Attention-Deficit/Hyperactivity Disorder (ADHD) and the influence of multisensory processes and sensorimotor integration on motor performance.

by

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An oral defense of this thesis took place on July 12th, 2022 in front of the following examining committee:

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Chair of Examining Committee	Adam Dubrowski
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The above committee determined that the thesis is acceptable in form and content and that a satisfactory knowledge of the field covered by the thesis was demonstrated by the candidate during an oral examination. A signed copy of the Certificate of Approval is available from the School of Graduate and Postdoctoral Studies.

Abstract

This thesis sought to investigate how adult Attention-Deficit/Hyperactivity Disorder (ADHD) influences processes relating to motor learning, sensory integration, and somatosensory processing. ADHD is associated with difficulties in motor control, including alterations to neural structure and function. However, it is unknown how these characteristics may influence motor control in adulthood. Results from study one suggests that those with ADHD exhibit an attenuation of neural activity in Brodmann area (BA) 2, right-hemispheric parietal lobe, in response to multisensory input. This may be reflective of alterations related to attentional resources and sensory processing when multiple simultaneous inputs are presented, as is the case during a multisensory condition. Differing activation within BA 2 provides important insight into the functioning of audiovisual multisensory processing in adults with ADHD. The second study, which utilized short-latency median nerve somatosensory evoked potentials (SEPs) paired with a novel visuomotor paradigm, yielded results of differing N18 and N30 SEP peak responses in those with ADHD. This suggests alterations to olivary-cerebellar-M1 processing and SMI when acquiring new motor skills, particularly those that are dependent on visuomotor input. Study three employed a novel force-matching motor paradigm and median nerve SEPs. Results indicated differential changes in the N18 SEP peak response after performing the novel force-matching task, suggesting a reduction in olivary-cerebellar-M1 inhibition. Finally, study 4 used source localization techniques to assess neural generator activity in response to median nerve stimulation after both visuomotor and force-matching motor paradigms. The ADHD group exhibited greater activation within BA 31 at post measures after performing the force-matching task, when compared to their baseline activity. This increased activity at post-measure may reflect activation of the Default Mode Network (DMN) and attentional changes, both of which are noted to be implicated in ADHD. As a whole, these findings provide a further understanding of the neurophysiological characteristics associated with ADHD, and their implications for motor control.

Keywords: Attention-Deficit/Hyperactivity Disorder (ADHD); sensorimotor integration (SMI); somatosensory processing; motor skill acquisition; somatosensory evoked potentials (SEPs)

Statement of Contributions

This thesis presents the research of Heather McCracken in collaboration with her Supervisors, Dr. Paul Yielder and Dr. Bernadette Murphy. The culmination of this work has resulted in the following contributions to the literature.

Published manuscripts included in this thesis:

McCracken, H., Murphy, B., Ambalavanar, U., Glazebrook, C., and Paul Yielder. Source localization of audiovisual multisensory neural generators in young adults with Attention-Deficit/Hyperactivity Disorder (2022). *Brain Sciences*.

Mrs. McCracken, Dr. Murphy, Dr. Glazebrook, and Dr. Yielder conception and design of research; Mrs. McCracken performed experiments; Mrs. McCracken and Miss Ambalavanar analyzed data; Mrs. McCracken, Dr. Murphy, Dr. Yielder, and Miss Ambalavanar interpreted results; Mrs. McCracken drafted manuscripts; Mrs. McCracken, Dr. Murphy, Dr. Yielder, and Dr. Glazebrook edited and revised manuscripts; Mrs. McCracken, Dr. Murphy, Dr. Yielder, and Dr. Glazebrook approved the final version of the manuscript.

Manuscripts submitted or to be submitted and included in this thesis:

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Mrs. McCracken, Dr. Murphy, and Dr. Yielder conception and design of research; Mrs. McCracken, Miss Ambalavanar, and Dr. Zabihhosseinian performed experiments; Mrs. McCracken, Miss Ambalavanar, and Dr. Zabihhosseinian analyzed data; Mrs. McCracken, Dr. Murphy, Dr. Yielder, and Miss Ambalavanar interpreted results; Mrs. McCracken drafted manuscripts; Mrs. McCracken, Dr. Murphy, and Dr. Yielder edited and revised manuscripts; Mrs. McCracken, Dr. Murphy, and Dr. Yielder approved the final version of the manuscript.

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McCracken, H., Murphy, B., Ambalavanar, U., Glazebrook, C., Yielder, P. Source Localization of Somatosensory Neural Generators in Adults with Attention-Deficit/Hyperactivity Disorder.

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Author’s Declaration

I hereby declare that this thesis consists of original work of which I have authored. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Slàinte mhath.

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List of Abbreviations

ADHD – Attention-Deficit/Hyperactivity Disorder

AASRS – Adult ADHD self-report scale

APB – Abductor pollicis brevis

ASD – Autism spectrum disorder

BA – Brodmann area

CNS – Central nervous system

DMN – Default mode network

EEG - Electroencephalography

EP – Evoked potential

ERP – Event-related potential

EHI – Edinburgh Handedness Inventory

FMT – Force matching task

M1 – Primary motor cortex

MSI – Multisensory integration

MTT – Motor tracing task

NSS – Neurological soft signs

PFC – Prefrontal cortex

PMC – Premotor cortex

PNS – Peripheral nervous system

S1 – Primary somatosensory cortex

SD – Standard deviation

SEP(s) – Somatosensory evoked potentials

sLORETA - standardized low-resolution brain electromagnetic tomography

SMA – Supplementary motor area

SMI – Sensorimotor integration

SnPM – Statistical non-parametric mapping

TMS – Transcranial magnetic stimulation

Chapter 1: Introduction

1.1 General Overview of Thesis

The process of sensorimotor integration (SMI) describes the nervous system's ability to integrate somatosensory afferents to refine motor commands and perform voluntary movement (Wolpert, Ghahramani, & Jordan, 1995). Additionally, successful motor control commands are integral to many, if not all, daily activities. When acquiring novel motor skills, the integration of peripheral sensory afferents is a necessary step in this process. The neuroanatomy associated with such processes has long been studied (Ghilardi et al., 2000; Jueptner, Frith, Brooks, Frackowiak, & Passingham, 1997a; Jueptner et al., 1997b; Müller, Kleinhans, Pierce, Kemmotsu, & Courchesne, 2002), and therefore can provide novel insight into differences in special populations, such as those with Attention-Deficit/Hyperactivity Disorder (ADHD). ADHD is associated with the presence of unique neural characteristics when compared to neurotypical controls. Furthermore, alterations to sensorimotor processing (Duerden, Tannock, & Dockstader, 2012; Valera et al., 2010) and difficulties with motor control exist (Brossard-Racine, Shevell, Snider, Bélanger, & Majnemer, 2012; Duda, Casey, O'Brien, Frost, & Phillips, 2019; Feifel, Farber, Clementz, Perry, & Anllo-Vento, 2004; Fliers, Franke, & Buitelaar, 2011). Previous work has suggested that sensory processing, in particularly multisensory integration (MSI), may have unique neural attributes in adults with ADHD (McCracken, Murphy, Burkitt, Glazebrook, & Yielder, 2020; McCracken et al., 2019). This eludes to the question, as to how SMI may be impacted in this population, and the effect this may have on motor performance and learning. The ability to perform and adapt motor commands to fit the ever-changing demands of everyday tasks is essential to many daily activities. The neural and behavioural correlates of ADHD may impair this process and have fundamental implications for day-to-day function.

Therefore, understanding the presence and relevance of behavioural and neural attributes of sensory processing in adult ADHD is important.

1.2 General Objective of Thesis

ADHD is typically described and diagnosed based on specific behavioural characteristics. However, more recently, the underlying neural substrates associated with ADHD have become a focus to better understand the symptomology and functioning of individuals with ADHD. The primary aim of this dissertation was to quantify variants of sensory processing, including MSI and SMI, which will provide an improved understanding of how adults with ADHD function in multisensory environments such as large lecture theatres or busy offices, as well as how this impacts their ability to learn novel motor skills that rely on the efficacy of sensory integration. Research assessing the impact of ADHD has disproportionally focused on children. However, the acquisition of motor skills is not exclusive to childhood or the early years of development, it is indeed an invaluable and common occurrence throughout the lifespan, including adulthood. For instance, adults are commonly in environments or scenarios that may require them to adapt their motor pattern or strategy. Examples of such occurrences may include being trained for a new job which requires the use of newly developed devices, such as running heavy equipment or the technical skills it may require to perform experiments in a laboratory. When considering this, it becomes clear that further understanding both the behavioural and neural mechanisms that are pertinent to motor acquisition and learning is fundamental to creating inclusive environments, both in workplace or academic settings, for those who may need such supports, such as young adults with ADHD. This leads to the overall aim of this thesis, which was to systematically assess sensory processing associated with motor skill acquisition in young adults with ADHD, specifically those between the ages of 18 – 35 years old.

ADHD impacts individuals throughout their life, and although limited literature has addressed these sensory processes in ADHD, even less has done so in adults with ADHD. Adults make up an invaluable part of the population, and may provide further insight into MSI and SMI differences that remain following development and into adulthood. This research is fundamental to better understanding differences in MSI and SMI in young adults with ADHD, which might indicate that some of the core characteristics of ADHD are not simply a result of impairments to attention, but may reflect underlying differences in SMI and MSI which are highly dependent on attentional processes. The findings from this research could assist our understanding of how to adapt environments to best suit sensory and behavioural characteristics associated with ADHD, to maximize functionality and performance in increasingly stimulating modern environments.

Chapter 2: Review of Relevant Literature

The following sections provide a review of the current literature as it relates to ADHD, SMI, MSI, motor learning, and motor control, with a particular emphasis on the neuroanatomy involved in these processes, including methodological techniques that can be employed to assess such processes.

2.1 Introduction

The ability of an individual to receive, integrate, and process afferent input is fundamental to the human experience. How individuals perceive the world is contingent on many factors, including, but not limited to, how they receive, process, and respond to sensory information from the dynamic world we find ourselves in. Sensory processing, meaning how the peripheral and central nervous system (PNS/CNS) work in unison to receive and process afferent input, has important implications for perception and action. Neural and behavioural characteristics associated with certain special populations may affect these sensory processes. One such group is individuals with alterations to attentional capabilities.

2.2 Attention

Attention is classically defined as a state of readiness, particularly involving a selective narrowing or focusing of consciousness and receptivity (Merriam-webster, 2002), whereas Schmidt and Lee (2005) define attention as a concept that can be a limiting factor on information processing. Attentional capacity, which can be thought of as a form of vigilance, describes one's ability to maintain conscious focus on an intended target while negating irrelevant concurrent input, has the potential to impact the success of sensory processing. This is due to the inherent role that attention has on sensory reception and integration, as what we're able to perceive is fundamentally affected by where attention is allocated (Pessoa, Kastner, & Ungerleider, 2003). For instance, visual attention requires similar neural circuitry as those that process stimulus characteristics, including motion and texture (Pessoa et al., 2003). Furthermore, when a visual stimulus is presented and attention is allocated to this stimulus, there is a notable increase in the firing rate of neurons responding to this stimulus, in comparison to the attenuated neural response after presenting a stimulus that is unattended (Pessoa et al., 2003). Neural regions that are critical to spatial attention processes have been localized to frontal and parietal brain regions, including the superior parietal lobule (SPL) and the intraparietal sulcus (IPS), and the frontal eye field (FEF) and the supplementary eye field (SEF) (Esterman et al., 2015; Pessoa et al., 2003; Rosen, Stern, Michalka, Devaney, & Somers, 2015; Wu et al., 2016).

Functionally, the ability to sustain attention on a given task is fundamental and has real-world implications, such as those influencing academic outcomes, social experiences, and employment (Esterman & Rothlein, 2019). Individuals with developmental disabilities are more likely to experience altered sensory processing for a multitude of reasons, including altered behavioural and neurophysiological characteristics associated with their diagnosis (Wallace & Stevenson, 2014). For instance, if the ability to perceptually bind sensory information is altered, this will result in atypical multisensory functioning, such as the multisensory dysfunction affecting speech perception in autism spectrum disorder (ASD) (Bebko, Schroeder, & Weiss, 2014; Gelder, Vroomen, & Van der Heide, 1991; Wallace & Stevenson, 2014). ADHD is one such developmental disability where sustained attention is notably impacted (Esterman & Rothlein, 2019).

2.3 Attention-Deficit/Hyperactivity Disorder (ADHD)

ADHD is a common neurodevelopmental disorder that impacts individuals throughout their life. ADHD is often thought of as a predominantly childhood disorder, with estimates suggesting that 11% of American children will be diagnosed with ADHD (Visser et al., 2014). However, 65% of individuals diagnosed in childhood continue to exhibit the disorder well into adulthood (Faraone, Biederman, & Mick, 2006); this translates to approximately 6.5% of individuals continuing to exhibit signs and symptoms of ADHD into adulthood (Kessler et al., 2005b; Kessler et al., 2006; Wender, Wolf, & Wasserstein, 2001). In childhood, it is more common for boys to receive a diagnosis, whereas in adulthood some literature has suggested that it is more prevalent or equivalent in women (Almeida Montes, Hernández García, & Ricardo-Garcell, 2007; Cortese, Faraone, Bernardi, Wang, & Blanco, 2016). There are a number of treatments that individuals with ADHD can take to aid in the management of their symptoms and improve function. Treatment may include both pharmacological and behavioural or psychological approaches. Stimulant medications are commonly prescribed and can be a part of a multifaceted treatment approach (Mattingly, Wilson, & Rostain, 2017). Psychostimulants, including methylphenidate and amphetamine, are the most common forms of pharmacological treatment, although non-stimulant medications such as norepinephrine reuptake inhibitors and α2-adrenergic receptor agonists may be used as well (Mattingly et al., 2017). Stimulant medications work via increases in dopamine and possibly norepinephrine, to improve neural signal transmission within the prefrontal cortex (Stahl, 2010). Non-pharmacological treatments include mindfulness and cognitive behavioural therapy (Catalá-López et al., 2017; De Crescenzo, Cortese, Adamo, & Janiri, 2017; Nimmo-Smith et al., 2020).

Those with ADHD have unique behavioural and neurological characteristics, such as inattentiveness and thinning of gray matter, that put them at an increased likelihood to experience various forms of maladaptive sensory processing which are not yet fully understood (Visser et al., 2014). Maladaptive sensory processing has the potential to alter motor control, which has been noted in children with ADHD (Goetz, Vesela, & Ptacek, 2014; Jung, Woo, Kang, Choi, & Kim, 2014; Sanz-Cervera, Pastor-Cerezuela, González-Sala, Tárraga-Mínguez, & Fernández-Andrés, 2017). This may be due to attentional alterations in this population, as attentional capabilities play a key role in the processing of various sensory inputs (Velasques, Cagy, Piedade, & Ribeiro, 2013). Nonetheless, alterations in sensory processing can influence how an individual will adapt to incoming sensory information, consequently influencing how they may learn a novel skill. There are numerous kinds of sensory processes, all of which are fundamental to everyday life, two in particular are pertinent to this dissertation and may be impacted in adults with ADHD.

2.3.1 Behavioural Characteristics of ADHD

There are several hallmark signs of ADHD, which are often noted as behavioural inattention, hyperactivity, and impulsivity (Faraone, Sergeant, Gillberg, & Biederman, 2003).

There is a high amount of heterogeneity in ADHD presentation, and current diagnostic criteria based upon the DSM-V include inattention, hyperactivity, and impulsivity that are exhibited consistently, being maladaptive and inconsistent with the current developmental level, and symptoms that have been persistent for more than 6 months (*Diagnostic and statistical manual of mental disorders: DSM-5*, 2013). Additionally, symptom onset must have been prior to the age of 12 and must be accompanied by a negative affect on social, academic, or occupational function (*Diagnostic and statistical manual of mental disorders: DSM-5*, 2013). ADHD in adulthood may present differently than symptoms in childhood, as adult ADHD is correlated with increased levels of depression and anxiety, lower levels of employment, relationship quality, and health and wellbeing, including an increased likelihood of experiencing financial difficulties (Biederman & Faraone, 2006; Das, Cherbuin, Butterworth, Anstey, & Easteal, 2012; Kessler et al., 2005a; Rösler, Casas, Konofal, & Buitelaar, 2010). This indicates that ADHD in adulthood has important implications for quality of life and functional abilities (Das et al., 2012).

2.3.2 Motor Control and ADHD

Aside from diagnostic criteria, literature has noted that alterations to sensorimotor processing and discrimination are also present but are far less understood (Dockstader, Gaetz, Cheyne, & Tannock, 2009; Duerden et al., 2012; Parush, Sohmer, Steinberg, & Kaitz, 2007). Motor impairments are common in children with ADHD in various domains of motor control, including balance, muscle tone regulation, and coordination (Goetz et al., 2014; Gustafsson et al., 2010; Zang, Gu, Qian, & Wang, 2002). These motor alterations are described as Neurological Soft Signs (NSS) (Gustafsson et al., 2010). For instance, ADHD is associated with difficulty performing tasks that require motor coordination and performance, such as writing and playing sports (Fliers et al., 2011; Kaiser, Schoemaker, Albaret, & Geuze, 2015; Karatekin, Markiewicz, & Siegel, 2003). Additionally, a potential hallmark of ADHD symptomology is deficient inhibitory motor control (Lijffijt, Kenemans, Verbaten, & van Engeland, 2005; Neely et al., 2017). Difficulties are present relating to performing tasks dependent on motor coordination, including those such as balance during a single task, walking, reaction time, motor timing, slower movement preparation, motor timing, and handwriting (Duda et al., 2019; Kaiser et al., 2015; Klimkeit, Mattingley, Sheppard, Lee, & Bradshaw, 2005; Klotz, Johnson, Wu, Isaacs, & Gilbert, 2012; Shorer, Becker, Jacobi-Polishook, Oddsson, & Melzer, 2012; Yan & Thomas, 2002). While behavioural characteristics are rather well described, there are also parallel neurological alterations present in those with ADHD that are not as clearly understood.

2.3.3 Neural Characteristics of ADHD

ADHD is defined a neurodevelopmental disorder, and is associated with alterations to function and structure within many neural substrates. Distinct neural characteristics are present in cortical and subcortical locations, including but not necessarily limited to, those related to the prefrontal cortex, anterior cingulate, precuneus, parieto-temporal regions, mesocorticolimbic networks, caudate, thalamus, and cerebellar regions (Castellanos et al., 2002; Castellanos et al., 2008; Ehlis, Bähne, Jacob, Herrmann, & Fallgatter, 2008; Liston, Cohen, Teslovich, Levenson, & Casey, 2011; Makris et al., 2008; McAlonan et al., 2007; Proal et al., 2011; Sidlauskaite, Caeyenberghs, Sonuga-Barke, Roeyers, & Wiersema, 2015; Sun et al., 2012). Unique neural attributes correlated to ADHD can be noted throughout the cortical regions of the CNS, such as diffuse cortical thinning of gray matter. In those with ADHD gray matter thinning is persistent throughout frontal, parietal, temporal, and occipital regions (Castellanos et al., 2002; Duerden et al., 2012; Proal et al., 2011; Valera, Faraone, Murray, & Seidman, 2007); while one study noted that in adolescents with ADHD there was an increased cortical grey matter volume in the right pre-supplemental motor area (SMA), and in the right primary somatosensory area (S1) in adulthood (Duerden et al., 2012). This is posited to be related to impaired inhibitory processes (Duerden et al., 2012), and similar patterns are found in chronic pain populations (DaSilva, Granziera, Snyder, & Hadjikhani, 2007). Volumetric reductions in subcortical regions such as within the caudate, globus pallidus, and thalamus have been found in children with ADHD (Rosch et al., 2018). It is postulated that one of the pathological mechanisms of motor hyperactivity in those with ADHD is a result of imbalanced excitatory and inhibitory activity between cortical layers III and V (Buchmann et al., 2006; Buchmann et al., 2003). Furthermore, cortical volumetric analysis indicative of reduced total cerebral volume may suggest that this is a key neurophysiological feature associated with ADHD in childhood, with alterations most prominent in right parietal lobe and left occipital lobe (Wolosin, Richardson, Hennessey, Denckla, & Mostofsky, 2009). Noted reductions in cortical volume may be associated with differences in cortical folding in this population (Wolosin et al., 2009). Additionally, predominant neurophysiological characteristics of ADHD are thought to be related to alterations to fronto-striatal-cerebellar network circuity (Krain & Castellanos, 2006; Proal et al., 2011).

Of particular relevance to this dissertation are cerebellar alterations in those with ADHD. It has been suggested that alterations to fronto-cerebellar circuitry are strongly related to behavioural symptomology associated with ADHD, including hyperactivity and inattention (Durston, van Belle, & de Zeeuw, 2011; Koziol, Budding, & Chidekel, 2013). It has been hypothesized that NSS may be a result of altered cerebellar function (Gustafsson et al., 2010; Thomann et al., 2009). The cerebellum and striatum of the basal ganglia, in conjunction with the frontal lobe, that contains both the premotor and primary motor cortices, form communication networks, known as fronto-cerebellar and fronto-striatal networks. These networks are involved in the formation, refinement, and learning of voluntary motor commands (Debas et al., 2010; Doyon & Benali, 2005; Doyon et al., 2002a; Hikosaka et al., 1999). Therefore, it is possible that the diffuse neurophysiological componentry of ADHD may be related to the behavioural signs mentioned above, such as difficulties with motor performance and hallmark attentional difficulties.

More recently, specific cerebellar alterations have been linked to ADHD symptomology (Almeida Montes et al., 2011; Bruchhage, Bucci, & Becker, 2018; Castellanos et al., 1996; Ivanov, Murrough, Bansal, Hao, & Peterson, 2014; Makris et al., 2015; Schneider, Retz, Coogan, Thome, & Rösler, 2006; Valera et al., 2007), and have important implications for motor function (Bruchhage et al., 2018). One particular study found reduced volume in the left hemisphere of the cerebellum in addition to cerebral alterations within the basal ganglia, particularly the right globus pallidus, and caudate volume symmetry significantly differed in those with a diagnosis of ADHD (Castellanos et al., 1996). A second study noted reduced volume in the superior cerebellar vermis, while those with more significant clinical outcomes of ADHD had reduced volume in the left and right inferior-posterior cerebellar lobes, with volume reductions relative to their peers continuing progressively into adolescence (Bruchhage et al., 2018; Mackie et al., 2007). In other words, increased significant clinical outcome measures of ADHD, as noted by physicians, were correlated with greater reductions in cerebellar volume (Bruchhage et al., 2018; Mackie et al., 2007). Similarly, Ivanov and colleagues noted that more severe symptoms of ADHD were associated with reduced cerebellar vermis volume (Ivanov et al., 2014). It is worth mentioning that many of these studies were completed in child and adolescent populations, therefore their generalizability to adulthood is unknown due to changes that may occur during the maturational process. However, one study did assess cortical volume in medication-naïve adults with ADHD and found significant reductions in overall cerebellar volume (Makris et al., 2015), suggesting that neurological characteristics of ADHD, as they relate to cerebellar volume, persist into adulthood.

In addition to these structural alterations, one study also noted reduced activation in the declive lobule of the cerebellar vermis, caudate nucleus, anterior cingulate, superior frontal gyrus, and the dorsolateral prefrontal cortex (Ortiz et al., 2015). Authors suggest that the bias for immediate reward in childhood ADHD may lead to altered function in fronto-cerebellar and fronto-striatal networks in adult ADHD (Ortiz et al., 2015). It has been hypothesized that cerebellar alterations may result in dysregulated dopaminergic transmission, thus influencing inattention, motivation, and effort characteristics in ADHD (Sonuga-Barke, Sergeant, Nigg, & Willcutt, 2008; Volkow et al., 2009). Cerebellar alterations are now being established as a prominent neurological characteristic of ADHD that may be linked to the long-noted behavioural characteristics. Some functions that may be affected, include the process of motor acquisition and learning, particularly during the acquisition phase of a novel task, while executive function, visuospatial processing, and linguistics may also be altered (Schmahmann & Sherman, 1997). There are several neurophysiological techniques that can be used to assess these neural characteristics.

2.3.4 Electroencephalography (EEG) and ADHD

There are several non-invasive modalities and techniques that can be used to infer neural functioning. One such modality is electroencephalography (EEG), which has been successfully used to assess differences in neural function in those with ADHD, suggesting that EEG is sensitive enough to discern unique neural characteristics in this population (Bresnahan & Barry, 2002; McCracken et al., 2020; McCracken et al., 2019). Although structural and functional alterations are present, it is unclear if and how these may negatively, or positively, influence the function of these structures, including the sensory and behavioural processes they are involved in. Recently, EEG neural markers, and their relevance for future ADHD objective diagnostics, have been assessed. The convolutional neural network (CNN) shows potential for future clinical utility in understanding ADHD (Chen, Song, & Li, 2019; Dubreuil-Vall, Ruffini, & Camprodon, 2020). Additionally, the utilization of a Go/No-Go task in conjunction with event-related potentials (ERPs) via EEG shows early promise as a neural biomarker of ADHD (Häger et al., 2021). Unique frequency band alterations are commonly observed in ADHD, such as exhibiting alterations in alpha, beta, and theta frequencies (Adamou, Fullen, & Jones, 2020; Arns, Conners, & Kraemer, 2013). Beta power is sensitive to medication status while theta is not, as differences persisted regardless of treatment (Isiten, Cebi, Sutcubasi Kaya, Metin, & Tarhan, 2017). However, due to inconsistencies in findings, the utility of frequency band alterations to assist diagnostics in this population has received scrutiny (Kiiski et al., 2020; Kitsune et al., 2015; Saad, Kohn, Clarke, Lagopoulos, & Hermens, 2018). This suggests that an enhanced understanding of the neural attributes of ADHD is needed, and with this, a potential to improve future screening and diagnostic criteria to include objective neurophysiological markers. Previous work utilizing EEG found unique neural characteristics related to multisensory processing in young adults with ADHD (McCracken et al., 2020; McCracken et al., 2019). This assessment was completed on multisensory ERPs and was based upon the principle of superposition of electrical fields. This suggests that processes related to sensory integration, potentially including SMI, may be observed using EEG in ADHD. The results of the current research may add to the body of literature supporting an objective technique to both understand and potentially clinically diagnose ADHD in the future, in addition to further understanding implications for alterations in multisensory processing for sensorimotor integration and subsequent motor learning and performance.

2.4 Multisensory Processing

Multisensory processing and integration describes the process occurring when an individual is presented with multiple, simultaneously occurring stimuli (Driver & Spence, 2000). MSI is a sensory process that can greatly influence an individual’s interactions on a day-to-day basis, depending on the success with which sensory afferents can be seamlessly processed and integrated by the CNS. For example, MSI occurs when you see a cat and hear a meow. This is an example of audiovisual multisensory processing of semantically congruent stimuli. When stimuli are semantically congruent, i.e. the individual does not have to dissociate the meaning from either the visual or auditory input, this can result in both behavioural and neural enhancements, including shorter response times (Driver & Spence, 2000; Laurienti, Kraft, Maldjian, Burdette, & Wallace, 2004). A variable of multisensory processing, that can have a profound influence on the integration effect, is the allocation of attentional demands to each constituent sensory component that encompasses the multisensory stimulus. This suggests that the level of selective attention can modulate MSI (Alsius, Navarra, Campbell, & Soto-Faraco, 2005; Busse, Roberts, Crist, Weissman, & Woldorff, 2005; Talsma, Doty, & Woldorff, 2007; Talsma, Senkowski, Soto-Faraco, & Woldorff, 2010; Talsma & Woldorff, 2005; Vroomen, Bertelson, & De Gelder, 2001). For instance, allocating attention to both the auditory and visual component of a multisensory condition can have a critical effect on the electrophysiological responses typically associated with MSI (Talsma et al., 2007). This is observed as the absence or attenuation of neural enhancements that are typically associated with MSI, when attention is limited to only one of the stimuli components. Therefore, alterations in attention may result in multisensory dysfunction.

Characteristics present in ADHD, at both neural and behavioural levels, suggest that these sensory processes may be altered and therefore influence their ability to function and perform in sensory-rich environments, such as workplace and academic settings.

2.4.1 Multisensory Processing and ADHD

Research on multisensory processing and integration in those with ADHD is limited. However, previous research conducted in the Ontario Tech Neurophysiology Laboratory found that young adults with ADHD respond differently to audiovisual multisensory stimuli, at both the behavioural and neurological levels of assessment, when compared to their neurotypical counterparts (McCracken et al., 2020; McCracken et al., 2019). This work showed that those with ADHD respond faster to both unisensory and multisensory inputs without having statistically significant decrements to accuracy (McCracken et al., 2020). Those with ADHD showed altered neural responses to multisensory inputs, with an enhanced multisensory event-related potential (ERP) over parieto-occipital brain regions from 110 – 130ms (McCracken et al., 2020). This difference at early sensory processing latencies suggests that those with ADHD process multisensory information differently during pre-cognitive sensory integration. Particularly, structural uniqueness in parietal and occipital regions may result in alterations at early multisensory processing latencies.

Prior to this research, few studies had assessed multisensory processing in those with ADHD. One such study noted neural alterations in those with ADHD, specifically adolescents, noting alterations to the right anterior insula, as those with ADHD had increased thickness when compared to neurotypical controls (Duerden et al., 2012). The insula, Brodmann area (BA) 13, is involved in multisensory processes, likely being associated with stimulus identification (Duerden et al., 2012; Renier et al., 2009). Furthermore, one study has suggested that response inhibition is modulated via conflicting multisensory information in ADHD when presented with semantically incongruent multisensory inputs (Chmielewski et al., 2018). This was correlated with attenuated activation within the medial frontal gyrus, BA 32, in adolescent ADHD when compared to neurotypical controls (Chmielewski et al., 2018). Forming an enhanced understanding of MSI in those with ADHD could have important implications for better understanding potential maladaptive neural processing and how this may influence behavioural outcomes. Understanding potential alterations in multisensory processing provides valuable knowledge to inform the development of ways to improve the experience of young adults with ADHD in both motor learning and workplace settings, which are highly dependent on multisensory inputs. The previous research was limited to ERP assessments, and therefore lacked insight on specific neural structures pertinent to the differences discovered (McCracken et al., 2020; McCracken et al., 2019). To improve this work, it is necessary to understand whether specific neural generators are responsible for these differences and whether these differences may be viewed as beneficial or maladaptive in multisensory environments, as some scenarios may require varying levels of accuracy and speed to ensure success.

2.5 Sensorimotor Processing

Sensorimotor processing and integration describe the process of utilizing afferent feedback to formulate and adapt motor commands. By definition, this is a form of sensory processing that can influence motor performance and consequently motor learning and retention (Andrew, Yielder, Haavik, & Murphy, 2018). An example of SMI is the use of visual feedback to enhance motor outputs to improve measures of task performance, such as accuracy and response time. Visual feedback is also thought to play a large role in motor performance (Jung et al., 2014; Schmidt & Lee, 2005; Shum & Pang, 2009), and the eye is considered the most critical sensory receptor providing information for motor output (Schmidt & Lee, 2005). Although vision is not essential for all motor commands, vision does allow for a tailoring of motor commands to meet environmental demands, such as processing the movement of objects within the environment allowing for a tailored motor response (Schmidt & Lee, 2005). The visual system is classically divided into two anatomical streams, the dorsal and the ventral (Ungerleider & Mishkin, 1982); where the dorsal stream projects to the posterior parietal cortex and the ventral stream to the inferotemporal cortex (Ungerleider & Mishkin, 1982). Each stream is proposed to play distinct roles. The dorsal is thought to be involved in the information processing for the visual control of movement (i.e. action), and the ventral provides cognitive input concerning objects within the environment (i.e. perception) (Ungerleider & Mishkin, 1982), and these streams function in unison. Vision, amongst other afferent input, allow for performance modifications in response to task variables. A previous study noted that children (1 male and 1 female) with ADHD benefited from receiving behavioural performance cues while completing an arithmetic task (Codding, Lewandowski, & Eckert, 2005). However, another study noted no differences in motor performance when presented with performance feedback in young boys with ADHD (Bishop, Kelly, & Hull, 2018). Thus, the ability to compare task demands with task performance is not well understood in ADHD, and could potentially prove to be a promising technique to enhance motor performance in those with an ADHD diagnosis.

2.5.1 Sensorimotor Integration (SMI) and ADHD

Although neural and attentional alterations present in those with ADHD suggest that altered SMI is likely impacted, little literature has looked at this process in adults. Structurally, there are alterations to cortical thickness in sensorimotor processing brain regions, including those with ADHD having increased thickness in the pre-supplementary motor area and the S1

(Duerden et al., 2012). Researchers have suggested that those with ADHD may have alterations present in SMI when sensory information is presented in the form of median nerve stimulation (Dockstader et al., 2009). Specifically, an attenuation of mu modulation (i.e. oscillation frequencies between 8 – 12 Hz over motor cortices) in adult ADHD may be related to deficits of perception-to-action systems (Dockstader et al., 2009). Although literature suggests that sensorimotor processing is altered in ADHD (Dockstader et al., 2009; Dockstader et al., 2008; Rubia, Noorloos, Smith, Gunning, & Sergeant, 2003; Rubia, Taylor, Taylor, & Sergeant, 1999; Toplak & Tannock, 2005; Valera et al., 2010; Werry et al., 1972), it is unclear the influence this may have on both behavioural and neural measures of learning and SMI. Much of the limited research assessing SMI in those with ADHD has focused on childhood measures; thus, lacking an important and fundamental understanding of how motor capabilities and learning are potentially altered in adulthood.

2.5.2 Motor Control and Learning

Learning through movement is fundamental to the human experience, and occurs through the modulation of task dependent variables (Schmidt & Wrisberg, 2008; Thelen, 1995), such as modulation of the location, velocity, and acceleration of planned movement (Schmidt & Lee, 2005). Adapted movement is an integrated stimulus response mechanism which depends on the contextual demands of a given scenario (Thelen, 1990). The process of learning occurs via changes in synaptic connectivity, and involves complex neural circuity loops, which have important behavioural implications, such as refined motor performance (Asanuma & Keller, 1991; Masao, 1993). Motor and sensory development begin before and continue immediately after birth, as newborns are constantly presented with an inundation of sensory information, which may be in the form of visual, auditory, proprioceptive, tactile, and olfactory afferent information. The process of motor development involves three primary levels of neural processing; first, being at the spinal level; second, at the subcortical level, including the superior colliculus, basal ganglia, cerebellum, and vestibular nuclei; thirdly, at the cortical level, which is thought to be involved in the refining of motor control (Velasques et al., 2013). This process largely continues well into adulthood, where older individuals may utilize sensory feedback to perform coordinated movements of a skill (Wishart, Lee, Murdoch, & Hodges, 2000). This can allow for the continued refinement and learning of performance for the optimization of resources and energy expenditure, improving accuracy, and reduced risk of injury, etc.

The development and learning of motor skills resulting in improved proficiency changes throughout the life span, and comparisons of motor performance can be drawn between older adults to adolescence, or between typical and altered states, to form an improved understanding of behavioural and neurophysiological mechanisms that are imperative to such processes (Magill & Anderson, 2010). Common examples of this can be seen early as learning to walk, which largely becomes automated in standard environments with skill acquisition, or riding a bike, and later in life while learning to drive a vehicle or learning new skills in workplace settings, such as learning to use graspers if you are training to be a surgeon where the force output from the digits is crucial for performance (Magill & Anderson, 2010). This process is described as motor learning and the development of motor skills (Magill & Anderson, 2010). Motor learning is defined as a set of internal processes associated with practice, that will result in relatively permanent changes in capability, whereas motor development is described as the changes associated with motor performance as a result of growth, maturation, and experience (Schmidt & Lee, 2005). There are several variables that can affect the proficiency and the performance of a learned skill, such as attentional characteristics or the number of resources available.

2.5.3 Attention

Attention can be defined as a limited and selective resource (Schmidt & Lee, 2005), whereas selective attention specifically describes one's ability to attend to a selected stimulus in the presence of distractors (Johnston & Dark, 1986; Theeuwes, 1993). In terms of motor behaviour, humans are limited in the number of things they can attend to at any given time (Schmidt & Lee, 2005), and certain disorders, such as ADHD, are characterized by alterations to attentional resources. When presented with multiple activities requiring attention, each activity, or stimulus, competes for limited attentional resources, which can additionally result in interference with the opposing activity or stimulus (Schmidt & Lee, 2005). Intentional attention will occur when we purposefully choose to allocate attentional resources to a stimulus, whereas an incidental focus of attention will occur when there is a jarring external stimulus presented (Schmidt & Lee, 2005). The attainment of skillful movement requires conscious awareness, and therefore attention, which can lead to the automaticity of movement patterns (Schmidt & Lee, 2005). When directing attention towards specific variables, such as an internal vs external focus, this can provide feedback allowing for the refinement of the movement (Schmidt & Lee, 2005). Research suggests that experts have optimal results when exerting an external focus of attention, whereas beginner learners benefit from an internal focus of attention (Castaneda & Gray, 2007; Perkins-Ceccato, Passmore, & Lee, 2003; Schmidt & Lee, 2005).

Studies have suggested that the neuroplasticity involved in motor learning can be altered by attentional capabilities (Rosenkranz & Rothwell, 2004; Stefan, Wycislo, & Classen, 2004). This is likely a result of the dependence of motor learning on attentional resources (Hazeltine, Grafton, & Ivry, 1997). Attention is also interplayed with arousal and anxiety. Arousal and anxiety both affect performance based upon the Inverted-U Principle, which posits that there is an optimal level of arousal, after which decrements in performance can occur (Martens & Landers, 1970; Schmidt & Lee, 2005; Sonstroem & Bernardo, 1982). However, the optimal range of arousal is dependent on the person, where some individuals function best under high arousal states, yet someone else may perform best in a low arousal state (Hackfort & Schwenkmezger, 1993). Perceptual narrowing under high-arousal states allows for eliminating distractions from peripheral input (Kahneman, 1973). However, with high levels of arousal, there are often numerous shifts in attention, some to irrelevant sources of information to the task at hand, resulting in missed relevant feedback which may be detrimental to performance (Schmidt & Lee, 2005). Therefore, high levels of arousal can result in decrements of the ability to discriminate relevant from irrelevant cues (Schmidt & Lee, 2005), which suggests that attentional resources can have a profound affect on one's ability to acquire and learn novel motor commands.

2.5.4 Motor Skill Performance

The variables of a motor skill that can affect performance, are largely related the individual performing the skill, the environment they are performing in, as well as the demands of the skill itself (Magill & Anderson, 2010). Attributes related to the individual include, but are not limited to, their attentional characteristics and their ability to attend to a given stimulus while suppressing unrelated distractors (Velasques et al., 2013). When being inundated with numerous afferent inputs from multisensory environments, it is necessary to process and utilize relevant sensory information while negating irrelevant sensory information. Thus, the ability to utilize selective attention effectively is highly relevant, and a determining factor in the efficacy of sensorimotor and multisensory processes affecting motor performance (Velasques et al., 2013). Motor command performance is defined in three stages; first, stimuli identification and selection;

second, motor command organization; and third, motor command execution (Velasques et al., 2013). Efficient motor learning processes may be dependent on the quality of afferent information provided to the CNS, which may be altered in individuals with both congenital and acquired conditions, such as in individuals with neck pain, social impairments, or inattentive tendencies, thus influencing their perception of the world (Andrew et al., 2018; Glazebrook, Elliott, & Szatmari, 2008). Understanding how motor learning is implicated in a given disorder or condition is paramount for forming an improved understanding of ways to optimize learning environments, and ultimately function, for these populations. One such population that is postulated to experience altered integration of sensory information and motor learning, are those with ADHD.

Dockstader et al. (2009) suggest that children with ADHD have reduced cortical activity in motor and parietal regions. They also found that adults with ADHD had decreased mu activity, which is described as the sensorimotor oscillation frequency (8 – 12 Hz), in response to median nerve stimulation. It is suggested that these alterations are a result of altered morphology in parietal regions, such as global thinning of gray matter (Duerden et al., 2012). The parietal lobe is highly involved in visuospatial SMI (Velasques et al., 2013), and SMI can be assessed with EEG in the form of both somatosensory-evoked potentials (SEPs) and frequency oscillations. The utilization of SEPs to quantify SMI and motor learning is a technique common to and well established in the Ontario Tech Neurophysiology Lab (Andrew et al., 2018; Zabihhosseinian, Gilley, Andrew, Murphy, & Yielder, 2020; Zabihhosseinian, Yielder, Wise, Holmes, & Murphy, 2021). In response to median nerve stimulation, children with ADHD exhibit larger peak-to-peak SEP amplitudes in the N20-P25 SEP peak (Miyazaki, Fujii, Saijo, Mori, & Kagami, 2007). While another study showed that children with ADHD exhibited larger

SEP peak amplitudes in the N13, N20, and P23 SEP peaks (Parush, Sohmer, Steinberg, & Kaitz, 1997). However, it should be emphasized that this work was completed in children and those with dual diagnosis of chronic tic disorder and tactile defensiveness, therefore limiting result transferability to adults with ADHD and those lacking this dual diagnosis.

Neural circuitry involved in fronto-striatal and cerebro-cerebellar networks are highly involved in the processes of learning and its motor counterparts, and are implicated in the pathophysiological mechanisms pertinent to ADHD (Koziol et al., 2013). Literature has posited that cerebellar alterations are a likely candidate resulting in behavioural characteristics of ADHD in children (Bledsoe, Semrud-Clikeman, & Pliszka, 2011; Mackie et al., 2007). Children with ADHD have noted difficulties with learning and automating fine motor skills, which may deter children with ADHD from participating in activities requiring motor proficiency (Kaiser et al., 2015; Koziol et al., 2013). Overall, the neural alterations in cerebellar and cerebral regions in this population suggest that motor learning alterations are likely. However, implicated behavioural outputs of motor learning in conjunction with neurophysiological measures, have not been quantified in conjunction with one another in young adults with ADHD, although they present a promising way to enhance our understanding of this population.

2.5.5 Assessments of Motor Learning

The assessment of motor learning will often involve a motor task that is novel to the participant or individual, i.e. they have not completed this task in the recent past. An example of a motor task that assesses visuomotor integration is a novel motor tracing task. This kind of task is commonly used in the Ontario Tech neurophysiology Laboratory, and allows for an assessment of motor learning and SMI (Andrew, Haavik, Dancey, Yielder, & Murphy, 2015a; Andrew et al., 2018; Dancey, Murphy, Andrew, & Yielder, 2016; Zabihhosseinian et al., 2020).

Although this task provides pertinent information into the process and variables surrounding motor learning particularly relevant to visuomotor integration, there are other motor processes that are fundamental to how an individual performs in a given motor task. For instance, incorporating a task that requires force matching will allow for an assessment of how force-modulation and proprioception may play a key role in the learning and performance of similar tasks, as alterations to force-modulation and proprioception are noted in those with ADHD (Neely et al., 2016; Sanz-Cervera et al., 2017). Therefore, as ADHD is a population with known proprioceptive and motor deficits, the incorporation of both a visuomotor tracing and force matching task are fundamental to further comprehend the neurophysiological characteristics involved in their motor performance.

2.5.5.1 Skill Transfer

Many motor tasks, and indeed those that elicit learning, involve some form of visual feedback, allowing for real-time performance feedback and consequent performance modulation. Including a transfer task, being a task that is similar to a learned skill, although being applied to a new task or context, can be an important component in the assessment of motor learning (Müssgens & Ullén, 2015). One way to assess skill transfer, would be to alter the inclusion or exclusion of feedback, whether that be the removal of specific forms of sensory feedback or performance feedback. Some research has suggested that those with ADHD may have an increased dependence on visual feedback, resulting in decrements to performance upon the removal of visual input (Eliasson, Rösblad, & Forssberg, 2004). In children with ADHD, knowledge of performance via prescriptive knowledge of performance feedback improves motor skill performance learning, to a greater extent than that of knowledge of results feedback only (Bishop et al., 2018). In children with ADHD, completing a motor task lacking visual feedback for goal directed movements, resulted in reduced performance, thus suggesting poorer motor programing in children with ADHD (Eliasson et al., 2004). In young adults completing a task utilizing grip force, those with ADHD had a faster rate of decay of force when visual feedback was removed, and this was associated with impulsivity and symptom severity (Neely et al., 2016). This suggests that adults with ADHD integrate visual feedback differently than neurotypical controls (Neely et al., 2016). Alterations are commonly noted in neural systems within the cortex, basal ganglia, thalamus, and cerebellum in those with ADHD (Makris, Biederman, Monuteaux, & Seidman, 2009), all of which are paramount in visuomotor control processes (Coombes, Corcos, & Vaillancourt, 2011; Neely, Coombes, Planetta, & Vaillancourt, 2013; Vaillancourt, Mayka, & Corcos, 2006). This suggests that differences in how visual feedback is integrated may affect motor control and performance in those with ADHD, where if visual afferents are removed, decrements to performance may occur. Therefore, including task iterations that both include and remove visual feedback may provide important information relating to the dependence on visual feedback versus proprioceptive feedback in those with ADHD during the learning process. Incorporating a transfer test without visual feedback or knowledge of the results, while keeping all other measures present during the learning or acquisition phase the same, may provide important information on the reliance on various sensory processes during motor learning between different cohorts (Mackrous & Proteau, 2007), allowing for adaptations to motor programs in the future to promote optimal skill acquisition. Typically, task versions that remove visual feedback, following practice with visual feedback, result in significant decrements to performance via reduced aiming accuracy (Mackrous & Proteau, 2007). Therefore, movement planning strategies are thought to be dependent on the form of afferent feedback available during the acquisition period (Mackrous & Proteau, 2007).

Although incorporating a transfer task that lacks visual feedback will almost certainly result in reduced performance, such a transfer test has the potential to provide novel and important insight on behavioural and sensory weighting, in addition to neural differences (Park et al., 2018).

The form of sensory feedback available during the learning and performance phases can have a profound effect on performance. When visual feedback is removed, those with ADHD have a substantially quicker rate of force decay compared to controls (Neely et al., 2016). With visual feedback available, adults with ADHD produce greater grip force than controls (Neely et al., 2016). Therefore, the type of sensory information available may have important implications for motor skill performance in those with ADHD. Children with ADHD score lower on tests assessing sensory processing, including differences in markers of touch and visual processing, suggesting impairments in sensory modulation (Shimizu, Bueno, & Miranda, 2014). Including trials both with and without visual performance feedback may provide insight into the role of motor learning and the reliance on visual input.

2.5.6 Proprioception

Proprioception describes the internal model of where an individual perceives their body and limbs to be in space, while utilizing and integrating the sensory information provided from the surrounding environment in the form of afferent input to form coordinated motor outputs (Kurtz, 2007). In other words, proprioception is an awareness of where your body is in space. Sensory receptors involved in proprioception include muscle spindles, Golgi tendon organs, and mechanoreceptors surrounding tendons and joints, which work in conjunction with the vestibular system (Purves et al., 2001). Developmental Coordination Disorder (DCD), a disorder most notable by an individuals functional impairments to motor control, is often dual-diagnosed in conjunction with ADHD (Lange, 2018). The motor impairments noted, and the neurological alterations specific to the cerebellum, suggests that coordination and proprioception may be related, with alterations that may be pertinent to those with ADHD.

Alterations to proprioception, being ones' ability to use their senses to understand where their limbs and body are in space, is a sensory characteristic that is inherent to ADHD symptomology (Sanz-Cervera et al., 2017). For instance, children with ADHD exhibit significant variability in speed and movement patterns (Izawa et al., 2012). Excessive variability in movement speed during the execution of movement is thought to be a characteristic unique to ADHD (Izawa et al., 2012). Although ADHD is associated with alterations in proprioception (Alba et al., 2016; Goulardins, Marques, Casella, Nascimento, & Oliveira, 2013; Jung et al., 2014; Sanz-Cervera et al., 2017), which is often inferred via an assessment of balance or body schema, the extent to which alterations to proprioception and force modulation affect motor learning in ADHD is unclear. For instance, balance dysfunction is present in ADHD, potentially associated with alterations to proprioception and vestibular function (Zang et al., 2002). Furthermore, one study used proprioceptive indicators of temperament to form an improved understanding of behavioural and personality indicators of ADHD in children (Liutsko, Iglesias, Tous Ral, & Veraksa, 2018). It is postulated that alterations to proprioception in those with ADHD are related to difficulties processing and integrating visual information (Jung et al., 2014; Sanz-Cervera et al., 2017). Young boys with ADHD score lower on balance, spatial organization, and fine and global motricity (Goulardins et al., 2013). One study utilized an intervention to assess performance in fine motor activities, where children with attention impairments wore a weighted vest, thus providing tactile and deep pressure sensory feedback, and saw improvements in on-task behaviour (VandenBerg, 2001). Children with ADHD are often reported to exhibit symptoms of idiopathic toe-walking (ITW), which notably is also common in ASD. ITW is thought to be related to vestibular and proprioceptive dysfunction (Insuga et al., 2018). Alternatively, one study noted a large proportion of athletes diagnosed with ADHD on a gymnastics team, a sport highly dependent on refined motor control (Kaufman, Bajaj, & Schiltz, 2011). The integration of sensory information and feedback may be inherent for task performance, where visual perception may have a significant impact on vestibular and proprioceptive function in children with ADHD (Jung et al., 2014). Alterations in cerebellar volume and activation may form a pivotal aspect of the neurophysiological mechanisms responsible for many of the behavioural cornerstones of ADHD, which require an improved understanding via the application of objective research techniques capable of measuring cerebellar and cortical function. Understanding the underlying neurological alterations associated with behavioural and proprioceptive function may have important and significant implications for function and performance in a wide array of tasks.

2.6 Relevant Neuroanatomy and Neurophysiology

In order to understand variants of sensory processing, it is necessary to comprehend the various anatomical structures and sites, including their function and how they are involved in such processes. Of particular relevance and importance to this dissertation is the neuroanatomy involved in MSI, SMI, and motor skill acquisition. Certain structures in their neurotypical states function in a reasonably well-understood manner; however, when neural alterations are present, such as those present in special populations, this may change how these processes occur and the efficacy of them. Two types of sensory processes that will be particularly emphasized here are MSI and SMI, both of which can have profound and important implications for how one perceives, responds to, and learns in many environments. MSI and SMI are both highly relevant when understanding neural responses to diverse forms of stimuli.

2.6.1 Cerebral Cortex

The cerebral cortex is the primary neural substrate allowing for cognitive abilities in humans, and is divided into regions based on both structure and function. The synaptic architecture within the cerebral cortex is what defines the capacity for specific neural processes (Rakic, Bourgeois, & Goldman-Rakic, 1994). This structural organization occurs through a process known as corticogenesis, where cortical layers undergo developmental migration and organization (Rakic et al., 1994). The neocortex is partitioned into six unique layers, all of which have differentiated composition and microstructure. Layer I is the most superficial and is the molecular layer; layer II is the external granule cell layer; layer III is the external pyramidal cell layer; layer IV is the inner granule cell layer; layer V is the inner pyramidal cell layer; and finally, layer VI, which is the deepest, is the multiform layer (Kandel, Schwartz, Jessell, Siegelbaum, & Hudspeth, 2013). Each layer has unique input and outputs. Layer I is composed of the dendrites of cells located in deeper layers and axons making connections to other regions. Layer II and III are comprised of smaller pyramidal neurons, which project to other neurons within neighbouring regions. This allows for intracortical communication (Kandel et al., 2013). Layer IV is the main receptor of sensory input via the thalamus, and is the most notable in the primary sensory regions, whereas this layer is almost absent in the primary motor cortex (M1) (Kandel et al., 2013). Layer V has the largest pyramidal cells, which form the primary output pathways to both cortical and subcortical regions. Finally, layer VI is composed of many different neuronal cell types and structurally blends into the deeper cortical white matter. The unique structural arrangement of each neural region allows for specific processes to transpire, with an example being the prominent layer IV in the primary visual cortex (Kandel et al., 2013).

2.6.2 Neural Attributes of Attention

The process of maintaining attention depends on several neural mechanisms. There is both endogenously and exogenously driven attention. Endogenous attention, otherwise termed top-down, describes enhanced focused relating to a current goal, for instance, writing this dissertation, whereas exogenous attention, also described as bottom-up, results in stimulus identification as a result of the physical salience of a stimulus (Mueller, Hong, Shepard, & Moore, 2017). When exerting attention towards visual stimuli, the frontal eye field in the prefrontal cortex, the lateral intraparietal area in the parietal cortex, and the superior colliculi are all inherently involved (Gregoriou, Rossi, Ungerleider, & Desimone, 2014; Mueller et al., 2017; Wardak, Olivier, & Duhamel, 2002; Zénon & Krauzlis, 2012), and these structures may facilitate attended stimuli within the visual cortex (Squire, Noudoost, Schafer, & Moore, 2013). In humans, there is a bias for right-hemisphere brain involvement in directed attention (Heilman & Van Den Abell, 1980; Mesulam, 1983; Spagna, Kim, Wu, & Fan, 2020). Transcranial magnetic stimulation (TMS) studies have assessed these attentional networks, and found that upon stimulation of the frontal eye field and lateral intraparietal sulcus in humans an impairment in performance is noted (Blankenburg et al., 2010). Impairments to attention can affect both endogenous and exogenous foci. Endogenous and exogenous attentional signals likely converge in the parietal cortex or prefrontal cortex (Sprague & Serences, 2013). Furthermore, dopamine signaling, which is altered in ADHD, may take part in endogenous attention (Mueller et al., 2017; Swanson et al., 2007). Thus, the neural networks that are attributed to attentional characteristics can assist in an assessment of how attention may be affected in certain populations or in response to various sensory and sensorimotor paradigms.

2.6.3 Neural Attributes of MSI

MSI describes the process by which the senses integrate multiple sensory inputs, that occur close in spatial and temporal proximity, which can have both complex and adaptive interactions, resulting in behavioural adaptations in response to stimuli (Bremner, Lewkowicz, & Spence, 2012; Calvert, Spence, & Stein, 2004; Spence & Driver, 2004). When presented with multiple simultaneously occurring stimuli, the process of integrating these stimuli is crucial to performance and neural enhancements. The modern world is stimulus rich, which results in the process of MSI being of the utmost importance from a sensory perception viewpoint, influencing both the perception of and response to stimuli (Brandwein et al., 2011; Foxe et al., 2000). This process can occur when presented with multiple stimulus modalities, including but not necessarily limited to auditory, visual, tactile, olfactory, and haptic inputs (Paraskevopoulos & Herholz, 2013). There are both behavioural and neural enhancements that can be assessed in response to multisensory inputs, such as neural efficiencies, shorter response times, and enhanced accuracy (Laurienti et al., 2004; Meredith & Stein, 1986). This process is highly influenced by activity within specific neural structures.

Neural structures known to be involved in MSI are the superior colliculi, parietal lobe, and the superior temporal sulcus (Brandwein et al., 2011; King, 2004; Wallace & Stevenson, 2014). Research utilizing EEG has found that cortical structures, including those found within parietal regions, are highly involved in the integration of audiovisual multisensory inputs (Brandwein et al., 2015; Brandwein et al., 2011; Molholm et al., 2006; Moran, Molholm, Reilly, & Foxe, 2008). Additionally, cortical regions including the superior temporal sulcus and posterior parietal cortex are two such multisensory regions (Molholm et al., 2002). These regions have a high density of multisensory neurons, being neurons that respond to both auditory and visual inputs (Andersen, Snyder, Bradley, & Xing, 1997; Molholm et al., 2002). The inferior parietal sulcus (IPS) and superior parietal lobule (SPL) are specific parietal regions where multisensory inputs have been localized to (Andersen et al., 1997; Calvert, Hansen, Iversen, & Brammer, 2001; Molholm et al., 2006). This suggest that parietal regions are heavily involved in AV multisensory processing. The insula has also been identified as a multisensory region (Duerden et al., 2012; Renier et al., 2009). A second form of sensory integration which is fundamental to learning novel motor skills, is sensorimotor processing.

2.6.4 Neural Attributes of SMI

Neural processing involving stimuli in the form of sensory afferents, such as visual or proprioceptive feedback, which are utilized to generate motor outputs, is known as SMI, which is involved in the process of motor learning (Machado et al., 2010). Motor learning describes the acquisition of a once novel motor task through performing said skill (Schmidt & Lee, 1988). Motor learning occurs via the acquisition of sequential movement patterns and behaviours, or through making alterations to movement patterns in response to environmental perturbations (Doyon et al., 2009). Through the process of learning a skill, task performance improves (Schmidt & Lee, 1988). Although learning cannot be directly observed, it can be inferred through alterations in motor behaviour performance, such as reductions in reaction time or percent error and accuracy plotted over time, which are known as performance curves (Doyon et al., 2009; Schmidt & Lee, 1988). A fundamental part of motor learning is skill retention, which can also be monitored via behavioural measures such as performance accuracy and response time (Schmidt & Lee, 1988). Motor learning can be shaped by the quality of both the augmented and intrinsic sensory information provided to the nervous system, as well as the nervous system’s ability to appropriately integrate this information to form efficient and correct motor outputs. If the integration of afferent input is altered, this may influence the success of SMI and consequently affect the extent to which motor learning occurs; these alterations may be due to altered structure or function of the neural structures involved in SMI.

2.6.4.1 Neural Networks of SMI

The process of motor learning and SMI involve structures at both cortical, subcortical, and spinal levels. The integration of sensory afferents occurs in circuitry involving the S1, secondary somatosensory cortex (SII), M1, premotor cortex (PMC), SMA, prefrontal cortex (PFC), amygdala, cingulate cortex, basal ganglia, thalamus, and cerebellum (Ciccarelli et al., 2005; Krakauer & Mazzoni, 2011; Nyberg, Eriksson, Larsson, & Marklund, 2006). The complex arrangement of relevant neural regions can influence processes related to the acquisition of motor skills. The prefrontal cortex is highly involved in many stages of motor learning, with a particular importance during the very early stages of learning when a novel task has first been introduced (Jueptner et al., 1997a; Jueptner et al., 1997b). Furthermore, the M1 within the frontal lobe, the striatum, and the cerebellum are all highly integral in adapting to task demands and acquiring new motor skills (Doyon, Ungerleider, Squire, & Schacter, 2002b; Hardwick, Rottschy, Miall, & Eickhoff, 2013). The cerebellum is a structure that has a prominent role in many forms of sensory and feedback processing and will be addressed in the following sections.

2.6.5 Motor Learning

Motor learning processes are performed by a number of unique neural structures and networks, which work in unison to refine and perform motor control. Adaptations that result in a refinement of behaviour, specifically those related to motor control and learning, occur via neural computations (Lan, Cheung, & Gandevia, 2016; Shadmehr & Wise, 2004). Such computations have been interpreted as computational models, and aim to aid our understanding of the complex processes that are inherent to the success of adapting motor commands to a given context (Lan et al., 2016). Todorov and Jordan (2002) proposed one such motor coordination theory, based upon the assessment of optimal feedback control which considers the numerous degrees of freedom that are involved in task constraints, as humans, our musculoskeletal and nervous system are composed of many synergies. The authors suggest that an optimal motor coordination strategy requires the allowance for variability in task conditions that are redundant, or those which are irrelevant to the task at hand (Todorov & Jordan, 2002). Subsequently, thoughtfully utilizing feedback and making corrections to those that impede the task goals. This is only one such computational theory, while many exist and each propose a unique perspective.

A fundamental theory to the neurophysiological processes involved in learning variants and memory in humans, is Hebbian theory and plasticity. The basis of Hebbian plasticity suggests that through consistent and repetitive stimulation of a postsynaptic neuron by a presynaptic neuron, resulting in depolarization of the postsynaptic cell, resultant adaptations will occur resulting in long term potentiation or learning (Hebb, 1949; Keck et al., 2017). In Hebb's words, "persistence or repetition of a reverberatory activity tends to induce long lasting cellular changes that add to its stability" (Hebb, 1949). A more colloquial verbiage for this theory is "cells that fire together, wire together". This is also termed long term potentiation, where through persistent stimulation of a neuron, resultant long term neuroplastic adaptations to the nervous system may occur, allowing for the strengthening of synaptic connections and enhanced neural communication (Keck et al., 2017). Long term potentiation can last for several hours to as long as many days (Datta, 2010); whereas short term potentiation is thought to describe time periods of fractions of milliseconds (Buonomano, 2000; Buonomano & Merzenich, 1995; Marder & Buonomano, 2003). Thus, Hebbian plasticity is occurring during the process of learning, which commonly requires consistent exposure to the same or similar stimuli while practicing or acquiring a particular skill, resulting in neural enhancements specific to the newly learned skill. This process allows for the encoding and retaining of information in neural networks, which can be retrieved for use at later time points (Fox & Stryker, 2017; Hebb, 1949), such as when learning novel tasks.

Electrophysiological techniques have been used to assess the neuroplastic adaptations that occur in response to learning. One study utilizing high-density EEG noted an increase in alpha functional connectivity between the left superior parietal cortex and the rest of the brain before a period of training, and a decrease in alpha functional connectivity in the same cortical locations after learning, and this activity was highly correlated with learning outcomes (Manuel, Guggisberg, Thézé, Turri, & Schnider, 2018). This suggests that alpha functional connectivity is involved in providing neural resources that are needed for forthcoming tasks (Manuel et al., 2018). Visuomotor adaptation, which occurs during motor acquisition, relies on neural networks involving motor cortical regions, parietal regions, and the cerebellum during the early stages of acquisition (Tzvi, Koeth, Karabanov, Siebner, & Krämer, 2020). When performing novel visuomotor rotation, one study noted increased activation within motor and parietal cortices which was associated with improved performance (Tzvi et al., 2020). The numerous cortical and subcortical regions described, which are integral to processes relating to motor learning, receive afferent input from the periphery.

2.6.6 Dorsal Column Medial Lemniscus Pathway

The dorsal column medial lemniscus pathway has a primary role in transmitting sensory information regarding fine-touch, proprioception, and vibration (Al-Chalabi, Reddy, & Alsalman, 2018). This pathway projects through the spinal cord in the dorsal column, and in the brainstem through the medial lemniscus (Al-Chalabi et al., 2018). This pathway is a three order neuron pathway system, with the first order neuron traveling from the periphery and the dorsal root ganglion to the medulla, the second order neuron decussating at the medulla and ascending to the thalamus in the ventral posterolateral (VPL) nucleus, and the third order from the thalamus to the S1 of the postcentral gyrus (Al-Chalabi et al., 2018). The dorsal column pathway has a somatotopic arrangement, and depending on the limb the afferent information is being transmitted from, either the fasciculus gracilis or fasciculus cuneatus may be involved. The fasciculus gracilis transmits lower limb afferents, and the cuneatus transmits afferent input from the upper limbs (Al-Chalabi et al., 2018). This acts as a conduit to transmit information on both conscious proprioception and tactile mechanoreceptors (Al-Chalabi et al., 2018). This pathway will transmit afferent information from the periphery to the CNS during the various stages of motor learning and otherwise.

2.6.7 Primary Motor Cortex

The M1 has a predominant function in the control and coordination of motor related commands. Anatomically, M1 is situated at the pre-central gyrus within the frontal regions of the human brain. The pyramidal neurons within M1 have descending projections allowing for the governing of movement in peripheral limbs as well as of the trunk and head (Canedo, 1997). The motor cortex is functionally and somatotopically organized into what is deemed the motor homunculus (Penfield & Rasmussen, 1950). During the stages of learning, and general motor execution, an increase in activation within contralateral M1 will occur (Setiz, Roland, Bohm, Greitz, & Stone-Elander, 1990; Van Mier, Tempel, Perlmutter, Raichle, & Petersen, 1998), allowing for performance modulation (Doyon et al., 1997; Honda et al., 1998; Pascual-Leone, Grafman, & Hallett, 1994). Research suggests that M1 may be heavily engaged during implicit motor learning, while the premotor cortex is involved to a greater extent during explicit learning (Galea, Albert, Ditye, & Miall, 2010; Grafton, Hazeltine, & Ivry, 1995; Hazeltine et al., 1997; Kantak, Mummidisetty, & Stinear, 2012). The motor cortices, in concert with other cortical and subcortical structures, allow for the control and refinement of motor commands through parietal, frontal, basal ganglia, and cerebellar neural networks

2.6.8 The Cerebellum

2.6.8.1 Cerebellar Gross Anatomy and Function

The cerebellum, Latin for "little brain", contains more than 50% of the neurons in the brain, whilst only comprising 10% of its volume (Kandel et al., 2013). Similar to the cerebral cortex it is composed of both white and grey matter. It is highly involved in the coordination of voluntary movement while also regulating balance and posture, and has more recently been noted for having a role in non-motor cognitive functions, including language (Funakoshi etaaL, Sebert, & Shooter, 1995; Kandel et al., 2013; Timmann & Daum, 2007). The cerebellum supports movement coordination by acting upon the cerebral cortex via the thalamocortical projection and on the brainstem (Takakusaki, 2017). Feedforward operations are informed via the cortico-ponto-cerebellar pathway, while sensory feedback is transmitted via the spinocerebellar tract, and the basal ganglia contributes to command modulation via GABA-ergic projection to the cerebrum (Takakusaki, 2017).

The cerebellum is often asserted as having a primary role in the learning or acquisition of novel skills, this is due to its involvement in feedback regulation and error monitoring (Doyon, Penhune, & Ungerleider, 2003; Hardwick et al., 2013; Houk, Buckingham, & Barto, 1996). Thus, the cerebellum has a pivotal role in motor refinement. However, the cerebellum has other functions that are not as well understood, but are still important to note. These functions may involve executive function, visuospatial processing, linguistics, and affect (Schmahmann & Sherman, 1997; Timmann & Daum, 2007). Support for cerebellar roles in non-motor functions can be observed in patients with Cerebellar Cognitive Affective Syndrome (CCAS), who experience deficits in these processes (Schmahmann & Sherman, 1997). It is now perceived that cerebellar lesions, regardless of if these lesions are congenital or acquired in nature, can result in intellectual, cognitive, language, attentive, and emotional deficits, outside of the typical motor impairments that were classically associated with such lesions (Aarsen, Van Dongen, Paquier, Van Mourik, & Catsman-Berrevoets, 2004; Levisohn, Cronin-Golomb, & Schmahmann, 2000; Riva & Giorgi, 2000). It is thought that the involvement of the cerebellum in non-motor function may be, in part, related to the projection from the dentate nucleus to the striatum of the basal ganglia, as well as a projection from the subthalamic nucleus to the cerebellum (Bostan, Dum, & Strick, 2010, 2013). Humans with cerebellar lesions, particularly those affecting the left hemisphere, exhibit alterations to motor patterns and learning (Molinari et al., 1997). Thus, the cerebellum is integral to a wide range of neural processes, shaping many aspects of how an individual may function.

The cerebellum is thought to contain the internal model that works to simulate a controlled object (Koziol et al., 2014). Internal models are neuronal representations of the external world, and allow for smooth and quick processing of afferent input (Ito, 2011; Koziol et al., 2014). The cerebellum acquires these internal models via sensorimotor interactions, and then will use predictive feedback signals to inform cortical regions of the current task demands (Koziol, Budding, & Chidekel, 2012). Using this internal model, the M1 can perform skillful movements without reliance on external feedback (Koziol et al., 2014). Impairments in cerebellar function reduce the ability to create predictive models and impair seamless automatic regulation when processing sensory information, resulting in disability and performance variability (Ghajar & Ivry, 2009; Koziol & Lutz, 2013). Thus, cerebellar function can have a prominent influence on many facets of an individual's function, including but not limited to motor characteristics (Aarsen et al., 2004; Levisohn et al., 2000; Riva & Giorgi, 2000). The cerebellum is comprised of several unique structures and regions, all of which play a unique but complementary role in cerebellar function.

2.6.8.2 Cerebellar Functional Anatomy

The role of the cerebellum in motor learning involves synaptic input via climbing and mossy fibers that are then integrated with Purkinje cells (Marr & Thach, 1991). Both climbing and mossy fibers have excitatory connections to cerebellar regions. Mossy fibers receive input from extracerebellar locations, while climbing fibers originate from the inferior olive (Gasbarri, Pompili, Pacitti, & Cicirata, 2003; Manzoni, 2007; Miall, 2013), both of which are thought to have unique roles in cerebellar function (Gasbarri et al., 2003). The cerebellum acquires learned spatiotemporal signals via mossy and climbing fibers (Koziol et al., 2014). Furthermore, Purkinje fibers learn via climbing fiber input, in response to a constant input from mossy fibers (Koziol et al., 2014). Purkinje fibers have a high degree of dendritic connections and synapses (Houk & Wise, 1995), and are considered the processing unit of the cerebellum, integrating afferents from the pons and inferior olive, having a primary role in inhibitory output (Snell, 1997). These cells are postulated to receive input to guide necessary adjustments during motor commands (Houk & Wise, 1995).

The early stages of cerebellar learning are regulated by climbing fiber systems within cerebellar regions (Ito, 2000), while later stages of learning are contingent on activity within cerebellar hemispheres and nuclei (Imamizu et al., 2000). When motor performance occurs with reduced error, a reduced activation within the posterior region of the right cerebellar cortex is noted, whereas activity within the ipsilateral deep cerebellar nuclei increases with a reduction in motor error (Nezafat, Shadmehr, & Holcomb, 2001). Similarly, Purkinje cells generally exhibit the greatest activity during the later stages of learning (Nezafat et al., 2001). When error monitoring is necessary, bilateral activation within neocerebellar structures is present, such as within the hemispheres, vermis, and nuclei (Jueptner & Weiller, 1998). Therefore, the cerebellum is thought to encode feedback from proprioceptive and visual information in the process of error monitoring (Halsband & Lange, 2006). This error monitoring allows for the optimization of movement via sensory afferents.

When motor skills become well learned, there is generally a reduction in cerebellar activation (Flament, Ellermann, Kim, Uğurbil, & Ebner, 1996). However, cerebellar functions include the storage of acquired motor skills, and activation within subcortical locations of the right cerebellar hemisphere, primarily the dentate nucleus (Doyon, Owen, Petrides, Sziklas, & Evans, 1996; Flament et al., 1996). Once a skill becomes well learned, the reliance on cerebellar function is reduced, and therefore motor patterns become more dependent on cortical function (Houk & Wise, 1995). The cerebellum, M1, and dorsal column pathway each have unique and important roles in shaping how individuals perform and retain new skills. Alterations in the structure and function of these neural regions, such as those found in ADHD, may have a profound influence on the process of sensory integration, motor performance, and learning. Thus, understanding unique neurophysiological characteristics in ADHD is pertinent.

2.7 Neurophysiological Techniques

There are many quantitative research techniques that can be used to discern the function or involvement of specific neural structures in motor learning, amongst other processes.

2.7.1 Electroencephalography (EEG)

EEG acts as a non-invasive method to assess neural activity at the cortical level, which also provides exceptionally high temporal resolution of the underlying neural activity (Gevins, Leong, Smith, Le, & Du, 1995). EEG records the post-synaptic potential activity of cerebral pyramidal neurons using an array of surface electrodes (Michel & He, 2019). The temporal acuity of EEG is that of millisecond accuracy (Gevins et al., 1995), providing important information on the level of cortical electrical activity involved in many cognitive and behavioural tasks. EEG electrode montages are based upon the International 10/20 system, and high-density EEG allows for improved spatial sampling of the underlying neural structures. Assessment techniques vary, and can include frequency (Hz), time-domain (ms), ERPs, and evoked potentials (EPs). Frequency alterations have been related to specific disorders. The Theta/Beta ratio is a common correlate of ADHD, where an increase in Theta or decrease in Beta over fronto-central electrodes is present in this population (Barry, Clarke, & Johnstone, 2003; Lenartowicz & Loo, 2014; Lubar, 1991). There is a robust body of literature utilizing single-electrode and whole-head EEG to elucidate the neurophysiological roles related to various somatosensory potentials, in both absolute and relative amplitude changes (Passmore, Murphy, & Lee, 2014). Changes in specific evoked potentials between different conditions or groups, allow for a comparison of activity within underlying neural substrates involved in a given task or sensory process. SEPs are a form of evoked potential that can be assessed at varying levels on their ascending pathway to the CNS, and provide insight into the processing associated with somatosensory afferent input to the CNS (Passmore et al., 2014).

2.7.2 Somatosensory Evoked Potentials (SEPs)

SEPs can be used to assess neuroplasticity in both clinical and research settings (Passmore et al., 2014). In research settings, SEPs can be used to infer alterations in neuroplasticity in response to learning novel perceptual, sensory, or motor tasks, i.e. in response to the process of motor learning (Murphy, Taylor, Wilson, Oliphant, & Mathers, 2003). This is done in a pre and post manner, where SEPs are elicited via stimulation of a peripheral nerve, and changes to SEP peak amplitudes post motor skill acquisition can be used to infer involvement or disruption of specific neural structures. This can be done in conjunction with a behavioural analysis of motor acquisition or learning, which is classically done by assessing improvements in accuracy and retention over a period of time. SEPs are often stimulated over a peripheral nerve, such as the median nerve, and the neural response is recorded at cortical and sub-cortical levels (i.e. spinal) through the use of single electrodes and high-density EEG (Passmore et al., 2014). SEPs are named based on their polarity and latency, where an upward deflection represents a negative peak, which is denoted with the prefix “N”, and a downwards deflection reflects a positive peak, denoted with the prefix “P” (Cruccu et al., 2008). For example, a negative deflection 20 ms after stimulation is labeled the N20. Early SEPs, those that occur less than 100 ms post-stimulus, are pre-cognitive and provide an objective way to measure changes in early somatosensory processing. SEP changes pre and post motor acquisition or intervention may be measured as differences in latency (ms) or peak-to-peak amplitude (μV) (Passmore et al., 2014). The amplitude of a given SEP peak, and the proportional change from baseline when utilizing a pre-post study design, infers the magnitude of activity within specific neural generators that have been established in previous literature (Passmore et al., 2014). The interpretation of changes to these SEP peaks allows for an improved understanding of how specific populations, such as those with ADHD, who exhibit known neurological and behavioural alterations, may respond to the acquisition of novel motor skills or how they integrate somatosensory inputs. For instance, this may allow for an improved understanding of whether specific neural structures or networks respond or adapt differently to stimuli than neurotypical controls do, such as neural connectivity within olivary-cerebellar regions. Examples of early SEP peaks that may be of interest in relation to motor learning include the N18, N20, N24, N30, etc.

2.7.2.1 Neural Generators

The area of the brain that generates a given SEP peak is termed the "neural generator" of that peak. The neural generators for various SEP peaks have been determined from recordings during neurosurgery, lesion studies, and more recently, advanced software solutions that use complex mathematics to determine the brain "source" of the electrical activity (Jatoi & Kamel, 2017). Research suggests that the N18 SEP peak reflects activity in the brain stem, particularly from within the midbrain-pontine region in conjunction with the medulla (Sonoo et al., 1999; Urasaki et al., 1992). The N18 is also thought to reflect cerebellar activity via activity in the cuneocerebellar tract, cerebellum, and accessory inferior olives (Noël, Ozaki, & Desmedt, 1996). The generation of the N20 is within the S1 (Desmedt & Cheron, 1980). The N24 SEP peak is thought to involve pathways between the cerebellum and S1 (Passmore et al., 2014; Restuccia et al., 2001). Researchers found that if the cerebellar cortex was disrupted, the N24 SEP peak would be enhanced, where conversely, the N24 SEP peak would be absent or reduced if the deep cerebellar nuclei are lesioned (Restuccia et al., 2001). The N30 SEP peak reflects sensory integrative processes and is thought to reflect activity within basal ganglia, thalamus, pre-motor areas, and M1 (Kaňovský, Bareš, & Rektor, 2003; Mauguière, Desmedt, & Courjon, 1983; Passmore et al., 2014; Rossi et al., 2003; Rossini et al., 1989; Rossini, Gigli, Marciani, Zarola, &

Caramia, 1987). The N60 is localized to fronto-central and secondary somatosensory cortex regions (Barba, Frot, Valeriani, Tonali, & Mauguiere, 2002; Frot & Mauguière, 1999). Thus, SEPs offer a non-invasive and objective means of assessing changes in early neurophysiological processing.

2.7.3 Source Localization

A neural technique that pairs individual EEG data collected at a high sampling frequency with a standardized MRI model, is source localization. Source localization allows for the localization of specific neural generators with high spatial acuity. This is done by estimating the three-dimensional (3D) current density distribution of the whole brain volume of the underlying neuronal activation (Michel & He, 2019). The modeled source represents a current dipole of the postsynaptic potential current that is flowing through apical dendritic trees of cortical pyramidal neurons (Michel & He, 2019). This technique can be applied to assess cortical activity during information processing and task execution (Michel & He, 2019). The high temporal acuity of EEG make it ideal for studying the time-course associated with neural activation and conductivity (Gevins et al., 1995), opposed to the delay in assessing the hemodynamic response using fMRI (Michel & He, 2019). Source localization techniques now have clinical application, including presurgical mapping where it can be used to assess brain tumors and epileptic foci (Michel & He, 2019). Furthermore, the precise location of the somatosensory cortex using SEPs, high-density EEG, and source imaging has been validated with fMRI (Michel & He, 2019).

Standardized low-resolution brain electromagnetic tomography (sLORETA) is a software that has been validated to locate the source of neural activity. sLORETA is a linear inverse algorithm, and provides an estimate of the 3D distribution of neural generators within the human cortex based on the Montreal Neurological Institute (MNI) MRI brain map (MRI-152) (Pascual-

Marqui, 2002). sLORETA has been found to provide the lowest localization error when being compared to other techniques using a linear inverse algorithm (Pascual-Marqui, 2002). One functionality of this software, is that it is capable of source localizing EEG data in the time-domain, and performs comparisons between or within groups. As sLORETA pairs a standardized MRI model with collected EEG data sets, it offers a non-invasive and cost-effective technique to assess neural activity within neural generators (Pascual-Marqui, 2002), which is accomplished via integration of the MNI-152 MRI model. This MNI model was created in partnership with the International Consortium for Brain Mapping (ICBM) project (Mazziotta et al., 2001; Mazziotta, Toga, Evans, Fox, & Lancaster, 1995), and is a digital template which is based on the average of many typical control MRI scans; specifically, the MNI-152 is based upon the average of 152 T1 scans. This template has improved resolution (1-2 mm^3) in contrast to prior versions such as the MNI-305 (Lancaster et al., 2007), allowing for better visualization of the upper portions of the brain and the cerebellum. The function of sLORETA is to solve the inverse problem, and this is done based on the assumption of neighbouring neurons firing in a synchronous and simultaneous manner, allowing for identification without a localization bias (Pascual-Marqui, 2002; Pascual-Marqui, Michel, & Lehmann, 1994; Sekihara, Sahani, & Nagarajan, 2005). Previous work has validated sLORETA for its accuracy, validation being based upon both EEG and fMRI data (Mulert et al., 2004). Therefore, this indicates the reliability of the estimated sources of neural activity found using sLORETA.

The method in which sLORETA functions is that it allows for the statistical comparison of sources of neural activity either within or between groups, depending on the methodological framework being utilized. Statistical significance is set to $p = 0.05$. The statistical analysis is done within sLORETA’s built in statistical tool (Navid et al., 2019; Pascual-Marqui, 2002), and this occurs in two main phases. The first step is to establish if and when the latency at which neural activity differs between the two groups by comparing t-statistics, and then the second step occurs to establish where this difference was present, which is based on the latency established in step one. sLORETA completes an independent or dependent two-tailed t-test, depending on the defined test-parameters, converting collected EEG data into t-values for each time frame, comparing two groups. This is done for a certain number of time frames or data points, which will be dependent on the sampling frequency and epoch utilized. This is accomplished using SnPM, which adjusts for multiple comparisons using Fisher’s random permutation test with 5000 randomizations (Nichols & Holmes, 2002). The software will then set a two-tailed t-value threshold, providing the t-critical, where if and once a value in the time-domain exceeds this threshold, a computation occurs within the software that localizes the area responsible for this difference in neural activity, while also providing the associated statistical significance (*p*-value). It may be important to note that it is possible that no statistically significant differences will be present between the two data sets being assessed, which will be reflected as a lack of a suprathreshold t-value (i.e. a t-value that does not exceed t-critical at any latency within a defined epoch). In this case, it may not be relevant to move onto step two of the sLORETA analysis if no statistically significant differences are present, which would typically be utilized to localize the area where such a difference occurred.Although EEG has high temporal accuracy, it does lack the spatial accuracy typically associated with techniques such as MRI, this is due to the scalp and underlying tissue substrates occluding the surface electrode signal. Modern technological advances allow for the pairing of individual EEG data with standardized averaged MRI head models, thus coupling the temporal and spatial strengths of each modality. sLORETA has a high-level of spatial resolution of neural structures when compared to an analysis strictly using surface-electrode EEG.

2.8 Conclusion and Significance

The overarching goal of the following experiments is to provide a comprehensive assessment of how the nervous system and related behavioural outcomes respond to dynamic sensorimotor environments in individuals with ADHD. The multisensory and sensorimotor tasks are similar to common daily tasks, allowing for an understanding of how multisensory processing influence their ability to learn motor skills in these environments. Including both behavioural and neurophysiological variables (i.e. EEG and SEPs) is a dual-pronged powerful approach to form an enhanced understanding of the brain-behaviour relationship in ADHD. Limited research has assessed these neural processes in this group, and furthermore, those with ADHD constitute an exceptionally heterogenous population (Mueller et al., 2017). More specifically, the present research will allow for a further understanding of how multisensory and sensorimotor processing may be altered, and how this may lead to maladaptive outcomes on motor learning and performance in workplace and educational settings in this population. In the future, results from these studies could lead to developments to support improvements in the way multisensory or sensorimotor stimuli are presented to those with inattentive or hyperactive tendencies, including busy workplace settings or crowded lecture halls. This could provide opportunities for this population to excel in situations where they otherwise struggle to adapt.

Chapter 3: Specific Research Objectives

All objectives serve to elaborate our understanding of sensory processing in young adults with ADHD when compared to their neurotypical counterparts. The forms of sensory processing being assessed include varying forms of multisensory and sensorimotor processes, and how this may influence their ability to learn, consolidate, and retain a novel motor task. Adults with ADHD likely experience altered somatosensory function and motor learning processes, yet very little is known at either a behavioural or neurophysiological level about either of these processes in those with ADHD in adulthood, although motor skill acquisition is necessary throughout the lifespan, including during adulthood. Overall, the findings from this research will aid in the understanding of the processes related to motor learning and SMI in those with ADHD. This information will lay a foundation to understand which modifications might be needed to provide the most suitable and productive learning and working environments for those with ADHD. Additionally, this information has the potential to inform how future adaptations can be developed to aid adults with ADHD in environments where the integration of sensory input to aid motor acquisition and learning are compulsory.

Research Objective 1

To determine the location of sources of increased or decreased neural activity in response to multisensory input in those with ADHD when compared to neurotypical controls.

Hypothesis 1

There will be differences in which cortical regions are primarily involved in sensory processing, particularly those involved in MSI, such as parietal brain regions.

Research Objective 2

To characterize differences in SMI in response to performing a novel visuomotor tracing task, measured via changes in short-latency SEP peaks and behavioural performance measures, in young adults with ADHD.

Hypothesis 2

Those with ADHD will show altered differences in neurological markers of SMI in the form of SEP peaks, particularly those peaks related to cerebellar function. Additionally, those with ADHD will achieve lower performance measures, likely having a reduced consolidation of motor performance, which is measured via accuracy at each phase of the motor paradigm.

Research Objective 3

To assess SMI and motor learning in response to a novel force matching task through assessment of both behavioural and neurophysiological measures in adults with ADHD.

Hypothesis 3

Those with ADHD will exhibit alterations to SEP peaks when compared to neurotypical controls, likely in peaks related to cortico-cerebellar processing. Additionally, those with ADHD and neurotypical controls will show performance improvements post-acquisition, and based on previous literature those with ADHD will likely have reduced improvements at retention measures when compared to controls.

Research Objective 4

To compare differences in neural generators pertinent to SMI and motor learning during both visuomotor and force-matching motor paradigms in young adults with ADHD compared to neurotypical controls.

Hypothesis 4

Adults with ADHD will exhibit differences in the source of neural activity after learning novel motor paradigms when compared to neurotypical controls.

Chapter 4: Study 1

4.1 Preface to manuscript 1

Multisensory processing is fundamental to everyday tasks, with a presence of audiovisual inputs being abundant. Alterations to this form of sensory processing may have important implications for performing a variety of daily functions. Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder that exhibits unique neurological and behavioural characteristics (*Diagnostic and statistical manual of mental disorders: DSM-5*, 2013). These characteristics may influence how adults with ADHD integrate and respond to multisensory stimuli (Duerden et al., 2012), particularly when in sensory-rich environments.

Our previous work noted distinct differences in how young adults with ADHD process audiovisual multisensory inputs when compared to neurotypical controls (McCracken et al., 2020; McCracken et al., 2019). The previous assessment included behavioural metrics and also involved surface electroencephalography (EEG). Although provided invaluable insight into the neural mechanisms predominant in multisensory processing in adults with ADHD, this was limited to the assessment of surface brain activity, therefore lacking clarity of specific neural structures or regions that may have been involved in these differences. The current study sought to further this by source localizing areas of neural activity, which is an important and cost-effective method to assess neural substrates and their function in diverse populations.

The current study sought to assess the differences in activity within neural generators in response to audiovisual stimuli in those with ADHD when compared to neurotypical controls. To do so, high-density EEG paired with standardized low-resolution brain electromagnetic tomography (sLORETA) analysis techniques were implemented, thus allowing for a form of neural assessment with a high-level of spatial and temporal acuity. This was done to localize the neural locations where responses to multisensory stimuli differed in those with ADHD compared to neurotypical controls.

Manuscript 1 – Source localization of audiovisual multisensory neural generators in young adults with Attention-Deficit/Hyperactivity Disorder – *submitted to Brain Sciences*

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4.2 Abstract

BACKGROUND: Multisensory integration (MSI) is a complex form of neural processing that significantly influences how individuals interact with their environment. MSI is defined as the processing of stimuli from more than one modality, with a predominance of audiovisual integration in everyday interactions. Attention-Deficit/Hyperactivity Disorder (ADHD) is considered to be a neurodevelopmental disorder that exhibits unique neurological and behavioural characteristics. These characteristics may influence how adults with ADHD integrate and respond to multisensory stimuli, particularly in sensory-rich environments. Our previous work using event-related potentials demonstrated that adults with ADHD process audiovisual multisensory stimuli somewhat differently than neurotypical controls. The goal of this present research was to identify specific neural substrates involved in this audiovisual processing, to determine whether there were underlying neurophysiological differences in those with ADHD compared to neurotypical controls. **METHODS:** This work utilized an audiovisual multisensory two-alternative forced-choice discrimination task. Stimuli included a unisensory visual (red, blue, or green circle), auditory unisensory (female verbalization), and a semantically congruent audiovisual stimulus. Participants responded using their right index and middle finger, using a Chronos response device. Continuous whole-head electroencephalography (EEG) was recorded at a sampling frequency of 2048 Hz while completing this task. Source localization (sLORETA) software was utilized to determine neuroanatomical differences in the contribution made by neural generators pertinent to audiovisual MSI, in those with ADHD versus neurotypical controls. **RESULTS:** Source localization techniques elucidated that controls had greater neural activity 164 ms post-stimulus onset when compared to the ADHD group, but only when responding to audiovisual stimuli. The source of the increased activity was found to be BA 2, postcentral gyrus, right-hemispheric parietal lobe referenced to Montreal Neurological Institute (MNI) coordinates of X = 35, Y = -40, and Z = 70 ($p < 0.05$). No group differences were identified during either of the unisensory conditions using sLORETA analyses. **CONCLUSIONS:** This work is the first to assess audiovisual multisensory processing through utilization of source analysis in young adults with ADHD. Differences in multisensory integration areas, particularly in the right-hemispheric parietal brain regions, were found in those with ADHD. These alterations may correspond to impaired attentional capabilities when presented with multiple simultaneous sensory inputs, as is the case during a multisensory condition. Structural alterations to parietal regions in ADHD may have important implications for the processing of complex sensory information, particularly when in audiovisual sensory-rich environments.

Keywords

standardized low-resolution brain electromagnetic tomography (sLORETA); Source-localization; multisensory; Attention-Deficit/Hyperactivity Disorder (ADHD); Brodmann area (BA) 2

4.3 Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder that is defined by specific behavioural characteristics (*Diagnostic and statistical manual of mental disorders: DSM-5*, 2013). Prominent behavioural characteristics described as being hallmarks of ADHD include hyperactivity, impulsivity, and inattention (Visser et al., 2014). Although the most common signs and symptoms relating to ADHD are behavioural in nature, literature has more recently suggested that there may be important neural alterations, with further research necessary to elucidate their relevance to ADHD symptomology. In the United States alone, it is estimated that 11% of children will receive a diagnosis of ADHD (Visser et al., 2014). In addition to this, approximately 65% of children diagnosed with ADHD will continue to exhibit symptoms as adults (Faraone et al., 2006). Each of the hallmark behavioural signs can have important implications for many day-to-day activities that can hinder physical and mental health in adults with ADHD, thus resulting in both internal and external life stressors (Brook, Brook, Zhang, Seltzer, & Finch, 2013). Therefore, further understanding these characteristics and their relevance to daily life is important. When comparing characteristics of ADHD in adulthood, adults are often noted as exhibiting reduced hyperactive tendencies when compared to children (Gentile, Atiq, & Gillig, 2006). The less overt and disruptive presentation in adulthood may, in part, explain why limited literature addresses the effects in adulthood. Nevertheless, there is increasing recognition and awareness of ADHD in adulthood. Improving the understanding of behavioural and neurophysiological mechanisms prominent in adult ADHD is key, and this will enable further enhancements to environments and supports to assist and promote barrier-free function in this population.

There are well noted neural alterations associated with ADHD, relating to both functional and structural characteristics that are unique to this population. This includes diffuse reductions in gray matter found throughout the cortex, including parietal, temporal, frontal, and occipital brain regions (Castellanos et al., 2002; Duerden et al., 2012; Makris et al., 2007; Proal et al., 2011; Valera et al., 2007). Although most research addresses such characteristic in children, persistent alterations are present in adults with ADHD as well (Makris et al., 2007; Proal et al., 2011). In addition to diffuse gray matter alterations, characteristic alterations are present within the prefrontal cortex and related neural circuits (Sowell et al., 2003). Alterations within the prefrontal cortex are some of the most commonly described neurophysiological characteristics of ADHD. These structural changes may have important implications for the behavioural characteristics associated with ADHD, including alterations to executive functions, which are commonly associated with activity in prefrontal brain regions (Barkley, 1997). Notably, structural alterations in the prefrontal cortex were evident in adults (Seidman et al., 2006). Additionally, adolescents with ADHD have noted alterations to the insula, specifically the right anterior insula, as those with ADHD had increased thickness when compared to neurotypical controls (Duerden et al., 2012). The insula, specifically BA 13, is involved in multisensory processes, likely those associated with stimulus identification (Duerden et al., 2012; Renier et al., 2009). This, in addition to parietal alterations, suggests that multisensory processing may be implicated in ADHD as a result of structural alterations, including, but not limited to, those related to the insula. Forming a deeper understanding of both neural structural and functional alterations present in this population will strengthen the overall understanding of ADHD and its effects on neural processes, many of which have a fundamental influence on function in day to day life.

Multisensory integration (MSI) is a form of neural processing that describes how the nervous system combines incoming sensory information, integrating this information in order to create a coherent perception of the surrounding environment (Stein & Wallace, 1996). Limited literature has assessed multisensory processing in ADHD. The capacity for multiple sensory inputs to be processed and integrated can have a profound effect on behaviour and function. For instance, when multiple stimuli are presented simultaneously and integrated by the nervous system, this can speed response times and result in neural enhancements (Brandwein et al., 2011; Laurienti et al., 2004; Meredith, Nemitz, & Stein, 1987). A specific type of MSI that is common to many everyday environments, is audiovisual (AV) MSI. AV integration occurs when an auditory and visual stimulus that are semantically congruent are presented closely in time and space. There are certain populations, such as those with autism spectrum disorder (ASD), that are thought to have altered AV MSI, potentially associated with difficulties in communication and social settings, where AV stimuli are abundant (Brandwein et al., 2015; Brandwein et al., 2013). This illustrates the importance of MSI, and how alterations to this process can have clinically and functionally significant implications. Due to the unique neural characteristics associated with ADHD, it is likely that alterations are also present in the way individuals with ADHD process multisensory inputs.

MSI is associated with functioning in specific brain regions. Previous research utilizing EEG has found that cortical structures, including those found within parietal regions, are highly involved in the integration of audiovisual multisensory inputs (Brandwein et al., 2015; Brandwein et al., 2011; Molholm et al., 2006; Moran et al., 2008). Cortical regions including the superior temporal sulcus and posterior parietal cortex are two such multisensory regions (Molholm et al., 2002). These regions have a high density of multisensory neurons, being neurons that respond to both auditory and visual inputs (Andersen et al., 1997; Molholm et al., 2002). The inferior parietal sulcus (IPS) and superior parietal lobule (SPL) are specific parietal regions where multisensory inputs have been localized to (Andersen et al., 1997; Calvert et al., 2001; Molholm et al., 2006). This suggest that parietal regions are heavily involved in AV MSI. The fact that they are cortical regions, as opposed to subcortical regions, allows for the ability to assess them using techniques such as EEG. Previous research found that there were unique differences in how young adults with ADHD process AV multisensory inputs when compared to neurotypical controls (McCracken et al., 2020; McCracken et al., 2019). These findings were based upon EEG data and noted several differences when compared to neurotypical controls (McCracken et al., 2020). For example, ADHD was associated with enhanced neural processing of multisensory inputs in parieto-occipital brain regions from 110-130 ms. Behaviourally, those with ADHD had faster response times, and although no significant accuracy differences were found, a medium effect size suggested increased error was associated with ADHD (McCracken et al., 2020). It is possible that the unique neural response in those with ADHD may be related to the quicker responses in that study. In order to further develop an understanding of how ADHD and potential neural alterations present in this population, identifying specific neural generators related to important sensory and multisensory processes is necessary to highlight the role of specific neural regions that may function differently in ADHD.

Previous work assessing MSI in ADHD involved analysis of event-related potentials (ERPs) using super-additive models (McCracken et al., 2020; McCracken et al., 2019). Although the previous work provided novel and important information into multisensory processing in adults with ADHD, further incorporating a form of neural assessment that exceeds an assessment involving strictly surface electrical activity will provide insight into the role of specific cortical structures involved in MSI in adults with ADHD. These analyses were outside the scope of a strictly surface activity EEG assessment. Source localization is an analysis technique that pairs the spatial resolution of magnetic resonance imaging (MRI) with the temporal resolution of collected EEG data. It is clear that those with ADHD exhibit unique neural characteristics, and therefore assessing the neurophysiological response to stimuli using an analysis technique that provides enhanced spatial resolution is important. The current analysis source localized the evoked potential data from McCracken et al., 2020. For the present study, standardized low-resolution brain electromagnetic tomography (sLORETA) was used to localize neural activity recorded using 64-electrode whole-head EEG. sLORETA is a linear inverse algorithm that provides an estimate of the 3D distribution of neural generators within the cortex (Pascual-Marqui, 2002). sLORETA has been found to provide the lowest localization error in comparison to other techniques using a linear inverse algorithm (Pascual-Marqui, 2002). Therefore, source localization acts as an important and cost-effective method to assess neural substrates and their function in diverse populations.

The research question that this work aims to answer is whether there are specific neural structures involved in the processing of multisensory inputs in adults with ADHD that differ from neurotypical controls? It is hypothesized that there will be differences in which cortical regions are primarily involved in sensory processing, particularly those involved in MSI, such as parietal brain regions.

4.4 Methods

4.4.1 Participants

This research received approval form the Ontario Tech University Research Ethics Board (REB) and participants gave written informed consent prior to participation. This study was performed according to the principles set out by the Declaration of Helsinki for the use of humans in experimental research. Participants included in the present analysis are identical to those whose multisensory ERP EEG peaks were assessed in McCracken et al., 2020. Participants were recruited from the Ontario Tech University student body and were contacted via in-course announcements and posters placed throughout the campus. Participants were young adults (18-35 years old) with ADHD, while the control group consisted of neurotypical adults. Participants in the ADHD group had previously received an ADHD diagnosis from a registered health care professional. They self-reported the age at which they were diagnosed and also any medication that they typically took to manage their symptoms of ADHD at the time of participation. The ADHD group (*n* = 10, three females) had a mean age of 23.7 ± 3.3 years, with a mean age of diagnosis being 13.7 ± 7.7 years old. The neurotypical control group (*n* = 12, four females) had a mean age of 21.7 ± 1.8 years old.

Inclusion and exclusion criteria: The Adult ADHD Self-Report scale (AASRS-v1.1) checklist questionnaire was completed by all participants prior to participation, this was done to quantify their ADHD symptomology. The AASRS-v1.1 consists of 18 questions that are highly correlated to the diagnostic criteria set out by the DSM-IV (Dankner, Shalev, Carrasco, & Yuval-Greenberg, 2017), and are rated on a five-point Likert scale ranging from “never” to “very often” for each question. This screening tool has been noted as highly effective for predicting ADHD symptomology (van de Glind et al., 2013) and is broken up into two parts, part A (inattentiveness) and part B (hyperactive/impulsive). When participants respond with “sometimes”, “often”, or “very often” it is highly suggestive of ADHD. This questionnaire was included as a part of the pre-participation screening to ensure that we did not inadvertently include any participants who may have unknowingly had ADHD in the “control” group, and likewise that we did not include any in the ADHD group whose symptoms has resolved since their diagnosis. To note, no specific total is associated with a definitive ADHD diagnosis; however, we were able to quantify the score for each participant and group (ADHD vs. control). The ADHD group had an average score for part A of 15.0 ± 3.33 (Controls: 6.25 ± 3.41) and 25.7 ± 5.29 (Controls: 10.17 ± 6.91) for part B. Six participants reported that they were taking medication relating to ADHD at the time of participation. The medications reported included: Adderall, Concerta, and Vyvanse. All participants completed the Edinburgh Handedness Questionnaire to determine their hand dominance. The number of left-hand dominant participants was made similar between groups. Specifically, the ADHD group had one left, five right, and four ambidextrous participants while the neurotypical control group had one left, 10 right, and one ambidextrous participant. An EEG safety checklist was completed to ensure that participants did not have a recent (past five years) history of epilepsy, concussion, stroke, or brain injury that could potentially affect the electrophysiological results or make the task unsafe for their participation.

4.4.2 Procedures

Stimuli

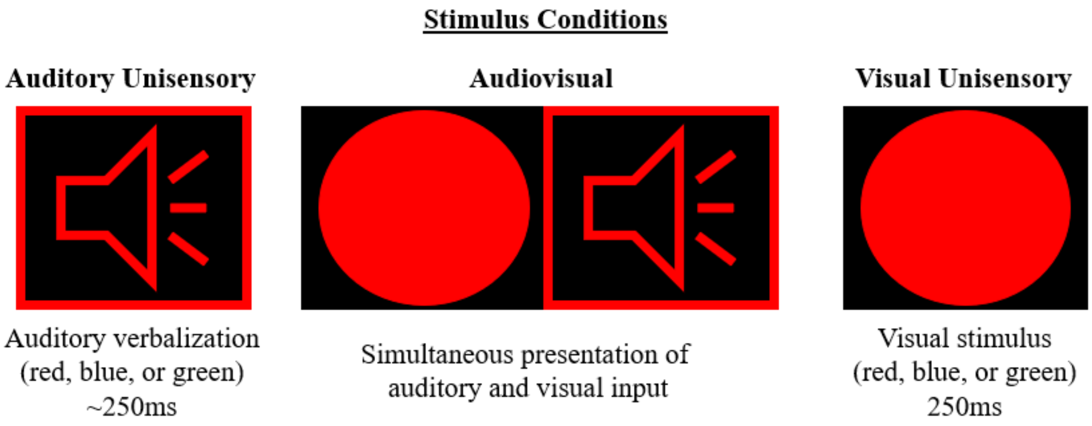

Figure 1 - Depiction of the various sensory conditions presented during the paradigm. Semantics associated with each condition were representative of "red", "blue", or "green".

Auditory Alone

A unisensory auditory stimulus was presented in front of the participant from speakers placed bilaterally from the computer screen. The stimulus was a female verbalization of the word red, blue, or green (duration ~250 ms, ~75 dB).

Visual Alone

A unisensory visual stimulus consisted of a circle (diameter 300 mm, seated ~23 inches away from screen) filled with the colour red, blue, or green. The circle was on a black background and lasted for a duration of 250 ms.

Audiovisual Multisensory

The multisensory stimulus consisted of the described auditory and visual conditions occurring simultaneously. The auditory and visual components were always semantically congruent. For example, when the blue circle appeared, the “blue” verbalization was emitted, etc. Conditions were never semantically incongruent.

To measure MSI, a two-alternative forced choice discrimination task was utilized that consisted of three unique stimuli that were semantically congruent. For example, a female verbalization of the word “red” was paired with a red circle, or a verbalization of the word “blue” was paired with a blue circle. Similar paradigms have been used previously to quantify multisensory processing (Farid, Yielder, Holmes, Haavik, & Murphy, 2018; Laurienti, Burdette, Maldjian, & Wallace, 2006; Laurienti et al., 2004; McCracken et al., 2020). E-Prime 2.0 Professional Software was used to develop and implement this paradigm (Psychology Software Tools, Sharpsburg, PA, USA). A previous study had described the EEG and behavioural results, with an emphasis on response time (ms) and accuracy (%) while assessing neural markers in the form of ERPs (McCracken et al., 2020). Thus, limiting the assessment of cortical activity to surface electrodes. Further details on the paradigm used are outlined in McCracken et al., 2020. The current study aims to use source localization via sLORETA to assess the neural generators involved during this task in a population of adults with ADHD compared to neurotypical controls.

A Waveguard™ 64-electrode EEG cap (ANT Neuro, Hengelo, The Netherlands) was used to collect surface brain electrical activity in response to performing forced choice task in each of the three sensory conditions. The Waveguard™ cap was connected to a TMSi REFA-8 amplifier (TMSi, Oldenzaal, The Netherlands) with 64 EEG channels, four bipolar channels, and four auxiliary channels and was collected through Advanced Source Analysis Lab™ (ANT Neuro) at a sampling frequency of 2048 Hz. EEG data was processed offline using ANT 4.10.1. Artifacts resulting from muscle activity and/or blinking were removed. A band-pass filter was utilized, with a low cut-off of 1.6 Hz to remove constant slow-wave activity, and a high cut-off of 45 Hz to remove any artifacts from surrounding electrical equipment, this was done with a slope of 24 dB/octave, which was applied to individual data sets. Artifact rejection was performed by excluding waveforms that exceeded ±100 μV. Electrodes still containing significant noise (e.g., electrical contamination not related to the EEG signal) were interpolated for the relevant individual participant using the nearest surrounding eight electrodes. This was done on an individual data set basis. EEG data were then averaged per condition into 600 ms epochs (−100 to 500 ms) surrounding stimulus onset, giving three averages for each participant (auditory, visual, and multisensory).

The primary objective for the research reported here was to build upon the novel findings in McCracken et al., 2020, and was therefore to assess whether there were differences in neural generators when those with ADHD were presented with multisensory and the constituent unisensory conditions when compared to neurotypical controls. Previous work was limited to the assessment of surface electrodes; however, the inclusion of source localization techniques in the present study allows for determination of particular neural generators and activity that are outside of the scope of surface EEG by itself.

4.4.3 Data Analysis

4.4.3.1 Source Localization – sLORETA Analysis

Source localization was performed to assess neural areas of greatest activity in response to each sensory condition, allowing for a comparison between groups. This was done using standardized low-resolution brain electromagnetic tomography (sLORETA) software (Fuchs, Kastner, Wagner, Hawes, & Ebersole, 2002; Jurcak, Tsuzuki, & Dan, 2007; Pascual-Marqui, 2002). sLORETA solves the inverse problem via the assumption of synchronous and simultaneous activation of neighbouring neurons without a localization bias (Pascual-Marqui, 2002; Pascual-Marqui et al., 1994; Sekihara et al., 2005). sLORETA has been validated for accuracy by comparing results with techniques such as EEG and fMRI (Mulert et al., 2004). The evidence from this validation research suggests that the estimated localized sources are reliable. The source localization analysis was completed in the time-domain to assess differences in areas of greatest neural activity between those in the ADHD group and those in the neurotypical control group in response to the: (1) multisensory, (2) visual unisensory, (3) and auditory unisensory conditions. Cortical grey matter consists of 6239 voxels with a spatial resolution of 5 mm. Voxel-wise randomization tests with 5000 permutations based on statistical nonparametric mapping (SnPM) were performed. This corrects for multiple comparisons and has the highest possible statistical power (Nichols & Holmes, 2002). The standardized current density at each voxel is calculated using a head model and electrode coordinates that are based on the Montreal Neurological Institute (MNI) average MRI brain-map (MNI-152).

4.4.3.2 Time-Domain Statistical Analysis

Statistical significance was set to $p = 0.05$. The statistical analysis was done within sLORETA's built in statistical tool (Navid et al., 2019; Pascual-Marqui, 2002). sLORETA completes an independent two-tailed Student's t-test, converting collected EEG data into t-values for each time frame, comparing two independent groups, in this case ADHD vs. controls. This was done for 1229 time frames, being 600 ms with a sampling frequency of 2048 Hz. This is done using SnPM, which adjusts for multiple comparisons using Fisher's random permutation test with 5000 randomizations (Nichols & Holmes, 2002). The software sets a two-tailed t-value threshold, providing the t-critical, where once a value in the time-domain exceeds this threshold, a computation occurs within the software that localizes the area responsible for this neural activity, while also providing the associated statistical significance (*p*-value).

4.5 Results

4.5.1 Multisensory

The comparison between multisensory responses concluded that neural generators differed significantly between groups when presented with an audiovisual multisensory stimulus. The area of greatest difference in neural activity between groups was right hemispheric, BA 2, postcentral gyrus, parietal lobe (MNI coordinates: X = 35, Y = - 40, Z = 70; $p < 0.05$). Controls had significantly greater activity in this region at 164 ms post stimulus onset when compared to those in the ADHD group. This region can be seen in Figures 2 and 3.

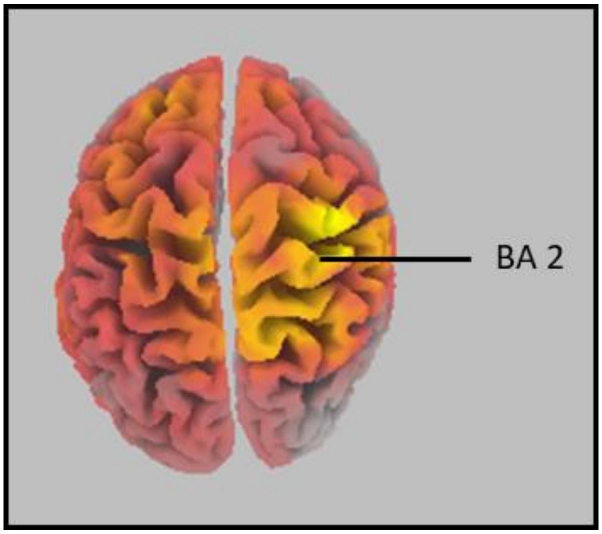

Figure 2 - sLORETA 3D Cortex. Area highlighted indicates the region of maximal difference between groups (Control vs. ADHD).

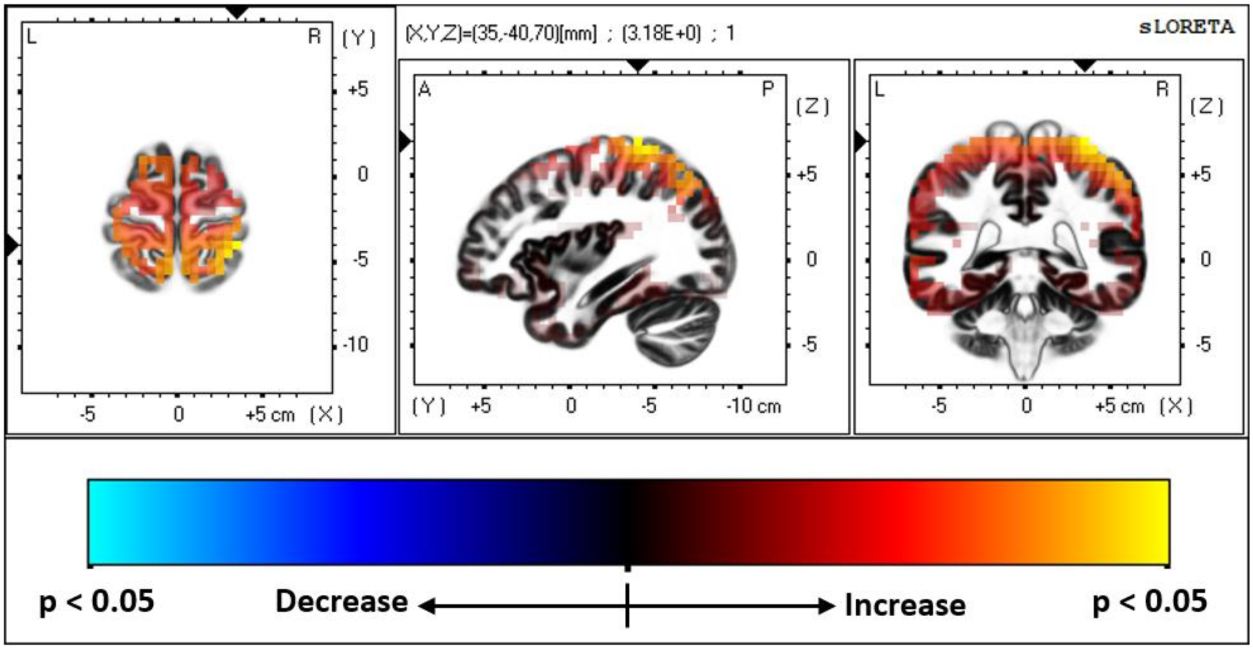

Figure 3 - sLORETA multisensory response, ADHD vs. Controls. Slice Viewer highlighting region of greatest neural activity difference between controls and those with ADHD. Views, from left to right, include a transverse, sagittal, and coronal cross-sectional area. Controls had greater activity in the region highlighted in yellow.

4.5.2 Visual Unisensory

There were no significant differences between groups when presented with the visual unisensory condition ($p > 0.05$). No timeframe surpassed t-critical.

4.5.3 Auditory Unisensory

There were no significant differences between groups when presented with the auditory unisensory condition ($p > 0.05$). No timeframe surpassed t-critical.

4.6 Discussion

This is the first study, to our knowledge, to assess the presence of unique neural generators, via source localization, related to multisensory processing in those with ADHD. Using source localization techniques and EEG data collected during an audiovisual multisensory task, we were able to compare cortical regions that differed in activation between young adults with ADHD and adult neurotypical controls. This additional analysis was an important next step from our previous work that assessed surface brain activity in those with ADHD during AV multisensory tasks (McCracken et al., 2020; McCracken et al., 2019). The previous work was done using a 64-electrode whole-head EEG system and analysis was based upon the principle of superposition of electrical fields (Molholm et al., 2002). Therefore, improving spatial resolution via source localization was important. Therefore, the current sLORETA analysis was performed on the evoked potential data from those in McCracken et al., 2020, please refer to the appendix for behavioural results from this study. This allows for the assessment of specific neural structures, including those that are deeper to the brain surface and therefore outside the scope of a direct surface assessment. In the current study, those with ADHD were found to have unique neural activation in response to an audiovisual multisensory stimulus when compared to controls. BA 2 had reduced activation in those with ADHD when compared to controls, and this unique activation occurred in the right-hemispheric parietal lobe at 164ms post stimulus onset. When comparing the neural response to each of the unisensory components, there were no significant differences between those with and without ADHD. This suggests that the difference discovered in BA 2 is unique to a multisensory response, related to altered neural function in ADHD.

4.6.1 Brodmann area (BA) 2

S1 has a fundamental role in processing afferent sensory input, particularly somatosensory input (Borich, Brodie, Gray, Ionta, & Boyd, 2015). Additionally, S1 allows for the integration of both afferent and efferent signals, making it a strong contributor to the processes necessary for movement (Borich et al., 2015). S1 encompasses BA 3, 1, and 2. Each of these areas are highly involved in motor learning, the localization of touch, and sensory perception (Nolte, 2008). Each BA has a specific function that are slightly unique to the others. Specifically, BA 3 is involved in processing vibration, pressure, and general tactile stimuli; BA 2 is involved in pressure and joint position sense; whereas BA 1 generally responds to vibrotactile stimuli (Sur, 1980). Lesions in any of these BA would result in alterations to proprioception and fine touch, due to the involvement of the dorsal column medial lemniscus (DCML) pathway (Nolte, 2008). More specifically, BA 2 is postulated to respond to pressure, joint position, and complex touch (Choi et al., 2015; Sur, 1980). The results from the current work suggest that BA 2 functions differently in those with ADHD when responding to multisensory afferent input.

The right-hemispheric difference specific to BA 2 is consistent with our previous work in ADHD. Specifically, we reported previously that when presented with an AV multisensory stimulus neurotypical controls had a more pronounced negative ERP over right-hemispheric central-parietal brain regions, specifically electrodes CP4 and P6, when compared to young adults with ADHD (McCracken et al., 2020). This prominent negative activity present in controls, but not those with ADHD, was evident from 160-180 ms post-stimulus onset (McCracken et al., 2020). The activity found in our previous work was in a similar location, and within the same time frame, to that of the results from the current study using source localization techniques analyzing the same participants EEG data.

Additionally, the previous analysis yielded results showing that those with ADHD had greater activity in areas related to multisensory integration in parietal-occipital brain regions (electrodes PO7, PO8, O1, and O2) at an earlier latency, from 110 – 130 ms (McCracken et al., 2020). Altered activity in BA 2 in ADHD may be related to differences in the way those with ADHD process and respond to multisensory stimuli, as BA 2 has a primary role in proprioception. For instance, one interpretation of this difference is an altered perception of the digits or limb used to respond to the stimulus. The multisensory condition resulted in greater activity in controls in BA 2 compared to those with ADHD, and this may be related to the faster responses recorded in an ADHD group (McCracken et al., 2020). Although this is unlikely, as this unique neural difference was only present during the multisensory condition. Reduced activation may reflect more efficient processing, and thus be associated with quicker responses found previously. However, there may be other, more likely, postulated mechanisms involved in this differed neural activation, such as impaired attention resulting in suboptimal multisensory processing, prioritizing speed of response over accuracy. This explanation will be further described in the subsequent section.

4.6.2 Parietal lobe

The current study established altered activity within BA 2 specific to the right hemisphere, in young adults with ADHD. BA 2 is found within the parietal lobe. The parietal lobe is generally associated with sensory processing, and contains the primary (S1) and secondary (S2) somatosensory cortices (Raju & Tadi, 2020). Parietal deficits are also well-noted in ADHD (Brandeis et al., 1998; Vance et al., 2007). Interestingly, previous work noted that a reduction, or attenuation, in parietal ERPs were associated with reductions in performance (Brandeis et al., 1998). Conversely, the opposite was found in adults where those in the ADHD group had shorter response times than controls (McCracken et al., 2020). Furthermore, previous research suggests that the right parietal lobe and its function may be implicated in the neurophysiology of ADHD (Aman, Roberts Jr, & Pennington, 1998; Chan et al., 2009). Neurophysiological evidence supports the role of altered right parietal lobe function in ADHD, including more left-sided errors than controls and reduced learning on right parietal dominant tasks (Aman et al., 1998). These previous findings suggest alterations to functions related to the parietal lobe and ADHD, which likely are related to structural alterations as well.

Anatomically, S1 is located at the postcentral gyrus of the parietal lobe, and altered structure may have important functional implications, and vice versa. Imaging studies have noted that children with ADHD have significantly reduced cortical volume in the right parietal lobe (Wolosin et al., 2009). Molholm et al. (2002) established that there is an AV multisensory effect focused over the right hemisphere at approximately 160 ms until 180 ms in neurotypical humans (Molholm et al., 2002). These regions and latency coincide with the results found in the current study, suggesting that both may have important functional implications for MSI. Thus, these changes established herein, have relevance to those with ADHD and how their nervous system processes such multisensory cues.

An fMRI study with both clinical and behavioural importance found right-parietal dysfunction in young boys with ADHD (Vance et al., 2007). Specifically, controls had greater activation in right parieto-occipital areas (BA 19) and right inferior parietal lobe (BA 40) compared to children with ADHD, further supporting the role of right parietal dysfunction in ADHD (Vance et al., 2007). This evidence further supports the suggestion of right striatal-parietal dysfunction in adolescents with ADHD. The right parietal lobe has an attributed role in spatial attention, including right-hemisphere involvement of the fronto-parietal network. Additionally, spatial attention has been localized to right-hemispheric fronto-parietal networks (Chan et al., 2009; Corbetta, Miezin, Shulman, & Petersen, 1993; Gitelman et al., 1999; Nobre et al., 1997; Vance et al., 2007). Alterations to right hemisphere parietal activation is associated with clinical outcomes in both adolescents and children, such as impaired control of attention (Carter, Krener, Chaderjian, Northcutt, & Wolfe, 1995; Chan et al., 2009; Silk et al., 2005; Vance et al., 2007). This was observed as children with ADHD have an impaired ability to attentionally orient to the left visual field (Carter et al., 1995). Alternatively, children with ADHD were found to have under activation in the right SPL during a visual selective attention task (Booth et al., 2005). This suggests that well-noted parietal dysfunction is present in both children and adolescents with ADHD. Attentional alterations are also present and characteristic of ADHD, and therefore the previously noted alterations to attentional networks and the findings from the current study localized to BA 2, suggest that right-parietal alterations impact multisensory processing and relate to the symptomology of ADHD.

Those with ADHD responded differently at a neural level in response to the multisensory condition, this unique difference in those with ADHD was found in BA 2, parietal lobe. It should be noted that this difference was unique to the multisensory condition, and no group differences were found in either unisensory condition. This further suggests that the unique neural activation is a result of the multisensory nature of the task. One potential explanation for these differences in sensory perception between groups could be that those with ADHD-like traits have a reduced ability to discern when multiple stimuli occur simultaneously (Panagiotidi, Overton, & Stafford, 2017). This is described as having an altered temporal integration window and may have important implications for the perception of multisensory inputs, as a result of alterations to attentional capabilities, leading to increased distractibility (Panagiotidi et al., 2017). For multisensory inputs to be processed and integrated as multisensory, and not two unique individual stimuli, it is necessary for each of the constituent components of the target stimulus to be attended to. In the case of the current study, individuals needed to attend to and process both auditory and visual unisensory afferents simultaneously. It is possible that the difference found within right-hemisphere BA 2, parietal lobe, is a result of altered attentional capabilities in those with ADHD. Thus, potentially reducing the activity within the parietal lobe in the ADHD group, as a result of their inability to allocate attentional resources to each of the multisensory components. This suggests that the structural alterations in parietal regions may have significant implications for how those with ADHD process sensory information and consequently respond in multisensory environments. Thus, having important implications for their sensory perception and how they experience everyday environments full of audiovisual stimuli.

4.6.3 Multisensory processing

Although limited literature has assessed MSI in ADHD, previous work has shown that there are differences in the way that adults with ADHD process and respond to multisensory inputs at both the behavioural and neurological levels. MSI is fundamental to how individuals experience the world, as many environments are multisensory in nature. For instance, at any given time individuals are presented with auditory, visual, and tactile stimuli. Therefore, alterations to multisensory processing may have fundamental implications for how one processes, perceives, and responds to their environment, potentially impacting day-to-day activities such as working and socializing. These differences can be observed using neurophysiological and behavioural measures. For instance, historically S1 is often thought of as unisensory, but has more recently been associated with being the initial site for processing associated with MSI (Borich et al., 2015; Driver & Noesselt, 2008). Therefore, neural changes in right-hemisphere S1 associated with ADHD (Mostofsky et al., 2006) may have important implications for MSI.

The previous unique neural alterations relating to MSI in ADHD were predominantly localized to parietal, occipital, and central electrode regions (McCracken et al., 2020; McCracken et al., 2019). These changes were found in conjunction with behavioural alterations, such as significantly shorter response times. Additionally, although there was not a significant effect found for accuracy, those with ADHD did show a pattern of increased error compared to controls, and a medium effect size was present (McCracken et al., 2020). The current work provides further insight into the neural mechanisms that may be related to these behavioural findings. The current work found that those in the ADHD group exhibited attenuated activity within the right-hemisphere parietal lobe. As previously discussed, this region is highly involved in attentional capacity (Carter et al., 1995; Silk et al., 2005; Vance et al., 2007). Therefore, the behavioural differences noted in prior research may be a result of, or related to, reductions in attention in ADHD as a result of right parietal dysfunction. This indicates the possibility of attenuated neural activity being related to impaired attention during the multisensory condition, potentially associated with important behavioural findings, such as increased error, although with shorter responses.

A tenet of multisensory processing, that can have a profound influence on the integration effect, is related to the allocation of attentional demands to each sensory component that encompasses the multisensory stimulus. This suggests that the level of selective attention can modulate MSI (Talsma et al., 2007). For instance, allocating attention to both the auditory and visual component of a multisensory condition can have a critical effect on the electrophysiological responses typically associated with MSI (Talsma et al., 2007). This is observed as the absence of, or reversal of, the neural enhancements associated with MSI when attention is limited to one of the constituent stimuli components. Therefore, reductions in attention may result in multisensory dysfunction, and this could have important implications for understanding the neural mechanisms involved in multisensory processing in those with ADHD, such as those found in the current study. Furthermore, a previous source localization study found hypoactivation within right-hemispheric frontal gyrus (BA 32) in response to incongruent multisensory inputs during incompatible NoGo trials in a Go/NoGo task in adolescents with ADHD when compared to neurotypical controls (Chmielewski et al., 2018). The authors postulated that this was related to compromised response inhibition as a result of impulsivity (Chmielewski et al., 2018). These findings compliment those found in the current study, suggesting reduced activation in right-hemispheric regions during multisensory conditions, and that this could be associated with impaired performance measures, such as accuracy. Additionally, the activation differences relating to S1 suggests relevance to other neural processes, as S1 has a primary role in many functions, such as those involved in sensorimotor integration in relation to motor learning. This suggests that distractibility and inattention, and their relation to learning and performance, may be impacted in ADHD.

4.6.4 Limitations

This study focused on university aged individuals recruited from the university campus. Thus, limiting generalizability of findings to those outside of this age group, such as children or adolescents with ADHD, or adults not affiliated with a university campus. Additionally, although utilizing sLORETA software provides a strong basis for the interpretation of neural generators, it should be noted that this involves pairing collected EEG data with a standardized average MRI. Therefore, although this is an acceptable, validated, and cost-effective technique to interpret neural activity, the MRI used for localization is not definitively reflective of each individual's specific neural structures. In the future, incorporating fMRI techniques and individual scans would enhance the findings noted above.

4.7 Conclusions

The present data analysis yielded results indicating that young adults with ADHD process AV multisensory stimuli differently than controls. In particular, neural differences were localized to the right hemisphere, over parietal regions associated with BA 2. No statistically significant differences in neural generator activity between groups were found for either unisensory condition. Therefore, the differences noted herein are unique to multisensory processing in those with ADHD. This result may have important implications for how they process and respond to multisensory inputs, while also reflecting alterations to attentional capacity when more than one stimulus is presented at a time. Previous literature found that neurotypical controls had greater activity in this brain region, specifically over right-hemispheric central-parietal brain regions from 160-180 ms (McCracken et al., 2020), suggesting a similar, yet more specific, pattern of activity yielded using sLORETA analysis techniques. This reflects the utility of source localization techniques to further elaborate on EEG findings in this population. In the future, continuing this stream of work via utilization of fMRI could prove beneficial. Overall, this work suggests that multisensory tasks and EEG in conjunction with source localization techniques may have the potential to serve as an objective measure of altered MSI in those with ADHD.

Furthermore, the activity alterations localized over the right-hemisphere in S1 indicate that other important alterations, such as those relating to attentional impairments, may be present in young adults with ADHD and have important implications for many functions, including motor learning and sensory integration.

Chapter 5: Study 2

5.1 Preface to manuscript 2

Sensorimotor integration (SMI) describes how one integrates sensory afferents to inform motor output, which is fundamental to the process of motor learning. There are a number of neural structures and networks that are implicated in the processes related to SMI and motor learning. Attention-Deficit/Hyperactivity Disorder (ADHD) is associated with impairments in motor control (Kaiser et al., 2015; Neely et al., 2016), in addition to alterations in somatosensory processing brain regions (Duerden et al., 2012). The results from the first study in this dissertation suggest that right-hemispheric BA 2 functions differently in adults with ADHD when presented with a multisensory stimulus, illustrating an attenuation of activity when compared to controls. Right-hemispheric parietal lobe is associated with spatial attention processes (Chan et al., 2009; Corbetta et al., 1993; Gitelman et al., 1999; Nobre et al., 1997; Vance et al., 2007), and BA 2 specifically processes sensory information related to pressure, joint position sense, and complex touch (Sur, 1980). This attenuation in neural activity, possibly related to attentional resources and joint position sense, may affect the central processing related to the acquisition and performance of novel motor tasks. Currently, little is known regarding the neural processes related to motor control and learning in adults with ADHD.

The second study sought to assess the neural processes related to motor learning and somatosensory processing in young adults with ADHD when compared to neurotypical controls. This assessment was implemented using a novel visuo-Motor Tracing Task (MTT), somatosensory evoked potentials (SEPs), and 64-electrode whole-head electroencephalography (EEG). Short-latency SEP peaks provide important insight into the role of specific neural structures and networks. The SEP peaks were compared prior to and after the practice of a novel motor paradigm. Participants practiced the task by tracing a sinusoidal waveform using their thumb on a trackpad. The stimuli were delivered in blocks of pre, acquisition, and post measures, and then participants completed a retention and transfer test the following day. Behavioural and neurophysiological measures were assessed, allowing for an interpretation of how neural responses may relate to performance outcomes such as accuracy.

Manuscript 2: Sensorimotor Integration and Motor Learning During a Novel Visuomotor Tracing Task in Young Adults with Attention-Deficit/Hyperactivity Disorder – *Submitted to the Journal of Neurophysiology*

Authors: Heather McCracken, Bernadette Murphy, Ushani Ambalavanar, Mahboobeh Zabihhosseinian, Paul Yielder

5.2 Abstract

Background: Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder with unique neurological and behavioural characteristics (Biederman et al., 2004; Proal et al., 2011). ADHD has been shown to alter motor performance and coordination (Kaiser et al., 2015; Neely et al., 2016), potentially affecting learning processes involved in the acquisition of motor skills. Additionally, there are alterations in somatosensory processing (Duerden et al., 2012) and the integration of multisensory stimuli (McCracken et al., 2020). It is currently unknown whether motor learning and performance may be altered, and whether there are neural markers relevant to these potential differences in adults with ADHD. This work will provide insight into the role of altered neural processing and sensorimotor integration (SMI) while learning a novel visuomotor task.

Methods: This work compared adults with ADHD (n = 12) to neurotypical controls (n = 16), utilizing a novel visuomotor tracing task, where participants used their right-thumb to trace a sinusoidal waveform that varied in both frequency and amplitude. This learning paradigm was completed in pre, acquisition, and post blocks, where participants additionally returned and completed a retention and transfer test 24 hours later. Right median nerve somatosensory-evoked potentials (SEPs) were collected pre and post motor acquisition. SEPs are named based on their

polarity and latency and are reflective of specific neural processes and structures. SEPs were stimulated at two frequencies, 2.47Hz and 4.98Hz, and were recorded using 64-electrode electroencephalography (EEG) at 2048Hz. Each SEP peak was normalized to each participant's baseline values.

Results: *Behavioural:* There was a main effect of time for both the normalized ($p < 0.001$) and absolute ($p < 0.001$) performance scores. *Neurophysiological:* N18: showed a main effect of group ($p < 0.05$) and a time by group interaction ($p < 0.05$), where the ADHD N18 increased post motor learning (1.26 ± 0.65) and controls decreased (0.83 ± 0.37). N20: showed a main effect of time ($p < 0.01$), where N20 increased for both groups post motor learning (ADHD: 1.10 ± 0.14; Control: 1.05 ± 0.12). P25: showed a main effect of time ($p < 0.001$), with P25 increasing for both groups post motor learning (ADHD: 1.10 ± 0.10; Control: 1.09 ± 0.13). N24: showed a main effect of time ($p < 0.05$), where N24 increased for both groups post motor learning (ADHD: 1.09 ± 0.16; Control: 1.14 ± 0.25). N30: showed a main effect of group ($p < 0.05$), as it decreased in ADHD (0.97 ± 0.15) and increased in controls (1.07 ± 0.11).

Discussion: This is the first work to utilize SEPs as a neurophysiological marker in conjunction with a visuomotor learning paradigm to assess processes involved in motor learning in adults with ADHD. These findings, particularly those related to the N18 and N30, suggest that there may be differences in cerebellar-cortical and prefrontal processing in response to this novel motor task in those with ADHD. Future work should further investigate the potential role of cerebellar function in response to motor learning in this population.

5.3 New and Noteworthy

Alterations to somatosensory evoked potentials (SEPs) were present in young adults with Attention-Deficit/Hyperactivity Disorder (ADHD), when compared to neurotypical controls. The N18 and N30 SEP peak had differential changes between groups, suggesting alterations to olivary-cerebellar-M1 processing and SMI in those with ADHD when learning a novel visuomotor tracing task. Therefore, this suggests the utility of short-latency SEPs in the assessment of motor learning in those with ADHD.

Keywords

Somatosensory evoked potentials (SEPs); Attention-Deficit/Hyperactivity Disorder (ADHD); motor learning; electroencephalography (EEG); sensorimotor integration (SMI)

5.4 Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is defined as a neurodevelopmental disorder, with the most common behavioural signs being hyperactivity, impulsivity, and inattention (Visser et al., 2014). These characteristics can have a profound affect on day to day life. In the United States, approximately 11% of children receive a diagnosis of ADHD (Visser et al., 2014). While ADHD is often associated with being a childhood disorder, up to 65% of those diagnosed during childhood, will continue to exhibit symptoms into adulthood (Faraone et al., 2006). This suggests that adults with ADHD make up an important part of the population, and further understanding their symptomology and the affects on day-to-day life, are fundamental to improving how we approach creating inclusive environments. Adults with ADHD often have reduced hyperactive tendencies, when compared to children with ADHD (Gentile et al., 2006), possibly explaining why limited literature addresses the effects in adulthood, neglecting an important cohort. Therefore, it is necessary to understand at both a behavioural and neurophysiological level how ADHD may affect those in adulthood, and the important implications this may have for day to day activities, including working and learning environments, for example.

In addition to the predominant behavioural characteristics, there are noteworthy signs and symptoms that are less commonly acknowledged. For instance, ADHD is associated with alterations to motor learning and performance (Barnes, Howard Jr, Howard, Kenealy, & Vaidya, 2010; Eliasson et al., 2004; Fliers et al., 2011; Harvey & Reid, 2003), as well as alterations to sensory processing (Ghanizadeh, 2011; McCracken et al., 2020; McCracken et al., 2019; Shimizu et al., 2014). There is robust evidence supporting the role of altered structure and function of neural substrates in those with ADHD, including alterations to both cortical and subcortical regions. Both functional Magnetic Resonance Imaging (fMRI) and electroencephalography (EEG) have shown distinct characteristics in those with ADHD when compared to neurotypical controls (Bresnahan & Barry, 2002; Castellanos et al., 1996; Makris et al., 2007; McCracken et al., 2020; McCracken et al., 2019; Proal et al., 2011). A common site of unique neural characteristics in those with ADHD is the prefrontal cortex (Castellanos et al., 2002; McAlonan et al., 2007), which often has reductions in gray matter when compared to neurotypical controls (Depue, Burgess, Bidwell, Willcutt, & Banich, 2010). Alterations to the prefrontal cortex have also been noted in young adults (Depue et al., 2010; Seidman et al., 2006). However, a robust body of literature now supports alterations that are diffuse throughout both cortical and subcortical regions, expanding upon the role of unique neural attributes in ADHD.

Neural alterations in this population include a global reduction in gray matter, found throughout parietal, occipital, and temporal regions, in addition to those found in the frontal cortex (Castellanos et al., 2002; Duerden et al., 2012; Proal et al., 2011; Valera et al., 2007). Reductions in grey matter within the right-hemispheric prefrontal cortex are associated with an increased difficulty to inhibit unwanted motor responses (Depue et al., 2010). Proal et al. (2011) identified reduced gray matter in right precentral, bilateral parietal, left temporal, and right cuneus. Additionally, this work yielded results showing reduced gray matter in the caudate, thalamus, and cerebellar hemispheres (Proal et al., 2011). Cerebellar alterations are noted in those with ADHD throughout the lifespan (Castellanos et al., 2002), with specific changes dependent on age. Children exhibit prominent alterations within the cerebellar vermis (Castellanos et al., 2001; Durston et al., 2004; Valera et al., 2007), and adult differences are apparent in the cerebellar hemispheres (Perlov et al., 2010; Proal et al., 2011; Valera et al., 2010; Wolf et al., 2009). This is in line with previous work suggesting that ADHD is at least partially related to fronto-striatal-cerebellar circuitry alterations (Krain & Castellanos, 2006; Proal et al., 2011). These neural attributes suggest important functional implications, such as those related to learning and motor performance.

Cerebellar alterations have been associated with difficulties with learning and automating fine motor skills, many of which are fundamental to daily life (Koziol et al., 2013). It is suggested that alterations to fronto-cerebellar circuitry are a strong indicator for the symptoms associated with ADHD, such as hyperactivity and inattention (Durston et al., 2011; Koziol et al., 2013). Additional alterations to the prefrontal cortex as they relate to ADHD include the dorsal frontostriatal and orbitofronto-striatal networks (Durston et al., 2011). Individuals with the most prominent clinical outcomes have reduced cerebellar volume (Mackie et al., 2007). Conversely, there are alterations to cortical thickness in sensorimotor processing brain regions, including those with ADHD having increased thickness in the pre-SMA and S1 (Duerden et al., 2012). These alterations in neural function and structure, suggest that there may be alterations to the functions associated with these areas. Some functions to note that are related to these structures, but are currently not fully understood in adults with ADHD, are sensorimotor integration and motor learning. These neural characteristics, as they pertain to cerebellar and sensorimotor regions, likely have profound behavioural implications, and are linked to the underlying characteristic signs of ADHD.

One's ability to control and perform motor outputs is fundamental to how they experience and interact with the world. At a behavioural level, those with ADHD are known to experience difficulties in tasks that require motor coordination and performance (Fliers et al., 2011; Kaiser et al., 2015; Karatekin et al., 2003). Those with ADHD may experience deficient inhibitory motor control, with this potentially being a hallmark deficit in ADHD (Lijffijt et al., 2005). Children with ADHD often exhibit difficulties with motor skills, such as handwriting, resulting in poor legibility and reduced speed (Brossard-Racine, Majnemer, Shevell, Snider, & Bélanger, 2011). In one study assessing children, regardless of medication status, it was found that difficulties in movement were present (Harvey et al., 2007). Conversely, Brossard-Racine et al. (2011) found that a proportion of children with ADHD improved in their motor skill performance after beginning treatment with stimulant medication, whereas 55.1% of participants had persistent motor impairment, regardless of medication status (Brossard-Racine et al., 2012). These alterations to motor performance affect motor learning as well (Karatekin et al., 2003). Karatekin et al. (2003) found that parents described their children with ADHD as having difficulties with learning complex motor skills, including motor tasks such as tying shoes and playing soccer. This suggests that difficulties are present in both activities of daily living as well as during leisure time. However, it is important to note that this data is based on parent perception, and not objective markers. Therefore, it is unknown whether alterations are inherently behavioural in nature, or if there may be important neural substrates involved in these motor and sensory characteristics that are key to how ADHD is understood. Although there is a reasonable body of literature assessing motor performance and learning in childhood, little is known on how ADHD affects these processes in adulthood.

With the limited literature addressing ADHD in adults, there is a lot that is currently unknown. One study noted that the consolidation of novel motor skills was reduced in young female adults with ADHD when compared to controls 24 hours after learning, although both the acquisition and memory consolidation were altered (Adi-Japha, Fox, & Karni, 2011). This was observed as those with ADHD had significantly reduced accuracy at the 24 hour retention test than compared to controls (Adi-Japha et al., 2011). These behavioural findings relating to motor performance may have important neurophysiological underpinnings. The cerebellum is noted as being fundamental in the processes related to learning of a new motor skill (Jueptner et al., 1997a). As previously noted, cerebellar alterations are common in ADHD. Therefore, it is likely that the noted cerebellar alterations in those with ADHD are associated with alterations in motor performance in adulthood (Kurdziel, Dempsey, Zahara, Valera, & Spencer, 2015). Interestingly, one study found that young adults with ADHD performed and learned better under noisy conditions, particularly conditions where a vibratory stimulus was introduced, even outperforming controls (Korman, Meir-Yalon, Egbarieh, & Karni, 2018). Depending on the environment and task demands, this may influence the extent to which motor alterations are observed. For instance, adults with ADHD achieved poorer performance on tasks that require manual dexterity, when compared to controls (Fietsam et al., 2022). Although limited studies have assessed motor performance and the likely alterations in those with ADHD form childhood through to adulthood, no studies have utilized a concurrent neurophysiological marker, such as SEPs, to understand the neural attributes of motor learning and their relation to performance in this population.

Combining behavioural and neurophysiological assessments provides a two-pronged approach to understanding motor performance. This may yield important details for designing learning environments to suit those with ADHD in the future. Motor learning is thought to be dependent on how one integrates sensory inputs in children with ADHD (Izawa et al., 2012). However, it is unclear whether this affects adults with ADHD to the same capacity, and if so, whether both the acquisition and consolidation of novel skills are affected. Additionally, there is even less known about the neural substrates affecting these processes, such as SMI, in either childhood or adulthood.

Sensorimotor integration (SMI) describes how the central nervous system (CNS) integrates sensory information from the periphery, to perform and refine motor outputs (Abbruzzese & Berardelli, 2003). Somatosensory evoked potentials (SEPs) are a tool that can be used to assess changes in SMI in response to novel motor skill learning and acquisition (Passmore et al., 2014). SEPs have successfully been used as a method to understand neural processing involved in SMI and motor learning in various populations, including those with subclinical neck pain (SCNP), neck fatigue, and those with neck pain who received spinal manipulation treatment (Andrew et al., 2018; Haavik & Murphy, 2012; Zabihhosseinian et al., 2021). Due to the cerebellum having a fundamental role in motor learning, and noted alterations in cerebellar structure in those with ADHD, suggests that SEPs in conjunction with a motor learning paradigm, may prove to be an invaluable method to assess neural changes in response to learning. SEPs have not been used to assess ADHD in adulthood, although limited studies have used SEPs as a method to assess somatosensory function in children with ADHD and tactile defensiveness (Parush et al., 1997; Parush et al., 2007). Children with ADHD and tic disorder were found to have distinct differences in the N20-P25 SEP peak, observed as a larger SEP peak amplitude when compared to neurotypical control children (Miyazaki et al., 2007). However, these studies were performed in childhood and in those with a dual diagnosis, reducing their generalizability to adulthood. Although literature suggests that SMI is altered in ADHD (Dockstader et al., 2009; Dockstader et al., 2008; Rubia et al., 2003; Rubia et al., 1999; Toplak & Tannock, 2005; Werry et al., 1972), it is unclear the influence this may have on both behavioural and neural measures of learning and SMI. SEPs are a promising method to provide a further understanding of the neural substrates involved in ADHD, motor learning, and SMI.

We sought to address the research question: Do adults with ADHD exhibit altered neural function and behavioural markers in response to learning a novel visuomotor task. We hypothesize that those with ADHD will show altered differences in neurological markers of SMI in the form of SEP peaks, particularly those peaks related to cerebellar function. Additionally, those with ADHD will achieve lower performance measures, likely having a reduced consolidation of motor performance, which is measured via accuracy at each phase of the motor paradigm.

5.5 Methods

5.5.1 Ethical Approval

Written and verbal informed consent was obtained prior to the start of data collection. This study was approved by the Ontario Tech University Research Ethics Board (REB). This study was carried according to the ethical standards set out by the Declaration of Helsinki statutes governing research on human subjects.

5.5.2 Participants

GPOWER statistical software indicated that for a large effect size, an alpha of $p = 0.05$, and a power ($1-\beta$) of 0.95 (β set at 0.05 to minimize the chance of a type II error), a sample size of 12 participants per group are needed for a pre-post experimental design (Faul & Erdfelder, 1992). Two groups participated, one group of adults with ADHD (n = 12, 8 females, mean age = 21.5 ± 1.93) and one group of neurotypical controls (n = 16, 9 females, mean age = 20.81 ± 2.46), all participants were right-hand dominant. Participants completed pre-screening questionnaires to ensure they met inclusion criteria, including being right-hand dominant, absence of any other known neurological conditions, or history of injury such as concussions.

Handedness was confirmed using the Edinburgh Handedness Inventory (EHI) self-report questionnaire.

The adult ADHD Self-Report Scale (ASRS-v1.1) was completed by every participant, and was used to assess symptoms associated with ADHD. The ASRS consists of 18 questions, which are in line with the ADHD diagnostic criteria set out in the DSM-IV (Dankner et al., 2017). Each question is rated on a 5-point Likert scale ranging from “never” to “very often”. This screening tool is highly sensitive for predicting ADHD symptomatology (van de Glind et al., 2013). Scores for part A and part B were recorded for each participant. Those in the ADHD group had an average of 21.58 ± 4.71 for part A, while controls scored 12.31 ± 3.53. Scores for part B for the ADHD group were 42.33 ± 8.03 and 22.94 ± 5.73 for controls.

5.5.3 Experimental Protocol

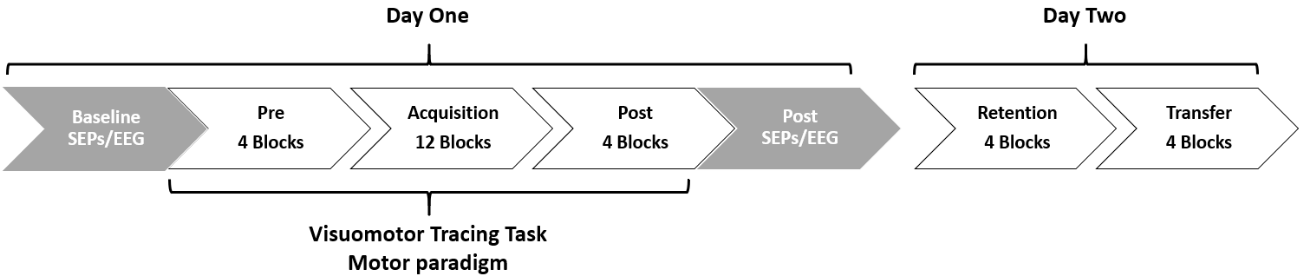

Figure 4 - Depicting the flow of the study on days one and two, where day two occurred 24 hours after the first session.

All participants attended two sessions, 24-48 hours apart. The first session included the EEG and SEP collections, where participants completed the pre and post motor tracing task blocks and motor skill acquisition. On day one, participants completed the informed consent documents. This was then followed by the setup of the EEG and SEPs. Baseline SEPs measurements were then recorded, including both 2.47Hz and 4.98Hz stimulation frequencies. Following baseline SEPs, participants completed the novel motor tracing task in blocks of pre-acquisition (4-blocks), acquisition (12-blocks), and post-acquisition (4-blocks). Prior to the start of the pre-acquisition phase, participants completed one familiarization trial so that they could acquaint themselves with the expectations of the paradigm. Post-SEP measurements were then recorded at the same two frequencies, 2.47Hz and 4.98Hz. This first session took approximately 3 hours total. 24-48 hours later, participants were asked to return to the lab and complete a brief retention (4-blocks) and transfer (4-blocks) test of the motor tracing task, which took approximately 10-minutes total. The transfer test was the same program as the retention test, the only difference was that participants did not receive live visual feedback indicating how accurately they were performing. The removal of visual feedback during the transfer test was done to further understand how reliant a participant was on the visual feedback during day one in order to modulate their performance. Previous literature has suggested altered dependence on visual feedback during motor performance in those with ADHD (Neely et al., 2016), therefore the transfer test was used to further elucidate this relationship. SEPs and EEG were not recorded on the second day, as previous research has shown that the majority of early corticospinal changes occur during the first day of early motor learning (Holland, Murphy, Passmore, & Yielder, 2015).

5.5.4 SEP Stimulating and Recording Parameters

Peripheral SEP recording electrodes were placed according to the International Federation of Clinical Neurophysiologists (IFCN) guidelines (Nuwer et al., 1994). Surface EMG electrodes (Ag-AgCl, Meditate, conductive adhesive hydrogel) were placed on the ipsilateral brachial plexus (Erb’s point) for the recording of the N9 SEP peak (Rossi et al., 2003), over the

C5 spinous process for recording of the N11 and N13 SEP peaks, and the anterior tracheal cartilage acting as a reference for the C5 electrode. A ground surface EMG electrode was placed over the contralateral lateral 1/3 of the clavicle. The brachial plexus electrode was referenced to the ipsilateral earlobe using electrode paste and an ear clip (Rossi et al., 2003). Prior to electrode placement, each site was cleaned and prepared by shaving, abrading using abrasive tape, and cleaned with an alcohol swab. Impendence was checked for peripheral electrodes to ensure that the impendence was below 5.0 KΩ.

The following SEP peaks were identified and the amplitude was recorded and analyzed at baseline and post motor learning. The peripheral N9, the spinal N11 and N13 were each recorded using Signal4 Software (Version 4.08, Cambridge Electronic Design, Cambridge, UK) , and the following were recorded using the 64-electrode EEG cap, including the far-field N18 (P14–N18 complex), the parietal N20 (P14–N20 complex), and P25 (N20–P25 complex), the frontal N24 (P22–N24 complex), the frontal N30 (P22–N30 complex), and N60 (P40-N60 complex).

SEPs were stimulated at two different sampling frequencies, this was to allow for the clear identification of the N24 SEP peak. The 2.47 Hz frequency was used to clearly identify the N30, while the higher 4.98 Hz frequency results in the attenuation of the N30 SEP peak, allowing for a better visualization of the N24 peak (Haavik & Murphy, 2013). The slow stimulation, 2.47 Hz, takes approximately 10 minutes, while the quick stimulation frequency, 4.98 Hz takes approximately 5 minutes. Each stimulation frequency took place for 1000 sweeps, allowing for a clear average of each SEP peak. SEPs at each stimulation frequency were collected twice, once prior to the novel motor tracing task and once after performing the tracing task. While SEP stimulation occurred, participants were instructed to sit still in a standard office chair, with their feet flat on the floor, in a comfortable posture that they could maintain throughout the collection.

5.5.4.1. Stimulation parameters

Median nerve SEPs were elicited via stimulation of the median nerve over the right wrist, just proximal to the distal crease of the wrist. Stimulation intensity was set at motor-threshold of Abductor Pollicis Brevis (APB) muscle for each participant, which was observed as the lowest possible intensity where a 1cm visible thumb twitch occurred. This motor response occurred as a result of the electrical stimulation of the median nerve, as the median nerve is a mixed-nerve. This ensured that the 1a afferents were being stimulated, which is important to elicit short-latency SEP peaks, due to their projection to the cerebral cortex (Gandevia, Burke, & McKeon, 1984). For the stimulating electrodes, the anode was placed proximal to the wrist while the cathode was placed distal to the wrist. SEP stimuli were sent via a stimulator (Digitimer DS7A constant current, Welwyn Garden city, UK), and were electrical square pulses that were 200 µs long, delivered at constant intensity at frequencies of both 2.47 Hz and 4.98 Hz through Ag/AgCl EMG conductive adhesive surface electrodes (Meditrace™ 130, Kendall, and Mansfield, MA, USA). As previously mentioned, impedance was checked and confirmed to be below 5.0 kΩ prior to commencing the collection. 1000 sweeps for each stimulation frequency occurred and were averaged.

5.5.4.2 EEG Recording Parameters

Central SEP peaks, including the N18, N20, P25, N24, N30, and N60, were recording us a Waveguard™ 64-electrode whole-head EEG cap (ANT Neuro, Netherlands). Utilizing the 64-electrode EEG caps allows for a robust analysis, including multiple electrode regions and the potential for source analysis. The Waveguard™ cap was connected to a TMSi REFA-8 amplifier with 64 EEG channels, four bipolar channels, and four auxiliary channels. This was run through asaLab™ (Netherlands), and collections were recorded at a sampling frequency of 2,048 Hz. SEP analysis was completed on a separate laptop using Advanced Source Analysis (ASA™; Netherlands) and SPSS® (Armonk, New York, NY, USA).

5.5.5 Motor Skill Tracing Task Parameters

Figure 5 - Depiction of the novel visuomotor task. Participants traced the sinusoidal waveform which traveled vertically down the screen, they did so using a wireless trackpad. The trace provided real time colour-coded accuracy feedback.

The novel motor tracing task was delivered via a custom-written Leap Motion software tool (Leap Motion, Inc., San Francisco, CA, USA) and delivered via Unity™ gaming software.

The motor tracing task consisted of various sinusoidal waveform patterns, consisting of continuous dots moving down vertically across the computer screen, while the horizontal axis was the actual cursor that the participant would use to trace the waveform. To trace the waveform, participants would perform variations of right-thumb adduction and abduction using an external wireless mousepad (Logitech, Inc., Fremont, CA, USA). There were four traces which varied in both frequency and amplitude, allowing for variability in task difficulty. This variation ensures that the task is unpredictable and may allow for continuous learning (Andrew et al., 2015a). Previous research using this same task has shown that it does not result in physiological fatigue (Holland, 2014), which otherwise may impact potential learning effects (Zabihhosseinian et al., 2021). The order of the traces presented to participants was pseudo-randomized, to ensure that there were not any order effects influencing the learning effect (Holland, Murphy, Passmore, & Yielder, 2017). Prior to tracing, dots remained red; however, once the participant began tracing the waveform the dots would change to variations of green and yellow. Green indicates a perfect trace match, whereas yellow indicated an imperfect trace match. This allowed participants to have real-time live updated feedback where they would see how well they were performing. During the transfer test 24 hours later, this visual feedback was removed and the dots remained red throughout the trace, regardless of trace accuracy. Motor tracing task phases included a pre-phase (4-blocks), acquisition phase (12-blocks), post-phase (4-blocks) and a retention and transfer test (4-blocks each). Performance error was analyzed via how far the participants trace varied from the template trace, with a value of 100% would be the same as the width of the dot. An average for each phase was obtained.

5.5.6 Data Processing

5.5.6.1 SEPs

SEP signals were amplified (gain of 10,000) and filtered (0.2–1000 Hz) on a laboratory computer (Zabihhosseinian et al., 2021). Peripheral SEPs were recorded and analyzed in Signal4 software (Version 4.08, Cambridge Electronic Design, Cambridge, UK). This includes the N9, N11, and N13 SEP peaks.

All SEP peaks were measured from the preceding trough/peak to the following peak/trough of interest. The change in amplitude in units of µV was recorded at baseline and post-motor skill acquisition. Latency in units of ms for each peak was also recorded.

It is necessary to determine that the afferent input between pre and post measures was stable, to ensure any changes in SEP peaks were a result of neural adaptations from learning and not a by-product of peripheral changes such as postural alterations. This was done by ensuring the stability of the N9 SEP peak over the brachial plexus. An inclusion criterion to include a participant's SEP data was that their N9 had to remain stable between pre and post measurements. Specifically, IFCN guidelines state that the N9 SEP peak had to be within ± 20% pre-post to include their neurophysiologic data (Nuwer et al., 1994). SEP peaks were normalized to a participant's baseline, i.e. a percentage of their pre-SEP peak amplitude, to account for differences in inter-participant baseline variability, allowing for comparisons between groups.

5.5.6.2 EEG Analysis

EEG was used to record and analyze central SEP peaks, including the N18, N20, P25, N24, N30, and N60. Data were cleaned and any artifacts were removed prior to running analyses. Artifacts which were a result of muscle activity and ocular activity were removed using ASA software, excluding signals that were ± 100 µV. EEG data were filtered using a band-pass filter with a low cut-off of 0.2 Hz and a high cut-off of 1000 Hz, slope steepness was set at 24 dB/octave. Data were then averaged, providing averaged 64-electrode signals to obtain central SEP peak amplitudes and latencies. Greater amplitudes are seen over electrodes closest to the neural generator of a given peak (Valeriani et al., 1998; Zabihhosseinian et al., 2021). Therefore, the N18 was recorded over the ipsilateral FC2 electrode, the N20 and P25 over the contralateral CP3, and the N24, N30, and N60 over the contralateral FC1 electrode.

5.5.6.3 Statistical Analyses

Statistical significance was set at $p \leq 0.05$ for all analyses (SPSS v.24, IBM Corporation, Armonk, NY, USA). Partial eta squared (η2) was used to report effect sizes, with a small effect of 0.01, a medium as 0.06, and a large effect as 0.14 (Richardson, 2011). All numeric values are expressed as mean ± standard deviation (SD). Normality was tested using Shapiro–Wilk’s test and Levene’s test assessed homogeneity of variance.

5.5.6.3.1 Behavioural

Motor performance was compared between groups. This was done for pre, post, retention, and transfer measures. A 2 x 3 mixed-design ANOVA was performed, with repeated measure of time (pre, post, retention) and between subject factor of group (ADHD and control). This was performed on both the absolute and normalized data, as the absolute can show differences in absolute motor performance, whereas the normalized data can show performance improvements relative to baseline as a result of learning. Additionally, for the last 11 participants’ data in each group, a 2 x 2 mixed-design ANOVA with repeated measures of time (pre and transfer) and between subject factor of group (ADHD and control) was performed, allowing for an assessment of how participants used knowledge of the results (KR) via visual feedback to perform the motor paradigm, and how performance may change upon removal of such feedback, thus providing insight into methods to promote optimal performance environments.

5.5.6.3.2 Neurophysiological

Neural adaptations were compared between groups using a 2 × 2 mixed-design repeated measures ANOVA with time (pre-acquisition vs. post-acquisition) as the repeated measure and group (ADHD and control) defined as the between subjects' factor for each SEP peak.

5.6 Results

5.6.1 Behavioural Data

All behavioural data were normally distributed. All performance scores can be seen in Table 1. ***Normalized:*** Normalized performance scores can be seen in Figure 6 and Table 1. There was a significant effect of time ($F_{2,26} = 92.746$; $p < 0.0001$; partial $\eta^2 = 0.781$) for the normalized performance scores. This shows that both groups (ADHD and control) improved from baseline to post-measures (ADHD: 0.79 ± 0.08 vs. control: 0.80 ± 0.12) and at retention compared to baseline (ADHD: 0.78 ± 0.12 vs. control: 0.76 ± 0.11). Post-hoc tests illustrated that pre-measures were significantly different than post and retention measures in both groups, whereas post and retention measures were not significantly different. An effect of group was not present ($F_{2,26} = 0.060$; $p = 0.809$; partial $\eta^2 = 0.002$). When comparing the transfer test to baseline, a main effect of time indicated that the transfer test results improved relative to baseline measures ($F_{1,20} = 49.749$; $p < 0.0001$; partial η2 = 0.713) overall, however there was no effect of group ($F_{1,20} = 1.497$; $p = .235$; partial η2 = 0.070). ***Absolute:*** Absolute performance scores can be seen in Figure 7. There was a significant main effect of time ($F_{2,26} = 67.671$; $p < 0.0001$; partial $\eta^2 = 0.722$) for absolute performance scores. This illustrates that both groups (ADHD vs. control) improved from baseline (ADHD: 91.06 ± 17.16 vs. control: 83.64 ± 14.18) to post-measures

(ADHD: 71.53 ± 14.36 vs. control: 65.91 ± 11.43) and from baseline to retention (ADHD: 70.19 ± 12.47 vs. control: 62.39 ± 9.54). Furthermore, post-hoc tests showed that pre-measures were significantly different than post and retention measures for both groups, although post and retention measures were not significantly different from each other. The effect of group (ADHD vs. control) was not significant, ($F_{2,26} = 2.400$; $p = 0.133$; partial $\eta^2 = 0.085$), although a medium effect size was present, suggesting that the ADHD group had a greater absolute error in all three phases. Additionally, when assessing transfer, a main effect of time indicated that the transfer test results differed from baseline measures ($F_{1,20} = 31.775$; $p < 0.0001$; partial $\eta2 = 0.614$), with no effect of group ($F_{1,20} =1.363$; $p = .257$; partial $\eta2 = 0.064$).

Percent Error (Normalized/Absolute)	**Pre**	**Post**	**Retention**	**Transfer**
ADHD	1	0.79 ± 0.08	0.78 ± 0.12	0.80 ± 0.11
	91.06 ± 17.16	71.53 ± 14.36	70.19 ± 12.47	73.82 ± 17.39
Control	1	0.80 ± 0.12	0.76 ± 0.11	0.86 ± 0.11
	83.64 ± 14.18	65.91 ± 11.43	62.39 ± 9.54	69.78 ± 9.99

Table 1 - Illustrating normalized and absolute performance values. All values represent mean ± SD.

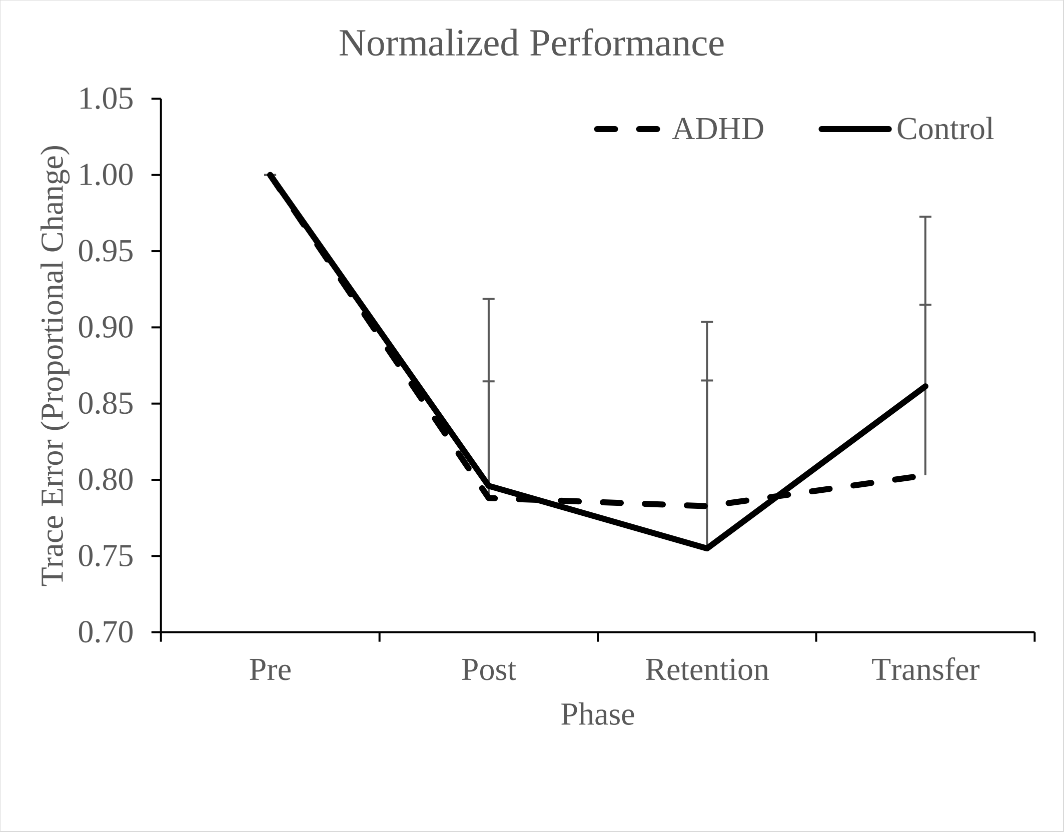

Figure 6 - Normalized mean percent error through each phase of the novel visuomotor paradigm. ADHD scores depicted in the dashed line, whereas controls are in the solid line. Values represent mean ± SD. Participants improved at post, retention, and transfer, when compared to baseline performance.

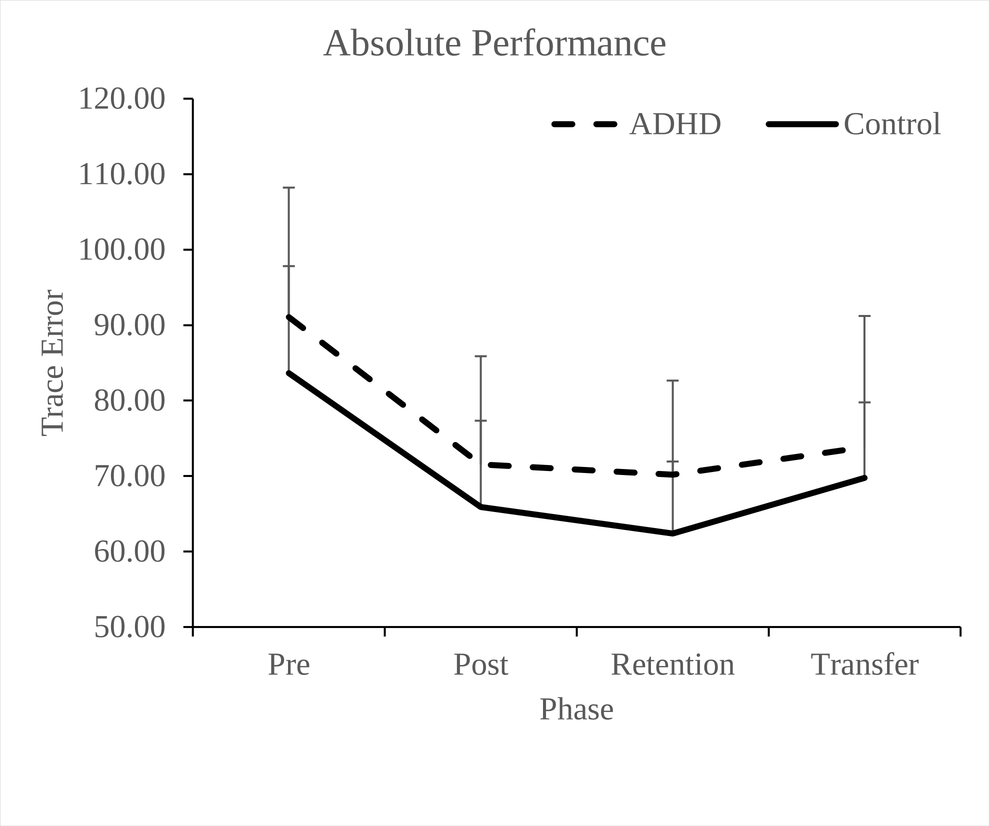

Figure 7 - Absolute score mean percent error through each motor skill phase of the novel visuomotor paradigm. ADHD scores depicted in the dashed line, whereas controls are in the solid line. Values represent mean ± SD. Participants performance improved at post, retention, and transfer, seen via a reduction in absolute trace error when compared to baseline.

5.6.2 Neurophysiological SEPs Data

All SEPs data were normally distributed. All participants SEP data met the inclusion criteria of the N9 SEP peak, which is recorded over the ipsilateral brachial plexus, differing by no more than ± 20% from baseline measures (Nuwer et al., 1994; Zabihhosseinian et al., 2021). This is done to ensure that any central SEP peak changes are not inadvertently a result of peripheral changes, such as to posture. This stability was further confirmed statistically. For the *N9*, no effect of time ($F_{1,26} = 0.362$; $p = 0.553$; partial $\eta^2 = 0.014$) or group were present ($F_{1,26} =$

0.482; $p = 0.494$; partial $\eta^2 = 0.018$). Therefore, all participants' data was included in SEP peak analysis and group averages for each peak can be seen in Figure 8.

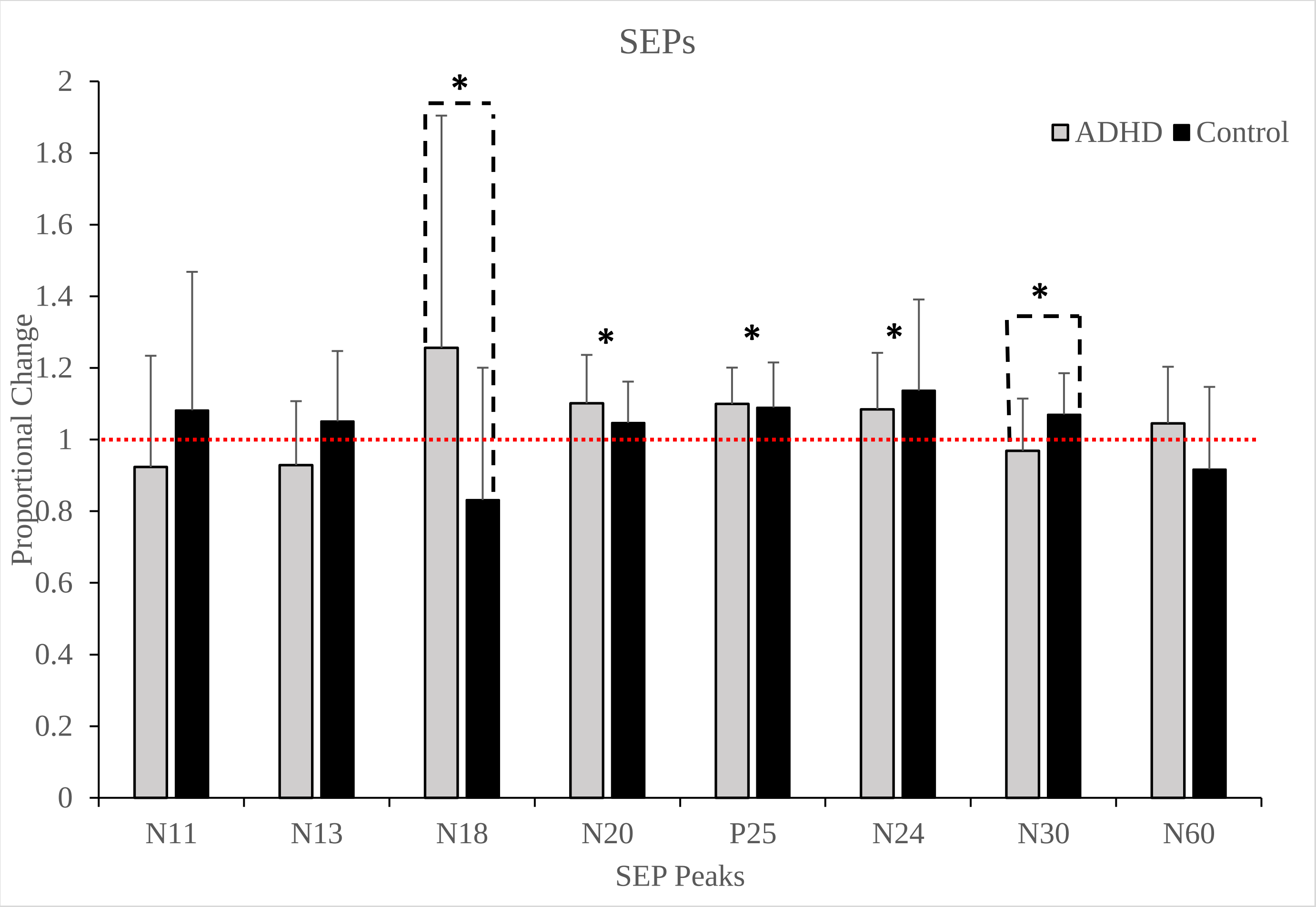

Figure 8 - Graphical representation of the averaged normalized SEP peak changes for each peak and group, comparing post to baseline. The red dashed line represents baseline, where a reduction at post measures is reflected as a bar below this line. Values represent mean ± SD. Dashed bars (---) and asterisks (*) indicate significant group interactions. Asterisks (*) only indicate significant effects of time.

<u>*N11:*</u> No effect of time ($F_{1,26} = 0.001$; $p = 0.971$; partial $\eta^2 = 0.000$) or group were present ($F_{1,26} = 1.356$; $p = 0.255$; partial $\eta^2 = 0.050$).

<u>*N13:*</u> No effect of time ($F_{1,26} = 0.077$; $p = 0.783$; partial $\eta^2 = 0.003$) or group were present ($F_{1,26} = 2.867$; $p = 0.102$; partial $\eta^2 = 0.099$).

<u>*N18:*</u> A main effect of time was not present ($F_{1,26} = 0.206$; $p = 0.654$; partial $\eta^2 = 0.008$). A significant effect of group ($F_{1,26} = 4.832$; $p = 0.037$; partial $\eta^2 = 0.157$) and a time x group interaction were present ($F_{1,26} = 4.832$; $p = 0.037$; partial $\eta^2 = 0.157$). The N18 increased in those with ADHD (1.26 ± 0.65) and decreased in controls (0.83 ± 0.37).

<u>*N20:*</u> A main effect of time was present ($F_{1,26} = 9.798$; $p = 0.004$; partial $\eta^2 = 0.274$), illustrating that the N20 SEP peak increased in both groups after motor learning (ADHD: 1.10 ± 0.14; control: 1.05 ± 0.12). A main effect of group was not observed ($F_{1,26} = 1.317$; $p = 0.262$; partial $\eta^2 = 0.048$).

<u>*P25:*</u> A main effect of time was present ($F_{1,26} = 18.120$; $p = 0.0002$; partial $\eta^2 = 0.411$), illustrating that the P25 SEP peak increased in both groups after motor learning (ADHD: 1.10 ± 0.10; control: 1.09 ± 0.13). A main effect of group was not observed ($F_{1,26} = 0.048$; $p = 0.828$; partial $\eta^2 = 0.002$).

<u>*N24:*</u> A main effect of time was present ($F_{1,26} = 7.014$; $p = 0.014$; partial $\eta^2 = 0.212$), illustrating that the N24 SEP peak increased in both groups after motor learning (ADHD: 1.09 ± 0.16; control: 1.14 ± 0.25). A main effect of group was not observed ($F_{1,26} = 0.390$; $p = 0.538$; partial $\eta^2 = 0.015$).

<u>*N30:*</u> No main effect of time was present ($F_{1,26} = 0.635$; $p = 0.433$; partial $\eta^2 = 0.024$). A significant effect of group ($F_{1,26} = 4.257$; $p = 0.049$; partial $\eta^2 = 0.141$) and a time x group interaction were present ($F_{1,26} = 4.257$; $p = 0.049$; partial $\eta^2 = 0.141$). The N30 decreased in those with ADHD (0.97 ± 0.15) and increased in controls (1.07 ± 0.12).

<u>N60:</u> Showed no effect of time ($F_{1,26} = 0.239$; $p = 0.629$; partial $\eta^2 = 0.009$) or group ($F_{1,26} = 2.755$; $p = 0.109$; partial $\eta^2 = 0.096$).

5.7 Discussion

To our knowledge, this is the first study to assess SMI and motor learning in adults with ADHD. This approach utilized both neurophysiological and behavioural variables, allowing for a robust interpretation of motor learning and SMI. The motor learning paradigm utilized here has successfully been used to assess neural and behavioural adaptations in response to motor learning in the past (Andrew et al., 2015a; Andrew et al., 2018; Zabihhosseinian et al., 2021). Although previous research has suggested that somatosensory processing and motor learning and performance are altered in those with ADHD, very limited literature exists exploring the role of neural alterations on these processes in adults with ADHD (Dockstader et al., 2008; Parush et al., 1997; Parush et al., 2007). The results in the current study demonstrate that ADHD is associated with alterations to neural processing in response to somatosensory stimuli after learning a novel visuomotor tracing task. Particularly, adults with ADHD had unique changes to the N18 and N30 SEP peak after motor learning when compared to neurotypical controls. Alternatively, the N20, P25, and N24 showed similar changes in both groups after motor learning, regardless of the presence or absence of ADHD. These changes to the N18 and N30 suggest that neural structures function differently in adults with ADHD, potentially affecting their perception and response when performing novel motor tasks. Both groups showed performance improvements at post and retention measures, when compared to baseline. An effect of group was absent, suggesting that behaviourally both groups performed similarly, although when looking at group scores, those with ADHD had increased absolute error at all phases of the motor paradigm. When considering both the behavioural and neurophysiological outcomes of the current study, we can form an improved understanding of the role neural structures play in motor learning in young adults with ADHD.

5.7.1 Neurophysiological Results

SEPs are named based on their polarity and their latency and reflect neural activity within and between specific neural structures (Passmore et al., 2014). A negative deflection is assigned a prefix of N, where a positive is assigned a prefix of P, where a negative deflection that occurs approximately 9ms after stimulation is called the N9 (Passmore et al., 2014). Each SEP peak has been localized to reflect activity within specific neural regions and structures, and thus provide invaluable information into the function of these structures during various processes and between groups. For instance, the N9 SEP peak recorded over Erb's point allows for an assessment of how stable the peripheral volley was on its way to the CNS, ensuring that any subsequent changes in SEP peaks are a result of neural adaptations, and not a result of postural changes, for example. The N11 and N13 are recorded over the C5 spinous process. The N11 reflects the afferent volley first arriving at the spinal cord, prior to its ascension to the cuneate nucleus (Wagner, 1991). The N13 indicates activity at the interneurons within the dorsal horn of the spinal cord, and is believed to reflect processes related to SMI at the spinal cord level (Cruccu et al., 2008; Desmedt & Cheron, 1981; Sonoo, Sakuta, Shimpo, Genba, & Mannen, 1991). The N60 is reflective of activity within the secondary sensory cortex (SII) in fronto-central brain regions contralateral to the stimulation site (Barba et al., 2002; Frot & Mauguière, 1999). The above SEP peaks did not change significantly post motor learning in either group in the current study. However, the N18, N20, P25, N24, and N30 all showed unique changes.

5.7.1.1 N18 SEP Peak

As noted above, each SEP peak is reflective of activity within specific neural generators. Particularly, the N18 reflects inhibitory activity from the midbrain-pontine region and between the lower medulla, more specifically within the dorsal column nuclei and accessory inferior olives (Noël et al., 1996; Sonoo et al., 1991; Urasaki et al., 1992). Additionally, the N18 may reflect activity within the cuneocerebellar tract, cerebellum, and accessory olives, as a result of activity within the medulla and medial lemniscus (Noël et al., 1996). The inferior olives act as a conductivity conduit between the spinal cord and cerebellum, working to integrate both motor and sensory information allowing for feedback to the cerebellum (Paul, 2019). Once the inferior olives receive information, the axons sending afferent signals branch into climbing and mossy fibers that ascend to the cerebellum and effect Purkinje cells (D'Angelo, Galliano, & De Zeeuw, 2016; Paul, 2019). Output from the inferior olives reflect what is termed an “error signal”, where the Purkinje cells will use this information to calculate movement patterns (Paul, 2019). It is therefore postulated that any alterations to the N18 SEP peak can provide insight into cerebellar SMI (Haavik & Murphy, 2013). Previous work utilizing a motor training task noted a significantly reduced N18 after motor learning in neurotypical control adults (Haavik & Murphy, 2013; Murphy et al., 2003). This reduction in the N18 in control participants may be a result of a reduction in inhibition or inhibitory activity at the level of the cuneate nucleus and inferior olives, thus resulting in changes to sensorimotor and cerebellar integration, in addition to enhanced processing at the level of S1 (Haavik & Murphy, 2013). It is hypothesized that a reduction in this process, reflecting a reduction in a filtering effect prior to cortical processing, is likely an important aspect of early motor learning (Haavik & Murphy, 2013).

Neurotypical controls in the current study exhibited the same, previously noted, reduction in the N18 SEP peak changes, which may reflect reduced inhibition of cuneocerebellar processing in response to the novel visuomotor task utilized. This potentially suggests a greater reliance on the visuomotor feedback needed in order to perform this motor task. Alternatively, in the current study, the N18 was noted to increase in those with ADHD. This suggests an up-regulation of olivary-cerebellar-M1 inhibitory activity in response to the novel visuomotor task, or increased inhibitory activity of cerebellar-cortical processing in ADHD. As a result of increased cerebellar inhibitory activity in those with ADHD, this may suggest a reduced ability to utilize relevant sensory feedback to create new synaptic connections through the learning process. This suggests that an increase in the N18 reflects that the cuneocerebellar structures may filter out more information than what is optimal prior to cortical involvement in those with ADHD, whereas a reduction in the filtering effect was found in controls in response to motor learning. In other words, those with ADHD may not use sensory feedback as efficiently as neurotypical controls during motor learning. Differences in cerebellar processing is in line with and an extension of previous work, which suggested that cerebellar processing is altered in ADHD (Castellanos et al., 2002; Perlov et al., 2010; Proal et al., 2011; Valera et al., 2010). The N18 alterations present in the ADHD group may very well be a result of alterations to cerebellar function in this population, potentially having important implications for the learning and acquisition of novel motor skills.

5.7.1.2. N30 SEP Peak

The N30 SEP peak is reflective of SMI (Rossi et al., 2003). Specifically, the N30 peak is reflective of sensory integration (Rossi et al., 2003) within both cortical and sub-cortical loops including the basal ganglia, thalamus, pre-motor areas, SMA, and M1 (Cebolla & Chéron, 2015;

Kaňovský et al., 2003; Rossi et al., 2003; Rossini et al., 1987). Alterations to the N30 may reflect deficits to the somatosensory synaptic network in response to sensory input (Cebolla & Chéron, 2015). Source localization techniques have localized N30 neural generators to four distinct locations, including the contralateral S1, prefrontal cortex, cingulate, and bilateral secondary somatosensory cortex (Lelic et al., 2016). Overall, the prefrontal cortex is the neural source with the greatest activity during the N30 latency (Lelic et al., 2016). Due to its overarching involvement in SMI, the N30 SEP peak provides invaluable information regarding neural activity within these regions during processes related to SMI.

The results of the current study, depicted that the N30 decreased in those with ADHD and increased in neurotypical controls post motor learning. The control findings are in line with previous work, which noted an increase in the N30 post motor learning (Andrew et al., 2018; Zabihhosseinian et al., 2021). This increase in the N30 is linked to increased excitability in pathways linked to motor learning (Zabihhosseinian et al., 2021). However, the findings related to the ADHD group are novel. One explanation for the group differences apparent with regards to the N30 in those with ADHD, when compared to neurotypical controls, may be a result of altered neural structure and function to prefrontal brain regions associated with ADHD, possibly resulting in an attenuation of early SMI processes. A prominent neural characteristic associated with ADHD is altered neural activity within prefrontal brain regions, amongst other unique neural characteristics (Barkley, 1997; Seidman et al., 2006; Sowell et al., 2003). The reduction in the N30 in those with ADHD in the current work may be a result of altered activity within and between brain regions in those with ADHD, such as neural regions that work in concert with prefrontal regions, such as the fronto-striatal network which has previously been noted to be altered in those with ADHD (Ortiz et al., 2015). These neural alterations in those with ADHD, when compared to neurotypical controls, may have important behavioural implications, particularly related to the performance of the motor learning paradigm utilized within the current study.

5.7.1.3 N20, P25, and N24 SEP Peaks

The N20, P25, and N24 all increased at post-measures in both those with and without ADHD. This suggests that the neural activity and sources associated with these peaks responded similarly in both groups, regardless of diagnostic status. Therefore, although there are differences in how those with ADHD process sensorimotor afferent input when compared to neurotypical controls with regard to the N18 and N30 and their associated structures, there are also similarities. The SEP peaks with group differences present post motor learning provide important information on the role of specific neural structures and learning in those with ADHD. In addition, those with an effect of time but lacking an effect of group, provide invaluable insight into similarities that also exist between those with and without ADHD.

The N20 reflects processing in S1 at the Rolandic fissure, this is reflective of BA 3b (Desmedt & Cheron, 1980, 1981). This reflects processing in response to contralateral tactile stimuli (Hlushchuk & Hari, 2006; Passmore et al., 2014). Additionally, BA 3b reflects processing of cutaneous inputs (Desmedt & Ozaki, 1991; Passmore et al., 2014). Previous studies have noted an increase in the N20 post motor learning, thus reflecting increased processing at S1 (Andrew et al., 2015a; Andrew et al., 2018). Both groups in the current study, those with and without ADHD, had an increase in the N20 SEP peak post motor learning. Therefore, these results as they pertain to controls are in line with results from previous studies. The increase in the N20 may suggest an increase in the neural activity associated with BA 3, located within the S1. This likely reflects enhanced activity within S1 in response to learning the novel visuomotor task, which was present to as similar extent in both groups.

The P25 is a positive deflection reflecting activity within the S1 and BA 1 (MacDonald et al., 2019; Mauguiere, 2005). The current results suggest that an upregulation of activity within S1 occurs in response to the novel visuomotor learning paradigm, regardless of whether an individual does or does not have ADHD. As BA 1 reflects processing of vibrotactile stimuli (Sur, 1980), the increase in P25 is likely a result of the tactile stimuli present from the thumb interacting with the track pad during the learning process. Thus, suggesting that adults with ADHD process tactile stimuli during the learning process of a visuomotor task in a similar manner as do neurotypical controls.

Finally, the N24 appears on the ascending slope of the N30 peak, the N24 is indicative of activity within BA 3b in the somatosensory cortex and the posterior wall of the central sulcus (Waberski et al., 1999), continuing to the cerebellar cortex and deep cerebellar nuclei (Molinari, Restuccia, & Leggio, 2009). An increase in the N24 post motor learning has previously been noted (Andrew et al., 2015a; Haavik & Murphy, 2013). The N24 originates in the S1, and is impacted in those with cerebellar lesions (Restuccia et al., 2001). This points to the cerebellum playing a fundamental role in early somatosensory processing. Therefore, the N24 increase in the current study may reflect afferent processing at the level of S1 as a result of cerebellar SMI. This suggests similar cerebellar-S1 connectivity in those with and without ADHD after exposure to the novel visuomotor task utilized, even though there was differing cuneocerebellar activity suggested by the N18 alterations.

5.7.2 Behavioural Performance

Both groups experienced significantly improved performance at post and retention measures, when compared to baseline. This improvement in performance suggests that motor learning did occur in response to the acquisition phase of the novel visuomotor paradigm. Learned movements via the process of motor learning occur through the process of repetition, allowing for central planning and the correction and calibration of ongoing movement (Abbs, Gracco, & Cole, 1984; Proteau, Tremblay, & Dejaeger, 1998). The normalized performance for each group was similar, suggesting that both groups learned to a similar extent. Although statistical significance was not reached, visually there was a trend suggesting that the control group may have further improvements at retention, whereas those with ADHD may have plateaued. This suggests that the consolidation of the learned task may occur or be observed differently in those with ADHD. Such findings were shown in previous work, which found that those with ADHD had reduced retention 24 hours after learning a novel task, when compared to controls (Adi-Japha et al., 2011). Although group differences did not reach statistical significance, a medium effect size was present when comparing between groups, possibly suggesting that the ADHD group had increased error at each phase of the novel visuomotor paradigm. Therefore, although we are unable to draw distinct group conclusions from this behavioural data, the error in those with ADHD may be related to the increased N18 and reduced N30 and their underlying neural activity. Further increasing the sample size in the future may allow for an improved understanding of how behavioural characteristics associated with learning a novel motor task may relate to the neural findings of the current study.

An additional measure that was included in the motor paradigm was the utilization of a transfer task, which removed the visual feedback providing moment to moment information on performance. The role of visual afferent feedback in early versus late stages of motor learning has been debated (Proteau et al., 1998). The results from the current study suggest that participants were reliant on the real-time accuracy feedback they received during the learning phases of the task. This was evident as when the visual performance feedback was removed during the transfer test, both groups showed decrements in their performance. Therefore, it becomes evident that the learning processes occurring were at least partially dependent on the form of afferent feedback present during the learning or practice phase, suggesting both groups performance were dependent on the knowledge of results (KR) provided in the form of visual afference (Proteau et al., 1998). This supports the specificity of practice hypothesis, as the visual feedback providing KR present during practice was important for how participants controlled their movement patterns (Proteau et al., 1998), and once removed, resulted in decrements to performance.

5.7.3 Limitations

Future work should recruit a larger sample size to reduce the chance of a type-II error. This may have been the case in the current study with respect to the behavioural results. Although, the goal sample size of n = 12 per group was reached, we would have ideally recruited an extra 3-4 participants in the ADHD group. Several COVID restrictions and lockdowns made data collection impossible for periods of time, therefore limiting opportunities for participant recruitment. Additionally, the sample was recruited from the general university population, reducing the generalizability to other age groups, such as children or older adults.

5.8 Conclusions

Overall, the present research found neurophysiological differences in the way that those with ADHD learn a novel visuomotor task. This was evident as an increase in the N18 in adults with ADHD in response to learning a novel motor task, in contrast to neurotypical controls who exhibited a decrease in the N18. Additionally, the N30 differed between groups, exhibited as a decrease in those with ADHD and an increase in neurotypical controls. These changes to SEP peaks illustrate potential differences in cerebellar and prefrontal processing in young adults with ADHD, having potentially important implications for how they learn and perceive somatosensory stimuli during practice. Both groups exhibited performance improvements after learning the novel task, and absolute performance may have been reduced, as indicated by increased error at all time points, in those with ADHD. This work shows the utility of SEPs in conjunction with motor paradigms to assess neural correlates of ADHD, providing novel and invaluable information into the neurology associated with this disorder. In the future, incorporating other forms of motor paradigms and neural assessment, that require varying forms of sensory integration, such as proprioception, can further provide important details into motor learning mechanisms and their relevance to those with ADHD. The current research suggested unique neural responses in those with ADHD when acquiring motor skills highly dependent on visuomotor feedback, whereas implementing a motor paradigm highly dependent on force for example, would enhance our understanding our how force and proprioceptive alterations in those with ADHD affect the acquisition of novel skills.

Chapter 6: Study 3

6.1 Preface to manuscript 3:

Sensorimotor integration (SMI) details the nervous system's ability to integrate sensory information to inform and refine motor output. Study 1 from this dissertation elucidated differences in right-hemispheric parietal lobe, localized to BA 2 in those with Attention-Deficit/Hyperactivity Disorder (ADHD) when processing multisensory input. Specifically, an attenuation of activity was found when compared to controls. Right-hemispheric parietal lobe is associated with spatial attention processes (Chan et al., 2009; Corbetta et al., 1993; Gitelman et al., 1999; Nobre et al., 1997; Vance et al., 2007), and BA 2 reflects processing of pressure, joint position sense, and complex touch (Sur, 1980), thus informing proprioception. Study 2, which utilized a novel visuomotor tracing task (MTT), noted unique differences in short-latency somatosensory evoked potentials (SEP) in those with ADHD. Particularly, the N18 and N30 SEP peak differed when compared to neurotypical controls, suggesting alterations to processes related to olivary-cerebellar-M1 function and SMI. Studies have shown that ADHD is associated with alterations to motor control and performance, including processes involving force-modulation and proprioception (Neely et al., 2016; Neely et al., 2017); whereas structural and functional differences to somatosensory processing brain regions are present (Duerden et al., 2012). Although little is known regarding how adults with ADHD process sensory information relating to the performance of a novel motor paradigm, our previous research suggests that ADHD is associated with unique neural responses to somatosensory input related to motor learning. It is important to extend this work to other forms of motor acquisition paradigms, to better understand the influence of ADHD on such processes at behavioural and neurophysiological levels, particularly during a task that is dependent on force output.

The current study aimed to compare metrics of motor learning when performing a novel task highly dependent on force-modulation and proprioception, allowing for a comparison between young adults with ADHD when compared to neurotypical controls. High-density electroencephalography (EEG) and short-latency SEPs were compared before and after the novel force-matching task (FMT). The neurophysiological data was collected in conjunction with behavioural variables, including performance accuracy and % force variability from the intended trace, to connect neural and behavioural changes. Specifically, including both behavioural and neural forms of assessment provides important insight into the relationship between performance and brain function when performing a force task in ADHD.

Manuscript 3: Motor learning and Sensorimotor Integration During a Novel Force-Matching Task in Young Adults with Attention-Deficit/Hyperactivity Disorder

Authors: Heather McCracken, Ushani Ambalavanar, Paul Yielder, Cheryl Glazebrook, Bernadette Murphy

6.2 Abstract

Background: Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder that exhibits unique neurological and behavioural characteristics (Biederman et al., 2004; Proal et al., 2011). Those with ADHD often have noted impairments in motor performance and coordination, including during tasks that require force modulation (Kaiser et al., 2015; Neely et al., 2016). There are alterations in the processing of somatosensory stimuli (Duerden et al., 2012) and the integration of multisensory stimuli (McCracken et al., 2020). However, there are many missing details regarding how motor learning and performance may be implicated, and whether there are neural markers relevant to these differences in young adults with ADHD. The present data provides insight into the role of altered neural processing and sensorimotor integration (SMI), particularly in response to a motor learning paradigm requiring force modulation and proprioception, which previous literature has suggested to be altered in those with ADHD.

Methods: Adults with ADHD (n = 15) and neurotypical controls (n = 15), performed a novel force-matching tracking task (FMTT), where participants used their right-thumb to match a trace template that varied from 2 – 12% of their Abductor Pollicis Brevis maximum voluntary contraction. This motor task was completed in pre, acquisition, and post blocks. Participants also completed a retention test 24 hours later. Median nerve somatosensory-evoked potentials (SEPs)

were collected pre and post motor acquisition on day one. SEPs were stimulated at two frequencies, 2.47Hz and 4.98Hz, and 1000 sweeps were recorded using 64-electrode electroencephalography (EEG) at 2048Hz. SEP amplitude changes were normalized to each participant's baseline values for that peak.

Results: *Behavioural data:* Both groups improved at post measures (ADHD: 0.85 ± 0.09; Controls: 0.85 ± 0.10), with improvements maintained at retention (ADHD: 0.82 ± 0.11; Controls: 0.82 ± 0.11), this improvement was evident when assessing both normalized and absolute performance scores. *Neurophysiological SEPs data:* The ADHD group had a decreased N18 post-acquisition (0.87 ± 0.48), while control N18 increased (1.91 ± 1.43). The N30 increased in both groups, with a small increase in the ADHD group (1.03 ± 0.21) and a more pronounced increase in controls (1.15 ± 0.27).

Discussion: This work is the first to utilize neurophysiological measures via SEPs in conjunction with a behavioural force-matching motor paradigm to assess processes involved in motor acquisition and learning in adults with ADHD. Results suggest that there are unique neural differences between groups, particularly in those relating to the N18, while the N30 had similar changes in both groups. The N18 differences suggest that those with ADHD have reduced olivary-cerebellar-M1 inhibition when learning a novel motor task dependent on force-modulation, potentially due to difficulties integrating the afferent feedback necessary to perform the task. This work suggests that young adults with ADHD have altered proprioceptive processing when learning a novel motor task when compared to neurotypical controls.

Keywords

Somatosensory evoked potentials (SEPs); Attention-Deficit/Hyperactivity Disorder (ADHD); motor learning; electroencephalography (EEG); sensorimotor integration (SMI); force-modulation

6.3 Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is described as a neurodevelopmental disorder. The hallmark characteristics associated with ADHD are behavioural signs, such as hyperactivity, impulsivity, and inattention (Visser et al., 2014). These noted behavioural changes can vary in their manifestation, but together have important implications for day to day life. Approximately 11% of children in the U.S. will receive a diagnosis of ADHD (Visser et al., 2014). However, ADHD commonly persists into adulthood, with approximately 65% of those diagnosed during childhood continuing to meet diagnostic criteria as adults (Faraone et al., 2006). How ADHD manifests in adulthood may vary when compared to childhood. Adults with ADHD are noted as having reduced hyperactive tendencies, when compared to children (Gentile et al., 2006), potentially due to developing coping mechanisms in their day to day life. The differences in how signs and symptoms manifest in adulthood may explain why limited literature focuses on ADHD in this age group. Thus, research has neglected an important cohort. Therefore, further research is needed in order to develop an improved understanding of ADHD symptomology, including underlying neural characteristics. This work is fundamental to improving how we approach creating inclusive environments for those with ADHD, particularly relating to adult symptomology, which is yet to be fully understood.

While ADHD is defined by behavioural alterations, there are neurological characteristics that are important to note, and that are relevant to the current work. Those with ADHD tend to have reduced cerebral gray matter, this finding is diffuse throughout the cortex (Proal et al., 2011). Duerden et al. (2012) assessed cortical morphology of adolescents and adults with ADHD using high-resolution 3D MRI, and cortical thickness was assessed using MNI analyses, with an emphasis on sensorimotor processing brain regions. Findings included that the pre-SMA in adolescents and the S1 in adults were thicker in those with ADHD when compared to neurotypical controls (Duerden et al., 2012). This may have relevance to the sensorimotor alterations found in ADHD, in conjunction with impaired motor and somatosensory processing (Duerden et al., 2012). Of relevance, are the roles that these neural structures are involved in, and particularly how they may relate to behavioural characteristics in this population. The pre-SMA is highly active in response to learning, particularly during tasks that require hand movements, and has projections to the dorsolateral prefrontal cortex (Nachev, Kennard, & Husain, 2008). The S1 plays a fundamental role in the processing and integration of incoming afferent somatosensory input, thus contributing to how sensory and motor signals are integrated for the performance of movement, which has important implications for motor learning and motor control (Borich et al., 2015). Increased thickness in S1 is also noted in other populations with altered somatosensory processing, including those who experience chronic pain (DaSilva et al., 2007). This increased cortical thickness in S1 has been linked to impaired inhibitory processes in pain populations, and altered inhibition is characteristic of ADHD. Therefore, it is likely that alterations to S1 in those with ADHD may be associated with alterations to motor performance and accuracy, potentially due to inhibitory alterations in S1. Additionally, ADHD is associated with hypoactivation in areas related to sensorimotor functions (Cortese, 2012). One such neurological characteristic that in recent years has become a potential hallmark for ADHD, is the overall reduction in cerebellar volume (Almeida Montes et al., 2011). The cerebellum is a neural structure that is fundamental to the processes relating to motor learning and SMI.

The cerebellum plays a fundamental role in how individuals utilize feedback to refine and control motor output, having important implications for motor learning (Koziol et al., 2014). The cerebellum is reduced in size throughout the lifespan in ADHD when compared to neurotypical controls (Castellanos et al., 2002). These cerebellar alterations, in conjunction with common behavioural characteristics, suggests that motor learning and motor performance may play an important role in how those with ADHD function in their daily life, including in occupational and educational settings. Many tasks that individuals perform daily, including tying shoes, typing, driving, etc. are all dependent on our ability to acquire new sensorimotor skills. Our ability to acquire these motor patterns will therefore dictate the level of success experienced with these tasks. The ease with which these skills are acquired can be either heightened or impaired as a result of neural function in specific neural structures and circuits. For instance, difficulties in the learning and automating of fine motor skills are strongly related to altered cerebellar function (Koziol et al., 2013). As a task is learned, the performance on said skill typically becomes more automatic in nature (Koziol et al., 2013). This process is regulated by the cerebellum. It is postulated that the behavioural characteristics noted to be associated with ADHD, including hyperactivity and inattention, are a result of or related to alterations within fronto-cerebellar circuity (Durston et al., 2011; Koziol et al., 2013). Additionally, the severity of clinical outcomes in those with ADHD are associated with cerebellar volume, as those with greater clinical outcomes have greater reductions in cerebellar volume (Mackie et al., 2007).

Despite the above advances, it is unclear how these neural characteristics will affect processes related to motor learning and performance in adults with ADHD. Utilizing techniques such as somatosensory evoked potentials (SEPs) can provide insight on the level of neural activity within cortical and subcortical structures in response to a novel motor task. SEPs are a non-invasive neurophysiological technique that allow for the assessment of neural structures via stimulation of a peripheral nerve, and are named based on their polarity and latency (Passmore et al., 2014). For instance, the N30 SEP peak, is a negative deflection that occurs 30 ms after stimulation of the peripheral nerve of interest, which will be the median nerve for the current study. The International Federation of Clinical Neurophysiology (IFCN) compiled information for the strategic and standard application of short-latency SEPs (Nuwer et al., 1994). Therefore, SEPs allow for the interpretation of specific neural generators that have been associated with specific peaks (Passmore et al., 2014). Thus, SEPs data can provide pivotal insight into neurophysiological mechanisms. The interpretation of SEPs may enhance the currently available information pertaining to the neurophysiological processes related to learning motor tasks, particularly those that are dependent on force modulation and proprioception in adults with ADHD.

Although limited literature has addressed motor performance, at either a behavioural or neurophysiological level in adults with ADHD, those with ADHD generally experience difficulties in tasks that require motor coordination and performance (Fliers et al., 2011; Kaiser et al., 2015; Karatekin et al., 2003). One such explanation for this may be that those with ADHD have alterations to their inhibitory processes (Feifel et al., 2004). This inhibitory alteration may be a hallmark deficit associated with ADHD (Lijffijt et al., 2005) that manifests as atypical behaviours, including learning new motor skills. Children with ADHD often exhibit difficulties with motor skills, such as handwriting, resulting in poor legibility and reduced speed (Brossard-Racine et al., 2011). Previous work has found that those with ADHD exhibit an attenuation of performance at retention measures 24 hours after learning, when compared to neurotypical controls (Adi-Japha et al., 2011). This suggests that ADHD may be associated with an impaired consolidation of motor skills. Additionally, force modulation alterations are associated with ADHD, specifically noting deficits in inhibitory force control in young adults (Neely et al., 2017).

Neely et al. (2017) used a Go/No-Go force task utilizing the thumb and index finger, and the load cell was calibrated to less than 15% of the MVC of the pinch grip (Neely et al., 2017). Specifically, those with ADHD elicit altered force output from their fingertips (Neely et al., 2017). This is a predictor for ADHD-related symptoms, showing alterations to inhibitory control in adults with ADHD when performing a task dependent on force modulation (Neely et al., 2017). ADHD was associated with greater and more varied force on the No-Go trials, thus suggesting hyperactivity in the motor systems in conjunction with alterations to inhibitory control mechanisms (Neely et al., 2017). With respect to motor control, optimal performance is associated with reduced variability (Selen, van Dieën, & Beek, 2006). Therefore, the increased variability in those with ADHD suggest they may experience difficulties with motor skills requiring force modulation. Additionally, force output was associated with ADHD diagnostic criteria (Neely et al., 2017). Neely et al. (2017) suggest that utilizing a force motor task can provide important information on the inhibitory mechanisms evident in this population. Additionally, using such a paradigm in conjunction with neural markers can provide important information on the neural substrates and processing mechanisms that are related to these changes. However, it remains unclear how alterations to force modulation in ADHD will affect their ability to learn and retain a novel motor task dependent on force, which are common to many day-to-day skills.

Many tasks require our ability to modulate force to elicit effective performance. Force modulation depends on proprioception via sensory feedback from several sensory structures, including muscle spindles, golgi tendon organs, Pacinian corpuscles, and the cutaneous receptors of the digits which are relevant to the task employed for the current research (Schmidt & Lee, 2005). Examples of such tasks in day to day life include applying pressure to a clutch or a gas pedal in a car and using a joystick controller while operating machines. Previous work utilizing a dynamic task requiring force matching of pinch grip, noted activation within brain regions involved in visual attention and proprioception (Brown et al., 2004). Although ADHD is associated with alterations in proprioception (Alba et al., 2016; Goulardins et al., 2013; Jung et al., 2014; Sanz-Cervera et al., 2017), the extent to which alterations to proprioception and force modulation affect motor learning in ADHD is unclear.

Proprioception, being ones' ability to use their senses to understand where their limbs and body are in space, is associated with the processing of somatosensory input and sensory function (Alba et al., 2016). Alterations to proprioception is a sensory characteristic that is intrinsic to ADHD symptomology (Sanz-Cervera et al., 2017). For instance, balance dysfunction is present in ADHD, potentially associated with alterations to proprioception and vestibular function (Zang et al., 2002). Furthermore, one study used proprioceptive indicators of temperament to form an improved understanding of behavioural and personality indicators of ADHD in children (Liutsko et al., 2018). It is postulated that alterations to vestibular function and proprioception in those with ADHD are a result of difficulties processing visual information, as visual input acts as a guide to inform body schema and spatial awareness (Jung et al., 2014; Sanz-Cervera et al., 2017). Young boys with ADHD score lower on balance, spatial organization, and fine and global motricity (Goulardins et al., 2013). It is thought that this may be related to delays in peak brain maturation in those with ADHD (Goulardins et al., 2013; Shaw et al., 2007).

Neurotypical children reach peak cortical thickness by the age of 7.5 years old, whereas children with ADHD reach this milestone by approximately 10.5 years old (Shaw et al., 2007). These maturational delays in the prefrontal cortex have been associated with the altered inhibitory characteristics in ADHD, whereas alterations to frontal regions including the premotor cortex are associated with the performance of motor commands (Goulardins et al., 2013). Fundamental sensorimotor abilities are impaired in children with ADHD compared to neurotypical controls, where many children fall below the 5th percentile range in the fundamental sensory-motor index for their age group (Iwanaga, Ozawa, Kawasaki, & Tsuchida, 2006). Additionally, finger localization and tactile discrimination may be impaired in children with ADHD (Iwanaga et al., 2006). Children with ADHD score lower on tests assessing equilibrium, somatosensory function, vestibular function, and visual ratios, which are related to the alterations in balance noted in this population (Shum & Pang, 2009). Therefore, the literature suggesting alterations to motor performance, proprioception, and cortical characteristics in children with ADHD is relatively robust and suggests important implications for many daily activities; however, due to insufficient literature that currently exists, it remains unclear as to how these motor and neural characteristics may present in adulthood and their influence on motor learning processes.

The purpose of the current work was to assess whether young adults with ADHD exhibit alterations in neural processes related to learning a novel force-matching task (FMT). Utilizing both behavioural and neural variables allows for a multifaceted approach to form an enhanced understanding of motor learning in those with ADHD. The research question that this work aims to address is, do young adults with ADHD experience alterations to motor learning when performing a task dependent on force modulation and proprioception? The primary neurophysiological and behavioural variables assessed were short-latency SEP peaks and performance via percent error at each phase of the motor learning paradigm. Specific hypotheses include: (1) those with ADHD will exhibit alterations to SEP peaks when compared to neurotypical controls, likely in peaks related to cortico-cerebellar processing; (2) those with

ADHD and neurotypical controls will show performance improvements post-acquisition, and based on previous literature those with ADHD will likely have reduced improvements at retention measures when compared to controls.

6.4 Methods

6.4.1 Ethical Approval

Written informed consent was obtained prior to the start of data collection. This study was approved by the Ontario Tech University Research Ethics Board (REB; # 15307). This study was carried according to the ethical standards set out by the Declaration of Helsinki statutes governing research on human subjects.

6.4.2 Participants

GPOWER statistical software indicated that for a large effect size, an alpha of $p = 0.05$, and a power (1-β) of 0.95 (β set at 0.05 to minimize the chance of a type II error), a sample size of 12 participants per group is needed for a pre-post experimental design (Faul & Erdfelder, 1992). This study consisted of two groups of participants, one group included adults with ADHD (n = 15, 9 females, mean age = 22.00 ± 2.51) and one group of neurotypical controls (n = 15, 9 females, mean age = 20.80 ± 1.97). Participants completed several pre-screening questionnaires to ensure they met the inclusion criteria, including being between the ages of 18-35 years old, right-hand dominant, the absence of any other known neurological conditions, or history of injury such as concussions. Handedness was confirmed using the Edinburgh Handedness Inventory (EHI) self-report questionnaire.

Each participant completed the adult ADHD Self-Report Scale (ASRS-v1.1). This was used to assess symptoms associated with ADHD in both groups. The ASRS consists of 18 questions, divided into part A and part B, these questions are in line with the ADHD diagnostic criteria set out in the DSM-IV (Dankner et al., 2017). Each of the 18 questions is rated on a 5-point Likert scale ranging from “never” to “very often”. The ASRS tool is highly sensitive to predicting ADHD symptomatology (van de Glind et al., 2013). Scores for part A and part B were recorded for each participant. Although no particular score is associated with a diagnosis, a higher score indicates a greater prevalence of signs and symptoms associated with ADHD. Those in the ADHD group had an average score of 22.40 ± 4.44 for part A, while controls scored 14.27 ± 4.46. The average score for part B for the ADHD group was 44.07 ± 8.16 and 24.93 ± 6.18 for controls.

6.4.3 Experimental Protocol

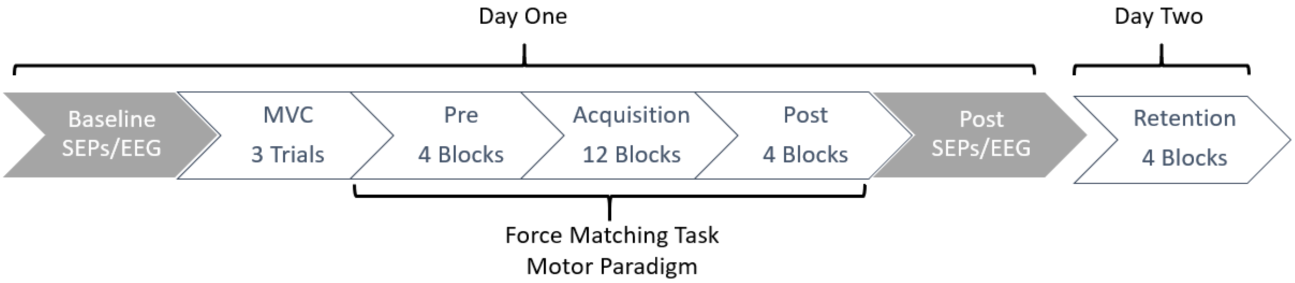

Figure 9 - Figure depicting the study flow. Collections occurred over a period of 24-48 hours, with the retention test occurring on the second day.

Data collection sessions occurred over two days. All participants attended two sessions, the second being 24-48 hours after the first. The first session included EEG and SEP collections, where participants completed the pre through to post motor task blocks of the FMT. On day one, participants completed the informed consent documents, giving both written and verbal informed consent prior to the commencement of the session. This was followed by the setup of the EEG and SEPs. Baseline SEPs measurements were then recorded, including both 2.47Hz and 4.98Hz stimulation frequencies. Following baseline SEPs, participants completed the novel FMT in blocks of pre-acquisition (4-blocks), acquisition (12-blocks), and post-acquisition (4-blocks) as depicted in Figure 9. Each block consisted of 3-5 traces. Post-SEP measurements were then recorded at both frequencies, 2.47Hz and 4.98Hz. This session on day one took approximately three hours total. 24-48 hours later, participants were asked to return to the lab and compete the retention (4-blocks) test of the FMT, which took approximately 10-minutes total. The second day was limited to behavioural measures, meaning SEPs and EEG were not recorded on the second day, as previous research has shown that the majority of early corticospinal changes occur during the first day of early motor learning (Holland et al., 2015).

6.4.4 SEPs Stimulating and Recording Parameters

As it pertains to peripheral SEPs, recording electrodes were placed according to the International Federation of Clinical Neurophysiologists (IFCN) guidelines (Nuwer et al., 1994). Surface EMG electrodes (Ag-AgCl, Meditate, conductive adhesive hydrogel) were placed on the ipsilateral brachial plexus (Erb’s point), allowing for the recording of the N9 SEP peak (Rossi et al., 2003). The Erb’s point electrode was referenced to the ipsilateral earlobe using electrode paste and an ear clip (Rossi et al., 2003). An additional electrode was placed over the C5 spinous process for recording the N11 and N13 SEP peaks, and the anterior tracheal cartilage acted as a reference for the C5 electrode. Finally, a ground surface electrode was placed over the contralateral lateral 1/3 of the clavicle. Prior to electrode placement, each site was cleaned and prepared by shaving, abrading using abrasive tape, and cleaned with an alcohol swab. Impedance was checked for peripheral electrodes; all signals had an impedance below 5.0 KΩ.

The following SEP peaks were identified and the amplitude was recorded and analyzed at baseline and post motor learning. Each participant’s “post” measurement was normalized to their baseline value, allowing for an assessment of proportional change in SEP peak amplitudes following motor acquisition. The peripheral N9 and the spinal N11 and N13 were each recorded using Signal4 Software (Version 4.08, Cambridge Electronic Design, Cambridge, UK), and the following were recorded using a Waveguard™ whole-head high-density 64-electrode EEG cap (ANT Neuro, Netherlands), including the far-field N18 (P14–N18 complex), the parietal N20 (P14–N20 complex) and P25 (N20–P25 complex), the frontal N24 (P22–N24 complex), the frontal N30 (P22–N30 complex), and N60 (P40-N60 complex). Each of these SEP peaks are reflective of activity within specific neural generators (Passmore et al., 2014).

SEPs were stimulated at two different sampling frequencies, this was to allow for the clear identification of the N24 SEP peak. The 2.47 Hz frequency was used to clearly identify the N30, whereas the faster stimulation frequency at 4.98 Hz results in the attenuation of the N30 SEP peak, allowing for a clear identification of the N24 peak (Haavik & Murphy, 2013). The slow stimulation, 2.47 Hz, takes approximately 10 minutes, while the faster stimulation frequency at 4.98 Hz, takes approximately 5 minutes. Therefore, each round of SEP stimulations and EEG recording took approximately 15 minutes. Each stimulation frequency took place for 1000 sweeps, allowing for a clear average of each SEP peak. Each stimulation frequency occurred twice, once prior to the novel motor tracing task and once after performing the FMT. While SEP stimulation occurred, participants were instructed to sit still in a standard office chair, with their feet flat on the floor, in a comfortable posture that they could maintain throughout the collection. The room remained quiet during this time.

6.4.5 Stimulation parameters

Median nerve SEPs were elicited via stimulation of the median nerve over the right wrist, just proximal to the distal crease of the wrist. Stimulation intensity was set at motor-threshold of the Abductor Pollicis Brevis (APB) muscle for each participant, which was observed as the lowest possible intensity where a 1cm visible thumb twitch occurred. This motor response occurred as a result of the electrical stimulation of the median nerve, as the median nerve is a mixed-nerve. This ensured that the 1a afferents were being stimulated, which will result in the short-latency SEP peaks, due to their projection to the cerebral cortex (Gandevia et al., 1984). For the stimulating electrodes, the anode was placed proximal to the wrist while the cathode was placed distal to the wrist. SEP stimuli were sent via a Digitimer, and were electrical square pulses that were 200 µs in duration, delivered at a constant intensity, at frequencies of both 2.47 Hz and 4.98 Hz through Ag/AgCl EMG conductive adhesive surface electrodes (Meditrace™ 130, Kendall, and Mansfield, MA, USA). 1000 sweeps for each stimulation frequency were delivered and were subsequently averaged.

6.4.6 EEG Recording Parameters

A Waveguard™ 64-electrode whole-head EEG cap (ANT Neuro, Netherlands) was used to record central SEP peaks, including the N18, N20, P25, N24, N30, and N60. The Waveguard™ cap was connected to a TMSi REFA-8 amplifier with 64 EEG channels, four bipolar channels, and four auxiliary channels. The collection was run through asaLab™ (Netherlands), and collections were recorded at a sampling frequency of 2,048 Hz. SEP analysis was completed on a separate laptop using Advanced Source Analysis (ASA™; Netherlands) and SPSS® (Armonk, New York, NY, USA).

6.4.7 Novel Force-Matching Tracking Task (FMT)

Participants were instructed to complete a novel motor task that required them to modulate their force from their right thumb via thumb adduction onto the force transducer, in order to accurately match a waveform trace that varied in force, based upon a percentage of their individual maximal voluntary contraction (MVC) of the APB muscle. The MVC was established as the average of 3 MVC trials. To collect MVCs, participants were instructed to “press as hard as you can against the force transducer using your right thumb, while limiting any forearm or upper arm involvement”. Two Velcro straps were used to secure the forearm to the table, one proximal to the wrist and the second was distal to the elbow. This was to limit the use of other muscles, aside from the APB, during the MVC and motor paradigm. Each trace was presented on a computer monitor in front of the participant, and the force transducer was stabilized on a height-adjustable table to the right of the participant. Table height was adjusted to a comfortable height for each participant.

The task was created and presented with a custom LABVIEW software program (National Instruments, Austin, TX, USA). To match the traces in the program, participants had to use their right thumb to adduct against a force transducer with a 50 kg load cell. The trace that participants were to match as accurately as possible was a continuous trace of white dots with two red error bars acting as a guide. The error bars were placed 0.05% above and below the dotted force trace. Throughout the duration of the task, participants were presented with augmented visual feedback in the form of a yellow solid line, representative of the force they were exerting against the transducer. This provided a visual depiction of how accurately they matched the intended trace. The traces varied between 2 – 12% of each participants APB MVC. Please refer to Figure 10, depicting an example of what the participant saw while completing the FMT.

When completing the task, participants were seated in a standard stationary work chair with feet flat on the floor. Their right arm and hand were pronated and resting on the table, with their right thumb to the left of the force transducer. Their forearm was strapped to the table using two Velcro straps. This was to limit the involvement of the shoulder and elbow in the task, assisting in ensuring participants were limited to using their right thumb. The task was completed in the following order: pre/baseline (4-blocks of traces), acquisition (12-blocks of traces), and post-acquisition (4-blocks of traces), 24-48 hours later participants returned to the lab and completed the retention (4-blocks of traces) test. Each block consisted of three to five traces, and each trial was 20 seconds long. Blocks were presented in a randomized order for each participant, to ensure that there was not an order effect on performance and learning. Prior to the start of the pre-acquisition phase of the FMT, participants completed one familiarization trial so that they could acquaint themselves with the expectations of the paradigm prior to beginning the motor acquisition paradigm.

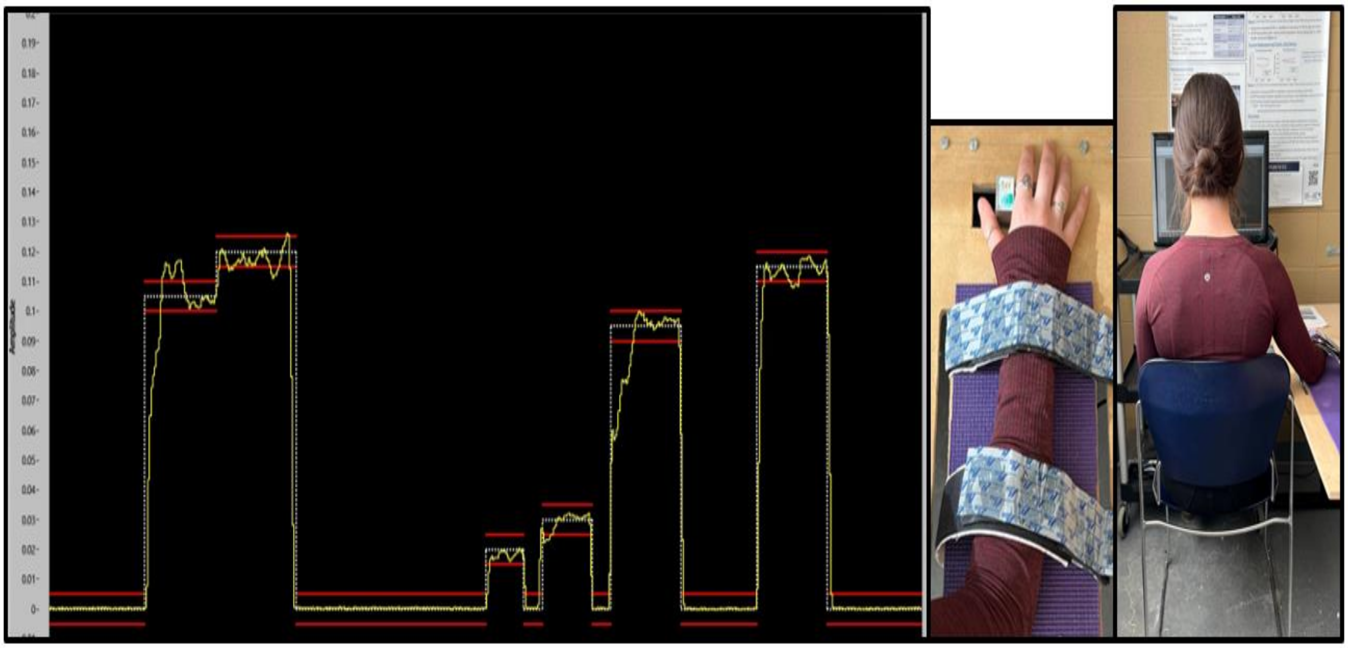

Figure 10 - Depiction of the FMT program. Yellow line indicates the participants force output on the transducer. The white line is the intended trace, while red lines reflect boundary guides. The

task was calibrated to each individual's APB MVC which was established prior to beginning the paradigm.

6.5 Data Processing

6.5.1 Force Data

A custom LabVIEW™ program was used to filter and analyze the force data. A 0.5 s moving average window was applied to the data for smoothing of the force signal (Sonne & Potvin, 2015). Variables that were assessed include average absolute percent error and standard deviation of error as a measure of force variability. Error was assessed by comparing the participant's force output to the force trace template target. Performance measures reported include both absolute values and those that have been normalized to each participant's baseline score.

To calculate percent error, the following equation was used:

Absolute % Error = $((\left(\frac{Participant\ Force\ Trace}{Force\ Trace}\right) x\ 100) - 100)$ (Ambalavanar, 2021)

6.5.2 SEPs

The SEPs signals were amplified (gain of 10,000) and filtered (0.2–1000 Hz) on a laboratory computer (Zabihhosseinian et al., 2021). Peripheral SEPs were recorded and analyzed in Signal4 software (Version 4.08, Cambridge Electronic Design, Cambridge, UK). This includes the peripheral N9, N11, and N13 peaks.

All SEP peaks were measured from the preceding trough/peak to the following peak/trough of interest. The change in amplitude in units of μV was recorded at baseline and at post measures. SEPs peak amplitude changes were then normalized to that peak's baseline value for each participant. This allows for an assessment of proportional change for each SEP peak.

Latency in units of ms for each peak was also recorded to ensure peaks were consistently identified for each participant.

To confidently say that SEP changes are not a result of peripheral changes, it is necessary to determine that the afferent input between pre and post measures was stable, to ensure any changes in central SEP peaks were a result of neural adaptations from motor acquisition and not a by-product of postural alterations, for example. This was done by ensuring stability of the N9 SEP peak over the brachial plexus/Erb's point. The N9 had to remain stable pre-post to use the data set. Therefore, the N9 SEP peak had to be within ± 20% pre-post to include that participant's neurophysiological data (Nuwer et al., 1994). All N9 SEP peaks met this inclusion criteria, and therefore no data sets were removed from analysis. SEP peaks were normalized to a participant's baseline, i.e. a percentage of their pre-SEP peak amplitude, to account for differences in inter-participant baseline variability, allowing for comparisons between groups.

6.5.3 EEG Analysis

Whole-head EEG was used to record and analyze central SEP peaks, including the N18, N20, P25, N24, N30, and N60. Data was cleaned and any artifacts, including eyeblinks, were removed prior to running analyses. Artifacts which were a result of muscle activity and ocular activity were removed using ASA software, excluding signals that were ± 100 µV. EEG data was filtered using a band-pass filter with a low cut-off of 0.2 Hz and a high cut-off of 1000 Hz, slope steepness was set at 24 dB/octave (Zabihhosseinian et al., 2021). Data was then averaged, providing averaged 64-electrode signals to obtain central SEP peak amplitudes and latencies. For each SEP peak, greater amplitudes are seen over electrodes closest to the neural generator responsible for that peak (Valeriani et al., 1998; Zabihhosseinian et al., 2021). Therefore, the

N18 was recorded over the ipsilateral FC2 electrode, the N20 and P25 over the contralateral CP3, and the N24, N30, and N60 over the contralateral FC1 electrode.

6.5.4 Statistical Analyses

Statistical significance was set at $p \leq 0.05$ for all analyses (SPSS v.24, IBM Corporation, Armonk, NY, USA). Effect sizes are reported using partial eta squared (η2), with a small effect as 0.01, medium as 0.06, and a large effect as 0.14 as defined by Richardson (2011). All numeric values are expressed as mean ± standard deviation (SD), unless otherwise stated. Normality was tested using Shapiro–Wilk's test and Levene's test was used as an assessment of homogeneity of variance.

6.5.4.1 Behavioural

Motor performance was compared between and within groups. This was done for pre-acquisition, post-acquisition, and retention. A 2 x 3 mixed-design ANOVA with repeated measures of time (pre, post, and retention) and between subject factor of group (ADHD and control) as measures was performed on both the mean percent error and the force variability (SD). This was performed on both the absolute and normalized data, as the absolute can show differences in absolute motor performance, whereas the normalized data can show performance improvements relative to baseline as a result of learning. Behavioural data was normally distributed, with the exception of the absolute "pre" scores for both groups. Therefore, log transformations were performed on the absolute performance scores to correct for this violation of normality.

6.5.4.2 Neurophysiological

Neural adaptations were compared between groups using a 2 × 2 mixed-design ANOVA with the factor of time (pre-acquisition vs. post-acquisition) as the repeated measure and group

(ADHD and control) defined as the between subject factor for each SEP peak. All SEP peak data were normally distributed.

6.6 Results

6.6.1 Behavioural

6.6.1.1 Mean Percent Error

Normalized mean scores: Normalized performance scores can be seen in Figure 11 and Table 2. There was a significant effect of time ($F_{2,28} = 61.645$; $p < 0.0001$; partial $\eta^2 = 0.688$) for the normalized performance scores. This shows that both groups (ADHD and control) improved from baseline to post-measures (ADHD: 0.850 ± 0.093 vs. control: 0.848 ± 0.103) and at retention compared to baseline (ADHD: 0.816 ± 0.114 vs. control: 0.825 ± 0.110). Post-hoc tests showed that pre-scores were significantly different than retention and post, while retention and post were not significantly different from one another. An effect of group was not present ($F1_{,28} = 0.008$; $p = 0.929$; partial $\eta^2 = 0.000$). *Absolute mean scores:* Absolute performance scores can be seen in Figure 12 and Table 2. There was a significant main effect of time ($F_{2,26} = 33.759$; $p < 0.0001$; partial $\eta^2 = 0.650$) for absolute performance scores. This illustrates that both groups (ADHD vs. control) improved from baseline (ADHD: 0.757 ± 0.184 vs. control: 0.696 ± 0.158) to post-measures (ADHD: 0.633 ± 0.107 vs. control: 0.578 ± 0.068) and from baseline to retention (ADHD: 0.601 ± 0.068 vs. control: 0.560 ± 0.052). Post-hoc tests showed that pre-scores were significantly different than retention and post, while retention and post were not significantly different from one another. An effect of group (ADHD vs. control) was not reached ($F_{1,26} = 2.036$; $p = 0.137$; partial $\eta^2 = 0.077$).

6.6.1.2 Force Variability (SD)

Normalized variability: Normalized force variability data can be seen in Figure 13. There was a significant effect of time ($F_{2,28} = 46.446$; $p < 0.0001$; partial $\eta^2 = 0.624$) for the normalized force variability. This shows that both groups (ADHD and control) became less variable from baseline to post-measures (ADHD: 0.90 ± 0.077 vs. control: 0.89 ± 0.093) and at retention compared to baseline (ADHD: 0.85 ± 0.091 vs. control: 0.89 ± 0.093). Post-hoc tests showed that variability at pre-measures were significantly different than retention and post, while retention and post were not significantly different from one another. An effect of group was not present ($F1_{,28} = 0.153$; $p = 0.698$; partial $\eta^2 = 0.005$). *Absolute variability:* Absolute variability can be seen in Figure 14. There was a significant main effect of time ($F_{2,26} = 42.168$; $p < 0.0001$; partial $\eta^2 = 0.601$) for absolute variability. This illustrates that both groups (ADHD vs. control) had less variable force output from baseline (ADHD: 0.1.32 ± 0.23 vs. control: 1.22 ± 0.19) to post-measures (ADHD: 1.17 ± 0.15 vs. control: 1.07 ± 0.089) and from baseline to retention (ADHD: 1.11 ± 0.12 vs. control: 1.07 ± 0.093). Post-hoc tests showed that variability at pre-measures were significantly different than retention and post, while retention and post were not significantly different from one another. An effect of group (ADHD vs. control) was not reached ($F_{1,26} = 2.820$; $p = 0.104$; partial $\eta^2 = 0.091$), although a medium effect size was present.

Percent Error (Normalized/Absolute)	**Pre**	**Post**	**Retention**
ADHD	1	0.85 ± 0.09	0.82 ± 0.11
	0.76 ± 0.18	0.63 ± 0.11	0.60 ± 0.07
Control	1	0.85 ± 0.10	0.83 ± 0.11
	0.70 ± 0.16	0.58 ± 0.07	0.56 ± 0.05

Table 2 - Illustrating normalized and absolute performance values for the novel FMT. All values represented are the mean ± SD.

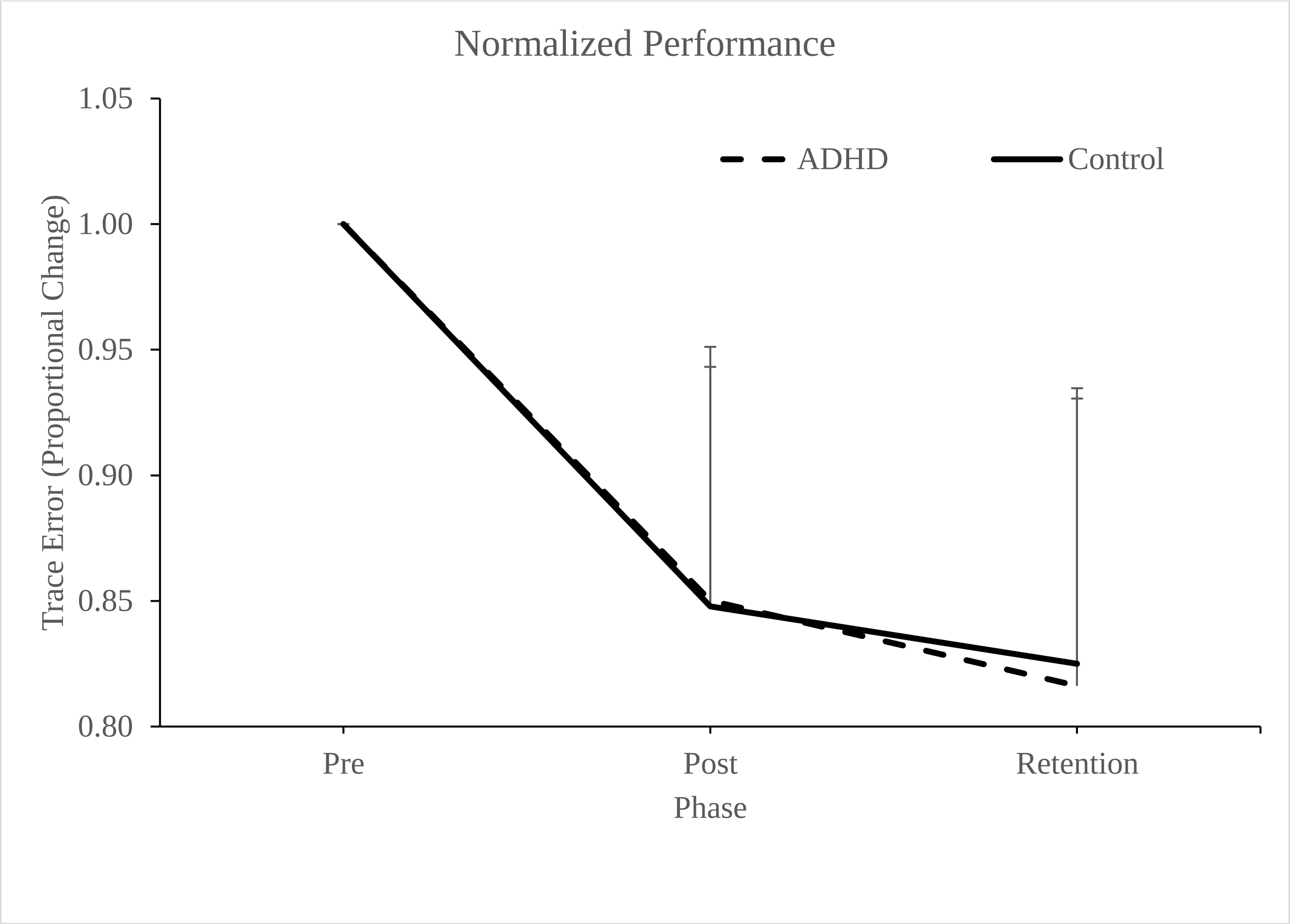

Figure 11 - Normalized performance scores for each phase. Pre and retention measures have been normalized to each individuals baseline (pre) score. ADHD scores are in the dashed line, controls are in the solid line. Values represent mean ± SD. Both groups improved at post-acquisition and retention when compared to pre-values.

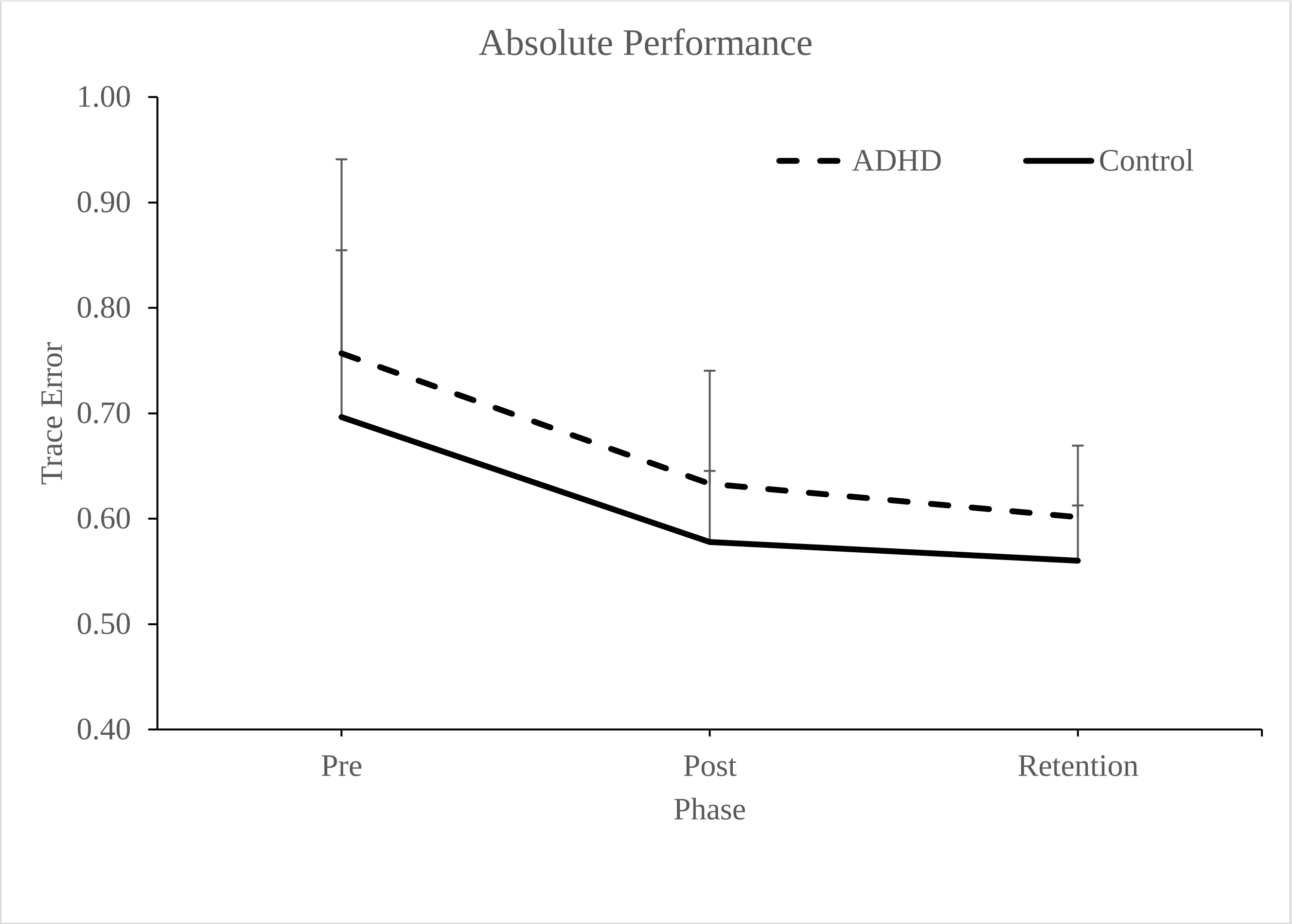

Figure 12 - Absolute (raw) performance scores for each phase. ADHD scores are in the dashed line, controls are in the solid line. Values represent mean ± SD. Both groups had improved performance at post-acquisition and retention when compared to baseline.

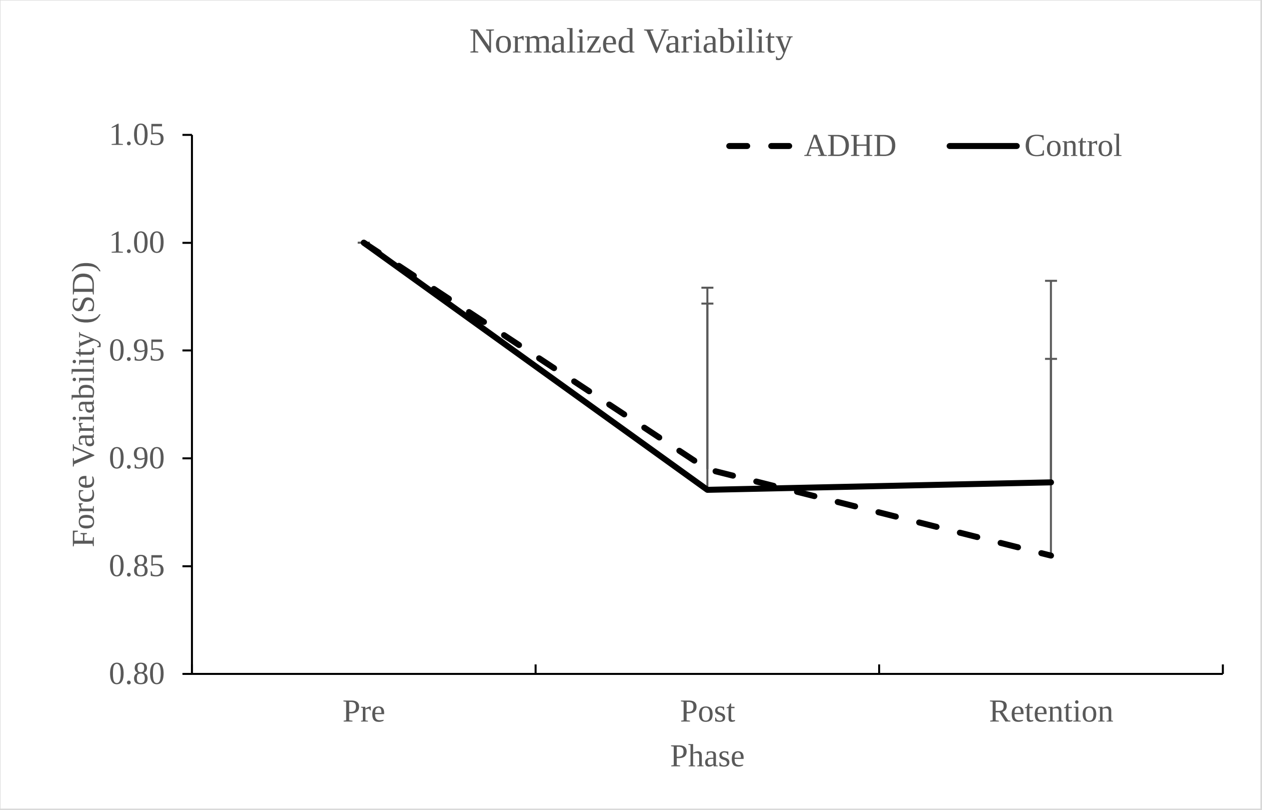

Figure 13 – Normalized force variability for each phase of the FMT. Variability is presented as SD of the force trace accuracy. Values represent mean ± SD. Variability reduced at post-acquisition and retention, when compared to baseline.

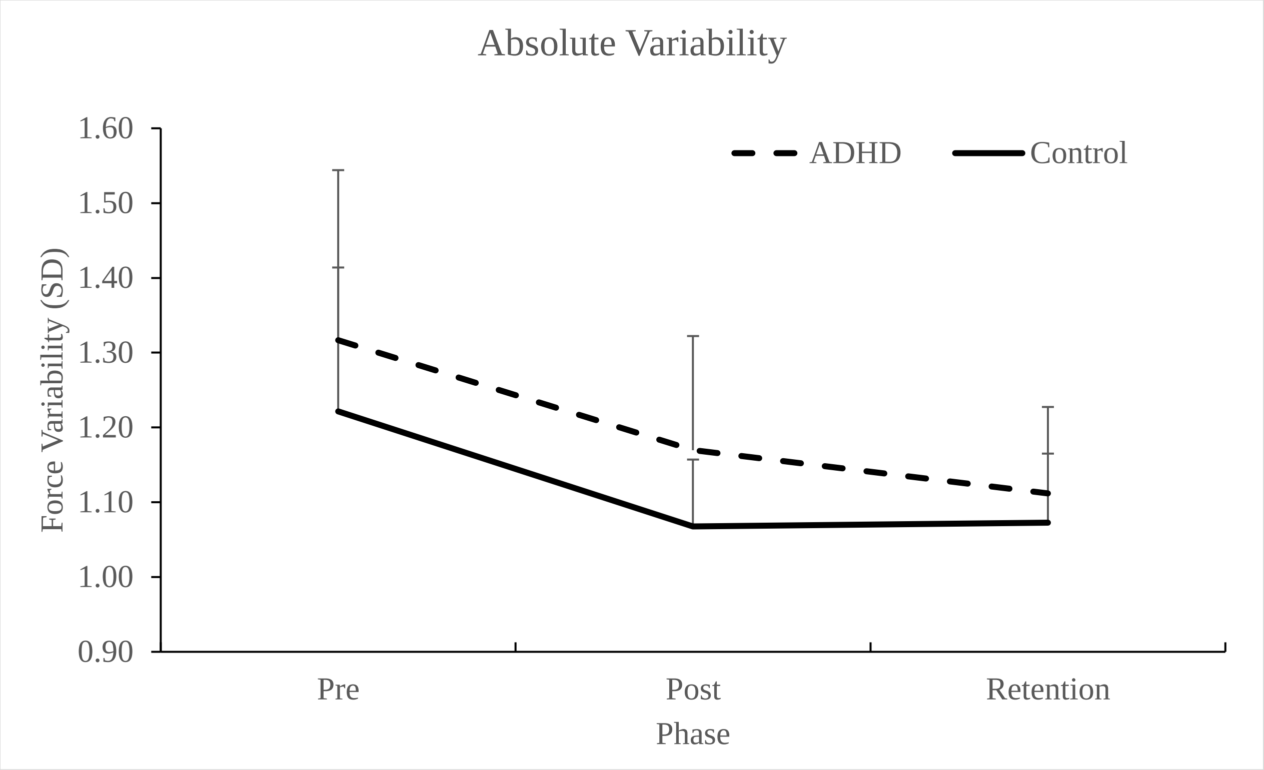

Figure 14 - Absolute force variability for each phase of the FMT. Variability is presented as SD for force accuracy. Values represent mean ± SD. Variability improved for both groups at post-acquisition and retention measures.

6.6.2 Neurophysiological SEPs Data

All participant's SEP data was included, as the inclusion criteria of the N9 SEP peak was met. The N9 was recorded over the ipsilateral brachial plexus, and when comparing pre-post measures, the N9 differed by no more than ± 20% from baseline measures (Nuwer et al., 1994; Zabihhosseinian et al., 2021). This assessment is done to ensure that any central SEP peak changes are not inadvertently a result of peripheral changes, such as to posture. This was also confirmed statistically, where the N9 had no effect of time ($F_{1,28} = 0.015$; $p = 0.903$; partial $\eta^2 = 0.001$) or group present ($F_{1,28} = 0.059$; $p = 0.811$; partial $\eta^2 = 0.002$). Therefore, all participants data is included in the SEP peak analysis. All SEP peak data can be seen below in Figure 15.

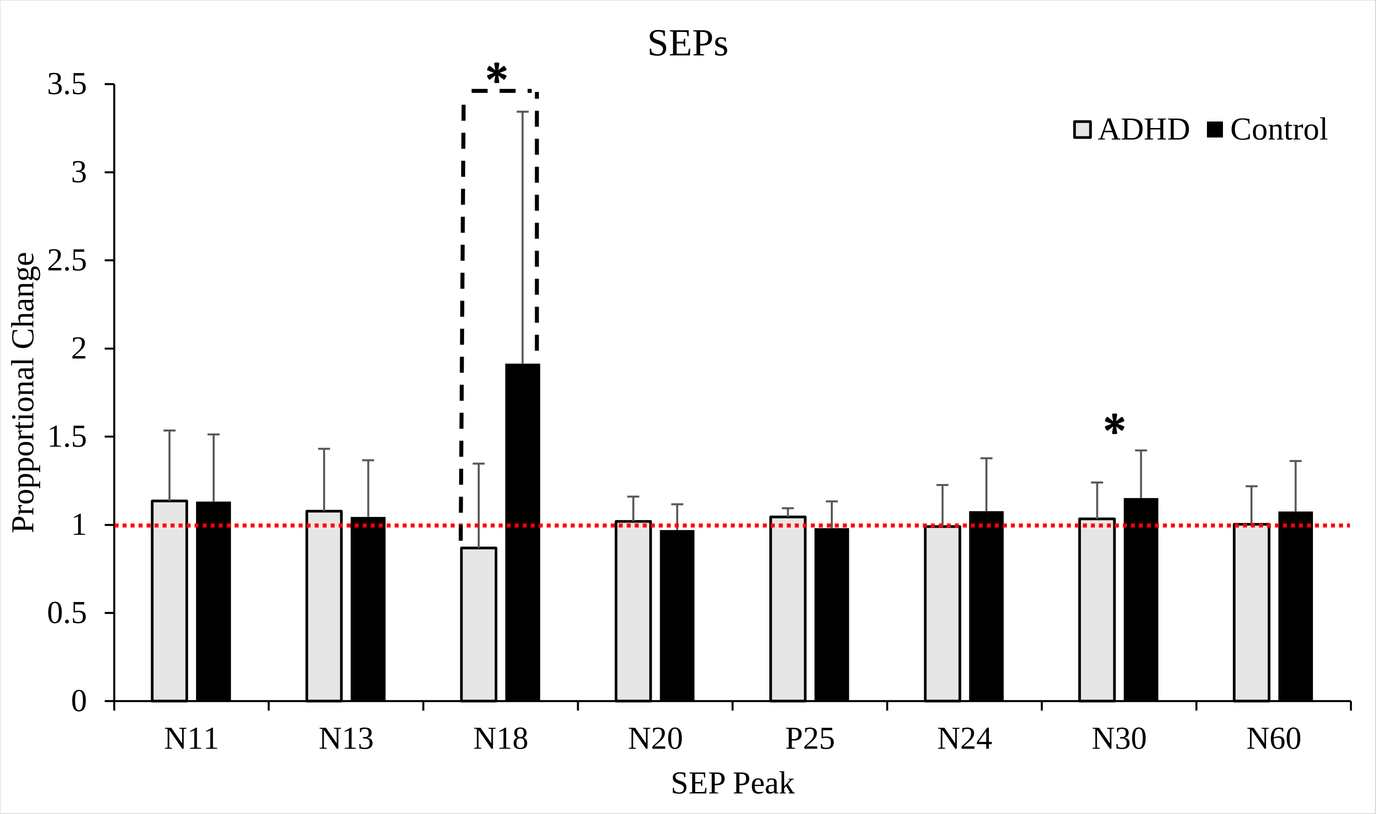

Figure 15 - Normalized SEP peak amplitudes relative to baseline (red dotted line). ADHD participants are in gray and controls are in black. Values represent mean ± SD. Dashed bars (- - -) and asterisks (*) denote significant group interactions, and asterisks (*) only indicate significant effects of time.

N11: No effect of time ($F_{1,28} = 3.523$; $p = 0.071$; partial $\eta^2 = 0.112$) or group were present ($F_{1,28} = 0.000$; $p = 0.984$; partial $\eta^2 = 0.000$), although a medium effect size was reached for time.

N13: No effect of time ($F_{1,28} = 0.990$; $p = 0.328$; partial $\eta^2 = 0.034$) or group were present ($F_{1,28} = 0.068$; $p = 0.797$; partial $\eta^2 = 0.002$).

N18: A main effect of time was not present ($F_{1,28} = 4.035$; $p = 0.054$; partial $\eta^2 = 0.126$), although it approached significance and a medium effect size was evident. A significant effect of group ($F_{1,28} = 7.212$; $p = 0.012$; partial $\eta^2 = 0.205$) and a time x group interaction were present

($F_{1,28} = 7.212$; $p = 0.012$; partial $\eta^2 = 0.205$). The N18 decreased in those with ADHD (0.87 ± 0.48) and increased in controls (1.91 ± 1.43).

N20: No effect of time ($F_{1,28} = 0.048$; $p = 0.829$; partial $\eta^2 = 0.002$) or group were present ($F_{1,28} = 0.888$; $p = 0.354$; partial $\eta^2 = 0.031$).

P25: No effect of time ($F_{1,28} = 0.379$; $p = 0.543$; partial $\eta^2 = 0.013$) or group were present ($F_{1,28} = 2.367$; $p = 0.135$; partial $\eta^2 = 0.078$), although a medium effect size was present when comparing between groups.

N24: No effect of time ($F_{1,28} = 0.459$; $p = 0.504$; partial $\eta^2 = 0.016$) or group were present ($F_{1,28} = 0.785$; $p = 0.383$; partial $\eta^2 = 0.027$).

N30: A significant effect of time ($F_{1,28} = 4.395$; $p = 0.045$; partial $\eta^2 = 0.136$) was present. The N30 increased in both groups (ADHD: 1.03 ± 0.21; controls: 1.15 ± 0.27). A main effect of group or a time by group interaction were not present ($F_{1,28} = 1.815$; $p = 0.189$; partial $\eta^2 = 0.061$).

N60: No effect of time ($F_{1,28} = 0.711$; $p = 0.406$; partial $\eta^2 = 0.025$) or group were present ($F_{1,28} = 0.588$; $p = 0.450$; partial $\eta^2 = 0.021$).

6.7 Discussion

This is the first work to assess a motor learning paradigm dependent on force modulation, in conjunction with neural markers in the form of SEPs, in young adults with ADHD. Results yielded indicate that there are differences in the way that those with ADHD process afferent information when learning a novel FMT, that differ from neurotypical controls. The SEP peaks that changed as a result of the novel FMT were the N18 and the N30. Specifically, the N18 SEP peak, which reflects activity within olivary-cerebellar-M1 networks, was unique in this population. The results from the current study also indicate that the N30 SEP peak increased in both those with and without ADHD, suggesting similar changes in each group. Additionally, both groups exhibited improvements in performance at post-acquisition and retention measures, suggesting that they did indeed learn throughout the acquisition phase of the paradigm. When assessing absolute performance measures, those in the ADHD group appeared to exhibit greater error at all phases of the paradigm, when compared to controls, although this did not reach statistical significance a medium effect size was present, and may be an important topic of inquiry in the future. Therefore, the normalized performance scores suggest that both those with and without ADHD learned to a similar extent, as seen by similar proportional improvement (i.e. reduction in error), although absolute values may suggest reduced overall performance in those with ADHD when compared to neurotypical controls.

6.7.1 Neurophysiological SEPs Data

SEPs offer a non-invasive technique to assess cortical and sub-cortical processing between groups and in response to various tasks. Each SEP peak is reflective of activity within specific neural structures (Passmore et al., 2014). Due to this, they provide an invaluable technique allowing for the assessment of the neural processes related to motor learning and SMI. Previous research has shown distinct SEP peak changes in response to visuomotor tasks and in many populations, including those experiencing fatigue and individuals with subclinical neck pain (SCNP), further validating their relevance associated with the interpretation of neural correlates of motor learning (Andrew et al., 2018; Zabihhosseinian et al., 2021). The current study is the first, to our knowledge, to use SEPs to aid the assessment of force-dependent motor learning in those with ADHD, thus providing novel insight into the neural underpinnings of motor learning in this population. The current study yielded results suggesting that two SEP peaks in particular had significant changes between groups or after motor learning, these peaks are the N18 and N30.

N18

The results from the current study showed that those with ADHD exhibited different neural processing after learning the novel FMT than did controls. This difference was evident for the N18 SEP peak, where those in the ADHD group exhibited a reduction in the N18 peak amplitude after performing the motor learning paradigm and controls exhibited an increase in peak amplitude. This is the first study to utilize a motor learning task highly dependent on proprioception and force modulation in those with ADHD, in conjunction with a neural measure to assess cortical and subcortical processing. The current work is in line with previous research utilizing similar methodology in controls, which saw as an increase in the N18 SEP peak in controls after acquisition of a novel FMT (Ambalavanar, 2021). The N18 is recognized as having neural generators within the brainstem, in particular between the lower medulla and the midbrain pontine regions (Haavik & Murphy, 2013; Noël et al., 1996; Sonoo et al., 1991). Furthermore, the N18 is reflective of inhibitory activity at the level of the medulla, as a result of activity within the dorsal column medial lemniscus nuclei (Noël et al., 1996; Rossi et al., 2003; Sonoo, 2000). However, the N18 is also a marker of activity generated within the cuneocerebellar tract, the cerebellum, and accessory olives, this being as a result of collaterals diverging from the medial lemniscus within the medulla (Noël et al., 1996). The cuneate nuclei relay both cutaneous and proprioceptive information to the thalamus, and then towards the cerebral cortex, in addition to its role in feed-back regulated cerebellar SMI (Berkley, Budell, Blomqvist, & Bull, 1986; Haavik & Murphy, 2013; Hand & Van Winkle, 1977; Marshall, 1984; Pascual-Leone & Torres, 1993). This posits that the N18 reflects alterations to cerebellar activity, such as activity related to cerebellar SMI (Haavik & Murphy, 2013). The increased N18 in controls at post measures may reflect increased inhibitory activity in olivary-cerebellar-M1 networks, suggestive of reduced dependence on cerebellar SMI processing related to force modulation in the thumb during this task as a result of learning (Ambalavanar, 2021). Therefore, the differences in the N18 in those with ADHD compared to controls may suggest differences in the olivary-cerebellar-M1 processing in response to learning the novel FMT.

The cerebellum is a neural structure that plays a fundamental role in the process of motor learning. Particularly, the cerebellum has increased activity during the initial stages of learning (Baarbé et al., 2014; Doyon et al., 2002a; Eliassen, Souza, & Sanes, 2001; Floyer-Lea & Matthews, 2005; Gao, Van Beugen, & De Zeeuw, 2012; Jenkins, Brooks, Nixon, Frackowiak, & Passingham, 1994; Penhune & Doyon, 2002). Consequently, reduced inhibition of the cerebellum to the M1 is noted after exposure to a novel motor task (Baarbé et al., 2014). Therefore, the novel finding from the current study, that those with ADHD had a reduction in the N18, may be reflective of reduced inhibitory activity of olivary-cerebellar-M1 networks after performance of the FMT. This may suggest that those with ADHD had reduced efficiency of sensory processing resulting in a greater reliance on proprioceptive input when learning this task than did controls, seen as a reduction in the filtering effect to continually refine motor output via proprioceptive and force feedback (Haavik & Murphy, 2013). Previous work illustrates that there are proprioceptive deficits in those with ADHD (Alba et al., 2016; Goulardins et al., 2013; Jung et al., 2014; Sanz-Cervera et al., 2017). Literature has noted that when a novel task is not learned well, this will result in increased activity within cerebellar brain regions (Andrew et al., 2018; Dancey et al., 2016; Doyon et al., 2002a; Floyer-Lea & Matthews, 2005; Manzoni, 2007). This is possibly a result of processing related to the ongoing error correction during the learning phase.

Therefore, the proprioceptive and motor control deficits noted in the literature previously in those with ADHD may be related to the N18 reduction in the current study, which may have occurred due to an enhanced reliance on proprioceptive feedback if this form of afferent input and processing is altered in this population.

Previous work, utilizing a 20 minute repetitive typing task, found an decrease in the N18 in controls, which was suggestive of a reduction in a filtering effect prior to cortical processing during the early stages of learning (Haavik & Murphy, 2013). The results from the current study suggest that those in the ADHD group may experience difficulty with the proprioceptive-centric demands of the current task, resulting in an enhanced dependence on force-modulation afferents via error monitoring, reflecting a reduction in inhibitory activity at the level of the olivary-cerebellar input as a reduction in the N18 post motor acquisition (Andrew et al., 2018). Interestingly, manuscript two from the current dissertation found contrasting results in those with ADHD when performing a motor acquisition paradigm utilizing different task demands. When completing a visuomotor task, those with ADHD exhibited an increase in the N18, whereas controls had a decrease. It is likely that the different task demands in the current study, which were heavily dependent on force-modulation and proprioception, resulted in the reduced N18 in those with ADHD. Therefore, this suggests that tasks that are heavily dependent on force-modulation via proprioception result in reduced inhibition of olivary-cerebellar-M1 processing in those with ADHD, when compared to neurotypical controls.

N30

The current study noted an increase in the N30 in both groups after completing the novel FMT. Previous work has found that motor learning paradigms result in an increase in the N30 SEP peak amplitude (Andrew et al., 2015a; Andrew, Yielder, & Murphy, 2015b;

Zabihhosseinian et al., 2020). Recent work utilizing a novel FMT found an increase in the N30 SEP peak after the learning paradigm was complete in a control group (Ambalavanar, 2021). The N30 SEP peak is reflective of activity at both cortical and sub-cortical levels, including the basal ganglia, thalamus, pre-motor areas, M1, and the SMA (Cebolla & Chéron, 2015; Kaňovský et al., 2003; Rossi et al., 2003; Rossini et al., 1987). This peak is generally thought to be reflective of SMI (Rossi et al., 2003). Source localization techniques have identified that the N30 neural generators have four distinct locations, including the contralateral S1, prefrontal cortex, cingulate, and bilateral secondary somatosensory cortex (Lelic et al., 2016). However, the prefrontal cortex is the neural source with the greatest activity during the N30 latency timeframe, and this region is related to SMI (Lelic et al., 2016). The increase in the N30 in the current study may reflect an upregulation of SMI neural processes, including those related to prefrontal function. Interestingly, the prefrontal cortex is one of the most commonly noted sites of neural alterations present in those with ADHD (Barkley, 1997; Seidman et al., 2006; Sowell et al., 2003).

The increase in the N30 in both groups suggests increased activity in brain regions heavily involved in SMI. Therefore, the demands of the novel FMT resulted in similar activation patterns in these brain regions in those both with and without ADHD. Although of potential relevance to note, a main effect of group was absent when assessing the N30, a medium effect size does suggest that there may be differences in the N30 between groups. For instance, the control group saw a mean increase in the N30 by 15% at post measures, whereas those in the ADHD group exhibited a modest mean increase of 3%. This suggests that there may be inherent differences in SMI processes in those with ADHD when completing a proprioceptive dominant motor learning task, such as the one utilized in the current study. Thus, resulting in an attenuated increase in the N30, when compared to neurotypical controls. If this is the case, it may be a result of altered neural structure and function in those with ADHD, such as those in prefrontal cortical regions (Barkley, 1997; Seidman et al., 2006; Sowell et al., 2003), affecting processes related to SMI. Previous work, specifically manuscript two within this dissertation, showed a reduction in the N30 in those with ADHD, compared to the control group which increased post motor acquisition. In the future, incorporating further assessment techniques that are sensitive to neural activity, such as fMRI or source localization as an initial cost-effective starting point, would elucidate the role of localized neural regions or structures in such processes, which may prove to be invaluable, to further enhance the understanding of how ADHD influences motor learning and SMI.

6.7.2 Behavioural Data

One way to behaviourally assess motor learning, can be via changes in performance, such as improvement in accuracy or reduced variability after the acquisition of a novel skill (Schmidt & Lee, 2005). Throughout the process of motor acquisition, there will generally be a progressive refinement in motor performance which can infer that learning has occurred. Additionally, the consolidation of a skill, observed via maintained or further improvement in performance at retention measures, can be assessed. Furthermore, the level of force-variability can provide insight into the level of motor performance and improvement at different stages of a task (Selen et al., 2006). The results from the current work suggest that both those with and without ADHD learned the novel FMT. This was observed as both groups had improvements in performance at post and retention measures, when compared to their baseline performance scores, in addition to exhibiting reduced variability at post and retention measures. These results suggest that both groups learned to a similar extent, as both groups exhibited approximately 15% less error at post measures, when their post scores were normalized to their baseline. Furthermore, when completing their retention test, scores remained similar to their post measures, if not ever so slightly improved, as error was approximately ~18-19% less than that of their baseline measures. Previous research has noted similar improvements in performance in response to learning a motor task dependent on force modulation (Ambalavanar, 2021). In the current study, similar results were present when assessing absolute performance scores, although those with ADHD had a pattern of increased absolute error and variability at each phase when compared to neurotypical controls. This may suggest that those with ADHD experience more difficulty with motor tasks dependent on force modulation and proprioception, than do neurotypical controls. Potential difficulties with proprioception, may be related to the reduction in the N18 in those with ADHD noted in the current study. The reduction in the N18, which is likely reflective of reduced inhibition, otherwise described as reduced inhibitory activity, of dorsal column nuclei, inferior olives, and cortico-cerebellar networks (Andrew et al., 2018; Haavik & Murphy, 2013; Noël et al., 1996; Rossi et al., 2003; Sonoo, 2000), may be a result of those with ADHD experiencing difficulty with the relative weighting of the visual versus force and proprioceptive feedback of the task. This, therefore, resulting in a greater reliance on the proprioceptive sensory afferents during the learning process, thus reducing inhibition of olivary-cerebellar-M1 processing allowing for the fine tuning of force-modulation to accurately meet the demands of the task.

6.7.3 Limitations

The nature of the design and formatting of the FMT may not have been optimal or conducive to motor learning, due to the slight delay between blocks/trials within LabVIEW. Thus, the discontinuous nature of the delivery may have made it more difficult, and limited further performance improvements at the retention measures. However, it should be noted that the delay was minimal. In the future, creating a delivery method that limits any lag between blocks and traces, that can be delivered automatically and continuously through the software, will allow for a more streamlined or continuous motor task. In the future, including a transfer task that requires a similar set of skills, yet under a somewhat different set of sensory conditions, would allow for an assessment of how well the motor skill was truly acquired and can be transferred to a related task. For instance, a transfer task that lacks the yellow force-feedback line staying present on the screen, and is replaced by a cursor that only shows the current, and not past force-output or accuracy, would allow for the assessment of how those with ADHD perform a motor task that was learned, lacking visual knowledge of results during the performance. Thus, providing insight into the relative weighting of sensory feedback utilized.

6.8 Conclusions

This work is the first to assess the neural mechanisms involved in force-dependent motor learning, heavily reliant on proprioception, in young adults with ADHD. The current technique involved the assessment of short-latency SEPs and behavioural improvements via performance accuracy. Those in the ADHD group exhibited a significantly reduced N18 SEP peak when compared to neurotypical controls whose N18 increased post-motor learning, suggesting reduced olivary-cerebellar-M1 inhibition in the ADHD group, in response to the novel motor task. This may reflect an increased reliance on proprioceptive feedback in order to perform the task, potentially as a result of difficulty in the processing and integration of the force and proprioceptive input in association with the visual feedback presented. Behaviourally this may be related to the increased absolute error present in the ADHD group. Although, both groups showed similar improvement in absolute performance, thus reflecting that learning occurred to a similar extent, in addition to a similar increase in the N30. In the future, utilizing forms of neural assessment that provide an improved form of spatial acuity, such as those offered by source localization techniques, or fMRI if feasible, could prove beneficial in improving our comprehension of how those with ADHD learn novel motor tasks, particularly those that require a high level of force modulation acuity. Overall, this work suggests that adults with ADHD exhibit different neural processing related to learning a force-dependent motor paradigm.

Chapter 7: Study 4

7.1 Preface to manuscript 4:

The previous work within this dissertation adds to the limited body of literature focused on adult Attention-Deficit/Hyperactivity Disorder (ADHD), with a specific focus on sensory integration and motor performance. The results from study one, utilizing standardized low-resolution brain electromagnetic tomography (sLORETA) techniques to source localize neural generators during an audiovisual multisensory task, suggested that BA 2 functioned differently in adults with ADHD when compared to neurotypical controls. Specifically, neurotypical controls exhibited greater activation at this brain source. This difference was evident when presented with an audiovisual multisensory stimulus. BA 2 has a primary function in processing pressure and tactile stimuli (Sur, 1980). Additionally, this difference was pronounced over the right-hemispheric parietal lobe, which has a well-known role in attentional attributes (Chan et al., 2009; Corbetta et al., 1993; Gitelman et al., 1999; Nobre et al., 1997; Vance et al., 2007). Moving sequentially forward, studies two and three, utilizing somatosensory evoked potentials (SEPs) and electroencephalography (EEG), elucidated the presence of unique neural differences relating to how adults with ADHD acquire novel motor skills and process somatosensory afferent input. These differences were evident in short-latency SEPs, such as the N18 and N30. Those in the ADHD group consistently exhibited alterations to the N18 SEP peak when compared to neurotypical control adults, regardless of whether the task was visuomotor (MTT) in nature, or whether it was a force-matching task (FMT). The unique difference in the N18 suggests that ADHD is associated with differences in olivary-cerebellar-M1 activity, particularly activity relating to inhibition, when performing novel motor skills (Andrew et al., 2018; Haavik & Murphy, 2013; Noël et al., 1996; Rossi et al., 2003; Sonoo, 2000). The reduction in the N18 in those with ADHD after learning the FMT likely reflects decreased inhibition of olivary-cerebellar-M1 networks (Andrew et al., 2018; Haavik & Murphy, 2013; Noël et al., 1996; Rossi et al., 2003; Sonoo, 2000). This may be indicative of difficulty processing the force and proprioceptive sensory afferents that are paramount to the performance of the FMT, as when a task is not well-learned, there is an increase in activity within cerebellar regions (Andrew et al., 2018; Dancey et al., 2016; Doyon et al., 2002a; Floyer-Lea & Matthews, 2005; Manzoni, 2007). These findings provide novel and crucial insight into the role of specific neural regions in the process of motor learning and somatosensory processing in adults with ADHD. Furthermore, they suggest the importance of applying sLORETA and SEP techniques to improve our understanding of ADHD.

Although the pairing of surface EEG and SEP techniques was an important first step in assessing somatosensory processing in adults with ADHD, and has provided invaluable insight into the processes related to SMI and motor learning, the analysis techniques utilized within studies two and three were restricted to surface cortical assessments, thus limiting the spatial acuity of the assessment. Given the fundamental importance of motor learning and performance in relation to daily function, utilizing neurophysiological techniques which allow for an assessment of neural source location is an important next step. Therefore, the aim of the current work was to localize areas of neural activity in response to learning both the MTT and FMT motor paradigms in those with ADHD and neurotypical controls. Utilizing sLORETA as an assessment tool allowed for the comparison between groups and also at pre and post measures, localizing areas that differed within a group (ADHD or control) after learning either of the novel motor tasks. This work provides invaluable insight into the role specific neural structures play in processes related to motor learning in adults with ADHD, thus indicating how ADHD affects the acquisition of motor paradigms that are dependent on force-modulation or not.

Manuscript 4: Source Localization of Somatosensory Neural Generators in Adults with Attention-Deficit/Hyperactivity Disorder

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7.2 Abstract

Background: Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder, which encompasses both behavioural and neurophysiological characteristics. Individuals with ADHD have noted alterations to motor performance and learning, including difficulties with various forms of sensory processing. Previous work within this dissertation elucidated unique patterns of neural activity in those with ADHD when performing both visuomotor and force-matching motor acquisition paradigms. The goal of the current work is to assess the sources of neural activity in response to somatosensory stimuli after two different motor acquisition paradigms, in both young adults with ADHD and neurotypical controls.

Methods: Two motor paradigms were used, one which was visuomotor and required variations of thumb adduction and abduction to trace a sinusoidal waveform, while the other was a force-matching task (FMT), requiring participants to apply force on a transducer to trace a waveform, the transducer was calibrated to their abductor pollicis brevis (APB) maximal voluntary contraction (MVC). Somatosensory evoked potentials (SEPs) were elicited via median nerve stimulation to the right wrist, while whole-head 64-electrode electroencephalography (EEG) was collected at a sampling frequency of 2048 Hz, both immediately before and after participants completed the motor paradigms. Source localization (sLORETA) software localized areas where neural activity significantly differed between those with ADHD and neurotypical controls.

Results: sLORETA localized greater activity post-FMT in those with ADHD, when compared to their baseline (pre) activity ($p < 0.05$). This difference was found at BA 31, precuneus, parietal lobe, referenced to Montreal Neurological Institute (MNI) coordinates of X = -5, Y = -75, and Z = 20 at 156 ms post stimulation. No significant differences were found for the other comparisons.

Discussion: This is the first work to assess sources of neural activity in relation to somatosensory stimuli and motor learning in young adults with ADHD. The increased activity within BA 31 in those with ADHD at post measures, when compared to the ADHD pre-measures, during the FMT, may be reflective of increased activation within the default mode network (DMN) or attentional changes. These neural activity changes are likely related to the force and proprioceptive demands of the FMT, and the way this form of proprioceptive sensory information is processed in those with ADHD, as similar changes were not present in response to the visuomotor task or neurotypical controls. Therefore, those with ADHD may perceive sensory input during tasks heavily dependent on force and proprioceptive input differently, particularly during tasks that require a refinement of motor performance such as the novel FMT utilized in this research.

Keywords

Attention-Deficit/Hyperactivity Disorder (ADHD); somatosensory evoked potential (SEP); source localization; sLORETA; motor learning

7.3 Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is classically defined as a neurodevelopmental disorder, with the most common behavioural characteristics being hyperactivity, impulsivity, and inattention (*Diagnostic and statistical manual of mental disorders: DSM-5*, 2013; Visser et al., 2014). Although ADHD is commonly described as having behavioural characteristics, there are also unique neural attributes associated with ADHD, which are relevant to the current work. ADHD is common in occurrence, with approximately 11% of children in the United States being diagnosed with ADHD (Visser et al., 2014). Although ADHD is commonly described as a disorder predominantly present during childhood, approximately 65% of children diagnosed with ADHD will continue to exhibit symptoms as adults (Faraone et al., 2006). Currently, limited literature exists addressing the signs and symptoms of ADHD in adulthood, including the neural and behavioural attributes that may be present, and their influence on sensory and motor functions. The hallmark behavioural characteristics described above can have important implications for how individuals function on a day to day basis, potentially hindering physical and mental health in adults with ADHD (Brook et al., 2013). ADHD in adulthood has been associated with increased levels of depression and anxiety, and lower levels of employment, relationship quality, and health and wellbeing, including increased likelihood of experiencing financial difficulties (Biederman & Faraone, 2006; Das et al., 2012; Kessler et al., 2005a; Rösler et al., 2010). This indicates that ADHD in adulthood, although presenting differently than in childhood, has significant implications for quality of life and functional abilities (Das et al., 2012). Due to the significant affect ADHD symptomology has on daily life, further research is necessary to improve the understanding of the unique neural characteristics in ADHD and their potential implications for behaviour. Furthermore, an improved understanding of the neural underpinnings associated with ADHD has the potential to aid our understanding of how alterations to sensory processing may affect day-to-day life in adults.

As ADHD is a neurodevelopmental disorder, it is associated with alterations to function and structure within many neural substrates and circuits. These distinct neural characteristics are present in cortical and subcortical locations, including but not necessarily limited to, those related to the prefrontal cortex, anterior cingulate, precuneus, parieto-temporal regions, mesocorticolimbic networks, caudate, thalamus, and cerebellar regions (Castellanos et al., 2002; Castellanos et al., 2008; Ehlis et al., 2008; Liston et al., 2011; Makris et al., 2008; McAlonan et al., 2007; Proal et al., 2011; Sidlauskaite et al., 2015; Sun et al., 2012). Additionally, predominant neurophysiological characteristics of ADHD are thought to be related to alterations to fronto-striatal-cerebellar network circuity alterations (Krain & Castellanos, 2006; Proal et al., 2011). It has been suggested that alterations to fronto-cerebellar circuitry are strongly related to symptoms associated with ADHD, including hyperactivity and inattention (Durston et al., 2011; Koziol et al., 2013). Duerden and colleagues noted differences in cortical thickness in sensorimotor processing brain regions, indicating increased thickness in the pre-SMA and the S1 in those with ADHD (Duerden et al., 2012). However, the influence that these unique neural characteristics may have on function, particularly those related to somatosensory processing and motor learning in adult ADHD, remains unclear.

Although there is notably limited literature assessing adult ADHD, existing literature suggests that somatosensory function and SMI are altered in this population (Dockstader et al., 2009; Dockstader et al., 2008; Duerden et al., 2012; Parush et al., 1997; Parush et al., 2007; Rubia et al., 2003; Rubia et al., 1999; Toplak & Tannock, 2005; Tucha et al., 2006; Werry et al., 1972). Functional and structural alterations to neural substrates involved in sensory integration may be related to performance-based outcomes. For instance, ADHD is associated with difficulty performing tasks that require motor coordination and performance (Fliers et al., 2011; Kaiser et al., 2015; Karatekin et al., 2003). A potential hallmark of ADHD symptomology is deficient inhibitory motor control (Lijffijt et al., 2005). Additionally, difficulties exist in performing tasks dependent on motor coordination, including balance during a single task, walking, reaction time, motor timing, slower movement preparation, motor timing, and handwriting (Duda et al., 2019; Kaiser et al., 2015; Klimkeit et al., 2005; Klotz et al., 2012; Shorer et al., 2012; Yan & Thomas, 2002). Difficulties in motor acquisition and performance associated with ADHD are likely related to, at least in part, alterations in sensorimotor processing.

Our previous work established the presence of an increased N18 and reduced N30 when utilizing a visuomotor tracing paradigm in adults with ADHD when compared to controls. Furthermore, a reduction in the N18 in those with ADHD after learning a novel force-matching task (FMT) was present. This reduction in the N18 after the FMT likely reflects decreased inhibition, or reduced inhibitory activity, of olivary-cerebellar-M1 networks (Andrew et al., 2018; Haavik & Murphy, 2013; Noël et al., 1996; Rossi et al., 2003; Sonoo, 2000). This may be indicative of difficulty processing the force and proprioceptive sensory afferents that are paramount to the performance of the FMT, as when a task is not well-learned, there is an increase in activity within cerebellar regions (Andrew et al., 2018; Dancey et al., 2016; Doyon et al., 2002a; Floyer-Lea & Matthews, 2005; Manzoni, 2007). Results from dissertation study 1, which utilized standardized low-resolution brain electromagnetic tomography (sLORETA), suggest that those with ADHD have attenuated activity within right-hemispheric BA 2 when presented with a multisensory stimulus. Literature has noted a role of the right-hemispheric parietal lobe with spatial attention processes (Chan et al., 2009; Corbetta et al., 1993; Gitelman et al., 1999; Nobre et al., 1997; Vance et al., 2007), whereas BA 2 in particular is reflective of neural processing of pressure, joint position sense, and complex touch (Sur, 1980). These findings provide novel and crucial insight into the role of specific neural regions in the process of motor learning and somatosensory processing in adults with ADHD. Furthermore, they suggest the importance of applying sLORETA and SEP techniques to improve our understanding of ADHD. Although the pairing of surface EEG and SEP techniques was an important first step in assessing somatosensory processing in adults with ADHD, and has provided invaluable insight into the processes related to SMI and motor learning, the analysis techniques utilized within studies two and three of this dissertation were restricted to surface cortical assessments, thus limiting the spatial acuity of the assessment. Given the fundamental importance of motor learning and performance in relation to daily function, utilizing neurophysiological techniques which allow for an assessment of neural source location is an important next step which we aim to address in the current study.

A form of neural assessment that pairs collected EEG data with a standardized MRI model, is source localization, which allows for the localization of specific neural generators with high spatial acuity. sLORETA offers a non-invasive and cost-effective technique to assess neural activity within neural generators (Pascual-Marqui, 2002). sLORETA has improved spatial resolution of neural structures when compared to an analysis strictly using surface-electrode EEG. sLORETA performs as a linear inverse algorithm that provides an estimate of the 3D distribution of neural generators within the human cortex based on the Montreal Neurological Institute (MNI) MRI brain map (MRI-152) (Pascual-Marqui, 2002). Furthermore, sLORETA has been found to provide the lowest localization error when being compared to other techniques using a linear inverse algorithm (Pascual-Marqui, 2002). One functionality of this software, is that it is capable of source localizing EEG data in the time-domain.

The rationale for the current work was to further improve our understanding of the neural characteristics in those with ADHD, particularly those related to motor learning and sensorimotor processing. This can be achieved by applying a form of neural assessment with a high-level of spatial acuity, such as sLORETA. The research question addressed within the current study, is: Do young adults with ADHD exhibit differences in neural activity source locations during visuomotor and/or force modulation tasks? This research aims to answer this question for two motor acquisition paradigms, one that is highly dependent on visuomotor processing, and the other that is more so dependent on force modulation and proprioception. Thus, allowing for an assessment of neural sources involved in motor paradigms that utilize differing sensory pathways. We hypothesize that adults with ADHD will exhibit differences in the source of neural activity after learning novel motor paradigms when compared to neurotypical controls.

7.4 Methods

7.4.1 Ethical Approval

This research study received approval from the Research Ethics Board (REB; # 15307) at Ontario Tech University. All participants gave written informed consent prior to participation. This study was performed according to the principles set out by the Declaration of Helsinki for the use of humans in experimental research.

7.4.2 Participants

Participants were recruited from the Ontario Tech University campus. All participants were between the ages of 18-35 years older, with one group of young adults with ADHD and a group of neurotypical controls per task. Participants were the same as those included in studies two and three within this thesis. Those in the ADHD group had received a previous clinical diagnosis from a health care professional. Two paradigms were used in this study: a novel visuomotor tracing task and a novel FMT. Those with ADHD (n = 15; 9 females) in the FMT group had a mean age of 22.00 ± 2.51, while controls (n = 15; 9 females) had a mean age of 20.80 ± 1.97. Those with ADHD (n = 12; 8 females) in the visuomotor task group had a mean age of 21.5 ± 1.93, while controls (n = 16; 9 females) had a mean age of 20.81 ± 2.46.

All participants were right-hand dominant, and this was confirmed using the Edinburgh Handedness Inventory (EHI). Additionally, participants completed pre-screening questionnaires prior to participating, to ensure they did not have a recent (past five years) history of epilepsy, concussion, stroke, or brain injury, that could have inadvertently affected the EEG, SEPs, and sLORETA results. All participants completed the Adult ADHD Self-Report scale (AASRS-v1.1) checklist questionnaire prior to participation. The AASRS-v1.1 quantifies the symptoms associated with ADHD, and consists of 18 questions that are highly correlated to diagnostic criteria for ADHD set out by the DSM-IV (Dankner et al., 2017). Each question is rated on a five-point Likert scale, with scores ranging from “never” to “very often”. This tool is effective at predicting ADHD symptomology (van de Glind et al., 2013). The checklist is broken up into part A and part B. Part A is related to inattentiveness, whereas part B is related to hyperactivity and impulsivity. To be clear, no specific score indicates a diagnosis of ADHD, rather it allows for a quantification of symptoms associated with ADHD, and therefore a comparison between groups

(ADHD vs. control). For the FMT task, those with ADHD had an average score of 22.40 ± 4.44 for part A (Controls: 14.27 ± 4.46) and 44.07 ± 8.16 (Controls: 24.93 ± 6.18) for part B. For the MTT those in the ADHD group had an average score of 21.58 ± 4.71 for part A (Controls: 12.31 ± 3.53), and an average score for part B of 42.33 ± 8.03 (Controls: 22.94 ± 5.73).

7.4.3 Procedures

7.4.3.1 SEPs Stimulation Parameters

SEPs were stimulated at a frequency of 2.47 Hz. SEPs were delivered via stimulation of the right median nerve at the right wrist, which was approximately 2 cm proximal to the distal crease of the wrist. Stimulation intensity occurred at motor threshold of the abductor pollicis brevis (APB) muscle, being the lowest intensity at which a 1 cm visible thumb twitch occurred. The noted motor response occurs due to the stimulation of the median nerve, which is a mixed nerve. This will ensure that the 1a afferents are stimulated, which is a fundamental part of eliciting the short-latency SEP peaks, as a result of their cortical projections (Gandevia et al., 1984). The anode of the stimulating electrodes is placed proximal to the wrist, and the cathode is distal. Stimuli are sent via a Digitimer Stimulator (Digitimer DS7A constant current, Welwyn Garden City, UK). These stimulations were delivered as square pulses, 200 μs in duration, at a constant frequency via Ag/AgCl EMG conductive surface electrodes (Meditrace™ 130, Kendall, Mansfield, MA, USA). Stimulations were delivered for 1000 sweeps, allowing for clear averages of SEP peaks. Stimulations occurred prior to and immediately after each of the novel motor learning paradigms occurred (MTT and FMT).

Peripheral SEP peaks, including the N9, were recorded over the ipsilateral brachial plexus, or Erb’s point (Rossi et al., 2003), using Signal4 software (Version 4.08, Cambridge Electronic Design, Cambridge, UK). This electrode was referenced to the ipsilateral earlobe using electrode paste and an ear clip (Rossi et al., 2003). Based on the IFCN guidelines, the N9 SEP peak had to remain stable (± 20%) between pre and post measures for each participant in order for their data to be included in the rest of the analyses (Nuwer et al., 1994).

7.4.3.2 EEG Collection Parameters

A Waveguard™ 64-electrode EEG cap (ANT Neuro, Hengelo, The Netherlands) was utilized in order to collect cortical electrical activity. The Waveguard™ cap was connected to the TMSi REFA-8 amplifier (TMSi, Oldenzaal, The Netherlands) with 64 EEG channels, four bipolar channels, and four auxiliary channels. Data was collected through Advanced Source Analysis Lab™ (ANT Neuro) software, and was collected at a sampling frequency of 2048 Hz. Each electrode had an impedance below 10 kΩ.

7.4.3.3 Paradigm(s)

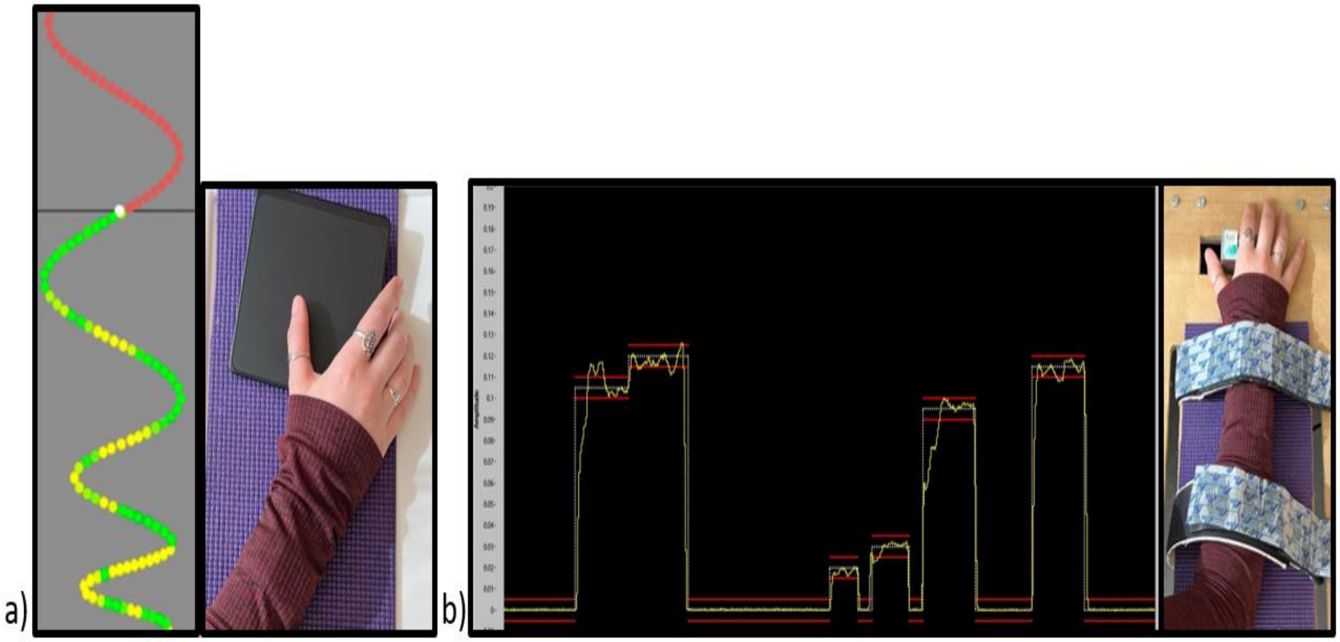


Figure 16 - Depiction of each motor paradigm. ***a)*** *visuomotor tracing task (MTT) and* ***b)*** *force-matching task (FMT). Each task was performed with the right hand and thumb, while real-time visual feedback was provided to the participant.*

7.4.3.3.1 Novel Visuomotor Task Parameters

The novel visuomotor tracing task was delivered via a custom Leap Motor software tool (Leap Motion, Inc., San Francisco, CA, USA), which was launched via a Unity™ gaming software. This paradigm consisted of sinusoidal waveform patterns, with four unique traces that varied in both frequency and intensity, thus allowing for variability in how difficult each trace was. This variation allows for an unpredictable task, potentially allowing for learning to occur (Andrew et al., 2015a). Traces were presented in a pseudo-randomized order, to ensure there were not any order effects present, affecting learning processes (Holland et al., 2017). The waveforms were a continuous stream of coloured dots that moved vertically down the computer monitor. The MTT paradigm can be seen in figure 16a. A red dot indicated that particular dot had not been traced yet, green indicating a perfect match, and variations of yellow-green indicating an imperfect match. To trace this waveform, thumb abduction and adduction was necessary, and performed on an external wireless touchpad (Logitech, Inc, Fremont, CA, USA). This task was completed in phases of pre-acquisition (4-blocks), acquisition (12-blocks), and post-acquisition (4-blocks), similar to that of the FMT behavioural paradigm. SEPs were collected prior to and immediately after participants completed this novel motor paradigm.

7.4.3.3.2 Novel FMT Parameters

Participants completed the novel FMT in several blocks, including pre-acquisition (4-blocks), acquisition (12 blocks), and post-acquisition (4-blocks). A block is defined as a group of trials, and each trial consisted of 3-5 traces. This task required force-modulation of their right thumb via adduction, allowing for them to trace a waveform on the screen. This can be seen in Figure 16b. The waveform varied in force, which was based on their maximal voluntary contraction (MVC) that was collected prior to the start of the learning paradigm. The MVC was an average of three trials, and was based on their abductor pollicis brevis (APB) muscle. The traces were delivered via a computer monitor that was placed directly in front of the participant, and the force-transducer was attached to a height adjustable table.

The task was delivered using LabVIEW custom programming (National Instruments, Austin, TX, USA). The force transducer utilized was calibrated with a 50 kg load cell. Each trace varied from 2 – 12 % of each individuals APB MVC. The intended trace was a series of white dots, and participants saw their force output on the computer monitor via a yellow line. Two red bars were placed on each side of the trace (white line), and these were placed 0.5% ± the white line, acting as a guide or boundary for participants to aim to stay within. While completing the behavioural paradigm, participants hand was pronated with their thumb resting against the transducer. SEPs were collected immediately prior to and after completion of this novel FMT paradigm.

7.4.3.4 Data Processing and Statistical Analysis

7.4.3.4.1 EEG/SEPs

EEG data was processed offline, using ANT 4.10.1 software, in order to remove artifacts, such as those from blinking, from the EEG signal. A band-pass filter with a low cut-off of 0.2 Hz and a high cut-off of 1000 Hz, and a slope of 24 dB/octave, was used. This process was done to each individual data set. Each EEG data set was then averaged into epochs starting from -10 ms and to 200 ms, making for a total epoch duration of 210 ms. This allows for the assessment of all short latency SEP peaks. Each participant’s data had two averages, one from the “pre” or baseline stimulation prior to the motor paradigm, and one from the “post” stimulation measures that occurred directly after completion of the motor paradigm.

7.4.3.4.2 Source Localization – sLORETA Analysis

Source localization was performed using sLORETA software (Fuchs et al., 2002; Jurcak et al., 2007; Pascual-Marqui, 2002). sLORETA software is a linear inverse algorithm and works as a method to solve the inverse problem, and is done so based upon the assumption of synchronous and simultaneous activation of neighbouring neurons, without a localization bias (Pascual-Marqui, 2002; Pascual-Marqui et al., 1994; Sekihara et al., 2005). This program has been validated for its accuracy, and was done so using both EEG and fMRI data (Mulert et al., 2004), indicating that the estimated sources of neural activity found using sLORETA are reliable. The template cortical grey matter is made up of 6239 voxels, with a spatial resolution of 5 mm. Voxel-wise randomization tests with 5000 permutations based on statistical nonparametric mapping (SnPM) were also performed. This randomization corrects for multiple comparisons, and provides the highest possible statistical power (Nichols & Holmes, 2002). The standardized current density at each voxel is calculated based upon the head model and electrode coordinates of the MNI average MRI brain-map (MNI-152).

This analysis was done in the time-domain, and was performed for the following comparisons:

1) Between groups (ADHD vs. control) at both baseline and post measures. Comparisons were done for both the MTT and FMT.
    a. Baseline ADHD vs. baseline control, to assess potential group differences at baseline measures.

    b. Post ADHD vs. post control, assessing group differences in source activity after the acquisition of the motor paradigm.

2) Within groups (pre-measures vs. post-measures) for both the ADHD and control group. Similarly, comparisons were done for both tasks, the MTT and FMT. This comparison was performed to assess whether locations of source activity differed within each group after acquisition of either of the motor paradigms.
    a. ADHD baseline vs. ADHD post
    b. Control baseline vs. control post
3) Finally, comparing between tasks, to assess whether somatosensory neural processing differed significantly between the two task conditions (MTT vs. FMT), discerning neural sources activated in response to visuomotor vs. force-matching demands of each task, respectively.
    a. ADHD
        i. Baseline MTT vs. baseline FMT
        ii. Post MTT vs. post FMT
    b. Control
        i. Baseline MTT vs. baseline FMT
        ii. Post MTT vs. post FMT

7.4.3.4.3 Time-Domain Statistical Analysis

Statistical significance for all tests was set to $p = 0.05$. All statistical tests were done within sLORETA's statistical tool in the time-domain (Navid et al., 2019; Pascual-Marqui, 2002). Statistical tests in sLORETA were performed using an independent (between group) and paired (within group) two-tailed Student's t-test, depending on the comparison being performed.

First, this converts all collected EEG data into t-values for each time frame. This process was completed on 430 time frames, as the epoch was 210 ms at a sampling frequency of 2048 Hz. The software provides the two-tailed t-value threshold, thus, providing t-critical. The SnPM adjusted for multiple comparisons by utilizing 5000 randomized permutations (Nichols & Holmes, 2002). Once t-critical threshold is established, the t-value output is assessed and if a t-value exceeds t-critical the sLORETA software will then perform a computation that localizes the neural location where the difference in activity occurred. In conjunction with this, the software provides the statistical significance (*p*-value) associated with the difference. Thus, illustrating whether the differences noted were statistically significant, or not.

7.5 Results

ADHD Pre vs ADHD Post, FMT Analysis: Results indicated that those with ADHD had increased neural activity at post SEP measures (or reduced at baseline/pre), after performing the novel FMT, when compared to their baseline SEP measures. Significantly greater activity was present in BA 31, precuneus, parietal lobe (MNI coordinates: X = -5, Y = -75, Z = 20; $p < 0.05$). This increased activity in BA 31 occurred at approximately 156 ms post median nerve stimulation. Figure 17 depicts the activity difference localized to BA 31 between pre and post conditions in those with ADHD.

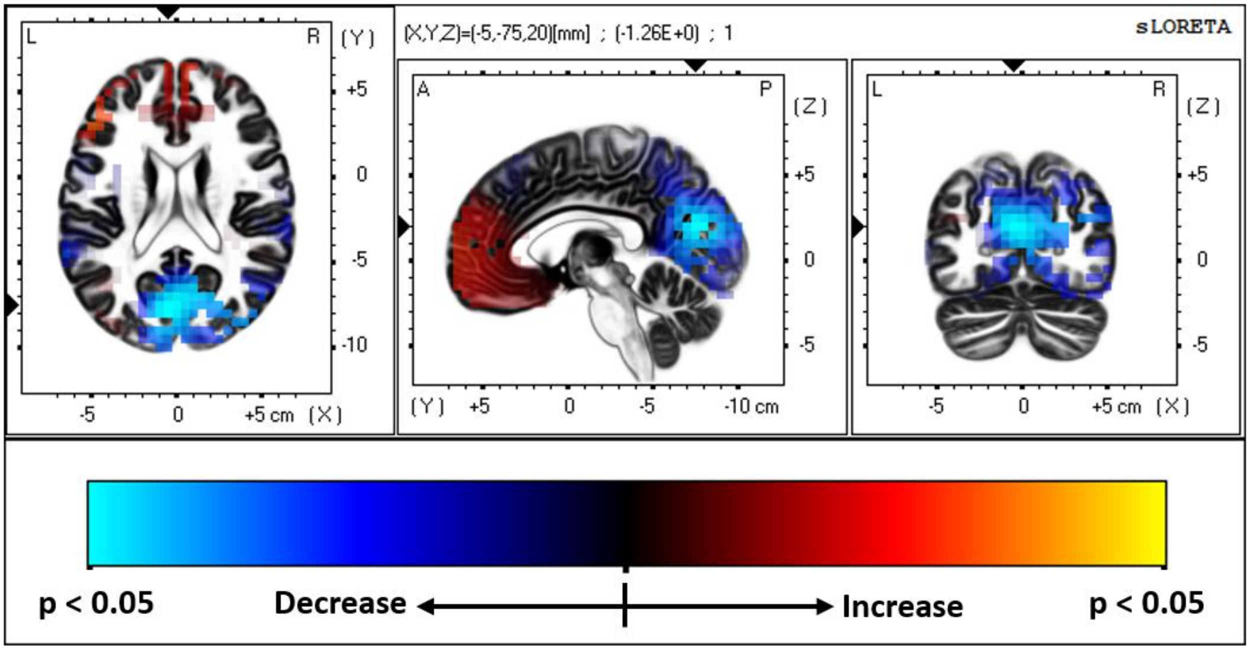


Figure 17 - sLORETA image, depicting area of neural activity where the greatest difference occurred between pre and post conditions in those with ADHD in the FMT condition ($p < 0.05$). Images from left to right include a transverse, sagittal, and coronal cross-sectional area. Abbreviations: ADHD – Attention-Deficit/Hyperactivity Disorder; sLORETA - standardized low-resolution brain electromagnetic tomography.

All other comparisons outlined in the methods: All other statistical tests, including within and between groups for both the MTT and FMT, yielded non-significant differences ($p > 0.05$).

7.6 Discussion

To the best of our knowledge, this is the first work to assess the source location of neural generators pertaining to somatosensory processing and motor learning in young adults with ADHD. The novel results from the current work indicate that when performing a novel motor paradigm dependent on force modulation and proprioception, those in the ADHD group have greater activation in BA 31, precuneus, parietal lobe, at post measures after acquiring this novel motor skill. This difference in neural activation was present at a latency of 156 ms post median nerve stimulation. When taking into consideration both the region of neural activation as well as the latency, this provides invaluable insight into the neural processing in those with ADHD when performing a motor paradigm that is highly contingent on proprioceptive feedback for success. We did not find differences in source activity with any of the other comparisons, suggesting that the source of the neural activity remained relatively consistent in controls and during the visuomotor task. The lack of differences in sources of neural activity in the other comparisons may be a result of similar neural sources being present between all compared groups, which may have been in contrast to the profound differences present in those with ADHD when completing the FMT at baseline when compared to post-acquisition. Postulated mechanisms for such differences after acquiring the novel FMT in those with ADHD, including possible explanations, will be discussed further below. Therefore, the difference found reflects that of unique processing in adults with ADHD after performing a motor task dependent on force-modulation.

7.6.1 Brodmann Area 31

BA 31, which is also commonly referred to as dorsal posterior cingulate area 31, is located at the medial border of the parietal lobe, between the cingulate and splenial sulci, and includes both posterior cingulate and precuneate cortices (Cavanna & Trimble, 2006; Hoesen, Morecraft, & Vogt, 1993). The neural generator within the current study was located specifically to BA31 and the precuneus. The posterior cingulate cortex has a major role in the default mode network (DMN) (Leech, Braga, & Sharp, 2012). The DMN describes a neural network including a number of brain regions, which exhibit deactivation or a reduction in activity during demanding cognitive tasks (Raichle et al., 2001). Broadly speaking, the DMN encompasses several brain regions, including the ventral medial prefrontal cortex, posterior cingulate, inferior parietal lobe, lateral temporal cortex, dorsal medial prefrontal cortex, and the hippocampus (Buckner, Andrews-Hanna, & Schacter, 2008). Previous work suggests altered connectivity between the precuneus and the anterior cingulate and DMN regions, such as the ventromedial prefrontal cortex, in adult ADHD (Castellanos et al., 2008). The reduction in neural activation during attentionally demanding cognitive tasks in the DMN is explained as this region being reflective of memory recollection or daydreaming (Buckner et al., 2008). However, there are competing hypotheses for the role of the DMN during cognitive tasks, one of which suggests an active role in working memory (Sormaz et al., 2018). When an individual performs a task that requires focused attention, such as goal directed behavioural tasks, generally there will be an attenuation of activity within the posterior cingulate cortex, which is reflective of a reduction in resources being allocated to this neural area during such tasks (Raichle et al., 2001). This is termed task induced deactivation, which is most prominent along the midline of the brain (Buckner et al., 2008). The activity difference in the current study was specific to the posterior cingulate cortex (BA 31) and precuneus. In the current study, the cortical structures underpinning this network exhibited an increase in activation in those with ADHD, after the performance of a novel FMT motor paradigm. Interestingly, the DMN is altered in those with autism spectrum disorder (ASD), where they fail to exhibit this deactivation (Kennedy, Redcay, & Courchesne, 2006). Another hypothesis for the role of the DMN during cognitive tasks, is explained as an exploratory state, when an individual has low-levels of attention dedicated to monitoring the external environment for unexpected events in an unfocused manner, as a form of information gathering (Buckner et al., 2008; Hahn, Ross, & Stein, 2007; Shulman et al.). This is in contrast to a task that requires a high level of attention to a specific target, such as visual acuity to a stimulus.

The increased activity at BA 31, parietal lobe, in those with ADHD after performing the novel FMT provides important insight into the neural function in response to this task. The DMN is commonly described as being altered in those with ADHD (Broyd et al., 2009; Castellanos et al., 2008; Sun et al., 2012; Tian et al., 2006; Uddin, Clare Kelly, Biswal, Xavier Castellanos, & Milham, 2009), and additionally altered precuneus connectivity within the DMN is associated with ADHD (Uddin et al., 2008). ADHD is correlated with connectivity alterations to the DMN, and this is likely due to alterations within fronto-striatal-cerebellar networks (Broyd et al., 2009). The increased activity within the posterior cingulate cortex and precuneus in the current study, may reflect a reduction in attention after the motor learning paradigm. In other words, it is possible that those in the ADHD group experienced difficulty focusing on the FMT, resulting in an attenuation of attentional resources at post measures. This may be related to the attenuated activity within BA 2, right-hemispheric parietal lobe, found in study one of this dissertation. BA 2 has a primary role in the processing of pressure, joint position sense, and complex touch (Sur, 1980), thus informing proprioception. Furthermore, the right-hemispheric parietal lobe reflects neural processing associated with spatial attention (Chan et al., 2009; Corbetta et al., 1993; Gitelman et al., 1999; Nobre et al., 1997; Vance et al., 2007). Therefore, the results from study 1, potentially reflective of attenuated neural processing of proprioceptive and spatial attention, may reflect the increased activity within the DMN of the current study. If this is the case, there are a number of potential reasons that this may have occurred in this particular group. One explanation for this increased activity in the DMN, which is the opposite of what is generally expected during a goal directed movement, where typically there would be an expected task-related deactivation, may be reflective of those in the ADHD group having a difficult time maintaining focus on the task. Inattention to the task at hand may be a result of the task being deemed “too boring” for this particular population, or possibly that it was difficult for them due to noted impairments with force matching and proprioception, thus resulting in a general disinterest for them. Of potential relevance to this, is that upon session completion, some participants in the ADHD group stated that they found the novel FMT to be “boring”. However, this is anecdotal, and in the future, incorporating a qualitative measure of self-perceived attention may aid in elucidating this potential relationship. Another interesting, yet important variable in the current finding, is the latency at which this difference was pronounced, as it aligns with a mid-late latency SEP peak, opposed to short-latency SEPs which were the objective of the previous studies two and three of this dissertation

7.6.2 Latency

The latency at which the difference in activation was found in BA 31 is in line with mid-late latency SEP peaks, as opposed to the latency of short-latency SEP peaks. Specifically, the latency of 156 ms may align with the somatosensory N140 peak. The N140 is often observable between 150 – 210 ms (Espenhahn et al., 2021). The N140 SEP peak is typically recorded over central or parietal brain regions, with the greatest amplitude over the midline or vertex electrodes, and activity is correlated with selective attention (Desmedt & Robertson, 1977; Hada, 2006). The N140 peak is commonly observable via median nerve stimulation (Hada, 2006). There is limited information specifying the neural generators underlying this activity (Desmedt & Tomberg, 1989; Hada, 2006). However, primary sensory area, the secondary sensory area, the prefrontal area, and the supplemental motor area are all cortical regions thought to be involved in the N140 (Desmedt & Tomberg, 1989). Spatial attentional modulation affects the amplitude of the N140 (Giabbiconi, Dancer, Zopf, Gruber, & Müller, 2004; Michie, 1984). Additionally, the N140 is thought to reflect the processing of tactile information (Espenhahn et al., 2021), and is also associated with cognitive functions, such as those related to selective attention and conscious stimulus perception (Forschack, Nierhaus, Müller, & Villringer, 2020; Schubert, Blankenburg, Lemm, Villringer, & Curio, 2006; Ueno, Hada, Shimizu, & Yamada, 2018). Those with adult ADHD exhibit reductions in right hemispheric superior longitudinal fascicle II (SLF II) connectivity, and the SLF II is related to visual spatial attention, providing input to the prefrontal cortex from parietal regions (Makris et al., 2008). Alterations to the N140 in those with autism, are thought to be related to excitation-inhibition balance and circuit hyperexcitability (Espenhahn et al., 2021). Therefore, the results from the current work suggesting increased activity post FMT in those with ADHD, may be a result of more resources being allocated for spatial attention or awareness. It is postulated that the N140 is related to motor execution and neural activity related to inhibition processing (Josiassen, Shagass, Roemer, Ercegovac, & Straumanis, 1982; Kida & Kakigi, 2008; Nakajima & Imamura, 2000; Nakata, Sakamoto, Honda, & Kakigi, 2015; Nakata, Sakamoto, & Kakigi, 2012). This can be seen as an increased amplitude response during NoGo trials and diminished in response to Go trials (Nakata et al., 2015). Although not directly related to somatosensory input, previous work utilizing visual afferents, noted that the visual N140 was increased in those with ADHD (Verbanck & Cheron, 2018). This increased activity was localized to BA 30, right posterior cingulate, in adults with ADHD , potentially due to increased attentional and cognitive demands (Verbanck & Cheron, 2018). Therefore, the activation within neural networks surrounding the latency of the N140 may be important in those with ADHD.

The increased activity within BA 31 at a latency that coincides with the somatosensory N140 after completing a novel motor task dependent on force-modulation within the current study, may suggest an increase in cognitive demands allocated to focus on body schema and proprioception associated with the limb and digit completing the task (i.e. right thumb) in those with ADHD. This may relate to self-perceived difficulties with the task, as if participants found the FMT difficult, they may have required greater focus during the motor acquisition paradigm. One way to account for this in the future, may incorporate asking participants to rate their mental state/attention before, during, and after performing a task. This would allow for a qualitative assessment of attentional levels at the different stages of the task, and then could aid in the interpretation of the neurophysiological results.

7.6.3 Limitations

Potential limitations include that participants were limited to young university-aged adults with ADHD, and therefore it is unknown whether they are generalizable to ADHD in childhood or older adults. Additionally, although sLORETA in conjunction with high-density EEG is a valid and cost-efficient form of neural assessment in the future, incorporating neurological techniques, such as functional MRI (fMRI), for each participant would further enhance these findings. The sample size for both the FMT and MTT protocols were modest, and although all samples met the sample size goal defined upon study inception, future work may benefit from increased sample sizes in order to ensure that possible additional differences are not missed due to a type II error.

7.7 Conclusions

This work demonstrated that young adults with ADHD exhibit increased activation within BA 31 after performing a motor learning paradigm dependent on force modulation, and this increased activity was localized to the precuneus, parietal lobe. The increased activity in BA 31 may reflect up-regulation in the DMN at post measures, in addition to alterations to selective spatial attention after such motor tasks. These findings are specific to motor tasks dependent on force, and were absent when assessing changes after the visuomotor task. Furthermore. these findings are inline with the neurophysiological characteristics associated with ADHD, such as unique functioning of the DMN and precuneus, while adding important contextual insight into the role that these networks play in motor learning in adult ADHD. Overall, greater neural activity has a focal point at BA 31 after force-modulation motor tasks in young adults with ADHD.

Chapter 8: General Discussion and Concluding Remarks

8.1 Conclusions

The overall objective of this thesis was to assess sensorimotor integration (SMI) and motor learning in young adults with Attention-Deficit/Hyperactivity Disorder (ADHD). ADHD is associated with a number of behavioural and neurophysiological characteristics that may affect the acquisition and performance of novel motor skills. Limited literature currently exists assessing these processes in ADHD during adulthood. The results from this work provide evidence of altered somatosensory processing in those with ADHD, providing important insight into the role that various neural structures play when adopting motor skills that require varying levels of proprioceptive and visuomotor sensory input.

Study 1

The first study yielded results suggesting that when presented with audiovisual multisensory input those with ADHD exhibit a different neural response than do neurotypical controls. Specifically, source localization techniques localized BA 2, right-hemispheric parietal lobe, as having attenuated activity in those with ADHD when compared to control adults. The attenuation of neural activity in this specific location, suggests potential alterations to attentional resources and sensory processing related to pressure and joint position sense. For multisensory inputs to be optimally processed as such, it is necessary to have attentional resources allocated to each of the constituent sensory components (Talsma et al., 2007). For instance, acknowledging both the auditory and visual components of an audiovisual input. The presence of attenuated activity in the ADHD group in response to the multisensory input, and neither unisensory input, may suggest impairments in multisensory processing in those with ADHD, which may be related to alterations in neural characteristics, including structural and functional differences. Therefore, the first study provides invaluable insight into the processing of multisensory stimuli in those with ADHD.

Study 2

The second study sought to assess behavioural and neural characteristics of motor learning and SMI in those with ADHD. This work provides evidence to suggest that ADHD is associated with alterations to activity within neural networks when performing a novel visuomotor paradigm. Specifically, the N18 and N30 somatosensory evoked potentials (SEPs) differed between groups, suggesting that ADHD is associated with alterations to olivary-cerebellar-M1 processing and SMI when acquiring novel motor skills. Behavioural markers of learning suggest that both groups learned the visuomotor task, as performance improvements were evident at post measures and retained at retention. Motor learning and the neuroplasticity associated with the related neural processes is dependent on and modulated by attentional resources (Hazeltine et al., 1997; McGaughy, Dalley, Morrison, Everitt, & Robbins, 2002; Rosenkranz & Rothwell, 2004; Stefan et al., 2004). As ADHD is characterized by attentional impairments, this likely has a fundamental effect on the altered motor control and performance that is often associated with this disorder. The current work suggests that alterations in neural networks, including those related to cerebellar inhibition and prefrontal processing, may be associated with the difficulties in motor learning often present in those with ADHD.

Study 3

The third study sought to address motor learning outcomes in those with ADHD when performing a novel motor paradigm that relies on force-modulation and proprioceptive afferent feedback. In addition to the difficulties in motor control and performance associated with ADHD, there are noted impairments to activities dependent on force and proprioception (Alba et al., 2016; Goulardins et al., 2013; Iwanaga et al., 2006; Jung et al., 2014; Neely et al., 2016; Neely et al., 2017; Sanz-Cervera et al., 2017), with very limited research addressing how this may affect motor learning. Results yielded indicated differential changes in the N18 SEP peak in those with ADHD when compared to neurotypical controls, suggesting a reduction in inhibition processes relating to olivary-cerebellar-M1 processing. Previous work has suggested that when a task is not learned well, there will be an increase in cerebellar processing (Andrew et al., 2018; Dancey et al., 2016; Doyon et al., 2002a; Floyer-Lea & Matthews, 2005; Manzoni, 2007). Therefore, the reduction in the N18 in those with ADHD, likely reflective of a reduction in olivary-cerebellar-M1 inhibition, may be associated with difficulties acquiring the motor paradigm dependent on proprioception via force input from cutaneous receptors of the right thumb.

Study 4

For the fourth and final study, the objective was to address the presence of differing neural generators in response to somatosensory stimuli, after acquiring motor tasks dependent on both visuomotor input and proprioceptive input. This comparison was done in those with ADHD and neurotypical controls. Results yielded suggest that performing a motor task dependent on force-modulation and proprioception results in increased activity within BA 31 at post-measures in those with ADHD. This increased activity may reflect increased activation within the default mode network (DMN) and attentional alterations as a result of performing the novel force-matching task (FMT) in the ADHD group. This pattern of activity is likely dependent on the sensory demands of the FMT in those with ADHD, as similar activity changes were not present for the visuomotor task or in neurotypical controls. This finding is inline with the changes to the N18 from study three, suggestive of difficulties associated with the proprioceptive and force-demands of the FMT. These findings provide further insight into the neural characteristics associated with motor learning and SMI in young adults with ADHD, suggesting potential neural activity alterations dependent on the sensory demands of the task.

8.2 Limitations

The primary objective of this thesis was to assess sensory processing and motor learning correlates of ADHD in adulthood. Limited literature has addressed adult ADHD, therefore it was important to address this due to the impact of ADHD symptomology on day-to-day function. However, the sample size consisted of young, university-aged adults with ADHD. Thus, limiting the generalizability of the findings to childhood or older adults with ADHD. Furthermore, sample sizes were moderate, and even though each study had a main finding it is possible that other findings were missed as a result of a type II error. All attempts were made to reach or exceed the pre-defined sample size goal, however provincial and federal restrictions related to COVID-19 made data collection sessions difficult and even impossible for periods of time, thus resulting in difficulties increasing the sample sizes in some instances. In the future, having an increased sample size will ensure that possible additional differences are not missed due to a type II error. Finally, for experiments one and four, sLORETA analysis techniques in conjunction with high-density EEG offer a validated and cost-efficient form of neural assessment, and provided an essential contribution to the methodology of this thesis. However, in the future, incorporating neurological techniques, such as functional MRI (fMRI), for each participant would further enhance these findings and allow for enhanced spatial acuity associated with this modality.

8.3 Future directions

In order to enhance our understanding of the neural correlates related to sensory processing and motor learning, a potential future direction for subsequent studies would entail incorporating individual MRI or fMRI to elucidate differences in neural structure and function in neural regions involved in processes related to motor learning and performance in ADHD. While the current dissertation provides evidence that locations of neural activity do differ in those with ADHD when compared to neurotypical controls, and additionally that the foci of neural activity within those with ADHD changes after acquiring novel motor skills dependent on force-modulation, subsequent research would benefit from modalities such as fMRI. Such assessment modalities would allow for high-level spatial accuracy to assess neural correlates related to sensorimotor circuitry in this cohort, complementing the high-level of temporal accuracy that high-density electroencephalography (EEG) offers. fMRI has been used extensively to study ADHD (Cortese et al., 2012), therefore lending to its application in the assessment of sensorimotor control.

Additionally, recent literature has elucidated the potential role of recently discovered neural biomarkers that could transform how ADHD is understood, diagnosed, and subsequently treated (Scassellati, Bonvicini, Faraone, & Gennarelli, 2012). ADHD is highly heterogenous and diagnoses are often accompanied by comorbidity of other disorders, such as anxiety or oppositional disorders, for example, further complicating diagnostic and treatment processes. Current diagnostic criteria are heavily reliant on subjective measures and recall, which may be prone to certain biases and therefore bringing into question their reliability. Research has consistently established unique neural characteristics in those with ADHD, including structural and functional alterations to circuitry relating to the prefrontal cortex, basal ganglia, and cerebellum (Curatolo, D'Agati, & Moavero, 2010), with prominent alterations present in neural regions associated with attention, inhibitory activity, and executive function (Curatolo, 2005; Suskauer et al., 2008). Recent discoveries related to neural markers of ADHD include the use of brain perfusion single-photon emission computed tomography (SPECT) imaging, where results yielded 100% specificity and 97% reliability when discerning adult ADHD from neurotypical adults (Amen, Henderson, & Newberg, 2021). Specifically, possible biomarkers were located within orbitofrontal cortices, anterior cingulate gyri, prefrontal cortices, basal ganglia, temporal lobes, and cerebellar regions (Amen et al., 2021). Moving forward, further studies are needed to clearly depict the reliability and validity of such measures, including their relevance and feasibility in a clinical setting.

Moving forward, a secondary analysis of SEP peaks to assess characteristics associated with mid-late latency SEP peaks in ADHD may be beneficial, as the current studies in this dissertation assessed short-latency SEPs. Currently, the application of mid-latency SEP peaks are less commonly assessed and their neural generators and physiological relevance are not as well understood (Kany & Treede, 1997), when compared to short-latency SEPs. In the future, supplementing the analysis via assessing mid and late latency SEP peaks in ADHD may be invaluable, including latencies and regions associated with the somatosensory N140 for example, which has the potential to provide an assessment of selective attention and conscious stimulus perception. Finally, adapting a variation of the FMT that lacks visual feedback in the form of knowledge of results (KR) would allow for an investigation with a behavioural context as to how those with ADHD rely on visual feedback to monitor error during the performance and acquisition of motor skills. Little is known on the role of integrating performance feedback to modulate motor behaviour in adult ADHD. Including such a transfer test would elucidate the role of visual feedback in adult ADHD when acquiring novel motor commands, as visual perception is thought to inform proprioceptive and vestibular function (Jung et al., 2014), both of which are impacted in ADHD.

8.4 Conclusion and Significance

The results from the four studies that compose this dissertation assist with our understanding of how Attention-Deficit/Hyperactivity Disorder (ADHD) in adulthood affects the neural and behavioural correlates associated with motor learning and sensory integration. Each study elucidated the presence of unique neural attributes associated with ADHD when compared to neurotypical controls, enhancing our understanding of sensory processes and the underlying neural structures and function as they may relate to motor performance in this population. Results suggested that those with ADHD experience differential neural processing, with SEP findings suggestive of alterations to olivary-cerebellar-M1 and sensorimotor pathways, and these differences were dependent on the contextual demands of a given task. For instance, differing responses, that were potentially reflective of olivary-cerebellar-M1 inhibition, were present if the motor paradigm was more heavily dependent on force modulation versus a task that did not require force input to the same extent. This work has real-world implications and will provide a basis for promoting barrier-free function in sensory rich environments for adults with ADHD via a comprehension of neural function, such as when being physically active or when learning new skills to participate in sport, both of which require a diverse array of sensory integration and consequential motor output. Understanding the sensory and motor processes that occur in such environments can provide a pivotal awareness of how to effectively adapt environments to promote optimal function in the future.

Additionally, the studies provide evidence of neural correlates that differ in ADHD, which could may have potential in identifying whether there are different ADHD subtypes, which may require different interventions in work and/or educational settings. As many jobs and educational settings become more focused on computer-based tasks, those with adult ADHD may be more impacted. Having a better understanding of the differences in neural processing could help to better tailor technology solutions so that those with ADHD have equity of opportunity to learn and work in ways that allow for their neural differences.

Appendix

A.1

Adult ADHD Self-Report Scale (ASRS-v1.1) Symptom Checklist

Instructions

from WHO Composite International Diagnostic Interview

The questions on the back page are designed to stimulate dialogue between you and your patients and to help confirm if they may be suffering from the symptoms of attention-deficit/hyperactivity disorder (ADHD).

Description: The Symptom Checklist is an instrument consisting of the eighteen DSM-IV-TR criteria. Six of the eighteen questions were found to be the most predictive of symptoms consistent with ADHD. These six questions are the basis for the ASRS v1.1 Screener and are also Part A of the Symptom Checklist. Part B of the Symptom Checklist contains the remaining twelve questions.

Instructions:

Symptoms

1. Ask the patient to complete both Part A and Part B of the Symptom Checklist by marking an X in the box that most closely represents the frequency of occurrence of each of the symptoms.
2. Score Part A. If four or more marks appear in the darkly shaded boxes within Part A then the patient has symptoms highly consistent with ADHD in adults and further investigation is warranted.
3. The frequency scores on Part B provide additional cues and can serve as further probes into the patient's symptoms. Pay particular attention to marks appearing in the dark shaded boxes. The frequency-based response is more sensitive with certain questions. No total score or diagnostic likelihood is utilized for the twelve questions. It has been found that the six questions in Part A are the most predictive of the disorder and are best for use as a screening instrument.

Impairments

1. Review the entire Symptom Checklist with your patients and evaluate the level of impairment associated with the symptom.
2. Consider work/school, social and family settings.
3. Symptom frequency is often associated with symptom severity, therefore the Symptom Checklist may also aid in the assessment of impairments. If your patients have frequent symptoms, you may want to ask them to describe how these problems have affected the ability to work, take care of things at home, or get along with other people such as their spouse/significant other.

History

1. Assess the presence of these symptoms or similar symptoms in childhood. Adults who have ADHD need not have been formally diagnosed in childhood. In evaluating a patient's history, look for evidence of early-appearing and long-standing problems with attention or self-control. Some significant symptoms should have been present in childhood, but full symptomology is not necessary.

If you have been diagnosed with ADHD/ADD, please complete the following 4 questions:

1. Have you been diagnosed with ADHD/ADD? YES ○ NO ○
2. At what age were you diagnosed? ____

3. Were you diagnosed with ADHD or ADD? ADHD ○ ADD ○ UNKNOWN ○
4. Do you normally take medication for ADHD? YES ○ NO ○

If yes, please list medication: ____

If yes, did you take your medication prior to participating today? YES ○ NO ○

	Never (1)	Rarely (2)	Sometimes (3)	Often (4)	Very Often (5)
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 A Total: ☐
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 directly to you?			▨	▨	▨
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?				▨	▨

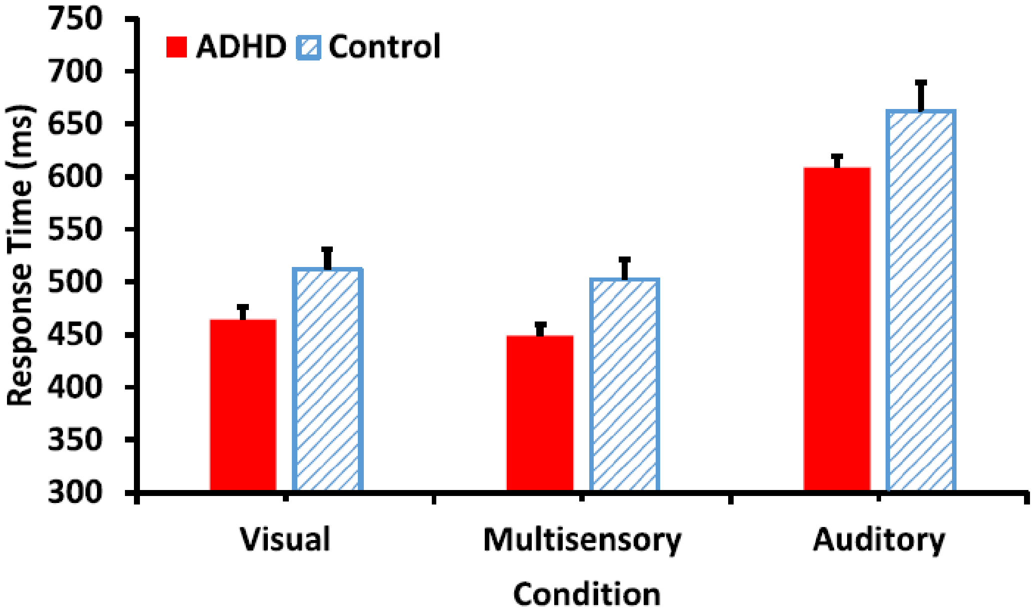
16. When you’re in a conversation, how often do you find yourself finishing the sentences of people you are talking to, before they can finish them themselves?			▨	▨	▨
17. How often do you have difficulty waiting your turn in situations when turn taking is required?				▨	▨
18. How often do you interrupt others when they are busy?			▨	▨	▨
Part B Total: ☐					

1. Do you read slowly? ☐
2. Did you have trouble learning how to read when you were in school? ☐
3. Do you often have to read something two or three times before it makes sense? ☐
4. Are you uncomfortable reading out loud? ☐
5. Do you omit, transpose, or add letters when you are reading or writing? ☐
6. Do you find you still have spelling mistakes in your writing even after *spell check*? ☐
7. Do you find it difficult to pronounce uncommon multi-syllable words when you are reading? ☐
8. Do you choose to read magazines or short articles rather than longer books and novels? ☐
9. When in school, did you find it extremely difficult to learn a foreign language? ☐
10. Do you avoid work projects or courses that require extensive reading? ☐

Total: ________

A.2

Response time and accuracy data from McCracken et al. (2020), as relevant to Study 1 from this dissertation.



The response times for each stimulus condition (visual, multisensory, and auditory) and each group (ADHD and control). Values are mean ± standard deviation and are presented in units of ms.

Accuracy (0-1.0)	**Visual**	**Multisensory**	**Auditory**
ADHD	0.9425 ± 0.0302	0.9551 ± 0.0257	0.9723 ± 0.0255
Control	0.9649 ± 0.0243	0.9735 ± 0.0219	0.9759 ± 0.0202

The average accuracy for each group (ADHD and control) and stimulus condition (mean ± standard deviation), where a score of 1.00 would imply a perfect score.

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