during the attentional-task. Similar to previous research, we again showed extensive positive BOLD responses in contralateral visual regions (Gandhi et al., 1999; Gouws et al., 2014; Kastner et al., 1999; Martínez et al., 1999; O'Connor et al., 2002; Somers et al., 1999; Tootell, Hadjikhani, et al., 1998), in addition to negative BOLD in ipsilaterally, mirroring the activity within our defined V1 and LGN regions (Gouws et al., 2014; Shulman, 1997; Slotnick et al., 2003; Smith et al., 2000, 2004; Tootell, Hadjikhani, et al., 1998; Tootell, Mendola, et al., 1998). Due to the larger field of view when recording MR activity, we were able to extend on Gouws' et.al (2014) previous findings where we see negative BOLD responses within parietal regions, including the SPL and IPL, in addition to the key visual areas. Attention-related suppression has previously been proposed to originate in the parietal cortex, as a region heavily involved in attentional-allocation (Behrmann, Geng, & Shomstein, 2004; Kanwisher & Wojciulik, 2000; Steinmetz & Constantinidis, 1995; Wojciulik & Kanwisher, 1999), before being fed back into earlier visual areas, potentially via the pulvinar (Gouws et al., 2014; Shipp, 2003), to influence suppression responses in both the LGN and V1. But we find that both Inattention groups respond differently within regions of the SPL, where those with few inattention traits exhibit negative BOLD suppression responses while those with high inattention show positive BOLD responses. Such group differences in parietal lobe activity may therefore feedback and contribute to the group differences observed within area V1 where V1 suppression responses are observed significantly more in those with no or few inattention traits. Such V1 suppression is therefore weaker or absent in those with many Inattention traits who have no suppression, or indeed an enhanced response, being fed back from the parietal lobe.

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Taken together, these results clearly demonstrate differences in cortical suppression mechanisms between those exhibiting low and high levels of Inattention traits often associated with ADHD, where those with more Inattention traits appear to show a lack of suppression. Moreover, such results indicate that there is no difference in how those with differing attention process attended visual stimuli, suggesting that inattention may be associated more with a lack of task-irrelevant suppression compared to problems with target processing. Previous literature has indeed show that those with ADHD can struggle to suppress behavioural responses and irrelevant information during executive functioning (Fassbender et al., 2009; Konrad et al., 2006; Willcutt et al., 2005), spatial attention (Pearson et al., 1995; Wood et al., 1999) and anti-saccade tasks (Feifel et al., 2004; Goto et al., 2010; Hanisch et al., 2005; Karatekin, 2006; Klein et al., 2003; Mahone et al., 2009; Munoz, 2003; O'Driscoll et al., 2005).

Research has also provided some evidence for a lack of suppression within neural responses within those with ADHD, however the majority of these have been confined to the default neural network, focusing on frontal and parietal regions (Fassbender et al., 2009; Liddle et al., 2010; Peterson & Potenza, 2009). Fassbender and colleagues found a lack of neural suppression response for those with ADHD within areas of the default mode network, where suppression is often associated with reduced distractibility and fewer attentional lapses, compared to controls. Additional studies have further found that psychostimulants medication, often prescribed to those with ADHD, can re-establish such absent suppression response (Liddle et al., 2010; Peterson & Potenza, 2009). Given the lack of suppression observed within these other high-level attention-related networks, it is plausible that increased distractibility and inattention may arise from problems eliciting top-down attentional control (Friedman-Hill et al., 2010). Indeed, the lack of negative BOLD responses we observe within parietal regions for those exhibiting many ADHD-associated Inattention traits may also support this notion, where a lack of top-down suppression from the parietal lobe results in a lack of suppression within the visual system and a continued processing of task-irrelevant locations and stimuli. Moreover, those showing low levels of Inattention traits are shown to exhibit such parietal suppression missing from the high inattention group, supporting the idea that parietal suppression may be linked to V1 suppression activity. Such results may therefore indicate that a general lack of cortical suppression is associated with increased Inattention and, under the assumption that the High

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Inattention group may represent a proxy for those with a clinical diagnosis, ADHD itself.

Interestingly, our results also suggest an abnormal spatial asymmetry within such neural suppression, where visual field was shown to play a significant role in Inattention group difference. Here we show differences in the suppression response between groups were larger when suppressing the RVF compared to the LVF. Similarly, this appears to support our previous research found within the Superior Colliculus (See Chapter 3) whereby there was a significant positive correlation between Inattention traits and MRI signal response, but only when the unattended stimuli appeared in the RVF and not the LVF. Previous research has often demonstrated some differences in attentional-responses to both LVF and RVF visual stimuli within those with ADHD, who often fail to suppress and are more distracted by stimuli in the RVF compared to the LVF (Chan et al., 2009; Epstein et al., 1997; Geeraerts et al., 2008; Hanisch et al., 2005; Huang-Pollock et al., 2005). It may therefore be likely that those at the other end of the ADHD Inattention spectrum, such as those in our Low Inattention group, are less distracted by RVF stimulation, possibly stemming from an extensive visual suppression mechanism within V1. Some evidence for these hemifield effects within controls have also been found behaviorally where Chan and colleagues found control children were less likely to experience interference from distractors in the RVF compared to the LVF (Chan et al., 2009), appearing to match the differences observed within the negative BOLD responses. Given the strong evidence for right-hemisphere dominance within the parietal attention network (De Schotten et al., 2011; Heilman & Van Den Abell, 1980; Shulman et al., 2010; Weintraub & Mesulam, 1987), this may further contribute to the RVF effect observed where group differences are maximal. Indeed, RVF displays have shown to exhibit negative BOLD within bilateral parietal regions for those with low inattention compared to right hemisphere only suppression for LVF displays. This may therefore indicate that the top-down suppression responses causing V1 negative BOLD are stronger, arriving from bilateral parietal regions, when the RVF is stimulated.

In conclusion, we have clearly demonstrated differences in V1 cortical suppression mechanisms between those showing low levels of ADHD-associated Inattention and those showing high levels. Here, the Low Inattention group displayed

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significantly greater negative BOLD responses within V1 when suppressing the RVF compared to the High Inattention group who shows a weak or absent suppression response. Regions of the Parietal lobe also exhibit similar patterns of an absent negative BOLD responses in those with High Inattention compared to Low Inattention. Such findings suggest that ADHD-associated Inattention may be linked to a lack of neural suppression, particularly within attentional and visual-regions, when processing the visual world.

Chapter Six: General Discussion

6.1 Overview

The primary aim of this thesis has been to explore potential differences within the visual system in relation to ADHD-associated Inattention traits within the typically developed adult population. Whilst there is a wealth of literature examining differences in neural responses in those with ADHD, very few choose to investigate visual-associated regions, instead preferring to examine frontal and parietal regions (Fassbender et al., 2009; Liddle et al., 2010; Peterson & Potenza, 2009). Given the extensive evidence for a visual attention deficit in those with ADHD (Huang-Pollock et al., 2005; Klein et al., 2006; Losier et al., 1996; Mowinckel et al., 2015; Oosterlaan et al., 1998; Wright et al., 2014), alongside the research showing interactions between the occipital cortex and attention network in maintaining attention (Shulman et al., 2009) and suppressing irrelevant distractors (Capotosto et al., 2009; Gouws et al., 2014; Schwartz et al., 2005), it is therefore possible that such deficits may be associated with functional abnormalities within the visual system. By measuring neural responses across the visual system during visual-attentional tasks, we aimed to explore the relationship between visual-deficits and Inattention. We also aimed to examine how this relationship may be dependent on task-attentional load and both the type and location of visual targets and distractors, with particular focus on difference between left and right visual fields. The first study aimed to address one specific theory regarding the relationship between activity within the superior colliculus and ADHD-associated Inattention. The latter two studies focus on difference in neural responses within occipital and early visual regions response to visual attention and suppression.

6.2 Summary of Findings

Here we will provide a brief overview of the three empirical chapters discussed above, outlining the background rationale and key results obtained. The implications of these results for Inattention and ADHD will be explored in the next section.

Our first experiment aimed to specifically explore the relationship between ADHD-associated Inattention traits and activity within the superior colliculus (SC): a

sub-cortical, mid-brain structure that forms part of the visual-system. Such region has previously been found to be involved with both head and eye (saccadic) orientating movements (Everling et al., 1999; Grantyn et al., 2004; Sparks, 1999) and covert orientation of attention (Ignashchenkova et al., 2003; Katyal et al., 2010; Rizzolatti et al., 1987). Research has also shown SC damage can often lead to changes in attention and distractibility (Albano et al., 1982; Gaymard et al., 2003; Goodale et al., 1978; Milner et al., 1978; Sprague, 1966). Given the links between the SC and distractibility, Overton and colleagues have proposed that the distractibility observed within ADHD could be attributed to dysfunction, specifically sensory hyper-responsiveness, of the SC (Overton, 2008; Overton & Clements, 2009; Panagiotidi, 2016). For the first time, this experiment aimed to test this possibility directly using fMRI, where healthy adults with varying levels of ADHD-associated Inattention undertook a sustained visual-attention task with peripheral distractors. fMRI BOLD responses in the left and right SC to stimuli presented in the right hemifield, showed significant positive correlations with Inattention traits, with those exhibiting more inattentive behaviours showing larger BOLD responses to motion versus static stimuli. However, when the same stimuli were presented in the left hemifield, there was no significant correlation between left or right SC responses to motion versus static stimuli and Inattention traits. A further behavioural task also measured anti-saccade performance, as a behavioural measure of SC functioning (Everling et al., 1999), where Inattention scores correlated positively with error rates.

Our second study aimed to expand on these results to examine separate neural responses to central targets and peripheral distractors during visual attention tasks. Previous literature has demonstrated that those with ADHD often experience increased interference from peripheral, task-irrelevant distractors during sustained attention tasks (Bellgrove et al., 2013, 2009; Chan et al., 2009; Forster et al., 2014; Geeraerts et al., 2008; Hanisch et al., 2005; Huang-Pollock et al., 2005). Such distractor interference is also more likely to occur during easy, low attentional load tasks, where excess attentional resources are allocated to process the distractors, compared to hard high-load tasks where attentional resources are already taken up by the central task (Lavie, 1995, 2005, 2010; Lavie & Tsal, 1994). Here we investigate how those with Low and High levels of Inattention process task-related targets and task-irrelevant distractors and whether such visual processing is influenced by attentional-load and both distractor location and type. Using EEG, we were able to measure separate SSVEP responses to

simultaneously presented central, task-relevant targets and peripheral, task-irrelevant distractors. Such distractors were presented to either the left visual field (LVF), right visual field (RVF) or bilaterally. During recording, participants performed both easy (low-load) and hard (high-load) sustained visual-attention tasks. Here we showed that those with few Inattention traits exhibited larger SSVEP responses towards the task-related stimuli than towards the unrelated distractors, regardless of attentional task, while the High Inattention group show the opposite effect, responding to the irrelevant distractors more than the task-related stimuli. Presentation hemifield and Distractor type were also found to significantly influence distractor processing, where those with High Inattention exhibited an increased response towards RVF distractors compared to those with Low Inattention. No group differences were found for responses towards LVF distractors. Group differences were too observed in the responses to unilateral and bilateral distractors where, whilst the Low Inattention group showed decreased responses to distractors presented bilaterally compared to unilaterally, the High Inattention group showed no difference.

Finally, our last study aimed to investigate whether those with low and high levels of ADHD-associated Inattention exhibit differences in attentional modulation within the visual system, specifically within suppression responses. Previous literature has often demonstrated that spatial attention can modulate neural responses within the visual system towards visual stimuli; increasing neural responses towards attended locations (Gandhi et al., 1999; Kastner et al., 1999; Luck et al., 1997; Martínez et al., 1999; McAdams & Maunsell, 1999; Moran & Desimone, 1985; Motter, 1993; O'Connor et al., 2002; Reynolds et al., 1999; Roelfsema et al., 1998; Somers et al., 1999; Thiele et al., 2009; Tootell, Hadjikhani, et al., 1998) while decreasing responses to unattended locations (Gouws et al., 2014; Shmuel et al., 2002; Slotnick et al., 2003; Smith et al., 2000, 2004; Tootell, Hadjikhani, et al., 1998; Tootell, Mendola, et al., 1998; Vanduffel, 2000). Given the increased distractibility seen in those with ADHD, it may be likely that Inattention problems are related to an absent or weakened suppression-mechanism where irrelevant stimuli and locations continue to be processed. To explore this, we ran an fMRI study to examine neural responses within regions of the Lateral geniculate nucleus (LGN) and Primary Visual cortex (V1) whilst Low and High Inattention participants undertook a lateralized sustained attention task. Responses were recorded separately from both regions contralateral to the task; corresponding to

the attended visual field and characterised by enhanced, positive BOLD responses, and from ipsilateral regions; corresponding to the unattended visual field and characterised by suppressive, negative BOLD responses. Due to the continuing influence of hemifield presented within the previous two studies, we also explored whether task hemifield influenced such neural responses. In keeping with previous literature, we show both Inattention groups exhibited extensive stimulus driven positive BOLD signals within contralateral LGN and V1 regions. Ipsilateral areas of V1 however showed significantly stronger negative BOLD signals for the Low Inattention group compared to the High group when participants attended to stimuli in the LVF. No differences were found within ipsilateral V1 when stimuli were presented to the RVF or for either visual field in the LGN. Extending our analysis to examine areas outside of the visual system, whole-brain analysis revealed significant group differences in BOLD responses within anterior regions of the Superior Parietal lobe, where the High Inattention group showed positive BOLD right hemisphere activity (LVF stimulus presentation) and bilateral activity (RVF stimulus presentation) while the Low Inattention group who showed negative BOLD responses in the same regions.

6.3 Implications of Results

The results of this thesis raise a number of important issues in regard to both Inattention traits and ADHD, and their relationship with neural responses within the visual system. Findings from these three empirical studies will now be addressed.

6.3.1 ADHD and the Visual System

While most research examining neural responses within ADHD has largely focused on differences within the prefrontal regions, the three chapters presented within this thesis demonstrate a clear relationship between functional responses from visually associated neural regions and Inattention traits. Whilst such research focused on adults from the typically developed population, some conclusions can be drawn on the relationship between visual processing and ADHD itself whereby High Inattention participant groups used in both Chapter 4 and 5 displayed Inattention traits above the suggested guideline for clinical diagnosis. Given such participants, these groups could be taken as a proxy for those with ADHD-I despite the fact they held no clinical diagnosis for the condition. This may be particularly true for Chapter 5 where nearly all

Chapter Six: General Discussion

High Inattention participants displayed Inattention traits two to three standard deviations above the population average. Nevertheless, while this suggestion is plausible, further research is required to explore it further.

Findings from Chapter 3 demonstrate clear associations between SC fMRI signals and Inattention traits supporting the suggestion by Overton and colleagues that a hyperactive SC may be related to Inattention within ADHD (Overton, 2008; Overton & Clements, 2009; Panagiotidi, 2016). Similarly, results from Chapters 4 and 5 find clear differences in neural responses from regions of the early occipital cortex, including area V1, between those with Low and High levels of Inattention traits. However, we fail to see any significant Inattention group differences within fMRI activity recorded from the LGN. Although, as noted in Chapter 5, the LGN is often difficult to record neural responses from whereby signals only show very small fluctuations. Whilst overall showing clear variation in visual responses between those with differing levels of Inattention, we show related differences within higher cortical regions. Indeed, Chapter 5 demonstrates that differences in neural responses within V1 are also mirrored within areas of the superior parietal lobe. Considering the extensive connections between the visual and attentional-networks (Bressler, Tang, Sylvester, Shulman, & Corbetta, 2008; Foxe & Simpson, 2002; Foxe, Simpson, & Ahlfors, 1998; Lauritzen, Esposito, Heeger, & Silver, 2009), this is unsurprising and suggests that Inattention-related differences observed within the visual system likely interact with other cortical regions, whether through feedforward or feedback mechanisms. Such findings overall clearly highlight the importance of vision and the visual-system within ADHD-associated Inattention, supporting the suggestion by Cortese and Castellanos that examining the visual-system within ADHD represent a ‘fruitful’ area of investigation (Cortese & Castellanos, 2012).

6.3.2 Differences in Visual Field Processing

Throughout our three empirical chapters, our investigations of the visual system allowed us to clearly explore potential differences in how both Inattention groups attended to and suppressed stimuli presented to either Left (LVF) or Right Visual Fields (RVF). Due to the clear retinotopic nature of the visual system (Engel et al., 1997; Holmes, 1918; Horton & Hoyt, 1991), neural responses recorded from visually-associated regions within the left hemisphere largely correspond to visual input from the

RVF while the right hemisphere largely responds to the LVF, particularly within low-level regions such as the LGN and V1. Based on the previous literature outlined within Chapter 1, we expected to observe a clear relationship between ADHD-associated Inattention traits and neural responses in response to distracting, task-irrelevant stimuli presented in each hemifield, particularly within the RVF. In Chapter 3, we show evidence that increased Inattention traits were associated with increased Superior Colliculus (SC) fMRI responses, but only when distracting stimuli were presented within the RVF. There was no relationship between Inattention and SC responses during presentation of LVF distractors. Our provisional interpretation of these data was that such stimuli are likely to be suppressed while participants engage in a central task and that those showing high levels of inattention are less successful at achieving this, particularly for peripheral target locations in the right hemifield. Unusually however, such results appears to defy the hemispheric division observed within the SC, where the LVF is processed by the right hemisphere and vice versa (Katyayal et al., 2010; Schneider & Kastner, 2005), in that such RVF effect was observed in both the left and right hemisphere SC. As noted in Chapter 3, this likely suggests that such VF differences may be modulated by cross-hemisphere, top-down attentional mechanisms in addition to some bottom-up sensory input. This is particularly likely given the fact such relationship was stronger within the contralateral SC, receiving both bottom-up visual input and top-down information, compared to the ipsilateral SC which may just receive top-down signals.

Using a related experimental design, these findings were replicated within Chapter 4 where neural responses were recorded from early occipital regions. Results showed those with high levels of Inattention exhibited increased responses towards RVF distractors compared to those with Low levels of Inattention, while no differences were observed for LVF distractors. Similarly, Chapter 5, examining responses to task-irrelevant hemifields, showed increased V1 neural activity towards the unattended RVF in those with the High compared to Low Inattention group, while no differences were observed for LVF activity. These results again support our initial interpretation and follows on from findings observed within the SC in Chapter 3, suggesting that those with increased Inattention traits are less successful as ignoring distracting stimuli and task-irrelevant locations in the RVF compared to those with few Inattention traits.

However, both Chapter 4 and 5 reveals that such RVF differences in attention and distractor processing may be driven primarily by those with Low Inattention. Results from Chapter 4 show that while High Inattention participants showed similar neural responses to LVF and RVF stimuli, those with Low Inattention showed reduced responses to RVF distractors compared to LVF. Comparably, Chapter 5 also showed the same effect where hemifield differences in V1 activity towards the un-attended VF are only observed in the Low Inattention group who demonstrate an extensive suppression response towards the RVF. This suggests that while Inattention traits are linked to RVF processing, hemifield differences are primary seen in the lower extreme of the ADHD-associated Inattention spectrum rather than within those with ADHD-level Inattention problems as first theorised. Previous literature has tended to find clear interactive effects in that those with ADHD are typically more distracted by RVF distractors (Chan et al., 2009; Epstein et al., 1997; Geeraerts et al., 2008; Huang-Pollock et al., 2005) while control participants are more distracted by those in the LVF (Geeraerts et al., 2008; Huang-Pollock et al., 2005). This does appear to somewhat fit with our current findings showing that, those with Low Inattention process LVF distractors more than RVF, although we fail to show any hemifield preference for those with High Inattention.

Given our consistent findings showing hemifield differences in neural responses between those with high and low levels of ADHD-associated Inattention, one would further speculate that such differences would be mirrored within the sustained attention task and its neural representation. Nevertheless, our results appear to show no influence of hemifield on task performance and neural responses to task-related target between those with differing inattention traits. In Chapter 4, we can firstly see no group difference in how both LVF and RVF distractors influence the central task and behavioural task performance. On a similar level, Chapter 5 shows no difference between how those with Low or High Inattention traits process the task-related hemifield, whereby similar neural responses were recorded for both groups towards LVF and RVF tasks within regions of the LGN and V1. Whilst surprising, such results appear to indicate that while RVF representations, and hence distractibility, increase with Inattention traits, this does not influence the sustained attention directed towards the task-related stimuli. This implies that Inattention-related differences within the visual system appear to relate to differences in distractibility and suppression rather than directed-attention.

There have been many previous theories regarding differences in VF processing within those with ADHD. As noted in Chapter 1, the majority of these have stemmed from research suggesting that ADHD Inattention may result from a right hemisphere deficit within parietal regions (for review see Hale et al., 2009; Stefanatos & Wasserstein, 2001). It has long been proposed that the right parietal lobe is dominant within spatial attention where, whilst the left parietal cortex controls spatial attention directed towards the right side of space, the right parietal cortex controls attention towards both left and right sides of space (Gonçalves et al., 2006; Heilman & Valenstein, 1979; Heilman & Van Den Abell, 1980; Kinsbourne, 1987). Due to this, any damage or abnormalities to the RVF may manifest in differences in attention between both sides of space, similar to that seen in unilateral neglect patients (Driver & Vuilleumier, 2001; Geeraerts et al., 2008; George et al., 2005), where the RVF is attended to more than the LVF. Upon initial examination, our results do not appear to entirely fit with this theory whereby, whilst there are clear differences in RVF processing between those with Low and High Inattention traits, we fail to see a rightward attentional bias in those with High Inattention. If anything, our results support the fact that those with few Inattention traits exhibit a more asymmetrical attentional-network showing ‘hyper-suppression’ towards the RVF, potentially arising from a heightened right hemisphere attention response. This is also mirrored in previous literature which has often found typically developing children and adults to show an attentional-bias towards the LVF with reduced interference from RVF stimuli (Geeraerts et al., 2008; Huang-Pollock et al., 2005). This was thought to be the result of a right-hemisphere dominance in attentional-control mechanisms or attention-related neural activity (De Schotten et al., 2011; Heilman & Van Den Abell, 1980). Given the idea that such asymmetries may be considered “normal” within the typically developed population, the lack of asymmetries observed within those with High Inattention may therefore indeed represent a weakened right-hemisphere attentional network, which is subsequently feedback to visual region. Furthermore, whilst our High Inattention population showed significantly more Inattention traits than their sex and age-matched peers, none had reported substantial detrimental effect of such traits nor had received a diagnosis of ADHD. It may therefore be possible that the lack of hemifield differences in attention observed within our High group represent a middle ground between the LVF-bias observed in the Low Inattention group and the RVF-bias previously reported in those with a clinical ADHD diagnosis (Chan et al., 2009; Epstein et al., 1997;

Geeraerts et al., 2008; Huang-Pollock et al., 2005). Further research is clearly needed to explore this suggestion whereby, similar to the way we now view ADHD-related behaviors (Larsson et al., 2012; Levy et al., 1997; Lubke et al., 2009; Martin et al., 2014; Polderman et al., 2007), we should assess whether Inattention-related differences in neural responses should also be considered as a continuum and whether those with increased Inattention traits with no clinical diagnosis can be considered a proxy for those with ADHD-I.

6.3.3 Inattention and Suppression Mechanisms

Throughout Chapters 4 and 5, our investigations allowed us to specifically examine neural responses corresponding to task-irrelevant stimuli and unattended spatial locations. Given such regions were irrelevant to the sustained attention task being performed, it would therefore be expected that neural responses towards these locations would be suppressed in order to reduce visual processing and allow increased attentional resources to be directed towards the task (Gouws et al., 2014; Shmuel et al., 2002; Slotnick et al., 2003; Smith et al., 2000, 2004; Tootell, Hadjikhani, et al., 1998; Tootell, Mendola, et al., 1998). Initially, we proposed that inattention and increased distractibility often observed in those with ADHD (Chan et al., 2009; Fassbender et al., 2009; Feifel et al., 2004; Goto et al., 2010; Hanisch et al., 2005; Huang-Pollock et al., 2005; Karatekin, 2006; Klein et al., 2003; Konrad et al., 2006; Mahone et al., 2009; O'Driscoll et al., 2005; Willcutt et al., 2005; Wood et al., 1999) may result from abnormalities in this suppression-mechanism, whereby a weaker or absent suppression can lead to continued processing of distractors and task-irrelevant regions. Within our non-clinical population, we therefore expected those in the High Inattention groups to show this reduced suppression response. Examining results from Chapters 4 and 5, our findings appear to somewhat support this suggestion whereby Chapter 5 demonstrated a reduced negative BOLD response within ipsilateral regions of V1 in those with High Inattention compared to Low Inattention – although this was only found when suppressing the RVF. Chapter 4 also showed those with High Inattention traits exhibited increased SSVEP responses towards peripheral distractors compared to individuals with Low Inattention, although this again only reached statistical significance for RVF distractors. In both cases, those with increased Inattention traits exhibited increased processing of these task-irrelevant locations compared to those with few Inattention traits. This could further indicate that such abnormal neural suppression

mechanism also occur in those with ADHD, whereby a lack of neural suppression for irrelevant locations and distractors may result in increased inattention and distractibility.

Such results also appear to suggest that abnormalities within the suppression-response may depend upon cortical location with abnormalities more likely in higher cortical regions. Indeed, Chapter 5 demonstrates that while reduced suppression was observed for the High Inattention group within regions of V1 and the Parietal lobe, it was not found within the LGN. Due to the extensive feedback connections between the Parietal lobe and Occipital cortex (Bressler et al., 2008; Foxe & Simpson, 2002; Foxe et al., 1998; Lauritzen et al., 2009; Rockland & Ojima, 2003), it is possible that the reduced suppression observed within the parietal lobe may have feedback to influence suppression response V1. This therefore suggests that such abnormal suppression observed within the visual system is likely to be mediated by top-down influences rather than bottom-up stimulus-driven mechanisms (Friedman-Hill et al., 2010). Moreover, such a lack of suppression observed within these vision and attention-associated regions may in fact be a characteristic of a more general suppression deficit in those with frequent Inattention problems, potentially including those with ADHD, rather than something specific to the visual system. Previous literature has also found suppression abnormalities in those with ADHD within frontal and parietal regions of the default mode network (Fassbender et al., 2009), where suppression is often associated with reduced distractibility and fewer attentional lapses, while others have shown that psychostimulants medication often prescribed to those with ADHD, can re-establish such absent suppression response (Liddle et al., 2010; Peterson & Potenza, 2009). Taken together, such findings suggest that, while there are clear differences in the suppression mechanisms in those with Inattention problems within early visual cortex, this may reflect a global deficit in neural suppression rather than something specific to the visual system.

6.3.4 Influence of Distractor Type

Within Chapter 4, we examine neural activity directly related to task-irrelevant peripheral distractors in order to understand the association between Inattention traits and influence of distractors. Whilst the above sections discuss how distractor influence may depend on hemifield, the current section covers differences in distractor type. Whilst there is research to show that those with ADHD show greater interference from

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distracting stimuli (Chan et al., 2009; Fassbender et al., 2009; Feifel et al., 2004; Goto et al., 2010; Hanisch et al., 2005; Huang-Pollock et al., 2005; Karatekin, 2006; Klein et al., 2003; Konrad et al., 2006; Mahone et al., 2009; O'Driscoll et al., 2005; Willcutt et al., 2005; Wood et al., 1999), very few have examined whether the type of distractor influences this relationship. Chapter 4 revealed that there were indeed differences in how both Inattention groups responded to distractors depending on whether they were presented unilaterally or bilaterally. Results showed that while those with few Inattention traits showed a reduced neural response to each distractor when presented under bilateral conditions compared to unilateral, those with high levels of Inattention show no difference between distractors. Bilateral stimuli presented across LVF and RVF are thought to promote bottom-up perceptual interference, or 'sensory competition', between stimuli whereby limited attentional resources are split across competing displays, resulting in a reduced neural representation (Desimone & Duncan, 1995; Moran & Desimone, 1985; Reynolds et al., 1999). Conversely, our current findings unexpectedly show that such competition appears absent in those with more Inattention traits. Interestingly, this effect was also seen across both easy, low-load and difficult, high-load attentional tasks, contradicting previous research who show increased sensory-competition during high attentional load tasks (Schwartz et al., 2005; Vuilleumier & Rafal, 2000). Upon first inspection, such results may imply that those with increased Inattention may show an increased attentional capacity whereby more attentional resources are available to split across each bilateral component reducing 'competition'. However, Chapter 4 shows that those with increased Inattention also demonstrate reduced responses towards the central task compared to the distractors. The Low Inattention group on the other hand show the opposite pattern where responses are higher for the central task compared to the distractor. This may therefore indicate that while those with Low Inattention direct their attention primarily towards the central task, leaving any remaining attentional capacity to be split across distractors, those with High Inattention primarily process the distractors. This would therefore indicate that, rather than a general difference in attentional capacity, those with Inattention problems may experience abnormalities in the level of attentional allocation between task-related and unrelated stimuli.

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6.3.5 Attentional Load

In Chapter 4, we explored the effect of task perceptual or attentional-load on neural responses towards attended and unattended stimuli where we show that increasing attentional load heightened neural responses towards task-related stimuli while reducing them for irrelevant distractors. Such results in general provide additional support for the Load Theory (Lavie, 1995, 2005, 2010; Lavie & Tsal, 1994), which puts forward that distractor processing can be reduced or eliminated if the level of task perceptual load is great enough to exhaust perceptual capacity. Our results also appear to be comparable to those showing reduced distractor-representations within LGN and V1 neural responses during high-load attention tasks (Bahrami et al., 2007; O'Connor et al., 2002; Rees et al., 1997; Schwartz et al., 2005). Furthermore, we found that the effect of attentional load was comparable in both Low and High Inattention groups. This supports previous researchers who have demonstrated that perceptual load influences both ADHD patients and healthy controls in a similar manner (Chan et al., 2009; Forster & Lavie, 2007; Forster et al., 2014; Friedman-Hill et al., 2010; Huang-Pollock et al., 2005). Overall, this indicates that increased levels of Inattention are unlikely to be associated with generalized deficit in attentional capacity. If such capacity restriction were the case, then we would expect the High Inattention group to show greater distractor influences under low-load conditions than the Low group, where attentional capacity is exhausted at a faster rate. Considering Chapter 4 showed similar effects of distractor presence on neural responses for both Inattention groups during low-load tasks, this reasons against such a general deficit.

6.4 Limitations and Future Directions

Throughout this thesis, all our findings have come from typically developed adults with varying levels of ADHD-associated traits as measured by the ASRS and CAARS self-report questionnaire. Whilst this is becoming a popular approach to studying some clinical conditions, particularly ADHD and Autism Spectrum Disorder, it is based on the idea that such traits exist on a continuum and that those with clinical diagnoses are taken as extremes of this spectrum. Within Chapters 4 and 5, we examine neural responses from those within both Low and High Inattention groups; each showing CAARS Inattention scores at least one standard deviation below or below the population mean. Given guidance for the CAARS indicates that trait score one standard

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deviation over the mean are indicative of ADHD-related behaviors; it is possible that those in the High Inattention group show similar traits to those with ADHD. This therefore raises an interesting question regarding whether those in the High groups can be considered a proxy for those with clinically diagnosed ADHD-I or whether, despite displaying similar Inattention scores, there is a distinct difference between healthy participants showing high Inattention traits and those with ADHD-I. In order to understand whether these groups are similar, future research is required where the same paradigms used here should be repeated with adults from the clinical population. This will allow us to further explore whether our findings showing neural differences in visually associated regions also exist on a continuum, as indicated by Chapter 3, where individuals with ADHD may sit at the extreme of the spectrum.

Another potential limitation of note involves the use of small sample sizes; ranging from 17 participants in our first study exploring the connection between Inattention and the Superior Colliculus, to 36 in our second study using EEG recording to measure SSVEP responses. Although these sample sizes gave us sufficient power to detect both group differences between those with Low and High Inattention traits (Chapters 4 and 5) and correlations between Inattention traits and neural responses, it was not possible to explore the influences of and control for other ADHD-associated traits. Larger samples for example may have allowed us to separate the influence of Hyperactivity/Impulsivity traits from the Inattention traits of interest, whereby additional groups containing participants with high Inattention traits, but low Hyperactivity could be directly compared to those displaying a high number of traits in both behaviours. Further large-scale studies will therefore allow us to determine whether the effects identified within this thesis are related to ADHD-associated traits in general or whether they relate specifically to inattention.

6.5 Practical Implications

From this thesis, there are a number of practical implications that can be taken from our three empirical studies.

Firstly, we have provided clear evidence for a link between ADHD-related Inattention traits and visual processing, whereby increased inattention problems are

associated with increases processing (or reduced suppression) of the RVF. Such hemifield differences in attention are indeed likely to influence attentional behavioural and level of distractibility within school and home settings. This may be particularly relevant for academic abilities involving reading, especially within societies reading left-to-right where a right-ward attentional bias may be beneficial (Chokron, 1993; Chokron & De Agostini, 1995; Rinaldi, Di Luca, Henik, & Girelli, 2014). Further studies are needed to assess the impact of such asymmetries in visual attention on those with differing levels of Inattention. Furthermore, we noted that both those with low and high level of inattention experienced similar increases in task-related activity and reduced distractor processing following increases in perceptual-load. Such results therefore suggest that, while some may be inclined to make tasks easier for those with ADHD and Inattention problems; increasing task perceptual load may be more beneficial in reducing distractibility. Within an educational setting, this may include using high visual-load materials and presentations rather than simple low-load versions.

Findings from this thesis provide further evidence to show that ADHD-associated traits similarly exist within the non-clinical population, where individuals range on a continuum from showing very few inattention traits to many traits. Given this, it may be logical to assume that neural differences relating to Inattention problems also occur on a continuum. Indeed, our research appears to support this suggestion where Inattention-related neural differences within the visual system are observed in those without a clinical ADHD diagnosis. This further supports the suggestion that ADHD should be considered as an extreme of a population distribution rather than a stand-alone disorder (Larsson et al., 2012; Levy et al., 1997; Lubke et al., 2009; Martin et al., 2014; Polderman et al., 2007).

6.6 Conclusion

The studies in present thesis set out to investigate whether ADHD-associated Inattention traits were associated with differences in neural responses within the visual-system. To achieve this, we used three experimental tasks to examine both attention and suppression-related responses within areas of the superior colliculus, lateral geniculate nucleus and early occipital cortex, including area V1. Overall, we have shown that those with high levels of inattention process visual stimuli differently to those with low

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inattention levels, particularly in regions of the SC and early occipital cortex. Furthermore, all three studies demonstrate significant asymmetries within visual suppression, where those with few inattention traits were more successful at ignoring and suppressing right visual field locations than those with more inattention traits. Although further research is needed to directly examine the source of such differences, whether from sensory-driven input or top-down feedback, these findings show the clear involvement of the visual-system within ADHD-associated Inattention. Our current theory proposes that such Inattention-related differences in neural activity may occur on a continuum rather than clear categorical differences between both clinical ADHD and typically developed populations. Further research is needed to explore this theory in relation to asymmetries observed within visual suppression.

References

References

- Adams, R., Finn, P., Moes, E., Flannery, K., & Rizzo, A. S. (2009). Distractibility in Attention/Deficit/ Hyperactivity Disorder (ADHD): the virtual reality classroom. *Child Neuropsychology : A Journal on Normal and Abnormal Development in Childhood and Adolescence*, *15*(2), 120–135.
<https://doi.org/10.1080/09297040802169077>
- Advokat, C., Martino, L., Hill, B. D., & Gouvier, W. (2007). Continuous Performance Test (CPT) of college students with ADHD, psychiatric disorders, cognitive deficits, or no diagnosis. *Journal of Attention Disorders*, *10*(3), 253–256.
<https://doi.org/10.1177/1087054706292106>
- Ågmo, A., Belzung, C., & Rodriguez, C. (1997). A rat model of distractibility: effects of drugs modifying dopaminergic, noradrenergic and GABA ergic neurotransmission. *Journal of Neural Transmission*, *104*(1), 11–29.
<https://doi.org/10.1007/BF01271291>
- Ahrendts, J., Rüsçh, N., Wilke, M., Philipsen, A., Eickhoff, S. B., Glauche, V., ... Tebartz van Elst, L. (2011). Visual cortex abnormalities in adults with ADHD: A structural MRI study. *The World Journal of Biological Psychiatry*, *12*(4), 260–270.
<https://doi.org/10.3109/15622975.2010.518624>
- Albano, J. E., Mishkin, M., & Westbrook, L. E. (1982). Visuomotor deficits following ablation of monkey superior colliculus. *Journal of ...* Retrieved from <http://srweb.net/Assets/NEIPages/BobWurtz/pdfs/AlbanoMishWestbroWur82.pdf>
- Allman, A.-A., Benkelfat, C., Durand, F., Sibon, I., Dagher, A., Leyton, M., ... O'Driscoll, G. A. (2010). Effect of d-amphetamine on inhibition and motor planning as a function of baseline performance. *Psychopharmacology*, *211*(4), 423–433. <https://doi.org/10.1007/s00213-010-1912-x>
- Allman, J. M., & Kaas, J. H. (1971). Representation of the visual field in striate and adjoining cortex of the owl monkey (*Aotus trivirgatus*). *Brain Research*, *35*(1), 89–106. [https://doi.org/10.1016/0006-8993\(71\)90596-8](https://doi.org/10.1016/0006-8993(71)90596-8)
- Almeida Montes, L. G., Prado Alcántara, H., Martínez García, R. B., De La Torre, L. B., Ávila Acosta, D., & Duarte, M. G. (2012). Brain Cortical Thickness in ADHD. *Journal of Attention Disorders*, *17*(8), 641–654.
<https://doi.org/10.1177/1087054711434351>
- Alvarez, J. A., & Freides, D. (2004). Research on Attention Deficit Hyperactivity

References

- Disorder Using the Covert Orienting Paradigm of Posner. *Developmental Neuropsychology*, 26(2), 627–645. https://doi.org/10.1207/s15326942dn2602_6
- Amano, K., Wandell, B. A., & Dumoulin, S. O. (2009). Visual Field Maps, Population Receptive Field Sizes, and Visual Field Coverage in the Human MT+ Complex. *Journal of Neurophysiology*, 102(5), 2704–2718. <https://doi.org/10.1152/jn.00102.2009>
- American Psychiatric Association. (2014). *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edit). American Psychiatric Association. <https://doi.org/10.1176/appi.books.9780890425596>
- Antshel, K. M., Zhang-James, Y., & Faraone, S. V. (2013). The comorbidity of ADHD and autism spectrum disorder. *Expert Review of Neurotherapeutics*, 13(10), 1117–1128.
- Antshel, K. M., Zhang-James, Y., Wagner, K. E., Ledesma, A., & Faraone, S. V. (2016). An update on the comorbidity of ADHD and ASD: A focus on clinical management. *Expert Review of Neurotherapeutics*, 16(3), 279–293.
- Armstrong, I. T., & Munoz, D. P. (2003). Attentional blink in adults with attention-deficit hyperactivity disorder. *Experimental Brain Research*, 152(2), 243–250. <https://doi.org/10.1007/s00221-003-1535-0>
- Ashtari, M., Kumra, S., Bhaskar, S. L., Clarke, T., Thaden, E., Cervellione, K. L., ... Ardekani, B. A. (2005). Attention-deficit/hyperactivity disorder: A preliminary diffusion tensor imaging study. *Biological Psychiatry*, 57(5), 448–455. <https://doi.org/10.1016/j.biopsych.2004.11.047>
- August, G. J., & Garfinkel, B. D. (1989). Behavioral and cognitive subtypes of ADHD. *Journal of the American Academy of Child & Adolescent Psychiatry*, 28(5), 739–748.
- Bahrami, B., Lavie, N., & Rees, G. E. (2007). Attentional Load Modulates Responses of Human Primary Visual Cortex to Invisible Stimuli, 17(6), 509–513. <https://doi.org/10.1016/j.cub.2007.01.070>
- Banaschewski, T., Poustka, L., & Holtmann, M. (2011). Autism and ADHD across the life span. Differential diagnoses or comorbidity? *Der Nervenarzt*, 82(5), 573–580.
- Banich, M. T., Burgess, G. C., Depue, B. E., Ruzic, L., Bidwell, L. C., Hitt-Laustsen, S., ... Willcutt, E. G. (2009). The neural basis of sustained and transient attentional control in young adults with ADHD. *Neuropsychologia*, 47(14), 3095–3104. <https://doi.org/10.1016/j.neuropsychologia.2009.07.005>

References

- Barkley, R. A., DuPaul, G. J., & McMurray, M. B. (1991). Attention deficit disorder with and without hyperactivity: clinical response to three dose levels of methylphenidate. *Pediatrics*, *87*(4), 519–531. Retrieved from <http://www.worldcat.org/title/brain-mechanisms-for-the-integration-of-posture-and-movement-international-symposium-okazaki-japan-on-march-18-22-2001/oclc/255637249>
- Barkley, R. A., Grodzinsky, G., & DuPaul, G. J. (1992). Frontal lobe functions in attention deficit disorder with and without hyperactivity: A review and research report. *Journal of Abnormal Child Psychology*, *20*(2), 163–188. <https://doi.org/10.1007/BF00916547>
- Barrett, G., Blumhardt, L., Halliday, A. M., Halliday, E., & Kriss, A. (1976). A paradox in the lateralisation of the visual evoked response. *Nature*, *261*(5557), 253–255. <https://doi.org/10.1038/261253a0>
- Baseler, H. A., Gouws, A., Haak, K. V., Racey, C., Crossland, M. D., Tufail, A., ... Morland, A. B. (2011). Large-scale remapping of visual cortex is absent in adult humans with macular degeneration. *Nature Neuroscience*, *14*(5), 649–655. <https://doi.org/10.1038/nn.2793>
- Basser, P. J., Mattiello, J., & LeBihan, D. (1994). MR diffusion tensor spectroscopy and imaging. *Biophysical Journal*, *66*(1), 259.
- Beck, D. M., & Kastner, S. (2009). Top-down and bottom-up mechanisms in biasing competition in the human brain. *Vision Research*, *49*(10), 1154–1165. <https://doi.org/10.1016/j.visres.2008.07.012>
- Beck, D. M., & Lavie, N. (2005). Look Here but Ignore What You See: Effects of Distractors at Fixation. *Journal of Experimental Psychology: Human ...*, *31*(3), 592–607. <https://doi.org/10.1037/0096-1523.31.3.592>
- Behrmann, M., Geng, J. J., & Shomstein, S. (2004). Parietal cortex and attention. *Current Opinion in Neurobiology*, *14*(2), 212–217. <https://doi.org/10.1016/j.conb.2004.03.012>
- Bellgrove, M. A., Barry, E., Johnson, K. A., Cox, M., Dáibhis, A., Daly, M., ... Kirley, A. (2007). Spatial Attentional Bias as a Marker of Genetic Risk, Symptom Severity, and Stimulant Response in ADHD. *Neuropsychopharmacology*, *33*(10), 2536–2545. <https://doi.org/10.1038/sj.npp.1301637>
- Bellgrove, M. A., Chambers, C. D., Johnson, K. A., Daibhis, A., Daly, M., Hawi, Z., ... Robertson, I. H. (2007). Dopaminergic genotype biases spatial attention in healthy

References

- children. *Molecular Psychiatry*, 12(8), 786–792.
<https://doi.org/10.1038/sj.mp.4002022>
- Bellgrove, M. A., Eramudugolla, R., Newman, D. P., Vance, A., & Mattingley, J. B. (2013). Influence of attentional load on spatial attention in acquired and developmental disorders of attention. *Neuropsychologia*, 51(6), 1085–1093.
<https://doi.org/10.1016/j.neuropsychologia.2013.01.019>
- Bellgrove, M. A., Johnson, K. A., Barry, E., Mulligan, A., Hawi, Z., Gill, M., ... Chambers, C. D. (2009). Dopaminergic haplotype as a predictor of spatial inattention in children with attention-deficit/hyperactivity disorder. *Archives of ...*, 66(10), 1135–1142. <https://doi.org/10.1001/archgenpsychiatry.2009.120>
- Biehl, S. C., Ehli, A.-C., Müller, L. D., Niklaus, A., Pauli, P., & Herrmann, M. J. (2013). The impact of task relevance and degree of distraction on stimulus processing. *BMC Neuroscience*, 14(1), 107.
- Billington, J., Wilkie, R. M., Field, D. T., & Wann, J. P. (2010). Neural processing of imminent collision in humans. *Proceedings of the Royal Society B: Biological Sciences*, 278(1711), 1476–1481.
- Boehnke, S. E., & Munoz, D. P. (2008). On the importance of the transient visual response in the superior colliculus. *Current Opinion in Neurobiology*, 18(6), 544–551. <https://doi.org/10.1016/j.conb.2008.11.004>
- Booksh, R., Pella, R. D., Singh, A. N., & Drew Gouvier, W. (2010). Ability of college students to simulate ADHD on objective measures of attention. *Journal of Attention Disorders*, 13(4), 325–338. <https://doi.org/10.1177/1087054708329927>
- Booth, J. R., Burman, D. D., Meyer, J. R., Lei, Z., Trommer, B. L., Davenport, N. D., ... Marsel Mesulam, M. (2005). Larger deficits in brain networks for response inhibition than for visual selective attention in attention deficit hyperactivity disorder (ADHD). *Journal of Child Psychology and Psychiatry*, 46(1), 94–111.
<https://doi.org/10.1111/j.1469-7610.2004.00337.x>
- Börger, N., van der Meere, J. J., Ronner, A., Alberts, E., Geuze, R., & Bögte, H. (1999). Heart rate variability and sustained attention in ADHD children. *Journal of Abnormal Child Psychology*, 27(1), 25–33. Retrieved from <http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=10197404&retmode=ref&cmd=prlinks>
- Brace, L. R., Kraev, I., Rostron, C. L., Stewart, M. G., Overton, P. G., & Dommett, E. J. (2015). Altered visual processing in a rodent model of Attention-Deficit

References

- Hyperactivity Disorder. *NEUROSCIENCE*, 303(C), 364–377.
<https://doi.org/10.1016/j.neuroscience.2015.07.003>
- Breen, M. J. (1989). Cognitive and behavioral differences in ADHD boys and girls. *Journal of Child Psychology and Psychiatry*, 30(5), 711–716.
- Breitmeyer, B. G. (1993). Express saccades: Attention, fixation or both? *Behavioral and Brain Sciences*, 16(3), 572.
- Bressler, S. L., Tang, W., Sylvester, C. M., Shulman, G. L., & Corbetta, M. (2008). Top-down control of human visual cortex by frontal and parietal cortex in anticipatory visual spatial attention. *The Journal of Neuroscience*, 28(40), 10056–10061.
- Brieber, S., Neufang, S., Bruning, N., Kamp Becker, I., Remschmidt, H., Herpertz-Dahlmann, B., ... Konrad, K. (2007). Structural brain abnormalities in adolescents with autism spectrum disorder and patients with attention deficit/hyperactivity disorder. *Journal of Child Psychology and Psychiatry*, 48(12), 1251–1258.
- Cao, Q., Zang, Y., Sun, L., Sui, M., Long, X., Zou, Q., & Wang, Y. (2006). Abnormal neural activity in children with attention deficit hyperactivity disorder: a resting-state functional magnetic resonance imaging study. *NeuroReport*, 17(10), 1033–1036. <https://doi.org/10.1097/01.wnr.0000224769.92454.5d>
- Cao, X., Cao, Q., Long, X., Sun, L., Sui, M., Zhu, C., ... Wang, Y. (2009). Abnormal resting-state functional connectivity patterns of the putamen in medication-naïve children with attention deficit hyperactivity disorder. *Brain Research*, 1303, 195–206. <https://doi.org/10.1016/j.brainres.2009.08.029>
- Caplan, R., Guthrie, D., & Komo, S. (1996). Blink rate in children with attention-deficit-hyperactivity disorder. *Neuron*, 39(12), 1032–1038.
[https://doi.org/10.1016/0006-3223\(95\)00315-0](https://doi.org/10.1016/0006-3223(95)00315-0)
- Capotosto, P., Babiloni, C., Romani, G. L., & Corbetta, M. (2009). Frontoparietal cortex controls spatial attention through modulation of anticipatory alpha rhythms. *J Neurosci*, 29(18), 5863–5872. <https://doi.org/10.1523/JNEUROSCI.0539-09.2009>
- Carrasco, M. (2011). Visual attention: The past 25 years. *Vision Research*, 51(13), 1484–1525. <https://doi.org/10.1016/j.visres.2011.04.012>
- Carter, C. S., Krenner, P., Chaderjian, M., & Northcutt, C. (1995a). Abnormal processing of irrelevant information in attention deficit hyperactivity disorder. *Psychiatry Research*, 56(1), 59–70. [https://doi.org/10.1016/0165-1781\(94\)02509-h](https://doi.org/10.1016/0165-1781(94)02509-h)

References

- Carter, C. S., Krenner, P., Chaderjian, M., & Northcutt, C. (1995b). Asymmetrical visual-spatial attentional performance in ADHD: evidence for a right hemispheric deficit. *Biological ...*, 37(11), 789–797. [https://doi.org/10.1016/0006-3223\(94\)00217-Q](https://doi.org/10.1016/0006-3223(94)00217-Q)
- Castellanos, F. X., & Proal, E. (2012). Large-scale brain systems in ADHD: beyond the prefrontal–striatal model. *Trends in Cognitive Sciences*, 16(1), 17–26. <https://doi.org/10.1016/j.tics.2011.11.007>
- Cerullo, M. A., Adler, C. M., Lamy, M., Eliassen, J. C., Fleck, D. E., Strakowski, S. M., & DelBello, M. P. (2009). Differential brain activation during response inhibition in bipolar and attention-deficit hyperactivity disorders. *Early Intervention in Psychiatry*, 3(3), 189–197. <https://doi.org/10.1111/j.1751-7893.2009.00132.x>
- Chan, E., Mattingley, J. B., Huang-Pollock, C. L., English, T., Hester, R. L., Vance, A., & Bellgrove, M. A. (2009). Abnormal spatial asymmetry of selective attention in ADHD. *Journal of Child Psychology and Psychiatry*, 50(9), 1064–1072. <https://doi.org/10.1111/j.1469-7610.2009.02096.x>
- Chee, P., Logan, G. D., Schachar, R., Lindsay, P., & Wachsmuth, R. (1989). Effects of event rate and display time on sustained attention in hyperactive, normal, and control children. *Journal of Abnormal Child Psychology*, 17(4), 371–391. Retrieved from <http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=2794253&retmode=ref&cmd=prlinks>
- Chokron, S. (1993). Influence of reading habits on line bisection. *Neuron*, 1(4), 219–222. [https://doi.org/10.1016/0926-6410\(93\)90005-P](https://doi.org/10.1016/0926-6410(93)90005-P)
- Chokron, S., & De Agostini, M. (1995). Reading habits and line bisection: A developmental approach. *Cognitive Brain Research*, 3(1), 51–58.
- Chou, K. H., Chou, Y. H., Chiu, F. Y., & Gao, W. Y. (2007). Structural abnormalities of adolescent males with attention-deficit/hyperactivity disorder: a DTI study. *The Joint Annual ...* Retrieved from https://www.researchgate.net/profile/Woei_Chyn_Chu/publication/266220705_Structural_abnormalities_of_adolescent_males_with_attention-deficithyperactivity_disorder_a_DTI_study/links/54becfcb0cf28ad7e7195a95.pdf
- Clark, K. A., Nuechterlein, K. H., Asarnow, R. F., Hamilton, L. S., Phillips, O. R., Hageman, N. S., ... Narr, K. L. (2011). Mean diffusivity and fractional anisotropy as indicators of disease and genetic liability to schizophrenia. *Journal of*

References

- Psychiatric Research*, 45(7), 980–988.
<https://doi.org/10.1016/j.jpsychires.2011.01.006>
- Clements, K. M., Devonshire, I. M., Reynolds, J. N. J., & Overton, P. G. (2014). Enhanced visual responses in the superior colliculus in an animal model of attention-deficit hyperactivity disorder and their suppression by d-amphetamine. *NEUROSCIENCE*, 274(C), 289–298.
<https://doi.org/10.1016/j.neuroscience.2014.05.054>
- Cocchi, L., Bramati, I. E., Zalesky, A., Furukawa, E., Fontenelle, L. F., Moll, J., ... Mattos, P. (2012). Altered Functional Brain Connectivity in a Non-Clinical Sample of Young Adults with Attention-Deficit/Hyperactivity Disorder. *The Journal of Neuroscience*, 32(49), 17753–17761. <https://doi.org/10.1523/JNEUROSCI.3272-12.2012>
- Cohen, M. S., DuBois, R. M., & Zeineh, M. M. (2000). Rapid and effective correction of RF inhomogeneity for high field magnetic resonance imaging. *Human Brain Mapping*, 10(4), 204–211. [https://doi.org/10.1002/1097-0193\(200008\)10:4<204::AID-HBM60>3.0.CO;2-2](https://doi.org/10.1002/1097-0193(200008)10:4<204::AID-HBM60>3.0.CO;2-2)
- Collings, R. D. (2003). Differences between ADHD inattentive and combined types on the CPT. *Journal of Psychopathology and Behavioral Assessment*, 25(3), 177–189.
- Conners, C. K. (2008). Conners third edition (Conners 3). *Los Angeles, CA: Western Psychological Services*.
- Conners, C. K., Erhardt, D., Epstein, J. N., Parker, J. D. A., Sitarenios, G., & Sparrow, E. (1999). Self-ratings of ADHD symptoms in adults I: Factor structure and normative data. *Journal of Attention Disorders*, 3(3), 141–151.
- Conners, C. K., Erhardt, D., & Sparrow, E. (2002). Conners's Adult ADHD Rating Scales—Self-Report: Long Version (CAARS—S: L).
- Conners, C. K., Sitarenios, G., Parker, J. D. A., & Epstein, J. N. (1998). The revised Conners's Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. *Journal of Abnormal Child Psychology*, 26(4), 257–268.
- Conners, C. K., Staff, M. H. S., Connelly, V., Campbell, S., MacLean, M., & Barnes, J. (2000). Conners' continuous performance Test II (CPT II v. 5). *Multi-Health Syst Inc*, 29, 175–196.
- Cortese, S., & Castellanos, F. X. (2012). Neuroimaging of Attention-Deficit/Hyperactivity Disorder: Current Neuroscience-Informed Perspectives for Clinicians. *Current Psychiatry Reports*, 14(5), 568–578.

References

- <https://doi.org/10.1007/s11920-012-0310-y>
- Cortese, S., Imperati, D., Zhou, J., Proal, E., Klein, R. G., Mannuzza, S., ... Castellanos, F. X. (2013). White Matter Alterations at 33-Year Follow-Up in Adults with Childhood Attention-Deficit/ Hyperactivity Disorder. *BPS*, 74(8), 591–598. <https://doi.org/10.1016/j.biopsych.2013.02.025>
- Cortese, S., Kelly, C., Chabernaud, C., Proal, E., Di Martino, A., Milham, M. P., & Castellanos, F. X. (2012). Toward Systems Neuroscience of ADHD: A Meta-Analysis of 55 fMRI Studies. *American Journal of Psychiatry*, 169(10), 1038–1055. <https://doi.org/10.1176/appi.ajp.2012.11101521>
- Cubillo, A. I., Halari, R., Ecker, C., Giampietro, V., Taylor, E., & Rubia, K. (2010). Reduced activation and inter-regional functional connectivity of fronto-striatal networks in adults with childhood Attention-Deficit Hyperactivity Disorder (ADHD) and persisting symptoms during tasks of motor inhibition and cognitive switching. *Journal of Psychiatric Research*, 44(10), 629–639. <https://doi.org/10.1016/j.jpsychires.2009.11.016>
- Cubillo, A. I., Halari, R., Smith, A., Taylor, E., & Rubia, K. (2012). A review of fronto-striatal and fronto-cortical brain abnormalities in children and adults with Attention Deficit Hyperactivity Disorder (ADHD) and new evidence for dysfunction in adults with ADHD during motivation and attention. *CORTEX*, 48(2), 194–215. <https://doi.org/10.1016/j.cortex.2011.04.007>
- Cynader, M., & Berman, N. (1972). Receptive-field organization of monkey superior colliculus. *J Neurophysiol*. Retrieved from http://invice.net/biblio_database_dyva/woda/data/att/f43e.file.02149.pdf
- Daselaar, S. M., Prince, S. E., & Cabeza, R. (2004). When less means more: deactivations during encoding that predict subsequent memory. *NeuroImage*, 23(3), 921–927. <https://doi.org/10.1016/j.neuroimage.2004.07.031>
- Day, R. F., Shyi, G. C. W., & Wang, J. C. (2006). The effect of flash banners on multiattribute decision making: Distractor or source of arousal? *Psychology & Marketing*, 23(5), 369–382.
- De Schotten, M. T., Acqua, F., Forkel, S. J., Simmons, A., Vergani, F., Murphy, D. G. M., & Catani, M. (2011). A lateralized brain network for visuospatial attention. *Nature Neuroscience*, 14(10), 1245. <https://doi.org/10.1038/nn.2905>
- Dean, P., Redgrave, P., & Westby, G. W. M. (1989). Event or emergency? Two response systems in the mammalian superior colliculus. *Trends in Neurosciences*,

References

12(4), 137–147.

- Desimone, R., & Duncan, J. (1995). Neural Mechanisms of Selective Visual Attention. *Annual Review of Neuroscience*, 18(1), 193–222.
<https://doi.org/10.1146/annurev.neuro.18.1.193>
- Dibbets, P., Evers, L., Hurks, P., Marchetta, N., & Jolles, J. (2009). Differences in feedback- and inhibition-related neural activity in adult ADHD. *Brain and Cognition*, 70(1), 73–83. <https://doi.org/10.1016/j.bandc.2009.01.001>
- Dickinson, A., Jones, M., & Milne, E. (2014). Oblique orientation discrimination thresholds are superior in those with a high level of autistic traits. *Journal of Autism and Developmental Disorders*, 44(11), 2844–2850.
- Dillo, W., Göke, A., Prox-Vagedes, V., Szycik, G. R., Roy, M., Donnerstag, F., ... Ohlmeier, M. D. (2010). Neuronal correlates of ADHD in adults with evidence for compensation strategies--a functional MRI study with a Go/No-Go paradigm. *German Medical Science : GMS e-Journal*, 8, Doc09.
<https://doi.org/10.3205/000098>
- Dorris, M. C., Klein, R. M., Everling, S., & Munoz, D. P. (2002). Contribution of the primate superior colliculus to inhibition of return. *Journal of Cognitive ...*, 14(8), 1256–1263. <https://doi.org/10.1162/089892902760807249>
- Driver, J., & Vuilleumier, P. O. (2001). Perceptual awareness and its loss in unilateral neglect and extinction. *Cognition*, 79(1–2), 39–88. [https://doi.org/10.1016/s0010-0277\(00\)00124-4](https://doi.org/10.1016/s0010-0277(00)00124-4)
- DuPaul, G. J., Schaugency, E. A., Weyandt, L. L., Tripp, G., Kiesner, J., Ota, K., & Stanish, H. (2001). Self-report of ADHD symptoms in university students: Cross-gender and cross-national prevalence. *Journal of Learning ...*, 34(4), 370–379.
- Durston, S., Pol, H. E. H., Schnack, H. G., Buitelaar, J. K., Steenhuis, M. P., Minderaa, R. B., ... van engeland, H. (2004). Magnetic Resonance Imaging of Boys With Attention-Deficit/Hyperactivity Disorder and Their Unaffected Siblings. *Journal of the American Academy of Child & Adolescent Psychiatry*, 43(3), 332–340.
<https://doi.org/10.1097/00004583-200403000-00016>
- Durston, S., Tottenham, N. T., Thomas, K. M., Davidson, M. C., Eigsti, I.-M., Yang, Y., ... Casey, B. J. (2003). Differential patterns of striatal activation in young children with and without ADHD. *Biological Psychiatry*, 53(10), 871–878.
[https://doi.org/10.1016/S0006-3223\(02\)01904-2](https://doi.org/10.1016/S0006-3223(02)01904-2)
- Edelman, J. A., & Keller, E. L. (1993). *Activity of Visuomotor Neurons in Primate*

References

- Superior Colliculus During Express Saccades to Single and Double Targets*. Retrieved from <http://scholar.google.com#>
- Eichele, T., Debener, S., Calhoun, V. D., Specht, K., Engel, A. K., Hugdahl, K., ... Ullsperger, M. (2008). Prediction of human errors by maladaptive changes in event-related brain networks. *Proceedings of the National Academy of Sciences*, *105*(16), 6173–6178. <https://doi.org/10.1073/pnas.0708965105>
- Engel, S. A., Glover, G. H., & Wandell, B. A. (1997). Retinotopic organization in human visual cortex and the spatial precision of functional MRI. *Cerebral Cortex*, *7*(2), 181–192. <https://doi.org/10.1093/cercor/7.2.181>
- Epstein, J. N., Conners, C. K., Erhardt, D., March, J. S., & Swanson, J. M. (1997). Asymmetrical hemispheric control of visual-spatial attention in adults with attention deficit hyperactivity disorder. ..., *11*(4), 467–473. <https://doi.org/10.1037/0894-4105.11.4.467>
- Epstein, J. N., Conners, C. K., Sitarenios, G., & Erhardt, D. (1998). Continuous performance test results of adults with attention deficit hyperactivity disorder. *The Clinical Neuropsychologist*, *12*(2), 155–168.
- Epstein, J. N., Erkanli, A., Conners, C. K., Klaric, J., Costello, J. E., & Angold, A. (2003). Relations Between Continuous Performance Test Performance Measures and ADHD Behaviors. *Journal of Abnormal Child Psychology*, *31*(5), 543–554. <https://doi.org/10.1023/A:1025405216339>
- Evans, A. C., Collins, D. L., Mills, S. R., Brown, E. D., Kelly, R. L., & Peters, T. M. (2004). 3D statistical neuroanatomical models from 305 MRI volumes. *1993 IEEE Conference Record Nuclear Science Symposium and Medical Imaging Conference*. IEEE. <https://doi.org/10.1109/NSSMIC.1993.373602>
- Everling, S., Dorris, M. C., Klein, R. M., & Munoz, D. P. (1999). Role of Primate Superior Colliculus in Preparation and Execution of Anti-Saccades and Pro-Saccades. *The Journal of Neuroscience*, *19*(7), 2740–2754. Retrieved from <http://linkinghub.elsevier.com/retrieve/pii/0165027088901604>
- EyeLink® 1000 User Manual* . (2009). Retrieved from [http://sr-research.jp/support/EyeLink 1000 User Manual 1.5.0.pdf](http://sr-research.jp/support/EyeLink%201000%20User%20Manual%201.5.0.pdf)
- Fallgatter, A. J., Ehlis, A.-C., Seifert, J., Strik, W. K., Scheuerpflug, P., Zillessen, K. E., ... Warnke, A. (2004). Altered response control and anterior cingulate function in attention-deficit/hyperactivity disorder boys. *Clinical Neurophysiology*, *115*(4), 973–981. <https://doi.org/10.1016/j.clinph.2003.11.036>

References

- Faraone, S. V. (2005). What Is the Prevalence of Adult ADHD? Results of a Population Screen of 966 Adults. *Journal of Attention Disorders, 9*(2), 384–391. <https://doi.org/10.1177/1087054705281478>
- Faraone, S. V., Biederman, J., & Mick, E. (2005). The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. *Psychological Medicine, 36*(02), 157–159. <https://doi.org/10.1017/S003329170500471X>
- Faraone, S. V., Sergeant, J. A., Gillberg, C., & Biederman, J. (2003). The worldwide prevalence of ADHD: is it an American condition. *World Psychiatry*. Retrieved from http://www.mednet.org.uy/spu/wp/WPA_2_2003.pdf#page=42
- Fassbender, C., Zhang, H., Buzy, W. M., Cortes, C. R., Mizuri, D., Beckett, L., & Schweitzer, J. B. (2009). A lack of default network suppression is linked to increased distractibility in ADHD. *Brain Research, 1273*(C), 114–128. <https://doi.org/10.1016/j.brainres.2009.02.070>
- Fayyad, J., De Graaf, R., Kessler, R. C., Alonso, J., Angermeyer, M., Demyttenaere, K., ... Jin, R. (2007). Cross-national prevalence and correlates of adult attention-deficit hyperactivity disorder. *The British Journal of Psychiatry, 190*(5), 402–409. <https://doi.org/10.1192/bjp.bp.106.034389>
- Feifel, D., Farber, R. H., Clementz, B. A., Perry, W., & Anllo-Vento, L. (2004). Inhibitory deficits in ocular motor behavior in adults with attention-deficit/hyperactivity disorder. *Biological Psychiatry, 56*(5), 333–339. <https://doi.org/10.1016/j.biopsych.2004.06.019>
- Filipek, P. A., Semrud-Clikeman, M., Steingard, R. J., Renshaw, P. F., Kennedy, D. N., & Biederman, J. (1997). Volumetric MRI analysis comparing subjects having attention-deficit hyperactivity disorder with normal controls. *Neurology, 48*(3), 589–601. <https://doi.org/10.1212/WNL.48.3.589>
- Fink, G. R., Driver, J., Rorden, C., Baldeweg, T., & Dolan, R. J. (2000). Neural consequences of competing stimuli in both visual hemifields: A physiological basis for visual extinction. *Annals of ...*, *47*(4), 440–446. [https://doi.org/10.1002/1531-8249\(200004\)47:4<440::AID-ANA6>3.0.CO;2-E](https://doi.org/10.1002/1531-8249(200004)47:4<440::AID-ANA6>3.0.CO;2-E)
- Fischer, B., & Weber, H. (1993). Express saccades and visual attention. *Behavioral and Brain Sciences, 16*(3), 553–567. <https://doi.org/10.1017/S0140525X00031575>
- Ford, T., Goodman, R., & Meltzer, H. (2003). The British Child and Adolescent Mental Health Survey 1999: The Prevalence of DSM-IV Disorders, *42*(10), 1203–1211.

References

- <https://doi.org/10.1097/00004583-200310000-00011>
- Forster, S., & Lavie, N. (2007). High Perceptual Load Makes Everybody Equal. *Psychological Science*, *18*(5), 377–381. <https://doi.org/10.1111/j.1467-9280.2007.01908.x>
- Forster, S., & Lavie, N. (2008). Attentional capture by entirely irrelevant distractors. *Visual Cognition*, *16*(2–3), 200–214. <https://doi.org/10.1080/13506280701465049>
- Forster, S., & Lavie, N. (2011). Entirely irrelevant distractors can capture and captivate attention. *Psychonomic Bulletin & Review*, *18*(6), 1064–1070. <https://doi.org/10.3758/s13423-011-0172-z>
- Forster, S., Robertson, D. J., Jennings, A., Asherson, P., & Lavie, N. (2014). Plugging the attention deficit: Perceptual load counters increased distraction in ADHD. ..., *28*(1), 91–97. <https://doi.org/10.1037/neu0000020>
- Foxe, J. J., & Simpson, G. V. (2002). Flow of activation from V1 to frontal cortex in humans. *Experimental Brain Research*, *142*(1), 139–150.
- Foxe, J. J., Simpson, G. V., & Ahlfors, S. P. (1998). Parieto-occipital ~ 10 Hz activity reflects anticipatory state of visual attention mechanisms. *NeuroReport*, *9*(17), 3929–3933. <https://doi.org/10.1097/00001756-199812010-00030>
- Fried, M., Tsitsiashvili, E., Bonne, Y. S., Sterkin, A., Wygnanski-Jaffe, T., Epstein, T., & Polat, U. (2014). ADHD subjects fail to suppress eye blinks and microsaccades while anticipating visual stimuli but recover with medication. *Vision Research*, *101*(C), 62–72. <https://doi.org/10.1016/j.visres.2014.05.004>
- Friedman-Hill, S. R., Wagman, M. R., Gex, S. E., Pine, D. S., Leibenluft, E., & Ungerleider, L. G. (2010). What does distractibility in ADHD reveal about mechanisms for top-down attentional control? *Cognition*, *115*(1), 93–103. <https://doi.org/10.1016/j.cognition.2009.11.013>
- Froehlich, T. E., Lanphear, B. P., Epstein, J. N., Barbaresi, W. J., Katusic, S. K., & Kahn, R. S. (2007). Prevalence, Recognition, and Treatment of Attention-Deficit/Hyperactivity Disorder in a National Sample of US Children. ... of *Pediatrics & ...*, *161*(9), 857–864. <https://doi.org/10.1001/archpedi.161.9.857>
- Fujita, N., Tanaka, H., Takanashi, M., Hirabuki, N., Abe, K., Yoshimura, H., & Nakamura, H. (2001). Lateral Geniculate Nucleus: Anatomic and Functional Identification by Use of MR Imaging. *American Journal of Neuroradiology*, *22*(9), 1719–1726. <https://doi.org/10.1001/archneur.1990.00530110059017>
- Furlan, M., Smith, A. T., & Walker, R. (2015). Activity in the human superior

References

- colliculus relating to endogenous saccade preparation and execution. *Journal of Neurophysiology*, *114*(2), 1048–1058.
- Furlan, M., Smith, A. T., & Walker, R. (2016). An fMRI investigation of preparatory set in the human cerebral cortex and superior colliculus for pro-and anti-saccades. *PLOS ONE*, *11*(7), e0158337.
- Furmanski, C. S., & Engel, S. A. (2000). An oblique effect in human primary visual cortex. *Nature Neuroscience*, *3*(6), 535–536. <https://doi.org/10.1038/75702>
- Gandhi, S. P., Heeger, D. J., & Boynton, G. M. (1999). Spatial attention affects brain activity in human primary visual cortex. *Proceedings of the National Academy of Sciences*, *96*(6), 3314–3319. <https://doi.org/10.1073/pnas.96.6.3314>
- Gaymard, B., François, C., Ploner, C. J., Condy, C., & Rivaud Péchoux, S. (2003). A direct prefrontotectal tract against distractibility in the human brain. *Annals of ...*, *53*(4), 542–545. <https://doi.org/10.1002/ana.10560>
- Geeraerts, S., Lafosse, C., Vaes, N., Vandenbussche, E., & Verfaillie, K. (2008). Dysfunction of right-hemisphere attentional networks in attention deficit hyperactivity disorder. *Journal of Clinical and Experimental Neuropsychology*, *30*(1), 42–52. <https://doi.org/10.1080/13803390601186676>
- George, M., Dobler, V. B., Nicholls, E., & Manly, T. (2005). Spatial awareness, alertness, and ADHD: The re-emergence of unilateral neglect with time-on-task. *Brain and Cognition*, *57*(3), 264–275. <https://doi.org/10.1016/j.bandc.2004.09.003>
- Goldberg, M. E., & Wurtz, R. H. (1972). Activity of superior colliculus in behaving monkey. II. Effect of attention on neuronal responses. *J Neurophysiol*. Retrieved from http://invibe.net/biblio_database_dyva/woda/data/att/6e08.file.pdf
- Gonçalves, S. I., de Munck, J. C., Pouwels, P. J. W., Schoonhoven, R., Kuijter, J. P. A., Maurits, N. M., ... Lopes da Silva, F. H. (2006). Correlating the alpha rhythm to BOLD using simultaneous EEG/fMRI: Inter-subject variability. *NeuroImage*, *30*(1), 203–213. <https://doi.org/10.1016/j.neuroimage.2005.09.062>
- Goodale, M. A., Foreman, N. P., & Milner, A. D. (1978). Visual orientation in the rat: A dissociation of deficits following cortical and collicular lesions. *Experimental Brain Research*, *31*(3), 445–457. <https://doi.org/10.1007/BF00237301>
- Goto, Y., Hatakeyama, K., Kitama, T., Sato, Y., Kanemura, H., Aoyagi, K., ... Aihara, M. (2010). Saccade eye movements as a quantitative measure of frontostriatal network in children with ADHD. *Brain and Development*, *32*(5), 347–355. <https://doi.org/10.1016/j.braindev.2009.04.017>

References

- Gouws, A. D., Alvarez, I., Watson, D. M., Uesaki, M., Rogers, J., & Morland, A. B. (2014). On the Role of Suppression in Spatial Attention: Evidence from Negative BOLD in Human Subcortical and Cortical Structures. *The Journal of Neuroscience*, *34*(31), 10347–10360. <https://doi.org/10.1523/JNEUROSCI.0164-14.2014>
- Gowan, J. D., Coizet, V., Devonshire, I. M., & Overton, P. G. (2008). d-Amphetamine depresses visual responses in the rat superior colliculus: a possible mechanism for amphetamine-induced decreases in distractibility. *Journal of Neural Transmission*, *115*(3), 377–387. <https://doi.org/10.1007/s00702-007-0858-6>
- Grantyn, A., Moschovakis, A. K., & Kitama, T. (2004). Control of orienting movements: role of multiple tectal projections to the lower brainstem. In *Brain Mechanisms for the Integration of Posture and Movement* (Vol. 143, pp. 423–438). Elsevier. [https://doi.org/10.1016/S0079-6123\(03\)43040-9](https://doi.org/10.1016/S0079-6123(03)43040-9)
- Greven, C. U., Rijdsdijk, F. V., & Plomin, R. (2011). A twin study of ADHD symptoms in early adolescence: hyperactivity-impulsivity and inattentiveness show substantial genetic overlap but also genetic specificity. *Journal of Abnormal Child Psychology*, *39*(2), 265–275.
- Hahn, B., Ross, T. J., & Stein, E. A. (2006). Cingulate Activation Increases Dynamically with Response Speed under Stimulus Unpredictability. *Cerebral Cortex*, *17*(7), 1664–1671. <https://doi.org/10.1093/cercor/bhl075>
- Hale, T. S., Bookheimer, S., McGough, J. J., Phillips, J. M., & McCracken, J. T. (2007). Atypical Brain Activation During Simple & Complex Levels of Processing in Adult ADHD: An fMRI Study. *Journal of Attention Disorders*, *11*(2), 125–139. <https://doi.org/10.1177/1087054706294101>
- Hale, T. S., Loo, S. K., Zaidel, E., Hanada, G., Macion, J., & Smalley, S. L. (2009). Rethinking a Right Hemisphere Deficit in ADHD. *Journal of Attention Disorders*, *13*(1), 3–17. <https://doi.org/10.1177/1087054708323005>
- Halliday, R., Gregory, K., Naylor, H., Callaway, E., & Yano, L. (1990). Beyond drug effects and dependent variables: the use of the Poisson-Erlang model to assess the effects of D-amphetamine on information processing. *Acta Psychologica*, *73*(1), 35–54. [https://doi.org/10.1016/0001-6918\(90\)90057-m](https://doi.org/10.1016/0001-6918(90)90057-m)
- Hamilton, L. S., Levitt, J. G., O'Neill, J., Alger, J. R., Luders, E., Phillips, O. R., ... Narr, K. L. (2008). Reduced white matter integrity in attention-deficit hyperactivity disorder. *NeuroReport*, *19*(17), 1705–1708.

References

<https://doi.org/10.1097/WNR.0b013e3283174415>

- Händel, B. F., Haarmeier, T., & Jensen, O. (2011). Alpha Oscillations Correlate with the Successful Inhibition of Unattended Stimuli. *Journal of Cognitive Neuroscience*, *23*(9), 2494–2502. <https://doi.org/10.1162/jocn.2010.21557>
- Handen, B. L., Breaux, A. M., Janosky, J., Mcauliffe, S., Feldman, H. M., & Gosling, A. (1992). Effects and noneffects of methylphenidate in children with mental retardation and ADHD. *Journal of the American Academy of Child & Adolescent Psychiatry*, *31*(3), 455–461.
- Hanisch, C., Radach, R., Holtkamp, K., Herpertz-Dahlmann, B., & Konrad, K. (2005). Oculomotor inhibition in children with and without attention-deficit hyperactivity disorder (ADHD). *Journal of Neural Transmission*, *113*(5), 671–684. <https://doi.org/10.1007/s00702-005-0344-y>
- Harrison, A. G. (2004). An Investigation of Reported Symptoms of ADHD in a University Population. *The ADHD Report*, *12*(6), 8–11. <https://doi.org/10.1521/adhd.12.6.8.55256>
- Harrison, A. G. (2006). Adults Faking ADHD: You Must Be Kidding! *The ADHD Report*, *14*(4), 1–7. <https://doi.org/10.1521/adhd.2006.14.4.1>
- Harrison, A. G., Edwards, M., & Parker, K. (2007). Identifying students faking ADHD: Preliminary findings and strategies for detection. *Archives of Clinical ...*, *22*(5), 577–588. <https://doi.org/10.1016/j.acn.2007.03.008>
- Hart, E. L., Lahey, B. B., Loeber, R., Applegate, B., & Frick, P. J. (1995). Developmental change in attention-deficit hyperactivity disorder in boys: A four-year longitudinal study. *Journal of Abnormal Child Psychology*, *23*(6), 729–749. <https://doi.org/10.1007/BF01447474>
- Hart, H., Radua, J., Mataix, D., & Rubia, K. (2013). Meta-analysis of fMRI studies of inhibition and attention in ADHD: exploring task-specific, stimulant medication and age effects. *JAMA Psychiatry*, *70*(2), 185–198.
- Haxby, J. V., Horwitz, B., Ungerleider, L. G., Maisog, J. M., Pietrini, P., & Grady, C. L. (1994). The functional organization of human extrastriate cortex: a PET-rCBF study of selective attention to faces and locations. *The Journal of Neuroscience*, *14*(11), 6336–6353. <https://doi.org/10.1523/JNEUROSCI.14-11-06336.1994>
- Heilman, K. M., & Valenstein, E. (1979). Mechanisms underlying hemispatial neglect. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society*, *5*(2), 166–170.

References

- Heilman, K. M., & Van Den Abell, T. (1980). Right hemisphere dominance for attention: the mechanism underlying hemispheric asymmetries of inattention (neglect). *Neurology*, *30*(3), 327.
- Hester, R. L., Murphy, K., Foxe, J. J., Foxe, D. M., Javitt, D. C., & Garavan, H. (2004). Predicting success: patterns of cortical activation and deactivation prior to response inhibition. *Journal of Cognitive Neuroscience*, *16*(5), 776–785.
- Hetzler, B. E., Meckel, K. R., & Stickle, B. A. (2014). Methylphenidate alters flash-evoked potentials, body temperature, and behavior in Long–Evans rats. *Pharmacology, Biochemistry and Behavior*, *116*(C), 75–83.
<https://doi.org/10.1016/j.pbb.2013.11.018>
- Hillyard, S. A., Vogel, E. K., & Luck, S. J. (1998). Sensory gain control (amplification) as a mechanism of selective attention: electrophysiological and neuroimaging evidence. ... *of the Royal ...*, *353*(1373), 1257–1270.
<https://doi.org/10.1098/rstb.1998.0281>
- Hines, J. L., King, T. S., & Curry, W. J. (2012). The adult ADHD self-report scale for screening for adult attention deficit–hyperactivity disorder (ADHD). *J Am Board Fam Med*, *25*(6), 847–853.
- Hinshaw, S. P., Carte, E. T., Sami, N., Treuting, J. J., & Zupan, B. A. (2002). Preadolescent girls with attention-deficit/hyperactivity disorder: II. Neuropsychological performance in relation to subtypes and individual classification. *Journal of Consulting and Clinical Psychology*, *70*(5), 1099–1111.
<https://doi.org/10.1037//0022-006X.70.5.1099>
- Holmes, G. (1918). Disturbances of Vision by Cerebral Lesions. *The British Journal of Ophthalmology*, *2*(7), 353–384. Retrieved from
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC513514/>
- Hooks, K., Milich, R., & Pugzles Lorch, E. (1994). Sustained and selective attention in boys with attention deficit hyperactivity disorder. *Journal of Clinical Child Psychology*, *23*(1), 69–77.
- Horton, J. C., & Hoyt, W. F. (1991). The representation of the visual field in human striate cortex: a revision of the classic Holmes map. *Archives of Ophthalmology*, *109*(6), 816–824.
- Huang-Pollock, C. L., Karalunas, S. L., Tam, H., & Moore, A. N. (2012). Evaluating vigilance deficits in ADHD: a meta-analysis of CPT performance.
<https://doi.org/10.1037/a0027205.supp>

References

- Huang-Pollock, C. L., Nigg, J. T., & Carr, T. H. (2005). Deficient attention is hard to find: applying the perceptual load model of selective attention to attention deficit hyperactivity disorder subtypes. *Journal of Child Psychology and Psychiatry*, *46*(11), 1211–1218.
- Humphrey, N. K. (1968). Responses to visual stimuli of units in the superior colliculus of rats and monkeys. *Experimental Neurology*, *20*(3), 312–340.
[https://doi.org/10.1016/0014-4886\(68\)90076-9](https://doi.org/10.1016/0014-4886(68)90076-9)
- Hupé, J.-M., Bordier, C., & Dojat, M. (2012). A BOLD signature of eyeblinks in the visual cortex. *NeuroImage*, *61*(1), 149–161.
<https://doi.org/10.1016/j.neuroimage.2012.03.001>
- Huss, M., Hölling, H., Kurth, B.-M., & Schlack, R. (2009). How often are German children and adolescents diagnosed with ADHD? Prevalence based on the judgment of health care professionals: results of the German health and examination survey (KiGGS). *European Child & Adolescent Psychiatry*, *17*(S1), 52–58. <https://doi.org/10.1007/s00787-008-1006-z>
- Ignashchenkova, A., Dicke, P. W., Haarmeier, T., & Thier, P. (2003). Neuron-specific contribution of the superior colliculus to overt and covert shifts of attention. *Nature Neuroscience*, *7*(1), 56–64. <https://doi.org/10.1038/nn1169>
- Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved Optimization for the Robust and Accurate Linear Registration and Motion Correction of Brain Images. *NeuroImage*, *17*(2), 825–841. <https://doi.org/10.1006/nimg.2002.1132>
- Jenkinson, M., Pechaud, M., & Smith, S. (2005). BET2: MR-based estimation of brain, skull and scalp surfaces. *Eleventh Annual Meeting of the Organization for Human Brain Mapping*. Toronto.
- Kanwisher, N., & Wojciulik, E. (2000). Visual attention: Insights from brain imaging. *Nature Reviews Neuroscience*, *1*(2), 91–100. <https://doi.org/10.1038/35039043>
- Karatekin, C. (2006). Improving antisaccade performance in adolescents with attention-deficit/hyperactivity disorder (ADHD). *Experimental Brain Research*, *174*(2), 324–341. <https://doi.org/10.1007/s00221-006-0467-x>
- Karatekin, C., & Asarnow, R. F. (1998). Components of Visual Search in Childhood-Onset Schizophrenia and Attention-Deficit/Hyperactivity Disorder. *Journal of Abnormal Child Psychology*, *26*(5), 367–380.
<https://doi.org/10.1023/A:1021903923120>
- Kastner, S., Pinsk, A., De Weerd, P., Desimone, R., & Ungerleider, L. G. (1999).

References

- Increased Activity in Human Visual Cortex during Directed Attention in the Absence of Visual Stimulation. *Neuron*, 22(4), 751–761.
[https://doi.org/10.1016/s0896-6273\(00\)80734-5](https://doi.org/10.1016/s0896-6273(00)80734-5)
- Katyal, S., Zughni, S., Greene, C., & Ress, D. (2010). Topography of Covert Visual Attention in Human Superior Colliculus. *Journal of Neurophysiology*, 104(6), 3074–3083. <https://doi.org/10.1152/jn.00283.2010>
- Kawai, N., & Yamamoto, C. (1969). Effects of 5-hydroxytryptamine, LSD and related compounds on electrical activities evoked in vitro in thin sections from the superior colliculus. *International Journal of Neuropharmacology*, 8(5), 437–449.
- Kelly, S. P. (2006). Increases in Alpha Oscillatory Power Reflect an Active Retinotopic Mechanism for Distracter Suppression During Sustained Visuospatial Attention. *Journal of Neurophysiology*, 95(6), 3844–3851.
<https://doi.org/10.1152/jn.01234.2005>
- Kessler, R. C. (2006). The Prevalence and Correlates of Adult ADHD in the United States: Results From the National Comorbidity Survey Replication. *American Journal of Psychiatry*, 163(4), 715–716. <https://doi.org/10.1176/appi.ajp.163.4.716>
- Kessler, R. C., Adler, L. A., Ames, M., Demler, O., Faraone, S. V., Hiripi, E., ... Walters, E. E. (1999). The World Health Organization adult ADHD self-report scale (ASRS): a short screening scale for use in the general population. *Psychological Medicine*, 35(2), 245–256.
<https://doi.org/10.1017/S0033291704002892>
- Kim, B.-N., Lee, J.-S., Shin, M.-S., Cho, S.-C., & Lee, D.-S. (2002). Regional cerebral perfusion abnormalities in attention deficit/hyperactivity disorder. *European Archives of Psychiatry and Clinical Neuroscience*, 252(5), 219–225.
<https://doi.org/10.1007/s00406-002-0384-3>
- Kim, J.-H., Lee, E.-H., & Joung, Y.-S. (2013). The WHO Adult ADHD Self-Report Scale: reliability and validity of the Korean version. *Psychiatry Investigation*, 10(1), 41.
- Kinsbourne, M. (1977). Hemi-neglect and hemisphere rivalry. *Adv Neurol*, 18, 41–49.
- Kinsbourne, M. (1987). Mechanisms of unilateral neglect. In *Advances in psychology* (Vol. 45, pp. 69–86). Elsevier.
- Klein, C., Fischer, B., Fischer, B., & Hartnegg, K. (2002). Effects of methylphenidate on saccadic responses in patients with ADHD. *Experimental Brain Research*, 145(1), 121–125. <https://doi.org/10.1007/s00221-002-1105-x>

References

- Klein, C., Raschke, A., & Brandenbusch, A. (2003). Development of pro- and antisaccades in children with attention-deficit hyperactivity disorder (ADHD) and healthy controls. *Psychophysiology*, *40*(1), 17–28. <https://doi.org/10.1111/1469-8986.00003>
- Klein, C., Wendling, K., Huettner, P., Ruder, H., & Peper, M. (2006). Intra-Subject Variability in Attention-Deficit Hyperactivity Disorder. *Biological Psychiatry*, *60*(10), 1088–1097. <https://doi.org/10.1016/j.biopsych.2006.04.003>
- Kollins, S. H., MacDonald, E. K., & Rush, C. R. (2001). Assessing the abuse potential of methylphenidate in nonhuman and human subjects: a review. *Pharmacology, Biochemistry and Behavior*, *68*(3), 611–627.
- Konrad, A., Dielentheis, T. F., El Masri, D., Bayerl, M., Fehr, C., Gesierich, T., ... Winterer, G. (2010). Disturbed structural connectivity is related to inattention and impulsivity in adult attention deficit hyperactivity disorder. *European Journal of Neuroscience*, *31*(5), 912–919. <https://doi.org/10.1111/j.1460-9568.2010.07110.x>
- Konrad, K., Günther, T., Hanisch, C., & Herpertz-Dahlmann, B. (2004). Differential effects of methylphenidate on attentional functions in children with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, *43*(2), 191–198.
- Konrad, K., Neufang, S., Hanisch, C., Fink, G. R., & Herpertz-Dahlmann, B. (2006). Dysfunctional Attentional Networks in Children with Attention Deficit/Hyperactivity Disorder: Evidence from an Event-Related Functional Magnetic Resonance Imaging Study. *Biological Psychiatry*, *59*(7), 643–651. <https://doi.org/10.1016/j.biopsych.2005.08.013>
- Kooistra, L., van der Meere, J. J., Edwards, J. D., Kaplan, B. J., Crawford, S., & Goodyear, B. G. (2010). Preliminary fMRI findings on the effects of event rate in adults with ADHD. *Journal of Neural Transmission*, *117*(5), 655–662. <https://doi.org/10.1007/s00702-010-0374-y>
- Larsson, H., Anckarsater, H., Råstam, M., Chang, Z., & Lichtenstein, P. (2012). Childhood attention-deficit hyperactivity disorder as an extreme of a continuous trait: a quantitative genetic study of 8,500 twin pairs. *Journal of Child Psychology and Psychiatry*, *53*(1), 73–80. <https://doi.org/10.1111/j.1469-7610.2011.02467.x>
- Lauritzen, T. Z., Esposito, M., Heeger, D. J., & Silver, M. A. (2009). Top-down flow of visual spatial attention signals from parietal to occipital cortex. *Journal of Vision*, *9*(13), 18.

References

- Lavie, N. (1995). Perceptual load as a necessary condition for selective attention. *Journal of Experimental Psychology: Human ...*, *21*(3), 451–468.
<https://doi.org/10.1037//0096-1523.21.3.451>
- Lavie, N. (2005). Distracted and confused?: Selective attention under load. *Trends in Cognitive Sciences*, *9*(2), 75–82. <https://doi.org/10.1016/j.tics.2004.12.004>
- Lavie, N. (2010). Attention, Distraction, and Cognitive Control Under Load. *Current Directions in Psychological Science*, *19*(3), 143–148.
<https://doi.org/10.1177/0963721410370295>
- Lavie, N., & Cox, S. (1997). On the Efficiency of Visual Selective Attention: Efficient Visual Search Leads to Inefficient Distractor Rejection. *Psychological Science*, *8*(5), 395–396. <https://doi.org/10.1111/j.1467-9280.1997.tb00432.x>
- Lavie, N., & de Fockert, J. W. (2003). Contrasting effects of sensory limits and capacity limits in visual selective attention. *Perception & Psychophysics*, *65*(2), 202–212. <https://doi.org/10.3758/BF03194795>
- Lavie, N., Hirst, A., de Fockert, J. W., & Viding, E. (2004). Load Theory of Selective Attention and Cognitive Control. *Journal of Experimental Psychology: General*, *133*(3), 339–354. <https://doi.org/10.1037/0096-3445.133.3.339>
- Lavie, N., & Tsal, Y. (1994). Perceptual load as a major determinant of the locus of selection in visual attention. *Perception & Psychophysics*, *56*(2), 183–197.
<https://doi.org/10.3758/BF03213897>
- Lawrence, K. E., Levitt, J. G., Loo, S. K., Ly, R., Yee, V., O'Neill, J., ... Narr, K. L. (2013). White Matter Microstructure in Subjects With Attention-Deficit/Hyperactivity Disorder and Their Siblings. *Journal of the American Academy of Child & Adolescent Psychiatry*, *52*(4), 431-440.e4.
<https://doi.org/10.1016/j.jaac.2013.01.010>
- Lee, D. H., Oakland, T., Jackson, G., & Glutting, J. (2008). Estimated prevalence of attention-deficit/hyperactivity disorder symptoms among college freshmen: Gender, race, and rater effects. *Journal of Learning ...*, *41*(4), 371–384.
- Lee, K.-M., Lee, S.-H., Kim, N.-Y., Kim, C.-Y., Sohn, J.-W., Choi, M. Y., ... Hyun Chang, K. (2001). Binocularity and spatial frequency dependence of calcarine activation in two types of amblyopia. *Neuroscience Research*, *40*(2), 147–153.
[https://doi.org/10.1016/S0168-0102\(01\)00220-6](https://doi.org/10.1016/S0168-0102(01)00220-6)
- Leigh, R. J. (2003). Using saccades as a research tool in the clinical neurosciences. *Brain*, *127*(3), 460–477. <https://doi.org/10.1093/brain/awh035>

References

- Levy, F., Hay, D. A., McStephen, M., Wood, C., & Waldman, I. (1997). Attention-deficit hyperactivity disorder: a category or a continuum? Genetic analysis of a large-scale twin study. *Journal of the American Academy of Child & Adolescent Psychiatry*, 36(6), 737–744.
- Liddle, E. B., Hollis, C., Batty, M. J., Groom, M. J., Totman, J. J., Liotti, M., ... Liddle, P. F. (2010). Task-related default mode network modulation and inhibitory control in ADHD: effects of motivation and methylphenidate. *Journal of Child Psychology and Psychiatry*, 52(7), 761–771. <https://doi.org/10.1111/j.1469-7610.2010.02333.x>
- Limbrick-Oldfield, E. H., Brooks, J. C. W., Wise, R. J. S., Padormo, F., Hajnal, J. V., Beckmann, C. F., & Ungless, M. A. (2012). Identification and characterisation of midbrain nuclei using optimised functional magnetic resonance imaging. *NeuroImage*, 59(2), 1230–1238. <https://doi.org/10.1016/j.neuroimage.2011.08.016>
- Lincoln, A., Lai, Z., & Jones, W. (2002). Shifting attention and joint attention dissociation in Williams syndrome: implications for the cerebellum and social deficits in autism. *Neurocase*, 8(2), 226–232. <https://doi.org/10.1076/neur.8.2.226.16199>
- Loo, S. K., Hale, T. S., Macion, J., Hanada, G., McGough, J. J., McCracken, J. T., & Smalley, S. L. (2009). Cortical activity patterns in ADHD during arousal, activation and sustained attention. *Neuropsychologia*, 47(10), 2114–2119. <https://doi.org/10.1016/j.neuropsychologia.2009.04.013>
- Losier, B., McGrath, P. T., & Klein, R. M. (1996). Error patterns of the Continuous Performance Test in non-medicated and medicated samples of children with and without Attention Deficit Hyperactivity Disorder: a meta-analytic review. *J. Child Psychol Psychiatry. OMS (1992): CIE-10. Trastornos Mentales y Del Comportamiento. Criterios Diagnósticos de Investigación, Décima Revisión. Meditor, Madrid.*
- Lubke, G. H., Hudziak, J. J., Derks, E. M., van Bijsterveldt, T. C. E. M., & Boomsma, D. I. (2009). Maternal ratings of attention problems in ADHD: evidence for the existence of a continuum. *Journal of the American Academy of Child & Adolescent Psychiatry*, 48(11), 1085–1093.
- Luck, S. J., Chelazzi, L., & Hillyard, S. A. (1997). Neural mechanisms of spatial selective attention in areas V1, V2, and V4 of macaque visual cortex. *Journal of ...* Retrieved from <http://jn.physiology.org/content/77/1/24.short>
- Mahone, E. M., Mostofsky, S. H., Lasker, A. G., Zee, D., & Denckla, M. B. (2009).

References

- Oculomotor Anomalies in Attention-Deficit/Hyperactivity Disorder: Evidence for Deficits in Response Preparation and Inhibition. *Journal of the American Academy of Child & Adolescent Psychiatry*, 48(7), 749–756.
<https://doi.org/10.1097/CHI.0b013e3181a565f1>
- Makris, N., Biederman, J., Valera, E. M., Bush, G., Kaiser, J., Kennedy, D. N., ... Seidman, L. J. (2007). Cortical Thinning of the Attention and Executive Function Networks in Adults with Attention-Deficit/Hyperactivity Disorder. *Cerebral Cortex*, 17(6), 1364–1375. <https://doi.org/10.1093/cercor/bhl047>
- Manly, T., Cornish, K., Grant, C., Dobler, V. B., & Hollis, C. (2005). Examining the relationship between rightward visuo-spatial bias and poor attention within the normal child population using a brief screening task. *Journal of Child Psychology and Psychiatry*, 46(12), 1337–1344. <https://doi.org/10.1111/j.1469-7610.2005.01432.x>
- Marrocco, R. T., & Li, R. H. (1977). Monkey superior colliculus: properties of single cells and their afferent inputs. *Journal of Neurophysiology*, 40(4), 844–860. Retrieved from <http://jn.physiology.org/lookup/doi/10.1152/jn.00575.2016>
- Martin, J., Hamshere, M. L., Stergiakouli, E., O'Donovan, M. C., & Thapar, A. (2014). Genetic Risk for Attention-Deficit/Hyperactivity Disorder Contributes to Neurodevelopmental Traits in the General Population. *BPS*, 76(8), 664–671. <https://doi.org/10.1016/j.biopsych.2014.02.013>
- Martínez, A., Anllo-Vento, L., Sereno, M. I., Frank, L. R., Buxton, R. B., Dubowitz, D. J., ... Hillyard, S. A. (1999). Involvement of striate and extrastriate visual cortical areas in spatial attention. *Nature Neuroscience*, 2(4), 364–369. <https://doi.org/10.1038/7274>
- Marx, I., Höpcke, C., Berger, C., Wandschneider, R., & Herpertz, S. C. (2013). The Impact of Financial Reward Contingencies on Cognitive Function Profiles in Adult ADHD. *PLOS ONE*, 8(6), e67002-16. <https://doi.org/10.1371/journal.pone.0067002>
- McAdams, C. J., & Maunsell, J. H. (1999). Effects of Attention on Orientation-Tuning Functions of Single Neurons in Macaque Cortical Area V4. *The Journal of Neuroscience*, 19(1), 431–441. <https://doi.org/10.1523/JNEUROSCI.19-01-00431.1999>
- McAlonan, G. M., Cheung, V., Cheung, C., Chua, S. E., Murphy, D. G. M., Suckling, J., ... Ho, T. P. (2007). Mapping brain structure in attention deficit-hyperactivity

References

- disorder: A voxel-based MRI study of regional grey and white matter volume. *Psychiatry Research: Neuroimaging*, 154(2), 171–180.
<https://doi.org/10.1016/j.psychresns.2006.09.006>
- McGee, R., Williams, S. M., & Silva, P. A. (1985). Factor structure and correlates of ratings of inattention, hyperactivity, and antisocial behavior in a large sample of 9-yr-old children from the general population. *Journal of Consulting and Clinical Psychology*, 53(4), 480.
- McLoughlin, G., Ronald, A., Kuntsi, J., Asherson, P., & Plomin, R. (2007). Genetic support for the dual nature of attention deficit hyperactivity disorder: substantial genetic overlap between the inattentive and hyperactive–impulsive components. *Journal of Abnormal Child Psychology*, 35(6), 999–1008.
- Meredith, M. A., Wallace, M. T., & Stein, B. E. (1992). Visual, auditory and somatosensory convergence in output neurons of the cat superior colliculus: multisensory properties of the tecto-reticulo-spinal projection. *Experimental Brain Research*, 88(1), 181–186. <https://doi.org/10.1007/BF02259139>
- Metin, B., Roeyers, H., Wiersema, J. R., van der Meere, J. J., & Sonuga-Barke, E. J. S. (2012). A meta-analytic study of event rate effects on Go/No-Go performance in attention-deficit/hyperactivity disorder. *Biological Psychiatry*, 72(12), 990–996. <https://doi.org/10.1016/j.biopsych.2012.08.023>
- Milich, R., Balentine, A. C., & Lynam, D. R. (2006). ADHD Combined Type and ADHD Predominantly Inattentive Type Are Distinct and Unrelated Disorders. *Clinical Psychology: Science and Practice*, 8(4), 463–488. <https://doi.org/10.1093/clipsy.8.4.463>
- Millstein, R. B., Wilens, T. E., & Biederman, J. (1997). Presenting ADHD symptoms and subtypes in clinically referred adults with ADHD. *Journal of Attention Disorders*, 2(3), 159–166. <https://doi.org/10.1177/108705479700200302>
- Milner, A. D., Foreman, N. P., & Goodale, M. A. (1978). Go-left go-right discrimination performance and distractibility following lesions of prefrontal cortex or superior colliculus in stump-tail macaques. *Neuropsychologia*, 16(4), 381–390. [https://doi.org/10.1016/0028-3932\(78\)90062-3](https://doi.org/10.1016/0028-3932(78)90062-3)
- Mohler, C. W., & Wurtz, R. H. (1976). Organization of monkey superior colliculus: intermediate layer cells discharging before eye movements. *Journal of Neurophysiology*, 39(4), 722–744. Retrieved from <http://jn.physiology.org/lookup/doi/10.1152/jn.00575.2016>

References

- Moran, J., & Desimone, R. (1985). Selective attention gates visual processing in the extrastriate cortex. *Science*, *229*(4715), 782–784.
<https://doi.org/10.1126/science.4023713>
- Morton, W. A., & Stockton, G. G. (2000). Methylphenidate abuse and psychiatric side effects. *Primary Care Companion to the Journal of Clinical Psychiatry*, *2*(5), 159.
- Mostofsky, S. H., Cooper, K. L., Kates, W. R., Denckla, M. B., & Kaufmann, W. E. (2002). Smaller prefrontal and premotor volumes in boys with attention-deficit/hyperactivity disorder. *BPS*, *52*(8), 785–794. Retrieved from <http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=12372650&retmode=ref&cmd=prlinks>
- Mostofsky, S. H., Lasker, A. G., Cutting, L. E., Denckla, M. B., & Zee, D. S. (2001). Oculomotor abnormalities in attention deficit hyperactivity disorder A preliminary study. *Neurology*, *57*(3), 423–430.
- Motter, B. C. (1993). Focal attention produces spatially selective processing in visual cortical areas V1, V2, and V4 in the presence of competing stimuli. *Journal of Neurophysiology*, *70*(3), 909–919. <https://doi.org/10.1152/jn.1993.70.3.909>
- Mowinckel, A. M., Pedersen, M. L., Eilertsen, E., & Biele, G. (2015). A meta-analysis of decision-making and attention in adults with ADHD. *Journal of Attention Disorders*, *19*(5), 355–367.
- Munoz, D. P. (2003). Altered Control of Visual Fixation and Saccadic Eye Movements in Attention-Deficit Hyperactivity Disorder. *Journal of Neurophysiology*, *90*(1), 503–514. <https://doi.org/10.1152/jn.00192.2003>
- Munoz, D. P., & Wurtz, R. H. (1992). Role of the Rostral Superior Colliculus in Active Visual Fixation and Execution of Express Saccades. *Journal of Neurophysiology*, *67*(4), 1000–1002. Retrieved from <http://jn.physiology.org/lookup/doi/10.1152/jn.00575.2016>
- Musso, M. W., & Gouvier, W. D. (2012). “Why Is This So Hard?” A Review of Detection of Malingered ADHD in College Students. *Journal of Attention Disorders*, *18*(3), 186–201. <https://doi.org/10.1177/1087054712441970>
- Newman, E., Jernigan, T. L., Lisdahl, K. M., Tamm, L., Tapert, S. F., Potkin, S. G., ... Castellanos, F. X. (2016). Go/no go task performance predicts cortical thickness in the caudal inferior frontal gyrus in young adults with and without ADHD. *Brain Imaging and Behavior*, *10*(3), 880–892.
- Nigg, J. T., Swanson, J. M., & Hinshaw, S. P. (1997). Covert visual spatial attention in

References

- boys with attention deficit hyperactivity disorder: lateral effects, methylphenidate response and results for parents. *Neuropsychologia*, 35(2), 165–176.
[https://doi.org/10.1016/S0028-3932\(96\)00070-X](https://doi.org/10.1016/S0028-3932(96)00070-X)
- O'Connor, D. H., Fukui, M. M., Pinsk, M. A., & Kastner, S. (2002). Attention modulates responses in the human lateral geniculate nucleus. *Nature Neuroscience*, 5(11), 1203–1209. <https://doi.org/10.1038/nn957>
- O'Driscoll, G. A., Dépatie, L., & Holahan, A. L. V. (2005). Executive functions and methylphenidate response in subtypes of attention-deficit/hyperactivity disorder. *Biological Psychiatry*, 57(11), 1452–1460.
<https://doi.org/10.1016/j.biopsych.2005.02.029>
- Oosterlaan, J., Logan, G. D., & Sergeant, J. A. (1998). Response Inhibition in AD/HD, CD, Comorbid AD/HD+CD, Anxious, and Control Children: A Meta-analysis of Studies with the Stop Task. *The Journal of Child Psychology and Psychiatry and Allied Disciplines*, 39(3), 411–425. <https://doi.org/10.1017/S0021963097002072>
- Overton, P. G. (2008). Collicular dysfunction in attention deficit hyperactivity disorder. *Medical Hypotheses*, 70(6), 1121–1127.
<https://doi.org/10.1016/j.mehy.2007.11.016>
- Overton, P. G., & Clements, K. M. (2009). Does collicular hyper-responsivity underlie increased distractibility in attention deficit hyperactivity disorder. *Advances in Psychology Research*, Vol, 67, 1–16.
- Panagiotidi, M. (2016). The Role of the Superior Colliculus in Attention Deficit Hyperactivity Disorder.
- Panagiotidi, M., Overton, P. G., & Stafford, T. (2016). Attention-Deficit Hyperactivity Disorder-Like Traits and Distractibility in the Visual Periphery. *Perception*, 1–14.
<https://doi.org/10.1177/0301006616681313>
- Panagiotidi, M., Overton, P. G., & Stafford, T. (2017). Increased microsaccade rate in individuals with ADHD traits. *Journal of Eye Movement Research*, 10(1).
- Parsons, T. D., Bowerly, T., Buckwalter, J. G., & Rizzo, A. A. (2007). A Controlled Clinical Comparison of Attention Performance in Children with ADHD in a Virtual Reality Classroom Compared to Standard Neuropsychological Methods. *Child Neuropsychology*, 13(4), 363–381.
<https://doi.org/10.1080/13825580600943473>
- Pavuluri, M. N., Yang, S., Kamineni, K., Passarotti, A. M., Srinivasan, G., Harral, E. M., ... Zhou, X. J. (2009). Diffusion Tensor Imaging Study of White Matter Fiber

References

- Tracts in Pediatric Bipolar Disorder and Attention-Deficit/Hyperactivity Disorder. *Biological Psychiatry*, 65(7), 586–593.
<https://doi.org/10.1016/j.biopsych.2008.10.015>
- Pearson, D. A., Yaffee, L. S., Loveland, K. A., & Norton, A. M. (1995). Covert visual attention in children with attention deficit hyperactivity disorder: evidence for developmental immaturity? *Development and Psychopathology*, 7(02), 351–367.
- Peirce, J. W. (2009). Generating stimuli for neuroscience using PsychoPy. *Frontiers in Neuroinformatics*, 2, 10.
- Peterson, B. S., & Potenza, M. N. (2009). An fMRI study of the effects of psychostimulants on default-mode processing during Stroop task performance in youths with ADHD. *Am Psychiatric Assoc*, 166(11), 1286–1294.
<https://doi.org/10.1176/appi.ajp.2009.08050724>
- Pironti, V. A., Lai, M.-C., Müller, U., Dodds, C. M., Suckling, J., Bullmore, E. T., & Sahakian, B. J. (2014). Neuroanatomical Abnormalities and Cognitive Impairments Are Shared by Adults with Attention- Deficit/Hyperactivity Disorder and Their Unaffected First-Degree Relatives. *BPS*, 76(8), 639–647.
<https://doi.org/10.1016/j.biopsych.2013.09.025>
- Plaisted, K., Swettenham, J., & Rees, L. (1999). Children with Autism Show Local Precedence in a Divided Attention Task and Global Precedence in a Selective Attention Task. *Journal of Child Psychology and Psychiatry*, 40(5), 733–742.
<https://doi.org/10.1111/1469-7610.00489>
- Polanczyk, G. V, de Lima, M. S., & Horta, B. L. (2007). The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *American Journal of Psychiatry*, 164(6), 942–948. <https://doi.org/10.1176/ajp.2007.164.6.942>
- Polanczyk, G. V, Willcutt, E. G., Salum, G. A., Kieling, C., & Rohde, L. A. (2014). ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. *International Journal of Epidemiology*, 43(2), 434–442. <https://doi.org/10.1093/ije/dyt261>
- Polderman, T. J. C., Derks, E. M., Hudziak, J. J., Verhulst, F. C., Posthuma, D., & Boomsma, D. I. (2007). Across the continuum of attention skills: a twin study of the SWAN ADHD rating scale. *Journal of Child Psychology and Psychiatry*, 48(11), 1080–1087. <https://doi.org/10.1111/j.1469-7610.2007.01783.x>
- Polner, B., Aichert, D., Macare, C., Costa, A., & Ettinger, U. (2015). Gently restless: association of ADHD-like traits with response inhibition and interference control.

References

- European Archives of Psychiatry and Clinical Neuroscience*, 265(8), 689–699.
- Posner, J., Park, C., & Wang, Z. (2014). Connecting the Dots: A Review of Resting Connectivity MRI Studies in Attention-Deficit/Hyperactivity Disorder. *Neuropsychology Review*, 24(1), 3–15. <https://doi.org/10.1007/s11065-014-9251-z>
- Posner, M. I. (1980). Orienting of attention. *Quarterly Journal of Experimental Psychology*, 32(1), 3–25. <https://doi.org/10.1080/00335558008248231>
- Posner, M. I., Nissen, M. J., & Ogden, W. C. (1978). Attended and unattended processing modes: The role of set for spatial location. *Modes of Perceiving and Processing Information*, 137(158), 2.
- Poynter, W., Ingram, P., & Minor, S. (2010). Visual field asymmetries in attention vary with self-reported attention deficits. *Brain and Cognition*, 72(3), 355–361.
- Proal, E., Reiss, P. T., Klein, R. G., Mannuzza, S., Gotimer, K., Ramos-Olazagasti, M. A., ... Castellanos, F. X. (2011). Brain Gray Matter Deficits at 33-Year Follow-up in Adults With Attention-Deficit/Hyperactivity Disorder Established in Childhood. *Archives of ...*, 68(11), 1122–1134. <https://doi.org/10.1001/archgenpsychiatry.2011.117>
- Punja, S., Zorzela, L., Hartling, L., Urichuk, L., & Vohra, S. (2013). Long-acting versus short-acting methylphenidate for paediatric ADHD: a systematic review and meta-analysis of comparative efficacy. *BMJ Open*, 3(3), e002312.
- Quinn, C. (2003). Detection of malingering in assessment of adult ADHD. *Archives of Clinical ...*, 18(4), 379–395. [https://doi.org/10.1016/S0887-6177\(02\)00150-6](https://doi.org/10.1016/S0887-6177(02)00150-6)
- Redgrave, P., Prescott, T. J., & Gurney, K. (1999). The basal ganglia: a vertebrate solution to the selection problem? *NEUROSCIENCE*, 89(4), 1009–1023. [https://doi.org/10.1016/s0306-4522\(98\)00319-4](https://doi.org/10.1016/s0306-4522(98)00319-4)
- Rees, G. E., Frith, C. D., & Lavie, N. (1997). Modulating Irrelevant Motion Perception by Varying Attentional Load in an Unrelated Task. *Science*, 278(5343), 1616–1619. <https://doi.org/10.1126/science.278.5343.1616>
- Reiersen, A. M., & Todd, R. D. (2008). Co-occurrence of ADHD and autism spectrum disorders: phenomenology and treatment. *Expert Review of Neurotherapeutics*, 8(4), 657–669.
- Reynolds, J. H., & Chelazzi, L. (2004). Attentional Modulation of Visual Processing. *Annual Review of Neuroscience*, 27(1), 611–647. <https://doi.org/10.1146/annurev.neuro.26.041002.131039>
- Reynolds, J. H., Chelazzi, L., & Desimone, R. (1999). Competitive Mechanisms

References

- Subserve Attention in Macaque Areas V2 and V4. *The Journal of Neuroscience*, 19(5), 1736–1753. <https://doi.org/10.1523/JNEUROSCI.19-05-01736.1999>
- Rihs, T. A., Michel, C. M., & Thut, G. (2007). Mechanisms of selective inhibition in visual spatial attention are indexed by θ -band EEG synchronization. *European Journal of Neuroscience*, 25(2), 603–610. <https://doi.org/10.1111/j.1460-9568.2007.05278.x>
- Rinaldi, L., Di Luca, S., Henik, A., & Girelli, L. (2014). Reading direction shifts visuospatial attention: An Interactive Account of attentional biases. *Acta Psychologica*, 151, 98–105.
- Rizzolatti, G., Riggio, L., Dascola, I., & Umiltá, C. (1987). Reorienting attention across the horizontal and vertical meridians: evidence in favor of a premotor theory of attention. *Neuropsychologia*, 25(1), 31–40. [https://doi.org/10.1016/0028-3932\(87\)90041-8](https://doi.org/10.1016/0028-3932(87)90041-8)
- Robertson, I. H., Manly, T., Andrade, J., Baddeley, B. T., & Yiend, J. (1997). Oops; Performance correlates of everyday attentional failures in traumatic brain injured and normal subjects. *Neuropsychologia*, 35(6), 747–758. Retrieved from <http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=9204482&retmode=ref&cmd=prlinks>
- Robinson, D. A. (1972). Eye movements evoked by collicular stimulation in the alert monkey. *Vision Research*, 12(11), 1795–1808. [https://doi.org/10.1016/0042-6989\(72\)90070-3](https://doi.org/10.1016/0042-6989(72)90070-3)
- Robinson, D. L., & Wurtz, R. H. (1976). Use of an extraretinal signal by monkey superior colliculus neurons to distinguish real from self-induced stimulus movement. *Journal of Neurophysiology*, 39(4), 852–870. Retrieved from <http://jn.physiology.org/lookup/doi/10.1152/jn.00575.2016>
- Rockland, K. S., & Ojima, H. (2003). Multisensory convergence in calcarine visual areas in macaque monkey. *International Journal of Psychophysiology*, 50(1–2), 19–26.
- Roelfsema, P. R., Lamme, V. A. F., & Spekreijse, H. (1998). Object-based attention in the primary visual cortex of the macaque monkey. *Nature*, 395(6700), 376.
- Rohde, L. A., Szobot, C., Polanczyk, G. V., Schmitz, M., Martins, S., & Tramontina, S. (2005). Attention-Deficit/Hyperactivity Disorder in a Diverse Culture: Do Research and Clinical Findings Support the Notion of a Cultural Construct for the Disorder? *Biological Psychiatry*, 57(11), 1436–1441.

References

<https://doi.org/10.1016/j.biopsycho.2005.01.042>

- Ross, R. G., Harris, J. G., Olincy, A., & Radant, A. (2000). Eye movement task measures inhibition and spatial working memory in adults with schizophrenia, ADHD, and a normal comparison group. *Psychiatry Research*, *95*(1), 35–42. [https://doi.org/10.1016/s0165-1781\(00\)00153-0](https://doi.org/10.1016/s0165-1781(00)00153-0)
- Ross, R. G., Hommer, D., Breiger, D., Varley, C., & Radant, A. (1994). Eye movement task related to frontal lobe functioning in children with attention deficit disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, *33*(6), 869–874.
- Rosvold, H. E., Mirsky, A. F., Sarason, I., Bransome Jr, E. D., & Beck, L. H. (1956). A Continuous Performance Test of Brain Damage. *Journal of Consulting Psychology*, *50*(5), 343.
- Rothman, D. L., Petroff, O. a, Behar, K. L., & Mattson, R. H. (1993). Localized 1H NMR measurements of gamma-aminobutyric acid in human brain in vivo. *Proceedings of the National Academy of Sciences of the United States of America*, *90*(12), 5662–5666.
- Rubia, K., Alegría, A. A., & Brinson, H. (2014). Brain abnormalities in attention-deficit hyperactivity disorder: a review. *Revista de Neurologia*, *58 Suppl 1*, S3-16. Retrieved from <http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=25252664&retmode=ref&cmd=prlinks>
- Rubia, K., Halari, R., Cubillo, A. I., Mohammad, A.-M., Brammer, M. J., & Taylor, E. (2009). Methylphenidate normalises activation and functional connectivity deficits in attention and motivation networks in medication-naïve children with ADHD during a rewarded continuous performance task. *Neuropharmacology*, *57*(7–8), 640–652. <https://doi.org/10.1016/j.neuropharm.2009.08.013>
- Rubia, K., Smith, A. B., Halari, R., Matsukura, F., Mohammad, M., Taylor, E., & Brammer, M. J. (2009). Disorder-Specific Dissociation of Orbitofrontal Dysfunction in Boys With Pure Conduct Disorder During Reward and Ventrolateral Prefrontal Dysfunction in Boys With Pure ADHD During Sustained Attention. *American Journal of Psychiatry*, *166*(1), 83–94. <https://doi.org/10.1176/appi.ajp.2008.08020212>
- Rubia, K., Smith, A., & Taylor, E. (2007). Performance of Children with Attention Deficit Hyperactivity Disorder (ADHD) on a Test Battery of Impulsiveness. *Child*

References

- Neuropsychology*, 13(3), 276–304. <https://doi.org/10.1080/09297040600770761>
- Rubia, K., Taylor, E., Smith, A. B., Oksannen, H., Overmeyer, S., & Newman, S. (2001). Neuropsychological analyses of impulsiveness in childhood hyperactivity. *The British Journal of Psychiatry*, 179(2), 138–143. <https://doi.org/10.1192/bjp.179.2.138>
- Sanders, G. S., & Baron, R. S. (1975). The motivating effects of distraction on task performance. *Journal of Personality and Social Psychology*, 32(6), 956.
- Sandson, T. A., Bachna, K. J., & Morin, M. D. (2000). Right hemisphere dysfunction in ADHD visual hemispatial inattention and clinical subtype. *Journal of Learning ...*, 33(1), 83–90. <https://doi.org/10.1177/002221940003300111>
- Santosh, P. J., Taylor, E., Swanson, J. M., Wigal, T., Chuang, S., Davies, M., ... Posner, M. I. (2005). Refining the diagnoses of inattention and overactivity syndromes: A reanalysis of the Multimodal Treatment study of attention deficit hyperactivity disorder (ADHD) based on ICD-10 criteria for hyperkinetic disorder. *Clinical Neuroscience Research*, 5(5–6), 307–314. <https://doi.org/10.1016/j.cnr.2005.09.010>
- Schiller, P. H., & Koerner, F. (1971). Discharge characteristics of single units in superior colliculus of the alert rhesus monkey. *J Neurophysiol*. Retrieved from http://invice.net/biblio_database_dyva/woda/data/att/544a.file.00158.pdf
- Schiller, P. H., Sandell, J. H., & Maunsell, J. H. (1987). The effect of frontal eye field and superior colliculus lesions on saccadic latencies in the rhesus monkey. *Journal of Neurophysiology*, 57(4), 1033–1049. Retrieved from <http://jn.physiology.org/lookup/doi/10.1152/jn.00575.2016>
- Schiller, P. H., & Stryker, M. (1972). Single-unit recording and stimulation in superior colliculus of the alert rhesus monkey. *Journal of Neurophysiology*. Retrieved from <http://jn.physiology.org/content/jn/35/6/915.full.pdf>
- Schiller, P. H., True, S. D., & Conway, J. L. (1980). Deficits in eye movements following frontal eye-field and superior colliculus ablations. *Journal of Neurophysiology*, 44(6), 1175–1189. Retrieved from <http://jn.physiology.org/lookup/doi/10.1152/jn.00575.2016>
- Schneider, K. A., & Kastner, S. (2005). Visual Responses of the Human Superior Colliculus: A High-Resolution Functional Magnetic Resonance Imaging Study. *Journal of Neurophysiology*, 94(4), 2491–2503. <https://doi.org/10.1152/jn.00288.2005>

References

- Schneider, M. F., Krick, C. M., Retz, W., Hengesch, G., Retz-Junginger, P., Reith, W., & Rösler, M. (2010). Impairment of fronto-striatal and parietal cerebral networks correlates with attention deficit hyperactivity disorder (ADHD) psychopathology in adults — A functional magnetic resonance imaging (fMRI) study. *Psychiatry Research: Neuroimaging*, *183*(1), 75–84.
<https://doi.org/10.1016/j.psychresns.2010.04.005>
- Schulz, K. P., Fan, J., Tang, C. Y., Newcorn, J. H., Buchsbaum, M. S., Cheung, A. M., & Halperin, J. M. (2004). Response inhibition in adolescents diagnosed with attention deficit hyperactivity disorder during childhood: an event-related FMRI study. *American Journal of Psychiatry*, *161*(9), 1650–1657.
- Schulz, K. P., Newcorn, J. H., Fan, J., Tang, C. Y., & Halperin, J. M. (2005). Brain Activation Gradients in Ventrolateral Prefrontal Cortex Related to Persistence of ADHD in Adolescent Boys. *Journal of the American Academy of Child & Adolescent Psychiatry*, *44*(1), 47–54.
<https://doi.org/10.1097/01.chi.0000145551.26813.f9>
- Schwartz, S., Vuilleumier, P. O., Hutton, C., Maravita, A., Dolan, R. J., & Driver, J. (2005). Attentional Load and Sensory Competition in Human Vision: Modulation of fMRI Responses by Load at Fixation during Task-irrelevant Stimulation in the Peripheral Visual Field. *Cerebral Cortex*, *15*(6), 770–786.
<https://doi.org/10.1093/cercor/bhh178>
- Schweitzer, J. B., Faber, T. L., Grafton, S. T., Tune, L. E., Hoffman, J. M., & Kilts, C. D. (2000). Alterations in the functional anatomy of working memory in adult attention deficit hyperactivity disorder. *American Journal of Psychiatry*, *157*(2), 278–280. <https://doi.org/10.1176/appi.ajp.157.2.278>
- Seidman, L. J., Biederman, J., Liang, L., Valera, E. M., Monuteaux, M. C., Brown, A., ... Makris, N. (2011). Gray Matter Alterations in Adults with Attention-Deficit/Hyperactivity Disorder Identified by Voxel Based Morphometry. *Biological Psychiatry*, *69*(9), 857–866.
<https://doi.org/10.1016/j.biopsych.2010.09.053>
- Seixas, M., Weiss, M., & Müller, U. (2012). Systematic review of national and international guidelines on attention-deficit hyperactivity disorder. *Journal of Psychopharmacology*, *26*(6), 753–765. <https://doi.org/10.1177/0269881111412095>
- Shaw, P., Lerch, J. P., Greenstein, D. K., Sharp, W., Clasen, L. S., Evans, A. C., ... Rapoport, J. L. (2006). Longitudinal mapping of cortical thickness and clinical

References

- outcome in children and adolescents with attention-deficit/hyperactivity disorder. *Archives of ...*, 63(5), 540–549.
- Sheppard, D. M., Bradshaw, J. L., Mattingley, J. B., & Lee, P. (1999). Effects of stimulant medication on the lateralisation of line bisection judgements of children with attention deficit hyperactivity disorder. *Journal of Neurology*, 66(1), 57–63. <https://doi.org/10.1136/jnnp.66.1.57>
- Shipp, S. (2003). The functional logic of cortico–pulvinar connections. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, 358(1438), 1605–1624. <https://doi.org/10.1098/rstb.2002.1213>
- Shmuel, A., Yacoub, E., Pfeuffer, J., Van de Moortele, P.-F., Adriany, G., Hu, X., & Ugurbil, K. (2002). Sustained Negative BOLD, Blood Flow and Oxygen Consumption Response and Its Coupling to the Positive Response in the Human Brain. *Neuron*, 36(6), 1195–1210. Retrieved from <http://linkinghub.elsevier.com/retrieve/pii/S0896627302010619>
- Shulman, G. L. (1997). Top-down modulation of early sensory cortex. *Cerebral Cortex*, 7(3), 193–206. <https://doi.org/10.1093/cercor/7.3.193>
- Shulman, G. L., Astafiev, S. V, Franke, D., Pope, D. L. W., Snyder, A., McAvoy, M. P., & Corbetta, M. (2009). Interaction of stimulus-driven reorienting and expectation in ventral and dorsal frontoparietal and basal ganglia–cortical networks. *J Neurosci*, 29(14), 4392–4407. <https://doi.org/10.1523/JNEUROSCI.5609-08.2009>
- Shulman, G. L., Pope, D. L. W., Astafiev, S. V, McAvoy, M. P., Snyder, A. Z., & Corbetta, M. (2010). Right hemisphere dominance during spatial selective attention and target detection occurs outside the dorsal frontoparietal network. *J Neurosci*, 30(10), 3640–3651. <https://doi.org/10.1523/JNEUROSCI.4085-09.2010>
- Silk, T. J., Newman, D. P., Eramudugolla, R., Vance, A., & Bellgrove, M. A. (2014). Influence of methylphenidate on spatial attention asymmetry in adolescents with attention deficit hyperactivity disorder (ADHD): preliminary findings. *Neuropsychologia*, 56, 178–183. <https://doi.org/10.1016/j.neuropsychologia.2014.01.015>
- Silk, T. J., Vance, A., Rinehart, N. J., Bradshaw, J. L., & Cunnington, R. (2009). White-matter abnormalities in attention deficit hyperactivity disorder: A diffusion tensor imaging study. *Human Brain Mapping*, 30(9), 2757–2765. <https://doi.org/10.1002/hbm.20703>
- Silk, T. J., Vance, A., Rinehart, N. J., Egan, G., Boyle, M., Bradshaw, J. L., &

References

- Cunnington, R. (2005). Fronto-parietal activation in attention-deficit hyperactivity disorder, combined type: functional magnetic resonance imaging study. *The British Journal of Psychiatry*, *187*(3), 282–283. <https://doi.org/10.1192/bjp.187.3.282>
- Skounti, M., Philalithis, A., & Galanakis, E. (2006). Variations in prevalence of attention deficit hyperactivity disorder worldwide. *European Journal of Pediatrics*, *166*(2), 117–123. <https://doi.org/10.1007/s00431-006-0299-5>
- Slotnick, S. D., Schwarzbach, J., & Yantis, S. (2003). Attentional inhibition of visual processing in human striate and extrastriate cortex. *NeuroImage*, *19*(4), 1602–1611. [https://doi.org/10.1016/S1053-8119\(03\)00187-3](https://doi.org/10.1016/S1053-8119(03)00187-3)
- Smith, A. T., Singh, K. D., & Greenlee, M. W. (2000). Attentional suppression of activity in the human visual cortex. *NeuroReport*, *11*(2), 271–278. <https://doi.org/10.1097/00001756-200002070-00010>
- Smith, A. T., Williams, A. L., & Singh, K. D. (2004). Negative BOLD in the visual cortex: Evidence against blood stealing. *Human Brain Mapping*, *21*(4), 213–220. <https://doi.org/10.1002/hbm.20017>
- Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping*, *17*(3), 143–155. <https://doi.org/10.1002/hbm.10062>
- Sokolova, E., Oerlemans, A. M., Rommelse, N. N. J., Groot, P., Hartman, C. A., Glennon, J. C., ... Buitelaar, J. K. (2017). A causal and mediation analysis of the comorbidity between attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). *Journal of Autism and Developmental Disorders*, *47*(6), 1595–1604.
- Sokunbi, M. O., Fung, W., Sawlani, V., Choppin, S., Linden, D. E. J., & Thome, J. (2013). Resting state fMRI entropy probes complexity of brain activity in adults with ADHD. *Psychiatry Research*, *214*(3), 341–348. <https://doi.org/10.1016/j.psychresns.2013.10.001>
- Solanto, M. V., Schulz, K. P., Fan, J., Tang, C. Y., & Newcorn, J. H. (2009). Event-Related fMRI of Inhibitory Control in the Predominantly Inattentive and Combined Subtypes of ADHD. *Journal of Neuroimaging*, *19*(3), 205–212. <https://doi.org/10.1111/j.1552-6569.2008.00289.x>
- Solanto, M. V., Wender, E. H., & Bartell, S. S. (1997). Effects of methylphenidate and behavioral contingencies on sustained attention in attention-deficit hyperactivity disorder: a test of the reward dysfunction hypothesis. *Journal of Child and Adolescent Psychopharmacology*, *7*(2), 123–136.

References

- Somers, D. C., Dale, A. M., Seiffert, A. E., & Tootell, R. B. H. (1999). Functional MRI reveals spatially specific attentional modulation in human primary visual cortex. *Proceedings of the National Academy of Sciences*, *96*(4), 1663–1668.
<https://doi.org/10.1073/pnas.96.4.1663>
- Sowell, E. R., Thompson, P. M., Welcome, S. E., Henkenius, A. L., Toga, A. W., & Peterson, B. S. (2003). Cortical abnormalities in children and adolescents with attention-deficit hyperactivity disorder. *The Lancet*, *362*(9397), 1699–1707.
- Sparks, D. L. (1999). Conceptual issues related to the role of the superior colliculus in the control of gaze. *Current Opinion in Neurobiology*, *9*(6), 698–707.
[https://doi.org/10.1016/s0959-4388\(99\)00039-2](https://doi.org/10.1016/s0959-4388(99)00039-2)
- Sparks, D. L., Rohrer, W. H., & Zhang, Y. (2000). The role of the superior colliculus in saccade initiation: a study of express saccades and the gap effect. *Vision Research*, *40*(20), 2763–2777. [https://doi.org/10.1016/S0042-6989\(00\)00133-4](https://doi.org/10.1016/S0042-6989(00)00133-4)
- Spinelli, S., Joel, S., Nelson, T. E., Vasa, R. A., Pekar, J. J., & Mostofsky, S. H. (2011). Different Neural Patterns Are Associated With Trials Preceding Inhibitory Errors in Children With and Without Attention-Deficit/Hyperactivity Disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, *50*(7), 705-715.e3.
<https://doi.org/10.1016/j.jaac.2011.03.014>
- Sprague, J. M. (1966). Interaction of Cortex and Superior Colliculus in Mediation of Visually Guided Behavior in the Cat. *Science*, *153*(3743), 1544–1547.
<https://doi.org/10.1126/science.153.3743.1544>
- Stefanatos, G. A., & Wasserstein, J. (2001). Attention deficit/hyperactivity disorder as a right hemisphere syndrome: selective literature review and detailed neuropsychological case studies. *Annals of the New York Academy of Sciences*, *931*(1), 172–195.
- Stein, B. E. (1998). Neural mechanisms for synthesizing sensory information and producing adaptive behaviors. *Experimental Brain Research*, *123*(1–2), 124–135.
<https://doi.org/10.1007/s002210050553>
- Stein, M. A., Blondis, T. A., Schnitzler, E. R., Brien, T., Fishkin, J., Blackwell, B., ... Roizen, N. J. (1996). Methylphenidate dosing: twice daily versus three times daily. *Pediatrics*, *98*(4), 748–756.
- Stein, M. A., Sarampote, C. S., Waldman, I. D., Robb, A. S., Conlon, C., Pearl, P. L., ... Newcorn, J. H. (2003). A Dose-Response Study of OROS Methylphenidate in Children With Attention-Deficit/Hyperactivity Disorder. *Pediatrics*, *112*(5), e404–

References

- e404. <https://doi.org/10.1542/peds.112.5.e404>
- Steinmetz, M. A., & Constantinidis, C. (1995). Neurophysiological Evidence for a Role of Posterior Parietal Cortex in Redirecting Visual Attention. *Cerebral Cortex*, *5*(5), 448–456. <https://doi.org/10.1093/cercor/5.5.448>
- Stins, J. F., Tollenaar, M. S., Slaats-Willems, D. I. E., Buitelaar, J. K., Swaab-Barneveld, H., Verhulst, F. C., ... Boomsma, D. I. (2007). Sustained Attention and Executive Functioning Performance in Attention-Deficit/Hyperactivity Disorder. *Child Neuropsychology*, *11*(3), 285–294. <https://doi.org/10.1080/09297040490916938>
- Storebø, O. J., Krogh, H. B., Ramstad, E., Moreira-Maia, C. R., Holmskov, M., Skoog, M., ... Gillies, D. (2015). Methylphenidate for attention-deficit/hyperactivity disorder in children and adolescents: Cochrane systematic review with meta-analyses and trial sequential analyses of randomised clinical trials. *Bmj*, *351*, h5203.
- Swanson, J. M., Posner, M. I., Potkin, S. G., Bonforte, S., Youpa, D., Fiore, C., ... Crinella, F. (1991). Activating Tasks for the Study of Visual-Spatial Attention in ADHD Children: A Cognitive Anatomic Approach. *Journal of Child Neurology*, *6*(1 suppl), S119–S127. <https://doi.org/10.1177/0883073891006001121>
- Sykes, D. H., Douglas, V. I., & Morgenstern, G. (1972). The effect of methylphenidate (Ritalin) on sustained attention in hyperactive children. *Psychopharmacology*, *25*(3), 262–274.
- Sylvester, R., Josephs, O., Driver, J., & Rees, G. E. (2006). Visual fMRI Responses in Human Superior Colliculus Show a Temporal-Nasal Asymmetry That Is Absent in Lateral Geniculate and Visual Cortex. *Journal of Neurophysiology*, *97*(2), 1495–1502. <https://doi.org/10.1152/jn.00835.2006>
- Takeda, T., Tsuji, Y., & Kurita, H. (2017). Psychometric properties of the Japanese version of the Adult Attention-deficit hyperactivity disorder (ADHD) Self-Report Scale (ASRS-J) and its short scale in accordance with DSM-5 diagnostic criteria. *Research in Developmental Disabilities*, *63*, 59–66.
- Tamm, L., Epstein, J. N., Lisdahl, K. M., Molina, B., Tapert, S., Hinshaw, S. P., ... Swanson, J. M. (2013). Impact of ADHD and cannabis use on executive functioning in young adults. *Drug and Alcohol Dependence*, *133*(2), 607–614. <https://doi.org/10.1016/j.drugalcdep.2013.08.001>
- Tan, H., Mooney, R. D., & Rhoades, R. W. (1999). Effects of norepinephrine upon

References

- superficial layer neurons in the superior colliculus of the hamster: in vitro studies. *Visual Neuroscience*, *16*(03), 557–570.
- Tantillo, M., Kesick, C. M., Hynd, G. W., & Dishman, R. K. (2002). The effects of exercise on children with attention-deficit hyperactivity disorder. *Medicine & Science in Sports & Exercise*. Retrieved from <http://psycnet.apa.org/record/2002-00614-002>
- ter Huurne, N., Onnink, M., Kan, C. C., Franke, B., Buitelaar, J. K., & Jensen, O. (2013). Behavioral consequences of aberrant alpha lateralization in attention-deficit/hyperactivity disorder. *BPS*, *74*(3), 227–233.
- Thiele, A., Pooresmaeli, A., Delicato, L. S., Herrero, J. L., & Roelfsema, P. R. (2009). Additive Effects of Attention and Stimulus Contrast in Primary Visual Cortex. *Cerebral Cortex*, *19*(12), 2970–2981. <https://doi.org/10.1093/cercor/bhp070>
- Thomas, N. A., & Nicholls, M. E. R. (2018). Asymmetries in Distractibility: Left Distractors Improve Reaction Time Performance. *Scientific Reports*, 1–9. <https://doi.org/10.1038/s41598-018-23498-w>
- Thut, G. (2006). α -Band Electroencephalographic Activity over Occipital Cortex Indexes Visuospatial Attention Bias and Predicts Visual Target Detection. *The Journal of Neuroscience*, *26*(37), 9494–9502. <https://doi.org/10.1523/JNEUROSCI.0875-06.2006>
- Tian, L., Jiang, T., Liang, M., Zang, Y., He, Y., Sui, M., & Wang, Y. (2008). Enhanced resting-state brain activities in ADHD patients: A fMRI study. *Brain and Development*, *30*(5), 342–348. <https://doi.org/10.1016/j.braindev.2007.10.005>
- Toffanin, P., de Jong, R., Johnson, A., & Martens, S. (2009). Using frequency tagging to quantify attentional deployment in a visual divided attention task. *International Journal of Psychophysiology*, *72*(3), 289–298. <https://doi.org/10.1016/j.ijpsycho.2009.01.006>
- Tootell, R. B. H., Hadjikhani, N. K., Hall, E. K., Marrett, S., Vanduffel, W., Vaughan, J. T., & Dale, A. M. (1998). The Retinotopy of Visual Spatial Attention. *Neuron*, *21*(6), 1409–1422. [https://doi.org/10.1016/s0896-6273\(00\)80659-5](https://doi.org/10.1016/s0896-6273(00)80659-5)
- Tootell, R. B. H., Mendola, J. D., Hadjikhani, N. K., Liu, A. K., & Dale, A. M. (1998). The representation of the ipsilateral visual field in human cerebral cortex. *Proceedings of the National Academy of Sciences*, *95*(3), 818–824. <https://doi.org/10.1073/pnas.95.3.818>
- Trommer, B. L., Hoepfner, J.-A. B., & Zecker, S. G. (1991). The go-no go test in

References

- attention deficit disorder is sensitive to methylphenidate. *Journal of Child Neurology*, 6(1 suppl), S128–S131.
- Tsubota, K., Kwong, K. K., Lee, T.-Y., Nakamura, J., & Cheng, H.-M. (1999). Functional MRI of brain activation by eye blinking. *Experimental Eye Research*, 69(1), 1–7.
- Tucha, O., Mecklinger, L., Laufkötter, R., Klein, H. E., Walitza, S., & Lange, K. W. (2006). Methylphenidate-induced improvements of various measures of attention in adults with attention deficit hyperactivity disorder. *Journal of Neural Transmission*, 113(10), 1575.
- Vaidya, C. J., Austin, G., Kirkorian, G., Ridlehuber, H. W., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. E. (1998). Selective effects of methylphenidate in attention deficit hyperactivity disorder: A functional magnetic resonance study. *Proceedings of the National Academy of Sciences*, 95(24), 14494–14499. <https://doi.org/10.1073/pnas.95.24.14494>
- Van der Oord, S., Prins, P. J. M., Oosterlaan, J., & Emmelkamp, P. M. G. (2008). Efficacy of methylphenidate, psychosocial treatments and their combination in school-aged children with ADHD: a meta-analysis. *Clinical Psychology Review*, 28(5), 783–800.
- Van Der Stigchel, S., Rommelse, N. N. J., Deijen, J. B., Geldof, C. J. A., Witlox, J., Oosterlaan, J., ... Theeuwes, J. (2007). Oculomotor capture in ADHD. *Cognitive Neuropsychology*, 24(5), 535–549. <https://doi.org/10.1080/02643290701523546>
- van Ewijk, H., Heslenfeld, D. J., Zwiers, M. P., Buitelaar, J. K., & Oosterlaan, J. (2012). Diffusion tensor imaging in attention deficit/hyperactivity disorder: A systematic review and meta-analysis. *Neuroscience and Biobehavioral Reviews*, 36(4), 1093–1106. <https://doi.org/10.1016/j.neubiorev.2012.01.003>
- van Gerven, M., & Jensen, O. (2009). Attention modulations of posterior alpha as a control signal for two-dimensional brain–computer interfaces. *Journal of Neuroscience Methods*, 179(1), 78–84. <https://doi.org/10.1016/j.jneumeth.2009.01.016>
- Vance, A., Silk, T. J., Casey, M., Rinehart, N. J., Bradshaw, J. L., Bellgrove, M. A., & Cunnington, R. (2007). Right parietal dysfunction in children with attention deficit hyperactivity disorder, combined type: a functional MRI study. *Molecular Psychiatry*, 12(9), 826–832. <https://doi.org/10.1038/sj.mp.4001999>
- Vanduffel, W. (2000). Attention-dependent Suppression of Metabolic Activity in the

References

- Early Stages of the Macaque Visual System. *Cerebral Cortex*, *10*(2), 109–126.
<https://doi.org/10.1093/cercor/10.2.109>
- Vuilleumier, P. O., & Rafal, R. D. (2000). A systematic study of visual extinction. *Brain*, *123*(6), 1263–1279. <https://doi.org/10.1093/brain/123.6.1263>
- Waldie, K. E., & Hausmann, M. (2010). Right fronto-parietal dysfunction in children with ADHD and developmental dyslexia as determined by line bisection judgements. *Neuropsychologia*, *48*(12), 3650–3656.
<https://doi.org/10.1016/j.neuropsychologia.2010.08.023>
- Wallace, M. T., Wilkinson, L. K., & Stein, B. E. (1996). Representation and integration of multiple sensory inputs in primate superior colliculus. *Journal of Neurophysiology*, *76*(2), 1246–1266. Retrieved from
<http://jn.physiology.org/lookup/doi/10.1152/jn.00575.2016>
- Wang, L., Zhu, C., He, Y., Zang, Y., Cao, Q., Zhang, H., ... Wang, Y. (2009). Altered small-world brain functional networks in children with attention-deficit/hyperactivity disorder. *Human Brain Mapping*, *30*(2), 638–649.
- Wang, P., Zhu, D., Li, X., Chen, H., & Jiang, X. (2013). Identifying functional connectomics abnormality in attention deficit hyperactivity disorder. ... *Imaging (ISBI)*, 544–547. <https://doi.org/10.1109/isbi.2013.6556532>
- Wechsler, D. (2011). *Wechsler Abbreviated Scale of Intelligence - Second Edition (WASI-II)*.
- Weintraub, S., & Mesulam, M.-M. (1987). Right cerebral dominance in spatial attention: Further evidence based on ipsilateral neglect. *Archives of Neurology*, *44*(6), 621–625.
- Weissman, D. H., Roberts, K. C., Visscher, K. M., & Woldorff, M. G. (2006). The neural bases of momentary lapses in attention. *Nature Neuroscience*, *9*(7), 971–978. <https://doi.org/10.1038/nn1727>
- Weyandt, L. L., & DuPaul, G. J. (2006). ADHD in college students. *Journal of Attention Disorders*, *10*(1), 9–19.
- Weyandt, L. L., Linterman, I., & Rice, J. A. (1995). Reported prevalence of attentional difficulties in a general sample of college students. *Journal of Psychopathology and Behavioral Assessment*, *17*(3), 293–304. <https://doi.org/10.1007/BF02229304>
- Wilens, T. E., Biederman, J., Faraone, S. V, Martelon, M., Westerberg, D., & Spencer, T. J. (2009). Presenting ADHD Symptoms, Subtypes, and Comorbid Disorders in Clinically Referred Adults With ADHD. *The Journal of Clinical Psychiatry*,

References

- 70(11), 1557–1562. <https://doi.org/10.4088/JCP.08m04785pur>
- Willcutt, E. G., Doyle, A. E., Nigg, J. T., Faraone, S. V., & Pennington, B. F. (2005). Validity of the Executive Function Theory of Attention-Deficit/Hyperactivity Disorder: A Meta-Analytic Review. *Biological Psychiatry*, *57*(11), 1336–1346. <https://doi.org/10.1016/j.biopsych.2005.02.006>
- Witt, S. T., & Stevens, M. C. (2015). Relationship between white matter microstructure abnormalities and ADHD symptomatology in adolescents. *Psychiatry Research: Neuroimaging*, *232*(2), 168–174. <https://doi.org/10.1016/j.psychresns.2015.02.009>
- Wojciulik, E., & Kanwisher, N. (1999). The generality of parietal involvement in visual attention. *Neuron*, *23*, 747–764. Retrieved from <https://www.sciencedirect.com/science/article/pii/S0896627301800337>
- Wolosin, S. M., Richardson, M. E., Hennessey, J. G., Denckla, M. B., & Mostofsky, S. H. (2009). Abnormal cerebral cortex structure in children with ADHD. *Human Brain Mapping*, *30*(1), 175–184. <https://doi.org/10.1002/hbm.20496>
- Wood, C., Maruff, P., Levy, F., Farrow, M., & Hay, D. A. (1999). Covert orienting of visual spatial attention in attention deficit hyperactivity disorder: Does comorbidity make a difference? *Archives of Clinical ...*, *14*(2), 179–189. [https://doi.org/10.1016/s0887-6177\(97\)00097-8](https://doi.org/10.1016/s0887-6177(97)00097-8)
- Worden, M. S., Foxe, J. J., Wang, N., & Simpson, G. V. (2000). Anticipatory Biasing of Visuospatial Attention Indexed by Retinotopically Specific α -Bank Electroencephalography Increases over Occipital Cortex. *The Journal of Neuroscience*, *20*(6), RC63–RC63. <https://doi.org/10.1523/jneurosci.20-06-j0002.2000>
- World Health Organization. (2018). International statistical classification of diseases and related health problems (11th Revision). Retrieved from <https://icd.who.int/browse11/l-m/en>
- Wright, L., Lipszyc, J., Dupuis, A., Thayapararajah, S. W., & Schachar, R. (2014). Response inhibition and psychopathology: A meta-analysis of go/no-go task performance. *Journal of Abnormal Psychology*, *123*(2), 429–439. <https://doi.org/10.1037/a0036295>
- Yantis, S., & Serences, J. T. (2003). Cortical mechanisms of space-based and object-based attentional control. *Current Opinion in Neurobiology*, *13*(2), 187–193. [https://doi.org/10.1016/S0959-4388\(03\)00033-3](https://doi.org/10.1016/S0959-4388(03)00033-3)

References

- Yeo, B. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., ... Buckner, R. L. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of Neurophysiology*, *106*(3), 1125–1165. <https://doi.org/10.1152/jn.00338.2011>
- Yi, J., Woodman, G. F., Widders, D., Marois, R., & Chun, M. M. (2004). Neural fate of ignored stimuli: dissociable effects of perceptual and working memory load. *Nature Neuroscience*, *7*(9), 992–996. <https://doi.org/10.1038/nn1294>
- Yong-Liang, G., Robaey, P., Karayanidis, F., Bourassa, M., Pelletier, G., & Geoffroy, G. (2000). ERPs and behavioral inhibition in a Go/No-go task in children with attention-deficit hyperactivity disorder. *Brain and Cognition*.
- Zeki, S. M. (1969). The secondary visual areas of the monkey. *Brain Research*, *13*(2), 197–226.