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The Role of the Superior Colliculus in Attention Deficit Hyperactivity Disorder

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"... the use of our intelligence quite properly gives us pleasure. In this respect the brain is like a muscle. When we think well, we feel good. Understanding is a kind of ecstasy."

Carl Sagan

Abstract

Attention-deficit hyperactivity disorder (ADHD) is the most common developmental disorder defined by an attentional dysfunction, hyperactive/impulsive behaviour or both. Recent evidence from animal studies suggest that the superior colliculus (SC), a multimodal laminar structure located in the midbrain that belongs to a distributed network of areas mediating saccadic eye movements, shifts of attention, and multimodal integration might be abnormal in individuals with ADHD.

The goal of this thesis is to investigate the role of the superior colliculus in humans. A comprehensive review of the existing evidence supporting the collicular hypothesis of ADHD is included. The following chapters present a series of experiments attempting to test collicular sensitivity in children with ADHD and healthy volunteers with varying level of ADHD traits (as assessed in the Adult ADHD Self-Report Scale). The first study examines distractibility by employing a new paradigm using intermittent far-peripheral distractors embedded on a sustained attention task and shows that individuals with high ADHD are associated with abnormal distractor processing. A second study investigates the temporal aspects of multisensory integration in individuals with high and low ADHD and presents preliminary evidence for abnormal multisensory integration in ADHD. A third study looks at the relationship between ADHD traits and the rate and characteristics of microsaccades during a sustained fixation paradigm. A positive relationship is shown between ADHD traits and microsaccade rates. Finally, a fourth study examines visual field differences between children with ADHD and age-matched controls using optical perimetry testing. Significantly smaller visual field sizes are reported in ADHD compared to controls.

Overall, this thesis offers initial support for the superior colliculus hypothesis of ADHD. The possibility of using collicular paradigms as biomarkers for ADHD is discussed.

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Background to ADHD

1.1 Chapter Summary

ADHD is the most common developmental disorder characterised by inattention, hyperactivity, or both. Even though it was initially thought of as a childhood disorder, recent studies have found that it persists into adulthood in roughly half of the children diagnosed with the disorder. This chapter offers a short review of the history of ADHD, starting from its first description by Alexander Crichton in 1798 until its current diagnostic criteria as defined by DSM V. The next section is dedicated to characteristics of ADHD such as co-morbidity with other disorders and gender differences. Furthermore, the treatment options available for individuals with ADHD are reviewed, as well as the etiology and the major theoretical models proposed for ADHD. The final section of this chapter is dedicated to the neural correlates of ADHD.

1.2 Attention - Deficit Hyperactivity Disorder: A Brief Description of its symptoms and epidemiology

Attention-deficit hyperactivity disorder (ADHD) is a behavioural disorder defined by either an attentional dysfunction, hyperactive/impulsive behaviour or both (DSM-V; American Psychiatric Association, 2013). ADHD is the most common neurodevelopmental disorder (Faraone, Sergeant, Gillberg, & Biederman, 2003a); (Barkley, 1997) and its worldwide prevalence in children and adolescence is between 0.85% and 10% (Ford, Goodman, & Meltzer, 2003b; Tannock, 1998; Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007; Seixas, Weiss, & Müller, 2012). A possible explanation for the wide range observed in prevalence of ADHD is due to methodological differences in studies than true differences in prevalence across populations (Polanczyk et al., 2007). Another explanation for the wide ranging prevalence could be due to the lack of good diagnostic criteria for ADHD.

In roughly half of the children diagnosed with ADHD, symptoms persist into adulthood (T. J. Spencer, Biederman, Wilens, & Faraone, 2002). Therefore, ADHD has also been validated as an adulthood disorder (Faraone & Biederman, 2005a), with remaining symptoms in adults including distractibility and difficulties with maintaining goal-directed behaviour rather than hyperactivity. Self-report rating scales, based on the DSM-IV-TR, have been developed to quantify symptoms of ADHD in adults (e.g. Kooij et al., 2008). Its prevalence nationwide in adults (18-44 years old) is between 0.5% and 4.4% (Fayyad et al., 2007; Ford et al., 2003b;

Kessler, Adler, et al., 2005). Some clinically impairing symptoms (such as inattention) persist into adulthood for about 65% of these children, while another 15% will exhibit the full-blown disorder as adults (Faraone & Biederman, 2005a). In most cases the hyperactivity component decreases as the child approaches adulthood, but the inattention and impulsivity symptoms are maintained and generally become the dominant features of the disorder in adult life (Seidman, Biederman, Weber, Hatch, & Faraone, 1998; Wilens et al., 2009). More specifically, adults with ADHD usually report difficulty with following directions, procrastination, sustained attention, losing things, fidgeting, interrupting others, and not listening (Weiss, Hechtman, & Weiss, 2001). Similarly, hyperactive symptoms of ADHD may persist into adulthood, but may manifest themselves in a different way.

Adult ADHD is less studied and often ignored by clinicians. A recent study by McCarthy and colleagues (2009) found that treatment of ADHD is prematurely discontinued in some adults, even when their symptoms persist and affect their everyday lives. Murphy, Barkley, and Bush (2002) compared groups of healthy adults with adults diagnosed with different subtypes of ADHD and found that all subgroups were associated with greater mental health issues and antisocial behaviour.

The diagnosis of ADHD in both children and adults is based on behavioural symptoms, clinical examination and reports filled in by the patients or their parents. Seixas et al. (2012) in a recent review identified 26 potential diagnostic guidelines from a number of countries, including the UK, for ADHD that can be used by clinicians. By analysing 13 of them, the authors identified similarities but also significant differences between them. These findings suggest the need for more uniform, universal criteria for ADHD diagnosis.

1.3 Background on ADHD

1.3.1 A Brief History

ADHD-related symptomatology was first described by physician Alexander Crichton in 1798 (Palmer & Finger, 2001). Crichton described a mental state with most of the features of the now called inattentive subtype of ADHD, such as restlessness, problems with attention, early onset and how its effect on school performance (Palmer & Finger, 2001). Description of ADHD symptomatology was also found in the mid-19th century by Heinrich Hoffman, a German physician who represented this disorder in two characters in his children's book “Der Struwewelpeter” published in 1848 (Wolraich, 2006). However, the history of ADHD is mostly associated with the early work of George Still in the 1900s (Barkley, 1997; Wolraich, 2006). Still described a condition found in children characterised by defective moral control, which resulted from brain damage or hereditary factors (Barkley, 1997). The belief that this syndrome was the result of brain damage was increased in 1917–1918 after an epidemic influenza with encephalitis, which in some children resulted in symptoms similar to the ones found in ADHD, such as restlessness, inattention, impulsivity, and hyperactivity (Wolraich, 2006). As a result the syndrome was renamed to “brain-injured child syndrome”. The name of the condition was changed to “minimal brain dysfunction” in the late 60s following the study of patients with similar behavioural manifestations, but no clear evidence of brain damage (Barkley, 1997; S. D. Clements, 1966). The association of ADHD with brain damage became less certain when the second edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-II) called it hyper-kinetic reaction of childhood disorder (American Psychiatric Association, 1967).

Initially ADHD was thought to be a childhood disorder that children eventually outgrew and this was reflected in the first editions of the diagnostic manuals. However, after the publication of studies showing the persistence of the symptoms in adulthood in many patients, the description of the condition was revised and characterised as developmental/lifetime disorder in DSM-III (American Psychiatric Association, 1980). The focus on attention deficits and hyperactivity symptoms changed throughout the revisions of the diagnostic manuals to finally recognise the existence of both in DSM-III-R (American Psychiatric Association, 1987) and DSM-IV (American Psychiatric Association, 1994) and give ADHD its current name, attention- deficit/hyperactivity disorder.

DSM 5 (American Psychiatric Association, 2013) characterises ADHD as a pattern of behaviour, present in multiple settings (e.g., school and home), which can result in performance issues in multiple settings (e.g., social, educational,work settings). Emphasis is put into the lifetime aspect of the disorder and more details are provided about the diagnosis of ADHD in adults. For example, to diagnose ADHD clinicians now look back to middle childhood (age 12) and the teen years when making a diagnosis for the beginning of symptoms, not all the way back to childhood (age 7) like in DSM IV.

1.3.2 Diagnosis

The most widely used diagnostic manual, DSM-IV (American Psychiatric Association, 2000), recognised 4 subtypes of ADHD: ADHD-Inattentive Type (ADHD-I), ADHD-Hyperactive/Impulsive Type (ADHD-H/I), ADHD-Combined Type (ADHD-C), and ADHD-Not Otherwise Specified (ADHD-NOS). ADHD-I was characterised by significant levels of inattention but sub-threshold levels of hyperactive/ impulsive symptoms. ADHD-H/I defined by hyperactivity/ impulsivity but not of inattention symptoms, and ADHD/C was characterised by maladaptive levels of both symptom clusters. In order to meet diagnostic criteria for ADHD-I or ADHD H/I, an individual must exhibit six symptoms related to either inattention or hyperactivity/ impulsivity. An individual meets criteria for ADHD-C when there are significant (i.e., six or more) symptoms of inattention and hyperactivity or impulsivity (American Psychiatric Association, 1994). Furthermore, in order to be diagnosed with ADHD symptoms must have an onset before the age of 7, have duration of at least 6 months, be present in two or more settings, and cause significant impairment in social, academic, or occupational functioning. Moreover, a diagnosis of schizophrenia, affective disorder, or severe mental retardation must be excluded. A diagnosis of ADHD-NOS is given when not all criteria are met for the other subtypes of ADHD, but there is a significant degree of impairment (American Psychiatric Association, 1994).

The current version of DSM (American Psychiatric Association, 2013) refers to three types of ADHD as “presentations" instead of subtypes. Furthermore, it reports that a person can change “presentations” during their lifetime. This change better reflect the ways the disorder affects an individual at different points of their life. Additionally, ADHD can now be mild, moderate or severe depending on the symptoms.

The International Classification of Diseases - 10th Edition (ICD - 10; World Health Organization, 2009) identified a condition similar to ADHD, the syndrome of Hyperkinetic disorder (HKD). ICD-10 operationalises the inattentive, hyperactive and impulsive criteria in a very similar way to DSM (Tripp, Luk, Schaughency, & Singh, 1999; Lee et al., 2008). However, there are a number of important differences. First of all, ICD-10 requires the symptoms of the syndrome to evident in two independent situations (e.g., home, school, workplace), while such requirement does not exist in the current version of DSM. Additionally, ICD-10 does not recognise the existence of different subtypes, but sees HKD as a single entity that manifests with symptoms of inattention, impulsiveness, and hyperactivity. Furthermore, ICD-10 excludes co-morbidity. Only conduct disorder can be diagnosed with HKD. In the case of any other co-morbid conditions, the manual encourages the diagnostician to diagnose the other disorder. It is clear from the above description that there is a significant overlap between the two diagnostic manuals. DSM 5 resolved some of the discrepancies described above. More specifically, a diagnosis of ADHD and autism spectrum disorders is no longer mutually exclusive. Furthermore, the three types of ADHD identified as “subtypes" in DSM IV are now referred to as “presentations".

According to the latest version of the DSM (American Psychiatric Association, 2013), there is no current measure that specifically assesses for the presence of

ADHD. As a result, clinicians use a combination of tools to diagnose this particular disorder. More specifically, since ADHD is a developmental disorder it is importance to obtain information about an individual's developmental history (Weiss, Murray, & Weiss, 2002). In addition to that, in children the parents and the teachers are requested to provide information about the child's behaviour in various settings (Conner's Rating Scale). The diagnosis of ADHD in adults is done through self-report measures which assess for the presence of ADHD and typically include questions about current and past symptoms (Conner's Adult ADHD Rating Scale CAARS; Conners, Erhardt, Sparrow, et al., 1999; Wender Utah Rating Scale; ASRS). Clinical interviews are essential in the cases of individuals who score high on self-report measures and offer a more comprehensive picture of an individual's functioning (Weiss et al., 2002).

1.3.3 Co-morbidity and Gender Differences

Regardless of subtype ADHD has been found to be two to four times more common among boys than girls across referred and non-referred samples. However, differences have been found between different subtypes. More specifically, the proportion of girls with ADHD/ IA is higher than in the other ADHD subtypes (Eiraldi, Power, & Nezu, 1997; Levy, Hay, Bennett, & McStephen, 2005). On the other hand, hyperactivity and impulsivity symptoms are more commonly reported in boys (Wilens et al., 2009). It is not clear whether this finding is related to different manifestation of the disorder in each gender. The disorder decreases equally in both sexes during development (Kessler, Berglund, et al., 2005).

Co-morbidity is very commonly reported in ADHD. More specifically, as many as 87% of children diagnosed with ADHD have one other disorder and 67% may have at least two other co-morbid disorders (Kadesjö & Gillberg, 2001). The most common co-morbid disorders with individuals with ADHD are Oppositional defiant disorder (ODD), conduct disorder (CD), depression, and juvenile-onset bipolar disorder (Biederman et al., 1996). Dyslexia is also commonly reported in children with ADHD, especially the more severe cases (Germano, Gagliano, & Curatolo, 2010). In addition to that, even though DSM-IV prohibits the co-diagnosis of ADHD and autism spectrum disorder (ASD) recent studies indicate that co-occurrence of ADHD and ASD symptoms is common (Reiersen & Todd, 2008; Simonoff et al., 2008). This finding was reflected in the updated version of DSM which allows co-diagnosis of ADHD and ASD.

1.3.4 Treatment of ADHD

Stimulant drugs, such as methylphenidate (MPH) and amphetamine (AMP) are by far the most widely prescribed class of drugs for ADHD. The pharmacological management of ADHD in children has been studied for nearly 80 years, with the first study on the benefits of stimulants being reported in 1937 when benzedrine was used to treat children in inpatient residential care (Wolraich, 2006). The first controlled studies of stimulant treatment were published in the early 1960s (Conners, 1966; Conners, Eisenberg, & Sharpe, 1964). A high percentage (over 70%) of children responds to stimulant medications showing improvements in ADHD symptoms and academic achievement (L. A. Johnson & Safranek, 2005).

Stimulants, however, often cause severe side-effects, such as increases in heart rate, blood pressure, weight gain and have a high potential for abuse (Rapport & Moffitt, 2002; Volkow & Swanson, 2003). As a result, alternative interventions are being sought. Specific behavioural modification interventions are less popular but exist as an alternative or additive treatment of ADHD. However, the results are mixed and depend on the subtype and the severity of symptoms. Such interventions can be successful in the case of adult ADHD. In particular, treatments employing cognitive-behavioural principles have been found effective especially when used in combination with pharmacotherapy (Safren et al., 2005).

1.3.5 Aetiology

ADHD is a heterogeneous disorder. A strong genetic component in the etiology of the disorder has been identified. Multiple family and twin studies have shown that ADHD has high heritability estimated between 70-80% (Faraone & Mick, 2010; Burt, 2009; Rietveld, Hudziak, Bartels, Beijsterveldt, & Boomsma, 2004). The relative risk for ADHD is 6 to 8 times higher among first degree relatives of probands with ADHD than the base rate of ADHD in the general population (Faraone & Biederman, 2005b). Recently, specific genes have been associated with ADHD. In particular, genes involved in dopamine regulation, such as dopamine transporter gene (DAT1) and the dopamine D4 receptor gene (DRD4). Results from these studies, however, remain inconclusive (Willcutt et al., 2010).

Non-genetic factors have also been associated with ADHD. Environmental factors can be classified as prenatal, perinatal, and postnatal according to their origin

(Millichap, 2008). Prenatal or perinatal complications seem to have a small but significant association with ADHD symptoms (Milberger, Biederman, Faraone, Chen, & Jones, 1996). More specifically, there is a high incidence of ADHD amongst babies who were born premature or/and with low birth weight (Mick, Biederman, Prince, Fischer, & Faraone, 2002; Indredavik et al., 2004). Brain injury can also result in behaviour characteristic to ADHD (Keenan, Hall, Marshall, et al., 2008; Zwi, Clamp, et al., 2008). Prenatal exposure to particular substances such as alcohol (Mick, Biederman, Faraone, Sayer, & Kleinman, 2002) and tobacco have been found to increase the risk for ADHD (Milberger et al., 1996). Studies looking at possible relationships between season of birth and ADHD suggest an association with seasonally mediated viral infections (Mick, Biederman, & Faraone, 1996). It is not clear whether these reported pre/perinatal factors act in an additive or interactive manner with genetic influences to increase risk for ADHD, or represent an alternative etiological pathway that can cause ADHD.

1.3.6 Neurocognitive models of ADHD

A number of possible neurocognitive models have been proposed for ADHD, most of which implicate a simple linear pathway in which a single causal factor is hypothesised to give rise to a core cognitive deficit that is both necessary and sufficient to account for all the cases of ADHD. The most prominent models suggest that ADHD is due to deficits in executive functioning (EF). This is consistent with the history of the disorder; as described above it was initially associated with brain damage, especially in the frontal lobes, which have long been seen connected with

EF. EF is an umbrella term for functions such as planning, working memory, inhibition, mental flexibility, as well as the initiation and monitoring of action. EF are necessary skills for purposeful, goal-directed activity (Welsh & Pennington, 1988; Stuss & Alexander, 2000; Stuss & Knight, 2013). EF are partly subserved by the frontal lobes. Kerr and Zelazo (2004) proposed a division of EF to 'cool' and 'hot'. Research with children with ADHD has focused on the more purely cognitive or 'cool' EFs such as response inhibition and WM, associated with the dorsolateral prefrontal cortex (Zelazo & Müller, 2002). Recently, 'hot' EFs, those involving emotional and motivational processes, such as measured by affective decision-making tasks (e.g. delayed aversion) and thought to be dependent on the ventromedial prefrontal cortex, have received more attention (Kerr & Zelazo, 2004). Some of them propose a general dysfunction in EF, while others propose specific aspects of EF, such as response inhibition (Barkley, 1997; Pennington & Ozonoff, 1996), aversion to delay (Sonuga-Barke, 2003), difficulty modulating behaviour in response to reward and punishment cues (Luman, Oosterlaan, & Sergeant, 2005), response inconsistency (Haenlein & Caul, 1987), and overall slow processing speed (Shanahan et al., 2006).

The first ever model that attempted to account for the clinical presentation of the disorder was by Barkley (1997), who suggested that the main problem in ADHD is a dysfunction in behavioural inhibition. Four executive functions were impaired according to this model; working memory, regulation of affect–motivation–arousal, internalized speech, and reconstitution (higher level analysis of behaviour).

Sonuga-Barke and colleagues proposed another prominent model of ADHD, the dual-pathway model (Sonuga-Barke, 2003; Sonuga-Barke & Sergeant, 2005; Sonuga-Barke, Sergeant, Nigg, & Willcutt, 2008). According to this model executive function deficits and abnormalities in the reward circuity can explain ADHD symptomatology. More specifically, the dual-pathway model proposes that ADHD patients avoid delay in reward due to impairments in delay aversion caused by defects in meso-cortical areas. Nigg and Casey (2005) further developed the dual-pathway model by adding the role of frontocerebellar dysfunction in timing deficits and frontoamygdalar abnormalities as the substrate of affective problems observed in ADHD.

Another model attempting to explain the different symptoms of ADHD was proposed by Sergeant (2000). The cognitive-energetic model draws attention to the fact that ADHD has effects at two levels: cognitive mechanisms (e.g., response output), energetic mechanisms (e.g. activation and effort and control systems of EF). This model is an attempt to encompass both top-down and bottom-up processes and assumes that multiple loci are implicated in ADHD (Sergeant, 2000).

It is clear that none of the existing theories can fully account for all the symptoms of ADHD. This is associated with the nature of the disorder; multiple loci and systems seem to be affected. More recent models have attempted to deal with this by hypothesising that ADHD is a heterogeneous conditions that arises from the combined effects of weakness in multiple cognitive domains (Nigg & Casey, 2005; Sonuga-Barke & Sergeant, 2005). A combination of different theories might be essential for fully explaining ADHD.

1.3.7 The Neural Correlates of ADHD

Even though pharmacological therapies seem to yield positive results in most patients ameliorating their symptoms, the neurological basis of ADHD is poorly understood. A few possible loci for ADHD have been identified by neuroimaging studies on children and adults but the results appear to be not consistent. Several recent functional imaging studies of ADHD have focussed on the possible role of the default-mode network (DMN) in ADHD. The DMN refers to a group of brain areas that are activated when a person engages in processes of self-referential nature such as mind wandering (Raichle et al., 2001). The areas that are part of the DMN, such as the medial prefrontal cortex have been implicated in processes affected in ADHD, such as attention. A large corpus of normative studies have identified and characterised this network, which includes medial prefrontal cortex (MPFC), the posterior cingulate/precuneus cortices (PCC), and the mediolateral inferior parietal cortices bilaterally (Schilbach, Eickhoff, Rotarska-Jagiela, Fink, & Vogeley, 2008; Raichle et al., 2001). The most consistent finding in resting-state studies on ADHD patients has been reduced functional connectivity between MPFC regions and the PCC cortices (Castellanos et al., 2008; Fair et al., 2010; Uddin et al., 2008). Evidence for increased resting-state activation in the primary sensory and sensory-related cortices of adolescents with ADHD is also available, which although indirect does point to abnormalities in DMN function (Tian et al., 2008). Another study by Peterson and colleagues (2009) found reduced deactivation of medial frontal cortices in unmedicated adolescents with ADHD compared to controls when performing a Stroop task. In addition to that, activity in the medial PFC was suppressed after the administration of stimulants in the ADHD group.

Electrophysiological studies also support the above findings (Helps, James, Debener, Karl, & Sonuga-Barke, 2008; Helps et al., 2010). The frontal lobes, also, seem to be dysfunctional in ADHD. More specifically, individuals with ADHD have behaviours common in disorders of attention following frontal lobe damage (e.g. difficulties sustaining attention, poor organisational skills, distractibility). This is reflected on the previously described executive function theory of ADHD.

Structural differences have also been identified between children diagnosed with ADHD and normally developing children. Shaw and Rabin (2009) identified a delay in regional cortical maturation in ADHD children, especially in the prefrontal cortices.

Chapter 2

The Superior Colliculus (SC) Hypothesis

2.1 Chapter Summary

The Superior Colliculus (SC) is multimodal laminar structure located in the midbrain, which is involved in various functions, such as eye movements, orientation of attention, and multisensory integration. The SC hypothesis of ADHD suggests that many of the debilitating symptoms of ADHD could be attributed to a hyper-responsive SC. A brief introduction to the SC and its role is presented. In the following section, preliminary evidence from animal and human studies supporting the hypothesis is reviewed. More specifically, findings from animal models of ADHD and studies on ADHD populations are discussed.

2.2 The Superior Colliculus (SC) Hypothesis

Distractibility, which is one of the main and most debilitating symptoms of ADHD, can be defined as a deficit in inhibiting responses to targets irrelevant to the ongoing task. Many studies have examined and confirmed that distractibility levels are increased among adults and children with ADHD (Friedman-Hill et al., 2010; Barkley & Ullman, 1975; Bedi, Halperin, & Sharma, 1994; Gumenyuk et al., 2005; Riordan et al., 1999). Distractibility in participants with ADHD can also be expressed through increased reaction time (RT) variability (Fassbender et al., 2009). Increased intra-individual variability seems to be a consistent finding in ADHD (Geurts et al., 2008; Klein, Wendling, Huettner, Ruder, & Peper, 2006).

Distractibility depends on various neural networks. One of the brain regions closely associated with distractibility is the dorsolateral prefrontal cortex (DLPFC), and the posterior parietal cortex. Both areas are directly connected with the SC (Sparks & Hartwich-Young, 1989; Kustov & Robinson, 1996).

A growing body of evidence suggests that increased distractibility in ADHD is caused by a hyper-responsiveness of the superior colliculus (reviewed by Overton (2008)), a sensory structure in the midbrain which is intimately linked to eye movements and distractibility (Dean, Redgrave, & Westby, 1989). Evidence supporting the implication of the SC in ADHD comes from animal studies, as well as studies examining eye movements in ADHD patients. In the following paragraphs I will provide a brief description of the SC and its role, as well as an account of the existing evidence in support of the SC hypothesis in ADHD.

2.2.1 The SC and its role

The SC is a multimodal laminar structure located in the midbrain that belongs to a distributed network of areas mediating saccadic eye movements, and shifts of attention.They are named 'colliculi' because of their resemblance to 'little hills,' though 17th Century scholars chose rather less savoury names for these protuberances (the cerebral 'buttocks' or 'testicles' according to Critchley (1966). The SC is common to all mammals and has been studied extensively in nonhuman primates and other species using anatomical and electrophysiological techniques (Everling, Dorris, Klein, & Munoz, 1999; Sparks, 1988).

It is subdivided into a superficial part, which is involved in processing visual information, and a deeper part, which plays a role in orienting head and eye movements in response to sensory stimuli (Schneider & Kastner, 2005a). The neurons in the superficial and the deeper layers of the SC respond to different stimuli. The superficial neurons respond to a wide range of transient or moving visual stimuli (Humphrey, 1968; Marrocco & Li, 1977; Schiller & Koerner, 1971; Schiller & Stryker, 1972). These neurons are not affected by the stimulus orientation, size, shape, or movement velocity. The deeper layer neurons respond to eye and head movements, immediately before a saccade is executed (Robinson & Wurtz, 1976; Schiller & Koerner, 1971; Schiller & Stryker, 1972; Sparks, 1975; Wurtz & Goldberg, 1971, 1972a). They are also sensitive to shifts of attention (Ignashchenkova, Dicke, Haarmeier, & Thier, 2004). Neurons in the deeper layers respond well to motion stimuli (Cynader & Berman, 1972; Marrocco & Li, 1977).

The SC is also thought to play an important role in multisensory integration. A number of studies looking mainly at the SC of cats have found that visual, auditory, and somatosensory inputs converge onto a common pool of SC neurons, creating a substantial population of multisensory neurons (Meredith & Stein, 1986). Neurons in the SC that receive input from multiple sensory modalities typically show enhanced responses to multisensory stimuli (compared to the largest unisensory response) provided that the stimuli from the two modalities are close together in space and time (Stein & Meredith, 1993; Wallace, Wilkinson, & Stein, 1996).

Only a few studies have examined the role of SC in visual stimuli in humans. This is mainly due to its small size and deep location. More specifically, the SC is located near vascular structures, which cause high levels of physiological noise (Poncelet, Wedeen, Weisskoff, & Cohen, 1992). The anatomical organisation of the human SC including its cellular morphology, distribution, and laminar pattern (Hilbig, Bidmon, Zilles, & Busecke, 1999; Laemle, 1982; Leuba & Saini, 1996), a possible columnar organization (Graybiel, 1979; Wallace, 1988), and connections between the colliculi (Tardif & Clarke, 2002) seem to be organised in a way similar to the SC of other primates. Activations in the human SC related to functions associated with its deeper layers have been reported by a number of studies; eye and head movements (Schmitz et al., 2004), visual search (Gitelman, Parrish, Friston, & Mesulam, 2002), selective attention to motion (Büchel, Price, Frackowiak, & Friston, 1998), and spatial navigation (Grön, Wunderlich, Spitzer, Tomczak, & Riepe, 2000), .

Schneider and Kastner (2005a) used high-resolution fMRI to study the retinotopic organisation and the basic visual properties of population responses in the SC. The stimuli they used were checkerboards of varying luminance contrast to obtain contrast response functions, and moving and stationary dot fields to study responsiveness to motion. They also monitored eye movements of their subjects during the experiment. SC was found to be highly sensitive to low stimulus contrast and stimulus motion. A number of studies have examined motion responsive regions in the human brain using moving versus static dot fields and other motion stimuli but none have reported SC or LGN activity (Cheng, Hasegawa, Saleem, & Tanaka, 1994; Claeys, Lindsey, De Schutter, & Orban, 2003; Cornette et al., 1998; Dukelow et al., 2001). The lower spatial resolution used in many of these studies, typically 3 x 3 x 3 mm3, may account for these negative findings.

2.3 Evidence for the SC hypothesis

No study so far has directly tested the SC hypothesis in a population with ADHD. However, preliminary evidence from animal studies, case-reports, and studies on children and adults with ADHD provide some support for collicular involvement in this disorder.

2.3.1 Evidence from Animal Studies

Lesion studies support the role of the SC in distractibility and attention. More specifically, damage to the SC in non human primates leads to a decrease in distractibility (Albano, Mishkin, Westbrook, & Wurtz, 1982; Milner, Foreman, & Goodale, 1978).

More recently, Dommett and Rostron (2011) tested the SC hypothesis on one of the most commonly used animal models of ADHD, the spontaneously hypertensive rat (SHR). The SHR displays the main symptoms of ADHD and appears to be responsive to psychostimulant therapies (Adriani, Caprioli, Granstrem, Carli, & Laviola, 2003). Dommett and colleagues (2011) assessed air righting behaviour, which depends on collicular function. They found that the SHR did show impairment in height- dependent modulation of righting in contrast to both control strains. Very similar deficits were found in a strain of rats with collicular lesions by Yan and colleagues (2010). These findings indicate the presence of a collicular abnormality in the SHR.

To further investigate this possibility, in a following study, K. Clements, Devonshire, Reynolds, and Overton (2014) recorded the extracellular activity and local field potential in the superficial visual layers of the SC in an animal model of ADHD, the New Zealand genetically hypertensive (GH) rat, in response to whole-field light flashes. They found that the peak amplitude and the sum activity of the SC was significantly greater in the GH animals compared to controls. The peak amplitude and the sum activity were both brought to control levels by d-Amphetamine, thus providing more evidence for the hyper-responsive SC hypothesis of ADHD.

2.3.2 Evidence from Human Studies

2.3.2.1 Neuropsychology studies

Lesions limited to the colliculus are extremely rare in humans, due to the high mortality rate associated with damage in brainstem lesions (Weddell, 2004). The first case study on a patient with collicular damage was published by Zihl and Von Cramon (1979). The patient suffered from a congenital malformation of the right SC, which resulted in decreased contrast sensitivity in the contralateral visual field. Weddell (2004) reported the case of 34 year old man with a midbrain tumour with clear evidence of damage to the SC, who presented with difficulties in orienting his attention to contralateral visual stimuli and sustaining attention. Furthermore, the patient had sustained right-neglect.

Sapir, Soroker, Berger, Henik, et al. (1999) reported the case of single patient with a small spontaneous hemorrhage in the right SC area who presented with abnormalities in orienting of attention to the hemifields projecting to the affected side of the SC. No deficits were found in the hemifield projecting to the healthy side of the SC.

Disconnecting the colliculus from the prefrontal cortices in humans has been associated with an increase in distractibility (Gaymard, François, Ploner, Condy, & Rivaud-P échoux, 2003). Gaymard et al. (2003) tested seven patients with a small lesion in the lateral intraparietal area, in a number of oculomotor paradigms and found that removal of the the frontal lobe influence on the SC in humans led to an increase in distractibility as expressed through an increase in reflexive saccades.

Recently, Mathis and colleagues (Mathis et al., 2014) examined distractibility in genetically modified mice in which the retino-collicular projection is duplicated. They found higher levels of collicular noradrenaline levels in these mice, which resulted in deficits in response inhibition. These findings suggest that structural abnormalities in the SC could be behind deficits in response inhibition, one of the most consistent findings in ADHD research.

2.3.2.2 ADHD impaired in tasks sensitive to SC

Various tasks have been used to compare performance of ADHD to healthy controls. Most of these studies did not aim to test the SC hypothesis but used tasks that are sensitive to collicular function. One such task is the attentional blink (AB) paradigm. The AB is a phenomenon in which stimuli are presented in a rapid serial order at the same location. In a typical AB study, a rapid serial visual presentation (RSVP) is used wherein visual stimuli are presented in rapid sequence and observers are required to detect or discriminate 2 targets on each trial (Carr, Henderson, & Nigg, 2010). In a single task condition, participants confirm or reject the presence of the probe letter, while in the dual-task condition, participants must also identify a target stimulus which in presented in one of several serial positions prior to the probe letter. Detection of the target letter is followed by a period where the participants have limited capacity to identify and encode. During this period the probe letter can be missed. Children and adults with ADHD show a larger attentional blink effect overall relative controls (Armstrong & Munoz, 2003; Mason, Humphreys, & Kent, 2005; Raymond, Shapiro, & Arnell, 1992). Most explanations for the AB suggest that it depends on higher order processes such as allocation of attentional resources or visual short term memory consolidation (Raymond et al., 1992; Di Lollo, Kawahara, Ghorashi, & Enns, 2005). However, an alternative explanation could be offered for the larger attentional blink effect in ADHD patients. Studies have shown that excessive eye movements result in poor performance when the attentional blink paradigm is employed both in healthy and ADHD participants (Armstrong & Munoz, 2003). As a result, it is possible that the impaired performance of participants with ADHD is not driven by a deficit in allocating resources but by a deficit in inhibiting eye movements (Munoz, Armstrong, Hampton, & Moore, 2003).

2.3.2.3 Pro-saccades and anti-saccades

The SC plays an important role in the preparation and the execution of saccades (Sparks, 1988; Everling et al., 1999; Sparks, Rohrer, & Zhang, 2000). Children and adults with ADHD have inefficient gaze control compared to healthy controls (Munoz et al., 2003). Two tasks have been widely used in studies investigating eye movements in ADHD; The prosaccade and the anti-saccade task. The prosaccade task is used to test the ability of subjects to generate reflexive, visually triggered saccades (Munoz, Armstrong, & Coe, 2007). The participants are asked to fixate on a central location and look at an eccentric target as soon as it appears. The anti-saccade task is used to test the ability of subjects to suppress reflexive saccades and instead generate voluntary saccades to specific targets (Munoz et al., 2007). Anti-saccade tasks are similar to prosaccade task but subjects are asked to suppress the saccadic response to the eccentric target and instead generate a saccade to the mirror position where no stimulus appears. The SC has been involved in the execution of pro-saccades and the generation of anti-saccades (Everling et al., 1999). In particular, the avoidance of unwanted pro-saccades seems to be depended on the attenuation of preparatory and stimulus-related activity in the SC (Everling et al., 1999).

The majority of studies on children and adults with ADHD have found deficits in anti-saccade tasks. More specifically, Munoz and colleagues (2007) measured eye movement performance in pro- and anti-saccade tasks in a sample of 114 ADHD and 180 control participants ranging in age from 6 to 59 years. Impairments in both tasks were identified for ADHD participants; they had longer reaction times, greater intra-subject variance, and saccades of reduced peak velocities and increased durations in the pro-saccade task. Furthermore, ADHD participants had greater difficulty suppressing reflexive pro-saccades toward the eccentric target compared to healthy controls in the anti-saccade paradigm. Even when performing a correct anti-saccade ADHD participants had increased reaction times, and greater intra-subject variance.

Similar results were reported in another study by Munoz et al. (2003) who tested 76 children and 38 adults diagnosed with ADHD in a number of oculomotor tasks requiring the suppression of reflexive or unwanted saccades. Additionally, participants with ADHD had a great difficulty to suppress reflexive saccades. Slower pro-saccadic reaction times, higher number of premature responses, and reduced proportion of express saccades in the pro-saccadic gap condition were also reported by Klein, Raschke, and Brandenbusch (2003).

Feifel and colleagues (2004) administered two versions of the prosaccade task, with and without a 200-ms gap before target onset, as well as an antisaccade task in 12 adults with ADHD and 12 controls. As reported in previous studies, participants with ADHD performed significantly more anticipatory saccades during the prosaccade task. Eccentricity of the target affected the performance of the ADHD group; no differences between ADHD and control subjects were found when the targets were presented at 5°) of eccentricity. Saccades toward the more peripheral 35°) targets, however, exhibited a non-significant tendency to be shorter in latency for ADHD than for control subjects. In addition to this, participants with ADHD made significantly more directional errors on the anti-saccade task compared to healthy age-matched controls. The effect of eccentricity reported by Feifel et al. (2004) seems to provide additional support for the possible role of the SC in ADHD; the SC has been shown to be more sensitive to peripheral stimuli (Sylvester, Josephs, Driver, & Rees, 2007; Posner, 1980).

Karatekin (2006) examined the effects of task manipulations on anti-saccade accuracy and response times in a sample of ADHD consisting of adolescents, children and young adults. When compared to a control group, adolescents with ADHD showed impairments in terms of accuracy and saccadic latency on the antisaccade task. Training seemed to improve the performance of the ADHD group in the antisaccade task, suggesting a potential role of attentional factors in oculomotor task deficits observed in ADHD. Overall, Karatekin (2006) found that participants with

ADHD executed more premature saccades and fewer corrective saccades relative to age-matched groups.

Mostofsky and colleagues (2001) administered a series of oculomotor tasks, including a pro- and anti- saccade paradigm, to children with ADHD, divided into two groups; a group tested after administration of methylphenidate, and an unmedicated group, who did not take any medication before testing. Contrary to previously reported studies, no significant differences in the pro-saccade reaction times was found, although a significantly greater variability in reaction times was found in unmedicated children with ADHD. The lack of effect of ADHD on saccadic latency could be due to the small number of children tested by Mostofsky, Lasker, Cutting, et al. (2001) relative to previous research. Even though no significant differences were identified in the pro-saccade task, poorer performance was found for both medicated and unmedicated children on the anti-saccade task. Compared to controls, ADHD children executed a significantly higher number of directional errors.

Another study by Mostofsky, Lasker, Singer, Denckla, and Zee (2001) assessed saccadic eye movements in boys with Tourette syndrome (TS) with and without attention-deficit hyperactivity disorder (ADHD), comparing performance with that of an age and gender matched group. Saccadic latency was prolonged in all patient groups compared with controls. Consistent with previous findings, variability in saccadic latency in the pro-saccade task was greater in the groups of boys suffering with both TS and ADHD relative to control groups and TS only children. Similarly, difficulties in inhibiting pro-saccades in the anti-saccade task were found in the TS group with ADHD but not in the TS only and the control group. These findings suggest that abnormal performance in the pro- and anti-saccade task is part of the ADHD endophenotype.

Goto et al. (2010) tested 50 normal subjects (6-35 years), 19 ADHD (6-11 years), and 4 patients with frontal lesions (13-15 years) in a number of oculomotor tasks, including an anti-saccade task. They computed latency, accuracy, and percentage of direction errors for each task. Significant differences were observed between ADHD and age-matched controls in saccade latency, accuracy, and percentage of direction errors in all tasks, including the anti-saccade paradigm. Interestingly, the performance of the ADHD was similar to that of the frontal lesions group.

Deficits in pro- and anti- saccade tasks in ADHD groups were reported by a number of studies (O'Driscoll et al., 2005; Loe, Feldman, Yasui, & Luna, 2009; Carr et al., 2010; Mahone, Mostofsky, Lasker, Zee, & Denckla, 2009). The effect of ADHD subtypes on oculomotor performance, however, appears to be inconsistent; O'Driscoll et al. (2005) reported that children with the ADHD-C subtype were more impaired compared to other groups, while Mahone et al. (2009) found no differences in the severity of the impairement between subtypes. Such inconsistencies could be due to differences in ADHD diagnosis or potential co-morbid disorders within the samples tested.

Finally, Schwerdtfeger et al. (2013) used neuroimaging to examine differences in brain patterns in participants with ADHD and controls, while performing saccades in an anti-saccade task. Adults with ADHD were found to be impaired in the anti-saccade task in various measures, such as saccadic latency, variability in reaction times, and directional errors. During the preparation phase of an anti-saccade, less activation in frontal, supplementary, and parietal eye fields, was found in the ADHD group compared to controls. However, activation in these areas was normal in the ADHD group during the execution of a correct antisaccade. Interestingly, unlike controls, adults with ADHD had greater activation than controls in the dorsolateral prefrontal cortex (DLPFC) during antisaccade execution. In non human primates DLPFC neurons have been identified as sending a direct projection to the SC during anti-saccade tasks (Johnston & Everling, 2006). More specifically, DLPFC neurons were shown to directly modulate SC activity during anti-saccade trials. In case of a hyper-responsive SC, the DLPFC would have to exert higher control to inhibit unwanted responses (Johnston & Everling, 2006). This is consistent with the findings reported by Schwerdtfeger et al. (2013).

Even though the majority of published studies report significant differences of similar nature between ADHD and control groups in pro- and antisaccade tasks, a small number of studies failed to find any differences between ADHD and control groups. For example, Hanisch and colleagues (2006) reported no difference between 22 children ADHD and 22 controls in a prosaccade and an antisaccade task. Both groups had similar saccadic response preparation and saccadic accuracy. Another study that reported no behaviour differences was published by Goepel et al. (2011) and looked at the neural correlate of the antisaccade task in a group of 9 unmedicated boys with ADHD and 14 healthy control children. An antisaccade task with visual and acoustic responses was administered while an electroencephalogram (EEG) was recorded. Both groups performed similarly behaviourally. No difference was found in antisaccade errors and saccadic latencies. When cues were acoustic, EEG-activity differences were found between ADHD and control groups in the anti-saccade task. When visual cues were used EEG-activity preceding antisaccades did not differ between groups. The lack of behavioural differences in the Goepel et al. (2011) study could be due to introduction of multimodal stimuli.

2.3.2.4 Fixation and Fixational Eye-Movements

Fixation partly depends on SC function (Goffart, Hafed, & Krauzlis, 2012; Munoz & Wurtz, 1993b, 1993a). A few studies on populations with ADHD have looked at performance on fixation tasks. The majority of previous research suggests an ADHD deficit in inhibiting unwanted saccades and maintaining fixation (Munoz et al., 2003; Gould, Bastain, Israel, Hommer, & Castellanos, 2001; Loe et al., 2009).

Children and adolescents often have difficulty fixating at a specific location for long time periods. In particular, in a study by Munoz and colleagues (2003) participants with ADHD generated more intrusive saccades during periods when they were required to maintain steady fixation. The performance of children and adults with ADHD on such tasks suggests a possible deficit in the saccade-generating circuitry.

Gould et al. (2001) assessed eye movements in 24 boys with DSM-IV combined type ADHD between the ages of 7 and 13. They compared their performance on a fixation task with large saccades away from the fixation point to that of

26 age-matched control boys. They found that children diagnosed with ADHD had difficulty maintaining fixation even in the absence of external or internal distractors. A deficit in maintaining fixation in individuals with ADHD was also reported by Munoz et al. (2007). Munoz and colleagues tested children and adults diagnosed with ADHD in oculomotor tasks requiring the suppression of reflexive or unwanted saccadic eye movements. These tasks are supported by regions such as the frontal cortex and basal ganglia that have been identified in the control of voluntary responses and saccadic suppression. One of the tasks administered required prolonged fixation. Munoz et al. (2007) found that ADHD participants generated more intrusive saccades during periods when they were required to maintain steady fixation. Similar findings were reported by Hanisch et al. (2006) and Loe et al. (2009)

Not all published studies, however, report differences in fixation between groups with ADHD and healthy controls. Feifel et al. (2004) examined the functional integrity of the frontostriatal system of ADHD adult subjects. They compared unmedicated ADHD participants to age-matched controls on a comprehensive battery of oculomotor paradigms. The battery included a simple fixation task. No differences were found between two groups. The lack of an effect could be partly due to the small sample of participants tested by Feifel and colleagues (2004); only 12 adults with ADHD took part in the experiment.

2.3.2.5 Smooth Pursuit

Smooth pursuit are slow, voluntary tracking eye movements that allow us to keep a moving stimulus on the fovea (Purves, Augustine, Fitzpatrick, & et al., n.d.). The SC plays a role in smooth pursuit (Krauzlis, Basso, & Wurtz, 2000; Basso, Krauzlis, & Wurtz, 2000). Activation and inactivation of the SC during pursuit suggest a direct involvement of the colliculus in the visual tracking of targets (Basso et al., 2000). A few studies have examined smooth pursuit in ADHD patients. Shapira, Jones, and Sherman (1980) investigated eye movements in 29 school children with hyperactivity with learning disabilities and a matched control group of 32 children. A smooth pursuit task was employed. The children had to track a moving target, maintain eye fixation on a stationary target and to read a standard reading material. The tracking accuracy was significantly inferior in the hyperactive children with learning disabilities as compared to the control group. Another study by Bylsma and Pivik (1989) examined the effects of methylphenidate and behavioural manipulation (cognitive training) on oculomotor control in a sample of 20 children with ADHD and 20 age-matched controls. The subjects performed a smooth pursuit eye task, while their eye movements were recorded electro-oculographically. The ADHD group when tested off medication showed an abnormal tracking pattern. Medication significantly improved the performance of the ADHD group on the smooth pursuit task by normalising their eye movement patterns. Abnormalities in smooth pursuit were also reported by Bala et al. (1981) who compared eye movements of a group of hyperactive boys and a control group during a pursuit task. Children with ADHD executed a higher number of unwanted saccades during the task compared to the healthy participants.

Not all studies, however, report abnormalities in smooth pursuit in participants with ADHD. A number of published studies suggest that smooth pursuit seems to be preserved in ADHD. Castellanos et al. (2000) assessed oculomotor function in 32 girls with ADHD and 20 age and gender matched controls. Smooth pursuit performance was statistically equivalent across subject groups. Another study by Ross, Olincy, Harris, Sullivan, and Radant (2000) recorded smooth pursuit eye movement during a 16.7° per second constant velocity task in 17 adults with ADHD, 49 adults with schizophrenia, and 37 normal adults. Deficits were observed in subjects with schizophrenia only. Participants with ADHD and controls showed no differences in performance during the smooth pursuit.

Participants in the study by Ross et al. (2000) were significantly older than the ones tested in previous studies (i.e. adults aged 25 -50 years). No study so far has looked at differences between subtypes or the effect of comorbidities in smooth pursuit. Such factors could contribute to the inconsistent findings reported in smooth pursuit research on ADHD. Additional experiments are required in order to establish the relationship between ADHD and such eye movements.

2.3.2.6 Express Saccades

Express saccades are saccades with very short reaction times (80–100 ms) made in response to visual stimuli (Sparks et al., 2000). These fast eye movements are usually observed after extensive practice in tasks that require subjects to look as quickly as possible to a visual target that appears immediately after the disappearance of an original fixation stimulus (Sparks et al., 2000). Introducing a temporal gap between the fixation point offset and the saccadic target onset is associated with an increase in the frequency of the express saccades (Schiller, Sandell, & Maunsell, 1987; Edelman & Keller, 1996). Express saccades occur more often when the subject is presented with predictable targets and when a gap occurs between fixation point and target appearance.

The SC seems to have an important role in the generation of express saccades. This is evident from electrophysiological studies on non-human primates and neuropsychology case studies (Sparks et al., 2000). Edelman & Keller (1996) recorded visuomotor burst neurons in the deeper layers of the SC while two monkeys made short-latency saccades to visual targets and found that visual burst of visuomotor neurons in the deeper layers of the superior colliculus plays a role in the initiation of express saccades. Express saccades - unlike regular saccades - survive lesions of the frontal eye fields but not lesions of the superior colliculus (Schiller et al., 1987). No recovery is evident after SC lesions, thus it appears that the cortical areas involved in express saccade generation send their signals to the brainstem through the superior colliculus (Haushofer, Schiller, Kendall, Slocum, & Tolias, 2002).

Abnormalities in the generation of expressed saccades have been reported in ADHD. Munoz et al. (2003) computed the percentage of express saccades generated by ADHD participants and controls during an occulomotor task. They found that children, in general, generated more express saccades than adults. Both adults and children with ADHD appeared to generate slightly more express saccades than controls. In another study Klein and colleagues (2002) found that express saccade frequency in ADHD subjects during a pro-saccade task was significantly increased after the administration of methylphenidate. Feifel et al. (2004) found more evidence of an increased number of express saccades in ADHD. More specifically, ADHD subjects executed more anticipatory saccades (reaction time <90 msec) during a pro- and an anti- saccade task. The latency of these saccades suggests that they could be classified as express saccades. Dyslexia is often co-mordid with ADHD (Germano et al., 2010). One study by Biscaldi, Fischer, and Aiple (1994) found that subjects with dyslexia executed a significantly increased number of express saccades in five tasks non-cognitive tasks, which required them to perform saccades to various targets presented in a number of eccentricities (Biscaldi et al., 1994).

2.3.2.7 Microsaccades

Another type of eye movements, microsaccades, which are generated (at least partly) by the SC (Hafed, Goffart, & Krauzlis, 2009; Hafed et al., 2009; Hafed, Lovejoy, & Krauzlis, 2011), seem to be abnormal in ADHD. Microsaccades refer to involuntary, small, fast eye-movements usually observed during fixation. Only one study so far has attempted to examine microsaccades in ADHD. More specifically, Fried and colleagues (2014) found that adults with ADHD make more microsaccades compared to a group of controls when performing a continuous performance task. This difference was more significant when ADHD adults were tested off medication. Medication normalised the microsaccade rate in the ADHD group, suggesting a possible link between ADHD medication and the generation of microsaccades.

2.3.2.8 Inhibition of Return

Two types of attentional orienting have been identified; endogenous and exogenous. Endogenous attention refers to voluntary attention (i.e., information about a potential targets in a central cue, "top-down"). Exogenous attention, which has been more linked with the SC and subcortical mechanisms, refers to the involuntary, automatic capture of attention (i.e, information about a potential target by a sudden peripheral cue, "bottom-up"). Exogenous cues have been consistently found to lead to faster orienting of attention (Posner, Rafal, Choate, & Vaughan, 1985). This could be due to evolutionary purposes; responding faster to sudden, peripheral targets could help humans avoid predators. Whereas, central cues always facilitate attention, peripheral cues can only lead to enhanced responses for a limited amount of time. In fact, if the cue remains on for 300ms or more, it leads to slower and/or less accurate responses at the location where the cue was presented than at the opposite location. This phenomenon was termed by Posner, Rafal, and colleagues (1985) as inhibition of return (IOR). An explanation for this phenomenon could be the preference of the attentional system for novel spatial locations, which results in inhibiting regions that have already been attended to (Posner & Cohen, 1984). As a result of the IOR, a more efficient visual-search strategy is adapted which favours novelty.

Neuroscientific studies suggest that IOR, when generated using the model cuing task pioneered by Posner, begins with the presentation of the cue but is not seen in behaviour until attention is disengaged from the cue, thus removing attention-related facilitation. Neuropsychological and developmental studies point to the SC as critical in the generation of IOR.

In a rare patient with a unilateral lesion restricted to the dorsal midbrain, Sapir et al. (1999) demonstrated that IOR is generated within the midbrain SC. They report the case of a single patient with a small spontaneous hemorrhage in the right side of the posterior midbrain, mostly in the right SC area who had intact IOR in the hemifields projecting to the intact left SC. However, no IOR was found in the hemifields projecting to the affected right SC (Sapir et al., 1999).

Dorris, Klein, Everling, and Munoz (2002) recorded the activity of single neurons in the superficial and intermediate layers of the SC while the monkeys performed a visual attention task. When the target was presented at a previously cued location the stimulus-related response in the colliculus was attenuated and the magnitude of this response was correlated with subsequent saccadic latencies. This finding suggests that the primate SC participates in the generation of the IOR. Dorris and colleagues (2002) proposed that the modulation of the SC during the IOR suggests a possible role of cortical regions in regulating SC activity.

Abnormalities in IOR could suggest a collicular involvement in ADHD. A small number of studies have examined IOR in individuals with ADHD. Li, Chang, and Lin (2003) found that the magnitude of IOR appears to be slightly smaller in ADHD subjects compared to controls.

Yuen, Bradshaw, Sheppard, Lee, and Georgiou-Karistianis (2005) investigated the nature and functioning of the visual-spatial IOR in children with "pure" TS, and those with co-morbid forms of TS. ADHD was one of the comorbidities studied by Yuen et al. (2005). Participants performed a IOR task, which involved responding to left and right visual targets preceded by congruent or incongruent exogenous visual cues. The TS group with co-morbid disorders (including ADHD) exhibited an atypical IOR pattern compared to controls and the pure TS group. In particular, no evidence for normal facilitatory and inhibitory effects for right visual field targets was found in the co-morbid TS group. These findings suggest that deficits in IOR are not an inherent feature of TS but could be due to the ADHD symptomatology.

Results from studies investigating IOR in ADHD, however, are not always consistent with a performance deficit. White (2007) found no differences in a spatial and a semantic IOR between adults with ADHD and controls. However, the paradigm they used had words as targets. This might have affected the results, since processing of words involves higher cognitive areas.

2.3.2.9 Drugs for ADHD act on SC

D-Amphetamine and methylphenidate are the most common pharmacotherapies of ADHD. However, their exact mechanism is not clearly understood. One theory postulates that d-amphetamine and methylphenidate lead to an increase in synaptic levels of the monoamines dopamine, noradrenaline and 5-HT (Azzaro, Ziance, & Rutledge, 1974; Easton, Steward, Marshall, Fone, & Marsden, 2007;

Heal, Cheetham, & Smith, 2009). According to this theory, the main cause of methylphenidate's cognitive and behavioural effects is thought to be its influence on dopamine neurotransmission. More specifically, methylphenidate is an indirect dopamine agonist, which by binding to the dopamine transporter (DAT) increases dopamine concentrations in the synapse extracellular space. The DAT has been found to play a crucial role in the organism's attention mechanisms by regulating its responses to salient stimuli (Volkow, Wang, Fowler, & Ding, 2005). In addition to its effect on the dopaminergic system, methylphenidate also increases the levels of noradrenaline by blocking its re-uptake (Kuczenski & Segal, 1997). However, assumptions about the role of dopamine in ADHD are often overly simplified. A recent review by Gonon (2009) identified a number of inconsistencies from neurochemical, genetic, neuroimaging, and pharmacological data which do not support this hypothesis. It is more likely that dopaminergic pathway is only one of the pathways affected by stimulants (Levy & Swanson, 2001). The SC was found to be one of the main loci affected by stimulants (Dommett, Overton, & Greenfield, 2009). Dommett and colleagues (2009) found that both D-Amphetamine and methylphenidate alter the signal to noise ratio in the SC of rats.

Low doses of methylphenidate reduce hyperactivity and improve attention in individuals with ADHD. This has often been attributed to an improvement in working memory. However, in a recent study by Rajala et al. (2014), it was shown that low doses of methylphenidate improved performance in a memory saccade task in non-human primates by reducing premature responses and not by improving working memory. It also reduced errors from failing to fixate at the start of each trial. Premature responses and fixation are closely associated with SC function.

methylphenidate and AMP have been consistently shown to reduce the main ADHD symptoms in 70% of children (Faraone, Spencer, Aleardi, Pagano, & Biederman, 2004)). Stimulants are also prescribed to adult patients and are similarly effective (Faraone et al., 2004). methylphenidate has also been found to have positive effects on healthy adults by improving vigilance, reaction times, and working memory (Mehta et al., 2000; Elliott et al., 1997).

Several studies have investigated the effects of methylphenidate on saccade control in participants with ADHD. Munoz, Hampton, Moore, and Goldring (1999) reported a (non-significant) 2–3% increase and a 5–6% decrease of the proportions of express saccades (overlap condition) and direction errors (gap condition), respectively, under the on- as compared to the off-medication condition. More recently, Klein et al. (2002) examined the effects of methylphenidate on different measures of saccade control and practice effects. Their sample was 26 boys with ADHD who performed a pro-saccadic overlap and an anti-saccadic 200-ms gap task. Methylphenidate was found to reduce pro- and anti-saccadic reaction times, error correction times, and the proportion of direction errors during the anti-saccade task. Furthermore, the drug augmented the proportions of express saccades and error corrections.

2.3.2.10 Abnormal Reward Sensitivity in ADHD

Previous studies have shown that people with ADHD are unusually sensitive to reward (Douglas & Parry, 1994) and prefer immediate rather than delayed rewards (including situations where the delayed reward is larger) (Luman et al., 2005). The SC is a part of the circuitry involved in reward processing. Most specifically, the colliculus receives inputs from many brain areas including the prefrontal cortex and the basal ganglia where reward information is thought to be encoded. SC neurons have been shown to encode reward information in non human primates (T. Ikeda & Hikosaka, 2007). Ikeda and Hikosaka (2007) found that presaccadic activity of SC neurons is enhanced when a larger reward is expected. More studies are needed to establish the possible role of SC in ADHD symptomatology.

2.3.2.11 Increased rates of ADHD in deaf children

Contrary to popular belief, ADHD seems to be more common amongst deaf children compared to hearing children (Hindley, 2005; Hindley & Kroll, 1998; Landsberger, Diaz, Spring, Sheward, & Sculley, 2014). An advantage for stimuli presented in peripheral locations relative to the ones presented centrally has been reported for deaf subjects (Bosworth & Dobkins, 2002; Bavelier et al., 2000). It has been hypothesised that this is due to reorganisation of visual attention networks in order to compensate for the lack of auditory input (Bosworth & Dobkins, 2002). A high sensitivity to peripheral stimuli has been found in the SC (Sylvester et al., 2007; Posner, 1980). The abnormal visual attention found in deaf individuals resembles the presentation of a hyper-responsive colliculus. This association could potentially explain the high incidence of ADHD in the deaf population.

Overall, children with disabilities present a higher incidence of ADHD (DeCarlo et al., 2014; Hindley & Kroll, 1998). However, prevalence of ADHD seems to be lower in groups of children with near or total vision loss (DeCarlo et al., 2014). These results should be interpreted with caution. The differences in prevalence of ADHD in normal and children with disabilities do not necessarily reflect a connection between disabilities and ADHD. This finding could be due to a number of reasons; misdiagnosis due to the lack of appropriate tests, increased parent sensitivity, and specific features of their disability.

2.4 Thesis Aims

2.4.1 Investigating the role of the SC in ADHD

Preliminary results from studies on ADHD patients and animal models of ADHD provide some support for the SC hypothesis. The majority of studies on oculomotor behaviour in children and adults with ADHD suggest deficits and abnormalities in a number of tasks, which have been shown to directly involve the SC. These findings could be interpreted as indicative of abnormal SC activity in ADHD. An alternative explanation would propose that abnormal SC activity could be the result of poor voluntary control over the saccade neurons found in the SC. For example, deficits in SC activity modulation by the DLPFC could also manifest in a similar manner.

No study so far has directly attempted to test the hypothesis on human subjects. This will be the main purpose of this thesis. A number of experiments employing tasks sensitive to collicular function will be performed on children with ADHD, as well as healthy participants with varying levels of ADHD traits (Figure 2.1).

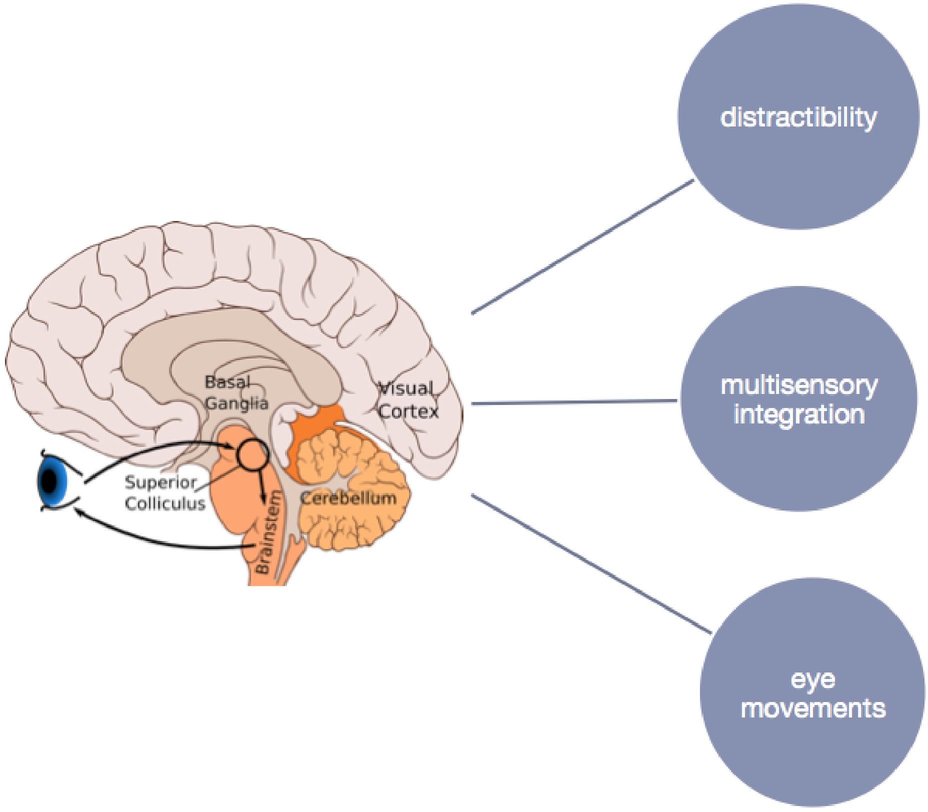


FIGURE 2.1: Approaches to the SC hypothesis in ADHD

2.4.2 Looking for potential biomarkers for ADHD

Using a prevalence rate of 5%, Pelham, Foster, and Robb (2007) estimated the annual societal "cost of illness" for ADHD in the US to be between between $36 and $52 billion. This is estimated to be between $12,005 and $17,458 spent annually per individual. Across 10 countries, it was projected that ADHD was associated with 143.8 million lost days of productivity each year. Most of this loss can be attributed to ADHD and not co-occurring conditions (de Graaf et al., 2008). In the UK, the annual mean cost for an individual patient in 2012-2013 ranged from £311.09 to as high as £1,410.00 (Telford et al., 2013; Holden et al., 2013; Snell et al., 2013; D'Amico et al., 2014). In addition to this, Kessler and colleagues (2009) found that ADHD was associated with a 4-5% reduction in work performance, a 2.1 relative-odds of sickness absence, and a 2.0 relative-odds of workplace accidents-injuries.

Currently, there is no objective test for ADHD. Several attempts for the creation of an objective test have been made. The most commonly used tests are continuous performance tests (CPT), which measure the patient's sustained and selective attention. The "test of variables of attention" (TOVA) developed by Greenberg and Waldmant (1993) is often used to help with diagnosis. However, the reliability of TOVA to serve as a screening diagnostic tool for ADHD has been debated (Zelnik, Bennett-Back, Miari, Goez, & Fattal-Valevski, 2012; Lindhiem, Yu, Grasso, Kolko, & Youngstrom, 2014).

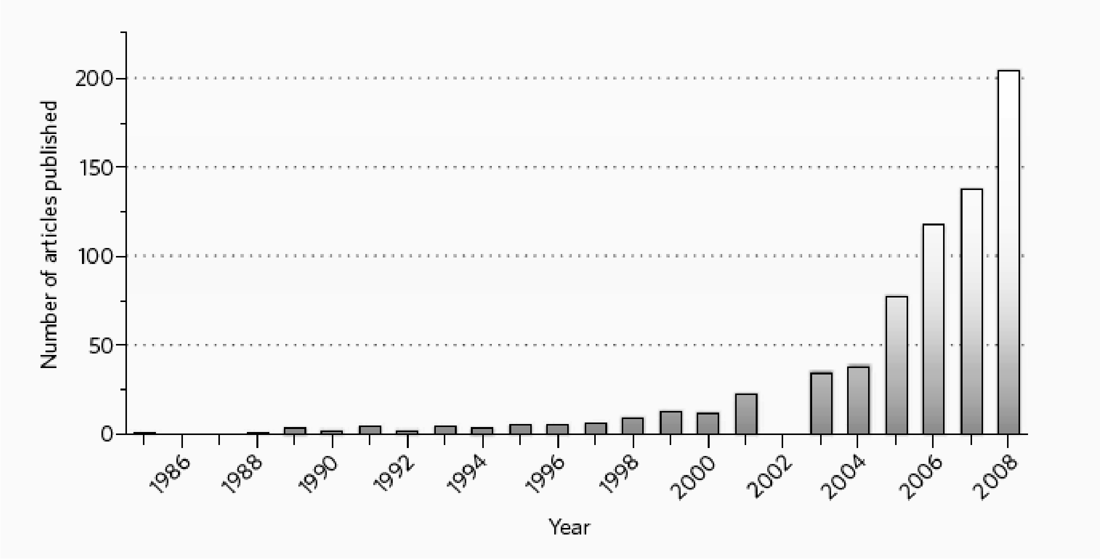


FIGURE 2.2: Rising interest in biomarkers and psychiatry: The increase in interest in objective biomarkers by researchers as reflected by the rise of number of journal papers focussed on this topic. The picture is adapted from Singh et al. (2009) and is based on data obtained from a search of the ISI Web of Knowledge in May 2009 for articles with the term 'biomarker' and the word stem 'psy' in the topic field.

Biomarkers are commonly used in medicine. Biomarkers are tests, biometric measurements that convey information about the biological condition of the subject being tested (LaBaer, 2005). For example, in the case of Alzheimer's Disease the concentration of a particular protein in the cerebral spinal fluid (CSF) is a biomarker for this specific disease. The last two decades psychiatry has also started looking for biological or physiological biomarkers for various disorders (Figure 2.2). Biomarkers in psychiatry could lead to a number of important advances. First, they could lead to tests to objectively detect and assess a psychiatric disorder. Second, they could potentially allow us to predict whether someone would develop a specific disorder. Third, biomarkers could be used to inform treatment and its effectiveness. Some example of potential biomarkers for psychiatric conditions involve neural patterns as assessed with neuroimaging techniques, abnormalities in eye-movements, and specific genetic characteristics.

From the brief summary of ADHD presented in the previous Chapter, it is clear that diagnosis of ADHD mostly depends on interviews and reports from the family of the ADHD patient. All these measures are defined by a high level of subjectivity. This subjectivity could potentially account for commonly reported discrepancies in ADHD literature. The identification of a biomarker for ADHD would help eliminate the subjective diagnoses based on interviews and potentially allow for earlier diagnosis and even personalised treatment (Moffitt et al., 2008; Singh & Rose, 2009).

One of the areas of investigation for potential biomarkers in ADHD is the visual system (visual field size, L. Martin, Aring, Landgren, Hellström, & Andersson Grönlund, 2008; eye blinks and eye movements, Fried et al., 2014). Identifying potential biomarkers for ADHD is the secondary goal of this thesis.

2.4.3 Plan of Work in the Thesis

Direct testing of the human SC is not possible. As a result, a number of alternative approaches were adopted to study its role in individuals with ADHD and varying levels of ADHD traits.

In Chapter 3 the dimensional approach in ADHD is presented, as well as the results of a study investigating the distribution of ADHD-like traits in the general population. The validity of a questionnaire as a tool to differentiate between participants with high and low ADHD traits is examined. The findings allow the use of a specific questionnaire and cut-off scores for the studies described in following chapters (Chapters 3, 4, 5, 6).

Distractibility is one of the main features of ADHD and is also linked to collicular function. Chapter 4 examines the effect far-peripheral distractors with features associated with collicular responses on a sustained attention paradigm in participants with varying ADHD traits. Differences in the processing of distractors between high and low ADHD could indicate a SC dysfunction in ADHD.

The role of the SC in multisensory integration is well established. Chapter 5 examines multisensory integration in participants with high and low ADHD traits by using two paradigms investigating the temporal aspects of multisensory integration. A collicular dysfunction could lead to atypical integration of multimodal stimuli.

The SC is thought to play an important role in the generation and the inhibition of microsaccades. An abnormality in microsaccade frequencies and properties could indicate a collicular involvement in ADHD. This was the main aim of the study described in Chapter 6. Differences between individuals with high and low ADHD traits are investigated with a simple sustained fixation paradigm, which has been previously found to elicit microsaccades.

The results of a study performed on a clinical population are described in Chapter 7. Visual field differences in ADHD and control groups are examined using a standardised perimetry test. The test assessing visual field size comprises of stimuli that have been found to activate the SC. An abnormality in the SC could manifest as an abnormal visual field.

Chapter 3

Investigating ADHD traits in healthy populations

3.1 Chapter Summary

ADHD is one of the most common developmental disorders. According to the dimensional approach developmental and psychiatric disorders such as ADHD can be seen dimensionally, with their symptoms distributed continuously in the population. In this study the distribution of ADHD traits in the general population of Sheffield was investigated. Three widely used questionnaires were administered; the ADHD Self-Report Scale (ASRS, Kessler, Adler, et al., 2005), the 6-item the Adult ADHD Self-Report Scale Screener (ASRS Screener, Kessler, Adler, et al., 2005) and the short version of the Wender Utah Rating Scale (WURS; Ward,

1993). All questionnaires showed high internal consistency and led to the identification of individuals with varying levels of ADHD. Both versions of the ASRS were strongly correlated with the WURS. The strong correlation between ADHD measures suggests that they are valid ways of measuring ADHD like traits. Cut-off scores were calculated for each questionnaire based on the observed distribution of ADHD scores. The implications of the current chapter findings for the studies described in the following chapters are discussed.

3.2 Introduction

There has been an ongoing debate about the nature of developmental disorders; are they dimensional or categorical? The categorical approach suggests that the difference between children or adults diagnosed with a developmental disorder and the norm is qualitative (Sonuga-Barke, 1998). The dimensional approach proposes that ADHD psychopathology can be viewed dimensionally, with inattentive and hyperactive-impulsive symptoms distributed continuously in the general population (Hudziak, Achenbach, Althoff, & Pine, 2007; Rodriguez et al., 2007). Preliminary evidence provides support for the hypothesis that ADHD represents the extreme end of traits present in the general population (J. Martin, Hamshere, Stergiakouli, O'Donovan, & Thapar, 2014; H. Larsson, Anckarsater, Råstam, Chang, & Lichtenstein, 2012; Levy, Hay, McStephen, Wood, & Waldman, 1997). This approach has been very popular in studies on other developmental disorders such as autism spectrum disorder (ASD) (Dickinson, Jones, & Milne, 2014; Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001). In particular, autistic traits in the general population seem to be highly heritable (Hoekstra, Bartels, Verweij, & Boomsma, 2007).

Sroufe (1997) by analysing data from 180 children who were followed from birth through sixth grade and using teacher Behavior Problem Checklist data as the outcome found that children who qualify for a diagnosis often differ quantitatively rather than qualitatively from their age-mates. The dimensional approach seems also to be consisted with multiple pathway models of ADHD (e.g., Nigg & Casey, 2005; Sonuga-Barke & Sergeant, 2005). A number of studies provide indirect support for a dimensional conceptualisation of ADHD. Marcus and Barry (2011) conducted a set of taxometric analyses using data from 1078 participants and revealed a dimensional latent structure across various analyses for ADHD, inattention, and impulsivity. A recent meta-analysis by Nikolas and Burt (2010) also found that each component of ADHD could be best explained as arising from a multi-locus genetic basis with a mix of additive and non-additive effects, along with non-shared environmental influences.

Even though the dimensional approach has been gaining popularity in developmental disorders research, only a limited number of studies have used ADHD checklists to assess the presence of ADHD symptoms in healthy populations. Dang et al. (2014) used the Barratt Impulsiveness Scale, a self-report measure that examines attentional, non-planning, and motor features of impulsivity and found that the score on this scale correlated with the ADHD score from the Test of Variables of Attention (TOVA), an objective measure of attentional deficits (Greenberg & Waldmant, 1993). J. Stevenson et al. (2007) investigated the relationship between digit ratios and ADHD symptoms in a group of college students not selected for ADHD. The ratio of the lengths of the 2nd finger to the 4th finger in each hand (2D:4D digit ratio) is regarded as a proxy for prenatal androgen exposure (Putz, Gaulin, Sporter, & McBurney, 2004). J. Stevenson et al. (2007) found that in females, the more masculine the left hand (LH) 2D:4D ratio, the more the ADHD/Combined symptoms and the more the ADHD/Inattentive symptoms and ADHD/Hyperactive-Impulsive symptoms. Furthermore, more masculine ratios correlated between the total WURS and right hand (RH) 2D:3D, RH 2D:4D, and LH 2D:3D; and between the inattentive DSM symptoms and LH 2D:5D, and between the ADHD/Hyperactive and Impulsive symptoms and RH 3D:4D. This suggests a potential role of genetics in the presence of ADHD traits.

Wodushek and Neumann (2003) examined inhibitory capacity in healthy adults with high and low scores on the WURS scale. Participants with greater ADHD symptomatology performed more poorly on cognitive measures of response inhibition (the Stop-Signal task) and visual attention, compared to those with fewer ADHD symptoms. Inhibitory performance and ADHD-like traits were further studied by Polner and colleagues (2014) in a large sample of healthy adults by combining a number of widely used tests of inhibition-related functions. ADHD like traits were found to correlate with poorer performance on various tasks. The relationship between inhibition performance and ADHD like traits was weaker than the one observed in clinical samples. Roy-Byrne et al. (1997) reported that adults with probable or possible ADHD exhibited poorer performance on the CPT and the reading section of the Wide-Range Achievement Test—Revised than those with low to moderate symptoms of ADHD, despite comparable rates of additional psychopathology in each group.

More recently, Biehl et al. (2013) investigated differences in suppression in the processing of task-irrelevant stimuli in participants with varying subclinical ADHD symptoms. Participants with high ADHD traits showed marginally higher mean amplitudes for irrelevant stimuli than participants with low subclinical symptoms. No difference was reported in the processing of relevant stimuli. The results point to enhanced processing of task-irrelevant stimuli in participants with high subclinical ADHD symptoms. This suppression deficit might lead to higher distractibility and in turn impaired task performance, and it is likely to be more pronounced in participants meeting full diagnostic criteria for ADHD.

Some studies on children and adults with ADHD have found that deficits in behavioural measures of attention are greater in the left versus right visual field (Geeraerts, Lafosse, Vaes, Vandenbussche, & Verfaillie, 2008; Epstein, Conners, Erhardt, March, & Swanson, 1997). Poynter, Ingram, and Minor (2010) used the Conners' Adult ADHD Rating Scales to measure self-reported attention problems in a group of healthy subjects without an ADHD diagnosis and found that visual field asymmetries in orienting attention correlated significantly with ADHD traits. The results in the non-clinical population with self-reported attention problems was similar to some findings from previous studies that used clinical samples.

Evidence from neurophysiology studies also provide support for the dimensional hypothesis of ADHD. Herrmann et al. (2009) used the ASRS and investigated the association between the amount of inattention and hyperactivity/impulsivity symptoms in a non-clinical population of healthy students and the neural correlates of error processing measured with event-related potentials. They found reduced amplitudes of error-positivity (Pe) with increasing symptoms of inattention. A similar finding was reported in a later study by Groom et al. (2013) that used a clinical population. Another study by Dang et al. (2014) investigated anatomical asymmetry of the caudate nucleus in 71 adults between 18 and 35 years with varying levels of ADHD as assessed with an objective measure of attentional problems, the ADHD score from the Test of Variables of Attention (TOVA). They found that larger right relative to left caudate volumes correlated with higher ADHD level. Higher ADHD traits in healthy populations have also been found to correlate with grey-matter volume in the right parietal lobe, right temporal frontal cortex, bilateral thalamus, and left hippocampus/amygdala complex (Geurts, Ridderinkhof, & Scholte, 2013).

Individuals with high ADHD traits have been found to have lower quality of life, similar to ADHD patients (Combs, Canu, Fulks, & Nieman, 2014). Seeing disorders as the high end of a spectrum suggests the possible existence of individuals on the lower end. Recently, Greven et al. (2015) examined the levels of ADHD and ASD traits in a population sample of 378 children and correlated them to parent-ratings of behavioural problems and performance in various cognitive tests. Children on the low ends of the ADHD and ASD trait spectrum had significantly fewer behavioural problems and performed better in cognitive tests.

The findings from the above studies provide support for the existence of a spectrum in neurodevelopmental disorders and show that measuring ADHD traits in healthy population and correlating them with their performance on various tasks is a useful approach in the study of developmental disorders. Recruiting clinical populations for research can be very challenging, especially when testing new ideas. In such cases, using healthy volunteers with high ADHD-like traits and comparing their performance to volunteers with low ADHD-like traits could be very informative.

3.2.1 Current Study

The aim of this study was to investigate the distribution of ADHD traits in the general population in Sheffield and identify the appropriate tool for assessing ADHD like symptoms. The characteristics of individuals with varying levels of ADHD were also investigated. Furthermore, a cutoff point for high and low ADHD groups, which was used in studies reported in the following chapters, was identified.

3.3 Methods

3.3.1 Participants

Subjects were 800 members of the Sheffield volunteers list. Members of the list were invited to participate by email. The research was approved by the Department of Psychology's Research Ethics Committee. 568 participants were female.

Age characteristics of the participants are presented on Table 3.6. The majority of the sample (78.9% were British citizens).

110 participants had been previously diagnosed with a mental health or a developmental disorder, including dyslexia and autism.

3.3.2 Materials

An online survey was administered to the University of Sheffield subject pool. 800 completed the questionnaire. Three scales for measuring ADHD symptoms were administered, the ADHD Self-Report Scale (ASRS, Kessler, Adler, et al., 2005), 6-item the Adult ADHD Self-Report Scale Screener (ASRS Screener, Kessler, Adler, et al., 2005) and the short version of the Wender Utah Rating Scale (WURS; Ward, 1993). The participants thought they were filling in a personality questionnaire and were not aware that ADHD symptoms were being measured.

3.3.2.1 ASRS and ASRS Screener

The ASRS is an instrument consisting of the 18 DSM-IV-TR criteria and was developed in conjunction with the World Health Organization (WHO), and the Workgroup on Adult ADHD. The scores obtained through the ASRS have been found to be predictive of symptoms consistent with ADHD (Adler, 2004). The ASRS contains eighteen items from DSM-IV-TR (American Psychiatric Association, 2000) but measures the frequencies of the symptoms. The subjects are asked to report how often they experience each symptom in a period of six months on a five point Likert scale which ranges from 0 for never, 1 for rarely, 2 for sometimes, 3 for often, and 4 for very often (Kessler, Adler, et al., 2005). The ASRS has a two factorial structure (Reuter, Kirsch, & Hennig, 2006) which includes an inattention scale and a hyperactivity/ impulsivity scale. Each subscale contains nine items. The ASRS examines only current adult symptoms of ADHD. The reliabilities (Cronbach's alpha) for the two subscales of inattention (.75) and impulsivity (.77) as well as for the total ASRS (.82) are satisfactory (Reuter et al., 2006). The ASRS is split into two parts; Part A and Part B. The Part A of the ASRS can be administered alone as the ASRS screener. It contains 6 questions mostly strongly associated with ADHD (Kessler, Adler, et al., 2005).

The original questionnaires are formatted with darkly shaded boxes in certain items which signify more severe symptoms. According to general convention, the ASRS Screener classifies an individual as highly likely to have an ADHD diagnosis if they have 4 or more responses marked in the dark-shaded boxes of the ASRS Screener. No agreed cutoff point exists for the ASRS. Stark et al. (2011) proposed that a sum score of under 34 suggests that a subject is unlikely to have ADHD, while a score between between 34 and 46 suggests the subject is likely to suffer from ADHD. Finally, scores greater or equal to 48 could indicate that the subject is most likely to have ADHD. However, it is not clear whether this cutoff point could be applicable in the UK.

In order to minimise any possibility that the darker shaded areas may motivate symptom exaggeration by the participants, we removed them from the ASRS .

3.3.2.2 WURS

The short version of WURS is a 25-item self-report questionnaire for the retrospective assessment of childhood ADHD symptoms; high scores indicate greater symptoms. It is based on the 61 item WURS developed by Ward (1993) but only includes the items that measure ADHD symptoms. The 25 items in the WURS describe ADHD behaviours and symptoms (for example "Concentration problems, easily distracted", see Table 3.1), which are rated on a 5-point scale, ranging from 0 ("not at all or very slightly") to 4 ("very much"). Possible total scores range from 0 to 100. A cut-off score of 46 was proposed to detect adults with ADHD (Philipsen et al., 2008; Fossati, Novella, Donati, Donini, & Maffei, 2002). The WURS has been found sensitive in detecting ADHD (McCann, Scheele, Ward, & Roy-Byrne, 2000; Ward, 1993), and has high internal consistency. It comprises of five subscales; Conduct Problems, Impulsivity Problems, Mood Difficulties, Inattention/Anxiety, Academic Concerns. Data suggest that when using a cutoff score of 46 or higher, WURS can correctly identify 86% of the patients with attention deficit hyperactivity disorder and 99% of the normal subjects (Ward, 1993)

The ASRS and the WURS have been successfully used in previous studies to estimate the prevalence and correlates of adult ADHD in population surveys (Kessler, Berglund, et al., 2005; Adler, 2004; Roy-Byrne et al., 1997; Herrmann et al., 2009; J. Stevenson et al., 2007).

Since these questionnaires have been previously found to misclassify individuals with other disorders as having ADHD (McCann et al., 2000; Roy-Byrne et al., 1997), the participants were asked to report whether they had ever been diagnosed having any dyslexia, ADHD, or any other mental or neurodevelopmental disorder.

3.3.3 Procedure

Potential participants were provided with a short paragraph describing the study and a hyperlink taking them to the study website (Qualtrics). All the questionnaires used in the survey were initially designed as "pen-and-paper". Our experiment was carried out online. However, this approach was not highly likely to affect the results, since evidence suggests that there is little variation in responses when pen-and-paper questionnaires are administered online (De Looij-Jansen, Petra, & De Wilde, 2008; Mangunkusumo et al., 2005). The participants thought they were filling in a personality questionnaire and were not aware that ADHD symptoms were being measured. In the end of the questionnaire, the participants were fully debriefed.

Completing the questionnaire took approximately 10 minutes.

3.4 Results

3.4.1 Questionnaires Characteristics

Internal consistency (Cronbach's alpha) of the total ASRS scale was .81. This is consistent with previous studies (.82, Reuter et al., 2006; .88, Adler, 2004). The reliabilities for the two subscales inattention (.76) and hyperactivity (.73) were also satisfactory. Internal consistency of the ASRS Screener was acceptable (.6).

The WURS reliability was high (.91). We used 5 subscales as previous studies (Suhr, Zimak, Buelow, & Fox, 2009; Kivisaari, Laasonen, Leppämäki, Tani, & Hokkanen, 2012). The reliabilities for each subscale are presented below (Table 3.1)

Table 3.1: The Items Constituting the Five Subscales of the WURS and the Cronbach's Alphas of Each

Conduct Problems	Impulsivity Problems	Mood Difficulties	Inattention/Anxiety	Academic Concerns
Short-tempered, low boiling point	Trouble with stickto-it-iveness, not following through	Sad or blue, depressed, unhappy	Concentration problems, easily distracted	Overall a poor student, slow learner
Temper outbursts, tantrums	Acting without thinking, impulsive	Low opinion of self	Anxious, worrying	Trouble with math and numbers
Stubborn, strong willed	Tend to be immature	Guilty, regretful	Nervous, fidgety	Did not achieve up to potential
Disobedient with parents, rebellious	Lose control of self	Unpopular with other children, did not keep friends for long	Inattentive, daydreaming	
Irritable	Tend to be or act irrational			
Moody, have ups and downs	Trouble seeing things from other's view			
Angry				
Trouble with authority				
a = .86	*a = .81*	*a=.77*	*a=.74*	*a=.65*

3.4.2 ASRS

The mean score in the overall ASRS score was 31.83 (SD= 8.5). The range of scores on the ASRS varied from 6 to 62 (Figure 3.1). The mean score in the inattention subscale was 17.48 (SD= 5.1, min= 4,max= 33) and the hyperactivity subscale 14.34 (SD= 5, min= 1,max= 33).

The mean score in the ASRS screener was 11.52 ($SD=$ 3.47,$min=$ 1,$max=$ 22).

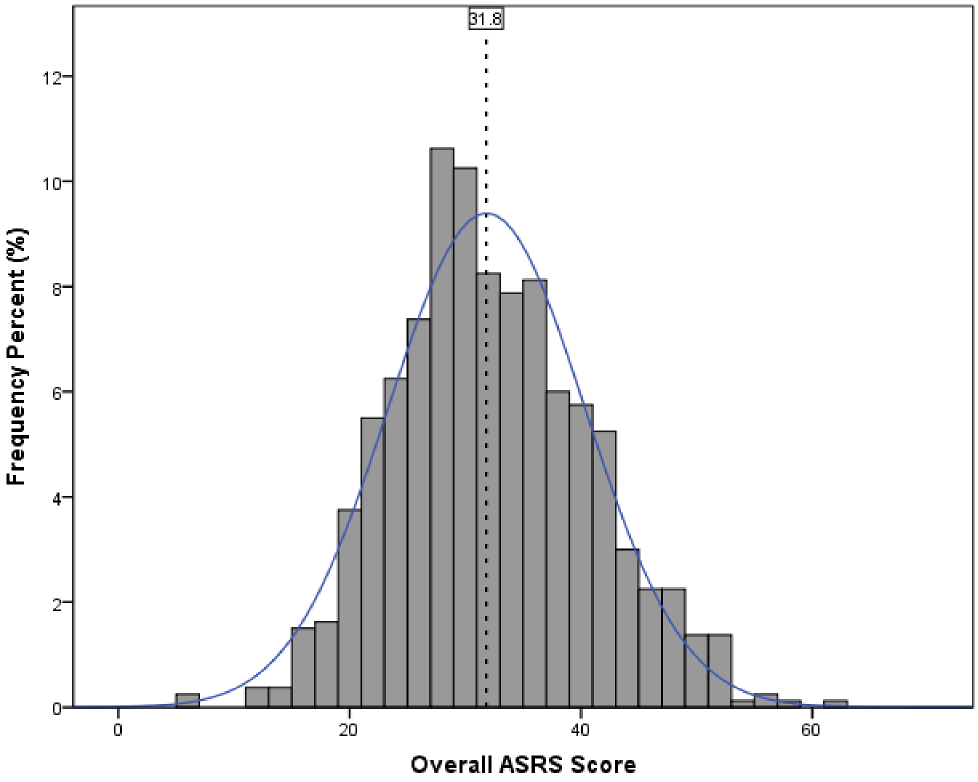


FIGURE 3.1: Histogram showing the distribution of ASRS Scores.

The two ASRS subscales were strongly correlated, r(800)=.418, p<.01. The overall ADHD score was correlated with both the inattention (r(800)=.844, p<.01) and the hyperactivity subscale (r(800)=.840, p<.01). The ASRS Screener was associated with the ASRS (r(800)=.820, p<.01) and the inattention (r(800)=.816, p<.01) and hyperactivity (r(800)=.564, p<.01) subscales.

The effect of mental or neurodevelopmental disorder diagnosis on the ASRS score was investigated. Participants previously diagnosed with a mental health disorder ($M=$ 36.15, $SD=$ 9.31, $min=$ 12,$max=$ 62) had significantly higher overall ASRS scores than participants without a past or current diagnosis ($M=$ 31.14, $SD=$ 8.16, $min=$ 6,$max=$ 56), (t(798)= -5.86, p<.01).

Participants diagnosed with a mental health disorder had also higher score on the ASRS Screener, $t(798) = -5.7$, $p < .01$) (Table 3.2)

Table 3.2: Mean Questionnaire Scores for participants with and without mental health disorders

Group	ASRS Score	Inattention Subscale	Hyperactivity Subscale	ASRS Screener	WURS Score
Previously Diagnosed With Mental Health Disorder (N= 110)	36.15 (9.31)	19.95 (5.33)	16.21 (5.35)	11.25 (3.27)	36.85 (16.68)
No Previous Diagnosis (N= 690)	31.14 (8.16)	17.1 (4.93)	14.06 (4.9)	13.25 (4.13)	24.34 (15.6)

Using the standard cutoff point of 4 answers in the shaded boxes, ASRS Screener identified 70% of the participants as highly likely to have ADHD. When the subjects previously diagnosed with other mental health disorders were removed from the analysis, the percentage dropped to 68%.

Percentiles were calculated for the ASRS using the data of participants never diagnosed with other disorders (Table 3.3).

Table 3.3: Percentiles for ASRS and Subscales

Percentiles	ASRS	Inattention Subscale	Hyperactivity Subscale
25	25	13	11
50	30	17	14
75	36	20	17

The effect of gender on the questionnaires administered was also investigated. There was no significant difference between makes and females in the ASRS Screener, $t(798)=1.31$, $p= .189$) ,the ASRS, $t(798)=-1.46$, $p= .145$) and the inattention subscale $t(798)=.342$, $p= .733$). The difference between males and females was significant in the hyperactivity subscale with females scoring higher than males, $t(798)=-2.83$ $p= .005$).

Table 3.4: Gender and Mean ASRS Score

Gender	ASRS	Inattention Subscale	Hyperactivity Subscale	ASRS Screener
Males (N= 232)	31.15	17.57	13.57	11.78
Females (N= 568)	32.11	17.44	14.67	11.42

3.4.3 WURS

The mean score in the WURS was 26.1 (*SD*=16.35). The range of scores varied from 0 to 81 (Figure 3.2).

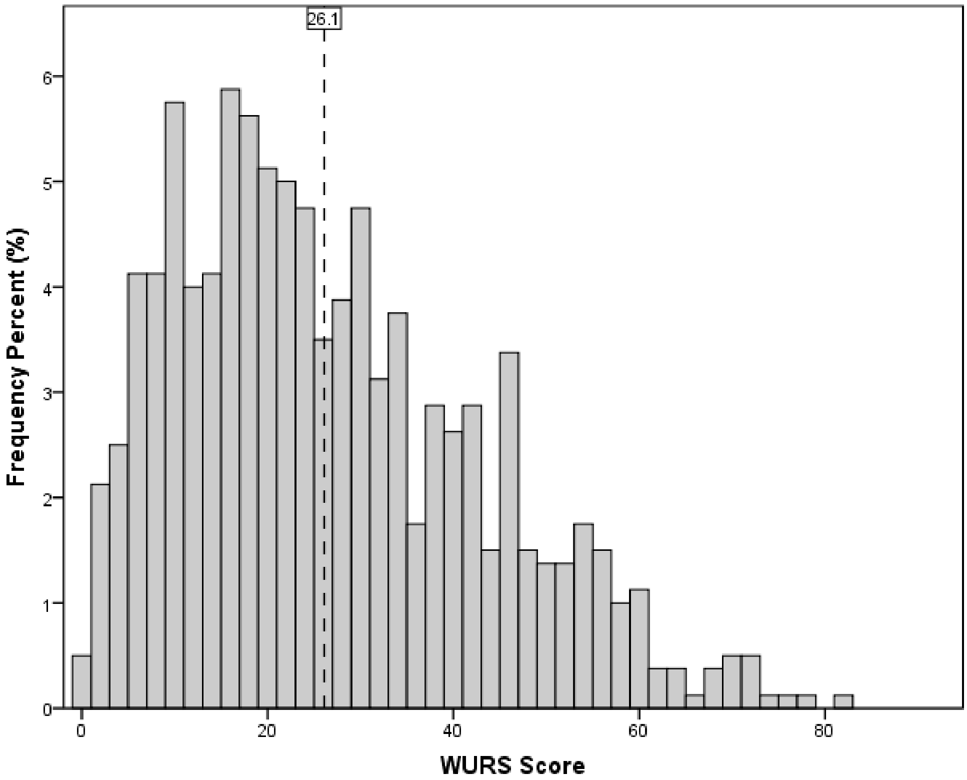


Figure 3.2: Histogram showing the distribution of WURS Scores.

The mean scores for each of the five WURS subscales are presented in Table 3.5

The effect of mental or neurodevelopmental disorder diagnosis on the WURS score was investigated. Participants previously diagnosed with a mental health disorder

Table 3.5: The mean scores in the five WURS Subscales

WURS Subscale	Conduct Problems	Impulsivity Problems	Mood Difficulties	Inattention/Anxiety	Academic Concerns
Mean (SD)	9 (6.66)	5.34 (4.55)	4.99 (3.8)	5.12 (3.7)	1.6 (2.24)

(M= 36.85, SD= 16.68, min= 0, max= 81) had significantly higher scores than participants without a past or current diagnosis (M= 24.34, SD= 15.63, min= 0,max= 77), (t(798)= -7.72, p<.01).

No difference was found between males (M= 27.3, SD= 15.5, min= 0,max= 71) and females (M= 25.6 SD= 16.7, min= 0,max= 81) in WURS, t(798)= 1.37, p=.173.

Using the cutoff point of 46, WURS identified 99 participants as highly likely to have ADHD. 27 of these participants reported being previously diagnosed with a mental health disorder.

3.4.4 The relationship between ASRS and WURS

The ASRS was strongly correlated with the WURS (Figure 3.3), (r(800)=.512, p<.01).

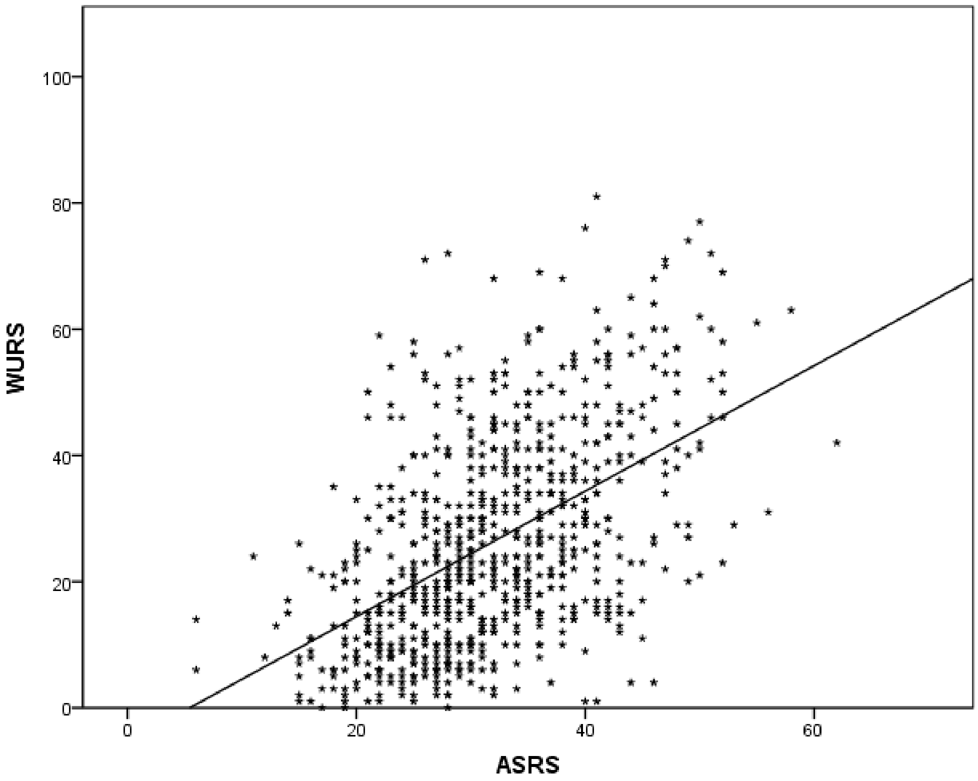


Figure 3.3: Scatterplot showing relationship between ASRS and WURS.

A strong correlation was found between the ASRS and all the WURS subscales (at p<.01 level). Higher ASRS scores were associated with more childhood ADHD symptoms as assessed on the WURS. The WURS was also significantly correlated with the inattention (r(800)=.445, p<.01) and the hyperactivity (r(800)=.416, p<.01). subscales of the ASRS.

The Kruskal-Wallis H test was used to examine whether questionnaires scores differed based on age. Fewer symptoms were reported in the older age group, but the difference was not statistically significant (Table 3.6).

Table 3.6: Characteristics of Age Groups

Age Group	ASRS Score	WURS Score	Frequency
18-24	32.05 (SD= 8.53)	26.7 (SD= 16)	440
25-34	31.8 (SD= 8.3)	25.6 (SD= 16.45)	158
35-54	31.97 (SD= 8.66)	26 (SD= 16.87)	156
55+	29.3 (SD= 9)	21.87 (SD= 17.82)	46

3.5 Discussion

The aim of this study was to investigate the distribution of ADHD traits in the general population in Sheffield using three standardised questionnaires; the ASRS, the ASRS Screener, and the WURS. All questionnaires showed high internal consistency and identified individuals with varying levels of ADHD. All the questionnaires used in this study were strongly correlated with each other.

Previous studies have found that individuals with depression or other psychiatric diagnoses often have high scores in ADHD screening questionnaires (McCann et al., 2000; Das, Cherbuin, Butterworth, Anstey, & Easteal, 2012) and questionnaires, such as the ASRS and WURS have been previously found to misclassify individuals with other disorders as having ADHD (Roy-Byrne et al., 1997; Caci, Bouchez, & Baylé, 2010). This finding was consistent with our results. Participants previously diagnosed with mental health or developmental disorders had higher scores in all three questionnaires administered in our study. It is, therefore, advised to exclude participants with existing or past mental health conditions when investigating subclinical ADHD-like traits.

Slightly higher means of ASRS scores were reported here than the ones in the existing literature. Initially, this was attributed to the presence of participants previously diagnosed with mental health and developmental disorders. However, even when these participants were excluded, the mean ASRS score was slightly higher than scores reported in previous studies. One possible explanation for this is the nature of online studies and the characteristics of participants subscribed to the volunteers' list. The study was advertised midweek via email. It is possible that people with higher ADHD traits are more likely to get distracted by such events and proceed to filling in an online questionnaire. Furthermore, internet addiction is more common in individuals with ADHD (Ko, Yen, Yen, Chen, & Chen, 2012). As a result, using an online test or survey is likely to include a higher number of participants with more ADHD-like traits. Another possible explanation for the higher mean scores reported in our study is the age of the participants. The sample in our study was younger compared to previous studies that employed ASRS (Reuter et al., 2006; Stark et al., 2011). Even though the difference between age groups not statistically significant in our case, the mean scores in all three questionnaires were lower in the older group. As a result, a study recruiting older participants could identify smaller number of ADHD like traits.

Even though the mean scores in the ASRS in our study were higher than previous studies, studies in clinical populations report even higher scores in groups of adults diagnosed with ADHD. More specifically, a study by Halleland, Lundervold, Halmøy, Haavik, and Johansson (2009) found that mean of total ASRS score on ADHD group was 45.8 (*SD*=12.2), inattention was 23.7 (*SD*=6.6) and hyperactivity was 22.1 (*SD*=6.8). Other studies also report similar scores; ASRS mean of 40.6 (*SD*=7.8) (Wilens et al., 2008) and 42.5 (Rydén, Johansson, Blennow, & Landén, 2009).

The two ASRS subscales were strongly correlated. This is similar to the results of Caci et al., 2010; Reuter et al., 2006 and Stark et al., 2011 who reported an inter-correlation of the two scales of .40, .61, and .56 respectively. However, in some people there are differences between subscale scores, which could possibly allow us to investigate differences between subtypes in a future study.

No significant differences were identified between females and males on the ASRS, the ASRS Screener, and the WURS. The mean scores for males and females were similar. The only exception was the hyperactivity scale of the ASRS. Females had higher scores than males. This was a surprising finding. Previous research examining gender differences on children and adults with ADHD has found the opposite; females tend to have lower hyperactivity scores (Gaub & Carlson, 1997; Gershon & Gershon, 2002; Levy et al., 2005). This unusual result in our study could be due to sample differences. 568 out of 800 participants were female. Since the population we studied was not clinical and the subjects were undiagnosed, it is possible that there is a difference in hyperactivity scores between males and females at a subclinical level. In fact, in a recent study by S. Gray, Woltering, Mawjee, and Tannock (2014) using a sample of 135 college students, females reported a higher frequency of ADHD symptoms on the ASRS. This finding, however, is not consistent in published studies using the ASRS. For example, Das et al. (2012) did not identify any gender differences in the ASRS Screener, or any of the ASRS subscales. The lack of gender difference in the overall ASRS score and the WURS is consistent with previous studies investigating ADHD traits in the general population (Das et al., 2012). Even though ADHD seems to be more common in males, especially in children (Kessler, Berglund, et al., 2005; Simon, Czobor, Bálint, Mészáros, & Bitter, 2009), research on subclinical populations show an even distribution of ADHD traits across genders (Das et al., 2012; Rao & Place, 2011; de Zwaan et al., 2012; Rao & Place, 2011).

Differences in mean scores in ADHD traits in the age groups that took part in our study as measured in all questionnaires were examined. No significant differences were found. However, the scores in both the ASRS and the WURS was slightly lower in the older age group (55+).

A limitation of the study is the nature of the administered questionnaires; they were all self-reported measures. However, there is evidence showing that adults can self-report symptoms of ADHD with high accuracy, without exaggerating or feigning them (S. Gray et al., 2014).

3.5.1 Implications for this thesis

The ASRS Screener internal reliability was acceptable (.6) but slightly lower than other studies. Kessler, Adler, et al. (2005) reported that the internal consistency reliability of ASRS Screener was in the range 0.63-0.72. Furthermore, the ASRS Screener using the recommended cut-off score, diagnosed the majority of our sample as highly likely to have ADHD. Due to these two factors we observed in the ASRS Screener, the 18 question version of the ASRS was chosen as a screening tool for ADHD like traits in the studies described later on in this thesis. ASRS has been found to be a well-validated tool used for the assessment of current ADHD symptoms in adults (Kessler, Berglund, et al., 2005; Kessler, Adler, et al., 2005). The strong correlation between the ASRS and the WURS provides further validation that the ASRS measures ADHD-like traits. Furthermore, the full version of the ASRS, unlike the ASRS Screener, allows the measurement of inattention and hyperactivity subscores, which could provide useful insights to possible subtype differences.

The higher ADHD scores observed in participants with a history of mental health disorders or other developmental disorders, led us to recruit subjects without any other disorders in the studies described in the following chapters.

Moreover, the lack of a significant gender and age effect on the questionnaire scores, would allow us to recruit participants from both genders and various age groups in our following studies.

After excluding participants previously diagnosed with other disorders, percentiles for the ASRS and its subscales were compiled. The mean ASRS score of 36, which belonged in the 75th percentile was used as a cutoff point in future studies. Previous studies have used lower cutoff points (e.g. 34 according to Stark et al., 2011), but after finding elevated scores in our sample, part of which would take part in future studies, the cutoff point was adjusted.

3.6 Conclusion

The results from our online study showed that the ASRS can be successfully used to identify individuals with high ADHD traits. The distribution of the scores allows us to recruit participants with varying ADHD traits and examine their performance on tasks sensitive to SC function, which are described in the following chapters.

Chapter 4

ADHD traits and distractibility

4.1 Chapter Summary

Distractibility is regarded as a defining symptom of ADHD. Despite this, studies investigating distractibility in ADHD populations remain inconclusive. Our aim here was to examine the performance of a sub-clinical sample on a new distractibility paradigm with far peripheral distractors and correlate it with the level of ADHD symptoms. In the first experiment we tested 34 healthy adults with low, mild, and high ADHD traits on a sustained attention task which required target selection in the presence of intermittent far peripheral distractors. The effect of distractors on performance was correlated with extent of ADHD traits. Higher ADHD traits were associated with a lower 'performance cost' of distractors. This counter intuitive finding was examined in two further experiments. The second experiment changed the onset time of the distractors so that they did not predict selection targets. This removed the relationship between ADHD traits and

distractability. The third experiment changed target frequency, making the task a continuous decision task. This change makes the relationship with extent of ADHD traits disappear. Overall, our results suggest two things: (1) Despite being a defining feature, high ADHD traits in a subclinical sample do not necessarily predict greater distractibility, and (2) When participants with higher ADHD-like traits process distractors differently it may be due to the stimulus contingencies of the environment.

4.2 Introduction

Attention-deficit hyperactivity disorder (ADHD) is a behavioural disorder defined by either an attentional dysfunction, hyperactive/impulsive behaviour or both (DSM-V American Psychiatric Association (2013)). ADHD is the most common neurodevelopmental disorder (Faraone, Sergeant, Gillberg, & Biederman, 2003b; Barkley, 1997) and its worldwide prevalence in children and adolescence is between 0.85 % and 10 % (Ford, Goodman, & Meltzer, 2003a; Tannock, 1998; Polanczyk et al., 2007; Seixas et al., 2012). In roughly half of the children diagnosed with ADHD, symptoms persist into adulthood (T. J. Spencer et al., 2002). Therefore, ADHD has also been validated as an adulthood disorder (Faraone & Biederman, 2005b), with remaining symptoms in adults including distractibility and difficulties with maintaining goal-directed behaviour rather than hyperactivity.

4.2.0.1 Distractibility in ADHD

Distractibility is often described as the main symptom of ADHD. Reports from teachers and parents suggest that children with ADHD have difficulties paying attention to one task without getting distracted by external events (Adler, 2004). This manifestation of the disorder is understood to play an important role in the negative impact that ADHD has on school and academic performance. Even though distractibility is a well-established symptom of ADHD, attempts to measure it in the lab have yielded mixed results (Fassbender et al., 2009; Gumenyuk et al., 2005; van Mourik, Oosterlaan, Heslenfeld, Konig, & Sergeant, 2007).

Typical visual tasks that assess sustained attention and distractibility require the participant to sustain attention over a continuous stream of stimuli (single letters, shapes, or digits which are presented serially) and to respond to a specific target (Keilp, Herrera, Stritzke, & Cornblatt, 1997; Shalev, Ben-Simon, Mevorach, Cohen, & Tsal, 2011). Sustained attention can be characterised as the ability to concentrate on a specific stimulus over a period of time while ignoring distracting stimuli (Manly, Robertson, Galloway, & Hawkins, 1999; Nichols & Waschbusch, 2004; Shalev et al., 2011). When attending to a target stimulus in the environment, individuals must select the relevant information on which to focus (attended stimuli), while simultaneously ignoring irrelevant information (distractors) (Godijn & Theeuwes, 2003; Nichols & Waschbusch, 2004). The most commonly used sustained attention tasks are the the Continuous Performance Task (CPT; Rosvold, Mirsky, Sarason, Bransome, & Beck, 1956; Cornblatt, Risch, Faris, Friedman, & Erlenmeyer-Kimling, 1988) and the Sustained Attention to Response Task (SART;

Robertson, Manly, Andrade, Baddeley, & Yiend, 1997). Performance on this task is measured by reaction times (RT), omission errors (times the participant fails to respond to the target stimulus), and commission errors (times the participant responds to a non-target stimulus). Distracting stimuli might, therefore, have an effect on sustained attention by increasing the rate of omission errors and commission rates. In addition to that, distractibility can be assessed by looking at the RT. More specifically, on trials when these lapses in attention occur, participants may miss cues to initiate responding, yielding longer RT values for those trials. This leads not only to an increase of the overall mean reaction time across trials, but also the range of reaction times thus resulting in greater intra-individual variability (RTSD) (Adams, Roberts, Milich, & Fillmore, 2011; Fassbender et al., 2009). Therefore, response time variability can be another measure of distractibility.

Studies on ADHD adults and children have found both higher rates of omission errors (Metin, Roeyers, Wiersema, van der Meere, & Sonuga-Barke, 2012), augmented RTs (Teicher, Ito, Glod, & Barber, 1996), and increased RT variability (Epstein et al., 2011b; Adams et al., 2011; Vaurio, Simmonds, & Mostofsky, 2009). However, the majority of tasks measuring distractibility have low ecological validity (Nichols & Waschbusch, 2004; Barkley & Ullman, 1975; Barkley, 1991). Most sustained attention tasks are administered in laboratory conditions and are free of distracting stimuli (apart from the non-target trials).

Studies using distractibility paradigms with more ecologically valid distractors have yielded mixed results. Uno et al. (2006) developed a noise-generated CPT, which included neutral, geometric stimuli (target/non-target), and auditory and visual distractors, which could be either tones or irrelevant letters). Uno and colleagues found that the addition of visual distractors led to a significant decrease in the number of omission errors in children with ADHD. On the other hand, healthy controls showed an increased in errors in trials with distractors. This finding was contrary to the results reported by Berger and Cassuto (2014), who used a similar task with visual distractors. Adolescents with ADHD were more impaired on a CRT when visual distractors were introduced. Cassuto, Ben-Simon, and Berger (2013) added environmental distractors in a continuous performance task and found significant differences in ADHD and control groups. More specifically, the addition of visual and auditory distracting stimuli which were not part of the non-target stimuli increased the number of omission errors in the ADHD group.

4.2.0.2 Collicular distractors

In everyday life, distractors can appear in different modalities, be irrelevant to the task, or appear in the far peripheral visual field (e.g., child attending to the teacher while other children are playing outside the classroom). The majority of tasks used in empirical investigations of distractibility in ADHD present stimuli in the central visual field while distractor stimuli are presented to the fovea or parafoveal area, (e.g. 4-8 degrees Loe et al. (2009). The maximum eccentricity reported so far was 21 degrees by Laasonen and colleagues (Laasonen et al., 2012). However, a typical visual field, is much larger than this, extending up to 200° laterally and 130° vertically (Henson, 2000). Neuroimaging work and single-cell recordings have found that peripheral and central visual fields project to different brain regions. More specifically, the central visual fields project mostly towards the ventral cortical processing streams, while the peripheral fields towards the dorsal cortical processing streams (Lavie, 2005; Overton, Dean, & Redgrave, 1985; Q. Chen, He, Chen, Jin, & Mo, 2010). It has been shown that there are stronger projections to the superior colliculus in the midbrain from the nasal hemiretina (which receives stimulation from the temporal hemifield) than from the temporal hemiretina (Sylvester et al., 2007; Posner, 1980). According to Rafal et al. (Rafal, Henik, & Smith, 1991), stimuli presented in the temporal hemifield drive a stronger tendency to make a saccade towards them than stimuli appearing in the nasal hemifield. The main mechanism behind this finding according to these authors is the neural pathway from the retina to the superior colliculus. No study so far has investigated distractibility in ADHD using far peripheral distractors. Neuroimaging work and single-cell recordings have found that peripheral and central visual fields project to different brain regions. More specifically, the central visual fields project mostly towards the ventral cortical processing streams, while the peripheral fields towards the dorsal cortical processing streams (Lavie, 2005; Overton et al., 1985; Q. Chen et al., 2010).

It has been shown that there are stronger projections to the superior colliculus in the midbrain from the nasal hemiretina (which receives stimulation from the temporal hemifield) than from the temporal hemiretina (Kristjánsson, Vandenbroucke, & Driver, 2004; Posner & Cohen, 1984). According to Rafal et al. (1991), stimuli presented in the temporal hemifield drive a stronger tendency to make a saccade towards them than stimuli appearing in the nasal hemifield. The main mechanism behind this finding according to these authors is the neural pathway from the retina to the superior colliculus.

The SC is known to play a critical role in reflexive, non-conscious orienting of attention (Rafal, Posner, Friedman, Inhoff, & Bernstein, 1988; Rafal, Smith, Krantz, Cohen, & Brennan, 1990). Rafal and colleagues (1988) specifically tested the role of the SC in non-conscious processing by presenting stimuli to the hemianopic fields of 3 patients. Retino-tectal projections are predominantly from the temporal rather than the nasal visual field. Consequently,by presenting stimuli either in the temporal or the nasal field under monocular viewing conditions, the investigators were able to establish the contribution of the SC. The results showed that saccadic movements towards targets in the intact visual field were inhibited only by distractors presented in the temporal hemianopic field. No effect was found when the distractors were presented in the nasal hemianopic field. This finding supports that the involvement of the SC in exogenous, unconscious attention-shifting.

Although clinical diagnoses are defined categorically, ADHD psychopathology can also be viewed dimensionally, with inattentive and hyperactive-impulsive symptoms distributed continuously in the general population (Rodriguez 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 (J. Martin et al., 2014; H. Larsson et al., 2012; Levy et al., 1997).

4.2.1 Current Study

To our knowledge, research on perceptual function in ADHD has involved only a small portion of the visual field and the sensitivity of non-central vision to task irrelevant distractors has not been examined in this population. The present study compared sustained attention and distractibility in adults with varying levels of ADHD traits, as indicated by distraction of visual task performance by task-irrelevant far-peripheral stimuli sensitive to collicural function.

4.3 Experiment 1

4.3.1 Methods

4.3.1.1 Participants

34 participants (23 female) were recruited from the volunteers' list of the University of Sheffield. The ages of the participants varied from 18 to 54 (M = 25.09, SD = 9.4). All subjects were right-handed, had normal or corrected-to-normal vision and were naive as to the purpose of the experiment. All the participants were healthy and none were previously diagnosed with ADHD or any other major mental illness. The subjects all gave their informed consent to take part in the experiment and the procedures were in accordance with the ethical standards of the Department of Psychology Ethics Sub-Committee and British Psychological Society Guidelines.

4.3.1.2 Materials

The experiment took place in a modified immersive dome (Figure 4.1), which wraps around the subject at a distance of 150 cm from the subject's head, and allows images to be projected over a horizontal range of 240° and a vertical range of 100° (as described in Yates & Stafford (2011)). All stimuli were presented on a black background and luminance was kept constant.

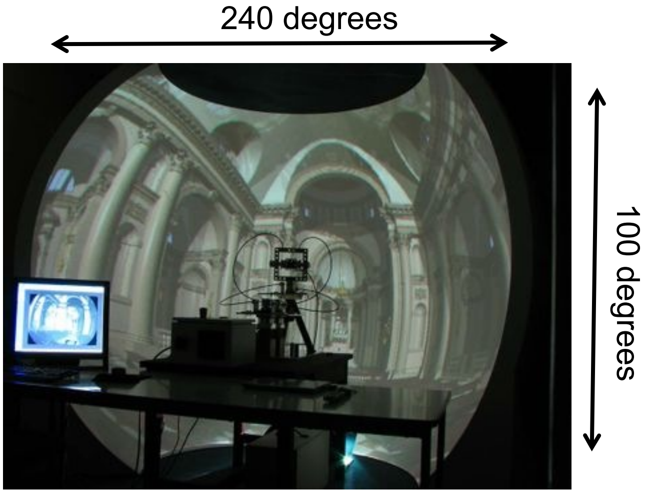


FIGURE 4.1: modified immersive Dome

A modified version of the SART with far-peripheral distractors was administered. In the original task participants are presented with a series of numbers of 1 to 9 and are instructed to respond by pressing a key whenever a number appears but to withhold their response when the number 3 appears. In our modified version participants were instructed to respond to all numbers by pressing "c", while press "m" for number 3. There were 225 stimuli overall and 11% were target presentations (number 3). Each stimulus remained on the centre of the screen for 1s and was followed by 1s of blank screen (black screen). The participant was allowed to make a response until the next target appeared. Far peripheral distractors were presented in some of the trials. Distractors appeared randomly with a chance of 10% 75 ms before the stimulus and stayed on for 100ms simultaneously with the central stimulus. The distractors were moving checkerboards and appeared in random positions in the periphery of the subject on the custom dome moving horizontally or vertically (for 7 frames on a 60 Hz display). Checkerboards were used as distractors as there have been found to stimulate the superior colliculus in human subjects (Calvert, Campbell, & Brammer, 2000; Schneider & Kastner, 2005b). The exact location of the peripheral distractors was not recorded but they were programmed to appear in random location in eccentricities over 40°. The size of the distractors was approximately 10 by 10 cm.

ADHD traits were measured with the World Health Organization Adult ADHD Self-Report Scale (ASRS, Kessler, Adler, et al. (2005)). The ASRS contains eighteen items from DSM-IV-TR American Psychiatric Association, 2000 but measures the frequencies of the symptoms. The subjects are asked to report how often they experience each symptom in a period of six months on a five-point Likert scale which ranges from 0 for never, 1 for rarely, 2 for sometimes, 3 for often, and 4 for very often (Kessler, Adler, et al., 2005). The ASRS has a two factorial structure (Reuter et al., 2006) which includes an inattention scale and a hyperactivity/ impulsivity scale. Each subscale contains nine items. The ASRS examines only current adult symptoms of ADHD. The reliabilities (Cronbach's alpha) for the two subscales of inattention (.75) and impulsivity (.77) as well as for the total ASRS (.82) are satisfactory (Reuter et al., 2006).

The original questionnaires are formatted with darkly shaded boxes in certain items which signify more severe symptoms. We removed the darkly shaded boxes in the ASRS-V1.1 to minimise any possibility that the darker shaded areas may motivate symptom exaggeration by the participants.

4.3.1.3 Procedure

Each participant was asked to complete a short practice SART with far-peripheral distractors (18 stimuli) before beginning the main task. After completion of the practice session the full version of the task was administered. The session lasted approximately 8 minutes.

When the participants finished the modified SART they were given a questionnaire which included the ASRS and some demographics questions. Afterwards, they were fully debriefed and thanked for their time.

4.3.2 Tracking eye movements

Eye movements were tracked during the experiment with the SMI Eye-tracking Glasses (SMI SensoMotoric Instruments), a portable, reliable eye tracking system (Mele & Federici, 2012). This was done to ensure that the participants maintained fixation during the task.

4.3.2.1 Data Analysis

Data from one participant were not recorded due to a technical problem, as a result data from 33 participants were included in the analysis. Reaction times from erroneous trials (trials where the participants made a wrong response) were removed from the analysis. In addition to that, RTs over 1s were not included in the analysis. The effect of the distractor was investigated by looking at the difference in RTs ('RT distractor cost'; RT in trials with distractors - RT in trials without distractors), and accuracy ('accuracy distractor cost'; accuracy in trials with distractors - accuracy in trials without distractors; positive values indicate the detrimental effect of distractor).

Intra-individual variability (IIV) was also calculated for each participant, measured by the standard deviation (SD) in the mean RT. The effect of the distractor on IIV was also calculated by measuring the difference in variability in trials with distractors and trials without distractors (IIV in trials without distractors - IIV in trials without distractors).

Eye tracking data were analysed with the SMI BeGaze^{TM} software. Eye tracking data was not recorded for one participant. Data from 6 participants were not included to the analysis due to poor data quality. Consequently, only eye tracking data from 26 participants were analysed. Fixation frequency, blink frequency, and saccade frequency values were calculated for each participant.

4.3.3 Results

4.3.3.1 ASRS scores

Scores on the ASRS checklist varied from 3 to 55 and the mean score was 35.45 (*SD*= 11.14). The maximum possible score on ASRS is 72. The mean score on the inattention subscale was 19.3 (*SD*= 6.64) and the hyperactivity subscale 16.18 (*SD*= 5.85). The two subscales were correlated, $r(33)=.587$, $p<.01$ (2-tailed). The overall ASRS score was correlated with both the inattention ($r(33)=.904$, $p<.01$) and the hyperactivity subscale ($r(33)=.876$, p<.01).

No correlations were found between the gender of the participant and overall ASRS score ($r(33)=-.262$, $p=.071$, 1-tailed). The age was also not correlated with the overall ASRS score ($r(33)=-.123$, $p=.248$, 1-tailed).

4.3.3.2 Reaction Time and Accuracy Data

Reaction time data reported below were normally distributed.

More specifically, skewness (.571), kurtosis (.240), and the Shapiro-Wilk ($S\text{-}W=.971$, $df=33$, $p=.42$) test determined that RT in trials with distractors met the assumption of normality.

RT in trials without distractors also appeared to be normally distributed (skewness:.433, kurtosis: -.359, Shapiro-Wilk:$S\text{-}W=.967$, $df=33$, $p=.5$).

Accuracy data were not normally distributed and were transformed (acsine transformation) prior to the analysis.

4.3.3.3 Distractor Cost on Performance

A paired samples t-test was conducted to examine the effect of the distractor on RT and accuracy in all participants. There was a significant difference in the

RTs in trials without distractors (M=468.51, SD=68.27) and trials with distractors (M=487.61, SD=72.84); $t(33)$= -3.387, p<.01). No difference was found between trials without distractors (M=97.83, SD=.94) and trials with distractors (M=97.82, SD=1.1) in accuracy; $t(33)$= .016, p= .99).

The RT distractor cost was negatively correlated with higher overall ASRS scores ($r(33)$=-.417, p=.016, as shown in Figure 4.2), as well as higher inattention ($p(33)$=-.354, p=.043) and hyperactivity subscale scores ($r(33)$=-.395, p=.023).

4.3.3.4 Modified SART with distractors performance

Total scores on the ASRS were negatively correlated with accuracy in trials when the target was presented ($r(33)$=-.416, p=.003). No difference was found in accuracy in trials without a target ($r(33)$=-.107, p=-.442). ADHD scores were negatively correlated with accuracy on non-distractor trials ($r(33)$=-.296, p=.022). No correlation was found between overall ASRS scores and accuracy in trials preceded by a distractor ($r(33)$=-.243, p=.093). Overall ASRS scores were negatively correlated with distractor cost on RT ($r(33)$=-.417, p=.016).

Higher scores on the inattention subscale of the ASRS were negatively correlated with performance on the modified version of the SART. More specifically, inattention scores were negatively associated with accuracy in target ($p(33)$=-.372, p=.008), but not on non-target trials ($r(33)$=-.099, p=.482). Inattention was also negatively correlated with accuracy on trials that were not preceded by a distractor (r(33)=-.290, p=027). Higher inattention scores were negatively correlated with distractor cost on RT ($p(33)$=-.354, p=.043).

Higher scores on the hyperactivity subscale of the ASRS were also negatively correlated with performance on the task. Higher hyperactivity scores were negatively correlated with accuracy in target trials ($r(33)$=-.373, p=.007). Hyperactivity scores were also negatively correlated with distractor cost on RT ($r(33)$=-.395, p=.023).

No correlation was found between ASRS score and RT in trials preceded by distractors ($r(33)$=-.169, p=.349) and trials without distractors ($r(33)$=.017, p=.926).

Overall ASRS scores were correlated with the effect of the distractor on RT variability ($r(33)$=-.365, p=.037). Inattention subscale scores were also related to distractor effect on RT variability, ($r(33)$=-.364, p=.037). No significant correlation was found between hyperactivity subscale score and the effect of distractors on IIV ($r(33)$=-.157, p=.387).

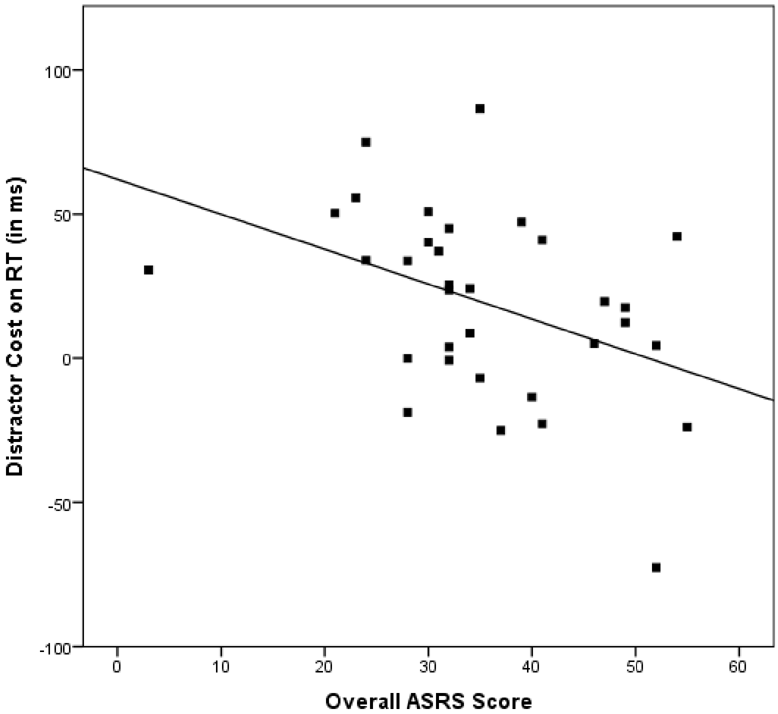


FIGURE 4.2: Scatterplot showing the correlation between overall ASRS score and the RT distractor cost

The accuracy distractor cost was not correlated with overall ASRS score ($p(33)$=-.126, p=.486), or any of the subscales (inattention, $p(33)$=-.033, p=.854; hyperactivity, $p(33)$=-.201, p=.262).

The relationship between ASRS scores and performance in trials with and without distractors are reported in detail on Table 4.1.

Table 4.1: Correlations between ASRS scores and variables in experiment 1

	Inattention	Hyperactivity	Overall ASRS
RT in trials with distractors	-.013	-.307	-.169
IIV in trials with distractors	.025	-.157	-.066
Accuracy in trials with distractors	-.366*	-.288	-.367*
RT in trials without distractors	.154	-.141	.017
IIV in trials without distractors	.344*	.090	.253
Accuracy in trials without distractors	-.397*	-.157	-.316

*Correlation is significant at the 0.05 level (2-tailed).

4.3.3.5 Predicting the effect of the distractor

Linear multiple regression analyses were conducted to test the extent to which the independent variables overall ASRS score, Inattention subscale score, and Hyperactivity subscale score predicted the distractor cost on RT (Table 4.2). Overall ASRS score significantly predicted the detrimental effect of the distractors in scores, β = -.417, $t(32)$ = -2.551, p =.016. Overall ASRS score also explained a significant proportion of variance in the effect of the distractor, R2= .147, F(1, 32) = 6.510, p =.016.

Table 4.2: Linear multiple regression between ASRS scores and distractor effect on RT

Variable	Model 1				
	B	SE(B)	β	t	sig *(p)*
Overall ASRS	-1.21	.475	-.417	-2.55	.016*

Linear multiple regression analyses were conducted to test the extent to which the independent variable overall ASRS score predicted the effect of the distractor on RT variability. overall ASRS score predicted the effect of the distractor on IIV. The results are presented in detail on Table 4.3.

Table 4.3: Linear multiple regression between ASRS scores and distractor effect on RT variability

Variable	Model 1				
	B	SE(B)	β	t	sig *(p)*
Overall ASRS	1.16	.531	-.365	2.18	.037*

4.3.3.6 Eye Tracking Data

A Pearson product-moment correlation coefficient was computed to assess the relationship overall ASRS score and subscale scores with the eye tracking measures. No relationship was found between overall ASRS scores and any of the eye tracking measures; fixation frequency ($r(26)$=-.069, p=.739), blink frequency ($r(26)$=-.108, p=.601), and saccade frequency ($r(26)$=.134, p=.513). A scatterplot summarises the results (Figure 4.3)

No correlation was found between the Inattention subscale score and fixation frequency ($r(26)$=-.042, p=.838), blink frequency ($r(26)$=-.062, p=.763), or saccade frequency ($r(26)$=.128, p=.532).

We found no relationship between Hyperactivity subscale score and any of the eye tracking measures; fixation frequency ($r(26)$=-.084, p=.685), blink frequency ($r(26)$=-.135, p=.511), saccade frequency ($r(26)$=.115, p=.575).

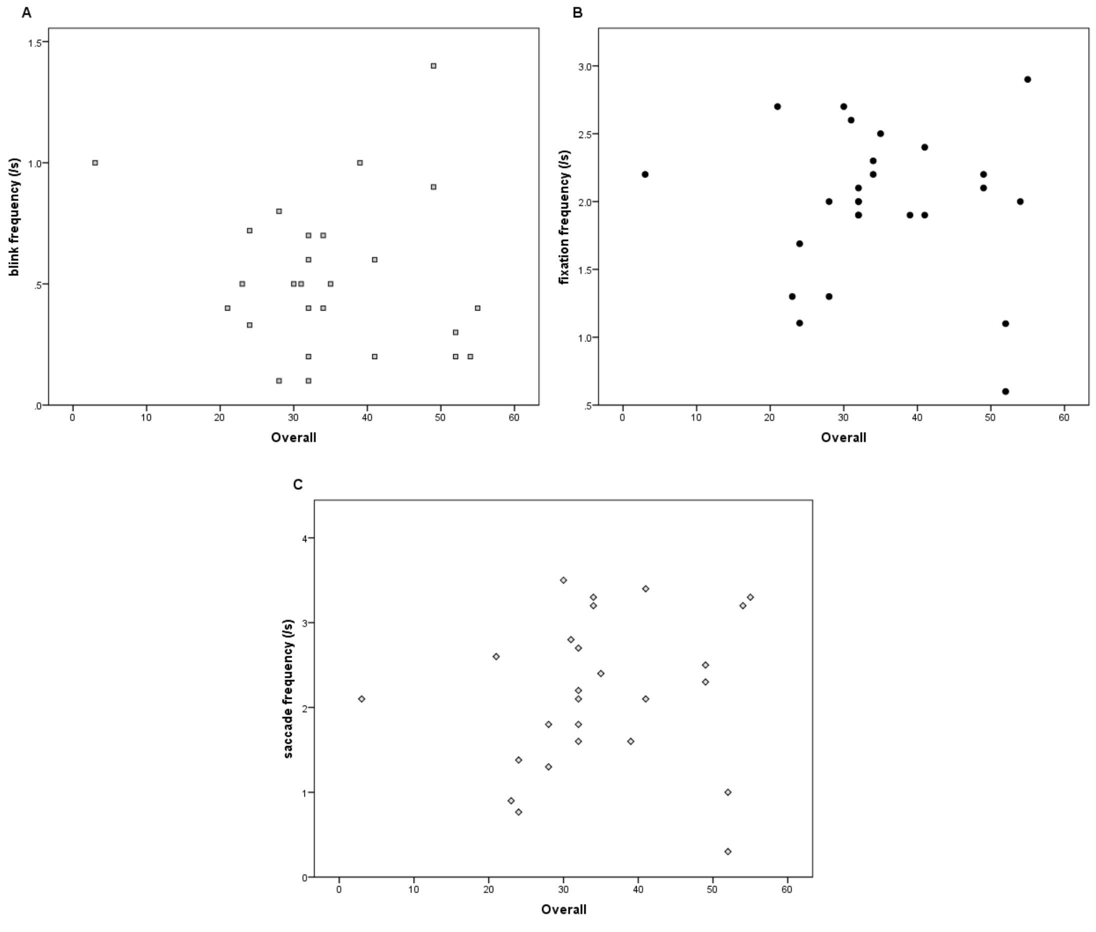


FIGURE 4.3: Scatterplots showing the relationship between overall ASRS score and A) blink frequency (/s), B) fixation frequency (/s), C) saccade frequency (/s)

4.3.4 Interim Discussion

The degree of ADHD traits was negatively correlated with RT distractor cost. Contrary to our hypotheses participants with higher ASRS scores were not more distracted by the moving checkerboards; in fact, their RTs were faster in distractor trials than in trials without distractors. Furthermore, no relationship was found between accuracy distractor cost and ADHD traits.

RT variability is another way to measure distractibility; in our paradigm participants with higher ADHD traits had reduced RT variability in distractor trials compared to participants with low ADHD traits.

A few possible explanations can be given for our unexpected findings. The onset of the distractor was the same in all trials; the moving checkerboard appeared in random positions in the left or right visual field of the participant 75 ms before the main stimulus. It is possible that the distractor had a cueing effect for participants with high ADHD traits, thus lowering their level of distractibility. Previous studies have shown that the informational content of the distractors influences their effect on task performance. More specifically, external distractors to the task which might offer information regarding the time or probability of occurrence of a visual target have a facilitative effect (Wetzel, Widmann, & Schröger, 2012; Parmentier, Elsley, & Ljungberg, 2010).

In our study, only a small percentage of the trials (10%) included distractors. In addition to this, the distractors appeared in different random locations and moved either horizontally or vertically. As a result, our distractors could be seen as novel distractors. Several studies have shown that individuals with ADHD process oddball stimuli differently than healthy individuals (Stevens, Pearlson, & Kiehl, 2007). Furthermore, novel distractors can often be less distracting or even have a facilitating effect on RTs. The novel related facilitation effect observed in the high ADHD group could be explained in terms of arousal. Novel or rare distractors could lead to an increase in motivation in participants with more ADHD-like traits.

A number of studies have found that children with ADHD benefit from extra-task distraction (Zentall & Meyer, 1987; Abikoff, Courtney, Szeibel, & Koplewicz, 1996; Leung, Leung, & Tang, 2000a; van Mourik et al., 2007). Performance between children with ADHD and normal controls can be evened out by the addition of extra-task stimulation. These findings support the optimal stimulation theory which proposes that task performance in children with ADHD benefits from task-unrelated distraction as it leads to an increase in their arousal levels closer to an optimal level (Zentall & Meyer, 1987). The cognitive energetic model can also explain these results as it supports that children with ADHD might suffer from an energetical dysfunction and are, therefore, unable to adjust their activation to meet task demands.

Stochastic resonance is the counterintuitive phenomenon that an optimal amount of noise may under certain circumstances improve cognitive performance (Söderlund, Sikström, & Smart, 2007). White noise, in particular, can be beneficial for cognitive performance in ADHD (Sikström & Söderlund, 2007; Söderlund et al., 2007). No study so far has investigated this phenomenon using visual distractors. It is possible that the onset of the distractor employed in this study had a similar effect to the performance of the participants with high ADHD traits. A way to investigate this further is by modifying the onset of the distractor in a future experiment. More specifically, we propose that the beneficial effect of the distractor will disappear if it appears at the same time or it is perceived as appearing at the same time as the stimulus. Changing the onset of the distractor might have implication for the collicular nature of the stimuli. In particular, studies in mammals have showed that most visually responsive cells in the superior colliculus are transiently activated 40 to 60 ms after the appearance, disappearance, or movement of a stimulus within a specific region of the visual field (Dommett et al., 2005). In the case of hyperactive SC the response to the moving checkerboard could be different, peaking at an earlier stage.

It is possible that the distractor had a negative impact on accuracy. Accuracy in our paradigm was very high across participants. Higher ADHD traits were associated with decreased accuracy in all conditions independently of the distractor's presence. In addition to this, only 11% of the trials included a target and 10% of all trials were preceded by a distractor. As a result, the effect of the distractors on accuracy was not clear. A way to examine the exact effect of the distractors on performance is by modifying the task, so that the chances of a target preceded by a distractor are 50%. This could be done by altering the task. As a result when a distractor appears the chances of responding with each key in the trial that follows would be 50%. This manipulation would make the effect of the distractor on performance more clear; are participants with high ADHD traits faster and more accurate, or do they trade accuracy for speed?

A limitation of our experiment was not measuring whether the participants were aware of the distractors. The distractors were far peripheral and appeared only for a short period of time. Even though some of the participants were asked whether they perceived the distractors, their answers were not formally recorded. The differences between high and low ADHD could be partially explained by the distractors not reaching awareness in individuals with high ADHD groups. Such a finding would be consistent with previous studies investigating the effect of task irrelevant distractors on performance by modulating the working memory workload (Schwartz et al., 2005). In these studies individuals diagnosed with ADHD (Forster, Robertson, Jennings, Asherson, & Lavie, 2014) or healthy volunteers with higher ADHD traits (Forster & Lavie, 2014) were in general more distracted by irrelevant distractors but the effect was significantly reduced when the mental workload was increased. As a result, increased workload was associated with less distractibility in individuals with ADHD.

Small differences were observed between ASRS subscale scores and performance measures; inattention was associated with impaired performance in trials with and without distractors. More specifically, inattention scores were correlated with lower accuracy and increased IIV in trials without distractors. The relationship between distractor cost on IIV and hyperactivity subscores was not significant. Interestingly, even though RT variability is commonly reported in ADHD research (Epstein et al., 2011b, 2011a; Kofler et al., 2013), it is usually observed in patients with ADHD-C or the ADHD-IA subtypes (Tamm et al., 2012). As a result, it is considered a feature of the inattentive spectrum of the disorder. Only a few studies suggest a similar relationship between hyperactive subtype and RT variability (Gómez-Guerrero et al., 2010). Our findings seem to support the hypothesis that RT variability in ADHD stems from inattentiveness.

No relationship was identified between ADHD traits and eye movements during the task. Blink rates, fixation and saccade frequencies were stable across participants with high and low traits. The saccade frequency might initially appear high. However, this was due to the size of stimuli presented on the customised immersive Dome. Subjects had to perform a number of saccades in order to read the numbers presented on the screen. The lack of relation between ASRS scores and eye movement measures suggests that eye movement differences cannot explain the effect of distractors on high and low ADHD traits.

4.4 Experiment 2

In the first experiment we found that, contrary to our hypotheses, higher ADHD traits were negatively correlated with the distractor cost on RT. The onset of the distractor was identified as a possible explanation for this unusual finding. We proposed that the appearance of the distractor 75ms before the main stimulus could have a cueing effect for participants with high ADHD. In experiment 2 we altered the onset of the distractor to 10ms in order to avoid possible cueing effects.

4.4.1 Methods

4.4.1.1 Participants

60 healthy participants (51 female, 8 left-handed) were recruited. The ages of the participants varied from 18 to 27 (M=19.07, SD=1.68). Data from 2 participants were not recorded due to equipment malfunction and data from one participant was not included in the analysis as they did not answer the ASRS. All subjects had normal or corrected-to-normal vision and were naive as to the purpose of the experiment. None of the subjects were previously diagnosed with ADHD or any other major mental illness. The subjects all gave their informed consent to take part in the experiment and the procedures were in accordance with the ethical standards of the Department of Psychology Ethics Sub-Committee and British Psychological Society Guidelines. They were all awarded for their time with credits needed for the completion of their undergraduate degree.

4.4.1.2 Materials

A modified version of the SART with far-peripheral distractors similar to the one used in experiment 1 was administered. The onset of the distractors was altered to 10ms before the appearance of the stimulus to control for possible priming effects. The distractor was perceived as appearing almost simultaneously with the main stimulus.

4.4.1.3 Procedure

Each participant was asked to complete a short practice modified SART with far-peripheral distractors (18 stimuli) before beginning the main task. After completion of the practice session the full version of the task was administered. The session lasted approximately 8 minutes.

When the participants finished the task they were given a questionnaire which included the ASRS and some demographics questions. Afterwards, they were fully debriefed and thanked for their time.

4.4.1.4 Data Analysis

Same as Experiment 1.

4.4.2 Results

4.4.2.1 ASRS Scores

Scores on the ASRS checklist varied from 16 to 56 and the mean score was 34.09 (*SD*= 8.66). The mean score on the inattention subscale was 19.46 (*SD*= 5.41) and the hyperactivity subscale 14.63 (*SD*= 4.46). The two subscales were correlated, $r(57)=.523$, $p<.01$. The overall ADHD score was correlated with both the inattention ($r(57)=.897$, $p<.01$) and the hyperactivity subscale ($r(57)=.844$, $p<.01$).

No correlations were found between the gender of the participant and overall ASRS score. Age and handedness were also not correlated with the overall ASRS score or any of the subscales.

4.4.2.2 Distractor Cost on Performance

A paired samples t-test was conducted to examine the effect of the distractor on RT in all participants. There was a significant difference in the RTs in trials without distractors (M=474.17, SD=73.24) and trials with distractors (M=483.55, SD=78.46); t(57)= -2.221, p=.030).

The RT distractor cost was not associated with ASRS scores (r(57)=.134, p=.319). The accuracy distractor cost was not correlated with overall ASRS score (r(57)=-.010, p=.942).

No relationship was found between ASRS scores and the effect of the distractor on IIV (r(57)=-.064, p=.635).

ASRS scores were positively correlated with RT in trials with distractors (r(57)=.015, p=.321) and trials without distractors (r(57)=-.036, p=.278) (Figure 4.4).

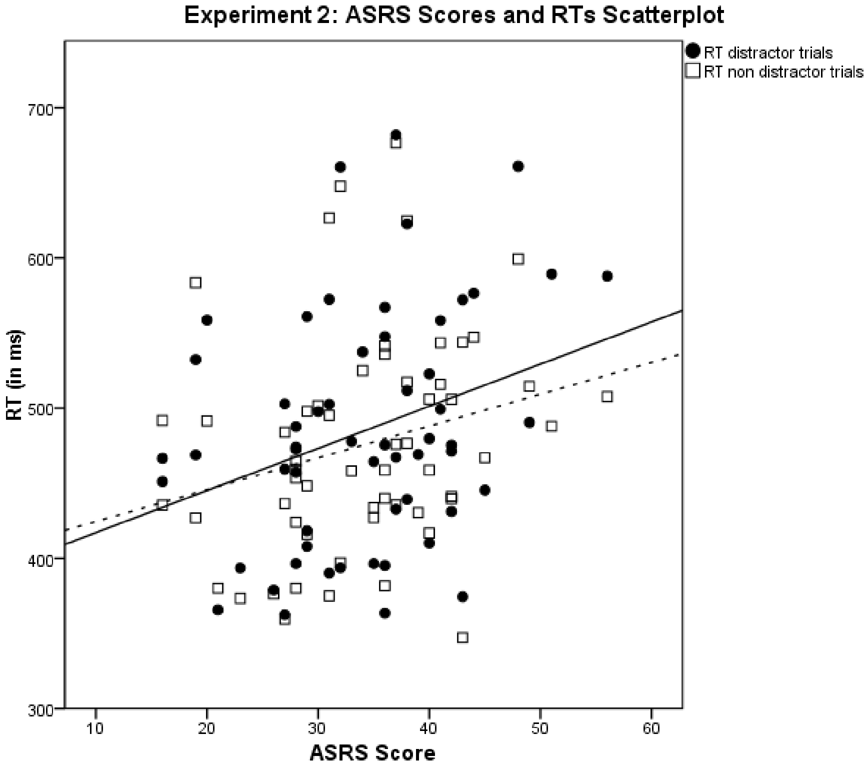


Figure 4.4: Scatterplot showing the relationship between overall ASRS score and the RT in trials with and without distractors in experiment 2

A positive correlation was found between ASRS scores and IIV in trials without distractors (*r*(57)=.020, *p*=.308). No relationship was found between ASRS and IIV in trials with distractors (*r*(57)=.776, *p*=.038).

Accuracy was high across participants in trials with (*M*=99.04, *SD*=2.7) and without distractors (*M*=98.4, *SD*=3.1).

The relationship between task performance and subscale scores was also investigated. The RT distractor cost was not associated with inattention (*p*(57)=.190, *p*=.157) or hyperactivity subscale scores (*r*(57)=.035, *p*=.799).

No relationship was found between the effect of the distractor on accuracy and the inattention (*r*(57)=.026, *p*=.849) and the hyperactivity (*r*(57)=-.042, *p*=.757) subscales.

The relationship between ASRS scores and performance in trials with and without distractors are reported in detail on Table 4.4.

Table 4.4: Correlations between ASRS scores and variables in experiment 2

	Inattention	Hyperactivity	Overall ASRS
RT in trials with distractors	.323*	.209	.321*
IIV in trials with distractors	.028	.032	.038
Accuracy in trials with distractors	.025	.180	.108
RT in trials without distractors	.257	.203	.278*
IIV in trials without distractors	.255	.269*	.308*
Accuracy in trials without distractors	.048	.141	.101

*Correlation is significant at the 0.05 level (2-tailed).

4.4.2.3 Did they see the distractors?

The majority of the participants reported seeing the distractors (52 participants). 34.5% could accurately describe the distractors (moving checkerboards), while 55.2% even though reported seeing the distractors could not describe them in detail. No correlation was found between ADHD traits and seeing the distractors ($r(57)$=.003, p=.985). Reporting seeing the distractors was not related to task performance.

4.4.3 Interim Discussion

In this second experiment we attempted to replicate the results of the first experiment in a sample of healthy volunteers with varying levels of ADHD traits. The relationship between ADHD traits and the distractor cost on RT was removed after modifying the onset of the distractor.

More specifically, trials with peripheral distractors resulted in slower RTs in both participants with high and low ADHD traits. Overall, participants who exhibited higher level of ADHD traits were slower in both distractor and non-distractor trials (Table B.4). No association was found between accuracy and level of ADHD.

Like in experiment 1, far-peripheral, task-irrelevant distractors were shown to have a detrimental effect on performance in all participants. The distractor cost, however, was not associated with ADHD traits. The only difference between the two reported experiments was the onset of the distractor.

Changing the timing of the distractor so that it could no longer predict the appearance of the central stimulus, removed the relationship between ADHD traits and distractor cost on RT. Participants with high ADHD traits no longer showed a benefit in RT in distractor trials. This finding suggests that the unusual finding from experiment 1 could be due to the timing of the distractor. By making the distractor less informative, participants with high ADHD traits performed no differently than participants with low traits.

In general, higher level of ADHD traits was correlated with slower RTs in both distractor and non-distractor trials (Table 4.4). Slower and more variable RTs are often reported in studies using clinical samples of children and adults with ADHD (Alderson, Rapport, Hudec, Sarver, & Kofler, 2010).

No correlation was found between level of ADHD and the distractor cost on accuracy. However, this could be due to ceiling effects. We attempted to solve this issue in experiment 3 described below.

4.5 Experiment 3

High accuracy was observed in both experiments 1 and 2 described above. The nature of task, did not allow us to effectively measure the impact of the distractors on accuracy; target trials were present only 11% of the time and distractors rarely appeared during such a trial.

In this experiment we attempted to look at the effect of distractors on accuracy by modifying the task.

4.5.1 Methods

4.5.1.1 Participants

The same 60 participants as in Experiment 2 took part. Data from 3 participants (different from the ones in Experiment 2) were not recorded due to equipment problems and data from one participant was not included in the analysis as they did not answer the ASRS.

4.5.1.2 Materials

The onset of the distractors was the same as in Experiment 1 (75ms). The nature of the task, however, was changed. The participant was presented with a series of numbers from 1 to 8 and they were instructed to respond by pressing “s” when the stimulus was an odd number and “l” when the stimulus was an even number. The chances of being presented with an even or an odd number were equal. This reduced the chances of responding correctly by chance after being presented with a distractor and allowed us to examine the effect of the distractor on accuracy.

4.5.1.3 Procedure

The participant were first given a practice test which included 16 trials. Then the main task began. All participants were instructed to respond as quickly and as accurately as possible. After completing both tasks, they were given a copy of the ASRS and a demographics questionnaire. All participants were asked whether they perceived the distractors and were asked to describe them to the experimenter.

4.5.1.4 Data Analysis

Same as Experiment 1.

4.5.1.5 ASRS Scores

Scores on the ASRS checklist varied from 16 to 56 and the mean score was 33.71 (*SD*= 8.62). The mean score on the inattention subscale was 19.02 (*SD*= 5.17) and the hyperactivity subscale 14.7 (*SD*= 4.7). The two subscales were correlated, $r(56)$=.516, p<.01. The overall ADHD score was correlated with both the inattention ($r(56)$=.884, p<.01) and the hyperactivity subscale ($r(56)$=.855, p<.01).

No correlations were found between the gender of the participant and overall ASRS score. Age and handedness were also not correlated with the overall ASRS score or any of the subscales.

4.5.1.6 Distractor Cost on Performance

A paired samples t-test was conducted to examine the effect of the distractor on RT in all participants. There was a significant difference in the RTs in trials without distractors (*M*=610.04, *SD*=75.87) and trials with distractors (*M*=619.02, *SD*=81.96); *t*(56)=-2.025 , *p*=.048). A paired samples t-test was conducted to examine the effect of the distractor on accuracy. The difference between accuracy in non distractor (*M*=94.32, *SD*=5.57) and distractor (*M*=93.57, *SD*=7.6) trials was not statistically significant; *t*(56)=1.094 , *p*=.279).

The RT distractor cost was not associated with ASRS scores (*r*(56)=.042, *p*=.757, as shown in figure 3), inattention (*p*(56)=-.005, *p*=.973) or hyperactivity subscale scores (*r*(56)=.074, *p*=.586).

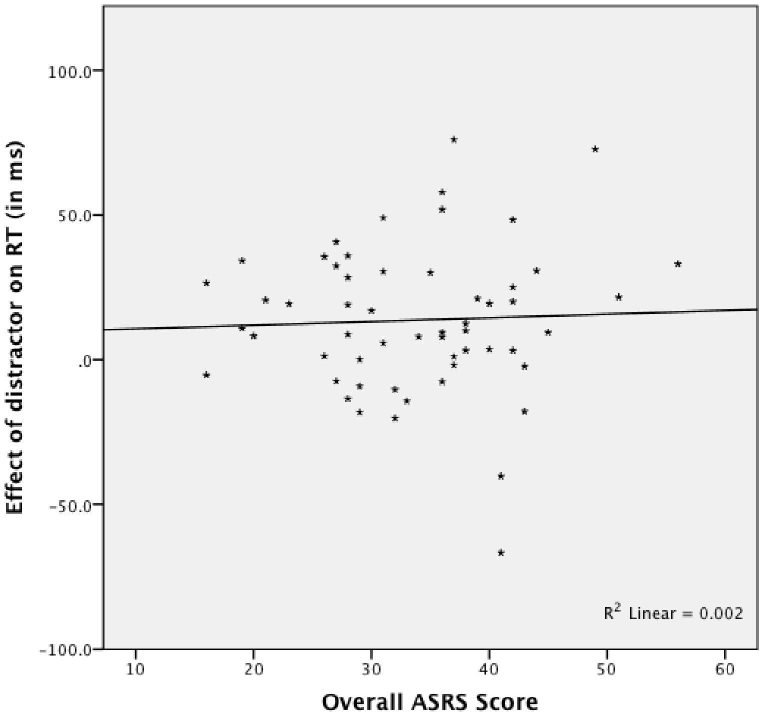


FIGURE 4.5: Scatterplot showing the relationship between overall ASRS score and the RT distractor cost in experiment 3

The accuracy distractor cost was not correlated with overall ASRS score ($r(56)$=-.192, p=.157). No relationship was found between the effect of the distractor on accuracy and the inattention ($r(56)$=-.112, p=.410) and the hyperactivity ($r(56)$=-.238, p=.077) subscales.

Overall ASRS scores were not correlated with the effect of the distractor on IIV ($r(56)$=-.049, p=.721). No association was found between ASRS subscales and the effect of the distractor on IIV.

Higher ASRS scores were associated with lower accuracy levels and slower reaction times in trials with distractors. The relationship between ASRS scores and performance in trials with and without distractors are reported in detail on Table 4.5.

TABLE 4.5: Correlations between ASRS scores and variables in experiment 3

	Inattention	Hyperactivity	Overall ASRS
RT in trials with distractors	.302*	.276*	.345**
Accuracy in trials with distractors	-.255*	-.238	-.283*
RT in trials without distractors	.329*	.265*	.355**
Accuracy in trials without distractors	-.241	-.102	-.205

*Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).

In trials with distractors higher ASRS scores were correlated with lower accuracy levels and slower reaction times (Figure 4.6).

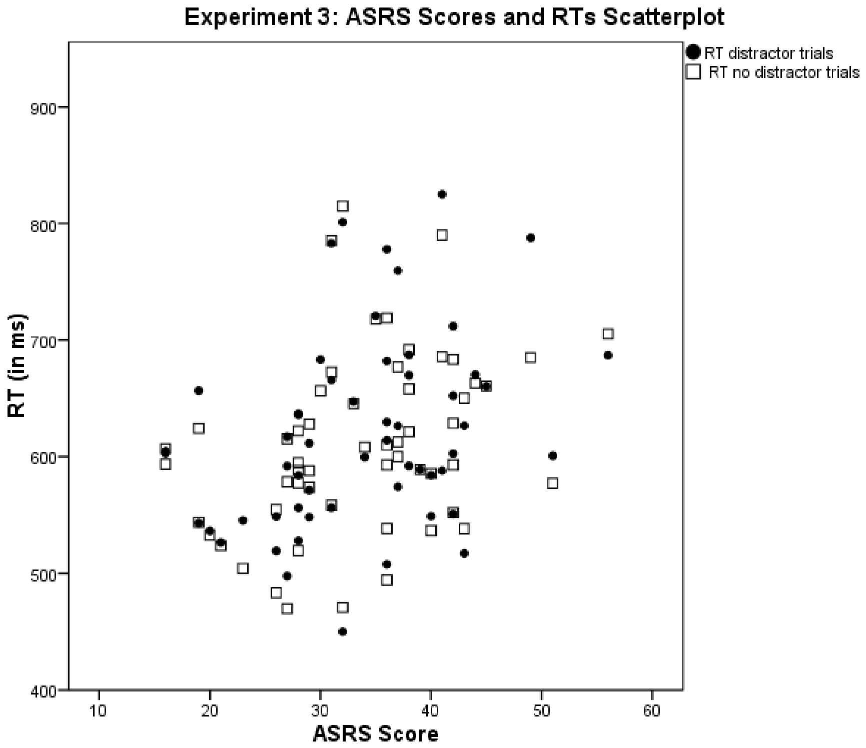


Figure 4.6: Scatterplot showing the relationship between overall ASRS score and the RT in trials with and without distractors in experiment 3

4.5.1.7 Did they see the distractors?

The majority of the participants reported seeing the distractors (52 participants). 36.8% could accurately describe the distractors (moving checkerboards), while 54.4% reported seeing the distractors but could not describe them in detail. No correlation was found between ADHD traits and seeing the distractors ($r(57)$=-.022, p=.874). Reporting seeing the distractors was not related to task performance.

4.6 Interim Discussion

In this experiment, we modified our paradigm so that we could examine the effects of far-peripheral distractors on accuracy as well as RTs. Overall, participants who exhibited higher level of ADHD traits were less efficient in the task as reflected by their augmented RTs and lower accuracy. This finding was observed both in trials preceded by distractors and non-distractor trials.

More specifically, the effect of the distractor on accuracy in this experiment was correlated with ADHD symptoms; higher scores on ASRS were associated with decreased accuracy on the odd-even task. The difference was not significant in trials without distractors. However, the results seemed to follow the same direction; participants with lower ADHD were more accurate.

The distractor cost on RT and accuracy was not correlated with ADHD traits. Even though the onset of the distractors was the same as experiment 1, higher ADHD was no longer associated with faster RTs in distractor trials. This could be due to the increased difficulty of the task for participants with high ADHD traits as reflected on their overall slower RTs and accuracy. However, it is worth noting that accuracy was slightly lower in trials with distractors than in trials without distractors, with the relationship between hyperactivity subscale score and distractor cost on accuracy almost approaches significance (.07).

Finally, the majority of participants reported noticing the far-peripheral distractors while doing the task. Whether they saw the distractors or not did not correlate with the level of ADHD traits or the performance in the task.

4.7 General Discussion

This study is, to the best of our knowledge, the first investigation of the effect of task irrelevant, far-peripheral distractors on healthy volunteers with varying level of ADHD traits. A new paradigm was employed to investigate the effect of intermittent far peripheral distractors on the performance of a sustained attention task.

In the first experiment, the presence of far-peripheral distractors led to decreased distractibility in participants with high ADHD traits as reflected in the diminished RTs in trials with distractors. Individuals with high ADHD processed the distractors differently and sped up their responses in distractor trials. This unexpected finding was further investigated in two experiments.

In the second experiment, the relationship between ADHD traits and distractibility in distractor trials was removed by modifying the timing of the distractor. More specifically, altering the onset of the distractor so that it no longer predicted the appearance of the next target stimulus, removed the beneficiary effect of the distractor on participants with high ADHD traits.

In the third experiment, the onset of the distractor was kept the same as in experiment 1, but the task was modified. Instead of a sustained attention task, participants were engaged in a odd-even task in which they had to decide whether a digit was odd or even. Since there was 50% chance of an odd or an even number in a distractor trial, distractors did no longer act as temporal cues for the upcoming targets. As a result the relationship between ADHD traits and distractor cost on RT was removed. No significant differences in accuracy scores were identified in the two previous experiments. However, the third experiment showed that higher ADHD traits were associated with lower accuracy in trials with and without distractors. Accuracy was slightly lower in far-peripheral distractor trials.

The results of our experiments suggest that high level of ADHD traits is associated with abnormal processing of far-peripheral distractors. This effect was not due to differences in mental workload; noticing the distractors was not related to level of ADHD traits. Distractors appearing a few ms before the main stimulus had a facilitating effect on participants with high ADHD traits only when they could predict the appearance of the main stimulus. When the nature of the task or the onset of the distractor was modified, the effect disappeared. It is unclear whether this effect is limited to the processing of far-peripheral distractors.

The SC has been previously shown to play a role in directing covert spatial attention (Müller, Philiastides, & Newsome, 2005). In addition to this, previous studies suggest that the SC is very sensitive to temporal factors (Meredith, Nemitz, & Stein, 1987) and cue onsets (Boehnke & Munoz, 2008). The distractors used in our paradigm are supposed to be sensitive to collicular function (moving checkerboards appearing in the far periphery; Calvert et al., 2000; Schneider & Kastner, 2005b). Even though it is highly speculative, our findings could be seen as preliminary evidence for the SC hypothesis of ADHD. Higher levels of ADHD were associated with increased sensitivity to collicular distractors when they were presented 75ms before the main stimulus. However, in our paradigm it is difficult to establish whether the correlation between ADHD traits and performance is due to collicular hypersensitivity alone. This problem could be solved in a future study by introducing distractors less sensitive to collicular function. A possible type of distractor could be colour sensitive stimuli. More specifically, short-wave-sensitive cones (S-cone) visual stimuli are thought to not directly access the SC (Thirkettle et al., 2013; B. J. White, Boehnke, Marino, Itti, & Munoz, 2009). By comparing the effect of S-cone and collicular distractors on task performance in participants with high and low ADHD traits we could establish whether this difference is driven by collicular function.

In all 3 experiments, infrequent, far-peripheral, task irrelevant distractors could capture the participants' attention as it was revealed by looking at their effect on the RTs. This is consistent with findings from studies using central and peripheral distractors (Forster & Lavie, 2008; Doyle & Walker, 2001), which have showed that in low workload conditions individuals tend to process task irrelevant stimuli.

Overall, in all three experiments, high ADHD traits were correlated with augmented RTs and lower accuracy. Even though the participants were recruited from a healthy population and were not diagnosed with ADHD or any other disorder, their performance was abnormal. This finding suggests that using subclinical populations could be a useful approach in the study of ADHD. Even thought this is a common methodology in ASD research, it is still rare in ADHD studies. Our results show that using undiagnosed populations with high traits of ADHD could provide useful information about the phenotype of the disorder. Furthermore, we managed to identify small differences between ASRS subscale scores and measures of task performance. This finding suggests that the ASRS could potentially be used to detect subtype idiosyncrasies.

4.8 Limitations

A number of limitations can be identified in our study. The paradigm we employed did not control for the exact location the distractors appeared. The distractors could appear on the left or right far-peripheral visual field of the participant. It was not possible to examine differences in right and left visual field distractors. Previous studies have shown that there are spatial asymmetries when it comes to attention allocation which seem to be reversed in individuals with ADHD (Chan et al., 2009a, 2009b). More specifically, an association between poor attention and a relative rightward bias in visual awareness has been observed in ADHD (Manly, Cornish, Grant, Dobler, & Hollis, 2005).

Finally, our study did not include any individuals diagnosed with ADHD and based the level of ADHD traits on self-reports. Even though ADHD traits exist on a continuum and clinical cases can be seen as its extreme end, differences between high ADHD level and diagnosed ADHD might exist. Future studies should administer our paradigm in a sample of ADHD children or adults.

4.9 Conclusion

To our knowledge, this is the first reported study to investigate the effect of far peripheral distractors on performance in individuals with high ADHD traits. Higher level of ADHD traits was correlated with impaired performance in all our experiments. Our results show that using the ASRS is a promising tool in the study of ADHD. This approach has been popular in studies of autism but has been rarely used in the case of ADHD.

Furthermore, our results suggest that individuals with high ADHD traits process far peripheral distractors differently depending on their time of onset and their informational content.

Chapter 5

Multisensory Integration and ADHD traits

5.1 Chapter Summary

Abnormalities in multimodal processing have been found in many developmental disorders such as autism and dyslexia. According to preliminary studies and anecdotal accounts, children and adults with ADHD often report hypo-responsiveness and/or hyper-responsiveness to sensory stimuli. However, surprisingly little empirical work has been conducted to actually test the integrity of multisensory integration in ADHD.

The main aim of this study was to examine links between symptoms of ADHD (as measured in a non clinical population using the ASRS) and the temporal aspects of multisensory processing. More specifically, differences in the temporal integration window between participants with low and high ADHD traits were using a simultaneity judgement (SJ) and a temporal order judgement (TOJ) task. Multisensory stimuli (e.g., an auditory beep and a visual pattern) were presented over a broad range of stimulus onset asynchronies (SOAs). In the SJ task, participants with high ADHD traits had a significantly smaller temporal window of integration. No difference was found in the point of subjective simultaneity (i.e. SOA at which participants are most likely to perceive the auditory and visual stimuli as occurring simultaneously). The TOJ task did not identify any differences between groups.

This is the first study to identify an abnormal integration window in individuals with ADHD traits. Perceived temporal misalignment of two or more modalities can lead to distractibility (e.g., when the stimulus components from different modalities occur separated by too large of a temporal gap, such as in a badly-dubbed movie). An abnormality in the perception of simultaneity could increase distractibility.

5.2 Introduction

The ability to use multisensory integration (MSI) (i.e., integrate information from multiple sensory modalities) allows us to interact adaptively and efficiently with our surroundings by creating a unified and coherent internal representation of the external environment. For example, locating a predator depends on accurately detecting and integrating information from multiple sources (e.g. hearing the sound of the predator, detecting movement), while differentiating it from other stimuli (e.g. sound of the wind). Therefore, combining information across senses can significantly increase survival chances. Additionally, by effectively integrating stimuli from multiple modalities we avoid being overwhelmed by the constant input of information and we can attend to specific aspects of the environment. MSI allows us to accurately discriminate or/and detect unisensory stimuli (Shams, Wozny, Kim, & Seitz, 2011; Schroeder & Foxe, 2005).

Even though the majority of studies investigating MSI focus on group analyses and do not report individual differences, there has been some evidence suggesting that certain conditions or life experiences can lead to altered MSI behaviour. For example, abnormalities have been found in early-blind participants (Liotti, Ryder, & Woldorff, 1998), animals deprived of early sensory input (Ghoshal, Pouget, Popescu, & Ebner, 2009), and certain developmental and psychiatric disorders (Laasonen, Tomma-Halme, Lahti-Nuuttila, Service, & Virsu, 2000; Kwakye, Foss-Feig, Cascio, Stone, & Wallace, 2010; Foss-Feig et al., 2010; Williams, Light, Braff, & Ramachandran, 2010; Foucher, Lacambre, Pham, Giersch, & Elliott, 2007). Previous studies have shown that the temporal window of integration (TWI; how close together in time stimuli must occur in order to be perceptually integrated into a single, multisensory object) is highly variable across individuals (R. A. Stevenson, Zemtsov, & Wallace, 2012) and abnormalities in multisensory integration have been observed in various disorders. For example, an extended temporal integration window has also been reported in dyslexia (temporal-order-judgement task; Hairston, Burdette, Flowers, Wood, & Wallace, 2005; simultaneity audiovisual task; Laasonen et al., 2000). In addition to this, certain activities, such as musical training and video-game experience, have been associated with altered multisensory integration profiles (Petrini et al., 2009; Donohue, Woldorff, & Mitroff, 2010)

5.2.1 Multisensory Integration in ADHD

Both empirical evidence and anecdotal accounts suggest the presence of sensory processing abnormalities in ADHD. A significant overlap between ADHD and "sensory processing disorder" (SPD) has been reported (Koziol & Budding, 2012). A specific type of SPD, "sensory modulation disorder" (SMD) which is characterised by hypo-responsiveness and/or hyper-responsiveness to sensory stimuli is more commonly reported in individuals with ADHD with estimates of comorbidity occurring 40% to 84% of the time (Hassan & Azzam, 2012). Yochman and colleagues (2004) used the Sensory Profile Questionnaire (SP) to examine sensory processing difficulties in 48 children with ADHD and 46 children without disabilities. Based on the measure of mothers' perceptions, children with ADHD demonstrated statistically significant differences from children without ADHD. One of the areas affected mostly by ADHD was that of multisensory integration. Furthermore, time processing, which is involved in integrating information from multiple modalities, seems to be abnormal in children and adults with ADHD (Toplak, Dockstader, & Tannock, 2006). In particular, a perceptual deficit of time discrimination in brief durations which differ by several hundred milliseconds has been observed (A. Smith, Taylor, Warner Rogers, Newman, & Rubia, 2002; Marusich & Gilden, 2014; Quartier, Zimmermann, & Nashat, 2010). Such deficits have also been found in non-clinical populations exhibiting ADHD-like traits (e.g., impulsivity) (Wittmann et al., 2011; Baumann & Odum, 2012). Such intervals play an important role in MSI.

Despite all the existing reports of MSI involvement in children and adults with ADHD, surprisingly little empirical work has been conducted to actually test the integrity of MSI in ADHD. Most studies of MSI in developmental disorders focus on MSI paradigms that involve speech (voice onset time, Breier et al., 2001; Breier, Gray, Fletcher, Foorman, & Klaas, 2002; Foxe et al., 2015; speech processing, Michalek, Watson, Ash, Ringleb, & Raymer, 2014). No differences between groups with ADHD and neurotypicals have been reported in studies using unisensory paradigms; visual simultaneity tasks (Brown & Vickers, 2004), visual temporal-order judgement tasks (Mueller, Berger, Tucha, & Falter, 2013) and auditory temporal-order judgement tasks (Breier et al., 2002).

A recent study by Donohue and colleagues (2012) looking at multimodal processing in ASD also examined the effect of ADHD symptoms. They found that ADHD symptoms as measured by the Jasper/Goldberg Adult ADHD Questionnaire (Jasper & Goldberg, 1993) were significantly correlated with multisensory processing in a study on 100 healthy volunteers. The authors reported that individuals in their sample with higher symptoms of ADHD had PSS values shifted to the left (i.e., they reported two stimuli as simultaneous when the auditory stimulus was leading). No differences in the temporal integration window size were reported. They also found that a stronger bias to perceive auditory stimuli occurring before visual stimuli as simultaneous was associated with greater levels of autistic symptoms. This finding is consistent with previous studies investigating MSI in ASD (Falter, Elliott, & Bailey, 2012; Foss-Feig et al., 2010; Russo et al., 2010) but also see Mongillo et al. (2008).

A growing body of evidence suggests that increased distractibility in ADHD is caused by a hyper-responsiveness of the superior colliculus (reviewed by Overton (2008)), a sensory structure in the midbrain which is intimately linked to orienting the eyes and head towards salient stimuli and has a role in distractibility (Dean et al., 1989). Evidence supporting the implication of the SC in ADHD comes from animal studies, as well as studies examining eye movements in ADHD patients.

5.2.2 The Role of the Superior Colliculus in Multisensory Integration

As reported on chapter 2, the SC is also thought to play an important role in MSI. Visual, auditory, and somatosensory inputs converge onto a common pool of SC neurons, creating a substantial population of multisensory neurons (Meredith & Stein, 1986). Neurons in the SC that receive input from multiple sensory modalities typically show enhanced responses to multisensory stimuli (compared to the largest unisensory response) provided that the stimuli from the two modalities are close together in space and time (Stein, Huneycutt, & Meredith, 1988; Stein & Meredith, 1993; Wallace et al., 1996). Typically, multisensory stimuli will be temporally linked together if they occur within about 150 ms of each other, and this time frame is referred to as the 'temporal window of integration' (see Figure 5.1) (Donohue et al., 2010; Powers, Hillock, & Wallace, 2009; Stone et al., 2001; Zampini, Guest, Shore, & Spence, 2005). The opposite effect (response depression) is observed when inputs are separated in space and time (Calvert, 2001; Calvert & Thesen, 2004; Calvert, Hansen, Iversen, & Brammer, 2001).

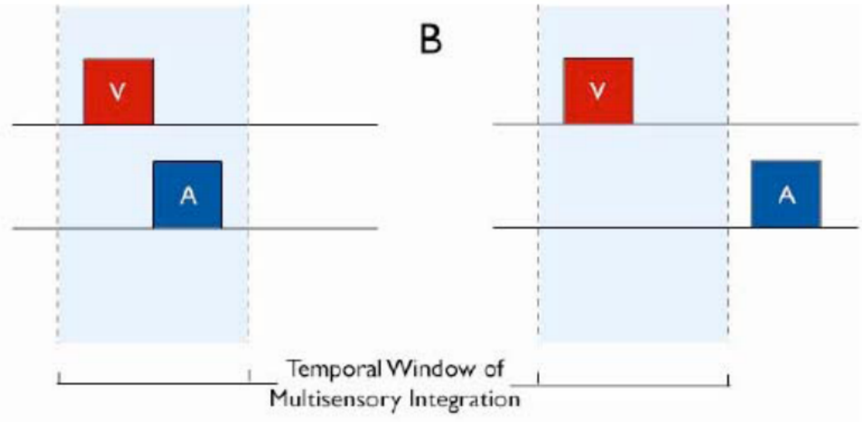


Figure 5.1: graphic representation of the temporal window of multisensory integration. Adapted from Powers and Wallace (2009)

Due to its small size and its location, the human SC has only been examined by a small number of studies. Few human neuroimaging studies have reported SC activations in MSI paradigms (Calvert, 2001; Powers, Hevey, & Wallace, 2012; Bushara, Grafman, & Hallett, 2001). The SC seems to be part of a larger network involved in MSI which includes the posterior parietal, superior temporal, prefrontal and insular cortices in addition to early visual and auditory areas and the posterior thalamus (Bushara et al., 2001, 2003; Calvert, 2001; Powers et al., 2012; Noesselt et al., 2007; Calvert et al., 2001). The SC receives both ascending and descending input from visual, auditory, and somatosensory areas. Bushara and colleagues (2001) investigated the neural correlates of temporal synchrony detection between multimodal sensory inputs during an audiovisual simultaneity paradigm using PET. They found that a large-scale neural network of insular, posterior parietal, prefrontal, and cerebellar areas was activated. The SC showed significant functional interaction with the right insula; the region with the highest and task-specific activity.

Similar results were also reported in a fMRI study of audiovisual temporal correspondence by Calvert et al. (2001). The paradigm they employed consisted of a visual stimulus, an 8 Hz reversing black-and-white checkerboard, which alternated every 30 s with a blank screen and an auditory stimulus, 1000 ms white noise bursts, which were timed either to coincide precisely with the reversal rate of the visual checkerboard (matched experiment) or were randomly shifted out of synchrony (mismatched experiment). The auditory stimulus alternated with a silent period every 39s. Calvert and colleagues (2001) found that the structure exhibiting the most significant crossmodal facilitation and suppression to synchronous and asynchronous bimodal inputs respectively was the superior colliculus. Powers et al. (2012) investigated the neural correlates underlying changes in multisensory temporal binding using a two-interval forced choice audiovisual simultaneity paradigm representing the substrate for a multisensory temporal binding window. The posterior superior temporal sulcus (pSTS) was the main region that appeared to play a role in training-induced changes. Resting state functional connectivity analysis revealed increased resting state functional coupling after training between the superior colliculus and the pSTS.

Evidence showing the involvement of the SC in MSI in humans also comes from behaviour studies. Frassinetti, Bolognini, and Làdavas (2002) and Bolognini, Frassinetti, Serino, and Làdavas (2005) investigated whether the spatial and temporal rules that have been previously observed in the animal SC (Stein & Meredith, 1993) can be also found in humans. They used a unimodal visual and a crossmodal audio-visual paradigm and they showed that when an auditory stimulus was presented at one spatial location, it facilitated responses to a visual target at that location. The detectability of the visual stimuli, however, did not improve when the same visual and auditory stimuli were presented at spatially disparate loci. Furthermore, they found that the capacity of an auditory stimulus to enhance the detectability of a visual stimulus was evident only when the two stimuli were presented simultaneously. Their results suggest that human multisensory integration follows the similar spatial and temporal rule that governs MSI at the collicular level (see also Odgaard, Arieh, & Marks, 2003; Lovelace, Stein, & Wallace, 2003; Noesselt et al., 2007).

McDonald et al. (2000) provided psychophysical evidence that a sudden sound improves the detectability of a subsequent flash appearing at the same location when the delay between the cue and the target was less than 300 ms. Noise has also been found to enhance the detection of subthreshold stimuli and diminish the detection of suprathreshold stimuli (e.g., Collins, Imhoff, & Grigg, 1996, 1997). This is consistent with the law of inverse effectiveness that has been observed in animal SC studies (Meredith & Stein, 1986; Wallace et al., 1996).

5.3 Current Study

The purpose of this study was to examine links between symptoms of ADHD (as measured in the ASRS) and the temporal aspects of multisensory processing. More specifically, differences in the temporal integration window (the period of time over which multisensory interactions are highly likely to occur) between participants with low and high ADHD traits will be examined. Furthermore, since SC plays an important role in MSI, this project will test the SC dysfunction hypothesis in ADHD. Evidence of MSI abnormalities in healthy individuals with high ADHD symptoms could potentially lead to a larger scale study involving patients diagnosed with ADHD.

The narrower the TWI, the more acute an individual's temporal perception in binding elements across audition and vision. According to the SC hypothesis, the colliculus is hyper-responsive in patients with ADHD. As a result, we anticipate that individuals with high ADHD traits will have an abnormal temporal integration window and point of subjective simultaneity.

5.4 Methods

5.4.1 Participants

47 participants (32 female) were recruited from the volunteers' list of the University of Sheffield. An example of data obtained from a participant that was excluded from the analysis is provided in the Appendix B. The ages of the participants varied

from 19 to 53 ((M=27.86, (SD= 7.29). All subjects had normal or corrected-to-normal vision and hearing and were naive as to the purpose of the experiment. None of the subjects reported having any history of neurological or psychiatric disorders or ADHD. 5 participants were left-handed.

The subjects all gave their informed consent to take part in the experiment and the procedures were in accordance with the ethical standards of the Department of Psychology Ethics Sub-Committee and British Psychological Society Guidelines. All participants were reimbursed with £5 for their time.

5.4.2 Materials

The ASRS was administered to determine ADHD-like traits in participants. The self-report questionnaire was used in our previous study (described in Chapter 4) and was found sensitive to behavioural measures. Two tasks were administered to examine MSI; a simultaneity judgement task and a temporal order judgement task. Each task is described in detail below.

5.4.2.1 Simultaneity Judgement Task

A simultaneity judgement task similar to the one described by Donohue and colleagues (2010, 2012) was employed. Previous studies have consistently found activations in the SC in similar paradigms (Powers et al., 2012). The simultaneity judgement task (Figure 5.2) is typically used to examine the dynamics of multisensory temporal integration (e.g., Donohue et al., 2010; Powers et al., 2012;

Zampini et al., 2005) and it includes fewer decisional components that other commonly used MSI paradigms (e.g., temporal-order-judgements, TOJ, García-Pérez & Alcalá-Quintana, 2012).

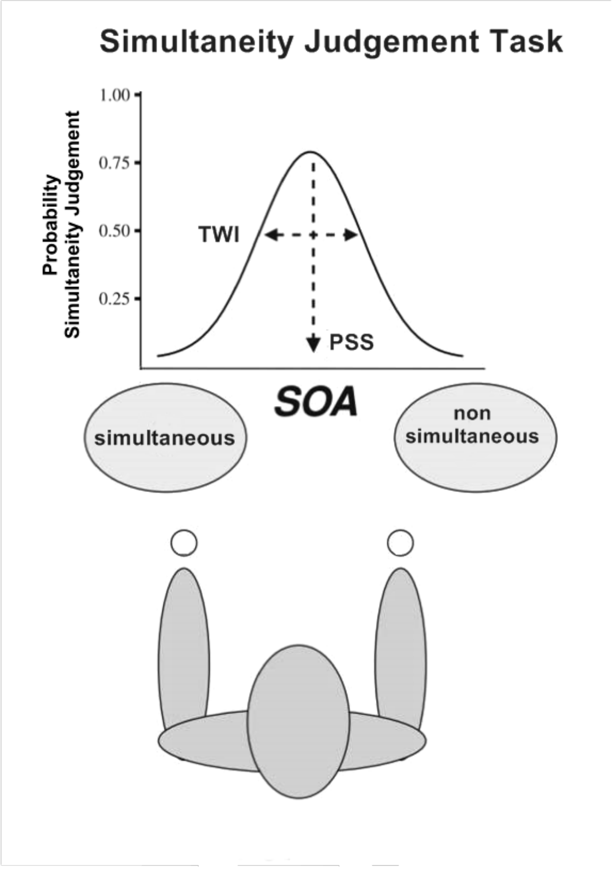


Figure 5.2: Graphic Representation of the Simultaneity Judgement task. *TWI= temporal window of integration, PSS = point of subjective simultaneity*

Multisensory stimuli (e.g., an auditory beep and a visual pattern) were presented over a broad range of stimulus onset asynchronies (SOAs) (Figure 5.2) using OpenSesame (Mathôt, Schreij, & Theeuwes, 2012) with the PsychoPy (Peirce, 2007) back-end. The stimuli used for this task were a black and white square checkerboard (5x5, 330 ms duration) and an auditory tone (330 ms duration, 60 dBSL, 5 ms rise-and-fall time, 1200 Hz) presented centrally. Both stimuli were presented for 330 ms. The auditory and visual stimuli were presented at thirteen stimulus onset asynchronies (SOAs in ms: -300, -250, -200, -150, -100, -50, 0, 50, 100, 150, 200, 250, 300), where negative SOAs represent the auditory stimulus appearing first and positive SOAs represent the visual stimulus appearing first, and 0 represents physical simultaneity. The typical range of window of integration is -150 to 150 ms. As a result, approximately half of the SOAs presented are perceived as simultaneous presentations even though only one is objectively simultaneous. The participants were instructed to press different keys to indicate whether the stimuli were presented simultaneously or asynchronously.

Participants were asked to determine if the auditory and visual stimuli occur at the same time or at different times by making self-paced key-press responses; one key ('S') was associated with presentations that were perceived as "simultaneous" and another ('J') with those perceived as "not simultaneous".

5.4.2.2 Temporal-Order Judgement Task

Temporal order judgement (TOJ) tasks are similar to SJ task; observers are presented with two stimuli (auditory and visual in our case) at a range of temporal offsets and are asked to choose which of the two appeared first (Figure 5.3). The same stimuli as in SJ task were used for the TOJ task. 12 SOAs were presented to the participants (-300, -250, -200, -150, -100, -50, 50, 100, 150, 200, 250, 300). Participants were asked to judge whether the auditory or the visual stimulus was presented first, again indicated with a keypress ('c', auditory first; 'm', visual first). The participants were instructed to be as accurate as possible, and that there was not a response time limit.

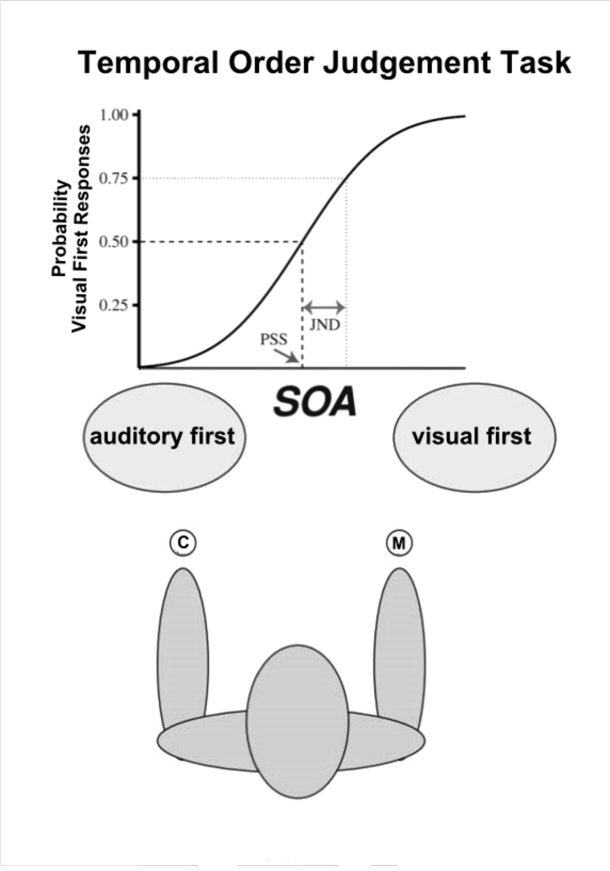


Figure 5.3: Graphic Representation of the Temporal Order Judgement task. *JND= Just Noticeable Difference, PSS = point of subjective simultaneity*

5.4.3 Procedure

Before signing up participants were screened using an online version of the ASRS which was presented as a personality test and assigned to high (ASRS over 35) or low ADHD group (ASRS under 29) according to their scores. The cutoff scores used were based on the results of previous studies undertaken in our lab (see Chapter 3). If the participant's score fell within 29 and 35 they were not allowed to take part in the study. The experimenter was blind as to which group the participant belonged at the time of testing.

The complete experimental session lasted approximately 45 minutes. All participants were first presented with the SJ task and were requested to complete a practice block of 13 trials. The practice session was followed by 260 test trials (20 trials for each of the 13 SOAs). The SOAs were presented in different random order to each participant. The SJ task was split into two parts.

After finishing the SJ task, participants had a short break during which they filled in a demographics questionnaire. Once they were ready for the second part of the study, the TOJ task was presented. Initially, participants completed a practice block of 24 trials. The practice session was followed by 288 test trials (24 trails for each of the 12 SOAs). The SOAs were presented in different random order to each participant. The task was split into two parts to allow the participant some time to rest.

The order of the task was kept the same for all participants. This was done as it has been shown that SJs could be more susceptible to the effects of adaptation to temporal asynchronies (Vatakis, Navarra, Soto-Faraco, & Spence, 2007).

5.4.4 Data Analysis

The primary measure of the simultaneity judgement task was the proportion of trials reported as ’simultaneous’ at each SOA. The data from each participant’s responses were fitted to a Gaussian function using a nonlinear least-squares fit (as in Zampini, Shore, & Spence, 2003; Donohue et al., 2010, 2012). Based on the above fit a point of subjective simultaneity (PSS), which reveals the specific SOA at which participants are most likely perceiving the auditory and visual stimuli as occurring simultaneously, was calculated. An ideal observer would have a PSS with an SOA of 0 msec. A negative SOA would mean that the observer has a bias to perceive auditory information before visual. For most people the PSS is when the visual stimulus comes slightly before the auditory stimulus (Stone et al., 2001; Donohue et al., 2012). The TWI was calculated by the width of each participant's distribution.

For the TOJ task, the proportion of visual first responses was calculated for each participant for each SOA. The data from each participant was fit with a Gaussian cumulative distribution function to further investigate the differences between the two groups (Donohue et al., 2012). The PSS was calculated from the 50% point from the TOJ curve. The 50% point on the function is used because this denotes the physical temporal offset at which the observer is maximally uncertain as to which of the two stimuli came first. The slope of the psychometric function can be used to measure sensitivity to temporal asynchrony, in the form of a Just-Noticeable Difference (JND)(Donohue et al., 2012). JND represents a numerical estimate of the sensitivity of the participant to changes in the stimulus characteristics. Specifically, high sensitivity to asynchrony would allow the participant to notice small changes in the physical temporal offset between the two stimuli. High sensitivity to asynchrony would be expressed as a low JND and relatively steeply sloping psychometric function.

A mean score for the proportion of responses reported as simultaneous for audio-first (SOAs: -300, -250, -200, -150, -100, -50) and visual-first (50, 100, 150, 200, 250, 300) responses was calculated for each participant. In addition to this, differences between groups in the probability of simultaneity report at each SOA were examined.

5.5 Results

5.5.1 ASRS Scores

Scores on the ASRS checklist varied from 7 to 66 and the mean score was 33.28 (*SD*= 13.03). The mean score on the inattention subscale was 17.36 (*SD*= 6.54) and the hyperactivity subscale 15.96 (*SD*= 7.57). The two subscales were correlated, $r(47)$=.698, $p<$.01 (2-tailed). The overall ADHD score was correlated with both the inattention ($r(47)$=.909, $p<$.01) and the hyperactivity subscale ($r(47)$=.933, p<.01).

An independent samples t-test was performed to examine the effect of gender of the participant on overall ASRS score ($t(45)$=2.417, p=.017). Males had higher overall and hyperactivity scores on the ASRS than females (Table 5.1). The effect of handedness on ADHD scores was also investigated but the differences in ASRS scores between left handed and right handed participants were not statistically significant ($t(45)$=-1.61, p=.114).

Table 5.1: Gender Differences in ASRS

Variable	*n*	*M*	*SD*
Males			
Overall ASRS	15	39.8	6.36
Inattention	15	20.4	6.36
Hyperactivity	15	19.4	5.82
Females			
Overall ASRS	32	30.22	12.81
Inattention	32	15.94	6.22
Hyperactivity	32	14.68	8.07

M = mean, *SD* = standard deviation

The participants were categorised into a two groups based on the overall ASRS scores. Initially, equal number of high and low ADHD participants were recruited but dropout rate was larger in the high ADHD group. 26 participants were in the low ADHD group and 21 in the high ADHD group. The characteristics of each group are presented in detail in Table 5.2.

Table 5.2: Table Characteristics of high and low ADHD groups

Variable	*n*	*M*	*SD*	*t*	*p*
ASRS				−9.28	<0.01
Low ADHD	26	23.9	5.7		
High ADHD	21	45	9.7		
Inattention Subscale				−7.48	<0.01
Low ADHD	26	13	4.03		
High ADHD	21	22.8	4.8		
Hyperactivity Subscale				−8.8	<0.01
Low ADHD	26	10.96	3.42		
High ADHD	21	22.14	6.67		
Sex				2.78	<0.05
Female					
Low ADHD	22				
High ADHD	10				
Male					
Low ADHD	4				
High ADHD	11				

M = mean, *SD* = standard deviation

5.5.1.1 SJ task

10 participants were disqualified from the analysis as they had cause PSS and/or TWI values over 600 msec (i.e., they fell outside the SOA range tested; cf. Spence et al., 2001 (Spence, Shore, & Klein, 2001), Vatakis et al., 2007 (Vatakis et al., 2007), for similar exclusion criteria), indicating that these 4 could not perform the task. Such exclusion rates are common in studies examining the temporal aspects of MSI. As a result the high ADHD was comprised of 17 participants and the low ADHD of 20 participants. More males were included in the high ADHD group.

The PSS for both groups was negative, which suggests that participants perceived the two stimuli as simultaneous when the auditory stimulus preceded the visual one.

An independent samples t-test was conducted to identify the differences in performance in the high and the low ADHD groups. There was a significant difference in the width of the TWI in the low (M=396.1, SD=89.34) and the high (M=326.6, SD=93.04) ADHD group ($t(35)=$ 2.33, p =.026). The high ADHD group had a significantly smaller window of integration compared to the low ADHD group (Figure 5.4). The effect size for this analysis ($d=$ .76) suggested a moderate to large effect.

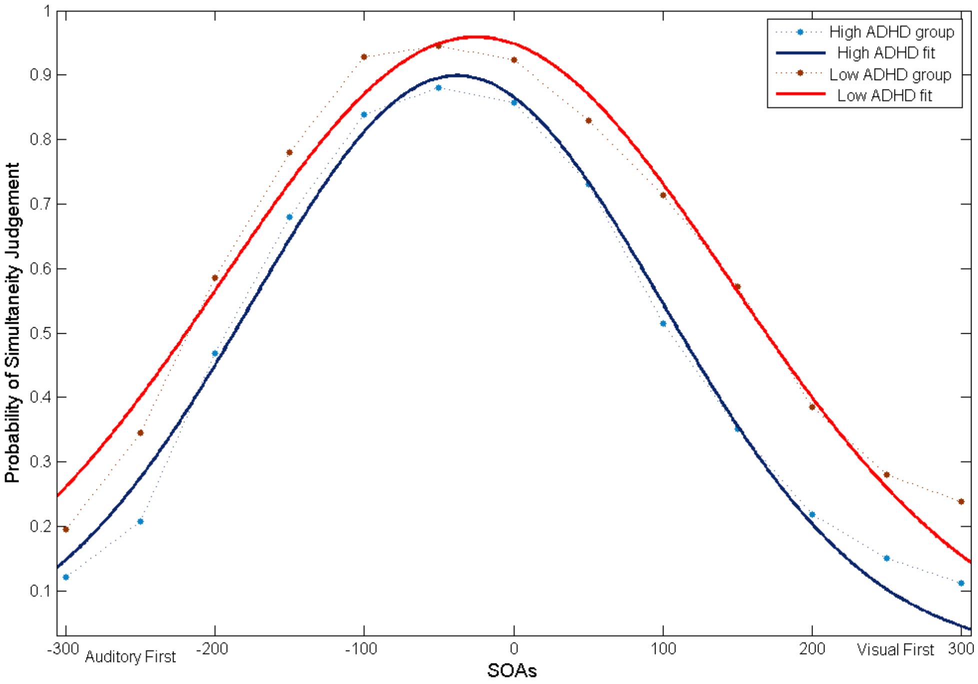


Figure 5.4: SJ Task Performance: Mean proportion of simultaneous responses as a function of the SOA between the auditory and the visual stimulus in high and low ADHD groups.

No difference was found between low (M=-20.21, SD= 58.94) and high (M=-43.64, SD= 36.74) ADHD in the PSS, $t(35)$= 1.42, p= .165.

An independent samples t-test was conducted to identify differences in high and low ADHD groups in the proportion of simultaneous responses in audio-first and visual-first SOAs (results summary can be found on Table 5.3). There was a significant difference between high and low ADHD groups in both visual-first, $t(35)$= 2.17, p = .036, and audio-first SOAs, $t(35)$= 2.07, p = .046.

Table 5.3: visual-first vs audio-first simultaneity judgements in high and low ADHD groups

Variable	*n*	*M*	*SD*
sound first			
low ADHD	20	0.63	0.13
high ADHD	17	0.53	0.15
visual first			
low ADHD	20	0.50	0.23
high ADHD	17	0.35	0.21

M = mean, *SD* = standard deviation

Since the difference between gender ratio in high and low ADHD groups was significant, an independent samples t-test was conducted to identify potential effects of gender on performance in the task. No differences were found between males (*M*=327.5, *SD*=107.5) and females (*M*=381.5, *SD*= 87.65) in the width of the TWI (t(35)=-1.63, p=.112). The difference in the PSS in males (*M*=-30.99, *SD*= 47.62) and females (*M*=-30.97, *SD*= 53.11) was not statistically significant (t(35)=-.001, p=.999).

5.5.1.2 TOJ task

Data from 10 participants were excluded from the TOJ task analysis due to poor performance (i.e., accuracy under 50% in the TOJ task, which resulted in their data not being fitted).

An independent samples t-test was conducted to identify the differences in performance in the high and the low ADHD groups (Figure 5.5). There was no significant difference in the JND in the low (*M*= 169.67, *SD*=70.35) and the high (*M*= 148.11, *SD*= 43.66) ADHD group (t(35)=1.076, p= .289).

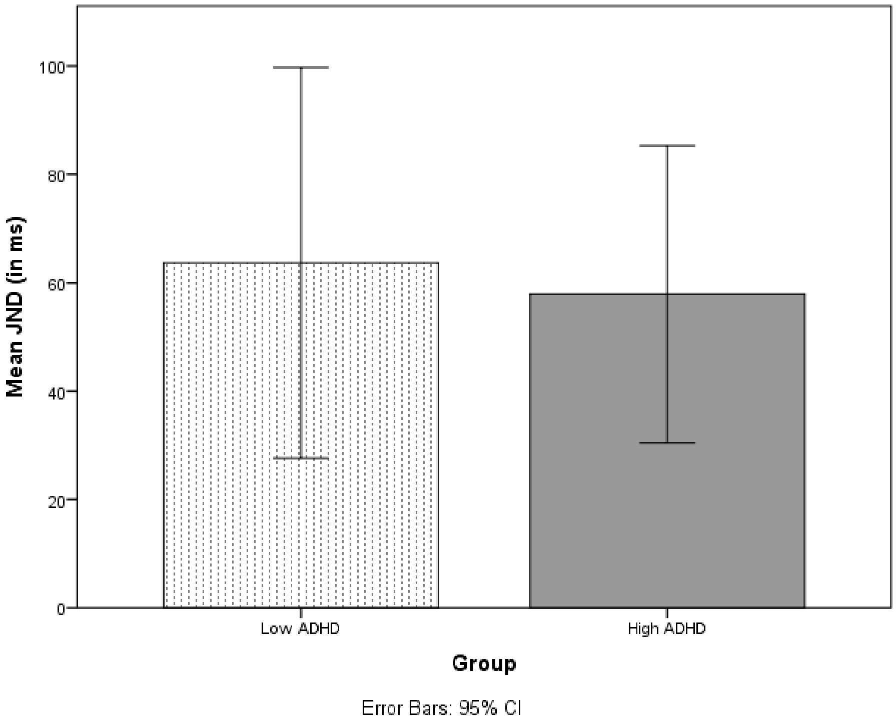


FIGURE 5.5: Bar chart showing the mean JND in high and low ADHD groups in the TOJ task

No difference was found between low (M=5.82, SD=105.33) and high (M=27.77, SD=81.98) ADHD in the PSS, $t(35)$=-.689, p=.495.

Accuracy scores were slightly higher in the ADHD group (table 5.4). This difference, however, was not significant ($t(35)$=-1.888, p= .068).

TABLE 5.4: Accuracy in the TOJ task in high and low ADHD groups

Variable	n	M	SD
Accuracy in TOJ			
low ADHD	21	78.89	10.42
high ADHD	16	83.95	5.66
visual first			
low ADHD	21	81.3	14.41
high ADHD	16	85.61	9.83
sound first			
low ADHD	21	76.49	14.3
high ADHD	16	82.29	7.28

M = mean, SD = standard deviation

5.6 Discussion

5.6.1 SJ Task

High ADHD had a significantly smaller TWI compared to participants with low ADHD. No significant difference was found in the PSS. The high ADHD group judged more SOAs as not being simultaneous both in visual-first and audio-first trials.

The TWI is related with the ability to create unified multisensory perception. Individuals with narrower windows are more likely to dissociate temporally asynchronous inputs.

Previous studies have found that the width of the TWI, specifically the right side, of an individual's TWI, where the auditory stimulus follows the visual, is significantly correlated with the strength of illusory percepts (R. A. Stevenson et al., 2012).

Perceived temporal misalignment of two or more modalities can lead to distractibility (e.g., when the stimulus components from different modalities occur separated by too large of a temporal gap, such as in a badly-dubbed movie). An abnormality in the perception of simultaneity could increase distractibility.

5.6.2 TOJ Task

No significant differences were found between high and low ADHD in the TOJ task. The PSS and the JND were similar in both groups.

When examining accuracy of responses across SOAs a trend was observed; participants with high ADHD tend to make more accurate estimations (i.e, they were more likely to accurately judge the order a tone and the checkerboard are presented).

5.6.3 General Discussion

To our knowledge, this is the first study to report abnormalities in MSI in individuals with high ADHD-like traits. Even though, sensory issues are often reported in patients with ADHD, this area of research has been neglected. Here, we investigated perceived simultaneity and the size of the temporal window of multisensory integration in participants with high and low ADHD traits as measured in a self-report questionnaire. Their performance in a SJ and a TOJ task were examined and compared. The high ADHD group has significantly smaller TWI than the low ADHD group in the SJ task. In addition to this, the difference between high and low ADHD groups was more pronounced when the visual stimulus appeared before the auditory stimulus; a higher percentage of simultaneous responses in visual leading asynchronies was observed in the low ADHD group. Participants with a higher level of ADHD traits appeared to have more negative PSS values but the differences between groups were not statistically significant.

No differences in the measures of simultaneity and the window of integration were found in the TOJ task. Similar PSS and JND values were found in participants with high and low ADHD.

The difference between high and low ADHD was significant only in the SJ task. In previous literature TOJs and SJs appear to have been used almost interchangeably to measure perceived simultaneity (Vatakis, Navarra, Soto-Faraco, & Spence, 2008). One would expect to be able to identify differences in groups in both tasks. However, it is worth noting that discrepancies between SJ and TOJ paradigms are very common. Previous research has shown that SJs and TOJs are supported by different perceptual and brain mechanisms (Love, Petrini, Cheng, & Pollick, 2013; Vatakis et al., 2007). A review by Van Eijk and colleagues (2008) found that in SJ tasks the PSS is usually video-leading. On the other hand, audio-leading PSSs are reported almost exclusively in the TOJ. Simultaneity judgement and temporal order judgement tasks are thought to tap into somewhat different underlying mechanisms (Van Eijk et al., 2008). Differences in estimates between SJ and TOJ tasks have been reported previously and are thought to be due to differences in the underlying perceptions that are being measured. More specifically, different aspects of temporal judgements are required for each task. The perception of successiveness is a necessary requirement for the perception of temporal order required in the TOJ (Allan & Kristofferson, 1974). The PSS estimate obtained in a TOJ task is shifted in the direction of the most sensitive part of the synchrony judgement curve, which is obtained in the SJ task. This results in a response bias that may affect the PSS by affecting the mid-point of the psychometric function

(Vatakis et al., 2008). Support for this was provided by a study by Van Eijk et al. (2008). Results showed that TOJ PSS values were not correlated with the equivalent SJ values. No relationship between TOJ and SJ task was found in any of the measures of observer sensitivity to asynchrony. These findings suggest that TOJ and SJ are probably measuring different aspects of the observers' perceived simultaneity.

Evidence suggests that different neural networks might be involved in SJ and TOJ tasks. Specifically, a cortical and subcortical network comprising the insula, cerebellum, inferior frontal gyrus, inferior parietal lobe, superior colliculus and posterior thalamus seems to be responsible for detection of asynchrony in a SJ task (Bushara et al., 2001). Given that SJ and TOJ may represent different measures of temporal processing, it is feasible that a TOJ task may employ a slightly different neural network. Fink and colleague (Fink, Ulbrich, Churan, & Wittmann, 2006) proposed that there might be more than three different neural mechanisms mediating TOJ, which process temporal order according to stimulus characteristics. Furthermore, the TOJ task has been found to be more complex and require more resources (e.g., decision making) than the SJ task (Yarrow, Shapiro, DiCosta, & Arnold, 2014). In general, the majority of published work suggests that the SJ task provides a more sensitive measure regarding the temporal aspects of a stimulus (i.e., PSS measure; Schneider & Bavelier, 2003; Vatakis et al., 2008)

The lack of significant differences in the TOJ task and the findings from the SJ task could pinpoint to the perceptual and neural mechanisms involved in ADHD. As reported in Chapter 3, the SC is one of the main areas involved in the SJ task (Bushara et al., 2001; Meredith et al., 1987). An abnormal SC function would lead to an altered temporal window of multisensory integration. This is consistent with our findings from the SJ task; the size of the TWI is smaller in participants with high ADHD traits. Since more mechanisms are involved in the TOJ tasks, participants with high ADHD traits could be compensating or relying on different strategies. Performance measures in TOJs have been found to depend more heavily on strategies and response biases than the ones in SJ.

Our results suggest that ADHD might be associated with abnormal processing of multisensory information. More specifically, it appears that higher ADHD traits are associated with smaller integration windows. This finding might at first appear counter-intuitive. A number of possible interpretations are offered for these results.

Attention seems to play a role in MSI paradigms as it can facilitate the detection and the identification of visual stimuli and this in turn could influence subsequent judgements. In a recent study by Donohue (2015), when individuals judged the simultaneity of a sound with the intersection of a moving visual stimulus, attention was found to widen the TWI, increasing the likelihood of simultaneity perception and the simultaneity judgement accuracy when the stimuli were actually physically simultaneous. When simpler stimuli were used (e.g. flashed visual stimulus and brief tone pip), however, attention had no effect on the measured TWI. It is possible that individuals with more ADHD traits reported fewer trials as simultaneous due to lapses of attention. In particular trials in which the stimulus order would have provided the most attentional capture (i.e., those with the auditory stimuli coming first) would explain the more negative PSS values reported in the SJ and

TOJ tasks. Notably, the most significant differences between high and low ADHD groups arose primarily when the visual stimulus preceded the auditory stimulus. Specifically, the high ADHD group appeared to be more sensitive to asynchrony. Lapses in attention could be a possible explanation. However, it should be noted that monitoring for visual stimuli requires visual selective attention, which seems to be preserved in ADHD (Barry, Klinger, Lyman, Bush, & Hawkins, 2001). Furthermore, our paradigm employed a brief tone and simple visual stimulus, similar to the ones described by Donohue et al. (2015). In this task attention had no measurable effect on the size of the TWI. As a result, the differences between high and low ADHD groups in TWI were not likely to be due to differences in attention or attention lapses in high ADHD.

Even though a smaller TWI might initially appear as a positive trait, it could contribute to the ADHD pathology. In everyday life perceived temporal misalignment of two or more modalities can lead to distractibility. A characteristic example of this is a badly-dubbed movie which occurs when the stimulus components from different modalities are separated by too large of a temporal gap. In the case of ADHD, it is possible that not integrating stimuli which appear within a neurotypical person's window of integration, could lead to increased distractibility. Thus, an abnormality in the perception of simultaneity could increase distractibility. A model of the above mechanism is presented on Figure 5.6.

Developmental and psychiatric disorders are often associated with disability and decreased ability relative to neurotypicals. However, enhanced perception in various tasks has been observed in other disorders such as ASD (visual acuity; Ashwin,

Ashwin, Rhydderch, Howells, & Baron-Cohen, 2009, visual search; O'Riordan, Plaisted, Driver, & Baron-Cohen, 2001, attention to detail; H. Smith & Milne, 2009) and dyslexia (creativity; Everatt, Steffert, & Smythe, 1999). A smaller integration window could also be seen as advantageous. Being able to parse audio-visual information when they occur closely together in time could reduce uncertainty in certain situations (Love, Pollick, & Petrini, 2012).

A curious finding in our study is the negative PSS reported for the SJ task. This is contrary to the popular opinion that an auditory stimulus has to be presented after a visual stimulus to be perceived as simultaneous (Hirsh & Sherrick Jr, 1961; Zampini et al., 2003; Dinnerstein & Zlotogura, 1968; Keetels & Vroomen, 2005). Only a limited number of studies report the opposite (Rutschmann & Link, 1964). A possible explanation for this according to Boenke, Deliano, and Ohl (2009) could be the higher intensity of the visual stimuli and/or lower intensities of the auditory stimuli. Stimulus intensity is therefore another factor that seems to influence perceived simultaneity (Boenke et al., 2009). This could explain the unusual findings of our study; the visual stimulus we used was a high-contrast black and white checkerboard, while the auditory stimulus consisted of a simple, low volume, sinewave. Most studies employ flashes or simpler visual stimuli. This, however, affected both high and low ADHD groups in a similar manner; both had negative PSS values.

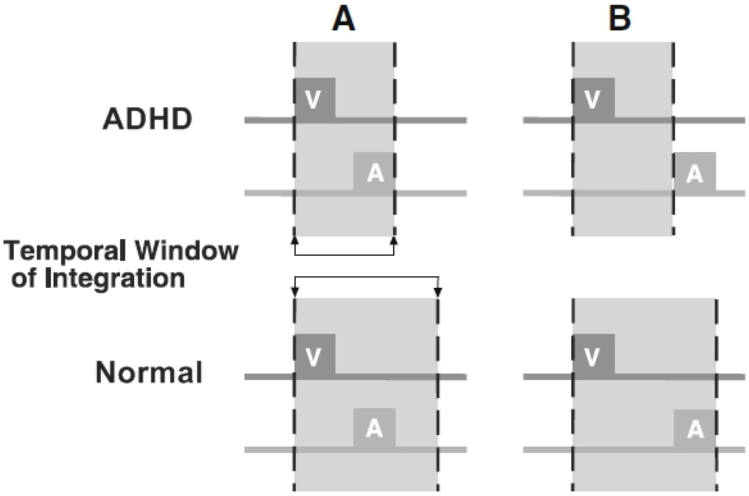


Figure 5.6: Model in which the temporal window of multisensory integration is narrowed in ADHD (a). Stimuli separated by smaller temporal intervals are processed as a unified event (b). Individuals with ADHD experience the two stimuli as distinct events.

The participants that took part in our study were not diagnosed with ADHD. Even though using non clinical populations with high levels of ADHD like traits can be very informative in the case of developmental disorders, future studies should examine MSI in children and adults diagnosed with ADHD to establish a relationship between ADHD and MSI. Since ADHD is a developmental disorder, and we tested adults, it might be possible to identify bigger differences in a younger sample. Preliminary evidence investigating time perception in adults and children with ADHD suggests that deficits in time processing might manifest in different ways with increasing age (Valko et al., 2010).

It is unclear whether the abnormal performance of the high ADHD group is associated with abnormal multimodal perception outside the lab. This is partly due to the low ecological validity of our paradigm. A number of ecologically valid MSI paradigms (the bouncing ball; Lewkowicz, 1996, audio and visual looming stimuli;

Maier, Neuhoff, Logothetis, & Ghazanfar, 2004) have been developed. In tasks such as the bouncing ball, a green disc is perceived as a moving stimulus, thus leading to an event with a causal interpretation. As a result, a more clear and predictable temporal relation exists (the visual component is expected to lead the auditory component). Future studies should attempt to replicate our results using such an ecologically valid paradigm (e.g. badly dubbed movie).

A limitation identified in our study was the lack of timing precision. Even though we employed the Psychopy back-end of OpenSesame, which has been found accurate enough for most psychology experiments (Garaizar & Vadillo, 2014), precision is crucial in MSI experiments. It would be suggested to repeat our study using a custom-made experimental set-up that allows millisecond timing precision (e.g., use of LEDs instead of a standard computer screen).

Like in studies reported in Chapter 4, the current results demonstrate that meaningful findings can come from studying a range of ADHD like symptoms in a general adult population. This is informative as it suggests cognitive deficits linked to ADHD can be explored without requiring clinical populations. Furthermore, the current study demonstrated widespread individual differences in temporal processing abilities across a young adult population. This highlights that individual variability should not be discarded as noise and should be taken into consideration when studying the binding of multisensory stimuli.

Recent evidence suggests that manipulation of the temporal integration window is possible (R. A. Stevenson, Wilson, Powers, & Wallace, 2013; Powers et al., 2012, 2009; Mégevand, Molholm, Nayak, & Foxe, 2013; Fujisaki, Shimojo, Kashino, &

Nishida, 2004). Thus, it is possible to develop behavioural interventions to attempt to normalise the window of integration in ADHD.

5.7 Conclusion

Integrating stimuli from multiple senses is an integral skill to survival which is affected in various clinical conditions and developmental disorders. So far, it has been neglected in ADHD research. We investigated possible relationships between ADHD traits and measures of MSI in a group of adults with high and low ADHD traits as measured in a self report questionnaire. Differences were found between participants with high and low ADHD in the SJ task alone. These findings suggest a new area of study for ADHD research and shed light to the possible mechanisms involved in the disorder.

Chapter 6

Microsaccades in individuals with high and low ADHD

6.1 Chapter Summary

Microsaccades are involuntary, small, jerk-like eye-movements with high-velocity that are observed during fixation. The SC is thought to play an important role in the generation and the inhibition of microsaccades. Abnormal microsaccade rates and characteristics have been observed in a number of psychiatric and developmental disorders. In this study, we further examined the role of the SC in ADHD, by looking at microsaccade differences in 43 participants with high and low ADHD traits, assessed with the ASRS. A simple sustained fixation paradigm, which has been shown to elicit microsaccades, was employed. A positive correlation was found between ADHD traits and microsaccade rates. No other differences

in microsaccade properties were observed. The relationship between ADHD traits and microsaccade rates provides support for collicular involvement in ADHD. Our results suggest that abnormal oculomotor behaviour is a core deficit in ADHD and could potentially serve as a biomarker for the disorder.

6.2 Introduction

6.2.1 Microsaccades

Our ability to see depends partly on being able to align our eyes with a visual target. Eye-movement behaviour is highly optimised to satisfy these needs; most of the time the eyes scan visual scenes in sequences of saccades and fixations. Saccades are rapid, ballistic eye movements, which are usually voluntary and their main purpose is to quickly bring the fovea to a specific portion of the visual field. Fixations, on the other hand, maintain the visual gaze to a specific location keeping a a target relatively stable with respect to the retina. Even though the definition of a fixation might suggest that the eyes remain stable, in reality the eyes are moving continuously. More specifically, when fixating on a stationary object rather than holding steady, our eyes perform tiny, seemingly erratic fixational eye movements. These eye movements, unlike saccades, are not performed voluntarily and we are generally not aware of their existence. The most prominent contribution to fixational eye movements is generated by small (a few arc min to 1.0°), jerk-like eye-movements with high-velocity that are embedded into slower drifting movements (Martinez-Conde, Macknik, & Hubel, 2004). These eye movements were first discovered by Dodge (1907) and are known as microsaccades, a term introduced by Zuber, Crider, and Stark (1964).

Before the term microsaccades was introduced and adopted in vision studies, they could be found in the literature with various names such as small, miniature, or fixational saccades, mini-saccades, jerks, flicks, jumps (Rolfs, 2009). An average person executes about 1-2 microsaccades per second and they can have a typical amplitude between 1 and 25 minutes of arc (min arc) (Dimigen, Valsecchi, Sommer, & Kliegl, 2009).

Despite early reports that fixational eye movements such as microsaccades are necessary to counteract neuronal adaptation and perceptual fading (Ditchburn & Ginsborg, 1952), a functional relevance of microsaccades for normal vision has been disputed. According to some, microsaccades have no useful purpose or function, and reflect oculomotor noise (Kowler & Steinman, 1980) or are a laboratory artifact. However, there is now mounting evidence that microsaccades are intimately linked to neuronal processing throughout the visual and attentional system. It has been found that certain stimuli and activities can increase or decrease the frequency of microsaccades. Fixating on static stimuli elicits a higher microsaccade rate (Hicheur, Zozor, Campagne, & Chauvin, 2013). The shape of the fixation target can also influence the microsaccade rate (Thaler, Schütz, Goodale, & Gegenfurtner, 2013), with circle and cross shapes being associated with higher rates of microsaccade activity, while a bulls eye and cross hair shape leads to more stable fixation.

Typically, microsaccade rate is reduced when the subject anticipates task-relevant stimuli (Hafed et al., 2011; Pastukhov & Braun, 2010; Steinman, Cunitz, Timberlake, & Herman, 1967). This phenomenon may serve to minimise the detrimental effects of ill-timed microsaccades on visual performance (Hafed & Krauzlis, 2010; Hafed et al., 2011) (e.g. moving the eyes before the target appears could have a detrimental effect on the target detection).

In humans, the occurrence of microsaccades has been linked to the detection of parafoveal and peripheral stimuli (Martinez-Conde, Macknik, Troncoso, & Dyar, 2006), as well as perceptual alternations during multistable vision (van Dam & van Ee, 2006; Troncoso, Macknik, Otero-Millan, & Martinez-Conde, 2008). Microsaccades are not only correlated with visual awareness, but also with visuospatial attention (Hafed & Clark, 2002; Engbert & Kliegl, 2003; Laubrock, Engbert, & Kliegl, 2005), and their rate is influenced by higher-level cognitive processes, such as the task relevance and relative frequency of visual or auditory stimuli (Valsecchi & Turatto, 2007, 2009; Valsecchi, Betta, & Turatto, 2007). Spatial attention is altered by microsaccade onset; foveal stimuli are perceived as more eccentric, while peripheral stimuli are perceived as more foveal (Hafed, 2013). This effect is closely related to covert attention, which has also been associated with the direction of microsaccades (Hafed et al., 2011). For example, attending to peripheral events can bias the direction of the observed microsaccades. The direction of microsaccades has been linked to shifts in spatial attention (Yuval-Greenberg, Merriam, & Heeger, 2014).

Furthermore, microsaccades have also been found to play an important role in the perception of various visual illusions (Murakami, 2003; Murakami, Kitaoka, & Ashida, 2006; Otero-Millan, Macknik, & Martinez-Conde, 2012). In particular, changes in the rate or/and the direction of microsaccades can predict the perception of certain illusions (Troncoso et al., 2008; Laubrock, Engbert, & Kliegl, 2008).

Microsaccades might also be involved in binocular rivalry (Sabrin & Kertesz, 1980, 1983; van Dam & van Ee, 2005; Hancock, Gareze, Findlay, & Andrews, 2012; Otero-Millan, Macknik, & Martinez-Conde, 2014). Binocular rivalry refers to a phenomenon that occurs when a subject is presented with two different images to each eye simultaneously. This results in the image presented to one eye competing with that presented to the other. The competition between the two percepts produces alternations in perceptual awareness over time. Microsaccade rate has been found to increase significantly (over 50% compared to normal viewing) when measured during binocular rivalry (Sabrin & Kertesz, 1980).

6.2.2 The Neural Correlates of Microsaccades

Animal studies have found that the SC plays a key role in the microsaccade generation (Hafed et al., 2009, 2009, 2011). Hafed (2009) investigated the temporal profile of microsaccade related activity in the colliculus. They found that microsaccade-related activity tends to increase gradually before the execution of a microsaccade, peaks around the time the eye movement begins, and gradually returns to baseline levels after the execution of the microsaccade. Goffart and colleagues (2012) showed a direct connection between the SC and microsaccades executed during sustained fixation periods. After deactivating the rostral deep SC of monkeys they observed a significant drop in the microsaccade rate during fixation. A causal role of SC in microsaccade generation was also found in another study by Hafed et al. (2009), who measured activity in monkey SC neurons, while the animals fixated on small stationary spot. They found that microsaccade activity was associated with SC neuron activity. Furthermore, reversible inactivation of the SC has been show to cause a disruption on the effect of peripheral cues on microsaccades (Hafed, Lovejoy, & Krauzlis, 2013)

A relationship between covert attention and the SC has also been established (Cavanaugh, Alvarez, & Wurtz, 2006; Hafed, Goffart, & Krauzlis, 2008). The effect of covert attention on microsaccade direction further supports an important role for the SC in microsaccades (Hafed et al., 2008, 2011; Hafed & Krauzlis, 2010; Hafed et al., 2013).

Even though the SC is thought of as the most important region in the generation and inhibition of microsaccades, a relationship between microsaccades and other brain areas has been shown. Preliminary results show that certain neurons found in the brainstem pause during microsaccades (Brien, Corneil, Fecteau, Bell, & Munoz, 2009). Recently, Arnstein, Junker, Smilgin, Dicke, and Thier (2015) showed that the fine-tuning of microsaccades is partly driven by the cerebellum.

6.2.3 Microsaccades in ADHD

Microsaccades have potentially an important role in ophthalmic and neurological disease. A very small number of studies, however, have examined microsaccades in patient groups.

Only one study so far has investigated microsaccades in ADHD. Fried and colleagues (2014) found that adults with ADHD off medication make more microsaccades compared to a group of controls when engaged with a continuous performance task. The difference between groups was pronounced in peri-stimulus trials; when the participant was anticipating a target and was required to suppress eye-movements. With medication (methylphenidate) the microsaccade rate in the ADHD group was normalised, suggesting a potential relationship between ADHD medication and microsaccade generation.

Variations in microsaccade rates across participants are a common finding in studies examining eye movements (Hermens & Walker, 2010; Engbert & Kliegl, 2003; Engbert, 2006). A study by Poynter, Barber, Inman, & Wiggins, 2013 who examined individual differences in eye-movement behaviour in 40 subjects found that normal individuals who reported relatively high levels of attention problems exhibited relatively frequent fixations of short duration and large size. The metric they developed measured the extent of all types of fixational eye-movements (i.e. tremors, drifts) not microsaccades exclusively.

Tasks correlated with microsaccadic activity have been shown to be abnormal in ADHD. More specifically, Casanova and colleagues (2013) used a binocular rivalry task in clinical ADHD groups and a control group and found that the time to onset of rivalry (the first dominance) was longer in the clinical groups than in the control group. Interestingly, the SC is a region associated with binocular rivalry. Zhang & He, 2010 used high-resolution functional magnetic resonance imaging to measure the activity of the SC during binocular rivalry and found that the BOLD signal level of the SC correlated with the subjects' perception.

Microsaccades are often seen as "smaller saccades" due to their similarities with saccades (Engbert, 2006; Engbert & Kliegl, 2003). Abnormalities in saccade inhibition have been previously reported in individuals with ADHD (Munoz et al., 2003; Gould et al., 2001; Loe et al., 2009). In particular, ADHD has been associated with a difficulty suppressing unwanted saccades during fixation (Munoz et al., 2003) and differences in saccadic latency (Mostofsky, Lasker, Cutting, et al., 2001). Medication has been shown to normalise oculomotor behaviour (Mostofsky, Lasker, Cutting, et al., 2001).

6.2.4 Blink Rates in ADHD

Blink rate has also been linked with attention, especially attentional shifts, mind wandering, and sustained attention (Anthony & Graham, 1985; Fairclough, Venables, & Tattersall, 2005). For example blink rate tends to decrease with increased attentional demands (Fairclough et al., 2005).

Abnormalities in blink rates have been found in patients with various mental health disorders (e.g. schizophrenia; E. Y. Chen, Lam, Chen, & Nguyen, 1996;

Jacobsen et al., 1996). Preliminary evidence suggests that there is a positive correlation between ADHD and blink rates (Fried et al., 2014; Caplan, Guthrie, & Komo, 1996). More specifically, patients with ADHD have been found to have an increased blink rate and difficulty suppressing blinks while anticipating the presentation of stimulus (Fried et al., 2014). Not all studies, however, seem to support this finding. Jacobsen et al. (1996) did not find any differences between ADHD patients and controls in blink rates. Methodological differences could be driving these inconsistencies; blink rates are modified by task demands.

6.3 Current Study

No study so far has looked at differences in microsaccade generation in people with high and low ADHD traits. This study examined differences in microsaccade rates and microsaccade characteristics in participants with varying ADHD traits by employing a sustained fixation task. Additionally, The relationship between blink rates and ADHD was investigated.

We predicted that participants with higher ADHD traits would exhibit a higher microsaccade rate compared to participants with lower ADHD. Furthermore, since the SC is directly implicated in microsaccade generation, we aimed to further investigate its role in ADHD. ADHD was also expected to correlate with blink rate, with higher level of ADHD being associated with increased blink rate.

6.4 Methods

6.4.1 Participants

43 participants (35 female) were recruited from the volunteers' list of the University of Sheffield. The ages of the participants varied from 18 to 30 (M = 20.72, SD = 3.33). All subjects had normal or corrected-to-normal vision and were naive as to the purpose of the experiment. 4 participants were left-handed. All the participants were healthy and none were previously diagnosed with ADHD or any other major mental illness.

They were all awarded for their time with credits needed for the completion of their undergraduate degree. The subjects all gave their informed consent to take part in the experiment and the procedures were in accordance with the ethical standards of the Department of Psychology Ethics Sub-Committee and British Psychological Society Guidelines.

6.4.2 Materials and Procedure

The ASRS was administered to determine ADHD-like traits in participants. The self-report questionnaire was used in our previous study (described in Chapter 3 and Chapter 4) and was found sensitive to behavioural measures.

The participant was seated in front of the eyetracker in a padded chair located about 100cm away from the screen. A keyboard was positioned within easy reach in front of the subject. A head rest was used and the participants were asked to maintain a stable posture and head position during the course of the experiment.

Before the main task begun, calibration and validation were performed. Calibration was manual and based on a number of 9 (grid) points. Participants were required to produce saccades towards 9 fixation points sequentially appearing at random on the screen. After calibration was performed, validation was performed by re-presenting the targets and determining the magnitude of the calibration error. In case the validation was unsuccessful, calibration was repeated. The process took approximately 2 minutes for each participant. Drift correction was performed before every trial. During the drift correction the participant was presented with a blank screen and the same black marker presented in the calibration and they were instructed to focus on the black marker fixation point. Calibration was performed twice for each participant; in the beginning of each block.

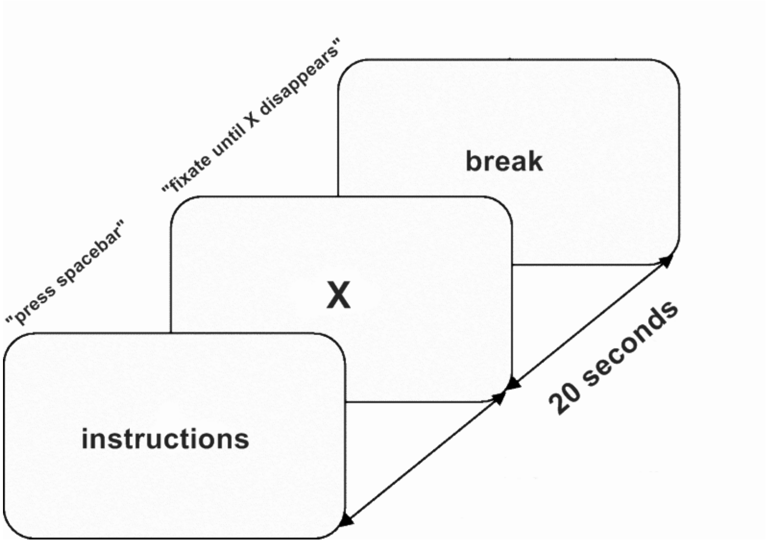


Figure 6.1: Graphical Representation of one Trial of the Sustained Fixation Task.

Once the calibration and validation were successfully performed, the main task was administered. It consisted of a simple sustained fixation task (Figure 6.1). Participants were instructed to fixate on a white cross (size) appearing on a black background in the centre of a 17 inch screen (frame rate 75 Hz) for 20 seconds. Overall, 2 blocks of 10 trials were presented to each participant. There was a break between each trial; the experiment was self-paced and the participant was asked to press the space-bar to begin each trial. Each trial we preceded by the instructions screen. The stimuli were presented with OpenSesame (Mathôt et al., 2012) using the PsychoPy (Peirce, 2007) back-end.

6.4.3 Tracking eye movements

Eye movements were measured using the Eyelink 1000 video-based eye tracker (SR Research Osgood, ON, Canada), which was mounted on a head-and-chin rest. Horizontal and vertical eye positions for both eyes were sampled at a rate of 500Hz (pupil-only mode, instrument noise 0.01 deg RMS) and stored for offline analysis.

6.4.4 Data Analysis

Microsaccades were detected using the algorithm of Engbert and Kliegl (2003) adapted to the 500-Hz sampling rate. This particular algorithm is one of the most commonly used in microsaccade research and has been found reliable in detecting microsaccades (e.g., Engbert & Kliegl, 2003; Engbert, 2006; Otero-Millan, Troncoso, Macknik, Serrano-Pedraza, & Martinez-Conde, 2008. The algorithm developed by Engbert and Kliegl (2003) allows the detection of binocular microsaccades (i.e., eye movements that occur in both eyes at the same time and at least one sample overlaps in time) and monocular microsaccades (i.e., movements that occur in one eye). Previous studies have found that 41% of all microsaccades are monocular (Engbert & Kliegl, 2003). As a result, both monocular and binocular microsaccades were included in our analysis. The average horizontal and vertical displacement across the two eyes was used to determine the amplitude and direction of binocular microsaccades (Engbert & Kliegl, 2003; Engbert, 2006; Otero-Millan et al., 2008). The distribution of the microsaccade angular orientations was also calculated using the Engbert and Kliegl algorithm.

Samples where no tracking data were detected were characterised as blinks and were excluded from the microsaccade analysis. This was done to avoid noise induced to data by blinks (Collewijn, Van der Steen, & Steinman, 1985; Thaler et al., 2013). Trials in which eye positions were not in the centre of the screen were also excluded from the analysis. The characteristics of the detected movements were manually checked and confirmed by plotting peak microsaccade velocity against amplitude (Figure 6.2, as well as by plotting amplitude distributions (Figure 6.3 like previous microsaccade research (Zuber et al., 1964; Hafed et al., 2009; Hafed, 2013).

All the trials from all the sessions were collapsed and included in the analysis. First, the position data was transformed to velocities using a moving average of 3 data samples (6 ms) for each eye. Second, the median-based standard deviation estimator as the velocity threshold was computed and then multiplied by the relative velocity threshold (6.0). If the average velocity exceeded the velocity threshold in at least three consequent samples, the movement was defined as monocular microsaccade. The microsaccades extracted from the algorithm showed a strong correlation between peak velocity and amplitude (r = 0.551, p<.01 (2-tailed)), and thus use of this algorithm to extract microsaccades is reliable and valid in this study (Figure 6.2). Microsaccades with amplitudes exceeding 1° and velocities over 200 were excluded from further analysis as in Yokoyama, Noguchi, & Kita, 2012.

Data from three participants were excluded from the analysis as they failed to complete all 20 trials. Another participant was excluded from the analysis due to high levels of noise in the data (e.g. the algorithm detected an unusual number of microsaccades in the sample). As a result, data from 38 participants were included in the final analysis. The mean proportion of excluded data from the analysis due to errors described above was 16.8% (*SD*=15.7).

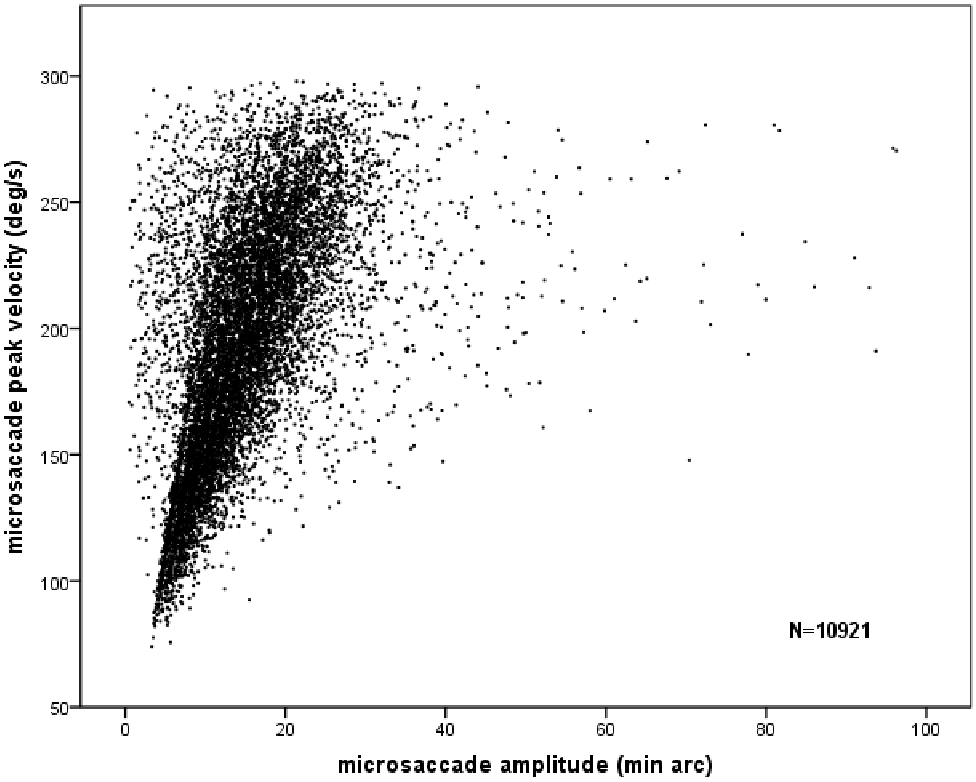


Figure 6.2: Peak velocities of microsaccades as a function of their amplitude. This graph includes all the microsaccades from participants from all trials

6.5 Results

6.5.1 ASRS Scores

Scores on the ASRS checklist varied from 23 to 58 and the mean score was 35.74 (*SD*= 9.6). The mean score on the inattention subscale was 20.29 (*SD*= 4.8) and the hyperactivity subscale 15.45 (*SD*= 6.39). The two subscales were correlated, $r(38)=.459$, $p<.01$. The overall ADHD score was correlated with both the inattention ($r(38)=.807$, $p<.01$) and the hyperactivity subscale ($r(38)=.896$, $p<.01$). Since the two subscales were strongly correlated, only overall ASRS scores were used in the analysis.

A simple t-test was performed to examine differences in ASRS scores between male and female participants. No significant difference in overall ASRS score was found between males (M=38, SD=10.81) and females (M=35.31, SD=9.49) , $t(36)$=.624, p=.536.

6.5.2 Microsaccade Features

A total of 10,921 microsaccades were recorded. More detailed information about the microsaccades are presented on Figure 6.3 and Figure 6.2.

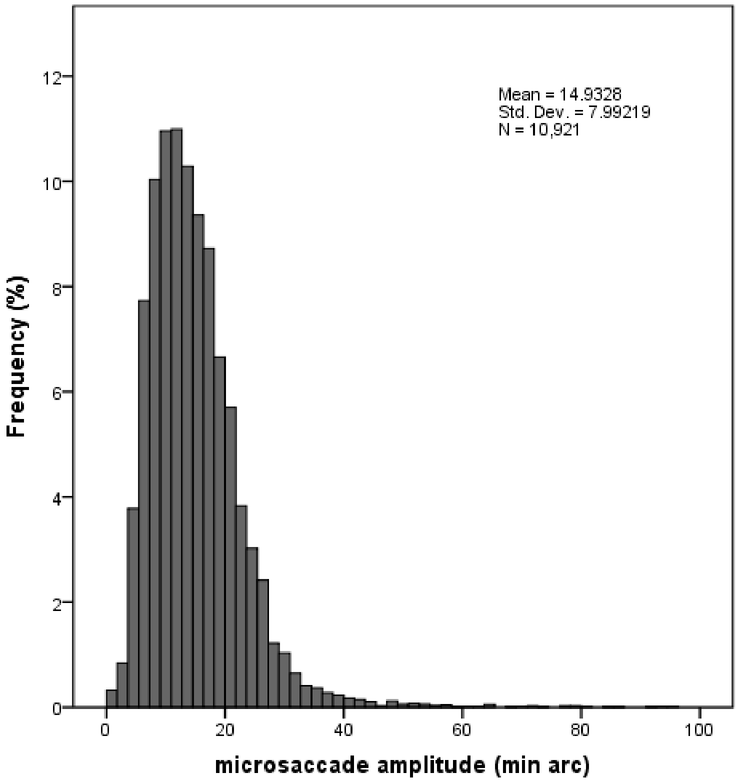


Figure 6.3: histogram of microsaccade amplitudes

Table 6.1 shows the average binocular and monocular microsaccade rates (number of microsaccades per second) across participants.

No difference in the mean microsaccade rate was found between males (M=1.1, SD=.74) and females (M=.84, SD=.4), $t(36)$=.766, p=.475.

TABLE 6.1: The mean microsaccade rate during sustained fixation across participants

type of microsaccade	mean microsaccade rate (sd)
binocular microsaccades	0.88 (.46)
left eye microsaccades	2.57 (0.98)
right eye microsaccades	2.37 (1.1)

6.5.3 Relationship between ADHD Traits and Microsaccades

A positive correlation was found between overall ASRS scores and binocular microsaccade rate (Figure 6.4), $r(38)$=.340, p=.036. Higher level of ADHD traits was associated with an increased rate of microsaccades.

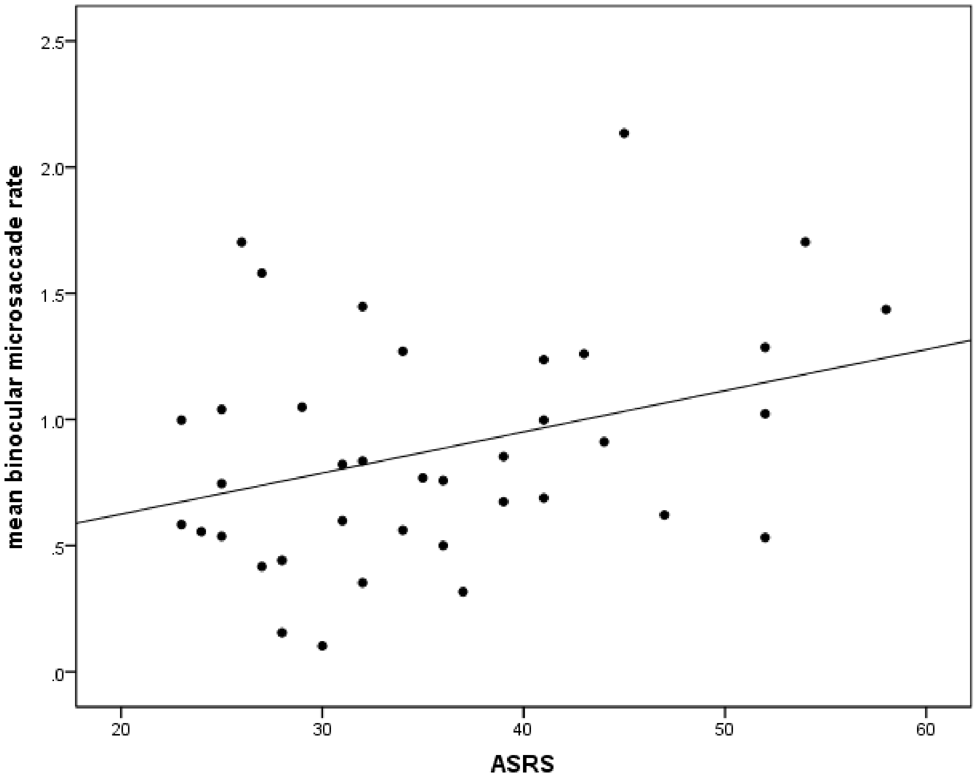


FIGURE 6.4: Scatterplot showing the relationship between ASRS score and microsaccade rate (/s)

Overall ASRS scores were also associated with increased monocular microsaccade rate (Figure 6.5; right eye $r(38)$=.429, p=.007, and left eye $r(38)$=.420, p=.009.

No correlation was found between ASRS scores and mean microsaccade peak velocity, $r(38)$=-.025, p=.882. There was no correlation between ADHD traits and microsaccade amplitudes, $r(38)$=.224, p=.177. The relationship between ASRS scores and microsaccade angular orientation was also investigated. No statistically significant relation was found between the two variables, $r(38)$=.115, p=.491.

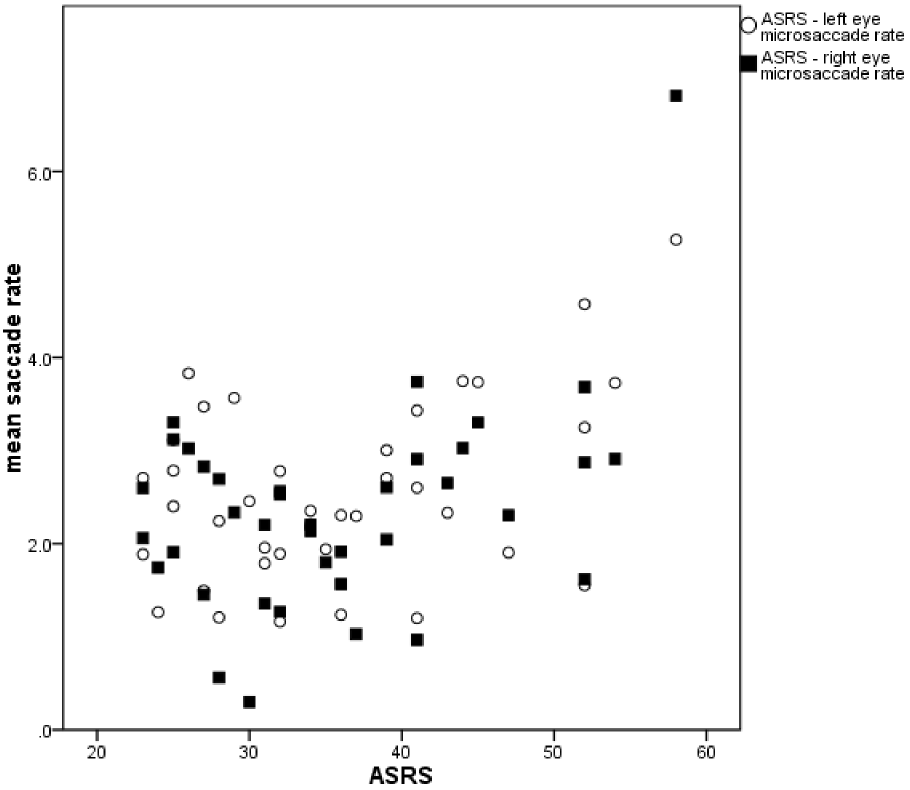


FIGURE 6.5: Scatterplot showing the relationship between ASRS score and monocular microsaccade rate (/s) detected in left and right eye

6.5.4 Predicting microsaccade rates

Linear multiple regression analysis was conducted to test the extent to which the independent variable ASRS score predicted the binocular microsaccade rate. ASRS score significantly predicted the rate of binocular microsaccades, $\beta = .340$, $t(37) = 2.17$, $p = .036$. Overall ASRS score also explained a significant proportion of variance, R2= .116, F(1, 37) = 4.72, $p = .036$.

The unique microsaccade rate from each eye was combined to a new value of monocular microsaccade rate. Linear multiple regression analysis was conducted to test the extent to which the independent variable ASRS score predicted the monocular microsaccade rate. ASRS score significantly predicted the rate of microsaccades, $\beta = .449$, $t(37) = 3$, $p = .005$. Overall ASRS score also explained a significant proportion of the variance, R2= .202, F(1, 37) = 9.1, $p = .005$.

6.5.5 Blinks

Blink rate per second values were calculated for each participant based on all the trials they completed. The blink rate scores were significantly non normally distributed, D=.169 , p=.008. The data were transformed with square-root transformation, which resulted in a normal distribution, D=.110, p=.200.

The average blink rate across participants was .17 blinks per second (SD=.14). The average blink rate of all subjects can be seen on Figure 6.6

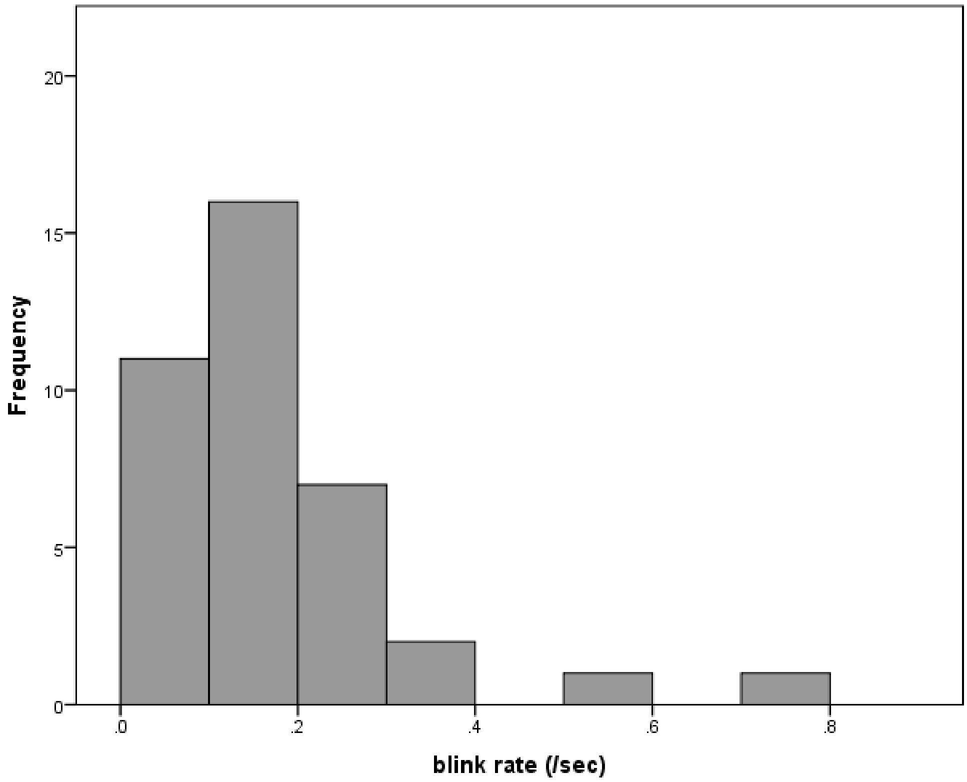


Figure 6.6: Histogram of average blink rates per second for all participants.

No correlation was found between ASRS scores and blink rates, $r(38)$=-.130, p=.438 (Figure 6.7.

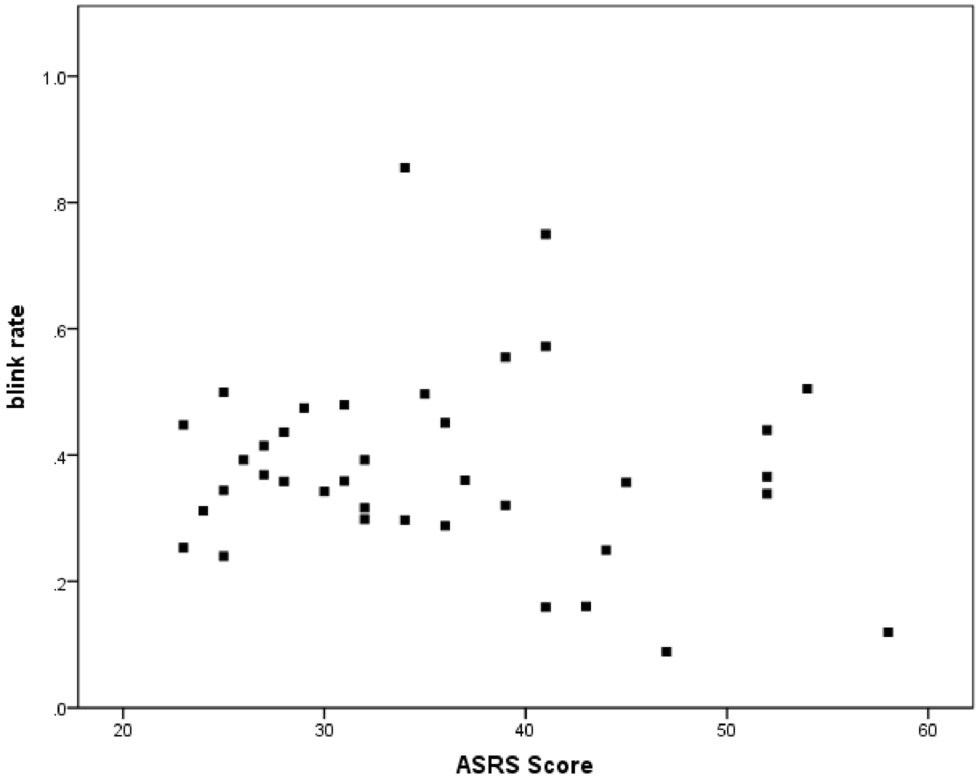


FIGURE 6.7: Scatterplot of blink rates for all participants and ASRS scores.

6.6 Discussion

This study examined microsaccade rates in participants with varying levels of ADHD traits during a prolonged sustained fixation paradigm. We found that higher level of ADHD traits as measured in the ASRS was associated with increased rates of microsaccades. Participants who reported more inattention and hyperactivity traits made more binocular and monocular microsaccades. No other differences in microsaccade properties were observed. This study also investigated differences in blink rates between participants with high and low ADHD traits. No association was found between self-reported ADHD traits and blink rates.

Substantial variability in microsaccade rates across participants was found in our study. This is a common finding in eye movement research (Poynter et al., 2013). ADHD traits could explain some of this variability. Even though our study used a subclinical population, a significant effect of ADHD like traits on oculomotor patterns was found. This is the second study showing a connection between ADHD and microsaccade rate (Fried et al., 2014). Increased number of microsaccades are found not only in children diagnosed with ADHD but also adults with ADHD symptoms. This finding suggests that abnormal eye movements could be part of the ADHD phenotype.

The SC plays an important role in the generation and inhibition of microsaccades. The SC hypothesis of ADHD, which was described in detail in Chapter 2 and is the main topic of this thesis, proposes that the SC is hyper-responsive in individuals with ADHD. Such an imbalance would lead to difficulty inhibiting eye-movements, and sustaining fixation. A hyper-responsive SC would also manifest through an increased number of microsaccades. In our paradigm the participants were required to maintain fixation for a specific amount of time in the absence of distractors. Such a simple task was chosen to reduce its cognitive demands, and allow us to examine possible abnormalities associated with ADHD that occur in a subcortical level (i.e. the SC).

In our study, higher ADHD traits were associated with an increased rate of monocular microsaccade rate. The existence of truly monocular saccades is still debated.

Even though, previous studies (Engbert & Kliegl, 2003; Kloke, Jaschinski, & Jainta, 2009; Rolfs, Laubrock, & Kliegl, 2006) report detecting purely monocular microsaccades using automatic algorithms, there is no known mechanism for the generation of such eye movements. Preliminary evidence suggests that monocular microsaccades are 60% more likely to appear in the dominant eye and their purpose is to find the preferred intra-foveal locus of fixation (Gautier, Hairol, Siderov, & Waugh, 2014). Kloke et al. (2009) speculated that microsaccades detected in one eye could also be occurring in the other but the direction change could be too small to allow detection. In such cases analysing monocular microsaccades could provide us with useful information. Microsaccades detected in one eye, however, can often induce noise to the data (Engbert, 2006; Laubrock et al., 2005; Engbert, 2006; Troncoso et al., 2008; Rolfs et al., 2006). As a result, our finding should be interpreted with caution. Further studies should investigate potential mechanisms involved in monocular microsaccade generation.

Our paradigm employed trials with fixed timing. It has been shown that fixed timing is a critical property and that people with ADHD have a specific impairment in the transient allocation of attention for anticipated and regular events (Greenberg & Waldmant, 1993; Shalev et al., 2011; Fried et al., 2014). Therefore, it is possible that participants with higher ADHD traits found the task more demanding. However, previous studies have found that non-visual cognitive processing leads to a decreased rate of microsaccades (Gao, Yan, & Sun, 2015). The opposite was observed in our study.

Individual measures of eye-movement behaviour have been shown to be consistent across tasks (Poynter et al., 2013). For example, Poynter and colleagues (2013) used six metrics (Fixation Rate, Duration, and Size; Saccade Amplitude; Micro-Saccade Rate and Amplitude) to measure individuals' eye-movement behaviour profiles and observed stable idiosyncrasies in measures of fixational eye-movement and consistent inter-metric correlations across tasks (e.g. participants who make more frequent saccades in one task, executed saccades more frequently in a different task). Similar findings have been reported by Hermens & Walker, 2010 who found that microsaccade rates within individuals were similar across different conditions. Consequently, ADHD traits could be associated with an increased number of microsaccades in different tasks. Failing to suppress microsaccades could be linked to attention problems. In our study, we used a simple sustained fixation paradigm. Future studies should attempt investigating microsaccades in subjects with ADHD or high ADHD traits in more attention demanding tasks and correlate their oculomotor pattern with symptom severity.

Blink rates of the participants in our study were lower than than blink rates usually reported in the existing literature. Previous research has found blink rates of 0.28/sec at rest, which can decrease to as low as 0.075/sec, when the subject is performing a reading task (Bentivoglio et al., 1997). The reduced blink rate observed in our data could be the result of our paradigm and the instructions given to the participants. Even though they were not instructed not to blink during fixation, participants were encouraged to blink and rest their eyes in between trials. This could potentially lead to a decrease in the blink rates during sustained fixation periods. No significant difference was found between participants with high ADHD and low ADHD traits in blink rates. Participants with higher ADHD traits tended to have slightly lower blink rates compared to participants with fewer ADHD like traits. Even though ADHD is thought to be associated with higher blink rates (Fried et al., 2014), this relationship seems to be reversed in cases of unmedicated ADHD subjects (Caplan et al., 1996). The medication prescribed for ADHD, therefore, could be the main reason why patients with ADHD blink more often. Future studies should examine whether this finding can be replicated in larger samples of healthy volunteers with a high number of ADHD like symptoms.

As in studies reported in previous chapters (Chapter 4, and Chapter 5), the current results demonstrate that studying subclinical populations can provide useful information to ADHD researchers. In this case, our findings were similar to the results of a clinical study. This suggests that abnormal oculomotor behaviour is a core deficit in ADHD, and supports the involvement of subcortical brain regions in the disorder. Furthermore, oculomotor tasks examining sustained fixation could have the potential to be used as biomarkers for ADHD.

6.7 Conclusion

Microsaccades are small, fast saccades that occur during fixation and are associated with the allocation of attention. The colliculus is one of the main areas linked to the generation and inhibition of microsaccades. This study examined the relationship between ADHD traits and microsaccades. Higher ADHD traits were associated with an elevated number of microsaccades. This result further supports the role of SC in ADHD.

These findings suggest a new area of study for ADHD research and shed light on the possible mechanisms involved in the disorder. The fact that our results are in line with research on clinical population provides further support for the use of subclinical populations in the study of ADHD.

Chapter 7

Testing the SC Hypothesis in children with ADHD: visual field size differences

7.1 Chapter Summary

The superior colliculus (SC), a sensory structure which lies deep within the brain, is particularly sensitive to certain types of visual stimuli, in particular small, moving things at the edges of vision. Visual field testing involves the detection of stimuli with properties associated with collicular function. In our study we presented such stimuli to ADHD patients using a specialised device called an Octopus semi-automated perimeter which is widely used by optometrists and orthoptists. We compared the performance of ADHD patients with age matched control subjects, and thus tested whether hypersensitivity in the superior colliculus plays a role in ADHD. Children with ADHD had faster reaction times to targets compared to controls. The visual field size of ADHD participants was found to be significantly smaller than the one in the healthy participants. The examination of differences between medicated and unmedicated subjects showed that medication tends to normalise the RTs of ADHD children, but decrease the size of their central visual field. Possible explanations for our findings are provided. Future studies could further examine the usefulness of optical perimetry testing as clinical tests for ADHD.

7.2 Introduction

There seems to be a discrepancy in the definition of central and peripheral visual field between optometrists and psychophysicists. Clinically, within 30° of fixation is referred to as the central visual field, while the rest referred to as the peripheral visual field (Buckley, Codina, Bhardwaj, & Pascalis, 2010). It is divided into nasal and temporal halves and superior and inferior altitudinal halves. The peripheral visual field, as defined by clinicians, is usually neglected by psychology research. However, in everyday life we heavily depend on the detection of events on the far periphery. For example, activities such as walking or driving require the ability to quickly detect movement in far peripheral locations.

One of the main roles of the SC is moving the eyes to bring stimuli in the peripheral visual field into central vision for more detailed analysis by the cortex. Neurons found in the SC that respond to visual stimuli have been shown to be particularly sensitive to the onset, offset and movement of small stimuli (Albano et al., 1982; Goldberg & Wurtz, 1972; Wurtz & Goldberg, 1972b). From studies on monkeys it is know that collicular lesions result in failure to detect small, moving, peripheral stimuli (Albano et al., 1982). Consequently, such stimuli could be used to assess collicular function psychophysically.

7.2.1 The Visual Field

A normal visual field extends approximately 100° temporally (laterally), 60° nasally, 60° superiorly, and 70° inferiorly (Anderson & Patella, n.d.). A physiologic scotoma (a blind spot) exists at 15° temporally where the optic nerve leaves the eye. Definitive location varies slightly on an individual basis (Armaly, 1969). The average blind spot is 7.5° in diameter, vertically centered 1.5° below the horizontal meridian (Hart & Burde, 1983).

The commonly used tests to examine the size of an individual's visual field are the Confrontation Visual Field Exam, Kinetic Perimetry, Static Perimetry, and Automated Perimetry (Walker, Hall, Hurst, & Spector, 1990). Confrontation visual field testing is usually employed as a screening test by clinicians suspecting visual field loss in patients. During this examination one of the patient's eyes is occluded, while the other eye fixates on a target object. Then the patient is asked to describe what they can see on their peripheral vision. This test is subjective and unreliable and it is mostly used as screening tool (L. N. Johnson & Baloh, 1991). In Kinetic Perimetry bright lights of varying colour, shape, luminosity, and size are used as targets and appear on a white background. A form of Kinetic Perimetry is Goldmann perimetry (Goldmann, 1945). The measurement of the visual field with this method requires highly trained perimetrists as it requires them to manually map the field. Static Perimetry assesses the ability of the patient to detect a static target in the visual field. The most well known form of Static Perimetry is the Humphrey Visual Field Test. Currently, the most objective and reliable way to assess visual field size is Automated Perimetry. Many forms of automated perimetry are available, but they require the patient to fixate on a central target and respond when they notice small flashes of light in their peripheral vision. The most widely used equipment for automated perimetry is the Octopus semi-automated kinetic perimetry (Bjerre, Codina, & Griffiths, 2014).

Automated perimetry is considered to involve the magnocellular pathways (Sample, Bosworth, & Weinreb, 1997; Delgado et al., 2002), which includes the SC. Neuroimaging work (Stephen et al., 2002) and single-cell recordings (Schiller & Malpeli, 1978) have found that the central visual fields project mostly towards the ventral cortical processing streams, while the peripheral fields towards the dorsal cortical processing streams.

7.2.2 The Visual Field in ADHD

Visual field examinations are typically used to assess abnormalities in the individual's non foveal vision. They also provide valuable information in different neurological and developmental disorders in children and young adults (E. Larsson, Martin, & Holmström, 2003). Preliminary evidence suggests abnormal peripheral vision in other developmental disorders, such as autism spectrum disorders (Milne, Scope, Griffiths, Codina, & Buckley, 2013; Frey, Molholm, Lalor, Russo, & Foxe, 2013), dyslexia (Geiger & Lettvin, 1987). Although ADHD is a disorder that affects both the structure and function of the brain, there is a very small number of published studies describing visual fields in children and adolescents with ADHD.

Even though many studies report abnormalities in visual-spatial working memory and eye movements in ADHD, only a small number of studies have actually investigated vision in children and adolescents with ADHD. Grönlund, Aring, Landgren, and Hellström (2007) examined 47 patients diagnosed with ADHD (mean age: 12) and reported that 76% of them had abnormal ophthalmological findings. In particular, children with ADHD compared to controls had reduced Visual Acuity, higher percentages of strabismus, reduced stereo vision, subnormal near-point of convergence, refractive errors, and other signs of cognitive visual problems. Some of these issues such as visual acuity, were not as common in subjects treated with stimulants. However, no direct relationship between ADHD medication and visual function could be established in this study. These fingings indicate an early disturbance of the development of low level vision.

To our knowledge, only one study has examined visual fields in ADHD (L. Martin et al., 2008). Martin and colleagues (2008) tested the visual acuity and visual fields of 18 children diagnosed with ADHD aged 6–17 years, both off and on medication in order to establish the role of medication in visual field size in ADHD. Computerised Rarebit perimetry was used to examine visual fields. Rarebit perimetry employs small bright dots, which are presented one or two at a time. The participant is requested to maintain fixation on a fixation mark which moves across the screen and at the same time make a response depending on the number of dots they perceive (McKendrick, 2005). Martin and colleagues (2008) found that significantly more subjects with ADHD off medication had subnormal visual field results compared to controls. This difference was no longer significant when the ADHD children were tested on medication.

7.3 Current Study

The main aim of the current study was to evaluate the visual fields in children with ADHD, and detect any abnormalities when compared to age-matched controls. The visual field testing employed here to assess visual fields uses small, bright stimuli that appear in the periphery and move towards the centre of vision. Given the collicular nature of these stimuli, visual field testing would allow us to test the collicular hyper-responsiveness hypothesis in ADHD. Unlike the previous study by Martin et al. (2008), here we used a different form of perimetry, semi-automated kinetic perimetry. Collicular hyper-responsiveness could appear as reduced reaction times, an increased apparent visual field for such stimuli and a increased likelihood of eye movements (losses of fixation) to such stimuli (in comparison to control subjects).

7.3.1 Method

7.3.1.1 Participants

39 children were recruited from a local ADHD clinic and local schools. 20 participants (4 female) diagnosed with ADHD took part in the study. The ADHD diagnoses were determined according to DSM-IV criteria by an experienced clinician. The mean age of the ADHD group was 12.11 (*SD* 1.66, range: 9-15). They all fulfilled the inclusion criteria of visual acuity of 0.3 LogMAR with or without refractive correction in either eye, no epilepsy, and no previous significant ophthalmological history. Only the right eye was tested, unless the right eye vision was worse than 0.3. 4 participants were left-handed. 19 participants (4 female) were used as controls. The control group data was collected in a previous study by Bjerre, Codina, and Griffiths (2014) using exactly the same protocol as the one employed in our study. 39 age and gender matched children picked randomly from a pool of 69 participants aged 9-15 were used as controls. The mean age of the control group was 12.11 (*SD* 1.66, range: 9-15). Previous research has found that obtaining reliable visual fields in children under 10 is problematic (Bjerre et al., 2014). This was the main reason, younger children were not recruited in our study.

The study was approved by The University of Sheffield Ethics Committee. Children were tested in the Sheffield Children's Hospital. The majority of patients tested were prescribed medication (15 out of 18) for their ADHD symptoms. 7 children were tested off medication (early in the morning) and the rest after having taken their medication as they normally do. 8 children were diagnosed with pure ADHD and the rest had at least one co-morbid disorder (27.8% autism, 33.3% dyslexia, 2% other learning difficulties).

Learning effects have been observed in previous Automated Perimetry studies in healthy and clinical populations (Castro, Kawase, & Melo Jr, 2008; Wild, Dengler-Harles, Searle, O'Neill, & Crews, 1989). Consequently, to avoid possible confounds, all participants recruited in this study were naive to automated perimetry.

7.3.1.2 Equipment

A 900 series Octopus perimeter (Haag Streit USA, Ohio) was used. While gaze remains directed to a central fixation point the observer's task is to press a button when they detect a spot of light, projected onto the inside of a white illuminated half-dome, that has moved along a radius from the outer periphery towards the fixation point. The device allows user defined stimuli to be presented in an automated manner at prescribed locations in the visual field. The device has been successfully used on previous occasions to map visual fields in clinical populations and to determine differences in visual field characteristics between patient groups (Buckley et al., 2010; Bjerre et al., 2014).

Two stimuli of the same size (0.25mm^2) were used but with different intensities to test the visual field. The far-peripheral visual field was assessed with the I4e stimulus ($328\ \text{cd/m}^2$) and the central visual field was assessed with the I2e stimulus ($20\ \text{cd/m}^2$). Throughout the testing, all stimuli appeared against a uniform white background with illumination of 10 cd/m^2. The light intensity of the equipment was calibrated before each session.

The same programme used by Bjerre et al. (2014) was used. Employing an automatic programme allowed us to to ensure standardised testing of each participant. The targets appeared at 12 meridia (15°, 45°, 75°, 105°, 135°, 165°, 195°, 225°, 255°, 285°, 315°, and 345°). In cases of loss of fixation during presentation of the stimuli, the examiner could repeat a meridian and manually test the blind spot if it occurred eccentric to the position expected by the automated programme. The RT-corrected visual field areas were determined using pre-programmed RT vectors presented within the isoptres.

7.3.1.3 Procedure

Participants with ADHD were recruited via Sheffield Community Child and Adolescent Mental Health Services (CAMHS). Informed written consent from parents and assent from children to participate and permission of access to medical records was obtained after explanation of the nature and the background of the study. The controls were recruited from schools in the area of Sheffield. None of them were diagnosed with ADHD or any other developmental disorders.

Testing took place in the Sheffield Children's Hospital. Visual acuity (VA) of each eye was assessed using the Crowded LogMAR Test (CLT) (Figure 7.1). This test is designed for accurate measurement of "crowded" visual acuity in children (McGraw & Winn, 1993) and incorporates several features to ease visual acuity testing in young children (Langaas, 2011). Each child stood 3 m from the visual acuity charts, and was instructed to read out loud the letters presented. A chart comprising of four letters was shown at each acuity level, starting with letters which could easily be seen. The letters size was reduced until the participants could not read them. Acuity in both eyes was tested.

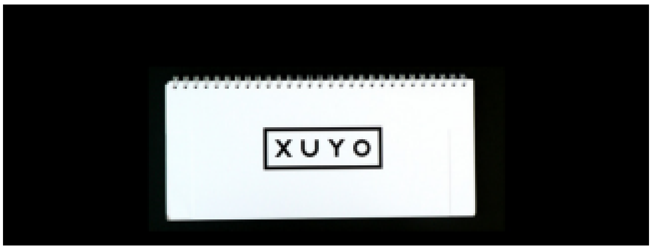


Figure 7.1: An example of stimuli from the Crowded LogMAR Test (CLT). Adapted from Norgett et al. 2011 (Norgett & Siderov, 2011)

The testing was conducted in a light proof room with extinguished room lights. The right eye was tested unless the right eye vision was worse than 0.3. The non-fixing eye of the participants was then occluded with a plastic, elastically secured patch. The participants were then given the response buzzer which they were instructed to hold in their dominant hand (defined as the hand used for writing). The participant's head was kept steady on a chin-rest. Small children were given an additional chin rest to elevate their head so that their pupil was centrally aligned with the fixation target. The Octopus was operated by a certified optometrist for all tests, whilst the experimenter monitored and counted fixation losses viewed on screen via an infrared camera.

A practice programme was administered first; this assessed response to six stimuli. More specifically, three stimuli were presented to the far peripheral visual field (up to 85° from fixation) and three were presented to the central visual field (up to 60° from fixation). Participants were instructed in age appropriate language to fixate a central green light within the perimeter bowl, whilst peripherally monitoring for a kinetic stimulus that appeared on 1 of 12 meridia. The stimuli were presented in a random order.

Only after successful completion of the practice test (maximum three practice tests per person) was the full test administered. The success measurement included the ability to maintain central fixation.

The full test consisted of an automatised programme that tested all meridians in a randomised order. To minimise inter-test differences, a specifically written programme ensured that the starting position of any test stimulus was identical for all participants.

The I4e kinetic stimulus was presented first, followed by the I2e. Static I2e stimuli were then randomly presented within each quadrant of the I2e stimulus area to identify the presence of any scotomas. Finally, the blind spot was plotted using the I2e stimulus starting in the centre of the expected blind spot and moving the stimuli outwards at $2^{\circ}/s$ along 4 cardinal and 4 intercardinal meridians. The RT vectors were assessed with four 2Ie stimuli in the central field area. If during testing any point was paused, or seemed inaccurate, it was replayed. Short breaks were included after the end of each field size, blind spot, and static point testing. This was to allow the participants to re-orientate themselves and to be able to verbally warn the patient of the change to the oncoming stimuli.

At the end of testing participants were asked to rate their experience of performing the visual field test by answering how difficult they thought it was ("easy", "okay", or "hard") and whether they could hear the noise the Octopus made during the test ("yes", "no") and what it meant. All subjects received Meadowhall vouchers (£10) as compensation for participating.

7.3.1.4 Data Analysis

The RT corrected values of the visual field as produced by the Octopus software were used in the analysis, as in previous studies (Bjerre et al., 2014). Initially, the performance of ADHD and control group was compared.

We also examined differences between medicated, unmedicated, and control subjects.

Data from 1 participant could not be obtained due to their inability to complete the practice session, and data from another participant were excluded from the analysis due to abnormally large visual field; the central visual field was over 10,000 deg^2, which is almost twice the size of the average central visual field (AppendixC).

7.3.2 Results

7.3.2.1 Feasibility

To discuss differences in visual field size in participants with ADHD and controls, it is necessary to first present feasibility data for the purpose of excluding unreliable data. No differences in fixation loss count between the two testing velocities were identified, so the fixation losses were collapsed into a single value. The difference between ADHD (*M*= 9.94, *SD*= 9.02) and control group (*M*= 7.53, *SD*= 10.21) was not statistically significant, *t*(35) = .762, *p* =.451.

7.3.2.2 Visual Field Size Differences

The mean and the SD of RT-corrected visual field area in deg^2 of all participants was calculated for the I4e and I2e targets. The mean visual field area using the I4e stimulus was 12046 deg^2 (*SD*= 1099) and deg^2 4686 (SD= 1282) for l2e, respectively. There was a significant difference between the ADHD (*M*=4001, *SD*= 974) and the control group (*M*=5333, *SD*= 1216) in the central visual field size, *t*(35)= -3.66, *p*=.001.

The difference between ADHD (*M*= 11651, *SD*= 1026) and control group (*M*= 12420, *SD*= 1056) in the far peripheral visual field size was also statistically significant, *t*(35)= -2.25, *p*=.031.

7.3.2.3 Blind Spot area

The mean blind spot area size in deg^2 was calculated for all participants (*M*= 38.87, *SD*= 18.21).

No difference was found in the RT corrected blind spot area in ADHD (*M*= 39.72,*SD*= 22.4) and non ADHD group (*M*= 38.1, *SD*= 13.71).

7.3.2.4 Reaction Times

The mean RT in both groups was 608.76 (SD= 196.76). The ADHD group (M= 516.67, SD= 176.87) had significantly faster RTs than the control group (M= 696, SD= 177.12), $t(35)$= -3.1, p=.004 (Figure 7.2).

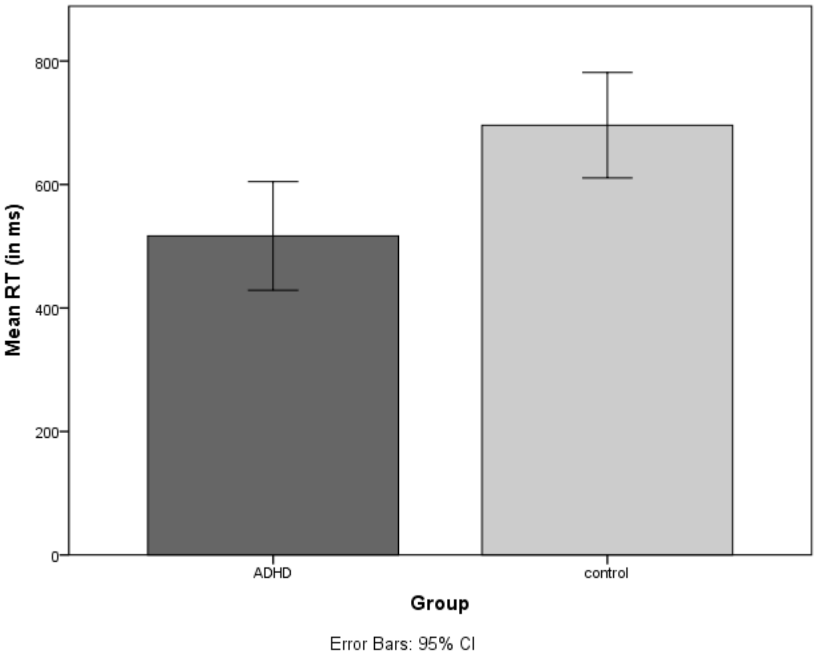


Figure 7.2: Reaction times (in ms) histogram showing the average RT in ADHD and control groups

7.3.2.5 Participant Difficulty Rating

No participants found the task difficult. 51.4% of the children found the test easy and 48.6% reported the test as being OK. Almost all the participants (36) were aware of the noise the Octopus makes during the stimuli presentation. 22 children associated the noise with the upcoming stimulus, while 15 were not aware of this relationship.

The difficulty ratings as a function of group condition is shown in Figure 7.3. No significant differences were found between ADHD and control groups in difficulty ratings, $\chi^2(1, \text{n}= 38)= 3.291$, p=.068.

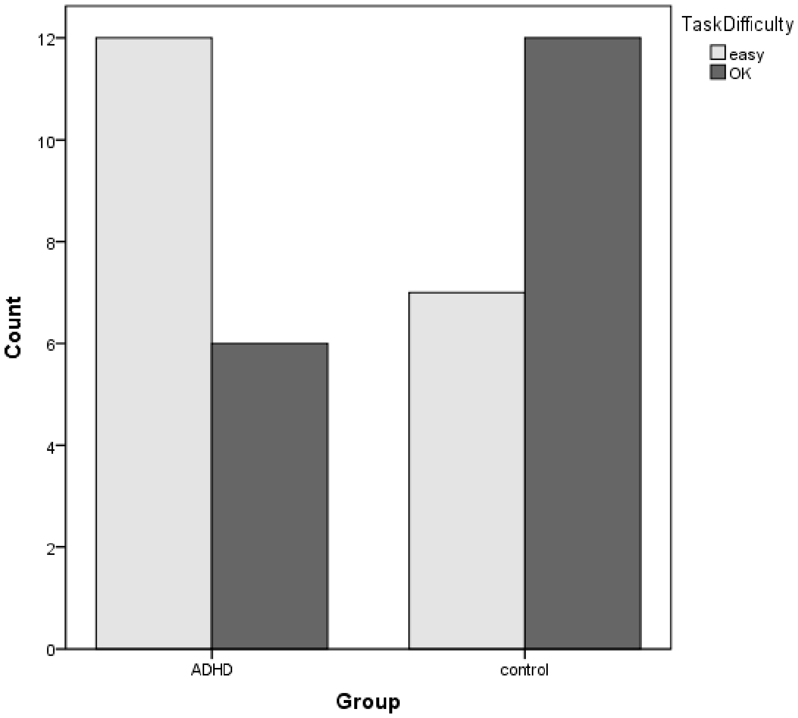


Figure 7.3: Bar Chart showing the difficulty ratings as a function of group condition

7.3.2.6 Effect of Medication Status

A one-way between subjects ANOVA was conducted to compare the fixation losses count between medicated ADHD, unmedicated ADHD, and control group (Table 7.1). No significant difference was found between groups, $F(2, 34)= .370$, p=.694.

Table 7.1: Mean Fixation losses, visual field size, Blind Spot size, and RT for each group.

Group	Fixation Losses	Far-Peripheral visual field Size	Central visual field Size	Blind Spot Area	RT
ADHD unmedicated	11.14	11650	1099	31.84	418.85
(N=7)	(12.4)	(946)	(415)	(24.5)	(92.13)
ADHD medicated	9.18	11651	931	44.73	578.9
(N=11)	(6.66)	(1119)	(280)	(20.5)	(192.7)
Control Group	7.53	12420	1216	38.1	696
(N=19)	(10.21)	(1056)	(279)	(13.7)	(177.1)

A one-way between subjects ANOVA was conducted to investigate differences between medicated ADHD, unmedicated ADHD, and control group in far-peripheral and central visual field size (Table 7.1) No significant difference was found between groups in far-peripheral visual field size, $F(2, 34)= 2.448$, p=.102. There was a significant effect on the central visual field size between groups, $F(2, 34)= 6.631$, p=.004. Post hoc comparisons using the Tukey HSD test indicated that the mean scores between medicated ADHD and control group were significantly different. The difference between unmedicated ADHD and control group approached significance (p=.055)(Figure 7.4).

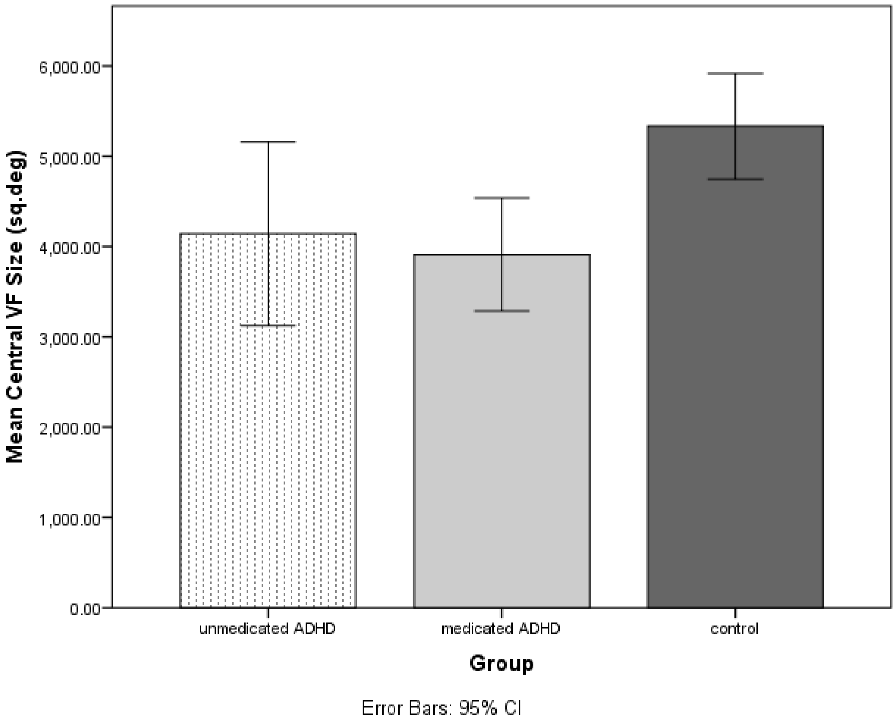


Figure 7.4: Bar Chart showing Central visual field Size as a function of group condition

No differences were found between groups in the blind spot area, $F(2, 34) = 1.118$, p=.339.

Finally, a one-way between subjects ANOVA was conducted to examine group differences in RT (Mean and SD values are presented on Table 7.1). There was a significant effect of group on RT, $F(2, 34) = 7.008$, p=.003 (Figure 7.5). Post hoc comparisons using the Tukey HSD test indicated that the mean scores between unmedicated ADHD and control group were significantly different. However, no other group differences were statistically significant.

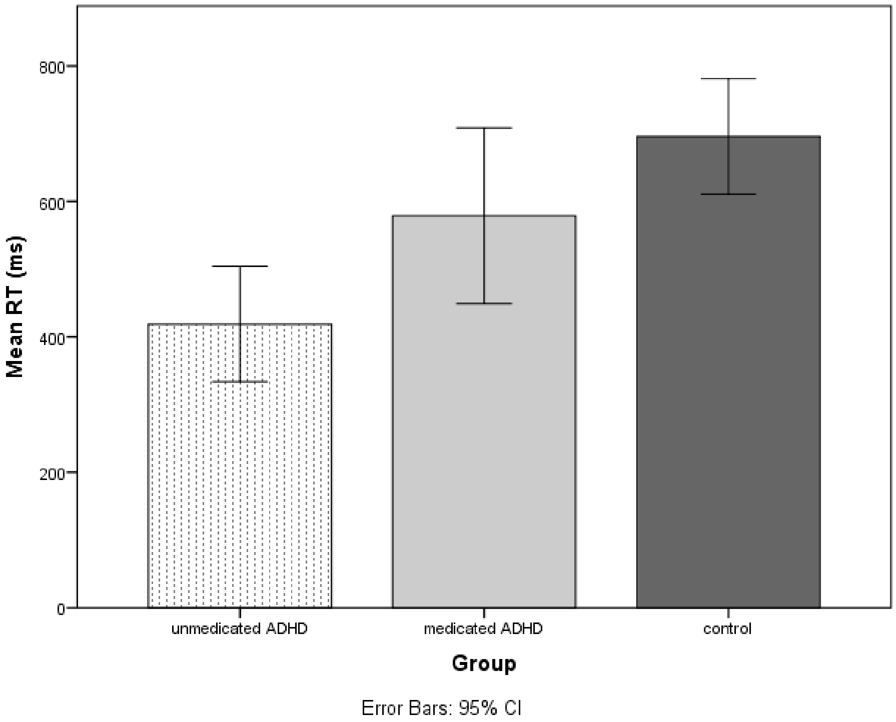


FIGURE 7.5: Reaction times (in ms) histogram showing the average RT in medicated ADHD, unmedicated ADHD, and control groups

7.3.2.7 Relationship between Central and Far Peripheral Visual Field

The relationship between central and far peripheral visual fields was investigated for the ADHD and the control group (Figure 7.6). The size of the far peripheral visual field was strongly correlated with the size of the central visual field in the control group, $r(19)=.707$, $p=.001$.

No correlation was found between the two visual fields in the ADHD group, $r(18)=.404$, $p=.096$.

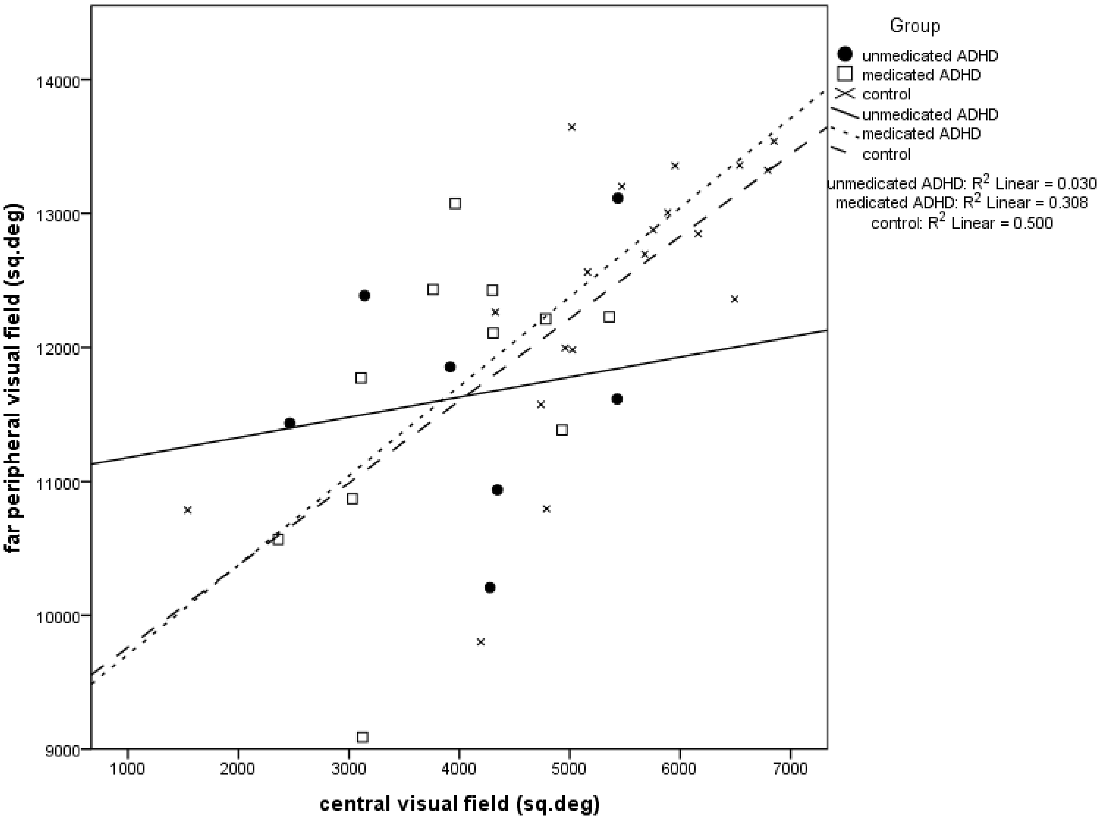


Figure 7.6: Relationship between far peripheral and central visual fields in medicated ADHD, unmedicated ADHD, and control groups

7.4 Discussion

This study investigated visual field sizes in participants with ADHD compared to control groups using Octopus semi-automated kinetic perimetry. An automatic programme was administered and the sizes of central and far peripheral visual field was examined. We found that children with ADHD had significantly smaller central and far- peripheral visual field than control groups. Furthermore, participants with ADHD had faster RTs. The effect of medication on visual field testing was also investigated. The medicated ADHD group had smaller central visual field than the control group. Furthermore, unmedicated ADHD participants had faster RT than the control group.

A recent study by Bjerre et al. (2014) found that semi automated kinetic perimetry is feasible in children, even though it might require physical adaptations to the machine (e.g. additional chin rest) and age appropriate instructions. More specifically, Bjerre et al. (2014) found that participants can reliably perform perimetry on the Octopus perimeter from the age of 10. Our study also supported this claim; only one subject aged 10 could not complete the task. The subjects in our study had visual fields similar in size with the ones reported in other studies using the Octopus (Rowe & Rowlands, 2014; Bjerre et al., 2014). We showed that children with ADHD can reliably perform Octopus perimetry. In addition to this, both ADHD and control participants found the task easy or relatively easy. Seeing how widely available automated permetry is in hospitals and how brief the test is, visual field testing could potentially be used as a diagnostic test for ADHD. ADHD diagnosis is currently based on interviews and measures with high subjectivity. The development of an objective biomarker could provide a very useful aid for the diagnosis of the disorder as well as its monitoring throughout the individual's lifespan. For example, the effect of medication could be examined by comparing differences in the visual field size, pre and post medication.

This is the first study to investigate visual field size using automated Octopus perimetry. Even though most existing types of perimetry measure the size of the subject's visual field, they employ different methods, which tap into different cognitive functions and brain mechanisms (McKendrick, 2005). Automated perimetry, such as the one employed in our study, is considered to engage the magnocellular pathways (Sample et al., 1997; Delgado et al., 2002)

ADHD is often associated with slow and variable RTs (Kofler et al., 2013; Tamm et al., 2012). The opposite was found in our study; ADHD children had significantly faster RTs than control children. The difference between mean RTs was bigger between unmedicated children and the control group. Medication slowed down the RTs of ADHD (Figure 7.5). Even though ADHD is associated with slower RTs, in certain cases participants with ADHD can have the same RTs or even faster RTs than controls. For example, fast-incentive conditions, fast paced tasks, or intrinsically salient, they tend to significantly reduce the RTs in individuals with ADHD (Andreou et al., 2007; Leung, Leung, & Tang, 2000b). Furthermore, slow RTs in ADHD seem to be task sensitive (Epstein et al., 2011a). Kofler et al. (2013) found that controlling for RT variability, extinguishes the RT difference between ADHD and controls. Contrary to our findings, administration of methylphenidate or stimulants has been shown to shorten the RTs and their variability (S. V. Spencer et al., 2009). Our paradigm was short and fast-paced. This could partly explain the faster RTs observed in the ADHD group.

Another explanation for the faster RTs in participants with ADHD could be the nature of the stimuli used in parts of the visual field testing employed in our paradigm. The subject was required to respond to moving, small lights appearing in the visual periphery. Such targets have been found to engage the SC (Albano et al., 1982; Goldberg & Wurtz, 1972; Wurtz & Goldberg, 1972b). According to the SC hypothesis, we expected the ADHD group to respond faster to targets in their periphery, thus having a larger visual field. Even though ADHD children appear to have smaller visual fields, their RTs were significantly faster. This could indicate an increased sensitivity to stimuli of such nature.

Automated perimetry requires the observer to respond to stimuli by pressing a button at the detection of the target light. Even though the visual field size as calculated by the Octopus software is RT corrected, one could argue that a difference in RT could partly account for our findings. However, faster RTs would result in larger visual fields (Buckley et al., 2010). The opposite was found in our study. Even though participants with ADHD have significantly faster RTs than the control group, they still have smaller visual fields. Consequently, RTs do not seem to confound our results.

Even though ADHD is linked to increased distractibility (Adler, 2004), over-focusing has been also reported (Kinsbourne, 1991). Previous research has shown that increased attentional demands can modify the detection of targets (Russell, Malhotra, & Husain, 2004) or the effect of distractors appearing in the peripheral visual field (Schwartz et al., 2005). In our paradigm participants had to focus on the centre of the Octopus screen and surpress eye movements. Over-focusing, while performing this task could potentially reduce sensitivity to stimuli appearing in the near or far periphery (Forster et al., 2014). Such a behaviour would result in seemingly smaller visual fields.

More demanding tasks have been shown to alter the functional visual field (M. Ikeda & Takeuchi, 1975). One could argue that our finding could be due to ADHD children having difficulties sustaining fixation and finding the task more challenging. However, the task difficulty as reported by each subject and the lack of differences in fixation losses, do not support this hypothesis. More specifically, the proportion of ADHD children who described the task as "easy" after its completion was higher than the proportion of control children, who in their vast majority characterised the task as "OK". In addition to this, the number of fixation losses could be used as an objective measure of task difficulty. Even though the ADHD group had a slightly higher number of fixation losses across conditions, this difference was not statistically significant.

Oculomotor deficits have been repeatedly reported in ADHD (Munoz et al., 2003; Bala et al., 1981; Klein et al., 2003). An abnormality in the visual field could potentially account for some of the eye motility dysfunctions associated with ADHD. The fast response to peripheral targets found in subjects with ADHD could be linked to their increased levels of distractibility and difficulties in sustaining attention (Adler, 2004; Metin et al., 2012; Teicher et al., 1996).

Automated perimetry as employed in the Octopus, the equipment used in our study, is based on the detection of stimuli as they move from peripheral locations to the centre of the visual field. Studies on monkeys have shown that the part of the striate cortex that projects to the peripheral visual field has a higher number of neurons that respond to moving stimuli (Battaglini, Galletti, & Fattori, 1993). Visual neurons responding to the far-peripheral visual field tend to be more sensitive to faster velocities. Battaglini et al. (1993) reported that in striate cortex the peripheral neurons responded to velocities over 10°/s. Neurons representing central portions of the visual field, however, tend to respond to slower velocities. SC neurons have been found to respond to most velocities (Goldberg & Wurtz, 1972), but velocities of movement of 10°/s and 50°/s have been identified as optimal (Stein & Arigbede, 1972). The maximum velocity used in our study was 5°/s. Higher velocities in automated perimetry have been associated with decreased reliability of the procedure, especially in the case of younger children (Hirasawa, Shoji, Okada, Takano, & Tomioka, 2014). Velocities over 10°/s are also reported as very fast by adult participants (C. A. Johnson, Keltner, & Lewis, 1987). It is, therefore, recommended to use slower velocities when examining visual fields with the Octopus.

In our study children with ADHD had smaller central visual fields. The stimuli presented on the central visual field had lower contrast than the ones in the far periphery. Animal studies have shown that the SC neurons respond to stimuli with lower contrast (Schneider & Kastner, 2005b). This finding could indicate that the colliculus is involved in ADHD.

An interesting finding of our study was the lack of significant correlation between far peripheral and central visual field in participants with ADHD. Anecdotal reports by clinicians suggest that in healthy subjects the size of the inner visual field is strongly correlated with the size of the outer field, as we observed in subjects without ADHD. The relationship between far peripheral and central visual field of medicated ADHD participants appears to resemble that of the control group. However, the small sample size does not allows us to draw any safe conclusions from the data. More research is needed to elucidate the meaning of this finding.

Finally, our results suggest that ADHD diagnosis should been taken into account by optometrists when examining visual fields of children.

7.4.1 The Effect of Medication

Contrary to previous studies, children on medication had significantly smaller central visual fields than children off medication and controls. This effect was not observed when examining the far peripheral visual fields. A possible explanation for this finding could be due to a limitation of the Octopus. Rowe and Rowlands (2014) compared different types of kinetic perimetry and found that when using the Octopus the I2e stimulus is better at identifying visual field defects. This could be due to the reduced intensity of the stimulus compared to the I4e one. The increased sensitivity of the I2e stimulus could explain why the difference found between ADHD and control group is more pronounced in the central visual field.

When comparing the performance of children who were on medication and children off medication on the day of testing, we found that even though the difference was not statistically significant medication led to a decrease in the number of fixation losses. This is consistent with findings from previous studies that have reported more intrusive saccades during fixation in unmedicated ADHD children (Munoz et al., 2003; Gould et al., 2001). Stimulant medication has been found to normalise oculomotor behaviour in ADHD (Bylsma & Pivik, 1989).

Medication, also, had an effect on RTs. Participants tested on medication had slower RTs; the difference between ADHD group on medication and the control group was not statistically significant. This is a seemingly unusual finding considering that previous studies report faster RTs in children with ADHD after administration of medication (Epstein et al., 2011b; Tamm et al., 2012). However, methylphenidate does not seem to decrease RT in ADHD, it tends to normalise responses. In our task normalisation of RTs would result in slower RTs similar to those recorded by control participants.

7.4.2 Limitations

A limitation in our study is recruiting children with ADHD, the majority of whom were on medication to treat their symptoms. Methylphenidate which is the most commonly prescribed drug for ADHD has the potential to affect brain development. The exact effect of long-term use of methylphenidate is not yet known. However, there is evidence suggesting that it leads to some changes in the brain, as well as behavioural changes (Coghill, Rhodes, & Matthews, 2007; Kline, Chen, Tso-Olivas, & Feeney, 1994; Nakao, Radua, Rubia, & Mataix-Cols, 2011). For example, chronic treatment with stimulant medication is associated with a decrease in the density of dopamine transporter in the basal ganglia (Singer et al., 2002) and differences in grey matter volume (Nakao et al., 2011) Another study reported that long term administration of methylphenidate in rats can lead to neurochemical changes in a number of brain regions including the hippocampal dentate gyrus and the medial prefrontal cortex (J. D. Gray et al., 2007). These areas are involved in a wide range of cognitive functions and behaviours. In our study, 15 children were prescribed medication for the management of their symptoms. Some of them had been taking medication for a long time. It is not possible to establish whether the differences we found are inherent to ADHD or result of the prolongued methylphenidate use. Future studies should recruit children with

ADHD who have never taken medication and compare their visual fields to those of children on medication and healthy controls. Such a study would allow us to clearly link visual field abnormalities to ADHD.

Another limitation in our study was the fact that the examiners in the present study were not masked to the diagnosis of the children tested. This was due to the nature of clinical settings. However, it would be useful for future studies to attempt double blind testing.

7.5 Conclusion

We examined the central and far peripheral visual fields of children with ADHD and control using semi automated kinetic perimetry. The stimuli used to identify visual field deficits were small, moving, bright lights. The SC, which has been hypothesised to be hyper-responsive in ADHD, is very sensitive to such stimuli. Participants with ADHD had faster RTs compared to controls, but significantly smaller visual fields. These findings show that perimetry testing could potentially discriminate ADHD from non ADHD patients and could even provide a much needed biomarker for the disorder.

Chapter 8

General Discussion & Conclusion

8.1 Chapter Summary

This chapter summarises the findings of this work. The implications of the results of four studies described in the previous sections are discussed and the current state of the SC hypothesis of ADHD is examined. Moreover, we present the main limitations of this thesis and conclude by proposing a number of future studies that could further our understanding of the collicular involvement in ADHD and could lead to the potential development of biomarkers for the disorder.

8.2 Introduction

Even though ADHD is a disorder affecting up to 10% of the population (Ford et al., 2003b; Tannock, 1998; Polanczyk et al., 2007; Seixas et al., 2012), many gaps exist in our knowledge about its aetiology and effective treatment. Until recently most theories attempting to explain its symptoms focussed on executive functions and proposed a frontal lobe involvement (Kerr & Zelazo, 2004; Barkley, 1997; Pennington & Ozonoff, 1996). However, an increasing amount of evidence suggests that more primitive, subcortical networks might be also impaired in individuals with ADHD (Munoz et al., 2003; Fried et al., 2014; Feifel et al., 2004). One potential locus of interest in ADHD is the SC (Overton et al., 1985). The SC has been extensively studied in animals (Robinson & Wurtz, 1976; Schiller & Koerner, 1971; Schiller & Stryker, 1972; Sparks, 1975; Wurtz & Goldberg, 1971, 1972a). Numerous studies (Robinson & Wurtz, 1976; Schiller & Koerner, 1971; Schiller & Stryker, 1972; Sparks, 1975; Wurtz & Goldberg, 1971, 1972a; Meredith & Stein, 1986; Stein & Meredith, 1993; Wallace et al., 1996) have shown that the colliculus plays an important role in covert attention, eye movements, and multisensory integration. It is also closely linked to distractibility (Albano et al., 1982; Milner et al., 1978). A small number of recent studies on animal models of ADHD have provided some preliminary proof for SC hypothesis, showing that animal models of ADHD have abnormal performance in tasks involving the colliculus (Dommett & Rostron, 2011; K. Clements et al., 2014). To our knowledge, no study so far had tested this hypothesis in humans.

The main aim of the present thesis was to investigate the predictions of the SC hypothesis in ADHD. More specifically, a combination of methods and tests that have been associated with collicular function were employed to test populations with high ADHD traits and a clinical sample. More specifically, we looked at distractibility induced by far-peripheral, collicular distractors, multisensory integration, microsaccade rates, and visual field sizes.

Another aim of this study was to examine potential biomarkers for ADHD based on the results in tasks involving the colliculus.

This final chapter of the thesis will summarise the findings relating to these aims and then address the issues that arise from these findings.

8.2.1 The Role of The SC in ADHD

The main purpose of this thesis was to investigate the SC hypothesis in humans. To our knowledge, this is the first project to investigate the role of the SC in human subjects with ADHD.

Isolating the function of one region in the brain is an almost impossible task. The small size and the location of the SC makes it difficult to study using traditional neuroimaging methods. Furthermore, other techniques such as Electroencephalography (EEG) and Transcranial magnetic stimulation (TMS), are only suitable for areas closer to the cortex and cannot be applied for the study of subcortical areas such as the colliculus. As a result, directly looking at SC activity in humans was not possible for this study. Therefore, behavioural and oculomotor tasks which partly depend on collicular activities were utilised.

In our first study, a novel distractibility paradigm was devised. Far-peripheral distractors were employed, the features of which, make them especially sensitive to SC function. In particular, the SC has been found to be particularly responsive to stimuli presented in the far-periphery (Sylvester et al., 2007; Posner, 1980; Meredith et al., 1987). Moreover, a link has been established between the SC and covert attention (Müller et al., 2005). The distractors employed in our paradigm were moving, far-peripheral checkerboards. Previous neuroimaging studies have found that stimuli of similar nature are related to collicular activation (Calvert et al., 2000; Schneider & Kastner, 2005b). Collicular hyper-responsiveness would manifest as abnormal processing of distractors resulting in differences in task performance. Three experiments were administered in a population with varying ADHD traits. In the first experiment, the distractors appeared in 10% of the trials, while the participants were performing a sustained attention task. The distractors appeared 75ms before the main stimulus. Their effect on response times and accuracy was investigated. Participants with high ADHD traits processed those collicular distractors abnormally; even though the presence of distractors led to slower RTs across participants, this effect was not found in subjects with a high level of ADHD traits. Furthermore, the effect of distractors on reaction time variability was examined. Higher ADHD traits were associated with decreased variability in trials with distractors. To sum up, the presence of a distractor had a facilitative effect on participants with high ADHD traits. In a second experiment we modified the onset of the distractor, so that they appeared almost simultaneously with the main stimulus. This diminished its informational content and removed any potential cuing effects. This manipulation removed the relationship between ADHD traits and distractor cost on RT. Distractor trials were associated with slower RTs in all participants independent of ADHD symptoms. In our first two studies accuracy was very high, thus it was difficult to establish the potential distractor effect on accuracy. This led to a third experiment, which required participants to decide whether the main stimulus was odd or even. Far peripheral distractors similar to those employed in the first study were used in 10% of the trials. This time, however, main stimuli appearing in distractor trials had a 50%-50% chance of being odd or even. As a result, the effect of distractors on accuracy could be examined. High ADHD traits were associated with poor performance in both distractor and distractor free trials. Our results provide some preliminary support for the role of the SC in ADHD. Higher ADHD traits were associated with abnormal processing of distractors of collicular nature. The onset of the distractor, as well as its informational content modulated this effect. It is worth noting that this difference was not due to mental workload effects; no relationship was found between noticing the distractors and ADHD traits or any performance measures. The presence of only one type of distractors in our paradigm does not allow us to draw definite conclusions about the role of the SC. Even though the SC has been found to particularly sensitive to temporal factors, such as stimulus onset (Meredith et al., 1987), it is possible that participants with high ADHD traits process stimuli with particular onsets differently, even when they are not of collicular nature. A future study employing both collicular and non collicular distractors could provide an answer to this. S-cone visual stimuli are thought to not directly access the SC (Thirkettle et al., 2013; B. J. White et al., 2009). Comparing the effect of S-cone and collicular distractors on task performance in ADHD would allow us to establish whether this difference we observed is driven by collicular function.

In the second study, MSI was investigated in participants with high and low ADHD symptoms. Multimodal integration has been associated with collicular function in animals and humans. More specifically, the temporal window of integration depends on collicular activity. The SC is only part of the regions involved in such a complex behaviour. However, the fact that it receives visual, auditory, and somatosensory inputs (Meredith & Stein, 1986) suggests that the SC serves like a multisensory integration hub, thus has a critical role in MSI. By employing a SJ and a TOJ task, two tasks widely used in MSI research, we showed that individuals with high ADHD had a significantly smaller window of integration in the SJ task alone. This effect was not observed in the TOJ tasks; both high and low ADHD groups had similar TWI when assessed with the TOJ. These two tasks are thought to engage different neural networks. The SJ has been associated with activations in a cortical and subcortical network comprising the insula, cerebellum, inferior frontal gyrus, inferior parietal lobe, superior colliculus and posterior thalamus, when synchrony is detected (Bushara et al., 2001). The TOJ task seems to depend mostly on cortical brain regions as it requires more resources and involves higher cognitive functions (Fink et al., 2006; Yarrow et al., 2014). The SJ task, which identified differences in our study is considered to be a more sensitive measure regarding the temporal aspects of a stimulus (i.e., PSS measure; Schneider & Bavelier, 2003; Vatakis et al., 2008). The lack of significant differences in the TOJ task could pinpoint to the perceptual and neural mechanisms involved in ADHD. As reported in Chapter 3, the SC is one of the main areas involved in the SJ task (Bushara et al., 2001; Meredith et al., 1987). An abnormal SC function would lead to an altered temporal window of multisensory integration. This is consistent with our findings from the SJ task; the size of the TWI is smaller in participants with high ADHD traits. Since more mechanisms are involved in the TOJ tasks, participants with high ADHD traits could be compensating or relying on different strategies. Performance measures in TOJs have been found to depend more heavily on strategies and response biases than the ones in SJ.

In a third experiment, the relationship between oculomotor performance and ADHD traits was examined. More specifically, we looked at differences in microsaccades in individuals with varying levels of ADHD. Saccades, including microsaccades, are highly depended on collicular function (Hafed et al., 2009, 2009, 2011). In particular, the SC has been found to play an important role in the generation and the inhibition of microsaccades (Hafed et al., 2009). In the case of a hyper-responsive colliculus, we would expect to find an increased number of microsaccades executed during fixation periods. In our paradigm, participants with high and low ADHD traits were instructed to fixate on a central target for a fixed period of time, while their eye movements were being recorded. Higher ADHD traits were correlated with an increase in both binocular and monocular microsaccade rate. This finding was consistent with the SC hypothesis; as we predicted, a higher level of ADHD traits was associated with the execution of a larger number of microsaccades during fixation.

In a fourth experiment the visual fields of children with ADHD were investigated and compared to those of age and gender matched controls. The task we used for this study was a clinical method widely used (Walker et al., 1990; Bjerre et al., 2014) to assess abnormalities in visual fields, Octopus semi automatic kinetic perimetry. This paradigm employs stimuli sensitive to collicular function; small, fast, moving, bright lights (Sylvester et al., 2007; Posner, 1980). Furthermore, the allocation of attention to stimuli appearing in the visual field has been associated with collicular function (Wurtz & Goldberg, 1972b). According to the SC hypothesis we predicted ADHD children to have faster response times to the targets, which would result in seemingly larger visual fields. Both medicated and unmedicated ADHD children were tested. Compared to control groups, ADHD children had significantly smaller visual fields. The difference between groups was more evident in the central visual field. Their response times, however, were significantly faster than those in control children. Faster RTs to collicular stimuli, could indicate a potential SC role in ADHD.

Overall, our findings suggest the possibility of collicular involvement in ADHD, a finding consistent with the existing animal literature (Dommett & Rostron, 2011; K. Clements et al., 2014). Both children with ADHD and individuals with high level of ADHD traits showed abnormalities in an array of tasks, which are hypothesised to tap into collicular function. A link between distractibility, multimodal integration, sensitivity to far-peripheral visual stimuli, as well as microsaccade execution with the SC has been well established.

8.2.2 A biomarker for ADHD?

ADHD diagnosis is currently based on interviews and parent/guardian/teacher reports. All these measures are characterised by high subjectivity. The subjective nature of ADHD diagnosis hinders ADHD research and its effective treatment.

Since there is no objective test for ADHD, other conditions with similar symptoms often get misdiagnosed as ADHD (Buttross, 2000). Several attempts have been made towards the development of an objective test for ADHD. Currently, there is no objective test for ADHD. The majority of developed tests depend on higher cognitive functions, such as sustained and selective attention (Greenberg & Waldmant, 1993) and have questionable reliability as screening diagnostic tools (Zelnik et al., 2012; Lindhiem et al., 2014). The development of an objective biomarker could lead to more accurate diagnosis and provide an effective way to monitor the effect of treatment (Moffitt et al., 2008; Singh & Rose, 2009). Oculomotor biomarkers are a possible area of interest for ADHD research. A few potential areas for future biomarker research arise from our studies. Two of our studies found evidence of abnormal eye movements and vision in both children with ADHD and healthy populations with high ADHD traits. In particular, children diagnosed with ADHD had significantly smaller visual fields than control children, as examined used the Octopus (Chapter 7). Additionally, ADHD symptoms were associated with an increased number of microsaccades during a simple sustained fixation task (Chapter 6). The findings from our study on the visual field differences in children with ADHD were very promising. A significantly smaller visual field was observed in ADHD. The difference was bigger in the central visual field. The fact that semi automated kinetic perimetry is feasible in young children (Bjerre et al., 2014) and in children with ADHD suggests that it could potentially be employed to test for ADHD symptoms. In our study children with ADHD could reliably perform Octopus perimetry as objectively verified by the small number of fixation losses recorded. In addition to this, all the children in the ADHD group reported no difficulties performing the task, which they found easy or relatively easy. Medication did not seem to have an effect on this; both subjects on and subjects off medication provided us with similar feedback. Perimetry is widely available in hospitals and the visual field test is very brief - taking less than 10 minutes. These characteristics suggest that visual field testing could potentially be used as a diagnostic test for ADHD.

In Chapter 6 we found a statistically significant correlation between the frequency of microsaccades executed during a sustained fixation task and ADHD traits. Participants with a higher level of ADHD symptoms, as assessed on the ASRS, made more microsaccades, while fixating on a target. A simple sustained fixation task requires minimum cognitive effort from the participants. We managed to identify differences in high and low ADHD by administering 20 trials each consisting of 20s fixation periods. Eye tracking systems are becoming increasingly popular. It is estimated that in the near future eye tracking will be integrated in gadgets we use on a regular basis. A biomarker based on eye movements could be a very effective way of testing for ADHD symptoms. Future research should focus on microsaccades.

Oculomotor deficits have been identified in various psychiatric and developmental disorders. To develop an accurate test for ADHD, it is necessary for future studies to include clinical groups as well as control groups when testing ADHD populations. This approach would allow us to identify factors associated exclusively with ADHD.

8.2.3 Positive ADHD?

Positive psychology aims at identifying specific strengths and skills of an individual and intervening to further develop them, thus leading to a more fulfilling life (Compton, 2005). This approach has been recently applied to dyslexia and other disorders.

A number of potential strengths of individuals with ADHD were identified in the studies described in the previous chapters. More specifically, participants with ADHD traits had smaller windows of temporal integration than participants with lower levels of ADHD traits. Even though this could in certain circumstances lead to increased distractibility, such a characteristic could also be advantageous. For example, it could allow to differentiate more accurately between stimuli appearing close to one another in time. Such an ability could lead to increased performance in certain tasks (e.g. sports, music). Further studies are required to examine this hypothesis.

In the first experiment described on Chapter 4 individuals with higher level of ADHD traits were less distracted by an external distractor appearing in their visual periphery at a predefined onset. In fact, higher ADHD traits had faster RTs in trials with distractors. It was shown that high ADHD is associated with different processing of distractors of collicular nature appearing 75ms before the main stimulus. Future research should attempt to replicate this finding in a clinical population. Specific learning strategies and methods could be developed for

ADHD, which could exploit this strength. For example, employing intermittent far peripheral distractors could benefit children with ADHD in the classroom.

8.3 Limitations

The majority of our findings come from healthy volunteers with varying ADHD traits as assessed on the ASRS, a self-report questionnaire. This approach has been very popular in ASD research. Since developmental disorders can be seen as the extreme manifestation of a spectrum of behaviours, using subclinical populations to examine new hypotheses can be informative. However, differences between clinical population and subclinical ones have been reported (Geurts et al., 2013) suggesting that even though there is evidence for an ADHD continuum, which extends to the general population, identifying ADHD solely as the extreme of a behaviour could be an oversimplification. Future studies should repeat our paradigms with clinical populations.

Another limitation of our studies was employing correlational analyses for two of the reported studies; the continuum approach . Even though examining the relationship between two factors can be highly informative, it does not allow us to infer that ADHD is the main cause of these effects.

The sample sizes employed in most of our studies were small. In particular, the study described on Chapter 7 recruited a limited number of ADHD children due to difficulties in accessing clinical populations. Even though we had sufficient power to detect group differences between ADHD and control groups, it was not possible to look into the potential effect of subtypes and/or co-morbidities. These effects could be examined by future studies using larger groups.

The SC hypothesis does not attempt to fully explain ADHD. This thesis only proposes that the colliculus is one of the brain areas affected in ADHD, which could explain part of its symptomatology and should be further investigated in future studies. This is of particular importance because the majority of previous research (e.g. Barkley, 1997; Kerr & Zelazo, 2004; Sonuga-Barke, 2003) on ADHD is focussed on frontal lobe abnormalities and executive dysfunction. Even though the role of the PFC has been established in this specific disorder, it does not exclude a possible vital role for subcortical areas, such as the SC. In fact, a PFC dysfunction could potentially lead to collicular hyperesponsiveness - by not inhibiting the SC. This could be the topic of future research.

8.4 Future Directions

Three studies reported in this project identified a relationship between ADHD traits and abnormalities in oculomotor behaviour, multimodal processing, and distractibility. Our results suggest that the dimensionality approach can provide us with useful information about ADHD, when access to a clinical population is not possible. Moreover, it is a quick way to test new theories before proceeding to examine a population diagnosed with ADHD. The spectrum approach is gaining increasingly popularity in psychiatry (Hudziak et al., 2007; Rodriguez et al., 2007; J. Martin et al., 2014; H. Larsson et al., 2012; Levy et al., 1997). Since ADHD can be seen as a continuous variable, it would be interesting for future studies to employ a different questionnaire and recruit individuals from both ends of the spectrum (e.g., with enhanced performance in attention task).

Multisensory integration is essential for survival. Our findings suggest that this area of research should be further studied in ADHD. Since we used a healthy population with high and low traits, further testing in clinical populations is required before making clear assumptions. In addition to this, possible abnormalities in the ability to integrate stimuli from various senses should be investigated in relation to ADHD deficits; does a higher level of current ADHD symptoms correlate with a more abnormal MSI profile? A number of studies suggest that MSI training can be effective at modulating the window of multisensory integration (R. A. Stevenson et al., 2013; Powers et al., 2012, 2009; Mégevand et al., 2013; Fujisaki et al., 2004). The effects of training on MSI in populations with ADHD could be another area worth investigating. If an abnormal integration window is linked to increased distractibility, it would be possible to decrease it by training.

Even though our results provide some preliminary support for the SC hypothesis, none of the reported studies looked directly at collicular activity. Future studies should employ neuroimaging to examine collicular activity in subjects with ADHD and controls during tasks that have been shown to engage the SC. Recent developments in neuroimaging (Calvert et al., 2001; Calvert, 2001; Wall, Walker, & Smith, 2009; Krebs et al., 2010) have made scanning the SC possible. Such a study could provide a more complete answer to the exact role of the colliculus in this disorder. Additionally, connectivity analysis could be conducted to examine brain regions (e.g. DLPFC), which interact with the colliculus. Such studies could allow us to identify whether there is a SC specific deficit, and identify its aetiology.

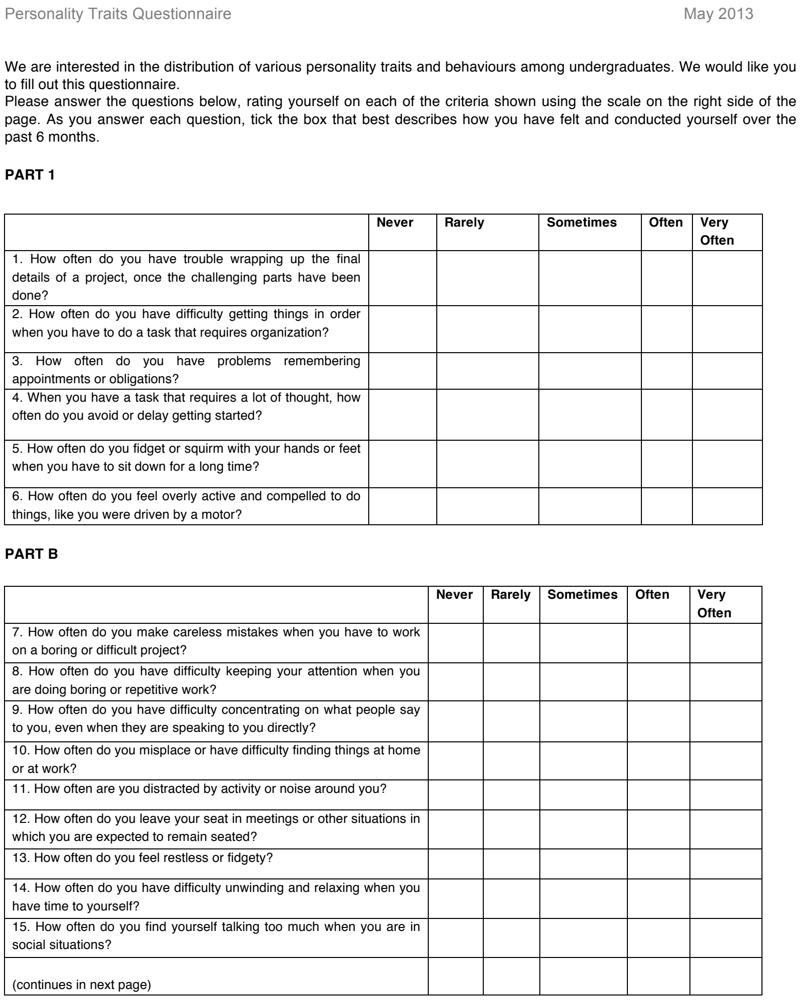
A few potential areas of research for biomarkers for ADHD were identified in our studies; microsaccade rate and visual field size. These findings suggest that oculomotor biomarkers could be developed for ADHD. Future research should be focussed on building upon our findings and attempt to create objective tests for ADHD.

8.5 Conclusion

The aim of the present thesis was to investigate the SC hyper-responsiveness hypothesis in ADHD in humans. Multiple tasks examining functions that have been associated with SC activity were employed. We found that healthy populations with high levels of ADHD, as well as children with ADHD, process collicular stimuli differently compared to individuals with low ADHD traits and controls. Furthermore, participants who report increased level of ADHD traits had abnormalities in multisensory processing, presenting with a smaller integration window relative to participants with low ADHD traits. These findings provide some initial support for the SC hypothesis of ADHD. Furthermore, oculomotor biomarkers are identified as potential areas for future ADHD research.

Appendix A

Appendix A



Personality Traits Questionnaire May 2013

We are interested in the distribution of various personality traits and behaviours among undergraduates. We would like you to fill out this questionnaire.
Please answer the questions below, rating yourself on each of the criteria shown using the scale on the right side of the page. As you answer each question, tick the box that best describes how you have felt and conducted yourself over the past 6 months.

PART 1

	Never	**Rarely**	**Sometimes**	**Often**	**Very Often**
1. How often do you have trouble wrapping up the final details of a project, once the challenging parts have been done?					
2. How often do you have difficulty getting things in order when you have to do a task that requires organization?					
3. How often do you have problems remembering appointments or obligations?					
4. When you have a task that requires a lot of thought, how often do you avoid or delay getting started?					
5. How often do you fidget or squirm with your hands or feet when you have to sit down for a long time?					
6. How often do you feel overly active and compelled to do things, like you were driven by a motor?					

PART B

	Never	**Rarely**	**Sometimes**	**Often**	**Very Often**
7. How often do you make careless mistakes when you have to work on a boring or difficult project?					
8. How often do you have difficulty keeping your attention when you are doing boring or repetitive work?					
9. How often do you have difficulty concentrating on what people say to you, even when they are speaking to you directly?					
10. How often do you misplace or have difficulty finding things at home or at work?					
11. How often are you distracted by activity or noise around you?					
12. How often do you leave your seat in meetings or other situations in which you are expected to remain seated?					
13. How often do you feel restless or fidgety?					
14. How often do you have difficulty unwinding and relaxing when you have time to yourself?					
15. How often do you find yourself talking too much when you are in social situations?					
(continues in next page)					

(continues in next page) 16. When you're in a conversation, how often do you find yourself finishing the sentences of the people you are talking to, before they can finish them themselves?					
17. How often do you have difficulty waiting your turn in situations when turn taking is required?					
18. How often do you interrupt others when they are busy?					

- I have previously been diagnosed with dyslexia.

☐ yes
☐ no

- I have previously been diagnosed with ADHD.

☐ yes
☐ no

- I have previously been diagnosed with autism.

☐ yes
☐ no

- I have previously been diagnosed with a mental disorder that I have been told might account for the types of experiences above, or I believe that I may be experiencing such a disorder. This might include Schizophrenia or other Psychotic Disorder, or something in the class of disorders included under the headings of Mood Disorder, Anxiety Disorder, Dissociative Disorder, or Personality Disorder.

☐ yes
☐ no

- Gender:

☐ male
☐ female

- Age: ……..

Appendix B

Appendix B

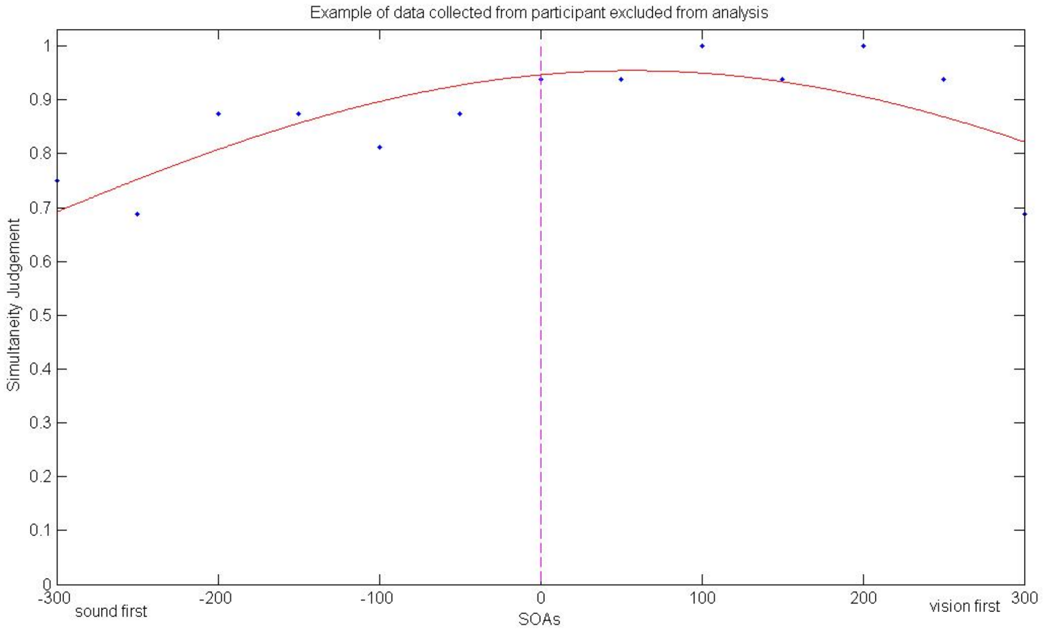


Figure B.1: Example of data obtained from participant excluded from data analysis in Chapter 5

Appendix C

Appendix C

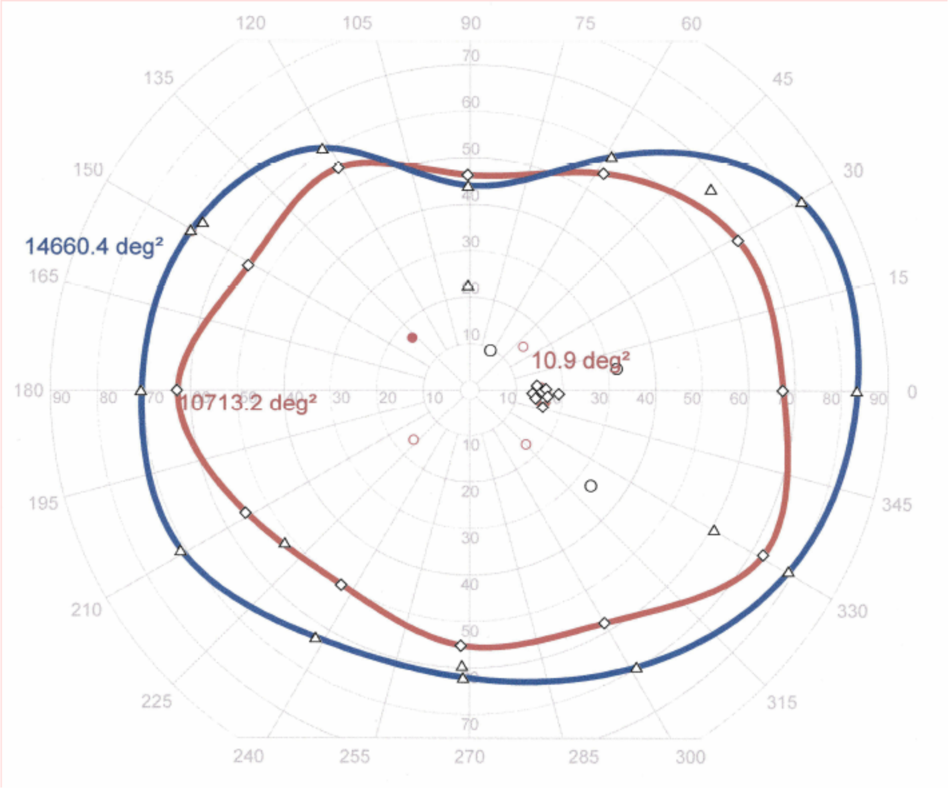


Figure C.1: Visual Field Printout obtained from participant excluded from data analysis in Chapter 7. The peripheral VF (14660 deg^2) and the central VF (10713.2 deg^2) as well as the blind spot (10.9 deg^2) are shown. All values were abnormal compared to those reported in previous research using the Octopus (Bjerre et al., 2014; Rowe & Rowlands, 2014)

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