

**Audiovisual Multisensory Integration in Young Adults with and without a Diagnosis of
Attention-Deficit/Hyperactivity Disorder**

by

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Abstract

Attention-Deficit/Hyperactivity Disorder (*ADHD*) is a neurodevelopmental disorder with behavioural and neurophysiological characteristics. Several cortical structures that are altered in *ADHD* are involved in the process of multisensory integration (*MSI*). *MSI* is a fundamental form of sensory processing involved in many everyday tasks. Therefore, it is important to know whether those with *ADHD* experience altered *MSI*. Two different paradigms were used to assess *MSI* in adults with a diagnosis of *ADHD*. First, a simple response time (*RT*) task was completed. Electroencephalography (*EEG*) analysis revealed that those with *ADHD* had *MSI* occur, while there were significant differences in brain activity between groups. Study two employed a two-alternative forced-choice discrimination task. Those with *ADHD* responded faster than controls. *EEG* analysis revealed that those with *ADHD* have enhanced *MSI*. Activity differences were found in brain regions that are structurally altered in those with *ADHD*, indicating that structural alterations in *ADHD* may promote sensory processing.

multisensory integration, *ADHD*, *EEG*, response time, audiovisual, two-alternative forced-choice discrimination

Statement of Originality

I hereby declare that, to the best of my knowledge, this thesis is my own original work unless otherwise stated throughout. This work has not been previously submitted as part of a degree to this or any other institution.

Certificate of Examination

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Abbreviations

Autism Spectrum Disorder (*ASD*)

Attention-Deficit/Hyperactivity Disorder (*ADHD*)

Central Nervous System (*CNS*)

Electroencephalography (*EEG*)

Event-related Potential (*ERP*)

Magnetic Resonance Imaging (*MRI*)

Multisensory Integration (*MSI*)

Response Time (*RT*)

Sensorimotor Integration (*SMI*)

Superior Colliculi (*SC*)

Introduction

How someone perceives the environment will have a profound effect on how they interact with the world. Some populations are more likely to experience altered sensory processing, or afferent input, when presented with varying sensory information such as the case with multisensory integration (*MSI*). For instance, various sensory processes change throughout development, and typically reach maturity by approximately 14 years old (Brandwein et al., 2011). Although this is the age when sensory maturation is typically reached, there are populations for which this may not be the case (Brandwein et al., 2015; Brandwein et al., 2013; Farid, Yelder, Holmes, Haavik, & Murphy, 2018). Certain populations have known sensory deficits, such as those with subclinical neck pain (*SCNP*) (Farid et al., 2018); however, there are some circumstances where this has yet to be investigated making it less clear whether certain special populations experience altered MSI. Adults with attention-deficit hyperactivity disorder (*ADHD*) are one population which may have altered sensory processing when in a multisensory environment. It is crucial to understand multisensory processing and MSI in adults with ADHD in order to more concisely comprehend how their nervous system functions in relation to the signs and symptoms of ADHD. This work can improve the comprehension of how the brain functions in response to various sensory paradigms and how this may be correlated to the behavioural responses that are elicited. This may have important future implication for diagnoses and supports available.

Multisensory Integration

We live in a stimulus-rich environment, therefore MSI plays a crucial role in how we perceive environments on a daily basis. For instance, when learning in a classroom, you are exposed to auditory stimuli from what the professor says, visual stimuli from the presentation

slides, and even tactile and proprioceptive stimuli; all of which are being received simultaneously in the form of afferent input. For two or more stimuli to be processed as a multisensory stimulus, the stimuli need to be presented at very similar onset latencies, close in space, and be semantically congruent (Driver & Spence, 2000; Laurienti, Kraft, Maldjian, Burdette, & Wallace, 2004). For instance, hearing a cat meow and seeing a cat are two semantically congruent stimuli; on the other hand, hearing a cat meow but seeing a dog are semantically incongruent. In order to effectively interpret and respond to your surroundings, your central nervous systems (*CNSs*) ability to do this is of the utmost importance (Brandwein et al., 2011).

The way that the nervous system processes and integrates afferent sensory input is crucial for forming meaningful connections between stimuli in order to form perceptions (Brandwein et al., 2011). This sensory processing may be in the form of sensorimotor integration (*SMI*), somatosensory processing, and *MSI*. *MSI* is a specific form of sensory processing that is integral to how an individual perceives and consequently reacts to the environment around them (Brandwein et al., 2011; Foxe et al., 2000). *MSI* describes how your nervous system integrates and processes simultaneously occurring stimuli which often originate from more than one sensory modality type (Paraskevopoulos & Herholz, 2013). There are several benefits to multisensory processing including faster and more accurate decision making and improved comprehension of certain tasks (Laurienti et al., 2004; Meredith, Nemitz, & Stein, 1987).

Simple response time (*RT*) and two-alternative forced-choice discrimination tasks require participants to respond to varying stimulus conditions and can be used to assess *MSI* (Brandwein et al., 2011; Farid et al., 2018). When multisensory stimuli are incorporated these tasks can be utilized to assess *MSI* and the resultant behavioural performance gains observed in different

populations (Laurienti et al., 2004). The utilization of a simple RT task provides data on a single variable of RT, while the utilization of a two-alternative forced-choice discrimination task adds a further level of complexity with a stimulus discrimination component to the task assessing accuracy (Brandwein et al., 2011; Farid et al., 2018). To investigate whether population differences in MSI are present these RT tasks can be employed individually or concurrently as a form of methodology to assess neurological activity.

As introduced above, a behavioural measure that can be indicative of enhanced or hindered multimodal processing is RT (Stevenson et al., 2014). Typically, in response to a multisensory stimulus that is presented in close spatial and temporal context, RT will be faster due to multisensory gain; in other words, when presented with a multimodal stimulus behavioural gains can occur such as shortened response latencies. Electroencephalography (*EEG*) and magnetic-resonance imaging (*MRI*) are two different techniques that can be utilized to quantify MSI from a neurological perspective (Stevenson et al., 2014). *EEG* and *MRI* allow for an inspection of the various brain regions and neural generators active in response to specific stimuli at specific latencies (Stevenson et al., 2014). More specifically, *EEG* allows for high temporal acuity, being that brain activity in response to sensory stimuli is observed with millisecond accuracy (Stevenson et al., 2014).

The way in which the nervous system processes sensory information will directly influence how people perceive and react to the environment around them (Brandwein et al., 2015; Molholm et al., 2002). For instance, if an individual experiences attenuated or non-existent afferent processing in response to auditory cues, this could hinder their ability to communicate when in a social setting (Brandwein et al., 2015; Foxe et al., 2013). The success with which these processes can be accomplished will be affected by the morphology and functionality of CNS

areas within the brain and spinal cord. There are several areas that are highly implicated in the processes of MSI, which occur at both the cortical and sub-cortical level. The superior colliculi (SC) is a sub-cortical structure that is directly involved in visually associated MSI; this being sensory processing in response to various visual afferents (Kandel, Schwartz, Jessell, Siegelbaum, & Hudspeth, 2000; Meredith et al., 1987). The SC's role in multisensory processing is likely due to its high density of multisensory neurons (Meredith et al., 1987). In conjunction, multiple cortical brain structures and regions are involved in MSI, such as the parietal region which plays a role in audiovisual multisensory processing, the intraparietal sulcus, superior temporal sulcus (STS), and frontal cortex (Brandwein et al., 2011; Paraskevopoulos & Herholz, 2013). Specific structural and functional brain changes have been associated with how certain subpopulations perceive their environment (Brandwein et al., 2015). Likewise, there are certain populations where altered cortical structures are prominent, which may imply altered MSI, but this has not yet been directly assessed. This is the case with adult ADHD.

Attention-Deficit/Hyperactivity Disorder

ADHD is a common neurodevelopmental disorder that is characterized by increased levels of behavioural inattention, impulsivity, and hyperactivity (Visser et al., 2014). The behavioural symptoms often result in difficulties in certain environments such as learning in a classroom. The onset of ADHD symptoms typically occur sometime during childhood, although the average age of diagnosis is 7 years old (Control & Prevention, 2014). Approximately 11% of all children have, or will receive, a diagnosis of ADHD (Visser et al., 2014). Although this disorder is quite common in childhood, it typically persists through development and is prominent in adults (Sadock, Sadock, & Ruiz, 2000). Approximately 50% of childhood cases will persist into adulthood (Sadock et al., 2000) meaning that 4.4% of adults would meet the

criteria indicating a diagnosis of ADHD (Kessler et al., 2005). There are significant sex-related differences in the prevalence of reported ADHD, as an ADHD diagnosis is much more common in men (5.5%) as compared to women (2%) (Amiri et al., 2014).

In order to receive a diagnosis of ADHD, a psychologist or neurologist is generally involved. The Diagnostic Statistical Manual (*DSM*)-VTM has specific criteria that are used to guide a diagnosis. These criteria are detailed and parsed into two different categories, inattention and hyperactivity (American Psychiatric & American Psychiatric Association, 2013). For an adult diagnosis to be achieved, five symptoms typically need to be present (American Psychiatric & American Psychiatric Association, 2013). These symptoms need to have been present for a period of 6 months or longer and are significant enough to impede an individual's ability to function normally in multiple settings (American Psychiatric & American Psychiatric Association, 2013). Given that ADHD can result in significant deficits in how individuals interact with the world and the associated inattention, it suggests that there is quite possibly altered sensory processes occurring, which makes this an important area for future scientific inquiry.

The clinical manifestations of ADHD also indicates that there is likely a spectrum of underlying brain structural changes (Castellanos et al., 2002; Duerden, Tannock, & Dockstader, 2012; Proal et al., 2011; Valera, Faraone, Murray, & Seidman, 2007). These alterations are functionally significant and it is likely that the ADHD syndrome influences the processing of multisensory stimuli. However, these differences may also influence how general sensory processing occurs and how successful the integration process is. Although adult ADHD is quite common, it is starkly underrepresented in the literature, as most ADHD research has focused on children and adolescents. The lack of literature on this topic indicates an important potential area

of inquiry. This thesis therefore sets out to elucidate whether adults with ADHD experience altered sensory processing in response to multimodal stimuli; These themes will be discussed in some detail in the Literature Review and Manuscript sections of this thesis.

Suggestion of Altered Sensory Function in Adult ADHD

Any alterations to the many processes performed by the brain and spinal cord could have detrimental, or conversely beneficial, influences on personal lived experience. Children with ADHD have altered somatosensory processing, reported as increased amplitudes of late somatosensory evoked potential (*SEP*) peaks (Parush, Sohmer, Steinberg, & Kaitz, 1997) as well as differences in their responsiveness to various sensory environments (Dunn & Bennett, 2002). These known functional differences have also been localised to specific brain regions with structural changes reported in this population (Castellanos et al., 2002; Duerden et al., 2012; Proal et al., 2011).

Differences in structure can, and have, been related to various functional differences. Certain techniques that can assess altered brain function include EEG and/or MRI (Stevenson et al., 2014). The use of surface EEG allows for an indication of the electrical activity occurring at the most superficial layers of the cortex (Najarian & Splinter, 2005). With the use of MRI, both sub-cortical and cortical regions of the brain can be studied in response to stimuli and tasks (Najarian & Splinter, 2005). Both of these modalities have had great utility when studying special populations, and more particularly in ADHD populations (Bresnahan & Barry, 2002; Castellanos et al., 2002).

EEG is a technique has high temporal acuity as these recordings are done so with millisecond accuracy (Najarian & Splinter, 2005). EEG can be used to assess the cortical activity

occurring in response to specific stimuli. The use of a multiple-electrode EEG cap allows for the analysis of multiple brain regions, as opposed to being limited to single electrode analysis. The research in this thesis was completed utilizing a 64-electrode EEG cap (ANT Neuro). EEG and MRI have been used to elucidate differences in cortical activation in both children and adults with ADHD (Bresnahan & Barry, 2002; Schneider, Retz, Coogan, Thome, & Rösler, 2006); however, adult ADHD is represented infrequently in the literature, negating the fact that adults with ADHD may be experiencing significant alterations to how they interact in certain settings.

The neuro pathophysiology and associated behavioural psychopathology of ADHD has been localised to numerous brain regions with structural and functional bilateral alterations to prefrontal cortices, temporal, occipital, and parietal regions as well as the basal ganglia, corpus callosum, and cerebellum being reported in the literature. (Aylward et al., 1996; Duerden et al., 2012; Durston, Pol, Schnack, Buitelaar, Steenhuis, Minderaa, & Kahn, 2004; Proal et al., 2011; Sowell et al., 2003; Valera et al., 2007). Dionne et al. (2015) mention that these changes to specific neurological structures may in fact alter the efficacy at which MSI can occur, as some of the structurally unique areas are heavily relied upon for the process of MSI. A recent study looked at multimodal processing in individuals with subclinical ADHD and their results suggested that ADHD may result in an impaired ability to perceive simultaneously occurring stimuli as truly occurring concurrently in time (Panagiotidi, Overton, & Stafford, 2017). In comparison, Doody (2013) investigated a subclinical ADHD population and found that this population had fewer behavioural gains when presented with a multisensory stimulus (Doody, 2013). These studies suggest that there are sensory differences in those who experience ADHD-like symptoms. However, the population studied was adults who have not received a clinical

diagnosis. The authors also did not include neurophysiological measures when assessing the ability to process audiovisual (AV) multisensory stimuli.

Individuals with developmental disabilities have an increased likelihood to experience maladaptive MSI, as a result of altered afferent processing when in a multisensory environment (Wallace & Stevenson, 2014). Attentional alterations are one of the hallmark signs of ADHD, and multimodal processing alterations may influence attentional capabilities (Dionne-Dostie, Paquette, Lassonde, & Gallagher, 2015). Similar brain regions are involved in sustained attention and in MSI, such as the SC and fronto-parietal and temporo-parietal regions (Dionne-Dostie et al., 2015). This suggests the possibility that those with a diagnosis of ADHD may in fact have altered multimodal functioning. It is hypothesized that the sensory process of MSI is likely altered in adults with ADHD, due to disorder symptomatology and the various cortical morphological changes present.

Purpose and Hypothesis

The purpose of this Master's thesis was to inquire into whether young adults between the ages of 18-35 who have at some point received a clinical diagnosis of ADHD demonstrate altered sensory processing and MSI. More specifically, audio-visual multimodal processing was assessed through the utilization of a simple RT task in study one as well as a two-alternative forced-choice discrimination task in study two. Both studies included the collection of continuous 64-electrode EEG. Whole-head EEG allows for the analysis of multiple brain regions because MSI occurs in diffuse brain locations. Therefore, it was important not to limit the analysis possibilities to one or few topographical locations. The EEG-analyses methodology employed was similar to that of Brandwein et al. (2011, 2015) and Molholm et al. (2002) who

characterized MSI through the utilization of EEG based upon the Principle of Superposition of Electrical Fields.

It is hypothesized that due to the various cortical alterations present in adult ADHD, that there will be alterations to the efficiency of multimodal processing and MSI. This will be seen via differed mean RT compared to neurotypical adults in conjunction with varied event related potentials (*ERPs*) when assessing activity amplitude after stimulus onset in response to a multisensory and unisensory stimulus. Due to the lack of previous research in this population and paradigm, we were unsure of how these differences would occur. The results of this research will further the understanding of how ADHD influences multisensory processing and if necessary will provide a foundation for the creation of technological advancements to support this population when in a multisensory environment.

The present thesis includes a thorough literature review on the common symptomatology and the associated documented neurological alterations associated with ADHD, with a particular emphasis on adult ADHD. Sensory processing of multisensory stimuli is described in depth, including but not limited to the relevant neuroanatomy involved, along with the assessment modalities that will be utilized to assess MSI.

Literature Review

Introduction

Developmental disability is defined as a life-long disorder where there are impairments, which are often significant in perception, motor output, and/or learning (Matson, Matson, Belva, & Hattier, 2011). Depending on the disability, cortical activity has been shown to differ in comparison to typically developing individuals (Davies & Gavin, 2007). Attention-Deficit/Hyperactivity Disorder (*ADHD*) is a developmental disability that has yet to be completely understood in terms of potentially associated neural changes. Adults with *ADHD* make up approximately 2-4% of the general population (Kessler et al., 2005) and up to 11% of children have been diagnosed with *ADHD* (Visser et al., 2014). However, these statistics vary from source to source. In adults, the most common traits that are present are inattentiveness and disorganization (Schneider et al., 2006). Generally, individuals with *ADHD* have been identified as having maladaptive alterations to both the structure and function of various brain regions (Schneider et al., 2006). Individuals with developmental disabilities are at an increased likelihood to experience maladaptive altered multisensory integration (*MSI*), arising from skewed afferent processing when in a multisensory environment (Wallace & Stevenson, 2014). If an individual is prone to altered *MSI*, this will in turn alter the way that they experience and interact with the world (Paraskevopoulos & Herholz, 2013). Duerden, Tannock, and Dockstader (2012) found cortical changes indicative of altered sensorimotor processing in adults with *ADHD*. However, the presence of altered *MSI* in adults with *ADHD* has yet to be identified if present, and consequently understood.

MSI describes the sensory processing of multiple sensory stimuli that are combined to form a perception (Paraskevopoulos & Herholz, 2013). *MSI* is involved in a wide range of every

day activities, shaping how individuals interact with and respond to stimuli. Successful MSI results in improved detection and discrimination of varying environmental events, enhanced response time (*RT*), and greater response accuracy (DeAngelis, Ohshiro, & Angelaki, 2011; Laurienti et al., 2004). There are multiple cortical areas and structures that are heavily involved in MSI which include but not limited to the superior colliculus (*SC*) (King, 2004), the parietal region (Brandwein et al., 2011), and the posterior superior temporal sulcus (*pSTS*) (Wallace & Stevenson, 2014). There are several task paradigms that are commonly used to assess MSI, which have shown differences between healthy and clinical populations (Brandwein et al., 2015; Brandwein et al., 2011; Farid et al., 2018; Laurienti et al., 2004). The more closely stimuli are presented both spatially and temporally leads to enhanced multimodal neural responses (Driver & Spence, 2000; Meredith et al., 1987). *RT* and accuracy are behavioural markers that have been used to measure MSI; however, there are neurological biomarkers that can also be utilized to discriminate neurophysiological differences that may underpin these behavioural responses (Brandwein et al., 2015; Brandwein et al., 2011; Stevenson et al., 2014). The Principle of Superposition of Electrical Fields is commonly used when assessing MSI through EEG analysis (Brandwein et al., 2015; Brandwein et al., 2011; Molholm et al., 2002). These MSI indices can be combined to identify differences between and within specific populations (Brandwein et al., 2015; Brandwein et al., 2011).

Farid et al. (2018) observed *RT* differences between a population of individuals with subclinical neck pain (*SCNP*) and a healthy control population using a *RT* task, finding that those with *SCNP* responded slower to multisensory tasks. Based upon their findings, further inquiry could focus on MSI using biological markers in conjunction with *RT*, in subpopulations. Populations that may be susceptible to altered sensory processing are those with structural

alterations present, as structure and function are often intimately related. Potentially maladaptive MSI neural changes have been partially distinguished in Autism Spectrum Disorder (ASD) (Brandwein et al., 2015; Brandwein et al., 2013). In developmental disabilities, such as in those with ASD, there are typically prominent communication barriers, and communication is heavily reliant on MSI (Wallace & Stevenson, 2014). Further studies by Brandwein et al. (2015) have distinguished neurophysiological markers relating to impaired MSI in children with ASD that are indicative of symptom severity. These variables were found using a simple RT task in conjunction with electroencephalography (EEG) technology and high-density electrical-mapping. The neurophysiological markers mentioned include an attenuated MSI response over parietal scalp 100-130ms post stimulus presentation (Brandwein et al., 2015). However, EEG has not yet, to our knowledge, been used as a direct biological measure of MSI in adults with ADHD.

Most research to date focusing on individuals with developmental disabilities and MSI has focused on ASD, which neglects to distinguish neurological characteristics in other populations, such as individuals with ADHD, although it is likely that those with ADHD have altered multimodal processing, due to the known cortical differences in areas related to MSI (discussed in the next section). Currently, there is not an EEG-centered diagnostic tool to distinguish biomarkers representative of ADHD (Loo & Makeig, 2012); although, past research has aimed to distinguish a reliable form of EEG-based diagnosis, but findings have been inconclusive (Lenartowicz & Loo, 2014). No such studies have focused on MSI in this population. The purpose of this literature review is to clearly show where scientific research currently stands regarding this topic, providing a basis for this thesis. This thesis proposes to investigate RT and accuracy variance during a multisensory-reliant task paradigm in conjunction

with analyzing high-density EEG to observe underlying neural activity in young adults with ADHD. It can be hypothesized that altered MSI EEG biomarkers will be observed in conjunction with a differed RT in adults with ADHD. The findings of this study will lead to a better understanding of multisensory processing and the neural plasticity in young adults with ADHD.

Neurological Differences in ADHD

ADHD is a disorder that is distinguished by developmentally inappropriate and persistent impairments in attention and hyperactivity (Duerden et al., 2012). The cause of ADHD is still unknown; however, research has focused on finding neurological indices of ADHD and their associated effects to see how this may correlate to clinical manifestations. This disorder results in both structural and functional changes to the brain (Castellanos et al., 2002; Duerden et al., 2012; Proal et al., 2011; Schneider et al., 2006; Valera et al., 2007). These neurological changes can be observed using various modalities, such as EEG and magnetic resonance imaging (*MRI*).

When interpreting EEG recordings there are 5 primary frequency bands of importance which can be used to assess cortical function in humans. Kovatchev et al. (2001) had individuals with ADHD perform attention-demanding tasks while recording EEG. Alterations in theta, alpha, and beta band frequencies were found in children with ADHD (Kovatchev et al., 2001; Loo & Makeig, 2012). Children with ADHD have been found to have an increased theta band frequency (Bresnahan & Barry, 2002). Subsequently, decreased beta band frequencies have also been identified (Bresnahan & Barry, 2002). Decreased frontal lobe activity in children with ADHD has also been observed (Kovatchev et al., 2001). It is suggested that increased low-frequency theta band activity and decreased beta band activity is a direct result of maturational delay and decreased cortical arousal in individuals with ADHD (Lazzaro et al., 1998). Although alterations in brain function have been found using EEG technology, there is not a sensitive EEG-centered

objective biomarker for ADHD as significant EEG heterogeneity is present between those diagnosed with ADHD (Loo & Makeig, 2012) . However, while findings are still inconclusive and controversial in childhood ADHD, even less is known about adults with ADHD.

The most prominent and commonly discussed brain structural changes in individuals with ADHD are a diffuse thinning of frontal, parietal, temporal, and occipital lobes (Castellanos et al., 2002; Duerden et al., 2012; Proal et al., 2011; Valera et al., 2007). These alterations in neural circuitry have been found to influence sensorimotor processing (Duerden et al., 2012). Duerden and colleagues (2012) set out to see if alterations were present in sensorimotor cortices. These researchers assessed cortical thickness in adults meeting the DSM-IV diagnosis for ADHD, using high-resolution three-dimensional MRI technology. Duerden et al. (2012) found that adolescents with ADHD had thicker cortical regions surrounding the pre-supplemental motor area and an increased thickness in the right primary somatosensory cortex, this was consistent through each age group ($P = 0.047$), while controls showed typical age-related thinning (Duerden et al., 2012). Increased cortical thickness in these areas is believed to play a role in the altered sensorimotor processing that is observed in individuals with ADHD (Duerden et al., 2012). An impairment in sensorimotor processing can result in an impaired discrimination of light touch and temperature, as well as altered pain processing and perceptions (Duerden et al., 2012). This may result in maladaptive neuroplasticity that may manifest as inappropriate responses in everyday situations.

Previous research has found more pronounced evoked potentials (*EPs*) in somatosensory cortices in children with ADHD, which was thought to be a direct effect of altered cortical inhibition (Parush, Sohmer, Steinberg, & Kaitz, 2007). Researchers have stated that these atypical findings in cortical regions tend to decrease with age and become similar to typically

developing controls (Shaw et al., 2007). Medication that individuals with ADHD take in order to control their symptoms have been associated with a decreased rate of cortical thinning that typically occurs with age (Eckstrand et al., 2009). Therefore, it is unknown whether these findings are a direct result of neurological characteristics of ADHD or a result of chronic consumption of medication prescribed for symptoms associated with ADHD. Conversely, Proal et al. (2011) found that frontal cortical structures exhibited greater cortical thinning in ADHD. The evidence states that ADHD results in altered sensory processing to an extent, however the question remains as to whether or not MSI is altered. There are several neural regions that are strongly involved in MSI, and due to the structural changes present in ADHD, MSI may be even more affected by ADHD when compared to single sensory processing.

Neuroanatomy Involved in MSI

MSI occurs via two main ways: 1. incoming afferent information activates nearby unimodal neurons from other sensory modalities, and; 2. multiple sensory modalities converge on one (multisensory) neuron (Stein & Meredith, 1993). These forms of MSI can result in both behavioural and neural enhancements. When discussing MSI, it is important to recognize the various brain regions and structures that play a fundamental role in this process. There are both subcortical and cortical regions involved in the processing and integration of afferent input.

Subcortical

Midbrain - Superior Colliculus

The colliculus, or corpora quadrigemina by its Latin name, composes the roof of the midbrain or mesencephalon. It is placed just posterior to the cerebral aqueduct. There are four colliculi found in this region, two inferior and two superior (Kandel et al., 2000). The superior

colliculus receives sensory information from two main brain regions, those being the lateral intraparietal area of the posterior parietal cortex and the frontal eye field in the prefrontal cortex (Kandel et al., 2000). Based on these pathways it is thought that this structure is involved in attention and saccadic eye movements. The superior colliculus is also heavily involved in the process of integrating afferent sensory input and is composed of seven layers. These layers are further segregated into superficial and deep layers, both of which have specific functions. The three most superficial layers encompass the stratum opticum which receives visual input from the retina as well as the visual cortex; while the two deeper layers and their constituent multisensory neurons are involved in receiving afferents from multiple sensory modalities (visual, auditory, and somatosensory) and are related to oculomotor actions (Kandel et al., 2000; Perrault Jr, Vaughan, Stein, & Wallace, 2005). The neurons are directionally tuned in the horizontal plane, meaning that an auditory stimulus on the left side of an individual will result in activity in the right superior colliculus (Kandel et al., 2000). The activity occurring in these layers may occur independently of one another, indicating that sensory activity may not always result in motor output and vice versa (Kandel et al., 2000).

Cortical

Superior Temporal Sulcus

One of the key cortical regions involved in MSI is the STS (Beauchamp, Lee, Argall, & Martin, 2004; Beauchamp, Yasar, Frye, & Ro, 2008; Noesselt et al., 2007). The STS is positioned within the temporal lobe and adjacent to the occipital lobe, while being inferior to the lateral fissure (figure 1). Due to its anatomical position, it has a large overlap in function between the auditory and visual cortices. This region has enhanced activity to congruent AV stimuli. (Paraskevopoulos & Herholz, 2013). The STS plays a fundamental role in several processes such

as social communication and stimulus integration, emotions, theory of mind (which is highly implicated in ASD), and face recognition (Allison, Puce, & McCarthy, 2000; Ojemann, Ojemann, & Lettich, 1992). The STS has enhanced multimodal activity, being that there is greater activity in this region in response to multiple stimuli than there is to a single unisensory stimulus. It is most active in response to auditory and visual afferent input (Beauchamp et al., 2004). Similar to other brain regions, the STS responds to stimuli in a contralateral manner. The STS is thought to play a role in assessing time and synchronicity, as there is greater activity in this region during synchronous and semantically congruent stimuli (Macaluso, George, Dolan, Spence, & Driver, 2004).

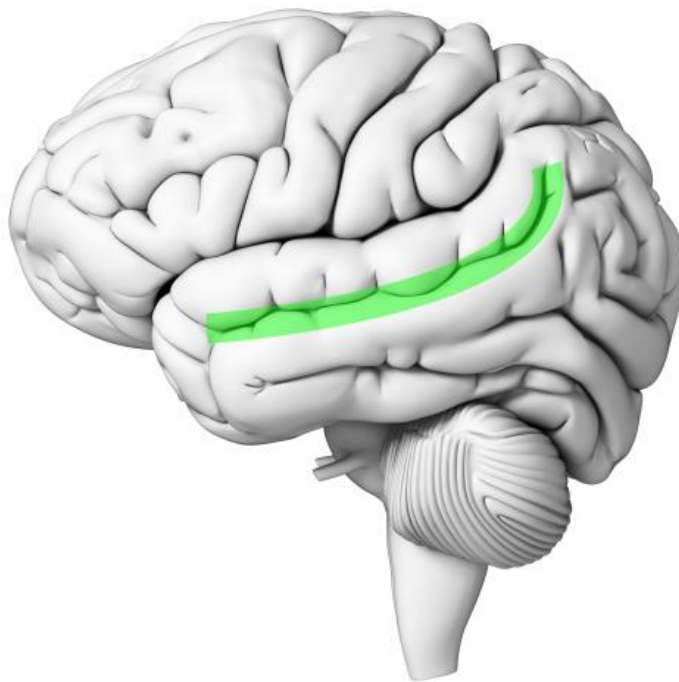


Image retrieved from <http://www.tulane.edu/~howard/BrLg/STS.html>

Figure 1 The STS in relation to other cortical regions.

Parietal Region

The parietal lobe has been widely discussed in the literature as being one of the main cortical regions involved in MSI (Brandwein et al., 2015; Brandwein et al., 2013; Brandwein et al., 2011; Giard & Peronnet, 1999). The parietal region is placed between the posterior occipital and lateral temporal lobes, which are involved in visual and auditory processing respectively. The parietal region is considered one of the key regions involved in the association of visual information and spatial perception (Kandel et al., 2000).

Literature has also associated a pattern of right-sided occipito-parietal activation in response to AV multisensory stimuli. (Giard & Peronnet, 1999). There are patterns of AV interactions within the right parieto-temporal area as well (Sams & Imada, 1997). Significant multisensory neural generators have been found within the parietal region (Brandwein et al., 2011; Molholm et al., 2006; Moran, Molholm, Reilly, & Foxe, 2008). The intraparietal sulcus is a more specific area within this region that is known to integrate multisensory inputs involved in speech (Andersen, Snyder, Bradley, & Xing, 1997), cross-modal spatial attention (Teder-Sälejärvi, Münte, Sperlich, & Hillyard, 1999), and AV object recognition (Werner & Noppeney, 2010) such as that in this research. As the parietal region is one of the most prominent cortical regions involved in AV MSI, it is one area that should be assessed using EEG.

Multisensory Neurons

Multisensory neurons are neurons that receive afferent input from more than one sensory modality (Perrault Jr et al., 2005). This characteristic allows these neurons to integrate simultaneous sensory information from more than one modality. Multisensory bimodal neurons respond to each independently occurring stimulus or when the stimuli are presented simultaneously (Allman & Meredith, 2007). However, MSI does not solely occur in bimodal neurons. Unisensory neurons are also involved in MSI (Allman & Meredith, 2007). Unisensory

neurons will respond to their constituent componentry of a multisensory stimulus, for example a visually responsive neuron responding to an audiovisual stimulus and a visual-alone unisensory stimulus, but would not respond to an auditory-alone stimulus. There are also trimodal neurons, which will respond to three given stimulus modalities (Meredith & Stein, 1986).

Multisensory Bimodal Convergence

Bimodal neurons are multisensory in nature, as they respond to a stimulus from more than one sensory modality. However, in order to evoke a response in these bimodal neurons, only a single stimulus presentation from one of its constituent modalities is necessary; however, when both stimuli are presented simultaneously (e.g. auditory and visual), significant behavioural and neurological enhancements may occur (James & Stevenson, 2012). These enhancements may be in the form of a shorter RT, increased accuracy, and an enhanced neural response as described by the Principle of Superposition of Electrical Fields. From a neurological perspective, enhanced bimodal neurons will result in decreased neuronal activity (i.e. decreased amplitude) when compared to the summed neural responses to both unisensory stimuli (i.e. auditory + visual) (James & Stevenson, 2012). In contrast, the neural response of a super additive bimodal neuron will be greater than that of the summed unisensory responses (James & Stevenson, 2012). Finally, bimodal neurons may have suppressed activity in response to a multisensory stimulus, with activity being lower than it is to either of the unisensory stimuli (James & Stevenson, 2012). The strength of the neural response (i.e. suppressed vs. increased) will vary for each given stimulus, and will be dependent on the stimulus characteristics at the time of stimulation (Meredith & Stein, 1986).

There are two main sensory processes that may result in multisensory facilitation if certain conditions are met. Which process occurs will depend on the sensory characteristics of

the stimuli. First, bimodal convergence occurs when afferent inputs can terminate in one area, being an area that responds to both auditory and visual sensory afferents (King & Palmer, 1985). These areas are thought to have a high number of bimodal or trimodal neurons, and thus respond to afferent input originating from multiple sensory modalities (Allman et al., 2008). Conversely, cross modal convergence is a process involved in MSI as well.

Cross modal Convergence

Cross modal convergence is an important theme to discuss regarding the neural characteristics of MSI, as this describes the neural circuitry involved in processing multisensory inputs. Cross modal convergence describes when one sensory area (i.e. visually dependant) has projections to another sensory area (i.e. auditory dependant) (Allman et al., 2008). Through cross modal convergence, afferent visual information may terminate in a predominantly auditory dependent area (Allman et al., 2008). There are two dominant patterns for which this convergence can occur. There are multiple sensory projections, where multiple modalities converge/terminate in a similar area (Rockland & Ojima, 2003). There are also cross modal projections, where for instance, an auditory stimulus will terminate in a visually dominant area (Allman et al., 2008). In order to attend to multisensory stimuli, or cross modal stimuli, distributing attention to various sensory stimuli is necessary (Perrault Jr et al., 2005). This poses the question, as to whether those with attention-deficits may experience altered cross modal convergence and the consequent integration of stimuli.

Selective Attention

How much attention one allocates to a given stimulus will have a direct influence on how that given stimulus is processed by involved brain regions. For instance, for the integration of

stimuli to occur it is important to have modality-specific attention evenly allocated to each sensory modality involved (Mozolic, Hugenschmidt, Peiffer, & Laurienti, 2008; Talsma, Doty, & Woldorff, 2006). If allocating attention to only a single modality, the behavioural response to the multisensory stimulus will likely resemble the response to the attended unisensory stimulus, negating any possible benefit of multisensory enhancements. This dependence on selective attention, suggests that those with ADHD may have a different integration process occur when presented with multisensory stimuli which requires attention allocation to more than one stimulus modality.

Past/Learned Experience

In order for stimuli to be processed in a multisensory fashion, it is important that they are semantically congruent (Laurienti et al., 2004). However, an individual's past experiences will shape what they associate with a given word/sound (auditory cue) and visual representation (visual cue). Depending on someone's experiences, they may not associate the same semantics with a given stimulus as most would, which will hinder the integration capabilities of the multisensory system. This semantic congruence is crucial, as the visual and auditory association areas need to communicate with one another as in cross-modal convergence. Research has shown that semantically incongruent stimuli will hinder the process of MSI, resulting in longer RTs (Laurienti et al., 2004). Therefore, the ability for MSI to occur is contingent on the spatial, temporal, and semantic characteristics of a given stimulus.

Behavioural Measures of MSI

Effective MSI is crucial in numerous daily tasks such as driving, crossing the street, holding a conversation with an individual, and learning in a classroom, among many others. The

integration as well as separating of multisensory stimuli when necessary is crucial to the performance of these tasks (Brandwein et al., 2011). There are multiple methods that can be employed for the purpose of measuring MSI. Some of which are methods that focus on behavioural measures relying on multisensory processing. Temporal order judgment (TOJ) tasks, simple RT tasks, and two-alternative forced-choice discrimination tasks use behavioural measures such as RT and accuracy to measure MSI (Farid, Murphy, & Yields, 2016). During a simple RT task and an audiovisual two-alternative forced-choice discrimination task, individuals are required to respond to varying stimuli conditions which are as follows: 1) a unisensory audio stimulus, 2) a unisensory visual stimulus, and 3) a combination of audio and visual stimuli which are presented synchronously or with a slight timing offset. The purpose of these tasks is to distinguish if there are differences in RTs and/or accuracy as well as neurological differences between two or more populations when presented with varying stimulus conditions. Differences in RT and EEG ERP variables can be associated with altered MSI.

SCNP results in altered afferent input which will in turn alter sensory processing and result in altered SMI (Haavik-Taylor & Murphy, 2007). If an individual experiences altered SMI, they are at an increased likelihood to elicit improper motor responses when presented with a task (Haavik-Taylor & Murphy, 2007). Based on findings from transcranial magnetic stimulation (*TMS*) and somatosensory evoked potentials (*SEPs*) studies it can be hypothesized that individuals experiencing SCNP may experience altered MSI as well. Based on this hypothesis, Farid et al. (2018) investigated MSI in individuals with SCNP using a MSI-dependant task. Their study used behavioural measures to assess MSI changes present in two populations, those with SCNP and healthy controls using a two-alternative forced-choice discrimination task. Overall, they found that adults with SCNP had significant differences in visual and multisensory RTs

(Farid et al., 2018). Specifically, SCNP resulted in a significantly longer RT for visual and multisensory conditions (Farid et al., 2018). Interestingly, for adults with SCNP, the shortest RT was to the visual-only condition rather than the multisensory condition (Farid et al., 2018). This result could indicate that having SCNP results in individuals having decreased efficiency of auditory stimuli processing, which will result in this population responding more quickly to visual unisensory stimuli and negating the benefits of an AV multisensory stimulus.

Response Time

Simple RT

A behavioural method to assess MSI can be implemented through the use of a simple RT task. This paradigm consists of multiple semantically congruent redundant stimulus types (e.g. auditory, visual, audiovisual multisensory) which occur with equal probability in a randomized order. In a simple RT task each stimulus condition requires the same response to be made, therefore response discrimination isn't necessary nor is there higher processing necessary such as decision making. Simple RT differentiates how participants respond to a multisensory stimulus when compared to a unisensory stimulus. If MSI is occurring, the RT to the multisensory stimulus (e.g. audiovisual) will be faster than that of the RT to either of its unisensory counterparts (e.g. auditory or visual). If MSI does not occur, the RT to the quickest unisensory stimulus would likely have the same RT as that of the multisensory stimulus. This paradigm has been used successfully in the past when used in conjunction with EEG to assess MSI (Brandwein et al., 2015; Brandwein et al., 2013; Brandwein et al., 2011).

Complex RT

A second method that has often been employed to distinguish the extent of MSI is the utilization of a two-alternative forced-choice discrimination task (Farid et al., 2018; Laurienti et al., 2004). In addition to solely RT, this paradigm also allows to the analysis of response accuracy (% correct). This task paradigm consists of multiple stimulus modalities (auditory, visual, and audiovisual multisensory), which are representative of multiple colours (e.g. blue, red, green). When the audiovisual stimulus occurs the stimulus will always be congruent (e.g. auditory verbalization of the word red combined with a red circle) and will never been semantically incongruent (e.g. auditory verbalization of the word blue combined with the red circle). This redundancy allows for a paradigm that is solely dependant on unisensory and multisensory processing, and not a dissociation process such as those necessary in a Stroop test consisting of semantically incongruent stimuli. There will typically be two stimuli that require a response (e.g. respond red with right index finger, blue with right middle finger, and ignore the green stimulus). The third stimulus not requiring a response is used to promote attention (e.g. not guessing with a 50% probability of being correct). The RT can be assessed, indicating how long it takes for an individual to make a choice in response to an auditory, visual, or audiovisual stimulus. Accuracy can also be analyzed to observe whether accuracy improved with the multisensory stimulus presentation. Although behavioural measures are important to consider for MSI, incorporating neurological measures such as EEG can provide a complementary measure, which is both robust and objective, and has the potential to provide a biomarker to discriminate ADHD from other conditions.

Neurological Measures of MSI using EEG

Due to the presence of multisensory neurons, several regions of the brain can be studied in order to obtain a better understanding of MSI. Multisensory afferent input goes through a

process of convergence, either by terminating in the form of multiple sensory projections (bimodal) or via cross-modal projections to different areas of the cortex as previously discussed.

EEG can be used to record the electrical activity of more superficial brain regions. EEG is an effective non-invasive method to study MSI and the associated neuronal activity by means of voltage (μV) and latency (ms) changes during different stimuli presentations and environmental conditions (Stevenson et al., 2014). Collected EEG data can be analyzed by looking at both the amplitude and frequency changes in specific populations and conditions (Stevenson et al., 2014). The parietal lobe and pSTS, which are located between the occipital lobe and the temporal lobe, are heavily involved in the temporal processing of AV multisensory afferent information (Brandwein et al., 2011; Wallace & Stevenson, 2014), and can be used as a topographical marker when quantifying MSI. Researchers have used EEG as a neurological measure to assess MSI in multiple age groups and in populations thought to experience altered MSI (Brandwein et al., 2011; Foxe et al., 2000; Giard & Peronnet, 1999; Molholm et al., 2002).

Brandwein et al. (2011) used EEG data to map event-related potentials (*ERPs*) in conjunction with analyzing behavioural measures during a MSI-dependant task. AV interactions were analyzed by means of summing auditory-alone ERPs and visual-alone ERPs (sum waveform) and comparing this wave to the multisensory response (multisensory waveform) (Brandwein et al., 2011). Any divergence of these two waveforms can be associated with the degree of MSI occurring (Brandwein et al., 2011). The above analysis is a common method used to assess MSI and is known as the principle of superposition of electrical fields (Brandwein et al., 2011; Giard & Peronnet, 1999; Molholm et al., 2002). This methodology has also been applied to study how individuals with ASD process multisensory stimuli.

Measuring MSI in Developmental Disabilities using EEG

ASD is a developmental disability that typically results in impaired social interactions and communication, in conjunction with atypical patterns of behaviour and movements (Lombroso, Ogren, Jones, & Klin, 2009). Communication is heavily reliant on the successful processing of both visual and other sensory stimuli (Brandwein et al., 2013). Individuals with ASD typically show signs of impaired social behaviour such as differences in eye contact and socially inappropriate gestures; therefore, it may be hypothesized that they are at an increased likelihood to process multisensory stimuli in a maladaptive manner and that these may be as a result of impaired multisensory processing at a basic level (Brandwein et al., 2013). ASD has also been characterized as having diffuse alterations in brain functioning and altered neural networks (Brandwein et al., 2015; Brandwein et al., 2013).

Brandwein and colleagues (2013) sought to determine if children and adults with ASD experience altered MSI. This research was carried out using EEG and behavioural measures to assess MSI in this population. Participants performed a simple RT task while wearing a 70-electrode EEG cap, to record the voltage changes occurring during different phases of the task (Brandwein et al., 2013). Individuals with ASD in both the young and older group had slower responses to all condition types when compared to the typically developing population (Brandwein et al., 2013). The typically developing group was found to have more prominent AV interactions when analyzing ERPs (Brandwein et al., 2013). Their overall findings indicate that individuals with ASD relied on different brain regions and therefore neural networks during early stages of multisensory processing, and that this integration was less effective than the typically developing cohort (Brandwein et al., 2013). This is in agreeance with the theory of disrupted connectivity in ASD, indicating that individuals with ASD's neural networks do not communicate optimally (Brandwein et al., 2013).

Brandwein and colleagues have also reported neurophysiological indices of ASD severity in early MSI using EEG (Brandwein et al., 2015). Specifically, individuals with more severe cases of ASD had smaller MSI responses over parietal regions 100-130 ms post-stimulus presentation (Brandwein et al., 2015). The strongest predictors for ASD severity were found within auditory responses, such that individuals with less severe ASD had smaller auditory N1a amplitudes and larger N1b amplitudes (Brandwein et al., 2015). This research suggested that there is impaired auditory processing in individuals with ASD (Brandwein et al., 2015). Through this research, robust findings in both the behavioural and neurological domains support the hypothesis that MSI is in fact altered in individuals with ASD (Brandwein et al., 2015). One future implication for this research could potentially involve beginning to incorporate EEG technology into the diagnosis of ASD, opposed to solely using subjective diagnostic methods.

Literature pertaining to data acquisition method

EEG is a non-invasive technique that is used to measure the electrical activity of the brain (Britton et al., 2016). The EEG signal is typically described as the recording of electrical potential changes that are influenced and change in relation to action potentials changing the membrane potential of neural generators (Najarian & Splinter, 2005). The recorded electrical changes are a summation of the excitatory and inhibitory postsynaptic potentials (*EPSP/IPSP*) (Britton et al., 2016). These electrical changes are then represented as important amplitude and frequency changes over a period of time (Najarian & Splinter, 2005). There are both clinical and research applications that utilize EEG. Clinically, EEG is typically used to monitor anesthesia levels during surgery and also in the diagnosis and monitoring of epilepsy (Britton et al., 2016; Najarian & Splinter, 2005). In neuroscience and research relating to rehabilitation, EEG can be

utilized in order to distinguish differences in brain activity in various special populations and in response to various tasks and environments.

Anatomical/Biological Aspects of the Signal

The pyramidal neurons in the brain, which are oriented perpendicular to the surface of the cranium, are where the EEG signals are thought to originate (Britton et al., 2016). The brain is composed of both white and gray matter, with the gray matter containing the majority of the cell bodies, while the white matter contains a majority of the axons and myelin (Najarian & Splinter, 2005). Surface EEG records the electrical activity that is closest to the superficial cortical regions of the brain, which is predominantly gray matter. Different regions of the brain have varying but specific functions. For instance, the temporal lobe is involved in the processing of auditory stimuli, language, and speech memory; the occipital lobe is responsible for processing visual stimuli; the parietal lobe is involved in spatial awareness and language; the frontal lobe is involved in active thinking, emotions, and problem solving (Sandilyan & Dening, 2015). When any of these regions are active, increased EEG activity may be observed. Deeper brain regions such as the basal ganglia and corpus callosum are very important, but are outside of the scope of surface EEG due to their depth in comparison to the most superficial regions of the brain. It is also important to distinguish that the manner in which the brain processes stimuli and forms motor output works in a mostly contralateral manner ("Brain Structure and Function," 2010), meaning that moving the right arm will likely result in greater neuronal activity in the left hemisphere of the brain in the region of the precentral gyrus which is oriented just anterior to the central sulcus.

Signal Origin

The EEG signal originates in the neurons of the brain and represents voltage fluctuations. When looking at an EEG signal, both amplitude, representative of voltage changes (μV), and frequency, which represents oscillations per second (Hz), can be isolated and related to biological fluctuations over a period of time or an epoch (Britton et al., 2016). Brain electrical activity can occur in response to varying stimulus presentations and/or motor output, otherwise known as afferent and efferent potentials (Britton et al., 2016). EEG records the summation of IPSPs and EPSPs (Najarian & Splinter, 2005). These recordings originate from the cyclic pattern of depolarization and repolarization, which are seen as voltage changes in the neuron membrane potential (Najarian & Splinter, 2005); this occurs in response to the summation of IPSPs and EPSPs once the membrane threshold of activation has been met. This cycle of voltage changes occurs from the sodium ions outside of the cell and the potassium ions inside of the cell moving across the cell membrane (Najarian & Splinter, 2005). Resting membrane potential is -70 mV , which is considered polarized (Najarian & Splinter, 2005). The peak of the depolarization of the action potential is approximately $+30$ to 40 mV (Najarian & Splinter, 2005). These voltage changes in response to stimuli are referred to as ERPs (Najarian & Splinter, 2005). These ERPs will appear as amplitude changes along the y-axis of the EEG digital output over time on the x-axis.

There are 5 primary EEG frequencies recorded from the human brain, these being: delta (1-3 Hz), theta (4-7 Hz), alpha (8-12 Hz), beta (13+ Hz), and gamma (25+ Hz) (Britton et al., 2016). Each frequency band can be associated with specific neurological states or functions in humans. For instance, a distinct alpha wave is termed mu and is commonly seen in adults, most often during drowsiness (Britton et al., 2016). Beta frequencies are associated with active problem solving and thinking in adults (Najarian & Splinter, 2005). The lower frequency bands,

delta and theta, are seen more commonly in younger children and become less prominent with age (Najarian & Splinter, 2005). To extract certain frequencies from a data set, a band-pass filter needs to be applied that is associated with that frequency's characteristics (Najarian & Splinter, 2005). For example, in order to extract alpha waves a band-pass filter of 8-12 Hz will be used. When analyzing EEG data in the frequency domain, this allows for an observation of the state of cortical functioning. This can give insight into possible changes in brain functioning. For instance, research has found elevated theta band activity in individuals ADHD as well as decreased beta and alpha band frequencies (Loo & Makeig, 2012).

Something important to consider when dealing with EEG, is that the signal originates inside of the brain and is recorded through the utilization of electrodes placed on the scalp. There are multiple biological layers that the electrical activity must pass through before it can be recorded. Some of these layers include the cerebrospinal fluid (*CSF*), the blood brain barrier (*BBB*), multiple layers of meninges, cranial bones, and the skin. These layers result in an attenuation of the raw signal from its original form, resulting in a smaller recording than what is actually occurring in the brain (Najarian & Splinter, 2005). Because the signal is so small, it must be amplified before it is digitally represented on the computer. The typical amplification settings are between 0.1 to 100 Hz, to make sure that there is not any important information that is unrepresented (Najarian & Splinter, 2005).

Application/Set-up

The EEG hardware can range in presentation and function. There are EEG caps that can range from less than 30 up to 300 electrodes. For the purpose of this thesis, a 64-electrode cap was used. This will allow for a spatially-dense representation of the brain activity, as to not miss the activity occurring in certain regions of the brain. These multi-electrode caps allow for a better

representation of the cortical activity occurring; however, certain studies may choose to utilize specific electrode locations instead of a whole-head cap, in order to look at certain ERPs or activity in specific brain regions. Each electrode is labeled with a letter prefix and a number suffix; the letter refers to the region of the scalp the electrode is overlapping and the number refers to the hemisphere, even numbers indicating the right hemisphere (Britton et al., 2016).

The 64-electrode cap is based upon an internationally standardized system, which is a variation of the 10-20 system (Britton et al., 2016). This standard system takes into consideration measurements using the nasion, inion, and the left and right tragus anatomical references, placing electrodes at 10 or 20 percent of the length measured between these landmarks (Britton et al., 2016). This allows for a standard EEG application between individuals. Before the EEG signal is observed on the computer screen, it goes through an analog to digital conversion that improves the visual representation of the raw biological signal and allows for signal storage.

In order to ensure that the quality of the signal is of the highest possible, there are several built-in quality assurance steps. When applying the electrodes to the scalp, there is a conductive gel that is used to fill each electrode. This results in a better connection with the skin and decreased impedance. The advanced source analysis (ASA) lab program that was used for the present collection of EEG data has a built-in impedance check. This aspect of the program allows for a visual representation of the impedance, with an associated number and colour. Ideally, the impedance should be as low as possible (0-20 k Ω), ensuring optimal connectivity. This step is crucial to collect noise-free data. When this occurs for each electrode, the researcher can move on from calibrating the EEG electrodes to the recording step of data collection.

Recording and Filtering

When collecting EEG data, all data first goes through a differential amplifier (Britton et al., 2016). This form of amplification references one electrode to another, in order to eliminate the common activity in the electrodes. This works to eliminate a large amount of the biological artifacts often present in EEG data (Britton et al., 2016). When sampling and observing an EEG signal in a specific time period, this is referred to as an epoch. EEG has very good temporal resolution, this is due to the fact that the EEG signal can be recorded in milliseconds instead of seconds (Najarian & Splinter, 2005).

Action potentials propagate down the axon of neurons extremely fast, making it important to record the EEG signal at a sampling rate that will reflect this, as not to miss important signal information. The NYQUIST theorem states that the sampling rate should be no less than double the highest frequency observed in the signal (Srinivasan, Tucker, & Murias, 1998). The most common sampling rates for EEG data range from 100 Hz to 200 Hz (Society, 2006), and can go up to 2500 Hz or higher depending on the equipment utilized. If this does not occur, the digital signal that is recorded will not be an accurate depiction of the raw biological signal.

When processing a raw EEG signal, it is important that appropriate filters are applied so that important information can be retrieved (Najarian & Splinter, 2005). The most common frequencies present in EEG data are 1-30 Hz; filtering techniques such as band-pass filtering result in these frequencies being easily distinguishable (Britton et al., 2016). Blinking and swallowing can result in EEG artifacts. The eye is a dipole, being there is both a positive and a negative end, and each movement results in a voltage fluctuation (Najarian & Splinter, 2005). Eye blink artifacts have a characteristic shape and are therefore easily removed. Another common artifact is when the electrodes on the scalp move, thus disrupting the equilibrium that

was established during the impedance check, this results in small voltage fluctuations (Najarian & Splinter, 2005). However, this can easily be extracted by applying a low-pass filter (Najarian & Splinter, 2005). Filtering can effectively remove these artifacts without decreasing the quality of the signal itself. Myofascial artifacts can also be present when facial muscles move drastically, although these are typically easy to distinguish, as they result in large frequency changes, and can therefore be removed easily (Najarian & Splinter, 2005). Typically a low-pass filter with a cut-off frequency of 12.5 Hz is applied to filter any muscle activity that interferes with the signal (Najarian & Splinter, 2005). Depending on the signal being analyzed, the filter will vary, this is where it is necessary to reference previous data analysis protocols.

In EEG studies looking specifically at MSI, there are several filtering and sampling techniques that have been used. A 512 Hz sampling rate was used when looking at MSI in varying childhood age cohorts (Brandwein et al., 2011). Brandwein and colleagues (2011) used a low-pass filter of 45 Hz to remove artifacts from electronic equipment, and a high-pass filter of 1.6 Hz to remove ongoing slow-wave activity. In order to analyze MSI directly, an average ERP was calculated, which generated a waveform for each stimulus (Brandwein et al., 2011). Brandwein et al. (2011) described their method to quantify MSI as summing the neural responses of both auditory-alone and visual-alone stimuli and comparing this waveform to the neural response of a multisensory stimulus. Any divergence between these two waveforms indicates an interaction between the auditory and visual stimuli, and therefore MSI occurring (Brandwein et al., 2011). This method has frequently been applied to adult populations as well (Giard & Peronnet, 1999; Molholm et al., 2002).

Rationale for the use of EEG to study MSI in ADHD

For the proposed research and thesis, EEG will be used to inquire into MSI by analyzing ERPs based upon the theory of superposition of electrical fields (Brandwein et al., 2015; Brandwein et al., 2011; Molholm et al., 2002). EEG is a reliable method to measure MSI (Stevenson et al., 2014). Historically speaking, EEG studies looking at MSI have typically analyzed ERPs in various brain regions (Stevenson et al., 2014). The parietal lobe is also often referenced when assessing MSI (Andersen et al., 1997; Brandwein et al., 2011). This is beneficial when implementing a technique to assess MSI using surface electrodes, such as those used in EEG. Therefore, EEG can be used to record the electrical activity over the more superficial brain regions such as the temporal, parietal, and occipital lobes.

Due to the fact that specific brain regions and frequency bands are associated with various sensory processes, EEG is an appropriate and effective modality to inquire into MSI (Stevenson et al., 2014). MSI inquiry using EEG has generally used an equation known as additive criterion (Stevenson et al., 2014), this is depicted as $ERP_{AV} \neq ERP_A + ERP_V$, where A refers to audio and V refers to visual (Stevenson et al., 2014). Another technique that can be utilized to isolate the multisensory ERP is to exclude any ERPs that occur after 200-250 ms post-stimuli presentation, this is when processes not directly related to early sensory processing occur (Hillyard, Teder-Sälejärvi, & Münte, 1998).

There are neurological alterations present in individuals with ADHD (Duerden et al., 2012). Some of these cortical changes are a thinning of the frontal, parietal, temporal, and occipital lobes, as well as a thickening of the primary somatosensory cortex (Duerden et al., 2012). These changes in neural circuitry have been observed as negatively influencing sensorimotor processing (Duerden et al., 2012). Individuals with ADHD are prone to having

altered cortical functioning and morphology; however, it is unknown whether this influences MSI and if it does, to what extent.

Where the literature on MSI and ADHD currently stands

In recent years, research surrounding MSI has become more frequent, filling in some of the gaps in this area of knowledge that once existed. This is important, as MSI is crucial to many tasks in our ever-increasingly busy lifestyle where we are constantly being stimulated from our technologically-enriched environment. Although optimal MSI is highly important, there are some populations that are at an increased risk of experiencing altered MSI. One of those populations are individuals with ADHD.

When reviewing the literature, it became apparent that individuals with ADHD experience altered cortical functioning; however, it is unknown how or even if these alterations effect MSI. If this is the case, that these alterations do in fact influence MSI, individuals with ADHD are an important necessary population to study MSI in. This can be studied through the utilization of EEG technology in conjunction with MSI-dependant tasks, similarly to Brandwein et al.'s (2011; 2015) and Farid et al.'s (2018) protocols discussed above. The methods of these studies can be replicated to an extent and applied to a population of adults with ADHD while performing a simple RT task and a two-choice audiovisual discrimination task, similar to Farid et al. (2018)'s research. This will result in an improved comprehension of how adults with ADHD experience the world around them.

Conclusion

When analyzing EEG data, it is important to distinguish which context or environment the data was recorded in when choosing the best method of analysis, as specific filtering

techniques and principles will apply. The use of EEG in multisensory processing and MSI has developed over the years. As described previously, the method that will be used to quantify MSI through EEG is the Principle of Superposition of Electrical Fields. This was chosen due to its ability to assess MSI when looking into early latency multisensory processing (Brandwein et al., 2015; Brandwein et al., 2011; Molholm et al., 2002; Stevenson et al., 2014). As mentioned, there is no research published on MSI in individuals with ADHD, although this is a population that is likely affected by altered MSI. Because of the accessibility and reliability of the EEG to quantify MSI, EEG will be used for the purpose of this thesis to inquire into MSI functioning in young adults with ADHD.

Study One Manuscript

Introduction

Attention-deficit/hyperactivity disorder (*ADHD*) is a common neurodevelopmental disorder. The most common symptoms associated with a diagnosis of ADHD are hyperactivity, impulsivity, and inattention (Visser et al., 2014). The symptoms typically associated with ADHD often arise during childhood, with approximately 11% of children receiving a diagnosis of ADHD (Visser et al., 2014). Although ADHD is typically associated with being a predominately childhood disorder, it is quite commonly present in adults as well (Wilens, Faraone, & Biederman, 2004). Of the children diagnosed with ADHD, approximately 50% will have symptoms persist into adulthood (Sadock et al., 2000). Adult males are more commonly diagnosed with ADHD than adult females (5.5% vs. 2%) (Amiri et al., 2014). Although there are common behavioural characteristics of ADHD, there are also neurological characteristics as well.

Those with ADHD have been found to have altered brain structures through the utilization of functional magnetic resonance imaging (*fMRI*) and electroencephalography (*EEG*) (Bresnahan & Barry, 2002; Castellanos et al., 2002; Duerden et al., 2012; Proal et al., 2011). For instance, a diffuse pattern of thinning in parietal, temporal, frontal, and occipital lobes are characteristic in those with ADHD (Castellanos et al., 2002; Duerden et al., 2012; Proal et al., 2011; Valera et al., 2007). Alternatively, thicker gray matter in the pre-supplemental motor area and in the right hemispheric primary somatosensory cortex are present (Duerden et al., 2012). The presence of alterations to several brain structures indicates that there may quite possibly be alterations to the functions related to these regions as well. For instance, MSI has been shown to occur in parietal and occipital cortical regions both of which are known to be altered in those with a diagnosis of ADHD (Brandwein et al., 2011; Proal et al., 2011).

MSI is a process that is crucial to how one interacts with and perceives the world around them. In order to make sense of various afferent input, it is necessary for the nervous system to effectively process these stimuli. For these stimuli to be processed as such, it is necessary for them to be semantically congruent and to occur simultaneously or with a slight timing offset (Driver & Spence, 2000; Laurienti et al., 2004). If sensory conditions aren't semantically congruent it can consequently result in worse performance such as greater response latencies (Laurienti et al., 2004). There are several behavioural enhancements that can result from MSI, such as a shorter response times (*RT*) and greater accuracy when responding (Laurienti et al., 2004; Meredith et al., 1987). Audiovisual (*AV*) MSI typically occurs throughout day to day life. When in a classroom setting, the nervous system is constantly processing all of the auditory stimuli from things that one is hearing as well as all of the visual stimuli from things that they are seeing. In most cases, these auditory and visual stimuli occur close in temporal and spatial proximity, and therefore such processing is highly important to the formation of perceptions (Foxy & Molholm, 2009). Semantic congruence is crucial, as the visual and auditory association areas need to communicate with one another as in cross-modal convergence (Laurienti et al., 2004). Previous studies have indicated that alterations to *AV* MSI can result in impairments in communication and sensory processing when in social settings (Brandwein et al., 2015; Brandwein et al., 2013). In order to assess MSI, there are several methods that can be employed.

A simple *RT* task can be utilized in order to promote and assess MSI (Brandwein et al., 2015; Brandwein et al., 2011). This task paradigm consists of multiple stimulus conditions (e.g. auditory unisensory, visual unisensory, and audiovisual multisensory). Each of these stimulus conditions would be representative of the same thing (e.g. the colour red). When a participant is presented with any of the stimulus conditions, the same response would be required (e.g. click of

a button with the right thumb). The utilization of the same response to each stimulus results in a truly simple RT task, where participants do not have to dissociate a certain response with a specific stimulus as seen in a two-alternative forced-choice discrimination task. While this task design alone allows for a strictly behavioural analysis, there are further methods that can be utilized in order to assess MSI from a neurological perspective (Stevenson et al., 2014).

The principle of superposition of electrical fields can be incorporated when assessing EEG in conjunction with behavioural methods of MSI (Brandwein et al., 2011; Molholm et al., 2002). This principle states that any significant divergence between a multisensory waveform and a “sum” waveform (derived from summing the auditory and visual unisensory waveforms) represents that MSI is occurring (Brandwein et al., 2011; Molholm et al., 2002). When comparing between groups (e.g. ADHD and neurotypical controls), analysis can indicate whether MSI is occurring in certain regions and latencies. Previous studies utilizing EEG have noted that there are specific regions involved in MSI, one of which is the parietal region (Brandwein et al., 2015; Brandwein et al., 2011; Molholm et al., 2006; Moran et al., 2008); this region is also altered in those with ADHD (Proal et al., 2011).

Due to the fact that ADHD is commonly described as a childhood disorder, literature pertaining to adult ADHD is lacking, even though ADHD is quite common in adulthood. It should be noted that there is evidence that adults with ADHD have specific brain structural changes present. Some of the regions which are altered in ADHD are also highly implicated in the process of MSI, such as the parietal region. However, no literature has yet to inquire into whether AV MSI is altered in any way in those who have received a diagnosis of ADHD.

The purpose of this study was to examine whether young adults who have received a clinical diagnosis of ADHD at some point in their lives have altered MSI compared to

neurotypical controls. The findings will help to elucidate if and when MSI occurs in both groups through RT differences in response to the AV multisensory stimulus and also through the divergence of the EEG waveforms (sum vs. multisensory). RT differences and event-related potential (*ERP*) differences between groups will then be analyzed to elucidate whether there is a main effect of group and/or condition (e.g. to what extent MSI occurs in those with ADHD). We hypothesized that due to the altered brain structure in regions involved in multisensory processing that MSI would occur differently in those with ADHD compared to controls.

Methods

Participants

Participants were recruited from the student body at the University of Ontario Institute of Technology (*UOIT*). Recruitment was done through the use of word of mouth, in-course announcements, and posters placed throughout the campus. Participants recruited were young adults between the ages of 18-35 years old that had and had not received a clinical diagnosis of ADHD at some point in their life. Adults that reported receiving a diagnosis of ADHD, self-reported the age at which they were diagnosed as well as any medication that was currently being taken to control their symptoms related to ADHD. The mean age for neurotypical controls (n=11, 3 females) was 21.3 ± 3.0 years old and for the ADHD group (n=10, 3 females) was 24.1 ± 3.5 years old. The mean age of ADHD diagnosis was 13.1 ± 7.4 years old.

The Edinburgh Handedness Questionnaire was used to determine which hand was the most dominant per participant, with the results indicating left, right, or ambidextrous. This was completed because the stimulus response was done with the right thumb. The number of left-handed participants per group was similar; so that any potential differences in behavioural, electrophysiological, or movement time were not related to a handedness-bias since the right

hand was not the dominant limb for each participant. The neurotypical control group had 3 left-handed, 7 right-handed, and 1 ambidextrous participant while the ADHD group had 2 left-handed, 3 right-handed, and 5 ambidextrous participants. The adult ADHD Self-Report Scale (ASRS-v1.1) was used to assess each participant's symptoms associated with ADHD. The ASRS has a total of 18 questions, which are in line with the ADHD diagnostic criteria set out in the DSM-IV (Dankner, Shalev, Carrasco, & Yuval-Greenberg, 2017). Participants were also asked to report whether they were currently taking medication for their ADHD. Six participants with ADHD reported that they were taking medication for ADHD at the time of participation, medications reported included Vyvanse, Concerta, and Adderall. This tool was chosen due to its high sensitivity in predicting ADHD symptomatology (van de Glind et al., 2013).

Participants completed pre-screening questionnaires prior to beginning the research protocol. An EEG safety checklist was completed to ensure that participants did not have any experiences that may be contraindicated for the collection of EEG. This includes a recent history of epilepsy, concussion, stroke, or brain injury, which may potentially alter the results and make the task unsafe for participation.

Stimuli

Auditory-alone

An audible female voice was presented speaking the word red (duration ~60ms) from speakers placed bilaterally to the computer screen.

Visual-alone

A red circle appeared on the screen for 60 ms, placed centrally in the vertical and horizontal plane.

Multisensory

The redundant auditory and visual stimuli occurred simultaneously from speakers and a computer screen adjacent to one another.

Procedures

A simple *RT* task was utilized to measure MSI. This paradigm was designed using E-Prime 2.0 Professional. The task consisted of three different stimuli conditions (visual, auditory, and multisensory) all presented in random order with an inter-trial interval of 1000-3000ms, similar to that of other studies that have utilized a similar paradigm to assess MSI. This is depicted below in figure 2. Stimuli were presented in 8 blocks, with each block consisting of 102 stimuli (34 per condition). The same response was required for each condition previously described, ensuring that there were no complex decision making processes necessary for a response, which would otherwise slow the response. Participants were instructed to respond with their right thumb and use the specified button on the Chronos® device to do so. A Chronos® response device was used to receive and collect responses. This device was used for its accurate collection of responses, which is done with millisecond accuracy and low-latency recordings (Schneider, Eschman, Zuccolotto, & Guide, 2002).

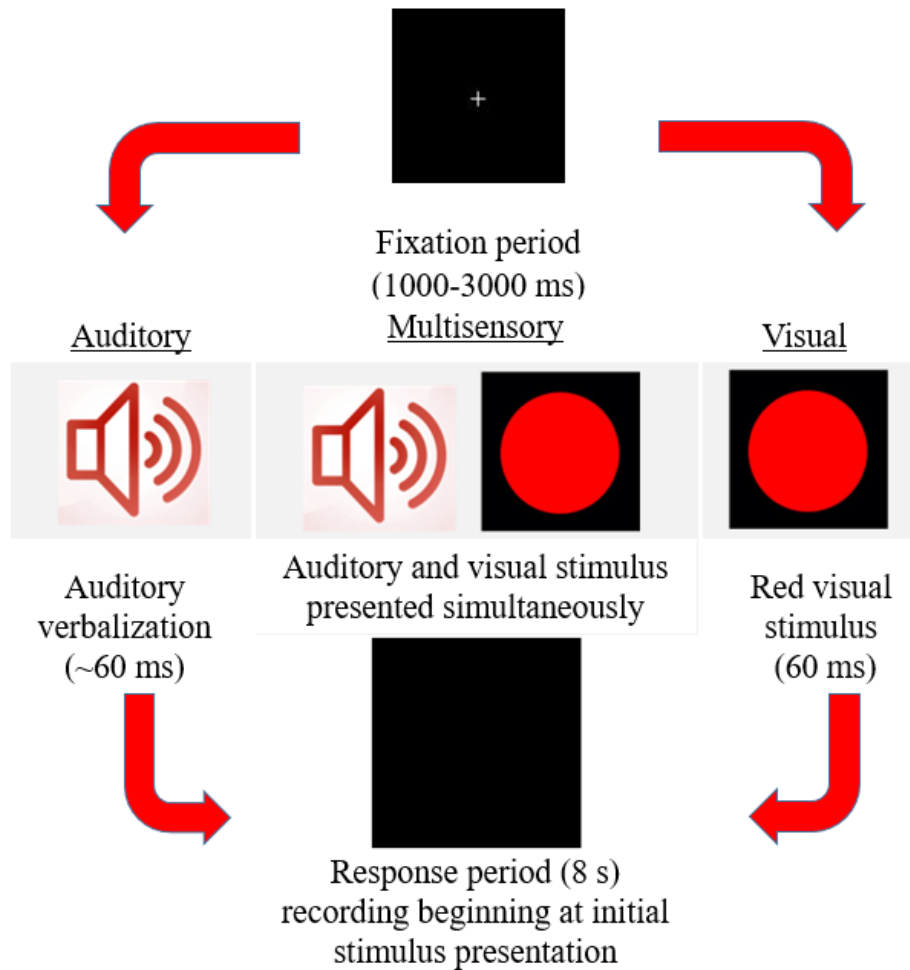


Figure 2 Example of the three possible stimulus conditions that participants may be presented with in the simple RT task

Data Acquisition and Analysis

Behavioural

E-Prime 2.0 Professional was utilized to run the simple RT task and record RTs. A Chronos® device was used to collect responses to all stimuli. While performing the simple RT task on a desktop computer, continuous EEG was recorded.

ERPs

A Waveguard™ 64-electrode EEG cap was used to collect surface brain electrical activity in response to each stimulus type. The use of a 64-electrode cap allows for a more robust analysis of brain activity, as acquisition is not limited to a few electrodes. The Waveguard™ cap was connected to a TMSi REFA-8 amplifier with 64 EEG channels, 4 bipolar channels, and 4 auxiliary channels; which was run through asaLab™ to collect and record each session at a 2048 Hz sampling frequency. ERP analysis was completed on a separate laptop using Advanced Source Analysis (ASA), Matlab, and SPSS.

Data was cleaned and removed of any artefacts prior to running any analyses. Artefacts which were a result of muscle activity and ocular activity were removed based on the manufacturer's recommendations. A band-pass filter with a low cut-off of 1.6 Hz and a high cut-off of 45 Hz and a slope of 24 db/octave was utilized. The low cut-off of 1.6 removes any slow-wave activity that would otherwise be represented doubly in the "sum" waveform during analysis. The 45 Hz high cut-off removes any artefacts that are a result of surrounding electrical equipment. Artefact rejection was performed, with the exclusion criteria being $\pm 100 \mu\text{V}$. Finally, data was averaged into 600 ms epochs per participant per condition, being 100 ms pre-stimulus and 500 ms post stimulus-onset (total 600 ms). This was done to each individual data set. Average waveforms for each unisensory condition were summed (auditory + visual) for comparison to the multisensory waveform (Brandwein et al., 2015; Brandwein et al., 2013; Brandwein et al., 2011; Foxe et al., 2000; Molholm et al., 2002). This was done in accordance with the principle of superposition of electrical fields and nonlinear summation. Based on this principle, any significant divergence between the sum and multisensory waveform indicates that the two stimuli presented simultaneously interacted (i.e. they weren't processed individually as unisensory stimuli) and were processed differently than their unisensory condition counterparts.

When completing the analysis, any significant divergence between these two waveforms would indicate if and when MSI occurred, and whether the pattern of MSI was different between the two cohorts (ADHD vs. neurotypical). In areas and time points where divergence between the two waveforms was significant (greatest difference from 0 μ V) it can be inferred that MSI was occurring. Similarly to other studies, time points for MSI ERP analysis were chosen based upon the grand-averaged head models where the greatest positive and negative activity occurred at various latencies, which can be seen in the included figures (5, 7, 9, and 11).

Statistical Analyses

Behavioural

RT is the sole behavioural variable that was assessed through the use of a simple RT task. Mean RTs were calculated per participant in response to each stimulus type (auditory alone, visual alone, and AV multisensory). Any responses that were ± 2 SDs from their individual condition average were excluded when calculating each participant's average per condition, with the caveat being that the lower limit could not be any faster than 100ms; for participants where -2 SDs was in fact lower than 100ms, the lower limit was then set to 100ms. A 2 group (ADHD vs neurotypical) by 3 sensory condition (A, V, multisensory) mixed factors ANOVA was completed, with repeated measures on the last factor; this was utilized to compare average RTs between groups (ADHD vs. control) and within conditions (A, V, AV) to elucidate whether there were any significant differences ($P < 0.05$) in RT dependant on diagnostic status and/or sensory condition. Partial eta-squared (η^2) was used to report effect size where results were reported as a trend, where a small effect was noted as 0.01, medium as 0.06, and a large effect as 0.14 (Richardson, 2011). An additional post-hoc analysis was done to compare RTs between males with and without ADHD; this was not done with females due to the small sample size. All statistical tests were run using SPSS version 24 (Nie, Bent, & Hull, 1970).

ERPs

All ERP processing was done offline using ASA, Matlab, and SPSS software. As has been done in the previous literature (Brandwein et al., 2015; Brandwein et al., 2013; Brandwein et al., 2011; Giard & Peronnet, 1999; Molholm et al., 2002), multisensory interactions were analyzed by comparing the AV multisensory waveform to a “sum” waveform. The sum waveform is created by summing the two unisensory conditions (A and V). Based on the principle of superposition of electrical fields, any significant divergence between the MSI and sum waveform indicates that multisensory integration did occur, or in other words, that the two simultaneously occurring stimuli interacted (i.e. were not processed in a unisensory fashion). An example of this divergence or difference can be seen below in figure 3. In order to not bias the analysis to the dependent measures (difference between multisensory and sum waveform per group) the electrodes and time frames for analysis were chosen based on an overall grand-average heat map for the AV multisensory stimulus. This grand average was created using all participants’ data (ADHD and neurotypical) as not to bias regions of interest to one groups activity. Time windows for analysis were constrained to early multisensory interactions, between 0 ms to 250 ms (Brandwein et al., 2011). Anything past this time frame becomes contaminated with unrelated neural activity. For each time frame and region chosen for analysis, averaged-data per participant was added to a 2 group (ADHD vs. neurotypical) vs 2 signal type (MSI vs. sum) mixed factors ANOVA with repeated measures on the last factor. Scalp regions were represented by an average of 2-4 composite electrodes, being the electrodes that showed greatest activity during that time frame. The regions and time-frames chosen are similar to those discussed in previous literature (Brandwein et al., 2015; Brandwein et al., 2013; Brandwein et al., 2011; Foxe et al., 2000; Giard & Peronnet, 1999; Molholm et al., 2002). Greenhouse-Geisser corrections were used when appropriate to report P values. All statistical tests were completed using SPSS

version 24 (Nie et al., 1970). All tests were checked for normality via Shapiro-Wilk’s test and homogeneity of variance using Levene’s test.

Alpha for all analyses was set to $P < 0.05$.

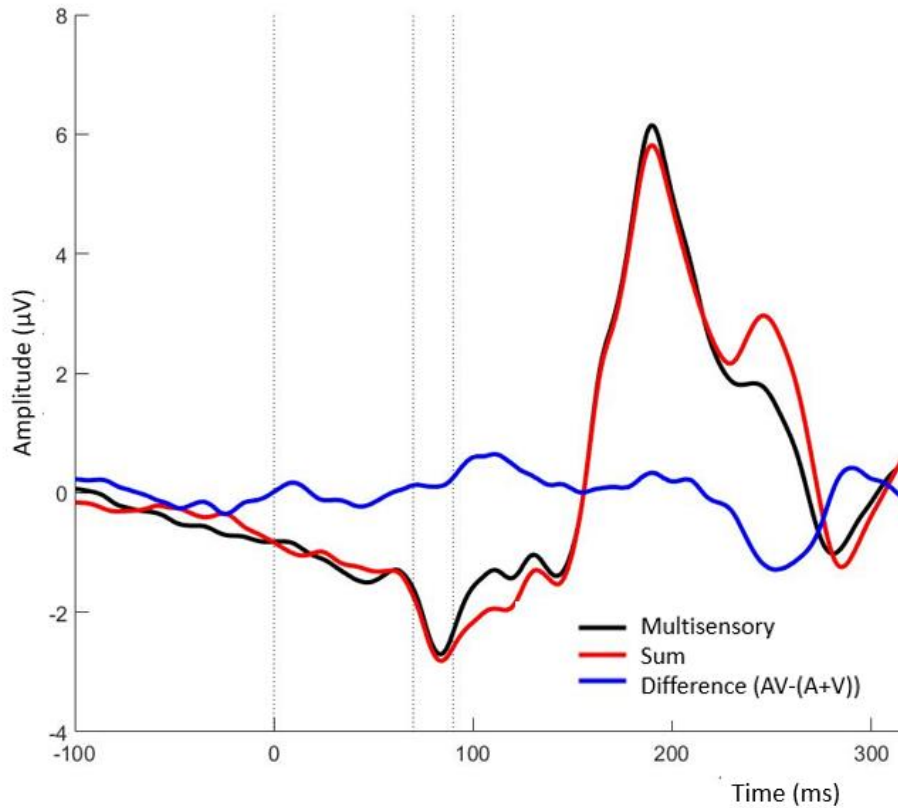


Figure 3 Graph highlighting areas of early MSI where there is a significant divergence between the multisensory and sum waveforms as indicated by a “difference” waveform in blue. This is based upon the Principle of Superposition of Electrical Fields.

Results

Behavioural

Response Time (ms)	Auditory	Visual	Multisensory
ADHD	308 (± 20)	243 (± 24)	236 (± 21)
Control	327 (± 34)	262 (± 29)	255 (± 31)

Table 1 The average response time (ms) for each group for each stimulus condition (mean \pm SD).

The mean RT for both the ADHD and control group are reported in table 1 above and in figure 4. A 2 group (ADHD vs neurotypical) by 3 sensory condition (A, V, multisensory) mixed factors ANOVA was completed, with repeated measures on the last factor. This revealed that response to the multisensory stimulus was significantly faster than the response to either of the unisensory conditions, revealing a main effect of stimulus condition ($F_{2,38} = 587.89$, $P < 0.001$). Both groups responded fastest to the multisensory stimulus (236 ms and 255 ms) and slowest to the auditory-alone (308 ms and 327 ms) stimulus. There is a potential trend for those with ADHD to respond faster to each stimulus type (308 ms vs. 327 ms; 243 ms vs. 262 ms; 236 ms vs. 255 ms) compared to their neurotypical counterparts; however, a significant group effect was not reached ($F_{1,19} = 2.709$; $P = 0.116$; partial $\eta^2 = 0.125$), indicating a medium effect size. Post-hoc analysis revealed that when comparing only the male participants between groups, a main effect of group was reached ($P = 0.042$) as males with ADHD ($n = 7$) responded faster to each stimulus condition than male controls ($n = 8$).

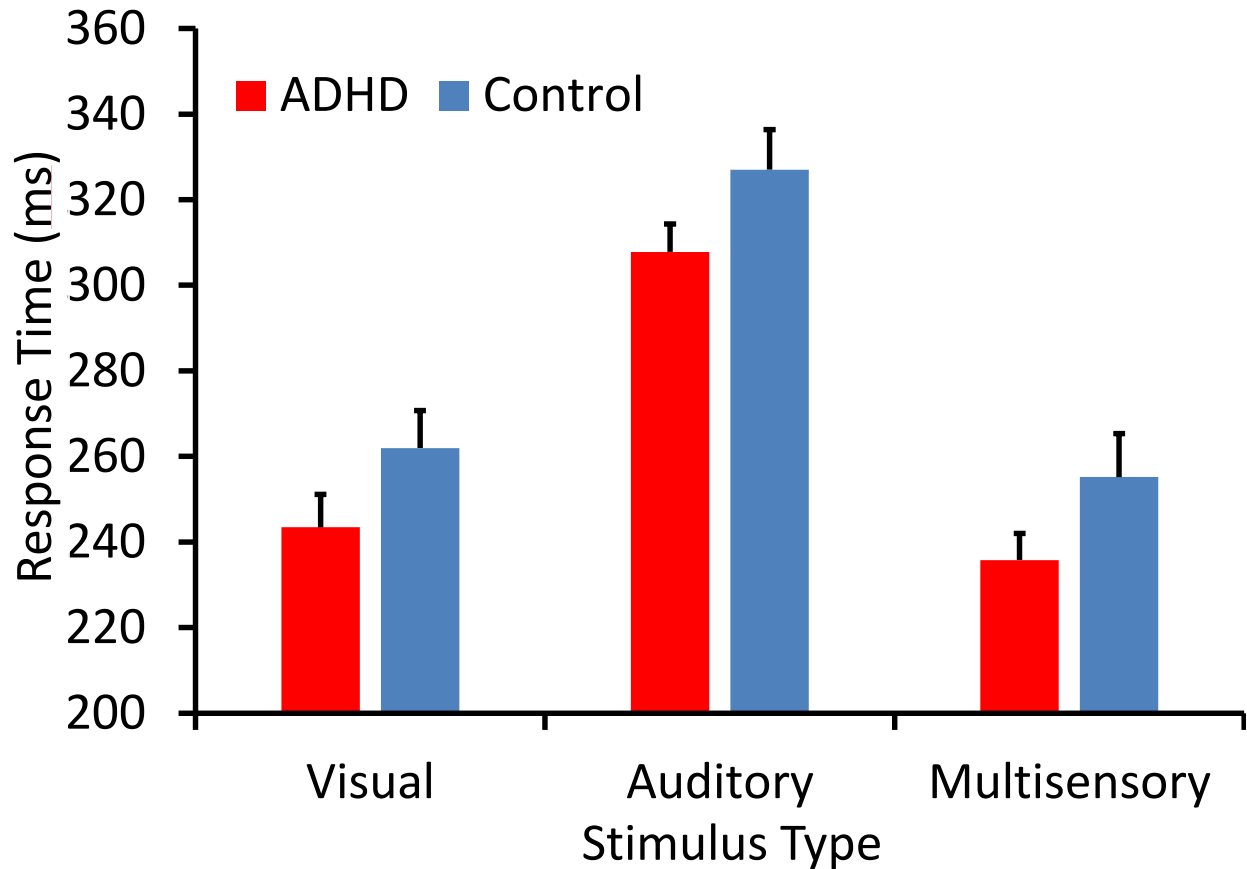


Figure 4 Average response time (ms) per condition, with ADHD responses represented in red and controls represented in blue.

Neurophysiological

When assessing the audiovisual multisensory responses, various distinct patterns of centralized activity were found in specific locations and at specific latencies. Latencies assessed were between 0-250ms. These time windows and areas of greatest activity were used to assess whether MSI was occurring in both study groups based on the principle of superposition of electrical fields, as previously discussed in the methods section. A 2 group (ADHD vs. neurotypical) by 2 signal type (MSI vs. sum) mixed factors ANOVA with repeated measures on the last factor was completed for each latency window, with the between subject’s factors of

diagnostic status (ADHD or control) and within subject's factor of multisensory or "sum" waveform; the sum waveform was described in the ERPs methods section.

For the time period of 100-140 ms in the central parietal region, there was localized negative activity. Running the ANOVA indicated that MSI occurred in both groups (ADHD and neurotypical controls) at this time point and region, as there was a significant difference between the average multisensory vs. sum activity in this latency window ($F_{1,19} = 16.293$; $P < 0.001$), indicating a main effect of stimulus condition (multisensory vs. sum). This indicates that MSI occurred in both groups in this region and time. There was not a main effect of group. This activity can be seen in the heat map from the overall group average (figure 5) as well as in figure 6 illustrating the time window assessed and showing the difference between the multisensory and sum waveforms for both groups.

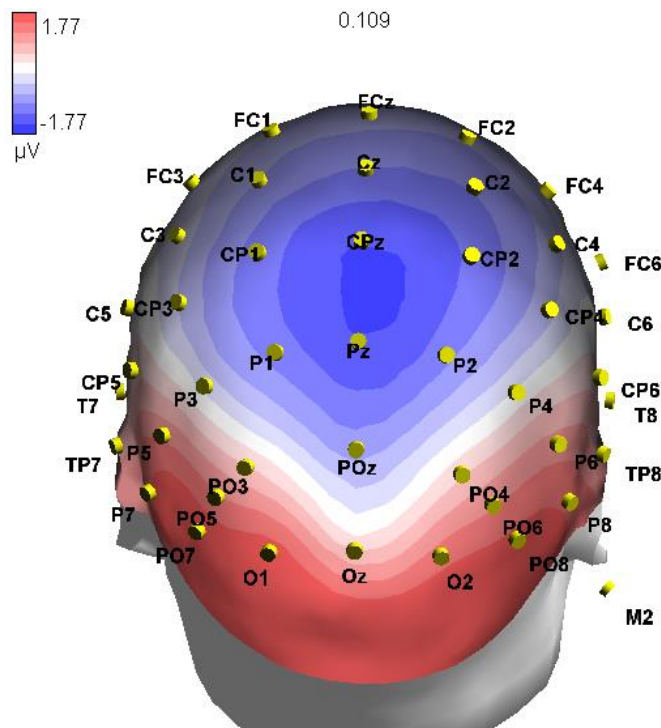


Figure 5 Localized negative activity in response to AV multisensory stimuli from 100-140 ms over CPz and Pz electrodes.

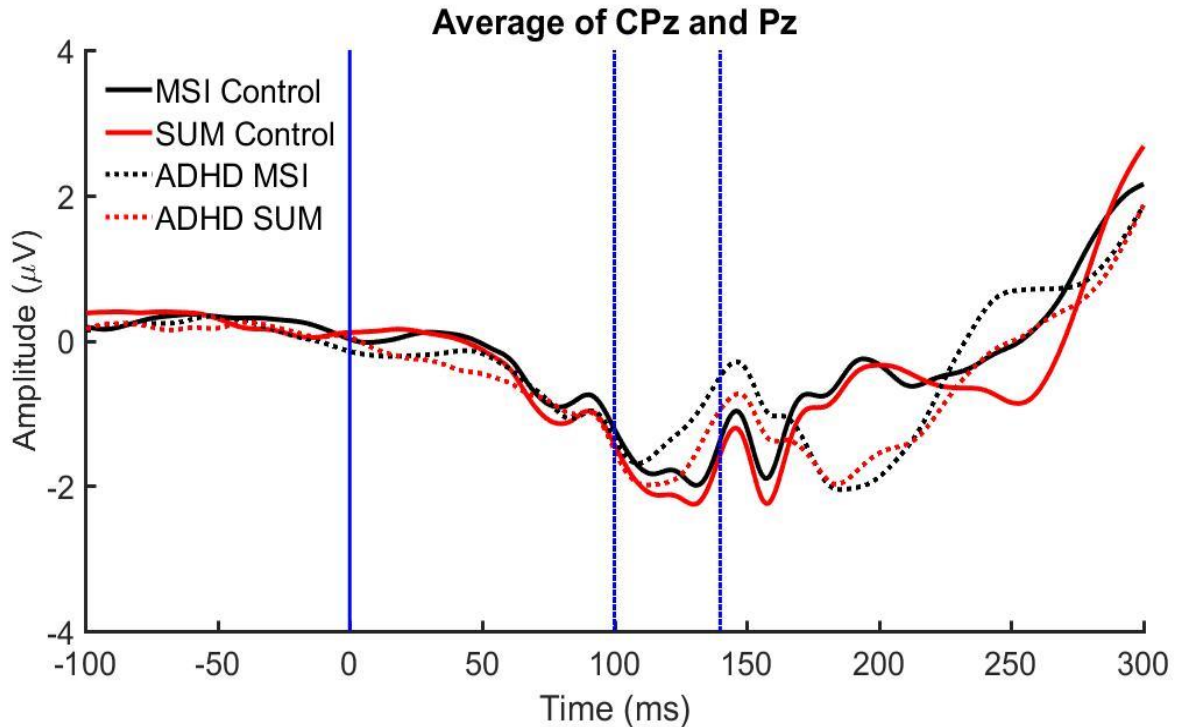


Figure 6 Graph highlighting negative activity from 100-140 ms over central-parietal brain regions, with an effect of condition (sum vs. multisensory) for both groups, as the sum waveform is significantly more negative than the multisensory waveform, indicating that MSI occurred in both controls and those with ADHD.

A second region and time window of analysis was from 140-160 ms over parietal occipital regions (Pz, P1, POz), which was observed as localized negative activity. This can be observed in the heat map in figure 7. The ANOVA revealed that there was a main effect of both group (ADHD vs. neurotypical control) and a main effect of stimulus condition (multisensory vs. sum), indicating that MSI occurred in both groups at this time and region but that the ERP pattern was different in each group. There was a significant difference between the multisensory and sum waveform ($F_{1,19} = 5.420$; $P = 0.031$) in both groups, as the sum waveform was more negative than the multisensory waveform; and there was a significant difference between the activity in the ADHD versus neurotypical control waveforms ($F_{1,19} = 7.295$; $P = 0.014$), as the

controls had significantly more negative activity than that of the ADHD group. These average waveforms can be seen in figure 8.

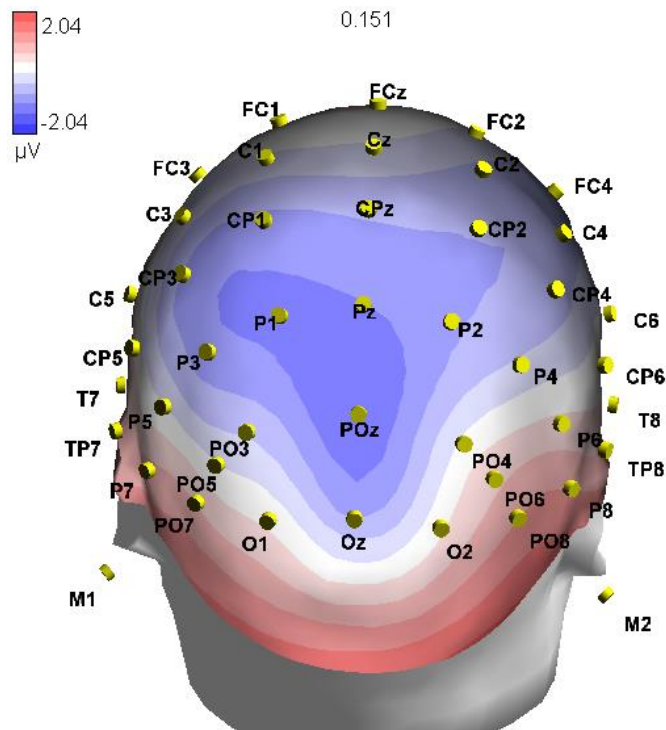


Figure 7 Localized activity over Pz, P1, and POz from 140-160 ms in response to the AV multisensory stimulus.

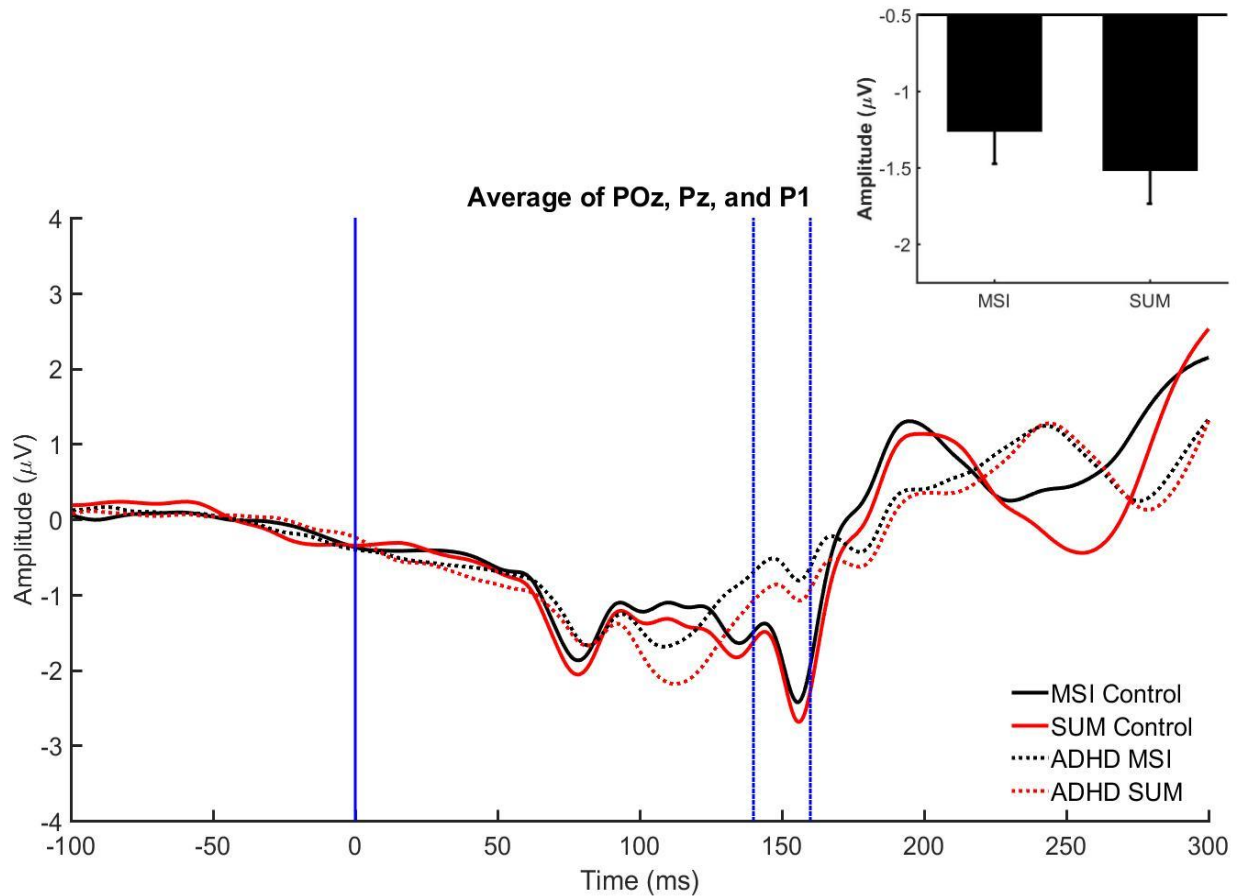


Figure 8 Graph highlighting the negative activity seen previously in figure 7 from 140-160 ms over parietal-occipital brain regions. MSI occurred in both groups (controls and ADHD) at this latency and brain region, although ERP activity was different in each groups as controls had more negative activity.

From 110-120 ms there was localized positive activity in pre-frontal regions (FPz, FP2, and FP1) as seen in the below figure 9. An ANOVA revealed that there was not significant MSI occurring at this time point and region; however, there was an interaction of stimulus condition and group, meaning that the electrical activity occurring in response to the multisensory stimulus was different between groups ($F_{1,19} = 4.988$; $P = 0.038$) which can be seen in figure 10, as the sum waveform was more positive than the multisensory waveform for controls while the inverse was found for the ADHD group.

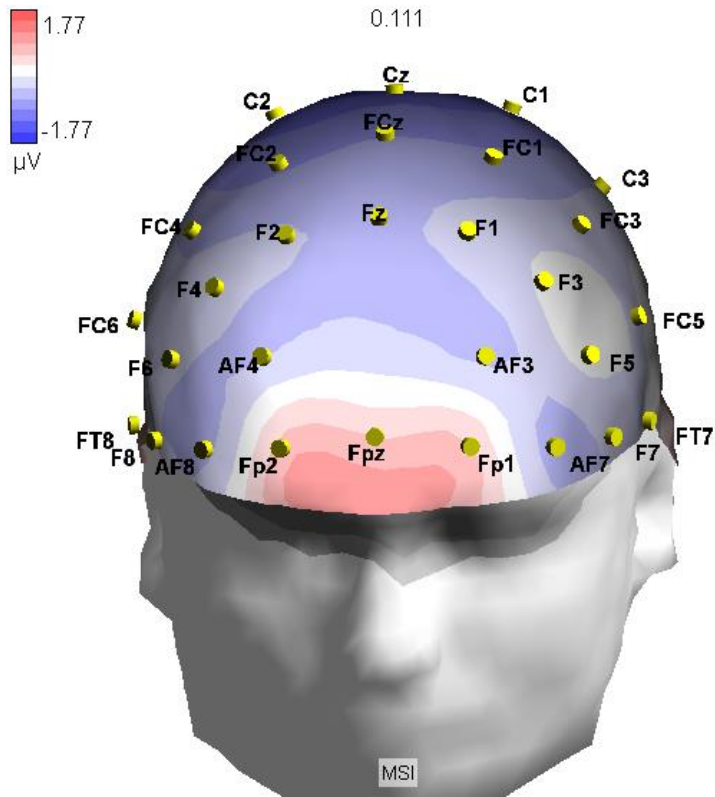


Figure 9 Showing a localized negative activity from 110-120 ms over FPz, FP2, and FP1 from the overall group grand averaged heat maps.

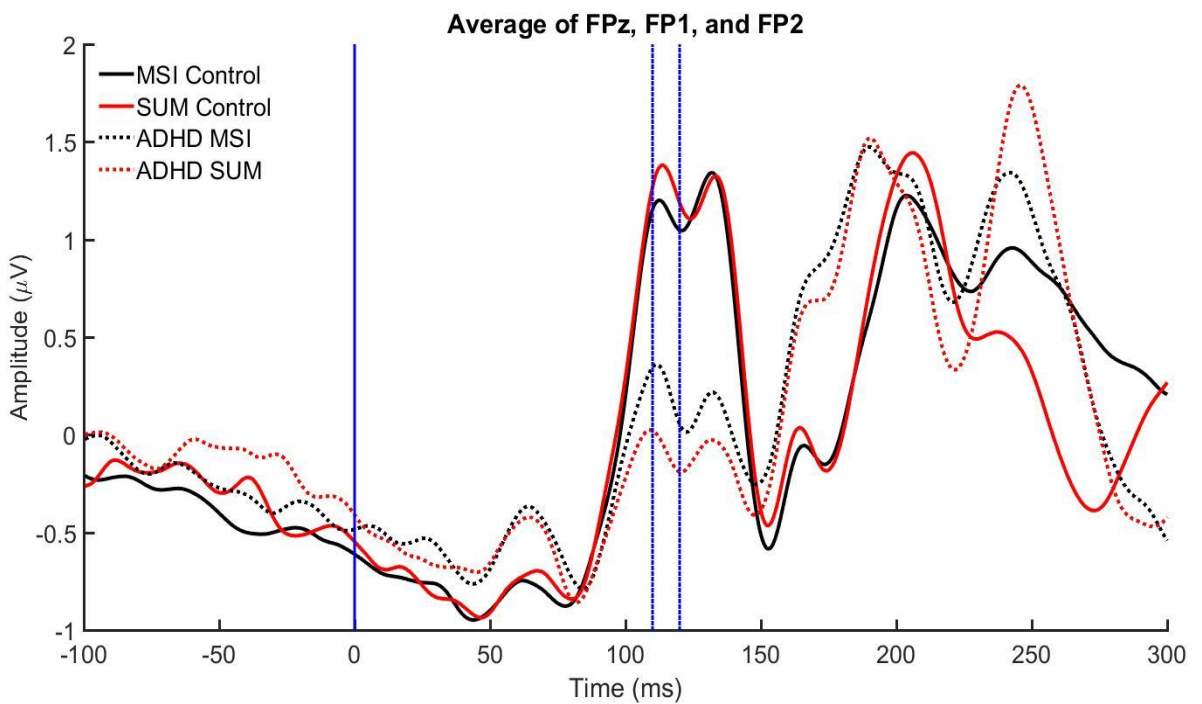


Figure 10 Graph highlighting the positive activity from 110-120 ms over frontal regions with a condition by group interaction. The MSI waveform is more positive in those with ADHD and the opposite is seen in the controls.

A final stimulus condition by group difference was found from a localized positive activity from 100-120 ms over parietal occipital regions (PO7, O1, O2, and PO8). This area is illustrated in figure 11. An interaction between sensory condition and group approached significance ($F_{1,19} = 4.336$; $P=0.051$), indicating that the pattern of electrical activity in response to the multisensory stimulus is different in both groups at this time point and brain region. This indicates that there is a difference in overall brain activity between those with and without ADHD in this brain region from 100-120ms. This can be observed in figure 12.

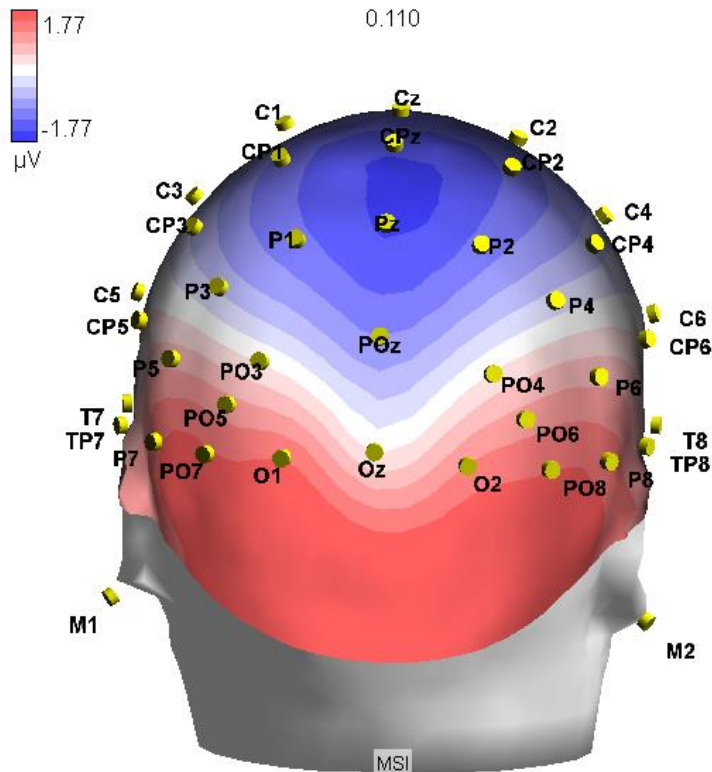


Figure 11 Localized activity in electrodes PO7, O1, O2, and PO8 from 100-120 ms from the overall grand averaged heat maps.

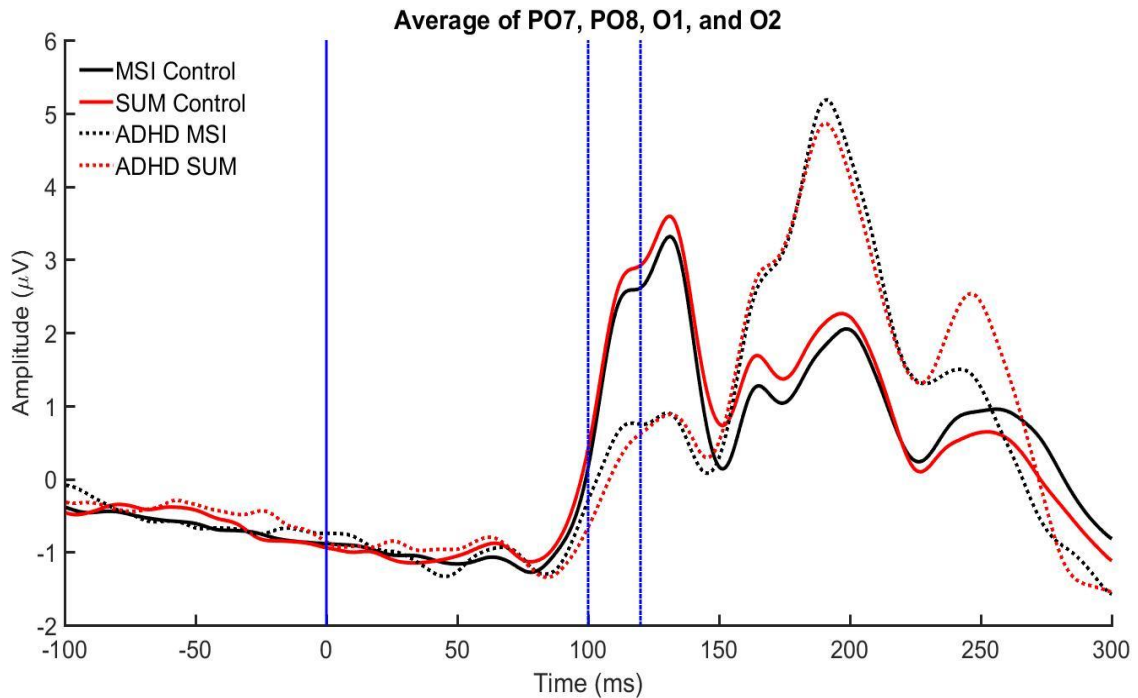


Figure 12 Graph highlighting 100-120 ms over parietal occipital regions where an interaction between condition and group was approached.

Discussion

Through the utilization of a simple RT task while recording continuous EEG, several distinct patterns of MSI were observed in both neurotypical controls and adults with ADHD. To our knowledge, this study is the first of its kind to inquire into the process of MSI in ADHD. Through doing so, both behavioural and neurological patterns of MSI can be discussed in relation to both RT differences and ERP differences both between conditions (A, V, and AV multisensory) and between groups (ADHD and neurotypical control).

Both groups responded fastest to the multisensory stimulus, which was predicted. Previous studies utilizing a similar paradigm had found that an AV multisensory condition resulted in the quickest RT when compared to an auditory or visual unisensory condition (Brandwein et al., 2015; Brandwein et al., 2013; Brandwein et al., 2011). Interestingly, both

groups responded slowest to the unisensory auditory stimulus; although unexpected due to the speed of typical auditory processing, a similar finding occurred in previous studies utilizing similar semantically congruent conditions (A, V, and AV multisensory) in different special populations (Farid et al., 2018; Laurienti et al., 2004). Although the auditory condition had the longest RTs in the current study, it had similar auditory RTs to that of other studies hovering around 300 ms (Brandwein et al., 2013; Brandwein et al., 2011) (i.e. the sample from our study had quicker responses to the visual and multisensory stimulus but similar auditory responses compared to previous research). Although there was not a significant main effect of group, post-hoc analysis revealed that males with ADHD responded faster than male controls.

The type of auditory stimulus utilized for this research may have influenced the behavioural results in this study, as an auditory verbalization was utilized as opposed to a pure-tone stimulus. When pure-tone auditory conditions are used, one would typically expect to see quicker responses than to those of a visual condition (Shelton & Kumar, 2010). Therefore, this indicates that the semantics involved in the auditory condition may have influenced the behavioural results observed as longer processing time would have been necessary. Other research has also elucidated that in certain multimodal paradigms, the visual stimulus may dominant over the auditory and drive the interaction (Colavita, 1974), possibly explaining why the visual stimulus was the quickest unisensory condition in the paradigm utilized here. However, because this study was investigating MSI, where the auditory and visual stimuli need to be semantically congruent for optimal integration, the verbalization of the word “red” was chosen as the auditory stimulus.

This study was the first of its kind to assess MSI in adults with ADHD, which left little guidance for how to best assess the process of MSI from a neurological perspective. Based on

methodology from previous literature assessing MSI in both neurotypical individuals and those with ASD, we found that specific patterns of MSI were apparent. MSI was found to have occurred in both groups, however, there were some differences in how that activity occurred in each group (i.e. the patterns of MSI were not exactly the same); this may be a result of attentional deficits in those with ADHD, as MSI is dependent on the level of attentional allocation to stimuli (Perrault Jr et al., 2005). MSI occurred in both groups over central parietal regions from 100-140ms. From 140-160 ms a main effect of both condition and group was found over parietal-occipital regions (MSI occurred in both, but different pattern). Interestingly, many of the differences found, were in regions that previous literature has found to be altered in those with ADHD (parietal, occipital, etc.) (Duerden et al., 2012; Proal et al., 2011; Valera et al., 2007), suggesting that the structural alterations result in different neural processing of multisensory stimuli.

Differences in brain activity between those with and without ADHD were found. For instance, from 110-120 ms it was found that those with a diagnosis of ADHD had significantly smaller ERPs than neurotypical controls. At this latency, controls also had a more positive sum waveform when compared to their multisensory waveform, while the opposite was true for the ADHD group as their multisensory waveform was more positive than their sum waveform. A second time period of 100-120 ms also demonstrated differences in brain activity over parietal-occipital regions, where the ADHD group again had much smaller ERPs than the neurotypical controls. The brain activity in response to the multisensory stimulus indicated that there is a difference in overall brain activity in this brain region and latency in those with a diagnosis of ADHD. The thinner cortical matter in these regions present in adults with ADHD may have influenced the electrical potentials that occur, resulting in an attenuated or altered signal.

The brain regions where a group difference was found between those with and without a diagnosis of ADHD coincides with the regions that are known to have altered structure in those with ADHD. For instance, the parietal and occipital regions of the brain are often thinner in those with ADHD (Duerden et al., 2012; Durston, Pol, Schnack, Buitelaar, Steenhuis, Minderaa, Kahn, et al., 2004; Proal et al., 2011; Valera et al., 2007) and were also the regions where this study found significant differences in activity. Although analysis was limited to regions and latencies of maximal multisensory activity, there are evident differences in general brain activity between those with and without ADHD. It is possible that the alterations to cortical matter structure resulted in altered function and electrical potentials at the latencies and region assessed in this study. Although the cortical activation differed between groups, there was evidence that those with ADHD did have MSI occur and seemed to have quicker responses to sensory conditions. This could indicate a behavioural enhancement, however the simple nature of the task did not require complex cognitive processing, only recognition, so the task does not allow us to draw conclusions about the impact of these faster responses on cognitive function. Given that this difference was significant when comparing only male participants (n = 7 ADHD and 8 control), it may be that females with ADHD have more variable responses, and future work should also endeavour to include sufficient females to allow sex to be included as a covariate

One potential limitation to this study was the small sample size, potentially underpowering the results resulting in type II error. However, overall this study was the first to elucidate that there are patterns present indicative of MSI in adults with ADHD. EEG revealed that those with ADHD have early MSI occurring over central, parietal, and occipital regions. An additional consideration is the use of an auditory verbalization which would have slowed auditory responses relative to a pure-tone auditory stimulus. However, this study purposely

utilized an auditory verbalization of the word red, in order to ensure semantic congruence with the visual stimulus of the colour red, which is essential for optimal MSI. A pure tone auditory stimulus would not have been semantically congruent, and hence was not utilized.

This is the first study of its kind to show behavioural and neural differences in MSI in young adults with ADHD. This current study only investigated simple response tasks, which did not require participants to discriminate between stimuli. Although there were specific behavioural patterns found between groups and conditions, future work should consider utilizing a more complex task where participants are to respond both as quickly and as accurately as possible, such as a two-alternative forced-choice discrimination task. Therefore, a second study was designed and carried out, which will be discussed in the next portion of this thesis, assessing the neurological and behavioural results of a more complex multisensory task.

Study Two Manuscript

Introduction

Attention-deficit/hyperactivity disorder (*ADHD*) is a neurodevelopmental disorder that is often diagnosed during childhood, with 11% of children receiving a diagnosis (Visser et al., 2014). A diagnosis of ADHD is usually given when symptoms are persistent and interfere with day-to-day activity. These symptoms include but are not limited to hyperactivity, impulsivity, and inattention (Visser et al., 2014). Although ADHD is common in childhood, it often persists into adulthood and affects 50% of adults that were diagnosed as children (Sadock et al., 2000). It is more common for men to receive a diagnosis of ADHD than it is for women to (5.5% vs. 2%) (Amiri et al., 2014). Although many of the characteristic symptoms of ADHD are typically described as behavioural, there are also neurological alterations present (Duerden et al., 2012; Proal et al., 2011).

Individuals with ADHD have been found to have alterations to their brain structure and function through the use of imaging modalities. The literature has identified that there is global thinning in temporal, frontal, parietal, and occipital lobes in those with ADHD (Duerden et al., 2012; Durston, Pol, Schnack, Buitelaar, Steenhuis, Minderaa, Kahn, et al., 2004; Proal et al., 2011; Valera et al., 2007). Although cortical thinning is a commonly found neurological difference in those with ADHD, there are also areas that have been found to have thicker grey matter (Duerden et al., 2012). The pre-supplemental motor area and right-hemispheric primary somatosensory cortex have increased grey matter volume (Duerden et al., 2012). These differences in brain structure are not merely limited to one focal area, indicating that there may quite possibly be differences to how those with ADHD perform many sensory processes due to altered structural composition.

Multisensory Integration (*MSI*) is a sensory process that is crucial for many day-to-day activities. When *MSI* is working well it can result in shorter response times (*RT*) and a better comprehension or understanding of a given stimulus. *MSI* describes how the nervous system processes and subsequently integrates all of the simultaneously occurring stimuli from the world around you. Individuals are constantly being exposed to afferent information from the environment in the form of auditory, visual, somatosensory, and olfactory stimuli for example. When in many common social settings, the extent to which your brain can integrate the auditory stimuli from things colleagues are saying and the visual stimuli associated with that is crucial, and this is known as audiovisual (*AV*) *MSI*. Previous literature has shown that any alterations to how individuals execute *AV* *MSI* can significantly change ones ability to socialize and interact with peers, as was found in those diagnosed with autism spectrum disorder (*ASD*) (Brandwein et al., 2015; Brandwein et al., 2013).

There are several brain regions that are highly implicated in the process of *MSI*. These regions include but may not be limited to the superior colliculus (*SC*) which is a subcortical structure, the region surrounding the superior temporal sulcus (*STS*), and the parietal region (Brandwein et al., 2011; Meredith et al., 1987; Paraskevopoulos & Herholz, 2013). The parietal region is often referenced in *MSI* literature as being one of the main sites where this process occurs (Brandwein et al., 2015; Brandwein et al., 2011; Molholm et al., 2006; Moran et al., 2008). Although *MSI* in *ADHD* has yet to be assessed, the alterations within the parietal region in this population indicate that *MSI* may be altered.

One of the common methods to assess *MSI* is by utilizing electroencephalography (*EEG*), and doing so based upon the Principle of Superposition of Electrical Fields. Based upon this principle, two waveforms must be created for analysis. First, a waveform in response to the

multisensory stimulus will be created. Secondly, a “sum” waveform will be created, which is done so by summing the waveforms to the two unisensory stimuli conditions (auditory and visual). Any significant divergence, $ERP_{AV} \neq ERP_A + ERP_V$, between the two waveforms (multisensory vs. sum) per participant indicates that MSI occurred. If MSI did not occur the two waveforms would be very similar if not identical, because the two components (auditory and visual) of the multisensory stimulus would have been processed as two unisensory stimuli. Therefore, any significant divergence can be taken as a quantitative method showing that MSI did occur at certain time points and brain regions.

Study one of this thesis utilized this method during a simple RT task in adults with ADHD. Through this we found that adults with ADHD do in fact have MSI occurring within certain brain regions. Interestingly, the main effects of group/diagnostic status (ADHD vs. no ADHD) were found over parietal/occipital regions, which are known to be altered in adults with ADHD (Duerden et al., 2012). In study one, those with ADHD responded faster to each stimulus type (auditory, visual, and AV multisensory) in the simple RT paradigm, with this effect being significant when comparing the males between groups. This led to a second question, as to whether this would be the case when faced with a more complex task, such as a two-alternative forced-choice discrimination task where both RT and accuracy were assessed. When both accuracy and RT are being assessed, the speed-accuracy trade-off may result in faster responses being less accurate while slower responses allow for a more accurate perception and therefore response (Heitz, 2014)

The purpose of the current study was to assess whether adults with ADHD respond faster than neurotypical adults when faced with a more complex decision making task, and whether those with ADHD trade accuracy for speed. Based upon the results of study one, it was

hypothesized that those with ADHD would have MSI occur when assessing EEG, and respond faster to each stimulus type, but that there would also be a speed-accuracy trade off resulting in decreased accuracy for those with ADHD.

Methods

Participants

This study was approved by the University of Ontario Institute of Technology Research Ethics Board (#14507) and participants were recruited from the student body, through the use of in-course announcements and posters placed around the campus. Prior to participating, participants gave written informed consent. The participants were young adults (aged 18-35 years old) with ADHD, with a control group of neurotypical young adults (18-35 years old). The participants with ADHD had previously received a diagnosis of ADHD from a health care professional, they self-reported the age at which they were diagnosed, as well as any medication that they were taking to control their symptoms at the time of participation. The mean age of the ADHD group was 23.7 ± 3.3 years old ($n = 10$, 3 females) and the mean age group of the neurotypical control group was 21.7 ± 1.8 years old ($n = 12$, 4 females). The mean age of ADHD diagnosis was 13.7 ± 7.7 years old.

The adult ADHD Self-Report Scale (ASRS-v1.1) checklist questionnaire was also completed by all participants at the beginning of the session. The ASRS-v1.1 encompasses 18 questions that are highly correlated to the diagnostic criteria set out by the DSM-IV (Dankner et al., 2017), and are rated on a 5-point Likert scale ranging from “never” to “very often” for each question. This screening tool is highly sensitive for predicting ADHD symptomatology (van de Glind et al., 2013). In this questionnaire, when participants indicate “sometimes”, “often”, or “very often” to many of the questions, it is suggestive of ADHD. The questionnaire was included

to ensure that we did not inadvertently include participants with potential ADHD in the control group, and equally that we did not include a participant in the ADHD group whose symptoms may have resolved. Responses indicated that those diagnosed with ADHD almost always selected “sometimes”, “often”, or “very often” with respect to each question, whereas the neurotypical control group selected “never” or “rarely” for almost all question. Participants reported whether they were currently taking medication for their ADHD, with 6 reporting that they were currently taking medication. Medications reported included Adderall, Concerta, and Vyvanse. Participants completed the Edinburgh Handedness Questionnaire, which was used to determine which hand was most dominant. Results indicated left-hand dominant, right-hand dominant, or ambidextrous. The number of left-handed participants in each study group was similar, this was to negate any differences in RT that may be due to the fact that not everyone is right-hand dominant (response hand), so that any electrophysiological and RT changes were not merely a result of a handedness-bias. The ADHD group had 1 left-handed, 5 right-handed, and 4 ambidextrous participants while the neurotypical control group had 1 left-handed, 10 right-handed, and 1 ambidextrous participant’s. An EEG safety checklist was also completed, to ensure that participants did not have a recent (past 5 years) history of epilepsy, concussion, stroke, or brain injury that may influence the electrophysiological results or make the task unsafe for them to participate in.

Some of the participants were also included in study one, however the current study utilized a different RT paradigm, meaning participants were naive to the two-alternative forced-choice discrimination task, thus indicating that there wouldn’t be any differences in results due to motor learning.

Stimuli

Auditory Alone

The unisensory auditory stimulus was representative of the colour red, blue, or green (duration ~300ms) which was in a female voice from speakers placed bilaterally to the computer screen.

Visual Alone

The unisensory visual stimulus was a circle filled with the colour red, blue, or green on a black background which lasted for 250ms.

Multisensory

The multisensory stimulus consisted of the auditory and visual stimuli occurring simultaneously. The stimulus was always semantically congruent, meaning that when the red circle appeared the auditory verbalization was also red, and when the blue circle appeared the auditory verbalization was also blue, and so on.

Procedures

Multisensory integration was measured utilizing a two-alternative forced-choice discrimination task with semantically congruent redundant stimuli, which is a similar paradigm that has been used successfully in previous research to dissociate differences in multisensory functionality (Farid et al., 2018; Laurienti et al., 2004). This task emphasizes both RT and response accuracy, assessing whether there are differences between these two variables when stimuli are auditory, visual, or multisensory in nature. This task was designed and implemented using E-Prime 2.0 Professional software by Psychology Software Tools, Inc.. When the multisensory stimulus occurred the visual and auditory components were always congruent.

Participants completed 2 blocks which were approximately 15-18 minutes each. Each block consisted of 110 auditory-alone stimuli conditions, 110 visual-alone stimuli conditions,

and 110 multisensory stimuli conditions, with there being 330 total stimuli per block. Fifty stimuli from each condition were representative of red, while fifty were representative of blue. Ten stimuli within each condition were representative of green (~10% of total trials), and did not require a response. These were used as “catch-trials” to promote attention maintenance. Each stimulus was preceded by a fixation cross which was utilized to decrease movement noise, as participants were instructed to sit as still as possible and maintain their attention on the cross. The stimuli were presented in random order with equal probability, with an inter-stimulus-interval (*ISI*) of 1000-3000 ms. This varied interval minimized participant’s ability anticipate the latency at which each stimulus was going to be presented, and therefore would respond upon hearing and/or seeing a stimulus and decrease the occurrence of them “jumping the gun”. To respond to a stimulus that was red the right index finger was used, while to respond to a blue stimulus the right middle finger was used. Participants were instructed to respond as quickly and as accurately as they could in response to each stimulus. Responses were recorded anytime at or after stimulus onset (0ms). This occurred while continuous EEG was recorded. It should be noted that although this study paradigm technically consisted of three possible stimuli (red, blue, or green), 2 where a behavioural response was necessary and quantified (red and blue), the necessary response inhibition in order not to respond to the green stimulus should be noted, although this was not included in the scope of the current study.

A low-latency Chronos® response box was used to receive and record RT (ms) and accuracy (red or blue) after each stimulus presentation. The Chronos device is designed by Psychology Software Tools and is highly compatible with E-Prime 2.0 Professional software. This device was used due to its high reliability and millisecond accuracy when recording RTs.

The response keys are also highly sensitive to pressure, and therefore the slightest button press will result in a recorded response, thus decreasing the latency associated with movement time.

Data Analysis

Statistical Analyses

Behavioural

RT and accuracy were the main variables of interest for this task. A 2 group (ADHD vs neurotypical) by 3 sensory condition (A, V, multisensory) mixed factors ANOVA was completed, with repeated measures on the last factor; this was done to assess whether any significant ($P < 0.05$) differences were present. Mean RT was calculated per participant in response to each stimulus type (A, V, MSI). Partial eta squared (η^2) was used to report effect sizes for results where trends are reported, with a small effect as 0.01, medium as 0.06, and a large effect as 0.14 (Richardson, 2011).

Accuracy was also analyzed, being the number of correct responses to each condition (A, V, MSI), and were compared between groups using an ANOVA. Correct being when the right index finger responded to a red stimulus (A, V, MSI) and when the right middle finger responded to a blue stimulus (A, V, MSI). Any RTs that were ± 2 SDs of a participants' average RT were not included in the analysis of RT or accuracy, as the participant likely "jumped the gun" or was not paying attention to the stimulus. The caveat for this being that the lower limit could not be less than 100 ms; in the cases where subtracting 2 SDs from the average resulted in a time value less than 100 ms, 100 ms was used in its place. Similar to Farid et al. (2018) and Laurienti et al.'s study (2006) incorrect responses were included when calculating RTs (Farid et al., 2018; Laurienti, Burdette, Maldjian, & Wallace, 2006). This was done to ensure that the data included in the RT and accuracy analyses were from the same participant responses.

ERPs

A Waveguard™ 64-electrode EEG cap was utilized to collect brain electrical activity. The Waveguard™ cap was connected to a TMSi REFA-8 amplifier with 64 EEG channels, 4 bipolar channels, and 4 auxiliary channels and was collected through asaLab™ at a sampling frequency of 2048 Hz. EEG data was processed offline using ANT 4.10.1 and Matlab R2017a. Artefacts resulting from muscle activity and blinking were removed based upon manufacturer specifications. A band-pass filter was utilized, with a low-cut off of 1.6 Hz to remove constant slow-wave activity which would otherwise be represented twice in the summed waveforms and a high cut-off of 45 Hz to remove any artefact from surrounding electrical equipment, this was done with a slope of 24 db/octave, which was applied to individual data sets. Artefact rejection was then also performed, excluding any waveforms that were $\pm 100 \mu\text{V}$. Data was then averaged per condition into 600 ms epochs (-100 to 500 ms) surrounding stimulus onset per participant, to give three averages for each participant.

Average waveforms from the visual-alone and auditory-alone conditions were then summed (known as the sum-waveform), which could then be compared to the multisensory ERP (multisensory waveform) (Molholm et al., 2002). If the neural responses were the same to the two unisensory stimuli (sum waveform) and the multisensory stimulus (multisensory waveform) (they did not interact), the ERPs would be the same according to the principle of superposition of electrical fields (Molholm et al., 2002). However, if interaction or multisensory facilitation did occur in response to the simultaneously occurring stimulus, then the two ERP waveforms would not be identical, they would diverge (Molholm et al., 2002). The ERP divergence between this summed-waveform and the multisensory waveform can then be compared between groups,

assessing whether there are differences in MSI. Group grand-averages were created for visualization of the overall peak-differences, which can be seen in the included figures.

All ERP processing was done offline using ASA 4.10.1 software. As has been done in the previous literature (Brandwein et al., 2015; Brandwein et al., 2011; Giard & Peronnet, 1999; Molholm et al., 2002; Molholm et al., 2006), multisensory interactions were analyzed by comparing the AV multisensory waveform to a “sum” waveform. Any significant differences between the multisensory activity and the sum waveform indicate that the two simultaneously occurring stimuli interacted (i.e. were not processed in a unisensory fashion).

In order to not bias the analysis to areas where we may find differences in cortical activity between neurotypical controls and those with ADHD the electrodes and time frames for analysis were chosen based on an overall grand-average heat map for the AV multisensory stimulus (i.e. grand-average including all participants regardless of diagnostic status). This grand average was created using all participants’ data (ADHD and neurotypical) so as not to bias regions of interest to one group’s activity. Time windows for analysis were constrained to early multisensory interactions, between 0 ms to 250 ms post stimulation. This was due to the fact that anything past this time frame becomes heavily noise induced with sensorimotor activity, and therefore is not strictly representative of early MSI. For each time frame and region chosen for analysis, averaged-data per participant was added to a mixed factors ANOVA with 2 groups (ADHD or neurotypical) and by 2 stimulus types (multisensory vs. sum) within a given time-frame. Scalp regions were represented by an average of 2-4 composite electrodes, being the electrodes that showed greatest activity during that time frame. The regions and time-frames chosen are similar to those discussed in previous literature (Brandwein et al., 2015; Brandwein et al., 2011; Foxe et al., 2000; Giard & Peronnet, 1999; Molholm et al., 2002). Greenhouse-Geisser

corrections were used when appropriate to report P values. All statistical tests were completed using SPSS version 24 (Nie et al., 1970). All tests were checked for normality using Shapiro-Wilk's test and homogeneity of variance using Levene's test. The assumption of sphericity was checked using Mauchly's test and when necessary Greenhouse-Geisser values were used to report more conservative p values.

Alpha for all analyses was set to $P < 0.05$.

Results

Behavioural

Response Time (ms)	Visual	Multisensory	Auditory
ADHD	464 (± 39)	449 (± 32)	609 (± 34)
Control	512 (± 68)	502 (± 67)	663 (± 91)

Table 2 The average response time (RT) in milliseconds for each group and stimulus condition (mean \pm standard deviation).

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

Table 3 The average accuracy to each group and stimulus condition (mean \pm standard deviation), where a score of 1.00 would imply a perfect score.

The mean RTs for both groups (ADHD and control) for each condition can be found above in table 2 as well as illustrated in figure 13. A 2 group (ADHD vs neurotypical) by 3 sensory condition (A, V, multisensory) mixed factors ANOVA was completed, with repeated measures on the last factor. This analysis revealed that participants in both the ADHD and control groups responded fastest to both the visual-alone stimulus (464 ms \pm 39; 512 ms \pm 68) and multisensory stimulus (449 ms \pm 32; 502 ms \pm 67) in comparison to the auditory-alone stimulus (609 ms \pm 34; 663 ms \pm 91), thus revealing a main effect of stimulus condition

($F_{1,313,26,250} = 277.972$; $P < 0.001$). Those in the ADHD group responded faster to each condition in comparison to neurotypical controls, revealing a main effect of group ($F_{1,20} = 4.397$; $P = 0.048$).

The average accuracy for both groups (ADHD and control) in response to each stimulus condition can be found above in table 3 and the overall average accuracy for each stimulus condition can be found in figure 14. A 2 group (ADHD vs neurotypical) by 3 sensory condition (A, V, multisensory) mixed factors ANOVA was completed, with repeated measures on the last factor. This revealed that both groups responded most accurately to the auditory-alone stimulus (0.9723 ± 0.0255 ; 0.9759 ± 0.0202) when compared to the visual-alone stimulus (0.9425 ± 0.0302 ; 0.9649 ± 0.0243) ($F_{2,40} = 8.933$; $P < 0.001$). There was a trend for those with ADHD to be less-accurate when responding to stimuli; however, this group effect doesn't reach significance ($F_{1,20} = 2.750$; $P = 0.113$; partial $\eta^2 = 0.121$), although a medium effect size was shown.

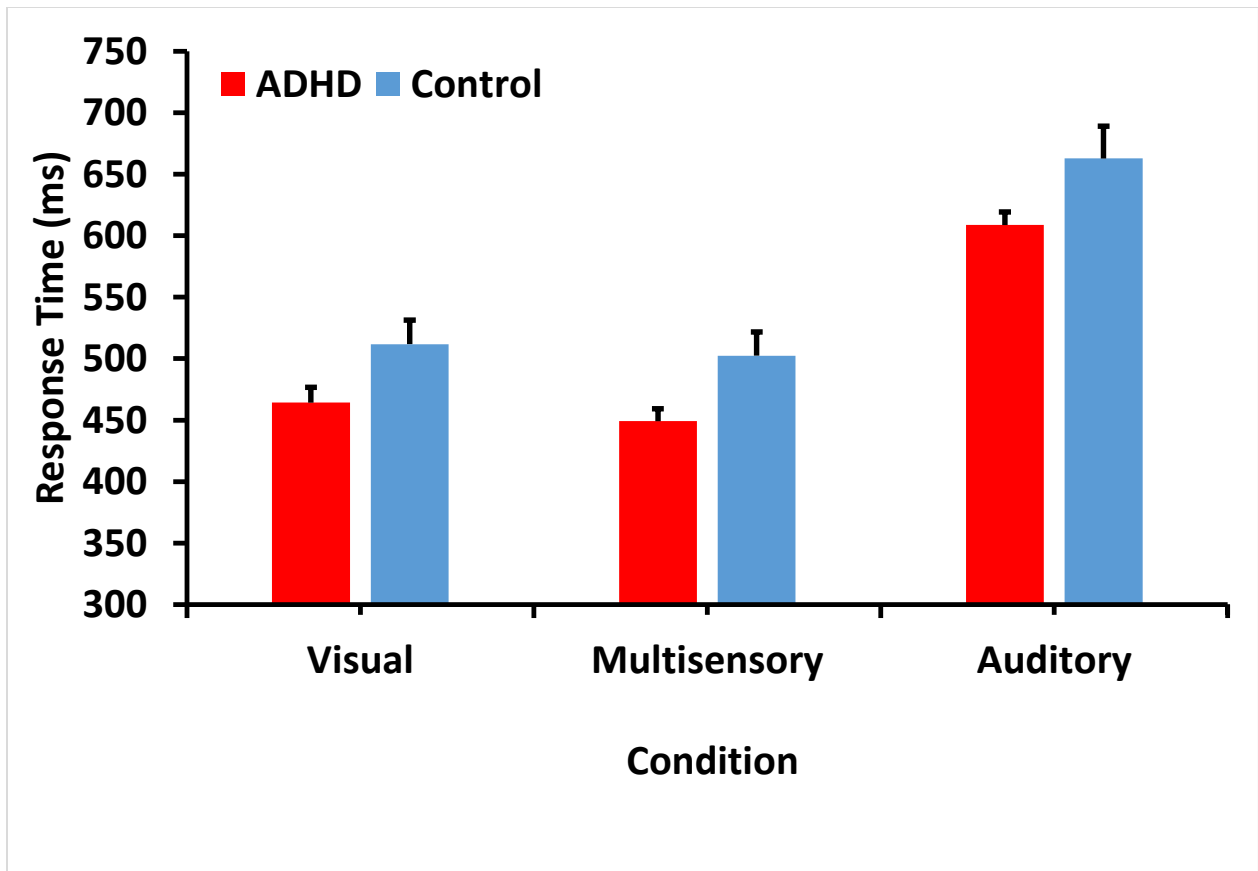


Figure 13 Mean response time (RT) per condition per group (ADHD and control), indicating a main effect of stimulus condition for both the visual-alone and multisensory conditions in comparison to the auditory-alone condition. Overall, those in the ADHD group responded faster to each condition compared to controls.

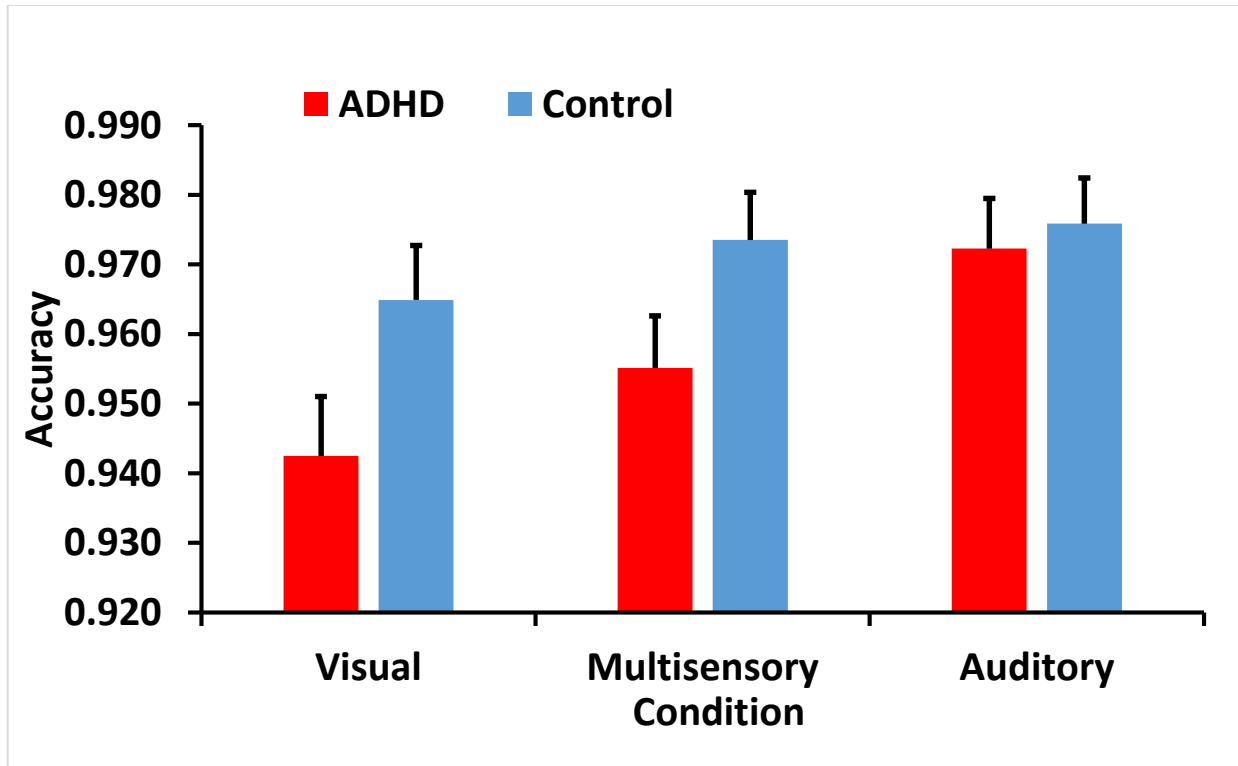


Figure 14 The average accuracy for each stimulus condition across groups (ADHD and control), where the auditory alone condition resulted in the most accurate responses. A value of 1.0 would indicate a perfect response.

Neurophysiological

When assessing the grand averaged topographical heat maps, several specific latencies and regions of interest became evident. These were distinguished as maximum negative and positive electrical potentials at distinct regions and times. These were identified as regions with the most prominent activity, as seen in several of the figures below (15, 17, 19, 21, 23, and 25).

For the latency window of 110-130 ms over parietal occipital regions (PO7, PO8, O1, and O2) there was prominent positive electrical activity (figure 15). The ANOVA revealed a main effect of stimulus condition (multisensory vs. sum waveform) and an interaction between stimulus condition and diagnostic status (ADHD vs. neurotypical control). The multisensory

waveform significantly deviated from the sum waveform ($F_{1,20} = 4.537$; $P = 0.046$), indicating that MSI occurred in both groups at this time and regions of interest. There was also a group (ADHD vs. neurotypical control) by stimulus condition (multisensory vs. sum) interaction, indicating that the pattern of MSI that was occurring was different in each group. Tukey's test indicated that the ADHD group had greater MSI occur within this brain region and at this latency ($F_{1,20} = 5.255$; $P = 0.033$). This can be seen in figure 16 below as a more pronounced deviation in the ADHD sum and multisensory waveforms.

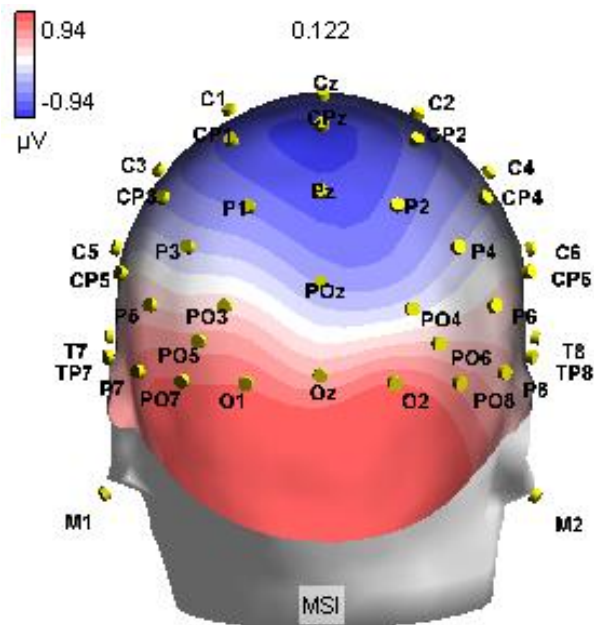


Figure 15 Localized positive activity in electrodes PO7, PO8, O1, and O2 from 110-130 ms from the overall group grand average heat map.

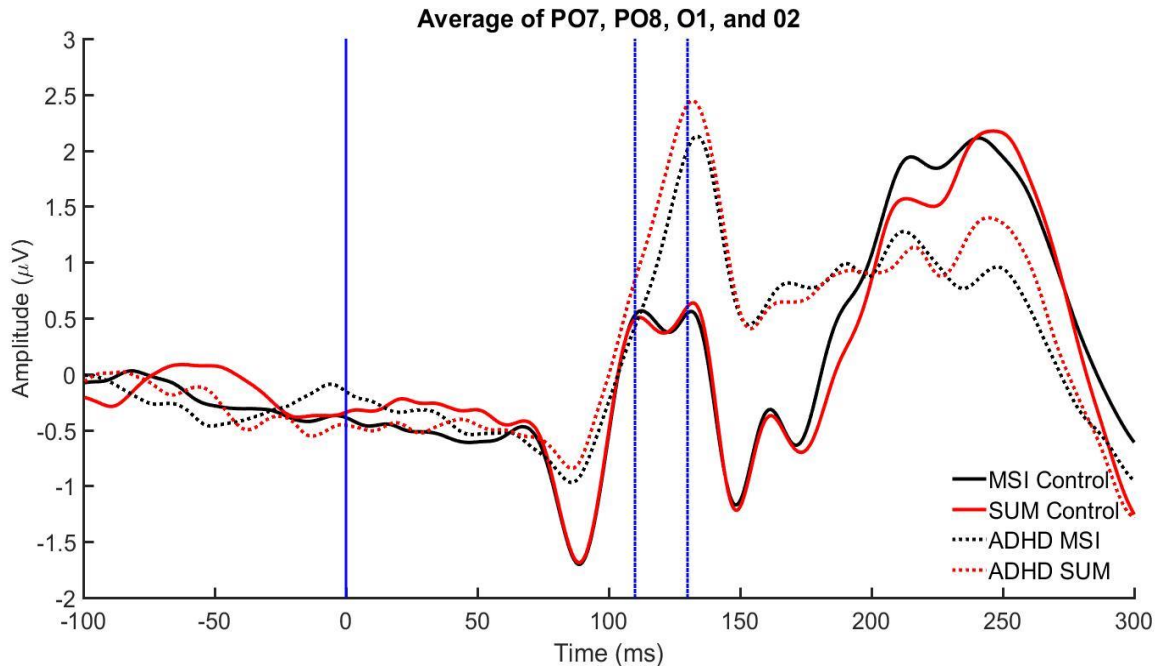


Figure 16 Graph highlighting the positive activity from 110-130 ms over parietal-occipital brain regions. Analyses indicated that the ADHD group had greater MSI occurring at this latency and brain region than controls, as indicated by a greater deviation between the sum and multisensory waveform.

A second region of interest occurred over right parietal occipital regions (O2 and PO8) from 130-140ms, which was observed as the most positive electrical activity at this latency (figure 17). A main effect was approached for both group (ADHD vs. neurotypical controls) and condition (multisensory vs. sum waveform). A main effect of stimulus condition was approached, indicating that MSI didn't quite occur in either group at this time point, as identified by an approaching significant divergence from the sum and multisensory waveform ($F_{1,20} = 3.907$; $P = 0.062$). The group differences approached significance as well ($F_{1,20} = 3.542$; $P = 0.074$). This relationship can be seen below in figure 18.

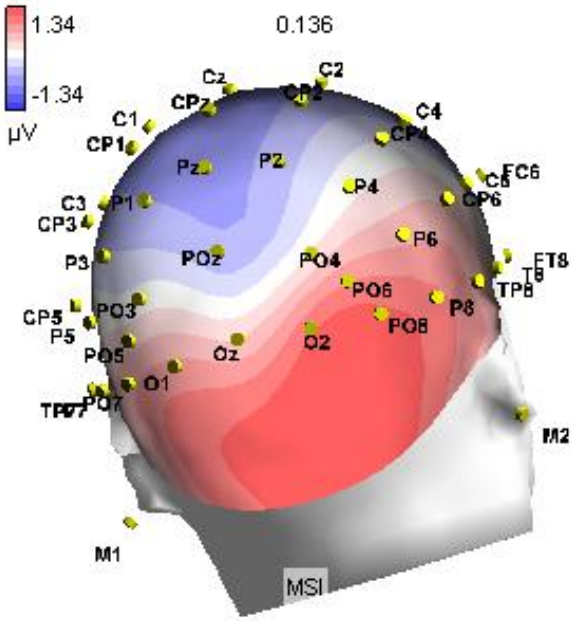


Figure 17 Localized positive activity over electrodes PO8 and O2 from 130-140 ms from the overall group grand average heat map.

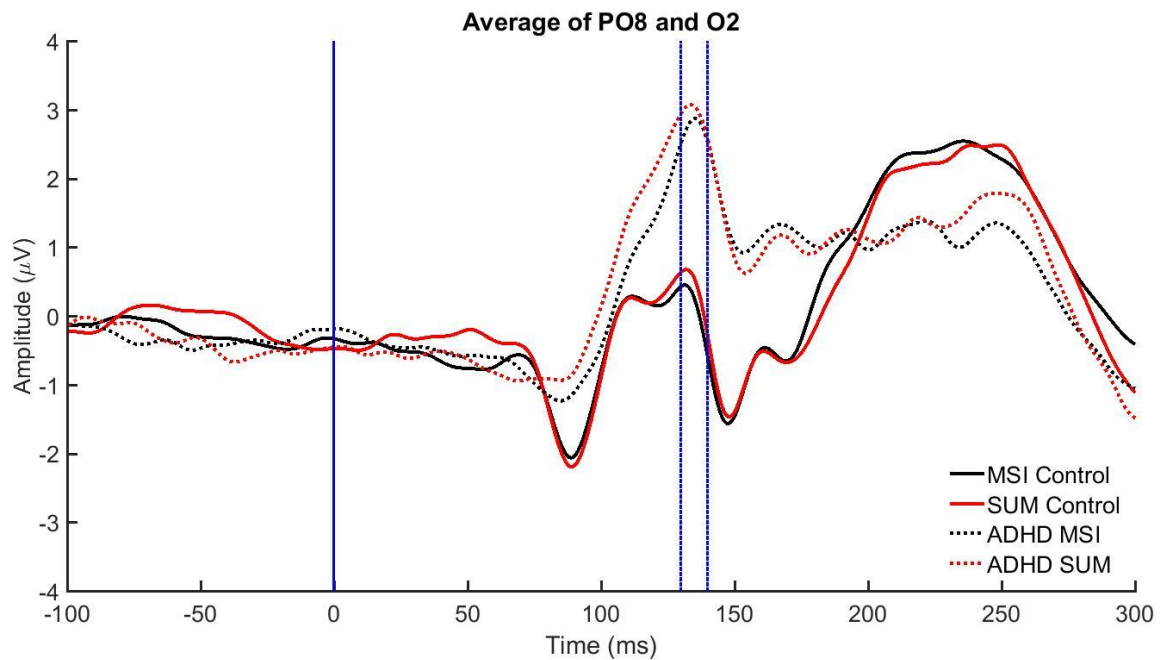


Figure 18 Graph highlighting the positive activity from 130-140 ms over parietal-occipital brain regions where an analysis of MSI approached significance ($P = 0.062$).

From 140-150 ms a main effect of group was identified over parietal occipital regions at electrode POz ($F_{1,20} = 7.225$; $P = 0.014$; figure 19) indicating that the control ERPs were significantly more negative than the ADHD ERPs. This can be seen in figure 20 below as a significant difference between the ADHD and neurotypical control cortical electrical activity. A graph depicting this can be found in figure 20.

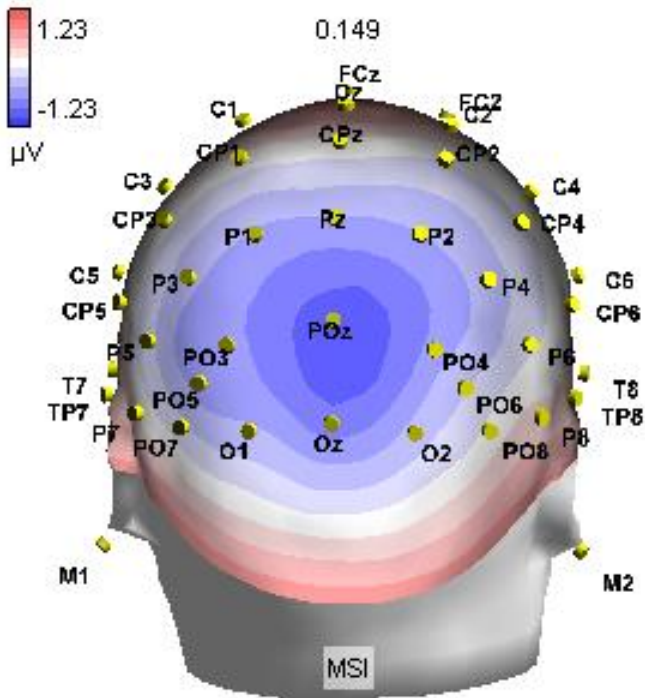


Figure 19 Localized negative activity from 140-150 ms over electrode POz from the overall group grand average heat map.

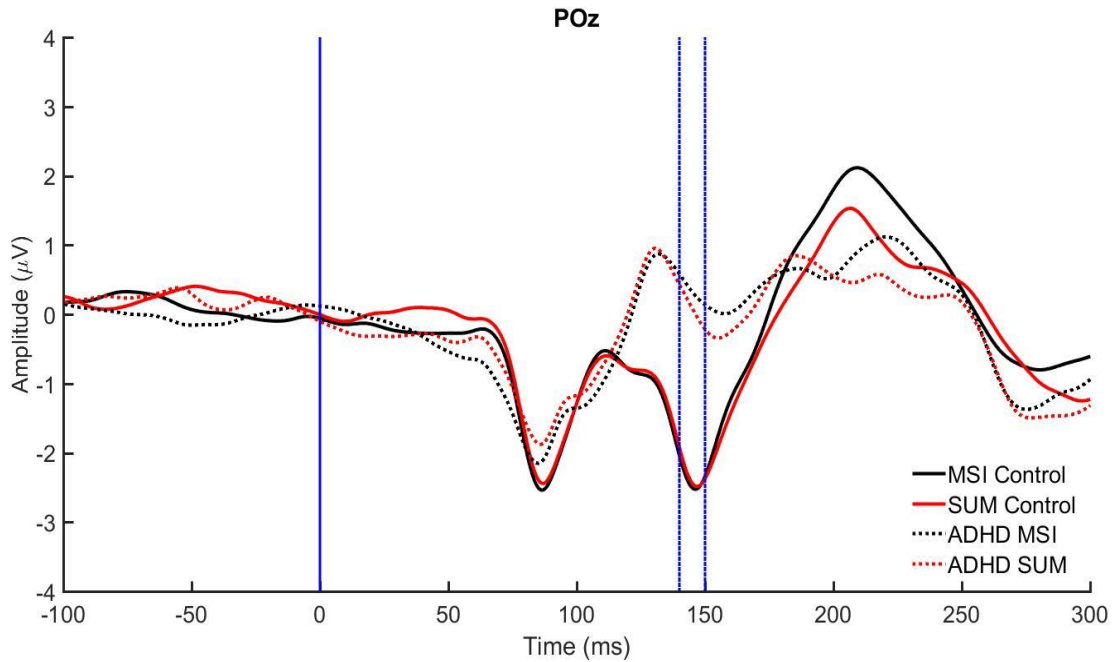


Figure 20 Graph highlighting negative activity from 140-150 ms over parietal-occipital brain regions where the control ERP is significantly more negative than that of the ADHD group.

From 170-220 ms over the occipital (Oz) region a main effect of stimulus condition (multisensory vs. sum waveform) was observed (figure 21). This was identified as a significant divergence between the multisensory and sum waveform ($F_{1,20} = 9.582$; $P = 0.0057$) as the multisensory waveform was more positive at this time point in both groups, indicating that MSI was occurring in both those with and without ADHD. An illustration of this can be seen in figure 22 below.

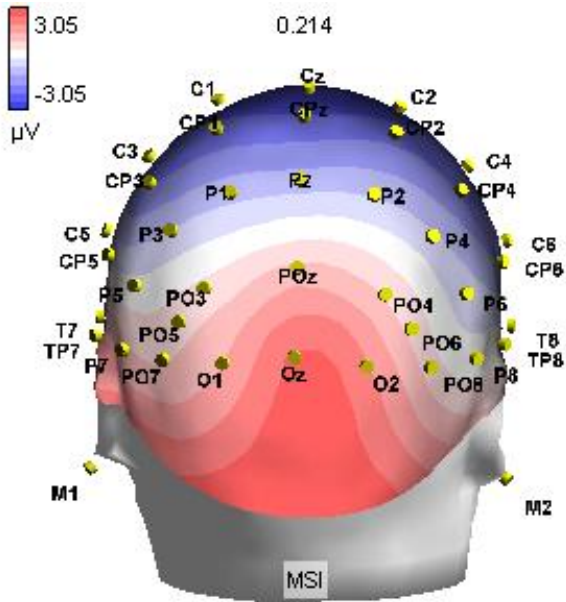


Figure 21 Localized positive activity from 170-220 ms over electrode Oz from the overall group grand average heat map.

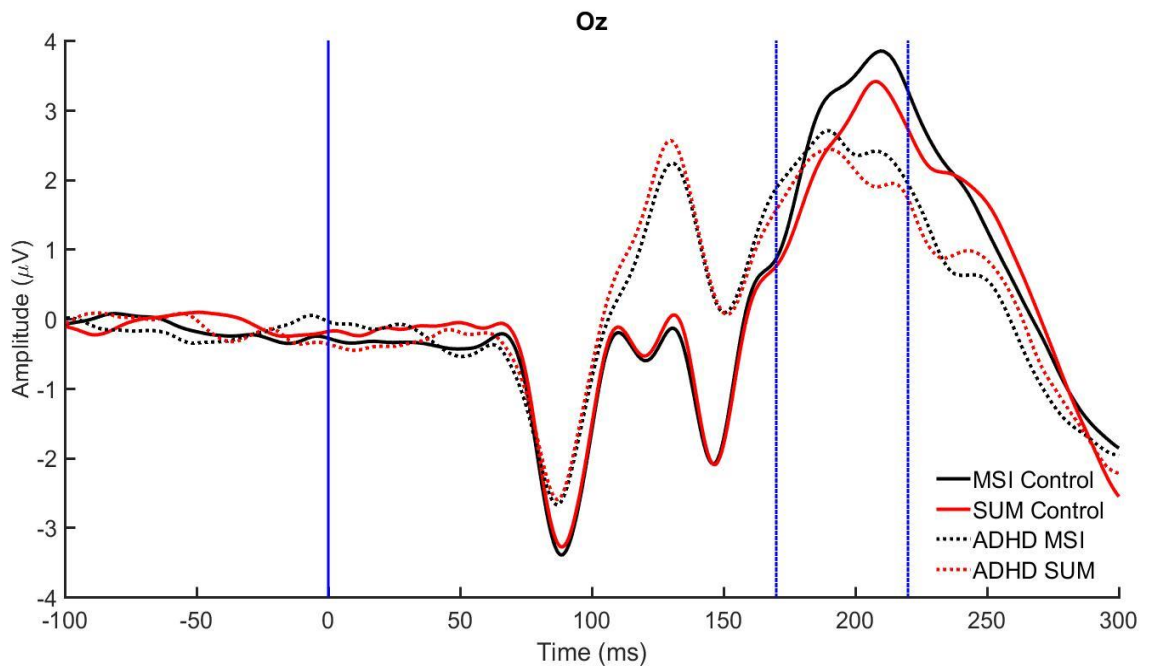


Figure 22 Graph highlighting the positive activity over occipital brain regions from 170-220 ms post stimulus presentation, indicating that MSI was occurring in both groups at this latency and brain region.

From 170-180 ms over the right hemispheric central parietal regions (CP4 and P6) a main effect of group was identified (figure 23). The cortical activity in those with ADHD was less-negative than that of the neurotypical controls ($F_{1,20} = 6.683$; $P = 0.018$). A main effect of stimulus condition was not identified at this time point. This is illustrated below in figure 24.

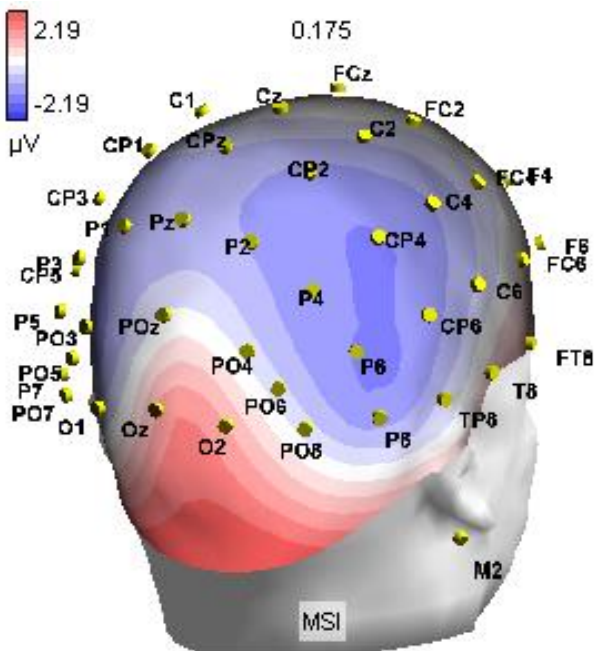


Figure 23 Localized negative activity over electrodes CP4 and PO6 from 170-180 ms from the overall group grand average heat map.

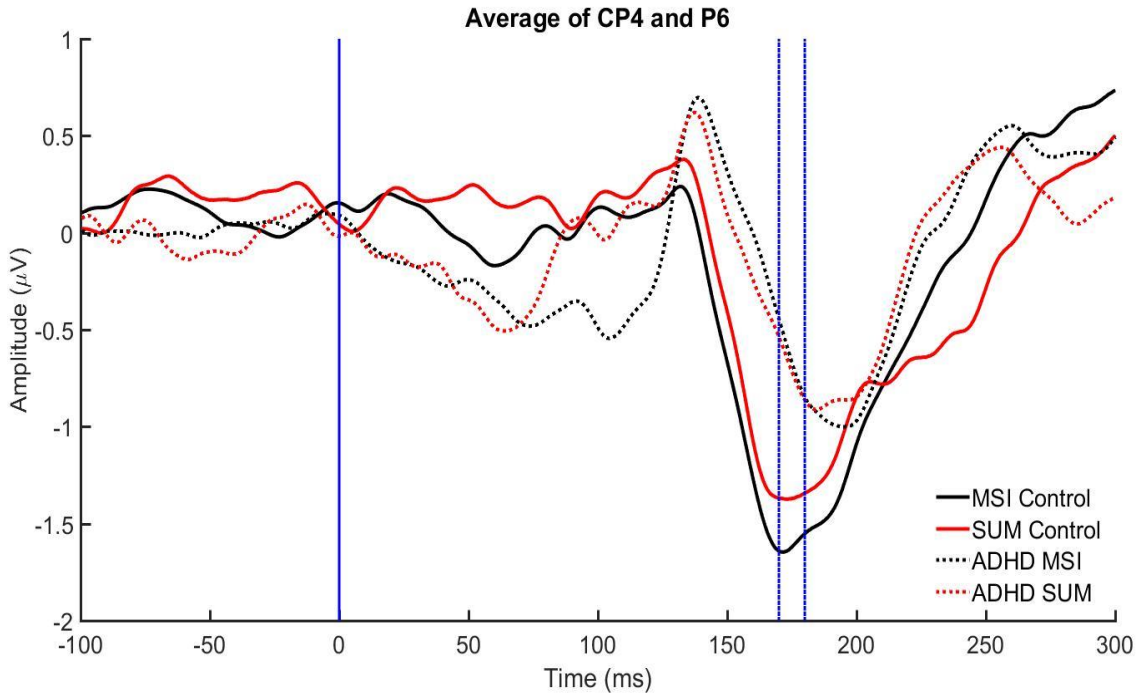


Figure 24 Graph highlighting negative activity over central-parietal brain regions from 170-180 ms where there is a significant difference between group activity, as the control ERPs are more negative than that of the ADHD groups ERPs.

Finally, from 180-220 ms over central electrodes (Cz, C1, and C2) a main effect of stimulus condition was identified (figure 25). The multisensory waveform was significantly more negative than the sum waveform over this region and at this latency ($F_{1,20} = 5.638$; $P = 0.028$), indicating that MSI was occurring in both groups. This can be seen in figure 26 below.

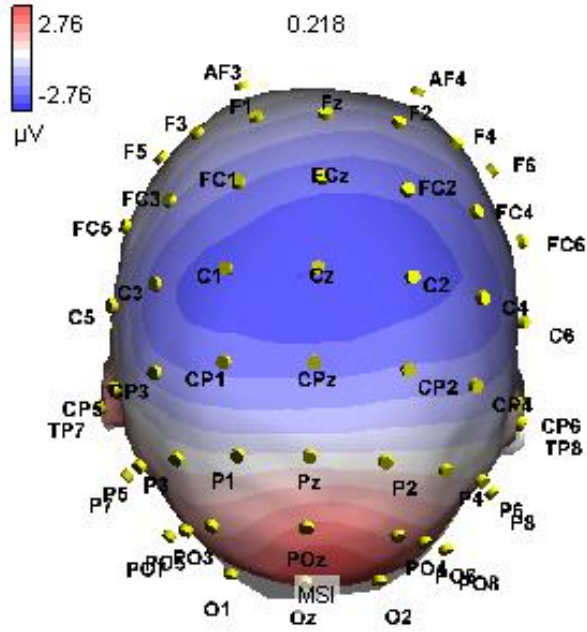


Figure 25 Localized negative activity over electrodes Cz, C1, and C2 from 180-220 ms from the overall group grand average heat map.

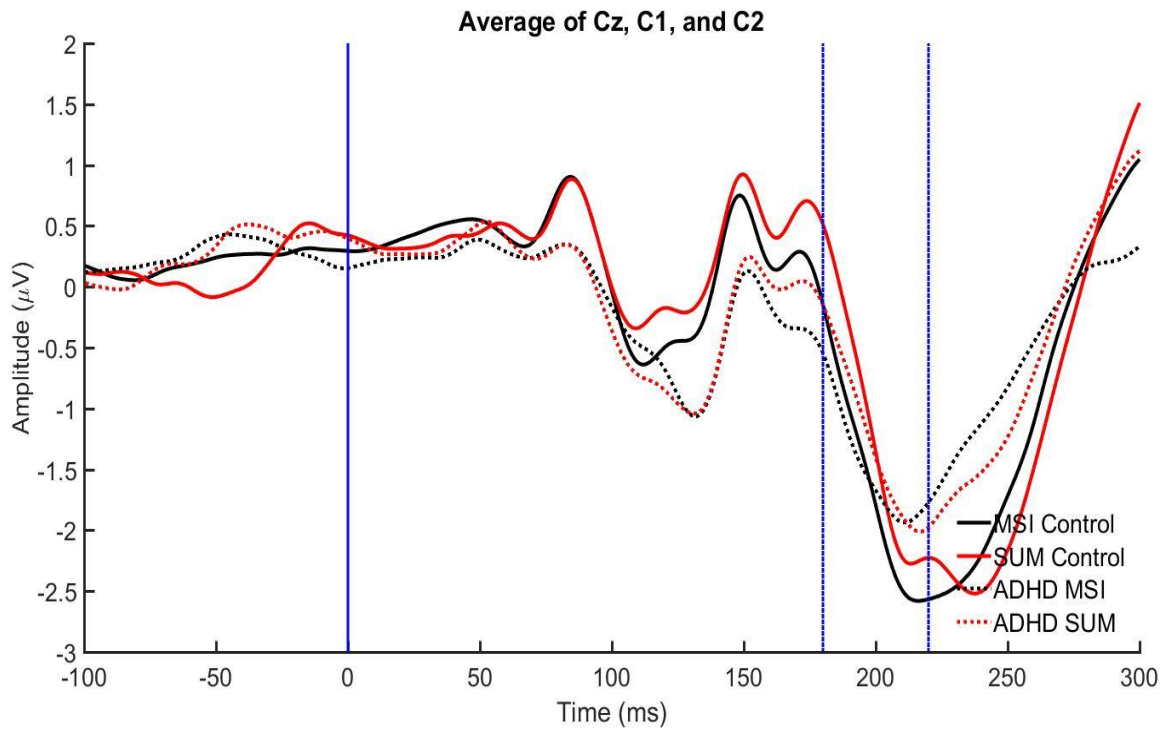


Figure 26 Graph highlighting the negative activity over central brain regions from 180-220 ms where a main effect of stimulus condition was identified, as the multisensory waveform (black) was significantly more negative than that of the sum waveform (red), indicating that MSI occurred in both groups (ADHD and controls) at this latency and brain region.

Discussion

Research on ADHD has often neglected to inquire into adults with ADHD, regardless of the fact that many children who are diagnosed with ADHD have symptoms that persist into adulthood. To date, no studies have inquired into MSI in individuals with a diagnosis of ADHD aside from study one in this thesis. Due to certain neurological characteristics it is probable that alterations to this important sensory process are likely present in adults with ADHD. This study is the first of its kind to utilize EEG and a two-alternative forced-choice discrimination task to assess MSI in adults with a diagnosis of ADHD. Through doing so, there were several significant findings in relation to both behavioural and neurological measures of MSI.

Both groups responded slowest to the auditory stimulus which was similar to our previous study and to other auditory RTs in the literature (Farid et al., 2018; Laurienti et al., 2004). In relation to the accuracy results this does make sense, as the auditory condition resulted in the most accurate response while also being the slowest response, this is in line with a speed-accuracy trade-off theory (Heitz, 2014). Both groups had faster responses to the AV multisensory and the visual unisensory conditions. This corresponds with literature indicating that a visual stimulus may tend to dominate an audiovisual interaction in certain response paradigms (Colavita, 1974). Although the multisensory stimulus had the shortest RT for both groups, this was not significantly different than the RT for the visual unisensory condition. Those with ADHD responded faster to each stimulus condition compared to controls when utilizing this

study paradigm, which may be related to the neurophysiological findings of this study as those with ADHD were found to have neural processing differences indicative of enhanced MSI. This may imply that the level of neural integration that occurs could have paralleled behavioural outcomes. The paradigm in this study allowed us to determine whether those with ADHD were faster at the expense of accuracy.

One of the main behavioural findings and an answer to one of our main research questions was that those with ADHD did in fact respond significantly faster to each stimulus condition (A, V, and AV multisensory) when compared to the neurotypical controls in this study. This finding was similar to the trend noted in study one. However, study one utilized a simple RT task, and therefore required far less complex cognitive processes to complete, as participants did not have to dissociate correct and incorrect responses from one another. This therefore led us to inquire into MSI with a more complex RT task to see how this would influence RT and accuracy in those with ADHD. This second inquiry was driven by the knowledge that executive function deficits are present in ADHD (Biederman et al., 2004), which includes decision making, potentially altering the multisensory processing capabilities when both accuracy and RT are assessed.

We hypothesized that the finding of adults with ADHD responding faster to stimuli may be related to the hyperactivity/impulsivity component of ADHD. However, this failed to acknowledge whether those with ADHD truly process sensory information faster and therefore form perceptions faster, or whether they have a quicker response due to impulsivity. The quicker RT may be a result of those with ADHD being hyper excitable and therefore able to respond to a given stimulus very quickly; however, they may not be fully-processing the stimulus that they are presented with, and therefore may not be able to respond accurately due to making a response

impulsively. Accuracy is an often essential component of responding to stimuli in day to day activities. Although those with ADHD did respond faster to each stimulus condition, they showed a trend to be less accurate than neurotypical controls, although this failed to reach significance with this paradigm and sample size, a medium effect size was found. This indicates that there may be a speed-accuracy trade-off present in those with ADHD, as those with ADHD do respond faster, but it seems to result in them becoming less accurate (Heitz, 2014), although a main effect of group for accuracy failed to reach significance. A similar effect can be noted for both groups when responding to the unisensory auditory stimulus. As mentioned earlier, the auditory stimulus resulted in the slowest RT, but interestingly resulted in the most accurate response; when in comparison, the visual stimulus had a quicker RT when compared to the auditory alone condition for both groups but also resulted in the least accurate responses.

EEG analysis has been used in the past to elucidate differences in cortical functioning in those with ADHD, however it has never been used as a method to assess MSI functionality in ADHD, other than in our previous study. EEG analysis showed that MSI occurred at early latencies in both study populations. These time periods and regions where MSI occurred coincide with other studies looking into AV MSI (Brandwein et al., 2015; Brandwein et al., 2011; Foxe et al., 2000; Giard & Peronnet, 1999). For instance, MSI occurred similarly in both groups over occipital scalp regions from 170-220 ms and central scalp regions from 180-220 ms. These are regions where the patterns of MSI were similar between study populations.

Although EEG analysis showed that MSI occurred in both neurotypical adults and adults that have received a diagnosis of ADHD, there were interesting differences in the patterns of MSI present. At early latencies, from 110-130ms, those with ADHD were found to have enhanced MSI over parietal-occipital regions, which was seen as a greater deviation from the

sum and multisensory waveforms than that of the controls. The parietal region is one of the main regions of MSI (Brandwein et al., 2011). Interestingly, this functional difference was found in a region that is known to be structurally unique in those with ADHD (Duerden et al., 2012; Durston, Pol, Schnack, Buitelaar, Steenhuis, Minderaa, Kahn, et al., 2004; Proal et al., 2011). Therefore, it is quite possible that the structural brain changes may result in adults with ADHD having enhanced MSI at early latencies, which may be related to the shorter RTs seen in this study. This may indicate that some of the neurological alterations present in those with ADHD could have beneficial implications for behaviour, especially when responding quickly to a given stimulus is advantageous.

MSI occurred in both study groups. However, there were also neurological differences between groups that were not necessarily related to MSI, but instead related to general cortical activity. These differences were identified at early stimulus latencies (0-250ms) over parietal, occipital, and central brain regions. Interestingly, all of the brain regions where differences in ERPs were found are also regions that previous literature has identified as being altered in those with ADHD (Duerden et al., 2012; Durston, Pol, Schnack, Buitelaar, Steenhuis, Minderaa, Kahn, et al., 2004; Proal et al., 2011). This indicates that EEG approach used in this study was sensitive enough to discern differences in cortical activity between those with ADHD and neurotypical adults.

Some possible limitations to this study may include the equipment that was used. Although reasonable consideration was given to all equipment involved such as the refresh rate of the monitor and the response pad, it is possible that there was a latency discrepancy between the refresh rate of the computer monitor and the speakers which may have impacted its ability to perfectly synchronize with the auditory stimulus. However, results are similar to those of other

studies with longer auditory RTs, relative to other stimulus conditions, when utilizing a speech-based auditory cue (Farid et al., 2018; Laurienti et al., 2004), however, the ERP analysis revealed that MSI did occur. Another possible limitation to this study was the small sample size which may have led to a Type II error, particularly the two trends that were reported with medium effect sizes.

Even though there was not a significant group finding for accuracy there was a trend approached toward those with ADHD being less accurate, suggesting the need for a larger sample size in the future. Another implication for the future would be to assess multisensory ERP latency differences in those with ADHD. Although this was outside the scope of the analysis methods adopted for the current study, from visual inspection there appeared to be differences in the neural regions involved at various post-stimulus latencies. Another future prospect for research within this domain in adults with ADHD, would be to assess MSI with stimuli that are more representative of important social and communication variables, as opposed to inanimate stimuli used in this study, such as incorporating facial expressions and/or words associated with lip movements when speaking.

Finally, this study revealed several new things in relation to MSI and ADHD. First, MSI does occur in adults with ADHD at early latencies and in specific brain regions. Some differences in MSI patterns were present in adults with ADHD when compared to controls, where adults with ADHD had greater MSI occurring at certain latencies and regions, associated with shorter RTs to all conditions, but with a trend towards less accurate responses to two out of the three conditions. This research has laid a foundation and provided insight for future work to assess MSI in ADHD utilizing different modalities and paradigms, which could potentially lead to the development of assistive-technologies to promote efficient integration and sensory

processing when in a multisensory-dependant environment, such as a lecture hall or busy office environment.

Summary and Conclusions

Rationale & Purpose

The purpose of this thesis was to identify whether adults with a confirmed diagnosis of ADHD at some point in their life have alterations to the process of multisensory integration (*MSI*). ADHD is a common neurodevelopmental disorder that often persists into adulthood. Those with ADHD have characteristic changes to various brain regions and structures (Duerden et al., 2012; Proal et al., 2011). Some of the brain regions that are altered in those with ADHD are also highly involved in the process of MSI. MSI is crucial for how you interact with and perceive the world around you, and many day-to-day tasks are heavily reliant on the success of how your nervous system integrates all of the stimuli that occurs around you. These neurological characteristics of ADHD led us to hypothesize that audiovisual (*AV*) MSI may be altered in adults with ADHD.

In order to assess AV MSI in adults with ADHD two different paradigms were employed. First, a simple response time (*RT*) task was utilized to show basic RT differences in response to multisensory stimuli in those with and without ADHD while recording continuous 64-electrode electroencephalography (*EEG*). The utilization of EEG allows for a more in-depth analysis of MSI based on the Principle of Superposition of Electrical Fields, and this is a method that has reliably been used in numerous other studies assessing MSI using EEG. Following this, a second study was undertaken that employed a more complex task that assessed AV MSI while still recording continuous EEG. This task was a two-alternative forced-choice discrimination task which has both an accuracy and a RT component to the behavioural analysis. The utilization of both behavioural (RT and accuracy) and neurological (EEG) measures of MSI allowed for a more robust assessment of MSI and underlying neural generators.

Summary of Findings

Our two studies have complimentary findings as the second study built upon the findings of the first study. The first study assessed simple RT and EEG data during a multisensory dependent task in adults with ADHD. We hypothesized that MSI would be altered or different in some way compared to neurotypical adults. However, due to the lack of previous literature inquiring into MSI in adults with ADHD we could not predict the direction that this relationship would be in.

In study one we report that adults with ADHD seemed to have faster RTs to each stimulus condition than controls, but this failed to reach significance. Both groups responded the slowest to the auditory unisensory condition and fastest to the multisensory condition, which was similar to findings in previous studies (Farid et al., 2018; Laurienti et al., 2004). Through EEG analysis it was found that adults with ADHD do have MSI occurring over parietal, occipital, and central brain regions at early latencies (0-250ms). The patterns of MSI varied between groups (i.e. one group had a greater difference between the sum and multisensory waveform while another group had more positive or negative peaks at specific latencies and regions). These findings from study one led to a second area of inquiry, which incorporated an assessment of accuracy.

Study two utilized a two-alternative forced-choice discrimination task while again recording continuous EEG in adults with and without ADHD. Based upon the results of study one we hypothesized that those in the ADHD group would respond quicker to each stimulus but be less accurate due to a speed-accuracy trade-off. The speed-accuracy trade-off describes how the more quickly a response is made that this will result in a deficit in accuracy, while consequently, slower responses will result in more accurate responses (Heitz, 2014).

Once again, the adults with ADHD responded faster to each stimulus condition than controls did, and this relationship did reach significance. A secondary analysis found that those with ADHD had a trend towards making less accurate responses. Both groups responded more accurately to the auditory alone condition which also had the longest RTs, which is in line with the theory involved in a speed-accuracy trade-off (Heitz, 2014). The EEG analysis elucidated that adults with ADHD do have MSI occurring at early latencies, similar to study one. However, from 110-130 ms over parietal-occipital regions those with ADHD were found to have greater MSI. This was found due to a greater divergence between the sum and multisensory waveforms when compared to the controls divergence.

Prospective Research Directions

Although these two studies have provided answers to some of the initial questions regarding MSI in adults with ADHD, they also provide insight into future directions. The paradigms from both studies showed differences in RTs, accuracy, and ERPs between groups (ADHD vs. controls) and between conditions (A, V, and AV multisensory). However, the RTs between the visual and multisensory conditions were not the same but they were similar. Future work may work to create a paradigm that is more sensitive to auditory and visual stimuli, ensuring that the monitors refresh latency is compatible with the audio equipment, which may result in further multisensory gains when lowering the stimulus offset deficit to be as synchronous as possible. In the future, a more robust analysis may take on a more exploratory method of analysis looking into latency of peaks opposed to solely amplitude differences as was done in these two studies, to see whether those with ADHD have earlier or later occurring multisensory ERPs.

Another future prospective for assessing MSI in this population may include eye-tracking software and/or a portable EEG system so that paradigms are not limited to a laboratory setting and can be implemented into a more real-world setting. For instance, recording EEG while in a lecture hall, where MSI is constantly necessary to promote comprehension of the simultaneous auditory and visual stimuli from the surrounding environment. Finally, since this research was completed in a population of adults with ADHD, it is unclear whether the same findings would be present when and if completed during childhood. Although studies have investigated subclinical ADHD, this fails to distinguish MSI characteristics in those with a clinical diagnosis. Therefore, future studies may investigate MSI in children with a diagnosis of ADHD. Another possibility for future work would be to address the research question as to whether the alterations in brain structure (Duerden et al., 2012) and function (Kovatchev et al., 2001; Loo & Makeig, 2012) result in ADHD onset, or whether ADHD results in these neurophysiological alterations.

Conclusion

To conclude this thesis, it was found that adults with ADHD do in fact have MSI occurring but there are some differences in the way in which this occurs compared to neurotypical adults. This difference was seen via varying degrees of divergence between a sum and multisensory waveform. There were differences in ERP activity between those with and without ADHD, with the most prominent differences occurring over parietal, central, and occipital scalp regions when assessing EEG data. Although there currently is not an EEG-centered diagnostic tool for ADHD, this research shows that there are MSI specific biomarkers present in those with ADHD. The fastest RT in both paradigms was to that of the AV multisensory stimulus. Study 2 elucidated that those with ADHD do respond faster to each stimulus condition while also having enhanced MSI occur when assessing EEG, and that there

was a potential trend approached towards those with ADHD also responding less accurately, possibly as a result of a speed-accuracy trade-off. This emphasizes that there may be a relationship between the behavioural results seen in the study paradigm 2 and the integration measured via cortical ERPs, i.e. behavioural results reflect the differences in brain activity. Future exploratory analysis may elucidate more patterns of altered MSI in both adults and children with ADHD, by utilizing different EEG outcome measures such as ERP amplitude and latencies, and/or different sensory modalities such as somatosensory stimuli.

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Appendix

Edinburgh Handedness Inventory

Please indicate your preferences in the use of hands in the following activities *by putting a check in the appropriate column*. Where the preference is so strong that you would never try to use the other hand, unless absolutely forced to, *put 2 checks*. If in any case you are really indifferent, *put a check in both columns*.

Some of the activities listed below require the use of both hands. In these cases, the part of the task, or object, for which hand preference is wanted is indicated in parentheses.

Please try and answer all of the questions, and only leave a blank if you have no experience at all with the object or task.

Task	Left	Right
1. Writing		
2. Drawing		
3. Throwing		
4. Scissors		
5. Toothbrush		
6. Knife (without fork)		
7. Spoon		
8. Broom (upper hand)		
9. Striking a match		
10. Opening a box (lid)		
Total (count check marks in both columns)		

Difference	Cumulative TOTAL	Result

Scoring:

Add up the number of checks in the “Left” and “Right” columns and enter in the “TOTAL” row for each column. Add the left total and the right total and enter in the “Cumulative TOTAL” cell.

Subtract the left total from the right total and enter in the “Difference” cell. Divide the “Difference” cell by the “Cumulative TOTAL” cell (round to 2 digits if necessary) and multiply by 100; enter the result in the “Result” cell.

Interpretation (based on Result):

below -40 = left-handed

between -40 and +40 = ambidextrous

above +40 = right-handed

ASRS-v1.1

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. Are you currently taking medication for ADHD? If so, what medication? YES NO

If yes, please list medication: _____

	Never (0)	Rarely (1)	Sometimes (2)	Often (3)	Very Often (4)
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					
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					

EEG/TMS Safety Checklist

Screening checklist:

The following questions are to ensure it is safe for you to have EEG data collected. If you answer yes to any of the questions below, we may need to exclude you from EEG experiments.

QUESTION	ANSWER	
1. Do you suffer from epilepsy, or have you ever had an epileptic seizure?	Yes	No
2. Does anyone in your family suffer from epilepsy?	Yes	No
3. Do you suffer from reoccurring headaches**?	Yes	No
4. Have you ever had a skull fracture or serious head injury?	Yes	No
5. Have you ever had any head surgery?	Yes	No
6. Are you pregnant?	Yes	No
7. Do you take any medication or use recreational drugs (including marijuana)*?	Yes	No
8. Do you suffer from any known neurological or medical conditions?	Yes	No

Comments _____

Name _____

Signature _____

Date _____

*Note if taking medication or using recreational drugs please read through the medication list on the next page to see if you use contraindicated drugs or medications. You do not need to tell the researcher which medications or drugs you use, unless you wish to. However, all researchers have signed confidentiality agreements and this information will not be recorded in writing, if you do wish to discuss this issue.

**Dr. Murphy will meet with participants who answer yes to this question to seek further information.

1) Tricyclic antidepressants

Name	Brand
amitriptyline (& butriptyline)	Elavil, Endep, Tryptanol, Trepiline
desipramine	Norpramin, Pertofrane
dothiepin hydrochloride	Prothiaden, Thaden
imipramine (& dibenzepin)	Tofranil
iprindole	-
nortriptyline	Pamelor
opipramol	Opipramol-neuraxpharm, Insidon
protriptyline	Vivactil
trimipramine	Surmontil
amoxapine	Asendin, Asendis, Defanyl, Demolox, Moxadil
doxepin	Adapin, Sinequan
clomipramine	Anafranil

2) Neuroleptic or Antipsychotic drugs

A) Typical antipsychotics

Phenothiazines:	Thioxanthenes:
o Chlorpromazine (Thorazine)	o Chlorprothixene
o Fluphenazine (Prolixin)	o Flupenthixol (Depixol and Fluanxol)
o Perphenazine (Trilafon)	o Thiothixene (Navane)
o Prochlorperazine (Compazine)	o Zuclopenthixol (Clopixol and Acuphase)
o Thioridazine (Mellaril)	· Butyrophenones:
o Trifluoperazine (Stelazine)	o Haloperidol (Haldol)
o Mesoridazine	o Droperidol
o Promazine	o Pimozide (Orap)
o Triflupromazine (Vesprin)	o Melperone
Levomepromazine (Nozinan)	

B) Atypical antipsychotics

Clozapine (Clozaril)	Quetiapine (Seroquel)
· Olanzapine (Zyprexa)	· Ziprasidone (Geodon)
Paliperidone (Invega)	· Amisulpride (Solian)
· Risperidone (Risperdal)	

C) Dopamine partial agonists: Aripiprazole (Abilify)

D) Others

Symbyax - A combination of olanzapine and fluoxetine used in the treatment of bipolar depression.

Tetrabenazine (Nitoman in Canada and Xenazine in New Zealand and some parts of Europe)

Cannabidiol One of the main psychoactive components of cannabis.

Regular Cannabis use more often than once per week and/or cannabis use in the past 4 days.

Regular use of other recreational drugs, or single episode within the past three weeks.



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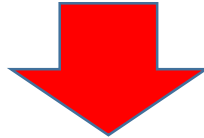
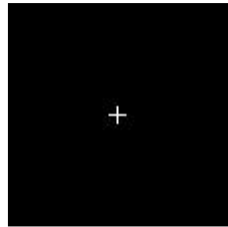
Title: *Multisensory Integration in Adults with and without Attention-Deficit Hyperactivity Disorder*. This study has received ethical approval from the UOIT ethics committee (REB [14507] on [September 14th, 2017]).

This study is being conducted by Dr. Bernadette Murphy and Dr. Paul Yelder in conjunction with MHS candidate Heather McCracken and fourth year research practicum students from the Faculty of Health Sciences at the University of Ontario Institute of Technology (UOIT), in Oshawa, Ontario, Canada. All researchers involved will have signed confidentiality agreements and completed the TCSP II tutorial on research ethical concerns.

Rationale for Research: Research has found that attention-deficit hyperactivity disorder (ADHD) results in changes to brain structure as well as sensory alterations. ADHD is a common disorder, which may potentially influence university-aged students with respect to how they process incoming sensory information, for example listening to a lecture while following along on PowerPoint slides. It has been hypothesized that ADHD may result in individuals experiencing altered multisensory integration (MSI) which is the ability of the brain to make sense of different types of sensory inputs. MSI is very important for many everyday tasks that individuals are involved in; for instance, MSI plays a key role in social communication, learning in a classroom, and while driving in a car. The current study aims to distinguish if there are differences in activity in different areas of the brain thought to be important in MSI between individuals with and without ADHD.

The research we are doing is showing how the brain responds to a multisensory task in a population of university-aged adults aged 18-30 both with and without ADHD and then comparing them between groups. A portion of this will consist of completing a task on a desktop computer, requiring you to click a button on the keyboard when you see a picture or hear a sound, please refer to the example below. The second portion will consist of this same task, but while wearing an electroencephalography (EEG) cap.

Fixation period (1000-3000ms)



Auditory



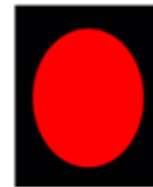
Auditory
verbalization
(~60ms)

Visual

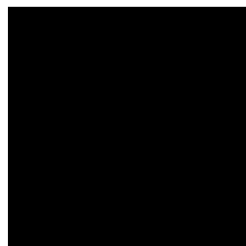
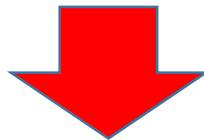


Red visual
stimulus
(60ms)

Multisenory



Auditory and visual stimulus
of the word red presented
simultaneously (~60ms)



Response period (8s)

Response recording begins at initial presentation and ends upon response

Information for participants: To do this research, we will ask you to complete questionnaires which will provide information regarding your handedness, general well-being, and ADHD symptomatology. We will then ask you to perform a task on the computer with pictures and audio cues while wearing an EEG cap.

For this study, we are seeking individuals who have been diagnosed with ADHD and are between 18 and 30 years of age. To participate in this study, you must complete an eligibility checklist in conjunction with one of the researchers to ensure you are eligible to participate. This includes ensuring that you don't have any other conditions which could impact the EEG measurements such as autism, multiple sclerosis, etc. You will also be given a chance to review the details of the study and ask any questions you may have.

The evaluation session will take between 2.5 and 3 hours and you will be given a chance to ask questions. It is recognized that research is fundamental to the university, and research experience allows one to grow intellectually, in support of the university tradition for creation of new knowledge. It is also recognized that volunteer work is an invaluable part of the undergraduate experience. Through participating in this study, you will be introduced, in some cases relatively early in your career, to the research tradition and be exposed to hand-on kinesiology work with state-of-the-art equipment. You will also be completing volunteer hours that could prove to be very useful for future job or graduate school applications. Participants who complete the study can ask for a letter confirming they have completed these hours. If you are a student enrolled in approved Kinesiology courses you may also have the opportunity to earn 1% extra credit which can be applied to one of your eligible kinesiology courses (see attached list in Appendix E). If you are interested in this option, the investigator will provide you with additional information. If you are not interested in this option or you are not a kinesiology student, your participation will be recognized with either a Tim Hortons or Aramark card of a ten-dollar (\$10) value.

Your participation in this study is entirely voluntary (your choice), and you are free to decline taking part in this study. You may also withdraw from the study up until the end of the data collection session. This will in no way affect your academic progress. Any questions regarding your rights as a participant, complaints or adverse events may be addressed to Research Ethics Board through the Research Ethics Coordinator – researchethics@uoit.ca or 905.721.8668 x. 3693.

Measurement sessions: Should you agree to participate we will need you to attend one session.
Measurement procedures:

❖ We are looking at how a multisensory integration dependent task will influence the human brain, through the collection of electroencephalography (EEG) data using a 64-electrode cap, which is non-invasive. The cap is placed on your head over your hair. We do need to apply electrode gel to your scalp which will need to be wiped off after the experiment. Once the cap is applied we will ask you to look at and respond to a series of events on a computer screen, as well as listen to a series of events while we record your EEG signal. This task is completed using E-Prime 2.0 which will also be recording your response time to each stimulus. The experiment itself may take less than half an hour; however, the full set-up of the EEG cap, and completion of the task may take up to 3 hours. During this time period, you will be encouraged to take mental breaks; however, due to the setup of the EEG equipment you will not be able to walk about freely.

Risks and benefits

The only risks associated with participation in this study are mental-fatigue and potential boredom while participating in the task, however, as a student this is not outside the normal risk associated with day-to-day life. Participation will take approximately 2.5-3 hours.

The benefit of participating in this study is that you will learn more about sensory integration. You will also be aiding our understanding of possible differences in neurological processing that is fundamental to many everyday tasks where we need to integrate visual and auditory information.

If the information you provide is reported or published it is done in a way that does not identify you as its source. There is a potential for the data from the study to be used as secondary-data at some point in the future and as such we are providing the option for you to tick a box indicating that you give consent to include this data in future research. The data will be stored in a locked area at UOIT for seven years from the completion of the study after which it will be destroyed. You are free to withdraw from the data collection at any time up until the end of the data-collection session. Taking part in this study is voluntary and your decision to take part in this study (or not) will in no way influence your academic progress or relationship with your Instructors or TAs. If you have opted for extra course credit as compensation, this information will be handled confidentially by the Faculty Research Development Assistant and your teacher will not be informed until your course is already complete.

Should you experience any discomfort or distress in response to this study and participating in it, please contact Heather McCracken at heather.mccracken@uoit.net. You can also contact local health services if necessary, such as the Canadian Mental Health Association Durham at 905-436-8760 or Durham Mental Health Services at 905-666-0831.

Participant Concerns and Reporting:

If you have any questions concerning the research study or experience any discomfort related to the study, please contact the researcher Heather McCracken at heather.mccracken@uoit.net.

Any questions regarding your rights as a participant, complaints, or adverse events may be addressed to Research Ethics Board through the Research Ethics Coordinator – researchethics@uoit.ca or 905.721.8668 x. 3693.

This study has been approved by the UOIT Research Ethics Board REB [REB # 14507] on [September 14th, 2017].

Thank you very much for your time and help in making this study possible. If you have any queries or wish to know more please contact Dr. Bernadette Murphy, a Professor at the University of Ontario Institute of Technology, Faculty of Health Sciences, 2000 Simcoe St North, Oshawa, Ontario, L1H 7K4 email: Bernadette.murphy@uoit.ca

The data from this research will be submitted to scientific conferences and peer reviewed journals. At the completion of the study, you will be sent a summary of the research findings and any place where the data has been published. All published data will be coded so that your data is not identifiable.

Please read the following before signing the consent form and remember to keep a copy for your own records if you wish.

- I understand that taking part in this study is voluntary (my choice) and that I am free to withdraw from the study up until the end of the data collection session without a reason and that this will in no way affect my academic progress.
- This consent form will be kept in a locked area in the Kinesiology Neurophysiology and Rehabilitation Research Laboratory at UOIT, Oshawa, Ontario for a period of seven years before being destroyed.
- The data collected in this study will be coded so that it is confidential from the consent form and stored in a locked area at UOIT, Oshawa, Ontario for a period of seven years before being destroyed.
- I have read and I understand the information sheet for volunteers taking part in the study. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.
- I have completed an eligibility checklist to ensure I am eligible to participant in this research.
- I understand that I can withdraw any data I supply up to the completion of my measurement session.
- I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports on this study.
- I have had time to consider whether to take part.
- I know who to contact if I have any side effects to the study.

I, agree to take part in this research.

I give consent for the data from this study to be used in future research as long as there is no way that I can be identified in this research. YES NO
(tick one)

I give consent for this data to be used as secondary-data at some point in the future (tick one) YES NO

I would like to receive a short report about the outcomes of this study (tick one) YES NO

Age: _____

Signed Date

RESEARCHER TO COMPLETE
Project explained by: _____
Project role: _____
Signature: _____