

Investigating cerebellar contributions to sensory processing

by

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A thesis

presented to the University of Waterloo

in fulfillment of the

thesis requirement for the degree of

Doctor of Philosophy

in

Kinesiology

Waterloo, Ontario, Canada, 2020

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revision, as accepted by my examiners.

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Abstract

Over the last two decades, the long-standing view of the cerebellum as a motor structure has been challenged with evidence highlighting the presence of cerebellar activation during non-motor tasks and functional connectivity studies emphasizing the importance of cerebellar input to associative cortical regions. The cerebellum has been widely agreed to be involved in coordinated movement. To successfully perform a smooth movement, we need to be able to gather information that is pertinent to completing the goal at hand and ignore erroneous information, which could be thought of as attention. Many of these studies have localized the right lateral cerebellum as the node primarily responsible for coordination of more cognitively driven processes, due to connectivity with prefrontal and frontal regions. Although it is widely agreed that the cerebellum aids in coordination via state estimation mechanisms, how it exerts this influence over higher order processes is not well understood; this is in part due to the variability of results from lesion studies. The purpose of this thesis is to investigate the nature of the cerebellum's influence on higher-order processes within a young, healthy population. The aim of the first study was to determine the cerebellum's influence over sensory processing without the need for an explicit movement task. Following the transient disruption of cerebellar activity using continuous theta burst stimulation (cTBS), Study 1 identified that the cerebellum was involved in distinguishing differences between types of sensory stimuli as indexed by changes in cortical electrical activity measured through electroencephalography (EEG). Specifically, decreases in the mismatch negativity (MMN) in response to the presence of deviant stimuli following administration of cTBS was observed. The aim of Study 2 was to further probe this concept using a sensory conflict task, which incorporated two different modalities of stimuli. Following cTBS to the right lateral cerebellum, the increases in the tactile N70 and visual P2

cortical peaks in response to irrelevant and distractor stimuli may be an indication of participants becoming less likely to ignore distractor stimuli. This is further supported by the concomitant decreases seen in accuracy. The final study of this thesis sought to strengthen our understanding of the nature of the cerebellar influence over attentional processes by assessing laterality and changing the side of cerebellar stimulation to the left side. In this way, it can be validated that the alterations observed in the previous studies are due to the hypothesized influence of right-cerebellum to left-side frontal areas as opposed to overall cerebellar control of sensorimotor processing. A lack of change within both somatosensory and visual peaks, the N70 and P2 respectively, following stimulation of the left lateral cerebellum supports the specificity of the cerebellum's influence. Together, these studies aid in our understanding of how the cerebellum exerts its influence on widespread, contralateral higher-order networks through the comparison of contextual sensory information. This work serves to broaden our understanding of how the cerebellum is involved in behaviours which encompass sensory processing, movement and cognition to execute purposeful behaviour.

Acknowledgements

The acknowledgements page: to me, it is one of the most important – it is the one page where you can truly get a snapshot into the author’s life. While it may just be my name that appears on the title of this thesis, I know all too well that this thesis was made possible from the efforts of many exceptional individuals.

To my Supervisor, Dr. Rich Staines, being able to work with you has been an absolute privilege. No matter how difficult the journey has been for me, your patience and unwavering support throughout this process allowed me to restore belief in myself at times where I thought I had lost it. You embody every aspect of what it is to be an incredible mentor and your dedication to your students knows no bounds.

To my committee members, Dr. Michael Barnett-Cowan, Dr. Sean Meehan and Dr. Laura Middleton, thank you for the time you dedicated to helping me to strengthen my research. Your questions have both challenged and broadened my thinking. Thank you also to Dr. Roxane Itier and Dr. Lauren Sergio for taking the time to serve on my examining committee. I am so grateful for your collective efforts to allow me to continue with this process even throughout these uncertain times we find ourselves in this year.

To my Labmates, both past and present, thank you for your encouragement, constructive feedback and humour. To the “lucky” few who have had the great joy of sharing an office with me, our chats have transcended far beyond research and you eased the sometimes treacherous path for me tremendously – I am fortunate to be moving forward from this phase with lifelong friendships. Honourable mentions go out to the many volunteers and participants who so graciously gave their time; this work would not have been possible without your enthusiasm.

To my circle of strength, my Family, there is simply not enough space to thank you for all the ways in which you have helped me. Your unconditional love and support has given me the strength to grow, encouraged me take chances and taught me to never back down from a challenge. Your unfailing faith in me has been my guiding light throughout life.

And last but certainly not the least, to Justin, thank you for being my rock and safe place. Somehow, you have always known exactly what I needed – whether it was strength when I felt weak or encouragement when I felt the confidence to face challenges head on. Your constant reassurance of “Everything will be okay in the end; and if it’s not okay, then it’s not the end” has resonated with me and has pulled me through so many times. So much in this life is uncertain but I know I’ll be fine because you are beside me.

Dedication

This thesis is dedicated to my parents, Fermen and Karen, who have always encouraged the pursuit of knowledge. It is your steadfast love and guidance that have taught me the most important lessons in life. All I have accomplished is a result of the sacrifices you have made and the values that you have instilled in me. Thank you for teaching me not only how to dream, but how to catch those dreams.

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List of Abbreviations

AB Attentional blink
ADHD Attention deficit hyperactivity disorder
AMT Active motor threshold
ANOVA Analysis of variance
APB Abductor pollicis brevis
ASD Autism spectrum disorder
BOLD Blood-oxygen level dependent
CCAS Cerebellar cognitive affective syndrome
CNS Central nervous system
cTBS Continuous theta burst stimulation
DAN Dorsal attention network
DCN Deep cerebellar nuclei
DTI Diffusion tensor imaging
EEG Electroencephalography
ERP Event related potential
iTBS Intermittent theta burst stimulation
M1 Primary motor cortex
MEP motor evoked potential
MMN Mismatch-negativity
OB Oddball
PA Picture Arrangement
PFC Prefrontal cortex
PMC Premotor cortex
PTSD Posttraumatic stress disorder
SD Standard deviation
SEP Somatosensory evoked potential
SI Primary somatosensory cortex
SII Secondary somatosensory cortex
SMA Supplementary motor area
SMI Sensorimotor integration
SO Standard omitted
TMS Transcranial magnetic stimulation
UCT Uniform cerebellar transform
WAIS-R Wachsler Adult Intelligence Scale Revised

Chapter 1: Introduction

1.1 Overview of thesis

The process of skill learning is almost exclusively discussed in the context of movement or motor control, whereby movements become performed effortlessly through repeated practice (Willingham, 1998). The neural correlates of this process have long been studied and more specifically, the role of the cerebellum has been emphasized as an accessory to motor adaptation structure. This stems from both a lack of being able to trace the cerebellum's polysynaptic circuitry (Strick, 1985; Schmahmann and Pandya, 1997) and the observation of uncoordinated movements in patients with cerebellar lesions without the presentation of gross sensory deficits (Holmes, 1939). This quite singular view has come to be challenged over the last two decades with the presence of cerebellar activation during cutaneous discrimination, auditory and visual non-motor tasks (Jueptner et al., 1995; Gao et al., 1996; Allen et al., 1997). Still, cerebellar connections and activations associated with these tasks have been viewed as a means of integrating information from widespread cortical areas to then be conveyed for use solely at the motor cortex for movement itself or motor imagery of movements associated with stimuli and tasks.

Technical advances have allowed for tracing of the multisynaptic circuits that exist between the cerebrum and the cerebellum in animal models. From these studies, it was determined that there is a sizable amount of output projected from the cerebellum to non-motor associative areas such as the prefrontal and posterior parietal cortices (Kelly and Strick, 2003; Middleton and Strick, 2001; Strick et al., 2009). This finding, coupled with cerebellar activation during hierarchically isolated non-motor tasks as well as deficits in sensory discrimination in

cerebellar lesion patients, adds to the evidence that the cerebellum exerts its influence over a plethora of functions beyond simple movements (Petersen et al., 1989; Molinari et al, 1997; Restuccia et al., 2001; Timmann and Daum, 2007; Glickstein 2007). However, it is still largely unclear as to how exactly the cerebellum is able to influence these processes, what this means for behaviour and how this structure could be implicated in sensory deficits and behavioural symptoms of various disorders.

1.1 General objective of thesis

The cerebellum is typically discussed as being essential for coordination of movement, which includes the gradual adaptation that occurs with experience in learning and sensorimotor integration (Krakauer and Mazzoni, 2011). This ability to adapt however could include larger, overlapping components that are not just motor in nature, but also cognitive. Resting state functional connectivity data support the presence of various, functionally segregated cerebro-cerebellar loops with both sensorimotor and association cortices with predominant contralateral projections between the cerebellum and cerebral cortex (Middleton and Strick, 2000; Krienen and Buckner, 2009). These well-studied frontal and parietal areas themselves are known to be involved in higher-order executive processes (Strick et al., 2009; Stoodley, 2012). It is suggested that the cerebellum's contribution to coordination and adaptation could span across domains to ensure appropriate behavioural performance beyond a simple movement such as reaching.

The uncertainties which surround the cerebellum still remain, in part, due to the variability that is associated with lesion studies and incomplete understanding of whether activations are due to being involved in a non-motor task or if it is specifically associated with motor components (Strick et al., 2009). Furthermore, many studies primarily focus on motor aspects of the cerebellum and more specifically, on learning studies of the arms and hands in

humans with primary outcome measures relying solely on reaction time or accuracy. A comprehensive model is still lacking in terms of how the cerebellum would exert its influence on these more associative areas in concert with its influence on motor areas in order to execute a well-informed behaviour in response to some stimuli or scenario.

The primary aim of this thesis was to investigate the cerebellum's influence on non-motor aspects of tasks following the alteration of the cerebellum's activity and measuring its effects on more widespread brain areas following the evaluation of specific sensory stimuli. The studies aim to address the questions of: 1. Whether the cerebellum is involved in evaluation of purely sensory stimuli without the need for a directed movement? 2. Is the ability to evaluate sensory stimuli related to a change in attention and does this process become compromised in the presence of sensory distractors following alteration of activity of the cerebellum? 3. How does the cerebellum link together different modalities of stimuli to allow individuals to perform meaningful behaviour and make appropriate responses?

Together, these studies form a comprehensive investigation of the potential processes by which the cerebellum serves its role as a prime mediator of stimuli integration beyond the scope of movement alone but behaviour in general. This research has the potential to inform a novel avenue for targeting the cerebellum in the treatment of behavioural anomalies that are present in many disorders today.

Chapter 2: Review of Relevant Literature

The following section is a review of current relevant literature that spans the domains of the thesis work. An overview of sensorimotor integration and the cortical and subcortical networks that subserve this large-scale process will be covered. Focus will be given specifically

to the cerebellum; its connectivity and functional organization will be further discussed. Traditional roles of the cerebellum will be briefly discussed followed by a further look into the more recent, non-traditional roles of the cerebellum that has been becoming more widely researched through higher order and executive functioning processes and conversely the implications of deficits within these processes. Lastly, the use of non-invasive neurophysiological techniques to investigate these processes as they relate to this thesis will be discussed.

2.1 Sensorimotor Integration

Communication between the central nervous system and periphery creates a fundamental feedback loop where sensory input is integrated and used for assisting in the execution of appropriate motor outputs; this dynamic process is termed sensorimotor integration (SMI) (Abbruzzese and Berardelli, 2003). The appropriate employment of this process is required for us to effectively adapt to the ever-changing environment that surrounds us. A main proponent of SMI is reduction of variability by using prediction from current incoming sensory information and previous exposure to stimuli or situations (Krakauer and Mazzoni, 2011; Flanders, 2011). Therefore, repeated behavioural training has been shown to induce resulting SMI use-dependent cortical changes necessary for learning and skill acquisition (Abbruzzese and Berardelli, 2003; Classen et al., 1998; Byl et al., 1997). While these adaptive changes are necessary; studies have shown that in various injuries and neurologic disorders, anatomical changes are correlated with unfavourable behavioural changes such as those seen in dystonia, carpal tunnel syndrome, stroke, and Parkinson's, thus making it critical to understand their mechanisms (Elbert et al., 1998; Tinazzi et al., 1998; Lewis and Byblow, 2002; Smania et al., 2008). Motor tasks have been used in combination with electrophysiological techniques to investigate this process following

repetitive voluntary movement (Murphy et al., 2003; Haavik Taylor and Murphy, 2007). This has allowed for interpretations of neural activity and accompanying performance measures without the delicate constraints associated with imaging techniques, allowing for greater real world transfer. Much of the emphasis in this domain is on the final result action of simple reaching or grasping movements, however more complex paradigms may provide new insight into the higher-order processes of recognition and intention of actions for the future, learning by observation and even understanding the behaviour of other people (Jeannerod, 2000). These processes, although they are of higher order functioning, would still require the aspects of prediction and learning that are thought to heavily govern the efficiency of SMI adaptation, leaving further exploration of these processes and the cortical networks that support them, necessary.

2.2 Networks that govern sensorimotor integration

The integration of sensory input is performed by networks at multiple levels within the central nervous system (CNS), taking place in the spinal cord, and widespread cortical and subcortical circuits (Flanders, 2011; Liepert et al., 2003; Nyberg et al., 2006). Functional imaging studies have demonstrated that these circuits include areas such as the primary somatosensory cortex (SI), secondary somatosensory cortex (SII), primary motor cortex (M1), premotor cortex (PMC), supplementary motor area (SMA), prefrontal cortex (PFC), amygdala, cingulate cortex, basal ganglia, thalamus and cerebellum (Ciccarelli et al., 2005; Nyberg et al., 2006; Krakauer and Mazzoni, 2011). These diverse, associative cortical and subcortical areas such as the PFC and basal ganglia are thought to be necessary for skill learning due to their involvement in developing task strategies and optimal decision making processes when learning a new skill or action.

Changes in activation patterns of the circuitry involved in SMI processes have been largely studied using learning adaptations based on upper limb reaching and throwing movements. These studies have given valuable insight into the speed and accuracy of performing a task and how these aspects become more efficient as a scenario is encountered more frequently. Apart from the changes in motor representations that occur alongside learning processes, these adaptations have generated rich discussions surrounding the potential mechanisms that govern this gradual change in efficiency and ability to recall skills. Specifically, changes within cortico-cerebellar circuits have been of interest with their hypothesized use of internal models. It is thought that the formation and alteration of these models allow us to adjust our movements depending on changes in environmental dynamics; for example: changing our gait when transitioning to walking on concrete to walking on ice, adjusting the effort required to lift a drink to our mouths as we consume its contents (Rabe et al, 2009; McDougle et al., 2016).

The role of the cerebellum with regards to learning has been long debated; however, it has emerged as a primary candidate for the usage of these internal models needed for SMI. The internal model concept has been useful for interpreting the coordinative role of the cerebellum, achieved via feedback projections from the somatosensory system which are then corrected through error-based learning and input is sent to primarily motor areas to adjust movements (Wolpert et al., 1995; Tseng et al., 2007). This quite singular model however seems to be insufficient in explaining the versatility of adaptations that may be more cognitive in nature and the complexity of integrating sensory stimuli for human performance beyond movement. The existence of outputs from the cerebellum that project to non-motor associative areas (Kelly and Strick, 2003; Middleton and Strick, 2001; Stick et al., 2009) suggests that there are higher order

functions of the cerebellum, although these are not well understood as to what strategies the cerebellum uses to communicate with these more associative areas.

2.3 The cerebellum

The cerebellum, or “little brain”, constitutes only 10% of the total volume of the brain but contains about half of the total neurons in the brain within this small space (Ito, 1984; Ramnani, 2006; Houk et al., 2007). These neurons subserve motor control, cognition, coordination and overall adaptations of sensorimotor relationships via dense and diverse reciprocal cortical connections (Middleton and Strick, 2000; Kelly and Strick, 2003; Doyon et al., 2009). This is supported by work which has shown that cerebellar trauma does not lead to the complete loss of motor function, suggesting that the contribution of the cerebellum is for refinement (Timmann et al., 2007; Grodd et al. 2001). A proposed mechanism of cerebellar influence on motor control is that it stores copies, or internal models, of motor commands to predict sensory effects of movements, thereby reducing dependence on delayed sensory signals and increasing our behavioural efficiency (Manto and Bastian, 2007). The cerebellum itself can be divided into functionally distinct regions; showing involvement in tasks which span beyond movement and include implicit learning, cutaneous sensory tasks and mental rotation tasks (Bussy et al., 2011; Baarbé et al., 2015). These findings have allowed for increased discussion of the cerebellum as more of a sensory acquisition structure than simply a structure involved in aiding motor coordination. This, coupled with findings of widespread cerebellar reciprocal connections to non-motor associative areas lends itself to the thought that the cerebellum may provide these predictive properties for higher order functions which help to facilitate motor responses and behaviours to complex scenarios. The cerebellum’s uniformly organized structure has been well

preserved throughout vertebrate evolution; this may be a good indication of its widespread role in neural processing. The circuitry of the cerebellum will be discussed to better frame this notion.

2.3.1 Cerebellar Gross Anatomy

Located at the base of the brain in the posterior fossa, the cerebellum consists of two lateral hemispheres which are separated by a midline ridge, the vermis. On a macrostructure scale, the cerebellum is composed of a continuous outer layer of grey matter which makes up the cerebellar cortex, dense masses of white matter are located internally to the cortex; embedded within the white matter are four pairs of cerebellar nuclei, the deep cerebellar nuclei (DCN).

There are two large fissures present within the cerebellar cortex which divides it into three large lobes; the primary fissure separates the anterior and posterior lobes and the posterolateral fissure separates the posterior lobe from the flocculonodular lobe. These lobes are each associated with broader functions, which include control of limb and trunk movements, movement planning and maintaining balance or coordination respectively. Smaller fissures within each of the lobes create smaller groups known as lobules, there are a total of 10 lobules which are designated I to X; lobules I-V are part of the anterior lobe, lobules VI-IX are part of the posterior lobe, and lobule X is part of the flocculonodular lobe (Schmahmann et al., 2000; Stoodley and Limperopoulos, 2016).

The cerebellum is connected to various parts of the CNS via afferent and efferent fibre tracts which are grouped together into three large roots or bundles called peduncles: the superior, middle, and inferior peduncles. The superior peduncle contains major efferent fibre tracts to the cortex via the thalamus; the middle peduncle is the largest of the three peduncles and contains afferent fibre tracts to the cerebellar cortex via the pontine nuclei; and the inferior peduncle

contains both afferent and efferent fibre tracts which connect the cerebellum to the vestibular system and spinal cord along with incoming projections from the inferior olive (Stoodley and Limperopoulous, 2016). The output areas of the cerebellum which use these peduncles or large tracts to communicate with the rest of the cerebral cortex are the DCN. There are four pairs of nuclei, embedded within the cerebellar core white matter, on either side of the cerebellum's midline, the medial (fastigial) nuclei, the interposed (globose and emboliform nuclei) and the lateral (dentate) nuclei, these nuclei give rise to the output fibres of the cerebellum. The cerebellum is organized in a somatotopic way such that the cerebellar cortex projections from the midline are sent to the fastigial nuclei, the medial paravermal regions project to the interpositus nuclei and the lateral hemisphere project to the dentate nuclei.

2.3.2 Intrinsic cerebellar cortex circuitry

Like the cerebrum, the cerebellum is comprised of both white and grey matter and is organized into layers, which are as follows from the outer to innermost layer: the molecular layer, the Purkinje layer, and the granular layer. The molecular layer contains two types of inhibitory interneurons, stellate cells and basket cells. The middle layer consists of inhibitory neurons known as Purkinje cells, lending to the name of this layer. The granular layer contains inhibitory Golgi cells and excitatory granule cells.

The axons of the inner layer granular cells travel through the middle Purkinje layer and bifurcate in the outer molecular layer; these bifurcations form parallel fibres, running transversely across the cerebellar cortex. The dendrites of the Purkinje cells also extend into the molecular layer where they form fan-like trees which are densely stacked in the sagittal plane of the outer layer. These become the sole output neurons of the cerebellar cortex, making them

essential to cerebellar-cerebral communications (Apps and Garwicz, 2005). The perpendicular arrangement of the parallel fibres and the dendritic trees allows for each Purkinje cell to intersect with a parallel fibre. This specific arrangement of the cells traverses throughout the cerebellum, leading to its uniquely uniform and geometric organization (Ito, 1984; Ramnani, 2006). This principle of uniformity of the cerebellum's structure coupled with cerebellar connections to distinct motor and non-motor associative areas has led to the prevailing modular view that the processing contribution the cerebellum performs on motor areas can also be generalized to other more associative areas, this has been referred to as the uniform cerebellar transform (UCT) (Schmahmann, 2000; 2004; Buckner, 2013).

2.3.3 Major cerebellar inputs

There are two major afferent inputs to the cerebellar cortex which originate from two primary pathways that stem from either various extracerebellar sites or the inferior olivary complex, mossy and climbing fibres. Both types of fibres have excitatory connections with cerebellar neurons, although they terminate at different locations within the cerebellum and influence the output Purkinje neurons differently. Pathways that stem from extracerebellar sites terminate in the cerebellar cortex as mossy fibres while those that stem from the inferior olive terminate in the cerebellum as climbing fibres (Gasbarri et al., 2003; Manzoni, 2007; Miall, 2016).

Mossy fibres synapse onto granule and Golgi cells in the granular layer, therefore large amounts of cerebral input reaches cerebellar output nuclei via a granule-Purkinje-cell loop (Miall, 2016). The Golgi cells are activated by both the mossy and parallel fibres which provides a feedforward-feedback inhibition to the granule cells (D'Angelo and Casali, 2013). Climbing

fibres directly target the Purkinje cells and also send collaterals to the DCN. The climbing fibres wrap around Purkinje cell dendrites, allowing for multiple synapses between a singular fibre and Purkinje cell. This influence of fibres on the Purkinje cells is a critical one as the Purkinje cell axons synapse on one of the previously mentioned DCN which provide outputs from the cerebellum to the rest of the cerebral cortex. This extensive circuitry forms closed-looped circuits with both the spinal cord and cerebral cortex, forming the basis of the cerebellum's functional topography where different regions of the cerebellum would be responsible for processing different types of information based on their input, although the mechanism of processing may be similar for various types of information.

2.3.4 Functional anatomy of the cerebellum

There are three major functional divisions of the cerebellum, distinguished by their major sources of input/information. The spinocerebellum receives somatic sensory inputs from the spinal cord and comprises the vermis and intermediate hemispheres of the anterior and posterior lobes; it also contains the fastigial and interposed nuclei. The cerebrocerebellum receives input directly from the cerebral cortex and consists of the lateral hemispheres of the anterior and posterior lobes. It contains the dentate nucleus. Lastly, the vestibulocerebellum receives input from the vestibular labyrinth, it corresponds with the flocculonodular lobe.

Due to its diverse connectivity with the cerebral cortex, the laterally situated cerebrocerebellum will be discussed in more detail here. The cerebrocerebellum is primarily involved in the planning of movement with major inputs originating from the contralateral cerebral cortex via cortico-ponto-cerebellar paths which link not only motor areas with the cerebellum but also sensory and association areas (Stoodley and Schmahmann, 2009). Inputs to

these lateral portions of the cerebellar cortex project to the dentate nucleus which in turn, projects its neurons to the ventrolateral thalamus and to the parvocellular red nucleus. The ventrolateral thalamus is known as the motor relay division of the thalamus, however, recent functional imaging studies have shown the dentate may mediate in higher-order brain functions via connections to prefrontal, frontal and parietal areas which are involved in working memory, perception, attention and action (Buckner, 2013; Stoodley and Schmahmann, 2009). Furthermore, the parvocellular nucleus projects to the inferior olivary nucleus, which, as discussed is a major source of input to the cerebellum; this is indicative of a feedback loop between the structures that may contribute to the internal models and prediction mechanisms that the cerebellum is so heavily discussed as being involved in.

2.3.5 Functional topography and connectivity of the cerebellum

Although it is well known that the cerebellum forms parallel loops with various cortical motor, non-motor and associative areas, the details and directionality of these connections still lack a comprehensive framework or understanding. Crick and Koch (2005), stated that in biology, when seeking to understand the function of something, it is perhaps a good idea to first take a look at the structure. This widespread cerebro-cerebellar connectivity pattern has been challenging to discern due to the technical limitations of mapping out multisynaptic pathways.

Viral transneuronal tracing techniques within animals have allowed for targets of cerebellar output to be identified, where diverse cortical areas receive input from a spatially separate set of neurons in the dentate (Hoover and Strick, 1999; Dum and Strick, 2003; Strick et al., 2009). Within these same studies, it was found that the region of the dentate which contains neurons that project to M1 occupies only 30% of the nucleus, implying that there are substantial

outputs to other cortical regions which are not primarily motor related (Hoover and Strick, 1999; Dum and Strick, 2003). As a follow up to this, it was found that pre-motor and supplementary motor areas were also targets of cerebellar output with output channels being located in the same dorsal areas of the dentate, essentially creating a motor domain (Akkal et al., 2007; Middleton and Strick, 1997; Dum and Strick, 2003). Output channels to prefrontal cortical areas are situated separately from those which target motor areas, this is the same for outputs which target the posterior parietal cortex, this finding supports the idea of domain specific areas within the cerebellum (Dum and Strick, 2003; Clower et al., 2004). Studies of the human dentate have demonstrated that it has expanded relative to other cerebellar nuclei; more so, this seems to be related largely to the increase in the size of the ventral areas of the dentate which has been shown to be the area concerned with projecting to non-motor areas (Middleton and Strick, 1997; Bostan et al., 2013). Kelly and Strick (2003) examined whether a specific region of the cerebellar cortex both received input from and projects to the same area of the cerebral cortex, for both a representative motor area (arm area of M1) and a non-motor area (area 46 in the prefrontal cortex), an area of the brain which plays a central role in attention and working memory. It was found that the arm area of M1 receives input mainly from lobules IV-VI while area 46 receives input largely from Crus II (Dum and Strick, 2003). The output back to the arm area of M1 and area 46 originate from the same areas within the cerebellum, giving rise to evidence that there are multiple closed loop circuits present within cerebro-cerebellar interactions so although the microarchitecture of the cerebellum is quite homogenous, this does not appear to be the case for its function.

The existence of these cortico-ponto-cerebellar and cerebello-thalamo-cortical loops which link the cerebellum with motor areas, non-motor association areas and paralimbic regions

of the cerebrum supports the basis of widespread cerebellar functions (Kelly and Strick, 2003). However, the confusion with detailing which regions of the cerebellum are involved in specific functions stems from failure to detect large pronounced, specific deficits in lesion studies. Meta-analytic studies have demonstrated that there are existing sensorimotor (anterior lobe), cognitive (posterior lobe) and affective (vermis) regions of the cerebellum, although there is inherent overlap between lobular areas due to the differences in data sets, specific task instructions and goals (Stoodley and Schmahmann, 2009). Recent functional parcellation data has demonstrated that perhaps the current lobular-functional distinctions are not as precise as once thought (Kansal et al., 2016; King et al., 2018). Using a large-scale diverse task-based approach, comprehensive maps of heterogeneous activity were found across the cerebellum during tasks within multiple domains (King et al., 2018). Further analysis showed that functional sub-regions that are typically defined within specific lobules often span multiple lobules, this may very well lead to the confusion that has surrounded the variability in symptoms seen with cerebellar degeneration or lesions and the subsequent classifications of function of the cerebellum.

2.3.6 The cerebellum and non-motor functions

The cerebellum, as discussed has a primary role in aiding in the coordination of movement processes by providing precise timing of feedback to the cortex from various signals that it receives and integrates from incoming sensory systems and the rest of the cerebrum. However, this coordination role could also underlie the implementation of processes such as prediction, detection of novelty, error detection, time matching and sequence ordering (Ivry et al., 2002; Ghajar and Ivry, 2009; D'Angelo and Casali, 2013). These processes are quite multi-dimensional and can contribute to diverse functions spanning from motor to cognitive in nature. The cerebellum itself may operate in a modular way, where its effects depend on the dominant

area within the cerebellum and the cortical area to which it receives input from and projects back to (D'Angelo and Casali, 2013). This can be better understood through the classical symptom that is seen with cerebellar damage, ataxia, characterized by a gross lack of coordination of muscle movements. This lack of coordination can present with abnormalities depending on which cerebellar structure has been damaged, impairment of balance or eye movement is due to dysfunction of the vestibulocerebellum, impairment of gait is due to dysfunction of the spinocerebellum, and difficulty of executing planned, voluntary movements are due to impairments within the cerebrocerebellum.

The presence of these deficits reiterates the presence of widespread cortico-cerebellar motor loops, however, upon closer inspection, patients with focal cerebellar lesions have been found to show cognitive-affective alterations (Schmahmann and Sherman, 1998). These deficits stem from the connections within prefrontal and parietal areas to and from the cerebellum. Impairments of executive functions, difficulties with spatial cognition, personality changes and language deficits have all been observed in cerebellar lesion patients, collectively, these symptoms are referred to as the cerebellar cognitive affective syndrome (CCAS) (Schmahmann and Pandya, 2008; D'Angelo and Casali, 2013).

Aspects of coordination, learning, predicting and behaving are also encompassed within higher-level cognitive processes when we make decisions on how to react or where to direct our focus to. These types of decisions are predicated on whether a situation is new to us or whether we have experienced it or something similar before. Although it is unclear exactly how the cerebellum contributes to these higher order processes, many studies have demonstrated its

activation during such tasks, even independently of overt motor components such as execution of button presses.

2.3.6.1 Attention

In order to perform even the simplest of tasks or movements, individuals need to orient themselves towards the task at hand and orient themselves away from potential distractors in the environment that are not relevant for the goal of the task. This concept is typically described as attention and requires a great deal of coordination, so perhaps it is not as surprising that the cerebellum is seen to be active during various attentional tasks. Patients with cerebellar lesions have been shown to be able to correctly orient visual attention, but their reaction times are slower as compared to those of healthy control subjects (Schlosser et al, 1999). Many studies require some type of overt movement as a response and therefore it is argued that the cerebellar activation is due explicitly to this. An fMRI study by Allen et al. (1997) sought to further investigate the nature of the cerebellum's involvement and found that the cerebellum was active during conditions in which participants were to visually orient their attention to a specific target without need for motor response, and during a movement response to the target. However, the voxels of interest were distinct from one another, their time courses of activation also differed, as during the motor task, attention voxels appeared highly activated at the start of the task but then decreased, while during the attention task, there were no marked increased activation of the motor voxels (Allen et al., 1997). Functional connectivity studies have shown that there is a cerebellar node within the dorsal attention network (DAN), a network comprised of frontal and parietal areas which are implicated heavily in attentional control (Brissenden et al., 2016). Cerebellar areas of activation within attentional tasks are generally present within Crus I/II and lobule VII (Halko et al., 2014). Inducing transient excitability to this cerebellar DAN node

resulted in participants having fewer attentional lapses during a gradual onset continuous performance task and during an attentional blink task (AB) (Esterman et al., 2017). Conversely, when the cerebellum is transiently inhibited, a decrease in accuracy in detecting a second target in a string of letters during an AB task was observed (Arasanz et al., 2012a).

2.3.6.2 Language Processing

Cerebellar pathology has been shown to impair acquisition of motor skills, resulting in the reduction of primary articulation ability (D'Angelo and Casali, 2013). Reliable cerebellar activation has been seen during language paradigms such as word/letter generation, word stem completion, semantic processing and verbal fluency tasks (Ojemann et al., 1998; Schlosser et al., 1998; Seger et al., 2000; Frings et al., 2006; Stoodley and Schmahmann, 2009). Word articulation tasks have been associated with activation of bilateral lobules V/VI whereas right lobule VI and Crus I/II have been shown in word generation and pseudoword tasks (Booth et al., 2007; Carreiras et al., 2007). The difference in activation patterns during overt speech compared to language processing suggests that the cerebellum contributes to higher order attentional processes which have a predictive or contextual component in addition to explicit movement to a target.

2.3.6.3 Imagery and Visuospatial Processing

Cerebellar engagement has been observed during mental rotation and transformation tasks, orientation judgement and spatial navigation (Zacks et al., 2002; Lee et al., 2005; Weiss et al., 2009). It is hypothesized that projections between the cerebellum and parietal lobe are what facilitate this activation. Engagement of the posterior cerebellum during motor imagery may be a crucial component within rotation and transformation, although it is argued that because there is

overlap in general cortical activation with movement and imagination of movement, that still this activation within the cerebellum is due to the motor component. Ultimately, movement, some type of acted on behaviour or reaction is the end result to any task demands and the need for task adaptation to changes across stimuli will be required.

2.3.6.4 Working Memory

Both verbal and non-verbal working memory tasks, like the Sternberg and *n*-back tasks, have been shown to reliably activate the cerebellum, particularly in lobules VI/VII, with cerebellar activity increasing in conjunction with increasing workload (Desmond et al., 1997; Chen and Desmond, 2005a; Stoodley and Schmahmann, 2010). These working memory tasks rely on the recall of specific items from lists or recall of stimulus similarities from a predetermined amount of earlier steps (“*n*” amount), respectively (Chen and Desmond, 2005a; Stoodley and Schmahmann, 2010). Differences in activation have been regarded throughout the encoding, maintenance and retrieval of items which may reflect, once again, its role in the monitoring of expected and observed outcomes.

2.3.6.5 Emotional Processing

Cerebellar activation has been observed during the processing of emotionally relevant stimuli which includes emotional images, facial expressions and vocal intonations (Lane et al., 1997; Paradiso et al., 2003; Lee et al., 2004). It is possible that the cerebellum is recruited in response to information that is relevant to subsequent actions. A lack of emotional modulation observed in some cerebellar patients and the symptomology of CCAS also strengthens the role of the cerebellum within this domain (Stoodley, 2012).

In order to accomplish specific aspects of the aforementioned paradigms, a common factor within all is the complex ability to integrate various stimuli and processes necessary to achieve a goal. To do this, individuals need to attend to specific aspects of a scenario and ignore others, it is possible then that on an over-arching level, that the cerebellum is involved in the process of executive process of attention regardless of the type of stimuli although there is no consensus on its specific contributions to the process. There are theories which aim to interpret the cerebellum's exact role within coordination and learning, whether it is for movement or cognition; these theories tend to revolve around the concepts of timing and prediction. The cerebellum is shown to be consistently activated following an attentional cue, independent of movement execution; attention itself is thought to have the primary role of generating time-based expectancies of sensory information (Ghajar and Ivry, 2009). It is therefore argued that the cerebellum is actively involved in an attentional network alongside the PFC and parietal lobe. Within this network, the cerebellum itself may be primarily concerned with encoding the precise timing of sensory predictions which works in a tight time frame to temporally bind stimuli and events, this predictive function of the cerebellum then is a defining trait of attention (Ghajar and Ivry, 2009). Precisely how the cerebellum exerts this input throughout the rest of the cortex is not as well elucidated although there are a few hypothesized mechanisms.

2.3.7 Hypothesized mechanisms of cerebellar control

Formation of these prediction trajectories is thought to be performed through the cerebellum's usage of internal models with repeated performance and feedback. In a broad sense, the term internal model is representative of any neural representation of the external world (Ito, 2008). This concept is well defined in the sensorimotor domain of control where as a movement is repeated, the cerebellum allows the movement to be executed skilfully without dynamic

feedback (Bucker, 2013). In keeping with the symptoms seen within CCAS and various patients with cerebellar abnormalities, it has been suggested that in the same way that the cerebellum regulates the rate, force, rhythm, and accuracy of movements, it might also regulate the speed, capacity, consistency, and appropriateness of mental or cognitive processes (Schmahmann and Sherman, 1998; Schmahmann, 2010). The cerebellum's internal models are necessary to compare the expected with the actual; however there can be detrimental changes with cerebellar alterations and the mismatch between not only expected and actual trajectories, but also with actual and perceived trajectories.

In order to be able to adapt to new movements, skills and situations, an adaptive control system is needed where a controller receives instruction from an operator, according to these instructions, the controller will generate signals to guide a controlled object. Internal models are required within this chain to help the system to learn. Within the realm of movement, the controlled object is a part of the periphery to be controlled by the CNS. For example, an internal model of the arm's (controlled object) dynamics receives input in the form of information on the current position and velocity of the arm along with an efference copy of the motor commands issued from the controller. The model forms an output, a prediction of the future position and velocity of the arm (Argyropoulos, 2016). Internal models are able to provide information about the future properties of a controlled object in rapid form, which is crucial in cases where sensory feedback may be absent; it is also a key component of learning. There have been two hypothesized types of control systems that have been proposed for the internal models and error monitoring, forward and inverse models. Forward models allow for prediction of the sensory consequences of a motor command which allows for rapid error detection when actual and

predicted feedback do not match. Inverse models are utilized to determine the motor commands necessary to achieve a desired action.

As discussed, the cerebellum is structurally uniform, contrasting with the regions of the cerebral cortex which can be distinguished from one another based on differences in their cytoarchitecture. These uniform areas of the cerebellum essentially form microcomplexes where internal models for specific functions can be formed depending on the functional input to the given region. Each microcomplex receives major input signals from the widespread cerebral cortex via mossy fibres and converts them to an output of cerebellar or vestibular neurons (Ito, 2008). The microcomplex also receives input from climbing fibres, originating from the inferior olive, which convey signals that represent changes or errors and that have the capacity to form and update the internal models. These signals form prediction errors, which are derived through the comparison of the outputs of a controlled object with those of the created forward model or the prediction (Wolpert et al., 1995; Ito, 2008). Massive amounts of sensory input enters the cerebellum and studies have shown that transmission of these error or change signals is reduced when input is predictable (Lawrenson et al., 2016). However, during unpredictable behaviour, signal transmission is increased in an effort to update the motor cortex and effectors to adjust current movement (Lawrenson et al., 2016; Sokolov et al., 2017). This finding supports the idea that cerebellar processing is crucial for taking in pertinent information to inform behaviours in the most efficient way possible and updating our behavioural repertoire when a novel stimulus is experienced. This circuitry is well discussed within the domain of movement with M1 acting as the controller, although it's role in higher order processes is now increasingly researched due to its massive connectivity across major subdivisions of the brain.

In keeping with the terminology utilized, it could be posited that the PFC acts as a controller for attentional processes with the cerebellum participating in feedforward and/or feedback control. For example, when participants are required to press a button in response to selectively attended to targets, there is greater cerebellar activation during moments of heightened attention and when errors were performed (Allen and Courchesne, 2003). Activity such as this may reflect the activation of internal models that need to be adjusted to correct errors during changes in perceptual or cognitive state that are then communicated through reciprocal connections to higher order areas, such as the PFC, in order to prioritize specific stimuli.

2.4 Potential implications of cerebellar dysfunction

Cerebellar patients have typically been classified as having large motor deficits, leading to the long standing belief that it was only involved in motor control. While certain sensory and perceptual deficits are difficult to assess, they have become increasingly detected within cerebellar patients and this is supported by the widespread connections between the cerebellum and cortex. Various behavioural and neuropsychiatric disorders present with findings of abnormal cerebellar processing; however, the presentations of these symptoms are quite ubiquitous and so the cerebellum has not been as primarily focused on as an avenue of these symptoms. The rate of psychiatric morbidity associated with cerebellar degenerative diseases is about double than it is in healthy subjects (Leroi et al., 2002). A diffusion tensor imaging (DTI) study revealed reduced white matter within the parietal association cortex and the cerebellum, furthermore, neurological signs in schizophrenic patients are inversely correlated with volume of the right cerebellar hemisphere (Bottner et al., 2005; Kyriakopoulos et al., 2008). Compared to healthy controls, psychiatric patients are not able to estimate the sensory consequences of their own actions (Synofzik and Voss, 2010). This is characteristic of a cerebellar lesion patient and

can be interpreted as an impaired comparison of an individual's actions with expectations, a primary predictive function of the cerebellum. Cerebellar patients and individuals with autism have shown impairments in attention shifting between auditory and visual stimuli (Courchesne et al., 1994). Reciprocal connections between the cerebellum and the surrounding cortex have been mapped out, providing a framework from which differences in connectivity in individuals with specific disorders can be compared to aid in understanding the etiology of symptoms, anatomical studies of individuals with autism have revealed a loss of Purkinje cells and hypoplasia within the cerebellum (Fatemi et al., 2012). While the extent of the link between cerebellar dysfunction and autism is not fully understood, these alterations in attention and feelings of stimuli overload in persons with autism once again validate the role of the cerebellum in evaluating stimuli to guide behaviours and position it as a potentially underutilized pathway for treating certain symptoms.

2.5 Neurophysiological techniques

Many of the studies which have found cerebellar activation during tasks involve imaging and are specifically fMRI studies, although many times the primary goal of the study is not to investigate cerebellar function and so its activation patterns are not further analyzed. In the last two decades, more studies have been focusing in on the cerebellum's activation within specific tasks, although its role still proves to be somewhat enigmatic. fMRI studies continue to show cerebellar activation within more passive tasks which range from viewing emotionally valenced photos to imagined movement (Paradiso et al., 2003; Lee et al., 2004; Hanakawa et al., 2008). Many studies produced inconclusive results within cerebellar patients due to differences in lesion locations and it was still unknown in what way that the cerebellum contributed to such processes and whether it was for motor intent or working alongside more widespread areas. Resting state

functional connectivity which focuses on brain activity while the cortex is not involved in an externally cued task posits that correlations in fluctuating spontaneous brain activity tend to reflect the intrinsic functional networks of the brain have been increasingly performed to investigate the potential cerebellar nodes within larger widespread networks (Fox and Raichle, 2007; O'Reilly, 2010). These studies have found that there are specific nodes within the cerebellum which are related to larger networks spanning sensorimotor and supramodal interactions (O'Reilly, 2010). More specifically, changes in these functional connectivity states have been implicated in conditions such as attention deficit hyperactivity disorder (ADHD), schizophrenia and Alzheimer's disease (Liang et al., 2006; Yu-Feng et al., 2007; Wang et al., 2007). These imaging studies rely on the blood-oxygen level dependent (BOLD) signal, a ratio of oxyhemoglobin to deoxyhemoglobin in a given cortical area (Matthews and Jezzard, 2004). Based on this principle, an increase of neural activity in a given area would lead to an increase in required blood flow which would mean an increased ratio of oxy- to deoxy-hemoglobin and therefore a higher BOLD signal. The changes observed during tasks can prove difficult to interpret when trying to determine causality to widespread changes in activation and time sensitivity of the task and activation observed within the cortex.

Studies have attempted to detangle the nature of these functional connections by modulating activity within the cerebellum to determine whether any changes can be seen in these widespread networks following specific cerebellar alterations (Fox et al., 2005; Habas et al., 2009; Buckner et al., 2011). These modulations have been performed using a specific type of transcranial magnetic stimulation (TMS) which is based on the principle of electromagnetic induction where a current pulse is produced and passed through a tightly wound copper wire coil placed on the scalp; this generates a magnetic field. The magnetic field is produced

perpendicularly to the plane of the coil that penetrates the scalp and skull, which in turn induces an electric field within the cortex; more specifically a change in the excitability of a focal pool of neurons depending on where the coil is placed over the cortex (Hallett, 2000; O'Shea and Walsh, 2007). The delivery of pulses of TMS can be applied at varying intensities and frequencies which alter whether the effect it has over the focal area it is applied over is excitatory or inhibitory. This method provides a unique opportunity to explore causal interactions between cortical areas and the specific contributions of cortical areas to defined tasks. Specifically, forms of repetitive stimulation known as continuous theta burst stimulation (cTBS) and intermittent theta burst stimulation (iTBS) have been shown to transiently decrease and increase M1 activity, respectively for about an hour in healthy participants (Huang et al., 2005). These techniques are now being used over the cerebellar cortex to understand how it communicates with distal cortical areas. A study by Halko et al. (2014), demonstrated that stimulating over Crus I/II using iTBS facilitated increases in functional connectivity with distal prefrontal and parietal areas. Similarly, following cTBS over the right lateral cerebellum has demonstrated a decrease in functional connectivity specifically with frontal and parietal cognitive regions (Rastogi et al., 2017). While work such as this demonstrates the strong connectivity of the cerebellum and non-motor areas, the exact effects of TMS over the cerebellum are not as well understood as they are for over M1. This poses a challenge given the unique structure of the cerebellum and its innately inhibitory nature. With the general inhibitory effects that is known to be exerted by cTBS (Huang et al., 2005), it is posited that the cTBS suppresses inhibitory GABAergic interneurons in the molecular layer of the cerebellum, leading to a reduction in inhibition of Purkinje cells; this would in turn increase their inhibitory output to the deep cerebellar nuclei, decreasing their excitatory output to the thalamus and cortex and possibly resulting in impaired cerebello-cerebral connectivity or

communication (Koch et al., 2008; Rastogi et al., 2017). Combining this technique with a high temporal resolution method such as electroencephalography (EEG) provides an avenue that can display the connectivity of cortical areas based on secondary effects at cortical areas distal to application of the TMS.

EEG is a valuable tool that allows for the functional mapping of neuronal activity associated with motor, sensory and cognitive functions across healthy and disease populations with high temporal resolution for characterizing changes in patterns of activation both over long periods of time and within session changes (Gevins et al., 1995). Using event related potentials (ERPs) and measuring their changes in response to interventions have helped to further understand the cortical networks involved in movement, emotion, working memory and attention (Näätänen and Escera, 2000; Popovich and Staines, 2014; Adams et al., 2017). Restuccia et al., (2007), demonstrated that an oddball paradigm using stimulation of 1st and 5th digits of hands ipsilateral to a cerebellar lesion showed attenuated responses of the somatosensory N140, a peak involved in stimulus evaluation, when compared to healthy controls. This study presents findings which indicate that the cerebellum may be a key evaluator of stimuli via attention. Cerebellar patients have also shown an impaired ability to rapidly shift their attention between visual stimuli along with a decreased cognitive P3 in response to rare stimuli (Akshoomoff and Courchesne, 1994), this was within one singular modality and these findings are replicated and more pronounced in the presence of multiple modalities (Akshoomoff and Courchesne, 1992). As mentioned, the use of cerebellar lesion patients sometimes poses a challenge with large amounts of variability due to differences in lesion size and location, therefore, studies which incorporate EEG with TMS modulating a specific area in a more standardized way across healthy participants may allow for further insight into these processes.

Evidence of the cerebellum's contributions to behaviour that is no longer restricted to just motor control is plentiful. As mentioned, this is not surprising given the extensive reciprocal connections that exist between the cerebellum and other cortical and subcortical areas. Despite the many imaging and cerebellar patient studies which link the cerebellum to these higher order functions, there is still a lack of understanding of how exactly it makes its contribution to these behaviours (Schmahmann and Sherman, 1998; Turner et al., 2007; Buckner et al., 2011; Darch et al., 2018). The modulatory effects of the cerebellum have been observed with imaging studies that have employed the use of cerebellar stimulation and measured the opposite effects of excitatory and inhibitory TBS on the connectivity with cognitive networks (Halko et al., 2014; Rastogi et al., 2018). Using non-invasive methods of neurostimulation to manipulate cerebellar function in both healthy and patient populations allows for the identification of how cerebellar alterations can lead to changes in a wide variety of behaviours (Darch et al., 2018). Furthermore, being able to use a technique such as TBS in a healthy population may help to give a clearer understanding of cerebellar function that can then be compared to patient populations in an effort to shed light on the progression of change. In order to understand more about a complex mechanism, we often use the concept of reductionism, where a real-world task is minimized to be fit for a laboratory setting and we draw large conclusions about real-world processes and behaviours. The studies of this thesis will start by utilizing basic tasks and will conceptually build off of the previous study by trying to manipulate the innate nature of the task in an effort to narrow in on how the cerebellum exerts its influence on higher-order tasks to help facilitate movement (e.g. prediction, attention, memory). Understanding the ways in which the cerebellum modulates these processes may highlight the potential of targeting this structure clinically for behavioural and cognitive impairments, which may be a result of cerebellar dysfunction.

Chapter 3: Specific research objectives

3.1 Research Objective 1

Characterize the influence of cerebellar input over sensory processing without the need for directed movement following inhibition of the right lateral cerebellum in a young healthy population

Although the cerebellum receives large amounts of sensory inputs, its lesions have been consistently shown to cause uncoordinated movements but not gross sensory deficits (Holmes, 1939). This discrepancy between the massive amounts of sensory input and lack of detection of obvious sensory deficits have long classified cerebellar sensory processing as a means for tuning voluntary movement but nothing more. Functional neuroimaging studies have demonstrated cerebellar activation during sensory tasks such as cutaneous discrimination, as well as auditory and visual non-motor tasks (Jueptner et al., 1995; Gao et al., 1996; Allen et al., 1997). It is still argued that these activations are present due to the associated motor response of the tasks. Little data exist on cerebellar influence during early sensory processing. Restuccia et al. (2001), found that patients with cerebellar lesions demonstrated decreased amplitudes of early somatosensory evoked potentials (SEPs) in response to median nerve stimulation at both frontal and parietal regions. A follow up study found that patients with cerebellar lesions were unable to effectively detect a change in stimulus presentation during an oddball paradigm where frequent and deviant stimuli were presented via median and ulnar nerve stimulation (Restuccia et al., 2007). This is a key finding as more recent concepts surrounding the cerebellum's function posits that it helps to facilitate behaviour due to state estimation of the body and what needs to be changed to perform desired movements or goals (Molinari et al., 2009). This function in itself is considered to be a higher-order function, the cerebellum's involvement in executive processes such as this is

supported by the widespread frontal and parietal connections that it is known to have, this is further strengthened by the changes observed within frontal and parietal cortical activity in relation to cerebellar lesions (Stoodley and Schmahmann, 2009; Bucker, 2013). Activation of the right lateral cerebellum has been shown to be associated largely with these higher-order executive tasks, as demonstrated within functional imaging studies (Allen et al., 1997; Stoodley and Schmahman, 2010). Although, there is much variability in the findings of such studies due to the vast differences in tasks utilized within healthy populations and due to the heterogeneity of lesions in studies using patients.

Research objective 1 aimed to investigate the cerebellum's contribution to sensory processing without the need for directed movement. It is hypothesized that if the cerebellum contributes to the detection of stimuli to predict our goals or behaviour, that following transient inhibition of its activity, participants would become less able to identify pertinent changes in the presentation of stimuli. Study 1 tests this hypothesis using an oddball paradigm task with median and ulnar somatosensory stimulation being presented as frequent and deviant stimuli and measuring the cortical responses to these stimuli before and after delivery of cTBS or sham stimulation over the right lateral cerebellum.

3.2 Research Objective 2

Determine whether the cerebellum's evaluation of sensory stimuli is related to a change in attention by evaluating changes to somatosensory and visual cortical peaks during a sensory conflict task

Navigating multisensory environments requires individuals to appropriately respond to the pertinent stimuli around them and ignore things in their surroundings that may distract them

or that are not necessary for their goals. This shifting of focus is defined as attention and is a common factor across many of the tasks that individuals perform on a daily basis. This may range from moving through a busy intersection or carrying out a conversation with someone, but in either case, it is critical to evaluate the information needed to behave appropriately and ignore anything not relevant to our needed response. The cerebellum has been shown to be active during attentional tasks and following attentional cues (Ghajar and Ivry, 2009; Esterman et al., 2017). Modulation of cerebellar activity has also been shown to alter functional connectivity with the dorsal attentional network which is heavily governed by frontal and parietal cortical regions (O'Reilley., 2010; Halko et al., 2014). This is perhaps not so surprising due to the vast connectivity between the cerebellum and these higher order associative areas. Still, confusion regarding the cerebellum's role in this prioritization of information for coordination is poorly understood namely due to ambiguity in tasks used and the inability to make inferences about causality. Previous work has utilized a sensory conflict task to understand the role of the prefrontal cortex in attentional processing, and has found that it contributes to the facilitation of relevant information. Given the connectivity of the cerebellum within this network, utilising the same task and evaluating the cerebellum's contribution to the same task will garner further insight into its role in this process. Therefore, research objective 2 is to further understand how the cerebellum may exert its influence via attention through means of evaluating or comparing stimuli differences. It was hypothesized that if the cerebellum contributes to the attentional process by means of comparing stimuli to task goals, then participants will be less likely to ignore irrelevant distractor stimuli and will perform with decreased accuracy following transient inhibition of cerebellar activity. To test this, the study utilized a sensory conflict task which required participants to provide a graded motor response to either tactile or visual stimuli which

were presented either unimodally or with a paired distractor. Cortical responses via EEG and accuracy were measured before and after delivery of cTBS to the right lateral cerebellum.

3.3 Research Objective 3

Understand how the cerebellum links together differing sensory modalities to facilitate meaningful behaviour and appropriate responses by assessing the laterality of the cerebellum's influence on contralateral attention networks

The previous study showed that participants were less efficient at ignoring information that was irrelevant to their task goal following an inhibition of right cerebellar activity; this was reflected in both EEG and behavioural data. There are various hypothesized mechanisms that explain how the cerebellum is able to prioritize the information it processes and communicates with the rest of the cortex to facilitate coordinative behaviour. These mechanisms revolve around the importance of spatiotemporal dynamics which can be easily understood through the traditional sense of failed motor coordination in cerebellar patients. This is a result of a lack of precise sequences of movements of one or more body segments due to deficient adjustments of position, velocity and acceleration, all aspects which are defined by changes in time and space (D'Angelo and Casali, 2013). Diverse behavioural symptoms observed in disorders may be a product of a lack of precision in the processing of various sensory stimuli in the environment (Moberget and Ivry, 2019). It has been argued that the specific role that the cerebellum plays within the behavioural domain is to funnel sensory information to inform movement. Reviews of imaging studies have shown the right sided cerebellum to be linked to higher-order attentional and cognitive processes, which has formed the basis of the use of right sided cerebellar stimulation for the current group of studies (Schmahmann, 2018). The results of study two lend further evidence to this specificity of the right sided cerebellum's involvement in higher-order

processes and although the primary factor of the task is attentional in nature, the task itself heavily relies on the integration of sensory information to make a graded motor response. Distinguishing the cerebellar role within movement and higher-order processes is challenging due to the overlap within the two domains and the necessity for both when it comes to everyday, meaningful behaviour. Therefore, in an effort to further specify the role of the cerebellum within these higher-order processes, a second group performed the same sensory conflict task but received left sided cerebellar stimulation. It was hypothesized that if the right side of the cerebellum was specifically involved in contributing to the modulation of the contralateral attentional network, then stimulation of the left side would not be associated with a difference in behaviour pre and post stimulation along with minimal EEG-related changes.

Chapter 4: Study 1

Transient inhibition of the cerebellum impairs change-detection processes: Cerebellar contributions to sensorimotor integration

Andrew, D., Ibey, R. J., & Staines, W. R. (2020). Transient inhibition of the cerebellum impairs change-detection processes: Cerebellar contributions to sensorimotor integration. *Behavioural brain research*, 378, 112273.

4.1 Overview

Patients with cerebellar lesions have shown altered responses to unpredictable stimuli leading to the belief that the cerebellum is involved in comparing incoming stimuli with previously experienced stimuli in order to predict and coordinate responses. It is thought that this purpose of the cerebellum could extend beyond motor control and to higher-order executive functions which allow for the evaluation of stimuli that influence our personal reactions, emotions, thoughts. This study sought to test the role of the cerebellum in the evaluation of isolated sensory stimuli being unattended by the participant. Median and ulnar nerve somatosensory evoked potentials (SEPs) were elicited by electrical stimulation via surface electrodes. Nerve stimulation was presented in an oddball fashion where median and ulnar stimulation were presented as frequent and deviant stimuli, respectively. Electroencephalography (EEG) was used to measure participants' cortical responses both before and after either continuous theta burst stimulation (cTBS) used to transiently inhibit cerebellar activity, or a sham condition. The N140 was shown to be modulated in response to deviant stimuli, resulting in a large negativity pre-cTBS, referred to as the mismatch-negativity (MMN). Following cTBS, the MMN was blunted, resulting in similar waveforms presenting to both frequent and deviant stimuli, with the decrease of the MMN being maximal approximately 30 minutes post-cTBS. The mechanisms thought to modulate this change within the N140 in response to deviant stimuli are believed to be different than those which govern its response to frequent stimuli. The cerebellum may be involved in pre-attentive change-detection processes that are critical for a wide-range of everyday processes.

4.2 Introduction

Communication between the central nervous system (CNS) and periphery creates a fundamental feedback loop wherein sensory input is integrated and used for assisting in the execution of appropriate motor outputs; this dynamic process is sensorimotor integration (SMI). SMI is flanked by the proponents of variability reduction and prediction estimates where with continued exposure to certain stimuli, error (or variability) can be reduced due to state predictions that are based on incoming sensory information and previous exposure to stimuli (Flanders, 2011; Krakauer and Mazzoni, 2011). Behavioural training has been shown to induce resulting SMI use-dependent cortical changes necessary for skill acquisition (Byl et al., 1997; Classen et al., 1998; Abbruzzese and Berardelli, 2003). While these adaptive changes are necessary, studies have shown that in various injuries and neurologic disorders, anatomical changes are correlated with unfavourable behavioural motor performance (Elbert et al., 1998; Tinazzi et al., 1998; Lewis and Byblow, 2002; Smania et al., 2008).

Cortical structures involved in the learning of motor skills have been the focus of studies for many years, with more investigations into the subcortical areas involved being increasingly performed over the last decade (Middleton and Strick, 2000; Doyon et al., 2002; 2009; Houk et al., 2007). Specifically, the role of the cerebellum with regard to motor learning has long been debated; however, it has emerged as a main candidate of stimuli integration and internal feedback, aspects which are critical for SMI (Doyon et al., 2002; Manzoni et al., 2007). Traditionally, the cerebellum has been regarded as an accessory motor structure in that its purpose was to receive massive amounts of somatosensory input and exclusively optimize and fine tune the regulation of voluntary movement (Restuccia et al., 2007). This idea of the cerebellum functioning solely as an accessory motor structure was supported by research which

demonstrated that cerebellar lesions do not produce gross sensory deficits, but rather uncoordinated movements (Holmes, 1939). This traditional view is now challenged as cerebellar activity has been observed following tasks that are not inherently motor in nature such as cutaneous discrimination, auditory, visual, and working memory tasks (Stoodley and Schmahmann, 2009; Stoodley, 2012; Buckner, 2013). It is now therefore thought that the cerebellum participates as a sensory acquisition controller and allows for the adaptation and coordination that is observed with skill learning (Bower, 2002). However, the concepts of adaptation and coordination are very large, overarching conditions that may have multiple, smaller underlying mechanisms or processes which extend beyond the realm of motor control only. This is further supported by cerebellar communication and influence on information processing throughout multiple regions of the cortex which is made possible through the dense connections with the thalamus which project to widespread areas including the frontal, motor and parietal cortices, involved in cognitive and emotional processes (Bugalho et al., 2006; Philips et al., 2015).

Past research has shown that the cerebellum is able to modulate the excitability of the primary sensory cortex at early stages of somatosensory input processing (Restuccia et al., 2001). Investigation of early latency evoked potentials in patients with lateralized cerebellar lesions revealed that inhibitory circuitries are low-functioning in cerebellar patients, suggesting that the cerebellum influences the inhibitory circuitries of S1 which may in turn modulate receptive fields and optimize sensory discrimination (Restuccia et al., 2001; 2007). Restuccia et al. (2007) demonstrated that an oddball paradigm using stimulation of the first and fifth digits of hands ipsilateral to a cerebellar lesion showed abnormal responses as measured by EEG when compared to healthy controls. This study presents findings which indicate that the cerebellum

may be a key evaluator of stimuli in a predictive and attentive way, however more work is needed to confirm this (Restuccia et al., 2007). Observations of somatosensory deficits such as difficulty in weight perception or kinesthesia have been reported in patients with cerebellar lesions (Gao et al., 1996); combined with evidence of widespread cerebellar connections with sensory and associative cortical areas, it is now thought that the cerebellum participates in high-level processes involved in planning, memory and attention (Stoodley and Schmahmann, 2009). Perhaps the cerebellum's coordinative function for motor learning operates in the same way for sensory and even cognitive tasks, this possibility is supported by the uniform cytoarchitecture of the cerebellum. It is still argued that the cerebellum's purpose is inherently motor related since its activation during perception tasks or memory tasks may have some aspect of motor imagery. Still, widespread evidence of the cerebellum's influence over S1's activity warrants further investigation of the cerebellum's ability to predict incoming sensory stimuli and how this may extend into the realm of higher-order functions.

The mismatch negativity (MMN) is a cortical event related potential (ERP) which is generated by an automatic cortical change-detection process where a difference is found between current input and the expected input or a representation of the regular aspects of the preceding input (Takegata et al., 2001; Näätänen et al., 2007). Research has tested this process by interspersing unattended, deviant stimuli between regular, frequent stimuli. This work is typically performed with the use of auditory stimuli but has also been shown with visual and olfactory stimuli as well (Nyman et al., 1990; Woods et al., 1992; Tales et al., 1999). Deviant stimuli have been shown to elicit a fronto-temporal negative response in the 120-180 ms latency range, the MMN. It is thought that this process can only be achieved if a representation of the standard or expected input is available for comparison with the current input. Due to the location

patterns of the negativity, it is thought to reflect a distributed network involving the prefrontal and parietal cortices (Alain et al., 2005). These areas of the cortex have been implicated in higher-order executive functioning (Corbetta et al., 2000; Langner and Eickhoff, 2013). Transneuronal tracing techniques have provided evidence that there are reciprocal circuits between the cerebellum and frontal and parietal areas from regions that do not have overlap with cerebellar motor circuitry (Kelly and Strick, 2003). This, paired with evidence that the cerebellum has the ability to modulate accessory cortical regions and high-order processes such as attention, leads to the questioning of whether the cerebellum acts as a regulator for these regions that are thought to hold the main responsibility of higher-order processes (Esterman et al., 2017). Functional topography studies have suggested that there are distinct areas of the cerebellum which receive dominant input from different cortical areas making distinctions between the cerebellar anterior lobe which is principally involved in motor control; the vermis which is involved in affective processing and the posterior cerebellum which contributes to higher-order and cognitive operations (Levisohn et al., 2000; Exner et al., 2004; Schoch et al., 2006; Schmahmann et al., 2007). Within such studies however, there are still contradictory results due to the differences in task demands and outcome measures, there is therefore value in trying to understand the cerebellum's role outside of the motor domain through the use of simple sensory stimuli.

In an effort to verify whether the cerebellum is capable of evaluating sensory stimuli and accordingly modulating cortical activity, Restuccia et al. (2001) performed an oddball paradigm in patients with unilateral cerebellar lesions and found that there was a lack of the change-detection mechanism (MMN) on the lesioned side. The use of a unilateral cerebellar lesion group provides a unique opportunity for being able to investigate both affected and unaffected sides in

the same individual; however, it does provide difficulties when considering the heterogeneity of lesion depth and location. Therefore, in order to further test this hypothesis, the goal of the current study is to investigate the cerebellum's involvement in stimuli prediction in a healthy population following transient inhibition of cerebellar activity. It is hypothesized that following this transient inhibition of the cerebellum, the MMN present at fronto-parietal sites in response to deviant stimuli will be blunted so that the cortical activity in response to deviant stimuli post transient inhibition will mimic that which is seen in response to frequent stimuli. The stimulation used to induce this transient inhibition will occur on the right side of the cerebellum, making it ipsilateral to the limb that is being stimulated with somatosensory stimuli.

4.3 Materials and Methods

4.3.1 Participants

Twenty healthy, right-handed participants with no known neurological conditions were recruited from the University of Waterloo community (10 males, 10 females; mean age \pm SD = 26 \pm 4.1). The cTBS stimulation group was comprised of ten volunteers and the remaining ten formed the sham stimulation group. All participants provided informed written consent. The University of Waterloo Office of Research ethics approved all experimental procedures.

4.3.2 Experimental Design

All participants entered a single-blind, pre-post design which required them to attend one session where they had EEG data collected. Each participant was administered the Edinburgh Handedness Questionnaire and a transcranial magnetic stimulation (TMS) Safety Checklist to ensure they were all right-handed and had no contraindications to receiving TMS, respectively. Participants' responses to electrical nerve stimulation were evaluated before and after the application of either cTBS to the right lateral cerebellum or sham stimulation (same location,

stimulation coil placed at a 90 degree angle away from the scalp and stimulus intensity at 10%). Participants in the sham group were naïve to cTBS/TMS procedures. Nerve stimulation was presented in an odd-ball paradigm where there were two types of stimuli, median and ulnar stimulation to the right side. Providing sensory stimulation to the right side was chosen as the right lateral cerebellum was being targeted with the cTBS and connectivity studies have demonstrated that stronger cerebellar input exists to the ipsilateral dominant hand and in turn, contralateral cortical hemisphere (Schlerf et al., 2014). The median nerve stimulation served as the frequent stimulation and the ulnar nerve stimulation served as the deviant stimulation; the stimuli were represented in an 80/20 fashion such that the median nerve stimulation occurred 80% of the time and the ulnar nerve stimulation occurred the remaining 20% of the time.

4.3.3 Experimental Paradigm

Participants were assigned to either the experimental stimulation (cTBS) or sham stimulation group, with both groups participating in the same oddball stimulation paradigm. Following EEG cap preparation, TMS thresholding and nerve stimulation set up, the participant was seated comfortably in front of a desk with a partition placed between where the participant sat and experienced the nerve stimulation and where the experimenter was sitting to isolate the participant as best as possible. Participants passively received nerve stimulation while gazing at a white fixation cross in the centre of a computer screen in front of them. The oddball nerve stimulation paradigm was delivered pre-and post-cTBS to the right lateral cerebellum. The pre-nerve stimulation trials consisted of two blocks of nerve stimulation, each consisting of 240 total stimuli with frequent and deviant stimuli presented in a 80/20 ratio. Therefore, in a block of 240 stimuli, 197 median nerve or frequent stimuli and 43 ulnar nerve or deviant stimuli occurred. Each block lasted approximately 6 minutes, with the stimuli occurring at an average of 1.36

seconds apart (range of 1.26-1.46 seconds), having a range for interstimulus intervals in order to decrease predictability. Following administration of cTBS to the right lateral cerebellum, the post- nerve stimulation trials began. The nature of the stimuli and oddball paradigm were identical to that of the pre- trials, however there were more blocks performed in an effort to quantify the timeline of the effects of cTBS on cerebellar function. For the post- trials, nerve stimulation was performed at 3 time points following cTBS (Post 1, 2, 3 - 0, 15, 30 min post-cTBS). During each post-cTBS time point, two blocks of nerve stimulation were delivered as in the pre- trials for a total of six blocks delivered. In total, the nerve stimulation post-cTBS lasted for a total of 36 minutes. During each time point, the blocks were performed twice to ensure that there were a sufficient number of deviant trials to average as they were significantly less in number than the frequent trials.

In order to ensure that the response being measured to deviant stimuli is in fact due to a change-detection process rather than activating different afferents due to the difference in stimulation parameters, a standard omitted (SO) protocol was also performed for one block before cTBS stimulation. This trial consisted of only the ulnar nerve stimulation identical to that used in the oddball paradigm (approximately 240 ulnar nerve stimuli).

4.3.4 Stimuli

Electrical stimuli were delivered to the distal and medial areas of the right wrist and hand so as to activate portions of the median and ulnar nerves respectively. The stimuli consisted of electrical pulses which were 0.1 ms in duration delivered at a rate of 0.98 Hz (GRASS, S88X stimulator, West Warwick, Rhode Island, USA). The stimuli delivered to the median nerve were done so through two Ag/AgCl ECG conductive adhesive skin electrodes (MEDITRACE™ 130, Ludlow Technical Products Canada Ltd., Mansfield, MA). These electrodes were placed over the

median nerve on the skin 2-3 cm proximal to the distal crease of the wrist, between the tendons of the flexor pollicis longus and palmaris longus with the anode distal. To familiarize participants to the stimulus and set an appropriate intensity, motor thresholding was performed and the recurring stimuli were delivered at this intensity for the median nerve. Motor thresholding is defined as the lowest possible intensity at which a visible muscle contraction of the abductor pollicis brevis (APB) was elicited. The stimuli delivered to the ulnar nerve were done so via ring electrodes placed on the fifth finger (anode distal). Intensity for the ulnar nerve stimulation was determined by sensory thresholding where the intensity was slowly increased until the participant reported a repeated sensation at which point the intensity was increased 2.5 times this and the stimuli to the ulnar nerve was delivered at this intensity for the remainder of the experiment (ie. 2.5 x perceptual threshold).

4.3.5 cTBS Parameters

Application of cTBS was performed using a MagPro R30 stimulation unit (MagVenture, Alpharetta, GA, USA) using a figure eight coil (MCF-B65). Stimulation intensity was set at 80% of the active motor threshold (AMT) for the right APB. In order to determine AMT, the stimulation coil was placed on the upper left surface of the participant's scalp at the optimal position over the motor cortex that would elicit motor evoked potentials (MEPs) from the contralateral APB. AMT was defined as the lowest stimulator output required to produce a MEP of >200 microvolts in 5 out of 10 trials during a 10% maximum voluntary isometric contraction. MEPs were measured using surface EMG from the right APB using two surface electrodes (MEDITRACE), two active electrodes were placed over the muscle belly and a ground was placed over the radial styloid. For the sham stimulation, the TMS unit was set to 10% of maximum output so that participants could hear the stimulus pulses but the coil was oriented up

and away from the scalp. It is important to note that the individuals in the sham group still received the protocol to determine the active motor threshold. During cTBS, bursts of three stimuli are presented at 50 Hz and repeated at 5 Hz (theta frequency) for 40 seconds, which yields a total of 600 pulses (Huang et al., 2005). In order to stimulate the right cerebellar hemisphere the centre of the coil was placed 1 cm below and 3 cm lateral to the right of theinion (Theoret et al., 2001; Arasanz et al., 2012a; 2012b).

4.3.6 EEG Parameters

EEG data was recorded using a full 64-channel EEG cap (Quick-Cap, Neuroscan, Compumedics, NC USA) to measure the electrical activity from the surface of the scalp in accordance with the international 10-20 system for electrode placement and referenced to the linked mastoids. Impedances were maintained $< 5 \text{ k}\Omega$ and continuous EEG data was collected, filtered (0.2-1000 Hz), digitized at 1000 Hz (Neuroscan 4.5, SynAmps2, Compumedics, NC USA) and subsequently stored on a computer for offline analysis. EEG analysis began with epoching to the nerve stimuli followed by baseline correction to the pre-stimulus interval. Epochs were 400 ms in length, beginning 100 ms before stimulus onset and epochs contaminated by muscle contractions, eye movements or blinks were removed by visual inspection before averaging. The final averaged traces for each block for frequent stimuli contained on average, 237 artifact-free epochs, minimum 132; and for deviant stimuli, 94 artifact-free epochs, minimum 57.

4.3.7 Data Analysis

The amplitudes of evoked potentials were measured peak-to-peak, from the peak of interest to the preceding potential of opposite deflection. All 20 participants who took part in this study were included in the analysis of EEG data.

The goal of this study was to test the hypothesis of the cerebellum's involvement in the processing of purely sensory stimuli and its role in modulating the cortical change-detection process in response to deviant stimuli. The goals of the statistical analysis were to test the specific hypotheses of (1) the presence of a much larger negativity in response to deviant stimuli versus frequent stimuli and (2) whether this large negativity was modulated by cTBS over the cerebellum in a way that decreased its amplitude in response to deviant stimuli post-cTBS. To do this, a three-factor mixed-model analysis of variance (ANOVA) was performed in SPSS (IBM, Version 25) to compare mean peak amplitude changes with factors of TIME (pre, post 1, post 2, and post 3) and STIMULUS (frequent, deviant) as within factors and a factor of GROUP (cTBS, sham) as the between factor. Statistical significance was set at $p=0.05$. Data was checked for normality to ensure that assumptions for performing the ANOVA were upheld.

A t-test was used to compare amplitudes pre-cTBS for the SO protocol of the single stimulation frequency of 0.98 Hz (referred to as deviant in the oddball paradigm). Amplitudes for the pre-cTBS time point of SO and oddball were compared. An alpha level of 0.05 was used to define statistical significance for any effects.

4.4 Results

The EEG traces demonstrated a clear N140 component in response to nerve stimulation, which was maximal parieto-occipally, in the 140-200 ms latency range. As stimulation of the cerebellum was delivered over the lateral right side, amplitude and latency measurements for the N140 were reported from electrode PO3. A small but reliable N60 was also regarded parieto-occipally and was maximal at the CP3 electrode in the 50-90 ms latency range and was therefore measured from this electrode site. Prior to cTBS stimulation of the cerebellum, there was a much larger cortical negativity parieto-occipally in response to the deviant nerve

stimulations when compared to the frequent nerve stimulations, taken to be the mismatch negativity response (MMN). Additionally, the P100 was also reliably observed within the 90-150 ms latency range and measured within parieto-occipital electrode, PO3. These components were visible in both cTBS and sham control groups as seen within Figures 4.1 and 4.2.

For the N60 peak, the three-factor mixed design ANOVA showed no significant interaction effects between any within-subjects factors (stimulus, or time), nor were any main effects observed. Furthermore, no main effects were observed for the between-subjects factor of group.

For the P100 peak, the ANOVA revealed a significant interaction of stimulus by time ($F_{3,54}=8.658$, $p=0.011$). To further investigate this interaction, two separate one way ANOVA analyses were performed for the stimulus types, frequent and deviant across the four time points. The ANOVAs revealed that there was a significant difference between time and the frequent stimuli ($F_{3,79}=2.718$, $p=0.037$). Post-hoc testing showed that this difference was specifically between time point one (pre) and time point four (post 3) for the frequent stimuli ($p=0.05$). Qualitatively, the peak amplitude of the P100 in response to frequent stimuli slightly decreased from baseline values when measured at the third timepoint.

For the N140 peak, the ANOVA demonstrated a significant 3-way interaction between factors of time by group by stimulus ($F_{3,54}=35.056$, $p<0.0001$). To further explore the interactions present and better represent the overall group difference that was observed for the N140 peak, separate two way ANOVAs were performed, separated by group, cTBS and sham respectively. Within the cTBS group, the ANOVA showed that there was a significant difference between frequent and deviant stimuli types for the N140 peak amplitude across the time points

($F_{3,36}=36.377$, $p<0.001$). Post hoc testing revealed that these differences were not present across all time points, but specifically during the pre ($p<0.001$) and post 1 ($p<0.001$) time points.

For the sham group, the ANOVA showed a significant difference between frequent and deviant stimuli types for the N140 peak amplitude across the timepoints ($F_{3,36}=13.397$, $p<0.0001$). Post hoc testing revealed that these differences between deviant and frequent stimuli were present across all time points pre ($p<0.0001$), post 1 ($p<0.0001$), post 2 ($p<0.0001$) and post 3 ($p=0.0001$).

Figure 4.1 shows the grand average traces which demonstrate the changes in peak amplitude that occur between frequent and deviant stimuli from the baseline trials to the post 3 time point for the cTBS group.

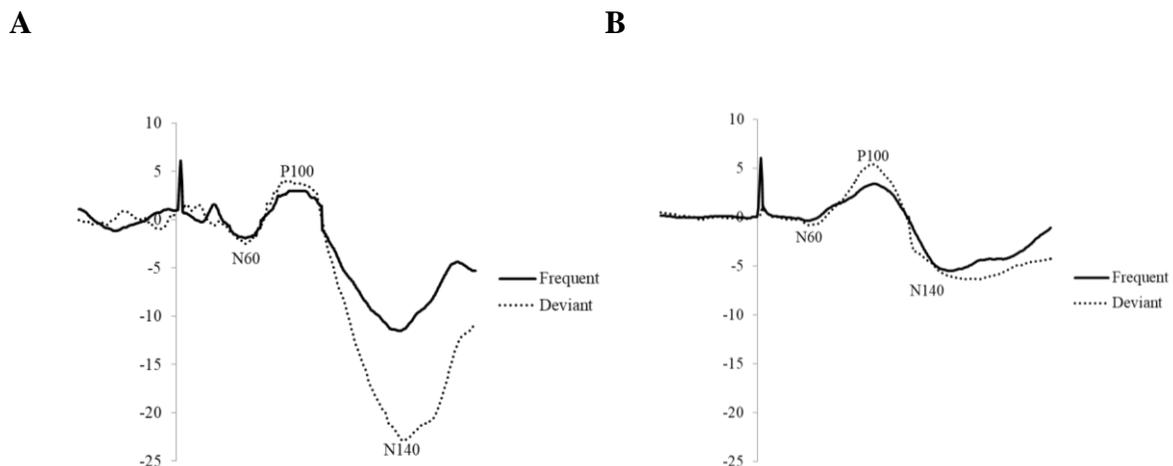


Figure 4.1. Grand average EEG traces for the N140 in the cTBS group. (A) Grand average waveform for the N140 peak in μV demonstrating the cortical response to frequent and deviant stimuli at baseline for the cTBS group (B) Grand average waveform for the N140 peak in μV demonstrating the cortical response to frequent and deviant stimuli at the Post 3 time point for the cTBS group. Measured from electrode PO3.

Comparison between groups can be observed in Figure 4.2 which shows the grand average traces of frequent and deviant stimuli across time points for the Sham group. The interactions observed are well demonstrated in Figure 4.3 which depicts the mean amplitude differences for the cTBS group. It is clearly seen here that within the cTBS group, that the mean amplitude difference is large during the pre time point and that the presence of this difference deteriorates as time continues. However, within the sham group, it can be seen that the presence of this large mean amplitude difference stays constant throughout all time points. The mean amplitude differences were calculated by subtracting the amplitude of the N140 peak in response to frequent stimuli from the amplitude of the N140 peak in response to the deviant stimuli.

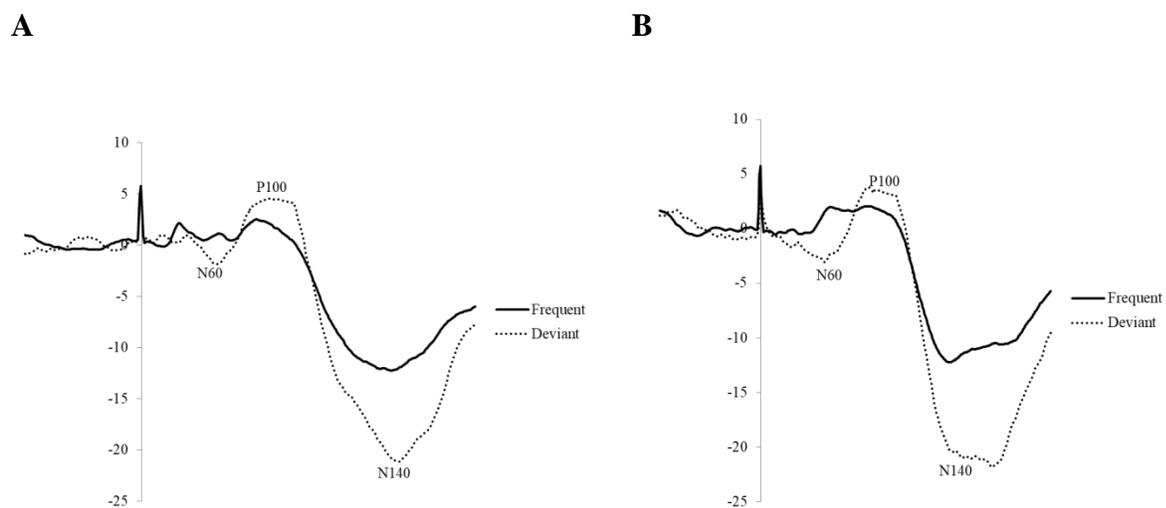


Figure 4.2. Grand average EEG traces for the N140 in the Sham group. (A) Grand average waveform for the N140 peak in μV demonstrating the cortical response to frequent and deviant stimuli at baseline for the Sham group (B) Grand average waveform for the N140 peak in μV demonstrating the cortical response to frequent and deviant stimuli at the Post 3 time point for the Sham group. Measured from electrode PO3.

It is quite clear that prior to cTBS stimulation, a large peak amplitude presents in concordance with a change detection mechanism required to identify a deviant stimulus, and

following cerebellar cTBS, this mechanism may be affected as there is a loss of amplitude difference between the two stimuli. As the main interest of this study was to determine whether cTBS does in fact have an effect on potential cerebellar processes, the lack of change demonstrated in Figure 4.3 which depicts the mean amplitude difference for the Sham group provides further support for this. No significant differences in latency were observed for any of the peaks.

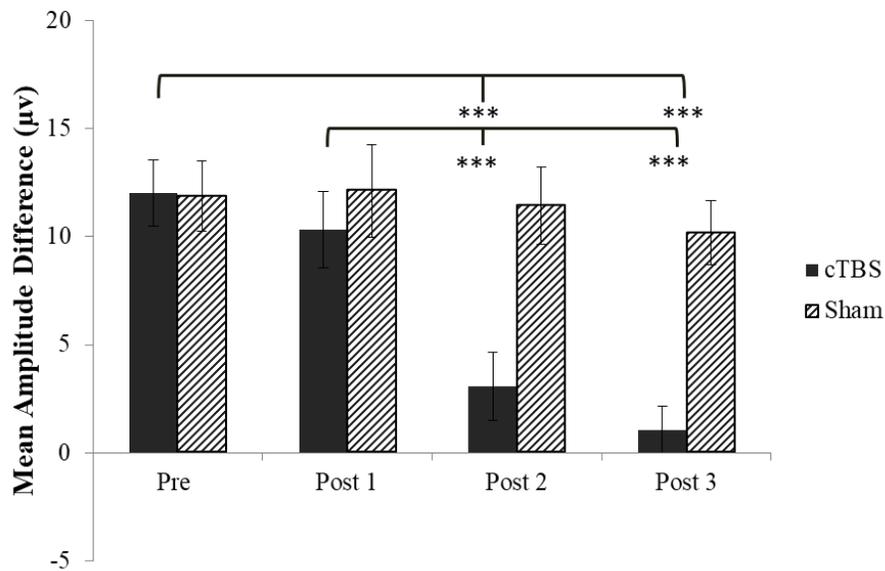


Figure 4.3. Mean amplitude differences shown for the cTBS and Sham groups. Mean amplitude difference of the N140 between responses to frequent and deviant stimuli. The cTBS group is represented by black bars and the Sham group is represented by hatched bars. (***) indicates $p < 0.001$; error bars indicate standard error)

In order to ensure that the differences seen in amplitudes between the frequent and deviant stimuli were in fact due to a change detection mechanism and not due to different afferents being activated in response to the altered stimuli, trials in which the ulnar nerve stimulation was the sole stimuli provided (SO) were compared to trials in which the ulnar nerve stimulation was delivered in the context of deviant stimuli (OB). For the comparison, amplitude averages of the N140 from baseline (pre) SO trials were compared to the baseline (pre) trials of

the cTBS group. The t-test indicated that there was a significant difference in amplitude ($p < 0.001$). There was also a significant difference in latency ($p = 0.04$) between the two groups. These differences are demonstrated in Figure 4.4.

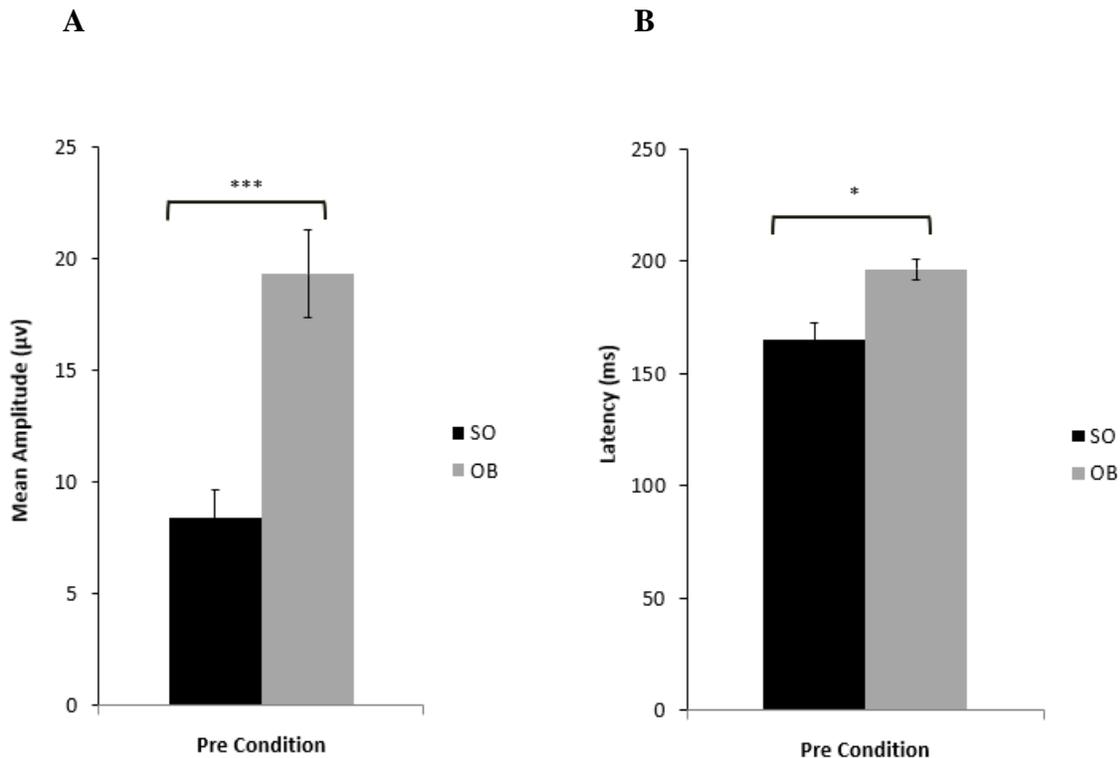


Figure 4.4. Comparison of response to ulnar stimulation in different contexts. (A) Mean peak amplitude of the N140 in response to ulnar stimulation presented as a deviant stimulus (OB, grey bar) and as a frequent stimulus (SO, black bar). Within a deviant context, the cortical response is much larger, and significantly so due to the presence of a large negativity (***) indicates $p < 0.001$). (B) The latency of the ulnar stimulus when presented as a deviant stimulus (OB, grey bar) is significantly larger than when it is presented as a frequent stimulus (SO, black bar) (* indicates $p < 0.05$).

4.5 Discussion

This work reiterates the body of research which posits that at some level, the cerebellum plays a role in the processing of sensory stimuli that is not needed for the purpose of a motor action or goal. The major findings of this study were (1) that interspersing deviant somatosensory stimuli amongst frequent stimuli elicits a clear parieto-occipital negativity, the

MMN and (2) that the characteristic MMN is modulated following transient inhibition of the right lateral cerebellum.

As previously mentioned, the MMN is defined as an electrical response evoked by a discriminable change in any regular or repeated somatosensory stimulation elicited in the absence of attention (Näätänen et al., 2005). Although this response has been routinely explored following exposure to auditory stimuli, it has also been elicited in response to visual, olfactory and somatosensory stimuli (Tales et al., 1999; Pause and Kraeul, 2000; Tamura et al., 2004; Akatsuka et al., 2005). Of these studies, MMN responses evaluated in response to somatosensory stimuli are the least studied, furthermore, replicating the MMN has not been consistent, potentially due to the nature of the stimuli used and variability in study participants (ie. vibrotactile stimuli, two-point discrimination tasks, lesion locations), which is why the use of a healthy population and a control group are so critical to the design of this study. Following the application of cTBS specifically to the right lateral cerebellum, the presence of a large negativity in response to deviant stimuli is gradually reduced, becoming maximally reduced 30 minutes following stimulation. This finding is further strengthened via the continuous presence of the large negativity in response to deviant stimuli across all time points in the Sham group.

In order for a change to be detected, there must be a preserved sensory representation of the regular or repeating stimuli. In observing that there is a clear difference in response to the deviant stimuli compared to the frequent stimuli, this provides evidence for the presence of a cortical mechanism responsible for recalling past events used in order to predict future events. While the neural correlates of this mechanism are still not fully known, it is thought that it differs from those circuits which are involved in the cortical responses seen as the N140 in frequent stimuli trials (Restuccia et al., 2007). This thought is further supported by the current study as the

cortical responses to the ulnar nerve stimulation in the standard omitted trials differed from that of the responses to the same stimuli following its presentation as a deviant stimulus in the oddball paradigm.

The cerebellum has long been discussed as having a comparator function in order to facilitate coordination in motor behaviour. The way in which the cerebellum is able to smoothly control these functions is thought to be via efference copies of the planned movement with the sensory feedback that is produced by the actual or current movement (Marr and Thach, 1991; Ito, 2005). The major route for information access to the cerebellum, the climbing fibres and the interactions with the mossy fibre system are considered to be the basis of this comparator function that the cerebellum is responsible for (Ito, 2005). During active, self-generated movements, transmission of major input to the cerebellum is found to be gated; however, the presence of altered or unpredictable stimuli increases the transmission of information in the cerebellum (Lawrenson et al., 2016). This pattern of information flow within the cerebellum would serve to initially store the expected outcome from a stimulus following repeated exposure to it and then update this previously stored event following the occurrence of an unfamiliar stimulus. A prominent feature of the cerebellum is its uniform organization that is repeated throughout its cortex (Schmahmann, 1991; Ramnani, 2006). It is known that the cerebellum receives input from a variety of higher-order, non-motor areas such as the cingulate cortex, posterior parietal cortex and frontal cortex and viral tracing techniques have demonstrated that there is a significant amount of output from the cerebellum to these non-motor areas (Schmahmann and Pandya, 1991). Based on the ubiquity of the cerebellum's organization and the presence of non-motor loops, perhaps the same processing role that the cerebellum performs for motor input is extended to input for these non-motor, association areas.

A major aspect of the oddball paradigm was the requirement of participants to passively receive nerve stimulation without having to overtly respond to the presence of the stimuli. The experiment was designed in this way in order to evaluate the cerebellum's role in the processing and integration of sole sensory stimuli. Measuring the MMN is best recorded using passive conditions where the individual's attention is not focused on the stimuli (Näätänen and Escera, 2000). One caveat however, is that in order to elicit the MMN response desired in this experiment the stimuli presented must differ substantially and it is therefore difficult to discern whether the participant's attention is covertly shifted to the stimuli as the sheer difference in stimuli may attract attention beyond the control of personal will and instructions. Attention is critical for all aspects of daily living and research has demonstrated that attentional deficits are related to sensory processing issues, demonstrating there is an overlap between the processes of sensory integration and attention (Schaaf and Miller, 2005; Zhang et al., 2011; Lin and Gau, 2017). This therefore poses a larger question with regards to the cerebellum's role in the processing of sensory information and its comparator responsibility. The relatively stable nature of N60 and P100 throughout the experiment in comparison to the N140/MMN lends support to the pre-attentive mechanism of the change detection as these peaks have been shown to be modulated by changes in attention (Desmedt and Tomberg, 1989; Garcia-Larrea et al., 1991; Schubert et al., 2008). The interaction effect that is observed for the P100 in response to deviant stimuli between the two groups at the sole Post 3 time point may be indicative of a stronger gradual shift of attention within the Sham group over time, although the slight difference in change of amplitude direction may be the main driving force behind this finding.

There are distinct networks that have been implicated in attention, namely the dorsal attention network (DAN), which is comprised of mainly frontal and parietal regions (Corbetta et

al., 2000; Langner and Eickhoff, 2013). Functional connectivity work has demonstrated that there are also cerebellar nodes involved in the DAN and that when these cerebellar nodes of the DAN are targeted with non-invasive stimulation techniques, improvements in attentional lapses are observed (Brissenden et al., 2016; Esterman et al., 2017). This is perhaps not surprising given the known presence of connections between the cerebellum and non-motor association areas, however more work needs to be performed to understand how the cerebellum may be exerting these effects upon distal cortical areas. Functional imaging has shown the presence of cerebellar activity during a visual attention task in an area completely distinct from areas of activation during motor performance (Arasanz et al., 2012a). Cerebellar patients have presented with impaired verbal fluency although, as mentioned, patient studies are often conflicting due to the nature of variability stemming from differences in cerebellar tumors, degeneration and lesions (Richter et al., 2007; Schweizer et al., 2010). To further investigate this, a study by Arasanz et al. (2012b) administered cTBS over the right lateral cerebellum in a fashion similar to as done in the current experiment and found that following cTBS, there was a reduction in phonemic fluency with specific regard to category switches. Category switches allow for the meaningful organization of word groups or clusters, this is reflective of executive and strategic mental processes (Troyer et al., 1998). An increased amount of category switches allows for increased word generation, generally within such tasks, most words are generated within the first 15 seconds, referred to as the early phase. Following cTBS, this ability to switch categories was found to be the most impaired during the early phase of the task, once again supporting the role of the cerebellum in executive functioning and cognition, which is heavily relied on in the early moments of category switches (Arasanz et al., 2012b). The ability to switch categories in a time sensitive manner can be linked back to the concept of attention and the cerebellum's potential

role in this higher order function. Another study by Arasanz et al. (2012a) found that following cTBS to the right lateral cerebellum, a decrease in accuracy to detect a second target in a string of letters when the second target was presented in a shorter time frame following the first or initial target (120-400 ms), this interference is known as the attentional blink phenomenon (AB). Studies have posited that the AB is predicted by the magnitude of attention resources that an individual places on the initial target (Shapiro et al., 2006; Arasanz et al., 2012a). It is possible that the cerebellum plays a role in modulation of attentional resources that are required to rapidly switch and detect the next target or event, a concept reminiscent of the rapid switch in attention needed for word generation as well (Arasanz et al., 2012a; 2012b).

Such highlights of these alterations of cerebellar activity once again demonstrates that the cerebellum is not solely equipped to perform just motor control, but is instead a system in and of itself that is made up of separate modules made to influence different behavioural functions such as cognition and attention in a similar fashion. These facets of behaviour work alongside movement in order to form meaningful actions in an ever changing multisensory environment. Therefore, a study which includes both transient modulation of cerebellar output in conjunction with directly orienting and/or manipulating a participant's attention towards target stimuli would allow for a better understanding of how the cerebellum can aid in facilitating higher-order processes. It could be possible that the cerebellum's role in comparison serves to act as the regulator of other cortical regions which are involved in execution of more specific functions.

Lastly, the current study did not include any behavioural measures; a critical next step would be to alter participant's attention while having them respond to target stimuli in a sensory task. Combining cortical responses and behavioural measures provides an avenue for us to better understand how the cerebellum may be involved in linking information that is required when we

engage in higher-order processes. This has the potential to increase our understanding of some of the challenges and deficits seen in attentional and behavioural disorders.

4.6 Conclusion

This work demonstrates that even during an unattended condition, deviant electrical somatosensory stimuli, when interspersed amongst frequent stimuli elicit a modulation of the N140 SEP peak. The use of cTBS to transiently inhibit the cerebellum validates the presence of cerebellar input to this peak as abnormalities are seen following cTBS. Specifically, this work lends important insight into the function of cerebellar input in somatosensory processing in observing that following its inhibition, responses to deviant stimuli, which had previously been established as unique from frequent stimuli, became similar to those responses. This is also further supported by the findings of the standard omitted protocol, in that no changes specific to the single stimulus change and that the N60, attentionally driven and related to frontal areas, remains relatively stable throughout all paradigms. Even with abnormal cerebellar input, the sensory information is still able to reach the cortex but with limited context relevance since the cerebellum is less efficiently able to perform its pre-attentive assessment of incoming information. Further work must be performed in order to understand the behavioural implications that cerebellar input, or the lack thereof has on performance, learning and potentially higher-order executive processes.

Chapter 5: Study 2

Cerebellar modulation of attention to distractor stimuli

5.1 Overview

The presence of cerebellar activation during non-motor tasks and its projections to non-motor cortical association areas have led to the hypothesis that it contributes to the coordination of higher-order functioning. To accomplish these higher order processes within multisensory environments, we need to orient ourselves to important stimuli and ignore distractions; this is essentially the description of attention. Studies have shown that nodes of the cerebellum are active during attentional tasks, although the exact mechanism of action is not clear. Understanding the mechanisms and networks by which we alter our attention is critical, as a deficit in its control may be a contributing factor to the deleterious symptoms observed in various behavioural disorders.

This study, therefore, sought to examine the cerebellum's role in attention by comparing changes to tactile and visual stimuli within a sensory conflict task before and after transient inhibition of the cerebellum using continuous theta burst stimulation (cTBS). Participants were asked to make a graded motor response to the amplitude of visual or tactile stimuli that were presented either individually or simultaneously. Attention was altered by having participants respond only to tactile or visual stimuli as instructed, prior to the start of each task block. This resulted in conditions in which participants received a relevant stimulus, an irrelevant stimulus, or a distractor stimulus. Somatosensory ERPs and performance were measured using electroencephalography (EEG) and grading accuracy, respectively, collected pre and post cTBS to the right lateral cerebellum.

The ERPs in response to both tactile and visual stimuli were larger when they were attended to than when they were not. Prior to cTBS, the presence of a distractor attenuated tactile N70 and visual P2 responses; post cTBS, the presence of a distractor resulted in increases in

these amplitudes, suggesting an affected ability to ignore distractors. Behavioural data demonstrates that after cTBS, grading of both visual and tactile stimuli is less accurate. Following transient inhibition of the cerebellum, participants are less likely to gate stimuli that are irrelevant.

5.2 Introduction

Vast connections exist between the cerebellum and cerebral cortex, including inputs from the frontal, parietal, temporal and occipital lobes (Glickstein et al., 1997; Schmahmann, 1996; Strick et al., 2009). It was thought that these inputs were channelled through cerebellar circuits then projected to the primary motor cortex (M1) by way of the thalamus (Brooks and Thach, 1981). This led to the longstanding belief that the cerebellum's only role was to perform a sensorimotor transformation, whereby sensory inputs were processed and then conveyed to M1 for the generation and coordination of movement (Strick et al., 2009). This view was supported by findings that cerebellar lesions led to largely uncoordinated movements but no gross sensory deficits (Holmes, 1939).

However, this simplistic view has been challenged by the presence of cerebellar activation during inherently non-motor tasks and the existence of cerebellar reciprocal projections from its nuclei back to non-motor cortical areas which include regions of the frontal, prefrontal, and posterior parietal cortex (Middleton and Strick, 2000; Kelly and Strick, 2003). In concordance with the uniform nature of the cerebellum, it is now hypothesized that the cerebellum not only aids in the integration of sensory information for the coordination of movement, but also to facilitate higher-order executive and cognitive functions. In order to accomplish these higher order mental processes in our everyday multisensory environments, we need to orient our attention to important stimuli and ignore the stimuli that are not necessary for our goals. Studies

have recently shown nodes of the cerebellum to be active during attentional tasks, furthermore changes in activity of these modes have been shown to modulate performance on these same tasks which include both transitory and continuous stimuli types (Halko et al., 2014; Brissenden et al., 2016; Esterman et al., 2017). Transient increases and decreases in cerebellar activity have been shown to elicit concomitant increases and decreases in functional connectivity with prefrontal attention networks (Fox and Raichle, 2007; O'Reilley, 2010; Halko et al., 2014). While these interactions of the cerebellum and the attentional network appear to be robust, the exact mechanism of its action is not well understood. It is critical to understand the mechanisms and networks by which we alter our attention to perform everyday tasks as a deficit in its control may be a contributing factor to the deleterious symptoms observed in various behavioural disorders.

Imaging studies have demonstrated cerebellar activation during tasks which range from language processing, spatial processing, working memory, and affective processing (Fink et al, 2000; Stoodley and Schmahmann, 2009; Hautzel et al., 2009). A common overlapping element of all of these tasks is the ability to coordinate previous and new information. This allows for the appropriate selection of relevant stimuli or information to perform a task where the concept of attention is needed in some capacity and the cerebellum's coordinative role may play a specific part in this. Further support of the cerebellum's involvement in attention come from studies which describe cerebellar alterations in patients with attention deficit hyperactivity disorder (ADHD), a disorder which is known to cause disturbances in executive functioning such as inattention to stimuli that should lead to action consequence and impaired response inhibition to those that should not (Castellanos, 2001). These impairments could potentially be a result of the

inability of the cerebellum to accurately perform comparisons of incoming sensory stimuli or an inability to distinguish pertinent stimuli from erroneous stimuli.

The invariant nature of the of cerebellar cortical cytoarchitecture is fundamental to the concept of the universal cerebellar transform (UCT); the idea that cerebellar processing remains similar across domains of actions depending on the specific circuitry of the area of the cerebellum and its connections. The cerebellum has been hypothesized as a global influencer of the coordination of movement, cognition and emotions through predicting internal conditions for a particular movement or mental operation and setting the corresponding conditions in preparation (Gottwald et al., 2003). The cerebellum's involvement in learning adaptation has been well studied, with imaging work showing that a novel task elicits strong cerebellar activations and once a task has been well learned, cerebellar activity decreases as internal predictions have become well set for use (Floyer-Lea and Matthews, 2005; Lehericy et al., 2005; Dayan and Cohen, 2011). These internal predictions allow for optimization of behaviour, which is why cerebellar damage does not completely eliminate these functions but increases suboptimal variability (Gottwald et al., 2003). This is perhaps the reason why its motor involvement is so much more emphasized, due to the explicit changes observed in ataxia as opposed to smaller, perceptual changes in sensory and executive functioning.

Attention can be guided volitionally through explicit goals and task demands or involuntarily drawn by a stimulus, these are referred to as top-down and bottom-up orienting, respectively (Buschman and Miller, 2007; Adams et al., 2017). Imaging and neurophysiological studies have consistently documented neural correlates of these processes within frontal and posterior parietal cortices (Corbetta and Shulman, 2002; Buschman and Miller, 2007). The convergence of these processes is a critical component, especially with regards to the complexity of tasks such as

detecting social cues or operating a vehicle. In these everyday situations we are required to maintain a goal while being able to allow important changes to alter our course while still ignoring those items which do not contribute to our goals or safety. This fine balance is a potential place holder of where the cerebellum could exert its contribution to the process of attention; through usage of its predictive and comparison mechanisms (Ito, 2005; 2008).

Previous work has shown that impaired cerebellar output affects an individual's ability to detect the differences in presented somatosensory stimuli, resulting in similar cortical responses to both frequent and novel stimuli (Restuccia et al., 2007). This impaired ability to detect important changes may be due to compromised cerebellar communication with higher-order areas and a lessened ability to prioritize the salience of stimuli, which is a component of attention.

Attentional blink (AB) protocols have demonstrated that following transient decrease of cerebellar output, individuals become worse at detecting a second target in a string of letters at longer delays as compared to controls (Arasanz et al., 2012a). This once again supports the idea of an impaired ability to detect rapid, salient changes in order to perform an appropriate behaviour. The cerebellum's use of internal models to perform and learn tasks has provided a useful tool to understand how people adjust their behaviour when there is some type of alteration in environmental dynamics (McDougle et al., 2016). The above-mentioned examples may indicate, through an alteration in attentional networks, the cerebellum is unable to convey the appropriate resources needed to adjust our behaviour or responses to dynamic changes. The use of these internal models has been well documented for successful adaptation in sensorimotor integration (SMI), but more recently, discussions of the versatile cognitive and executive functions that need to take place to make SMI possible have revolved around the cerebellum and its feedforward-feedback interactions with more associative areas in the cortex. A better

understanding of how the cerebellum may aid in the prioritization of communication with widespread attentional networks is needed.

Many studies utilize single modality tasks; however, we interact with multisensory environments and must orient ourselves to and away from specific stimuli, therefore, a study that examines how the cerebellum processes different modalities is needed. Previous work utilizing a cross-modal task found that cortical responses to tactile and visual stimuli are attenuated when they are not relevant, this was specifically seen within the somatosensory N70 peak (Adams et al., 2017). It was hypothesized that the prefrontal cortex (PFC) was a mediator of this top-down attentional control. Following the transient inhibition of the PFC, this task relevance modulation was abolished (Adams et al., 2017; 2019). Given the relationship of the cerebellum and PFC, perhaps the cerebellum aids in this same process to allow for appropriate stimuli selection.

The current study investigated the cerebellum's role in attention in a sensory conflict task by transiently inhibiting cerebellar activity using continuous theta burst stimulation (cTBS). It is hypothesized that if the cerebellum is involved in the comparison of stimuli to facilitate an appropriate response, then following cTBS, the attenuation of irrelevant information will be suppressed resulting in increased amplitudes of somatosensory and visual event related potentials (ERPs), as measured by electroencephalography (EEG). It is also expected that behaviourally, accuracy of sensory grading will be decreased due to the inability to selectively attend to the appropriate stimulus.

5.3 Materials and Methods

5.3.1 Participants

Fifteen healthy, right-handed participants with no known neurological conditions were recruited from the University of Waterloo community (7 males, 8 females; mean age \pm SD = 26 \pm 3.6). All participants provided informed written consent. The University of Waterloo Office of Research ethics approved all experimental procedures.

5.3.2 Experimental Design

All participants completed pre-post design, which required them to attend one session where they had EEG data collected. Each participant was administered the Edinburgh Handedness Questionnaire and a transcranial magnetic stimulation (TMS) Safety Checklist to ensure they were all right-handed and had no contraindications to receiving TMS, respectively.

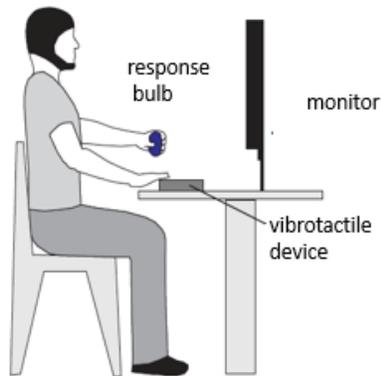
Participants performed a graded sensory conflict task where they were asked to make a graded motor response to the amplitude of unimodal visual (V) or tactile (T) stimuli that were presented either individually or simultaneously (VT), while their attention was randomly oriented to specific stimuli during blocks of trials. This formed two attention response conditions, attend to T or attend to V, as well as three stimulus presentation conditions where each stimulus would either be relevant, irrelevant or a concurrent distractor. 10 blocks of trials were presented, divided evenly and between the two attention conditions (attend T and attend V) and presented in randomized order. Each experimental block contained 54 stimuli which were presented for 500 ms each with a 2.5 s interval between trials, therefore each block lasted approximately 3.5 minutes. Participants' response to the attended stimuli was performed using a pressure-sensitive bulb where the participants would squeeze the bulb using a force graded response to indicate the approximate amplitude of the T or V stimuli depending on the instructed

attended condition, the experimental set up is demonstrated in Figure 5.1. The 10 blocks were presented as a pre-condition, followed by administration of cTBS over the right lateral cerebellum and then performance of another 10 blocks as a post-condition.

5.3.3 Experimental Paradigm

Following EEG cap preparation and TMS thresholding, the participant was seated comfortably in front of a desk with a computer screen where they were required to fix their gaze for the duration of the experimental task blocks. The computer screen in front of the participant presented visual stimuli and tactile stimuli were delivered through a custom made speaker device which has a flat plastic tip which the participant rested the palmar surface of their right second digit on. Participants were asked to judge the amplitude of the stimulus type that they were instructed to attend to prior to the start of each block (V or T). Their response was provided by squeezing a pressure-sensitive rubber bulb which was held in their left hand.

A



B

Stimulus: Relevant, Irrelevant or Distractor	Grade Tactile	Grade Visual
Tactile Stimulus 	 Response	----- No response
Visual Stimulus 	----- No response	 Response

Figure 5.1. Experimental setup and paradigm. (A) Participants were seated in front of a monitor with a pressure-sensitive bulb held in their left hand. Their right hand was rested in a vibrotactile delivery device which delivered vibrotactile stimulation to the distal digit of the right index finger. Fixation was maintained on the computer screen which presented visual stimuli. (B) Each experimental trial consisted of a unimodal tactile stimulus, a unimodal visual stimulus, or tactile and visual stimuli being presented simultaneously. After each trial was presented, participants were required to make a

force-graded response by squeezing the pressure bulb to approximate the amplitude of the target stimulus. Prior to the start of a task block, participants were instructed which stimulus to attend to, this defined the target stimulus and created trials where stimuli were either relevant, irrelevant or a concurrent distractor.

As with Study 1, sensory stimulation to the right side was chosen as the right lateral cerebellum was being targeted with the cTBS and we wanted to probe these changes within the widespread cerebellar networks that exist to the ipsilateral dominant hand and contralateral cortical hemisphere (Schlerf et al., 2014). When asked to attend to tactile stimuli, participants would apply enough pressure to the bulb proportional to the vibration amplitude of the tactile stimulus. As mentioned, stimuli were presented either unimodally (T_T or relevant condition, V_T or irrelevant condition), or simultaneously with visual stimulus (T_VT or concurrent distractor condition), regardless, responses were only to be made in regards to the tactile stimulus. Similarly, when asked to attend to visual stimuli, participants would apply proportional pressure to the bulb that would match the height of a yellow horizontal bar on the computer screen in front of them regardless of whether it was presented by itself (V_V or relevant condition, T_V or irrelevant condition) or in combination with a tactile stimulus (V_VT or concurrent distractor condition), this is illustrated in Figure 5.1. No single stimulus presented ever required the participant's maximum force output to ensure ease and comfort of responses. Feedback of responses was not provided during the experimental blocks.

Prior to the experimental blocks, participants performed a five minute training session which allowed them to become familiar to the presentation of the stimuli. For the visual stimuli, the yellow horizontal bar which represented the stimulus was also accompanied by a blue horizontal bar which represented the visual feedback that was present only for the training. When the yellow bar was presented at varying heights, the participant was to squeeze the bulb during the experimental blocks, in a proportional way to the height or amplitude of the visual stimulus.

During training, this would also change the height of the blue bar, providing visual feedback so that the participant could match the feedback and stimulus bars, becoming acquainted with the pressure needed to match varying visual stimulus heights. In tandem with this, the amplitude of the tactile stimulus applied to the participant's second digit changed to match the force applied to the pressure bulb. This allowed for the participants to create somewhat of a gauge for themselves to connect the varying amplitudes of the tactile and visual stimuli and the corresponding force that should be applied during trials without feedback. It is important to note that during experimental trials, the amplitude of the tactile stimulus varied independently from that of the visual stimulus, unlike the training trial.

5.3.4 Stimuli

The visual stimuli were presented as a yellow bar (6 cm wide), which was centered within a black box, which was 11 cm wide and 15 cm high, on a computer screen which the participant was seated in front of. At the start of each trial, the bar would be at the bottom of the box and would then appear at randomized heights on the screen (ranging from 1.5-14.5 cm in height) for 500 ms before returning to the bottom. The tactile stimuli were presented to the palmar surface of the second digit using a custom-made vibrotactile device which converted digitally created waveforms to analog signals (DAQCard 6024E, National Instruments, Austin, TX) which was then amplified (Bryston 2BLP, Peterborough, ON, Canada). The average tactile amplitude across all conditions was the same and the frequency of the vibrations were presented at 25 Hz consistently. Within each trial, the amplitude of each vibration was constant and varied randomly between trials (ranging from driving voltages of 132 mV – 500 mV). The tactile stimuli were audible, so in effort to decrease the likelihood of dependence on audition to gauge amplitude, participants wore ear bud headphones for the duration of the experiment which delivered a

constant volume of white noise (White Noise Ambience Lite, Logicworks Version 2.70, Apple App Store). Both visual and tactile stimuli were delivered using a custom written LabVIEW program, behavioural data were also recorded using this same program (Version 8.5, National Instruments). The bulb which participants used to make their graded responses was connected to a clear, enclosed rubber tube which led to a pressure change detected by a pressure sensor which was then converted into a measurable voltage.

5.3.5 cTBS Parameters

Application of cTBS was performed using a MagPro R30 stimulation unit (MagVenture, Alpharetta, GA, USA) using a figure eight coil (MCF-B65). Stimulation intensity was set at 80% of the active motor threshold (AMT) for the right APB. In order to determine AMT, the stimulation coil was placed on the upper left surface of the participant's scalp at the optimal position over the motor cortex that would elicit motor evoked potentials (MEPs) from the contralateral APB. AMT was defined as the lowest stimulator output required to produce a MEP of >200 microvolts in 5 out of 10 trials during a 10% maximum voluntary isometric contraction. MEPs were measured using surface EMG from the right APB muscle with two surface electrodes (MEDITRACE), two active electrodes were placed over the muscle belly and a ground was placed over the radial styloid. During cTBS, bursts of three stimuli are presented at 50 Hz and repeated at 5 Hz (theta frequency) for 40 seconds, which yields a total of 600 pulses (Huang et al. 2005). In order to stimulate the right cerebellar hemisphere, the centre of the coil was placed 1 cm below and 3 cm lateral to the right of theinion (Theoret et al., 2001, Arasanz et al., 2012a, 2012b).

5.3.6 EEG Parameters

EEG data was recorded using a full 32-channel EEG cap (Quick-Cap, Neuroscan, Compumedics, NC USA) to measure the electrical activity from the surface of the scalp in accordance with the international 10-20 system for electrode placement and referenced to the linked mastoids. Impedances were maintained $< 5 \text{ k}\Omega$ and continuous EEG data was collected, filtered (0.2-1000 Hz), digitized at 1000 Hz (Neuroscan 4.5, SynAmps2, Compumedics, NC USA) and subsequently stored on a computer for offline analysis. EEG analysis began with epoching to the stimulus onset followed by baseline correction to the pre-stimulus interval. Epochs were 600 ms in length, beginning 100 ms before stimulus onset and epochs contaminated by muscle contractions, eye movements or blinks were removed by visual inspection before averaging.

5.3.7 Data Analysis

5.3.7.1 ERP Analysis

The amplitudes of the ERPs were measured peak-to-peak, from the peak of interest to the preceding potential of opposite deflection. All 15 participants who took part in this study were included in the analysis of EEG data. This study aimed to test the hypothesis of the cerebellum's mediating role in attention orienting and the ability to ignore distractors. The goals of the statistical analysis were to test the specific hypotheses of (1) successful gating of irrelevant stimuli prior to cTBS as demonstrated by decreased amplitudes of somatosensory peaks in response to distractors and (2) following cTBS to the cerebellum, modulation of the peaks in response to distractors would reflect an impaired ability to ignore distractors as seen by increased amplitudes of somatosensory peaks in response to irrelevant information. It was further

hypothesized that behavioural data would support these findings with decreases in accuracy present during trials presented with a distractor following cTBS.

To do this, a three-way repeated measures ANOVA was performed on amplitudes of each potential with within-subject factors of attention instruction (T or V), stimulus presented (T, V or VT) and time (pre and post cTBS) in SPSS (IBM, Version 25). Statistical significance was set at $p=0.05$. Data was checked for normality to ensure that assumptions for performing the ANOVA were upheld.

5.3.7.2 Behavioural Analysis

Behavioural data were analyzed by comparing the amplitude of the target stimulus to the amplitude of the actual response that was created by the participant through use of the pressure-sensitive bulb. Since it was of primary interest to understand whether the cerebellum was involved with the ability to ignore distractors, a cost of distractor was calculated pre and post cTBS and these were compared using t-tests with statistical significance set at $p=0.05$. The cost score was calculated by dividing the percent ideal response during distracted conditions by the percent ideal response during the undistracted conditions and multiplying by 100.

5.4 Results

The EEG traces demonstrated clear somatosensory P50, N70, P100 and N140 components in response to vibrotactile stimuli as can be seen from the waveform in Figure 5.2, taken from electrode CP3, overlying contralateral somatosensory cortex.

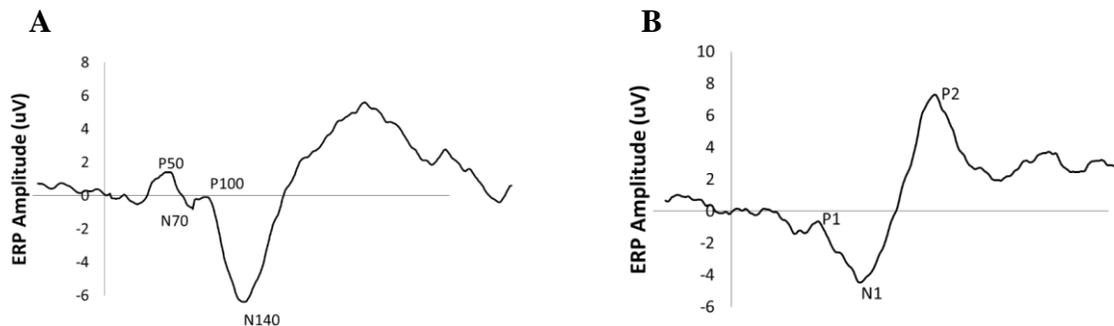


Figure 5.2. Representative traces in response to tactile and visual stimuli. (A) Tactile ERPs, measured at electrode CP3. (B) Visual ERPs, measured at electrode Pz.

The P50 potential, occurring maximally at electrode CP3 in the 45-68 ms range in response to tactile stimuli was not observed during the unimodal visual conditions. The ANOVA did not demonstrate any significant interaction effects nor were there any main effects.

The N70 potential also occurred maximally at electrode CP3, within the 60-80 ms range during tactile stimuli presentation. The ANOVA revealed a significant interaction of time x attention instruction x stimulus presented ($F_{2,42} = 59.49$, $p < 0.001$). In order to explore this interaction, two separate two-way ANOVAs were conducted, these tests were separated by time (pre and post cTBS). Within the pre-cTBS timepoint, the ANOVA showed that there was a significant difference between stimulus presented and attention condition ($F_{1,42} = 4.856$, $p = 0.013$). Post hoc testing revealed that these differences were present between PreT_T (relevant condition) and PreV_T (irrelevant condition), ($p = 0.032$); and between PreT_T (relevant

condition) and PreT_VT (concurrent distractor condition), ($p=0.014$). Within the post-cTBS timepoint, there were no significant findings present.

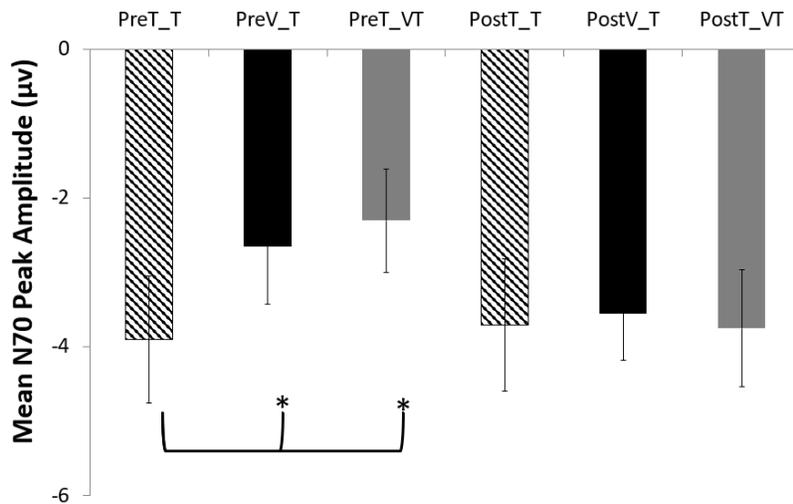


Figure 5.3. N70 ERP amplitudes in response to tactile stimuli. N70 amplitude to tactile stimuli when attending to tactile stimuli (hatched bar; relevant), when attending to visual stimuli (black bar; irrelevant), when being presented with a simultaneous distractor (grey bar). The N70 was significantly attenuated when attention was directed toward visual stimuli and in the presence of a visual distractor (* indicates $p<0.05$). This attenuation is no longer seen following application of cTBS to the right lateral cerebellum.

In keeping with previous studies that have utilized a similar task, pre-cTBS, it was found that N70 peak amplitudes were modulated by the relevancy of the presented T stimulus which was predicated on the attention condition, attend to T or attend to V (Adams et al., 2017). Therefore, when participants were instructed to attend to T stimuli and received a T stimulus, N70 amplitudes were largest. When participants were instructed to attend to V stimuli but were receiving T stimuli, the N70 amplitudes were attenuated and when participants were instructed to attend to T stimuli and received a T stimulus alongside a concurrent V stimulus distractor, N70 amplitudes were observed to be the most attenuated, on average. Following cTBS, these clear

changes in attenuation depending on stimulus relevancy appear to be abolished, with no differences between the three stimulus presentation conditions, as can be seen in Figure 5.3.

P100 and N140 components were reliably observed within the 90-148 ms and 140-200 ms latency ranges respectively in response to the vibrotactile stimuli and maximal at electrode FCz. For the P100, the ANOVA revealed a significant interaction of attention instruction x stimulus presented ($F_{1,42} = 76.70$, $p < 0.001$). In order to explore this interaction, three separate ANOVAs were conducted, these tests were separated by stimulus presentation (T, V or VT). The ANOVA revealed a significant difference between PreT_VT (attend tactile with a concurrent distractor) and PostT_VT (attend tactile with a concurrent distractor), ($F_{1,29} = 8.861$, $p = 0.006$). This difference is demonstrated in Figure 5.3 with the pre concurrent distractor trials being larger than the post concurrent distractor trials. No other significant findings were reported. Of note, both P100 and N140 peak amplitudes were largest during trials in which there was the presentation of a concurrent distraction. Conversely, following cTBS, both P100 and N140 peak amplitudes were on average, lowest during trials with the presentation of a concurrent distractor.

For the cortical peaks measured in response to visual stimuli, no significant effects were reported for either the P1 or N1, both occurring maximally at the Pz electrode and within the 120-140 ms and 165-188 ms time ranges respectively.

The visual P2 occurred maximally at the Pz electrode within the 230 – 255 ms range. For the P2, the ANOVA revealed a significant interaction of time x attention instruction x stimulus presented ($F_{2,42} = 62.58$, $p < 0.001$). To further explore this, two separate two-way ANOVAs were conducted, these tests were separated by time (pre and post cTBS). Within the pre-cTBS timepoint, the ANOVA showed that there was a significant difference between stimulus

presented and attention condition ($F_{1,42}= 5.723$, $p=0.027$). Post hoc testing revealed that these differences were present between PreV_V (relevant condition) and PreT_V (irrelevant condition), ($p=0.043$); and between PreV_V (relevant condition) and PreV_VT (concurrent distractor condition), ($p=0.027$). No significant effects were observed for the post-cTBS timepoint.

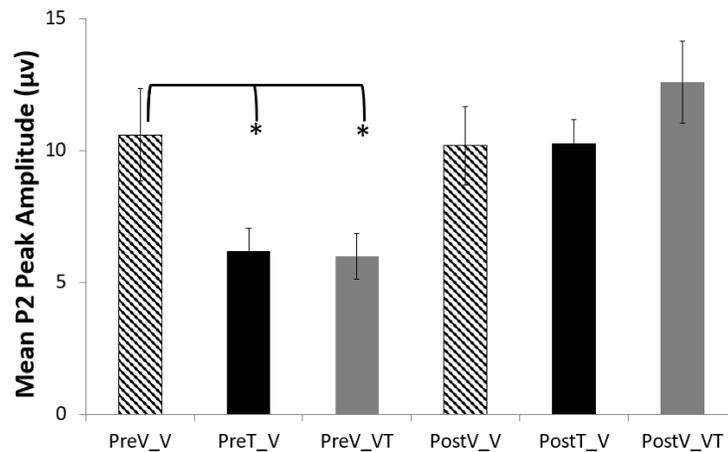


Figure 5.4. P2 ERP amplitudes in response to visual stimuli. P2 amplitude to visual stimuli when attending to visual stimuli (hatched bar; relevant), when attending to tactile stimuli (black bar; irrelevant), when being presented with a simultaneous distractor (grey bar). The P2 was significantly attenuated when attention was directed toward tactile stimuli and in the presence of a tactile distractor (* indicates $p<0.05$). As with the pattern seen within the N70, this attenuation is no longer seen following application of cTBS to the right lateral cerebellum.

A similar pattern as observed for the N70 was also observed for the visual P2 component in response to visual stimuli. With regards to the P2, the peak amplitude was largest when participants were instructed to attend to V stimuli and received a V stimulus. When participants were asked to attend to T stimuli and received a V stimulus, P2 peak amplitudes were attenuated and these P2 peaks were further attenuated when participants were asked to attend to V stimuli and received a V stimulus with a concurrent T distractor. Post cTBS, these trends were

modulated, such that the presence of an irrelevant stimulus or concurrent distractor appear to have similar cortical responses to that of a relevant stimulus, that is, increased peak amplitudes, as demonstrated in Figure 5.4.

To assess a change in performance, paired t-tests were conducted within each modality (tactile and visual) to determine the cost of a distractor to performance accuracy pre and post cTBS. For tactile grading, there was a significant difference in grading between pre and post cTBS when a visual distractor was present ($t_{14}= 9.91, p<0.001$).

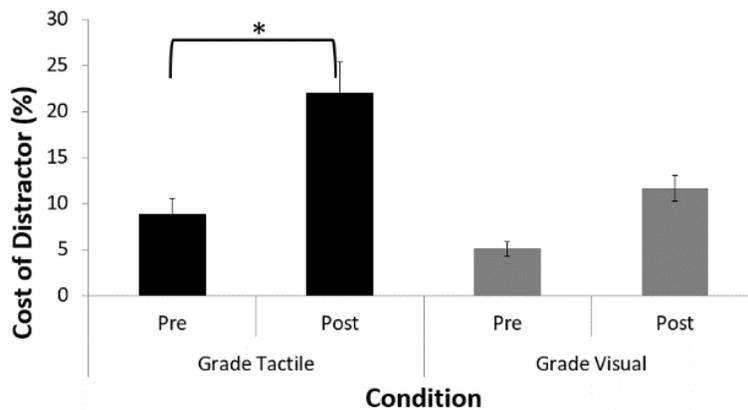


Figure 5.5. Behavioural results. Cost of the distractor was calculated by dividing the percent ideal response during the distracted conditions by the percent ideal response during the undistracted condition. When grading tactile stimuli (black bars), the presence of a visual distractor significantly affects accuracy following cTBS (* indicates $p<0.05$). When grading visual stimuli (grey bars), the presence of a tactile distractor does qualitatively affect accuracy, this however, is not significant.

For visual grading, there was a significant difference in grading between pre and post cTBS when a tactile distractor was present ($t_{14}= 6.38, p<0.01$). Behaviourally, accuracy was decreased in trials where a distractor was present prior to cTBS (for tactile trials, a simultaneous visual distractor and for visual trials, a simultaneous tactile distractor), the difference in accuracy between trials with and without a distractor became larger following cTBS, as seen in Figure 5.5.

5.5 Discussion

This work highlights the importance of cerebellar communication with widespread cortical associative networks. With the emphasis of the cerebellum being a motor structure shifting to its role as more of a global facilitator or modulator, and given its known connectivity to prefrontal areas implicated in higher-order processing, this study sought to use the method of attention modulation to gain more insight on the mechanism by which the cerebellum exerts its influences on these widespread cortical areas (Middleton and Strick, 1994; Kelly and Strick, 2003; Dum and Strick, 2003). It is hypothesized that cerebellar inhibition causes an attentive dysfunction, specifically related to the ability to process stimuli in which conflict signals or errors are present (Mannarelli et al., 2019). This hypothesis is supported by the findings of the current study as transient inhibition of the right lateral cerebellum resulted in increased somatosensory cortical peak amplitudes in response to irrelevant and distractor stimuli in both the somatosensory N70 and visual P2. This finding is further supported by decreased task performance following the administration of cTBS. Prior to the stimulation of the right lateral cerebellum with cTBS, it was found that cortical peaks in response to relevant stimuli, specifically the somatosensory N70 and visual P2, were larger in amplitude compared to when the stimuli were unattended or irrelevant. These findings pre-cTBS replicate past work which has used a similar task (Adams et al., 2017; 2019). The diminished cortical responses to unattended and distractor stimuli are representative of sensory gating to ensure that extraneous input does not hinder task performance to what has been previously instructed as relevant for the task goal.

This past work however, although it used a similar cTBS paradigm, sought to test the mechanism underlying the mediation of task relevance by means of the PFC (Adams et al., 2019). In the study by Adams et al. (2019), it was hypothesized that down-regulating PFC

excitability would result in the elimination of the amplitude differences between the three presented conditions observed in the somatosensory N70 responses to task-relevant and irrelevant stimuli. Following cTBS to the right PFC, although it was found that there was a lack of difference in the N70 amplitudes between attended and unattended stimuli, this finding was driven by the attenuation of cortical excitability in response to task-relevant stimuli more so than the hypothesized loss of inhibition in response to the task-irrelevant stimuli.

Given the nature of the cerebellum's inhibitory output, when this is paired with evidence of reciprocal connectivity between the PFC and cerebellum and the ability to modulate functional connectivity between cerebellar and PFC nodes, it perhaps comes as no surprise that the cerebellum facilitates this inhibitory control of irrelevant stimuli (Kelly and Strick, 2003; Rastogi et al., 2017). The de-differentiation between conditions that follows the administration of cTBS to the right lateral cerebellum showcases a loss of the typical inhibitory control that the cerebellum is thought to exert on more widespread cortical areas. This function of the cerebellum is widely discussed in the context of the motor domain and is thought to revolve around adaptation that occurs by way of predictive models that are formed based on past experience which are compared to the current state (Moberget and Ivry, 2017). Linking these same predictive functions to broader, higher-order functions, previous work has demonstrated that cerebellar TMS affects associative linguistic priming when the association between words is based on sequential probabilities, cerebellar activations have also shown positive correlations with contextual probabilities of target words (Argyropoulos, 2016). These alterations are a depiction of the error-based learning that is central to the theories of cerebellar control (Doya, 1999; Ito, 2012). In our previous work, it was demonstrated that following transient inhibition of the right lateral cerebellum, cortical responses to deviant and frequent stimuli were similar in

amplitude when compared to pre-cTBS and responses to deviant stimuli resulted in a large negativity (Andrew et al., 2020). This prior study highlighted the importance of cerebellar processing for the comparison of stimuli even without the need for an overt movement goal (Andrew et al., 2020).

Within the current study, the instructions prior to each block specified which stimulus was to be attended to and the subsequent experience of the task pre-cTBS formed an expectancy, with the cerebellum contributing to the inhibition of irrelevant information based on the context as determined by the instructions provided prior to each block of the task. Following cTBS, in a similar way in which there was a loss of differentiation between the processing of the frequent and deviant stimuli in our prior study (Andrew et al., 2020), there was a loss of differentiation between the processing of relevant and irrelevant information in the current study. This type of influence over the processing of sensory stimuli in a more global way is supported by the similar changes seen in response to both the vibrotactile and visual stimuli seen within the N70 and P2 respectively, following transient cerebellar inhibition.

With regards to both the P100 and N140, the cortical peaks were largest during concurrent distractor trials pre-cTBS and was smallest during concurrent distractor trials post-cTBS. These peaks are generated within the secondary somatosensory cortex and have been shown to be influenced by attention; furthermore, they are generated in a cortical area which is associated with assessing differences in stimuli for higher-order elaborations; more cognitively driven (Frot and Mauguiere, 1999; Chen et al., 2008; Staines et al., 2014). The presence or conflict of two stimuli being presented at the same time may drive the increase in amplitude that is seen in the pre-cTBS trials. Following cTBS, the small amplitude may be a result of impaired cerebellar function and therefore an inability to detect the inherent conflict present between the

two stimuli. This duality of the amplitude decrease in the presence of distractors in the longer latency peaks versus the increase in amplitude in the presence of distractors in the earlier latency peaks demonstrates the complexity of the cerebellum's influence on sensory processing.

Behaviourally, the participants' accuracy decreased following cerebellar cTBS; however, this was not the main interest of the behavioural analysis. Specifically, transient inhibition of cerebellar activity altered how costly the presence of a concurrent distractor was, as evidenced by the increased cost percentage post-cTBS. The cost of the distractor increased for both tactile trials (when the visual stimulus was a distractor) and for the visual trials (when the tactile stimulus was a distractor). Responses on the grading task coupled with the increase in distractor cost post-cTBS highlight the sensitive nature by which the cerebellum can influence sensory deficits. Although the cost of the visual distractor was more pronounced in comparison to the cost of the tactile distractor, this is likely a product of characteristics of the stimuli presentation and the saliency of the visual stimulus.

Links between the cerebellum and attention are frequently reported, where attentional deficits are associated with morphological cerebellar abnormalities. Individuals with cerebellar neurodegenerative disorders, autism spectrum disorders (ASD) and attention deficit hyperactivity disorder (ADHD) have similar difficulties in behaviour and cognition (Carper and Courchesne, 2000; Lupo et al., 2018, Schmahmann, 2019). The P300, implicated in attentional processes has been shown to be significantly reduced following the transient inhibition of the cerebellum using transcranial direct current stimulation (tDCS), validating the cerebellum's involvement of the processing of a stimulus during attention orienting and discrimination of the stimulus (Mannarelli et al., 2015; 2019). Attention is defined as the ability to appropriately allocate processing resources to relevant stimuli (Mannarelli et al., 2019). However, this is not a unitary

concept and will require multiple interacting processes and networks. Functional and anatomical neuroimaging studies have linked network disturbances between cerebellar nodes and the PFC. Within posttraumatic stress disorder (PTSD) and schizophrenia, negative symptoms such as anhedonia, amotivation and expressive deficits may relate to changes in the regulation of consistency, capacity and appropriateness, which are also relevant to maintain attention to complete a goal (Brady et al., 2019). Aberrant connections within these same networks is also being implicated in pathological aging and dementia, making it critical to understand the cerebellum's influence to advance efforts towards using non-invasive brain stimulation to alter the cerebellum's activity to modulate these large-scale cognitive networks.

The current study did not use sham cTBS, given the nature of the cTBS protocol, participants who are not naïve to the technique would be well aware of the difference in sensation. Furthermore, the purpose of the study was to investigate the cerebellum's unique roll within a larger attentional network and given that previous work by Adams et al. (2019), had used a similar and validated protocol, comparing our findings to the previous studies findings demonstrates a novel role of the cerebellum. However, given the complex nature of the cerebellum's connectivity, it would be beneficial to perform a similar paradigm with cerebellar stimulation on the left side. In doing so, this would discern the cerebellum's role within the process as specific to a higher-order domain or as part of one that is fulfilling more of a sensorimotor function as it is difficult to disentangle behaviour and movement. As mentioned, although there was a cost of the tactile distractor, the cost of the presence of the visual distractor was much more pronounced in comparison perhaps due to the way it was presented. Participants were instructed to maintain their gaze in front of them, which would be centered on the screen, allowing for the visual stimulus to always be captured regardless of the relevancy in comparison

to the tactile stimulus. A task in which the stimulus presentation is altered to be presented in a more perceptual way (ie. Change in spatial location), would perhaps help to further understand the characteristics the cerebellum utilizes to aid in informing predictions to facilitate appropriate behaviour.

5.6 Conclusion

The current study demonstrated that during a sensory conflict task, the presence of relevant information elicits larger cortical peak responses from somatosensory areas. During the presentation of irrelevant stimuli or concurrent distractors, these same cortical peaks are attenuated, demonstrating that defining stimulus context by means of attention creates a cortical gating effect. Following cTBS over the right lateral cerebellum, the ability to ignore distractors is impaired, leading to the processing of unattended stimuli, as indicated by increased ERP amplitudes. Decreased grading accuracy following cTBS also supports the role of the cerebellum in the process of orienting oneself away from information that is not necessary to coordinate the behaviour needed to perform a specific task. The current study found that the cerebellum may aid in the modulation of attention via the inhibition of irrelevant information, giving it a unique role in the larger attentional network. Due to the complex nature of the cerebellum's structure and connectivity, altering the side of cerebellar stimulation and side of somatosensory stimulation will allow for a further understanding of the cerebellum's role in higher-order functions. Conducting follow up studies in this nature will help to examine how the cerebellum interacts with differing modalities and to distinguish cerebellar motor aspects from cerebellar cognitive aspects across multiple domains. This itself may prove be an important pathway to treat in behavioural disorders.

Chapter 6: Study 3

Specificity of the cerebellum's influence on sensory processing

6.1 Overview

The previous two studies demonstrated the cerebellar role in attention and selection of stimuli that are needed to accomplish specific goals. Although the presentation of the stimuli differed between the two studies, a similar pattern for cerebellar processing of incoming sensory stimuli can be observed throughout both. Transient inhibition of the cerebellum resulted in the processing of the varying stimuli to be impaired, such that cortical responses to changes in stimuli presentation become similar due to potential alterations in the way that the cerebellum identified pertinent aspects of stimuli in order to alert widespread cortical areas depending on the resultant changes in goals or actions. There are various hypothesized mechanisms which explain the cerebellum's role in the processing and communication of sensory information to coordinate behaviour. Although reciprocal connections between the cerebellum and widespread associative cortices exist, it is argued that the specific role of the cerebellum within the behavioural domain is to funnel sensory information to inform movement and that imaging evidence may be confounded by eye movements (Glickstein, 1993; Glickstein and Doron, 2008). Given the complex nature of the cerebellum's connectivity with the rest of the cortex and the nature of behavioural tasks, it is difficult to discern the specificity of its influence over higher order functioning since there is much evidence for its involvement, it is not so much whether the cerebellum exerts its influence over these processes but what its mechanism is.

Based on the previous two studies, the current study sought to further distinguish the nature of the cerebellum's influence on higher-order processing, specifically with regards to laterality. Therefore, the same protocol and sensory conflict task were utilized as outlined in Study 2, however, participants received continuous theta burst stimulation (cTBS) to the left lateral cerebellum. Although the sensory conflict task requires a graded motor response, the

added manipulation of stimulus attention requires higher-order strategy. Performing the same task with opposite side stimulation provides a means of narrowing the specificity of cerebellar influence and disentangling the general sensorimotor influence from the higher-order processing influence specifically within the broader attentional network and its communication with contralateral prefrontal areas. Somatosensory ERPs and performance were once again measured using electroencephalography (EEG) and grading accuracy, respectively, these were collected pre and post cTBS to the left lateral cerebellum.

Prior to cTBS, the ERPs in response to both tactile and visual stimuli were attenuated in response to unattended stimuli versus when they were attended to. This pattern replicates the findings seen in Study 2 prior to cTBS, demonstrating the robust nature of the task and the attentional conditions. Following cTBS to the left side cerebellum, this same pattern is reproduced with decreased tactile N70 and visual P2 cortical peaks in response to unattended and distractor stimuli. Behaviourally, there is negligible change in grading accuracy following cTBS. This work demonstrates a distinct duality with the previous study, indicating specificity of the cerebellar contribution to the attentional task.

6.2 Introduction

Given the extensive interconnectivity that the cerebellum has with frontal and parietal attentional and associative areas, it is not so surprising that the cerebellum has some involvement in orientation towards or away from specific stimuli (Stoodley and Schmahmann, 2009; Stoodley and Schmahmann, 2010; Buckner, 2013). Increasingly, literature suggests that the cerebellum is involved in non-motor behaviours, however it is also argued that ultimately, the cognitive processes involved in non-motor tasks may still have the long-term goal of behaviour.

Sensorimotor adaptation tasks have been widely used to characterize the processes which underlie the calibration between desired outcomes and motor commands (McDougle et al., 2016). Many complex behaviours however, involve higher-order cognitive processes which help to coordinate precise actions such as adjusting our movements when lifting up a drink as we consume its contents and it becomes lighter or engaging in conversation with a person who we know very well versus someone who we have just met. In these situations, we need to be very cognisant of our environment to inform our behaviours which includes integration of external elements, our personal past knowledge, changes in our surroundings and social cues. This large influx of information needs to be rapidly processed in order to coordinate smooth and accurate behaviours. To do this, we need to be able to focus on those aspects which are relevant to successful completion of our goals and ignore pieces of information that we do not need. Therefore, there is a large contribution of cognitive strategies to sensorimotor learning that enable individuals to rapidly evaluate novel situations and perform adaptive behaviour.

Theoretical models have emphasized the cerebellum's predictive role which coordinates motor output as a means to anticipate the consequences of potential motor commands (Wolpert and Kawato, 1998; Ebner et al., 2011; Sokolov et al., 2017). These predictions can be compared with past experiences as well as current afferent input to determine whether the predicted and actual match, if not, the difference or error between the two allow for the rapid adjustment of actions (Sokolov et al., 2017). Such a process is essential for actions that involve coordination across multiple effectors, specifically those that are higher order and more complex in nature.

The cerebellum's high level of connectivity with much of the cerebral cortex supports the role of its integration of multiple inputs although there is still much to be learned about how these inputs are prioritized, the cerebellum may provide a means for hierarchically arranging this

with predictions at lower and higher levels depending on the specificity and amount of input e.g. one reaching movement or a longer chain of interactive events (D'Angelo and Casali, 2013). Furthermore, it is difficult to quantify what an error might look like or be perceived as when it comes to more complex behaviours. These cerebellar concepts of adaptation and prediction can be successfully accomplished by breaking down into the simplest of terms, identifying and attending to relevant information and ignoring irrelevant information. The difficulty of performing this task changes with respect to the task demands which can be manipulated based on the saliency of the stimuli, the amount and types of stimuli presented and previous experience. Manipulating attention provides a useful tool for understanding the higher-order processes that the cerebellum may be involved in. Utilizing a complex attentional task can provide insight into broader cognitive processes that help to facilitate movement and behaviour as a whole.

Previous work has shown a clear connection between cerebellar activity and attention and/or stimulus selection although the nature of the tasks presented have not necessarily been complex enough to showcase the higher-order processes that facilitate these behaviours. Selective attention to goal-relevant stimuli that appear amidst distraction involves perception, something that can be unique to each individual based on their personal experience and contexts (MacLellan et al., 2017). When individuals search for two predefined visual targets placed within a rapid sequence of visual stimuli, selection of the first target (T1) is often followed by a temporary reduction in the ability to identify or detect the second target (T2), this phenomenon is termed the attentional blink (AB) (Raymond et al., 1992; Soto-Faraco et al., 2002). A majority of AB studies use purely visual stimuli although several studies have shown that AB is also present with different modalities (Arnell and Jolicoeur, 1999; Soto-Faraco and Spence, 2002). Soto-

Faraco et al. (2002), demonstrated that the AB phenomenon is also present cross-modally, using visual and tactile stimuli. They found that the effects of the AB were larger for visual stimuli in comparison to tactile stimuli when presentation of T1 and T2 were consistently blocked, however the AB became similar for both types of stimuli when presentation of the targets were randomized (Soto-Faraco et al., 2002). The authors concluded that the occurrence of a cross-modal AB is determined by the selection processes afforded by the stimuli and/or demanded by the task, this is a process that the cerebellum has been increasingly found to help facilitate (Allen et al., 1997; Ghajar and Ivry, 2009; Stoodley and Schmahmann, 2010). Previous work has also demonstrated that transient inhibition of the cerebellum has led to increases in AB magnitude while transient excitation of cerebellar activity has led to increases in target detection during AB tasks; these tasks however utilized a single modality of stimulus (Arasanz et al., 2012a; Esterman et al., 2017). Therefore, the continued use of a multimodal attentional task may lend to a deeper understanding of how the cerebellum modulates communication with higher-order associative cortical areas in an effort to coordinate a wide-spectrum of behaviours. Given the involvement of the cerebellum in these attentional processes, perhaps it is its responsibility to monitor sensory acquisition to ensure that the quality of the incoming stimuli is conducive to behavioural goals. Individuals with cerebellar degenerative disease have significantly poorer thresholds for somatosensation, proprioception, and pitch discrimination (Parsons et al., 2009; Tinazzi et al., 2013). These more perceptual tasks attempt to distinguish cerebellar function as broader than strictly for the purpose of motor behaviour.

It is the aim of the current study to provide further evidence for this broader role of the cerebellum by attempting to narrow the scope of its function within a sensory conflict task. Should the cerebellum's role be focused on general sensorimotor adaptation, then stimulation of

the left side cerebellum will result in similar cortical peak changes and behavioural changes as observed in Study 2. However, if the cerebellar role is more focused on higher-order interactions with its contralateral prefrontal connections, then differential results should be expected if stimulation is now applied over the opposite side cerebellum. Specifically, it is hypothesized that following left sided stimulation, that the communication between the right side cerebellum and contralateral prefrontal cortex will not be affected and since somatosensory stimulation is being applied to the right side, the processing of the stimuli will not be compromised. Therefore, the post cTBS cortical responses will mimic the pre-cTBS responses.

6.3 Materials and Methods

6.3.1 Participants

Fifteen healthy, right-handed participants with no known neurological conditions were recruited from the University of Waterloo community (8 males, 7 females; mean age \pm SD = 27 \pm 4.1). All participants provided informed written consent. The University of Waterloo Office of Research ethics approved all experimental procedures.

6.3.2 Experimental Design

All participants completed a pre-post design study which required them to attend one session where EEG and behavioural data was collected. Each participant was administered the Edinburgh Handedness Questionnaire and a transcranial magnetic stimulation (TMS) Safety Checklist to ensure they were all right-handed and had no contraindications to receiving TMS, respectively.

Participants performed a graded sensory conflict task, identical to that which was performed in Study 2. For this task, participants were asked to make a graded motor response to the

amplitude of unimodal visual (V) or tactile (T) stimuli that were presented either individually or simultaneously (VT), while their attention was randomly oriented to specific stimuli in blocks. This formed two attention response conditions, attend to T or attend to V, as well as three stimulus presentation conditions where each stimulus would either be relevant, irrelevant or a concurrent distractor. 10 blocks of trials were presented, divided evenly and between the two attention conditions (attend T and attend V) and presented in randomized order. Each experimental block contained 54 stimuli which were presented for 500 ms each with a 2.5 s interval between trials, therefore each block lasted approximately 3.5 minutes. Participants' response to the attended stimuli was performed using a pressure-sensitive bulb where the participants would squeeze the bulb using a force graded response to indicate the approximate amplitude of the T or V stimuli depending on the instructed attended condition, the experimental set up is identical to that as described in Study 2 (Section 5.3.2). The 10 blocks were presented as a pre-condition, followed by administration of cTBS over the right lateral cerebellum and then performance of another 10 blocks as a post-condition.

6.3.3 Experimental Paradigm

Following EEG cap preparation and TMS thresholding, the participant was seated comfortably in front of a desk with a computer screen where they were required to fix their gaze for the duration of the experimental task blocks. The computer screen in front of the participant presented visual stimuli and tactile stimuli were delivered through a custom-made speaker device which has a flat plastic tip which the participant rested the palmar surface of their right second digit on. Participants were asked to judge the amplitude of the stimulus type that they were instructed to attend to prior to the start of each block (V or T). Their response was provided by squeezing a pressure-sensitive rubber bulb which was held in their left hand. Sensory stimulation

to the right side was chosen as the right lateral cerebellum was being targeted with the cTBS and we wanted to probe these changes within the widespread cerebellar networks that exist to the ipsilateral dominant hand and contralateral cortical hemisphere (Schlerf et al., 2014). When asked to attend to tactile stimuli, participants would apply enough pressure to the bulb proportional to the vibration amplitude of the tactile stimulus. As mentioned, stimuli were presented either unimodally, or simultaneously with a visual stimulus, regardless, responses were only to be made in regards to the tactile stimulus. Similarly, when asked to attend to visual stimuli, participants would apply proportional pressure to the bulb that would match the height of a yellow horizontal bar on the computer screen in front of them regardless of whether it was presented by itself or in combination with a tactile stimulus, as performed in Study 2. No single stimulus presented ever required the participant's maximum force output to ensure ease and comfort of responses. Feedback of responses was not provided during the experimental blocks.

Prior to the experimental blocks, participants performed a five minute training session which allowed them to become familiar to the presentation of the stimuli. For the visual stimuli, the yellow horizontal bar which represented the stimulus was also accompanied by a blue horizontal bar which represented the visual feedback that was present only for the training. When the yellow bar was presented at varying heights, the participant was to squeeze the bulb during the experimental blocks, in a proportional way to the height or amplitude of the visual stimulus. During training, this would also change the height of the blue bar, providing visual feedback so that the participant could match the feedback and stimulus target bars, becoming acquainted with the pressure needed to match varying visual stimulus heights. In tandem with this, the amplitude of the tactile stimulus applied to the participant's second digit changed to match the force applied to the pressure bulb. This allowed for the participants to create somewhat of a gauge for

themselves to connect the varying amplitudes of the tactile and visual stimuli and the corresponding force that should be applied during trials without feedback. It is important to note that during experimental trials, the amplitude of the tactile stimulus varied independently from that of the visual stimulus, unlike the training trial.

6.3.4 Stimuli

The visual stimuli were presented as a yellow bar (6 cm wide), which was centred within a black box, which was 11 cm wide and 15 cm high, on a computer screen which the participant was seated in front of. At the start of each trial, the bar would be at the bottom of the box and would then appear at randomized heights on the screen (ranging from 1.5-14.5 cm in height) for 500 ms before returning to the bottom. The tactile stimuli were presented to the palmar surface of the second digit using a custom-made vibrotactile device which converted digitally created waveforms to analog signals (DAQCard 6024E, National Instruments, Austin, TX) which was then amplified (Bryston 2BLP, Peterborough, ON, Canada). The average tactile amplitude across all conditions was the same and the frequency of the vibrations were presented at 25 Hz consistently. Within each trial, the amplitude of each vibration was constant and varied randomly between trials (ranging from driving voltages of 132 mV – 500 mV). The tactile stimuli were audible, so in effort to decrease the likelihood of dependence on audition to gauge amplitude, participants wore ear bud headphones for the duration of the experiment which delivered a constant volume of white noise (White Noise Ambience Lite, Logicworks Version 2.70, Apple App Store). Both visual and tactile stimuli were delivered using a custom written LabVIEW program, behavioural data were also recorded using this same program (Version 8.5, National Instruments). The bulb which participants used to make their graded responses was connected to

a clear, enclosed rubber tube which led to a pressure change detected by a pressure sensor which was then converted into a measurable voltage.

6.3.5 cTBS Parameters

Application of cTBS was performed using a MagPro R30 stimulation unit (MagVenture, Alpharetta, GA, USA) using a figure eight coil (MCF-B65). Stimulation intensity was set at 80% of the active motor threshold (AMT) for the right APB. In order to determine AMT, the stimulation coil was placed on the upper left surface of the participant's scalp at the optimal position over the motor cortex that would elicit motor evoked potentials (MEPs) from the contralateral APB. AMT was defined as the lowest stimulator output required to produce a MEP of >200 microvolts in 5 out of 10 trials during a 10% maximum voluntary isometric contraction. MEPs were measured using surface EMG from the right APB muscle with two surface electrodes (MEDITRACE), two active electrodes were placed over the muscle belly and a ground was placed over the radial styloid. During cTBS, bursts of three stimuli are presented at 50 Hz and repeated at 5 Hz (theta frequency) for 40 seconds, which yields a total of 600 pulses (Huang et al. 2005). In order to stimulate the left cerebellar hemisphere, the centre of the coil was placed 1 cm below and 3 cm lateral to the left of the inion (Theoret et al., 2001, Arasanz et al., 2012a, 2012b).

6.3.6 EEG Parameters

EEG data was recorded using a full 32-channel EEG cap (Quick-Cap, Neuroscan, Compumedics, NC USA) to measure the electrical activity from the surface of the scalp in accordance with the international 10-20 system for electrode placement and referenced to the linked mastoids. Impedances were maintained < 5 k Ω and continuous EEG data was collected, filtered (0.2-1000 Hz), digitized at 1000 Hz (Neuroscan 4.5, SynAmps2, Compumedics, NC

USA) and subsequently stored on a computer for offline analysis. EEG analysis began with epoching to the stimulus onset followed by baseline correction to the pre-stimulus interval. Epochs were 600 ms in length, beginning 100 ms before stimulus onset and epochs contaminated by muscle contractions, eye movements or blinks were removed by visual inspection before averaging.

6.3.7 Data Analysis

6.3.7.1 ERP Analysis

The amplitudes of the ERPs were measured peak-to-peak, from the peak of interest to the preceding potential of opposite deflection. All 15 participants who took part in this study were included in the analysis of EEG data. This study aimed to test the specificity of the cerebellum's mediating role in attention orienting. The goals of the statistical analysis were to test the specific hypotheses of (1) successful gating of irrelevant stimuli as determined by attention instruction prior to cTBS as demonstrated by decreased amplitudes of somatosensory peaks in response to distractors and (2) following cTBS to the left lateral cerebellum, there would be a lack of modulation of peaks in response to distractors, and the cortical peaks would demonstrate a similar pattern as observed pre-cTBS. It was further hypothesized that behavioural data would support these findings with little change in accuracy being observed following cTBS to the left lateral cerebellum.

To do this, a three-way repeated measures ANOVA was performed on amplitudes of each potential with within-subject factors of attention instruction (T or V), stimulus presented (T, V or VT) and time (pre and post cTBS) in SPSS (IBM, Version 25). Statistical significance was set at $p=0.05$. Data was checked for normality to ensure that assumptions for performing the ANOVA were upheld.

6.3.7.2 Behavioural Analysis

Behavioural data were analyzed by comparing the amplitude of the target stimulus to the amplitude of the actual response that was created by the participant through use of the pressure-sensitive bulb. Since it was of primary interest to understand whether the cerebellum was involved with the ability to ignore distractors, a cost of distractor was calculated pre and post cTBS and these were compared using t-tests with statistical significance set at $p=0.05$. The cost score was calculated by dividing the percent ideal response during distracted conditions by the percent ideal response during the undistracted conditions and multiplying by 100.

6.4 Results

The EEG traces demonstrated somatosensory P50, N70, P100 and N140 components in response to vibrotactile stimuli, measured from electrode CP3, overlying contralateral somatosensory cortex.

The P50 potential was observed maximally at electrode CP3 in the 40-72 ms range in response to tactile stimuli and was not observed during the unimodal visual conditions. The ANOVA did not demonstrate any significant interactions or main effects.

The N70 potential also occurred maximally at electrode CP3, within the 60-84 ms range during tactile stimuli presentation. The ANOVA revealed a significant interaction of time x attention instruction x stimulus presented ($F_{2,42}= 56.01$, $p<0.001$). In order to explore this interaction, two separate two-way ANOVAs were conducted, these tests were separated by time (pre and post cTBS). Within the pre-cTBS timepoint, the ANOVA showed that there was a significant difference between stimulus presented and attention condition ($F_{1,42}= 3.952$,

p=0.014). Post hoc testing revealed that these differences were present between PreT_T (relevant condition) and PreV_T (irrelevant condition), (p=0.041); and between PreT_T (relevant condition) and PreT_VT (concurrent distractor condition), (p=0.038). Within the post-cTBS timepoint, the ANOVA showed that there was a significant difference between stimulus presented and attention condition ($F_{1,42}= 4.637$, p=0.023). Post hoc testing revealed that these differences were present between PostT_T (relevant condition) and PostV_T (irrelevant condition), (p=0.036); and between PostT_T (relevant condition) and PostT_VT (concurrent distractor condition), (p=0.032).

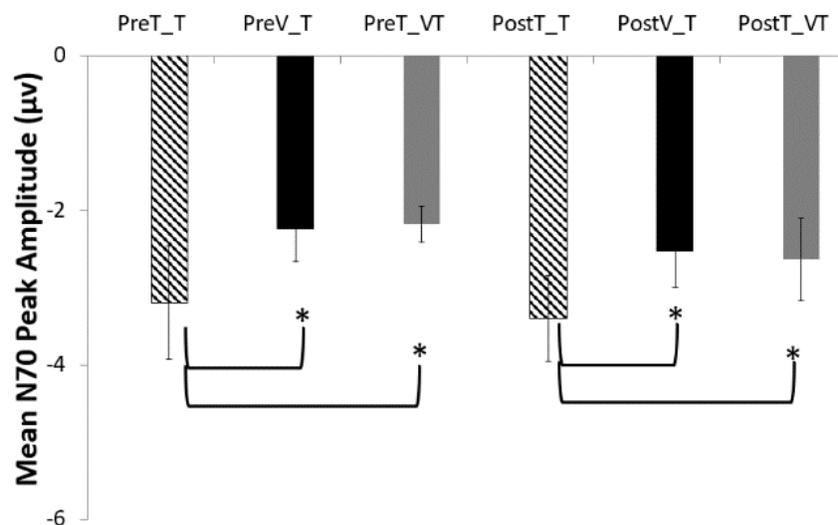


Figure 6.1. N70 ERP amplitudes in response to tactile stimuli. N70 amplitude to tactile stimuli when attending to tactile stimuli (hatched bar; relevant), when attending to visual stimuli (black bar; irrelevant), when being presented with a simultaneous distractor (grey bar). The N70 was significantly attenuated when attention was directed toward visual stimuli and in the presence of a visual distractor (* indicates p<0.05). This same pattern is replicated following cTBS to the left lateral cerebellum.

The pattern of cortical peak attenuation in response to the presence of irrelevant and distractor stimuli prior to cTBS is replicated in this study as was observed in Study 2. It was also found that N70 peak amplitudes were modulated by the relevancy of the presented T stimulus

which was predicated on the attention condition, attend to T or attend to V (Adams et al., 2017; 2019). Following cTBS to the left lateral cerebellum, these changes in attenuation depending on stimulus relevancy persist, with the three post condition responses appearing very similar to the three pre-condition responses, as can be seen in Figure 6.1. This finding is in stark contrast to the findings of Study 2 in which cTBS to the right lateral cerebellum resulted in a loss of attenuation of cortical peaks in response to irrelevant and distractor stimuli.

P100 and N140 components were reliably observed within the 89-146 ms and 138-200 ms latency ranges respectively in response to tactile stimuli and were observed maximally at electrode FCz. For the P100, the ANOVA revealed a significant interaction of time x attention instruction x stimulus presented ($F_{2,42} = 18.35$, $p < 0.003$). In order to explore this interaction, two separate two-way ANOVAs were conducted, these tests were separated by time (pre and post cTBS). Within the pre-cTBS timepoint, the ANOVA showed that there was a significant difference between stimulus presented and attention condition ($F_{1,42} = 7.194$, $p = 0.043$). Post hoc testing revealed that these differences were present between PreT_T (relevant condition) and PreT_VT (concurrent distractor condition), ($p = 0.032$); and between PreV_T (irrelevant condition) and PreT_VT (concurrent distractor condition), ($p = 0.024$). Within the post-cTBS timepoint, the ANOVA showed that there was a significant difference between stimulus presented and attention condition ($F_{1,42} = 6.158$, $p = 0.031$). Post hoc testing using Tukey's test revealed that these differences were present between PostT_T (relevant condition) and PostT_VT (concurrent distractor condition), ($p = 0.026$); and between PostV_T (irrelevant condition) and PostT_VT (concurrent distractor condition), ($p = 0.018$).

For the N140, the ANOVA revealed a significant interaction of time x attention instruction x stimulus presented ($F_{2,42} = 48.72$, $p < 0.001$). In order to explore this interaction, two

separate two-way ANOVAs were conducted, these tests were separated by time (pre and post cTBS). Within the pre-cTBS timepoint, the ANOVA showed that there was a significant difference between stimulus presented and attention condition ($F_{1,42} = 5.728$, $p=0.012$). Post hoc testing revealed that these differences were present between PreT_T (relevant condition) and PreT_VT (concurrent distractor condition), ($p=0.023$); and between PreV_T (irrelevant condition) and PreT_VT (concurrent distractor condition), ($p=0.020$). Within the post-cTBS timepoint, the ANOVA showed that there was a significant difference between stimulus presented and attention condition ($F_{1,42} = 5.342$, $p=0.014$). Post hoc testing revealed that these differences were present between PostT_T (relevant condition) and PostT_VT (concurrent distractor condition), ($p=0.026$); and between PostV_T (irrelevant condition) and PostT_VT (concurrent distractor condition), ($p=0.022$). Both P100 and N140 peak amplitudes were largest during trials in which there was the presentation of a concurrent distraction.

For the P1 and N1 cortical peaks measured in response to visual stimuli, no significant effects were reported. Both peaks were observed maximally at the Pz electrode and within the 118-140 ms and 162-187 ms time ranges respectively.

The visual P2 was maximal at the Pz electrode within the 232 – 260 ms range. For the P2, The ANOVA revealed a significant interaction of time x attention instruction x stimulus presented ($F_{2,42} = 57.03$, $p < 0.001$). To further explore this, two separate two-way ANOVAs were conducted, these tests were separated by time (pre and post cTBS). Within the pre-cTBS timepoint, the ANOVA showed that there was a significant difference between stimulus presented and attention condition ($F_{1,42} = 7.342$, $p=0.035$). Post hoc testing revealed that these differences were present between PreV_V (relevant condition) and PreT_V (irrelevant condition), ($p=0.032$); and between PreV_V (relevant condition) and PreV_VT (concurrent

distractor condition), ($p=0.037$). No significant effects were observed for the post-cTBS timepoint.

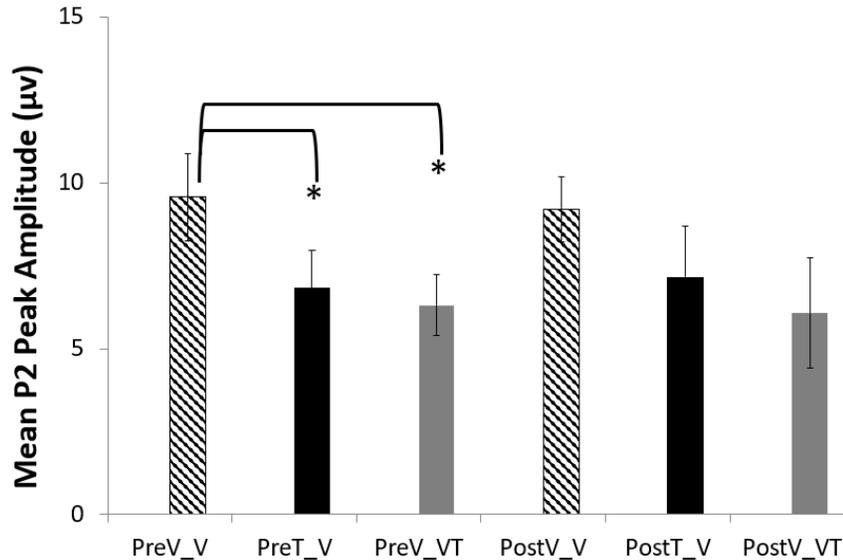


Figure 6.2. P2 ERP amplitudes in response to tactile stimuli. P2 amplitude to visual stimuli when attending to visual stimuli (hatched bar; relevant), when attending to tactile stimuli (black bar; irrelevant), when being presented with a simultaneous distractor (grey bar). The P2 was significantly attenuated when attention was directed toward tactile stimuli and in the presence of a tactile distractor (* indicates $p<0.05$). This pattern, although it is replicated following cTBS to the left lateral cerebellum is not significant.

Once again, similar patterns were observed for both the tactile N70 and the visual P2 prior to cTBS. For the P2, the peak amplitude was largest when participants were instructed to attend to V stimuli and received a V stimulus, as demonstrated in Figure 6.2. When participants were asked to attend to T stimuli and received a V stimulus, P2 peak amplitudes were attenuated and these P2 peaks were further attenuated when participants were asked to attend to V stimuli and received a V stimulus with a concurrent T distractor. Post cTBS, these trends remained constant, in contrast to what was observed in Study 2 where cortical peaks were modulated, such that the presence of an irrelevant stimulus or concurrent distractor elicited similar cortical responses.

To determine how detrimental to performance the presence of a distractor was, paired t-tests were conducted within each modality (tactile and visual) to determine the cost of a distractor to performance accuracy pre and post cTBS.

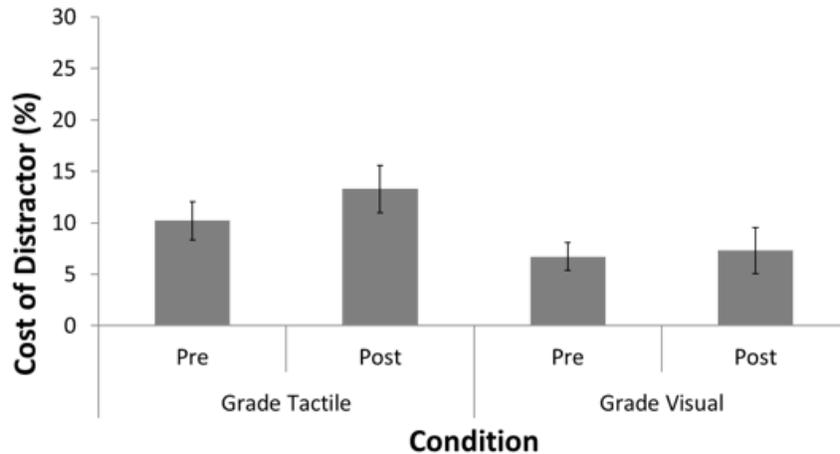


Figure 6.3. Behavioural results. Cost of the distractor was calculated by dividing the percent ideal response during the distracted conditions by the percent ideal response during the undistracted condition. When grading tactile stimuli, the presence of a visual distractor does not significantly affect accuracy following cTBS to the left lateral cerebellum. No significant changes in accuracy are seen when grading visual stimuli and there is a presence of a tactile distractor following left cerebellar stimulation.

Although the presence of a distractor did appear to decrease accuracy somewhat, as can be seen in Figure 6.3, no significant findings were reported for both tactile grading (presence of a visual distractor) or visual grading (presence of a tactile distractor).

6.5 Discussion

The current study sought to build upon the findings of Study 2 that demonstrated the influence of the right lateral cerebellum within the process of attention modulation via the inhibition of irrelevant information. Previous work has utilized the same sensory conflict task and has demonstrated similar findings as seen in both Study 2 and 3 prior to the application of any intervention or non-invasive stimulation. Specifically, cortical peaks in response to sensory

stimuli are largest when the presented stimuli are deemed relevant, as classified by prior instruction; these same peaks are shown to be attenuated in response to the same stimuli when they are presented in an irrelevant context or with a concurrent distractor (Adams et al., 2017; 2019). The nature of the sensory conflict task placed constraints on the environment that the participant needed to adapt their responses to (attend to T and respond, do not respond to V and vice versa). In an effort to respond appropriately within this dynamic task, an individual's perception must be consistently tuned to the ever-changing environment, to do this effectively, prediction capabilities must be embedded in the process, a function for which a consensus exists on the importance of the cerebellum (Popa et al., 2012; Paquette et al., 2013; Leggio and Molinari, 2015). As previously mentioned, past imaging work has shown cerebellar activity is enhanced after an unpredictable omission is inserted into a familiar train of somatosensory stimuli (Tesche and Karhu, 2000). Furthermore, studies have shown that altered cerebellar input results in impaired processing of unpredictable stimuli interspersed amongst a sequence of frequent stimuli (Restuccia et al., 2007; Andrew et al., 2020). The responses observed are a result of a loss in the predictability of a sensory pattern as governed by the cerebellum.

Within the context of Study 2 and the sensory conflict task, the appropriate responses are governed by the instruction that is given prior to the trials of what stimulus is to be attended to. In this way, the participant is able to set expectancies for what is and is not a relevant piece of information. These expectancies are compared to what stimuli are being presented and are a driving factor for the gating of irrelevant and distractor stimuli that are observed prior to cerebellar cTBS. Following the transient inhibition of the right lateral cerebellum, an impairment in cerebellar prediction results in similar cortical responses to all attention conditions, regardless of the stimulus presentation type.

In the current study, the stimulation to the left side of the cerebellum resulted in negligible loss of modulation of the cortical peaks, namely the tactile N70 and visual P2. Given that the presentation of somatosensory stimuli was still delivered to the right hand, this is perhaps not so surprising. However, these findings do lend themselves to the specificity with which the cerebellum is able to modulate sensory input for the facilitation of coordinated and meaningful behaviour. The cerebellum predominantly projects to the contralateral cortex by means of the thalamus, therefore it would be expected that in the previous study, that transient inhibition of the right lateral cerebellum, where attentional nodes are hypothesized to be, would alter its communication with higher-order areas on the left side of the cortex, as was observed. However, although the sensory conflict task provides a unique means of blending higher order processing sensory integration, it is difficult to isolate the general motor component of the task and the potential this may have for influencing the changes seen following cerebellar cTBS. A key challenge is discerning the cerebellum's function within higher order processes is in part due to this pairing of the integration of sensory stimuli for the ultimate purpose of some type of movement or behaviour, whether it be physically performed or mentally rehearsed. Given the lack of modulation of both the N70 and P2 post left cerebellar cTBS, more confidence can be placed on the nature of the communication between the right side cerebellum and its influence in higher order processing within the attentional network.

For both the P100 and N140, the peak amplitude was the largest of the three conditions within the concurrent distractor condition for pre and post left cerebellar cTBS. These two peaks originate from the secondary somatosensory cortex and are implicated in assessing alterations in stimuli (Frot and Mauguier, 1999). During the concurrent distractor trials, regardless of which stimulus is to be attended to (T or V), the stimulus of the opposing modality is presented at the

same time. This would require a more complex processing of the stimuli to distinguish the relevant from the irrelevant in order to accurately evaluate which stimulus to perform a graded response for between the two. This is supported by the increased amplitudes observed in response to the presence of the double stimuli. Following cTBS of the left cerebellum, this increased amplitude in both the P100 and N140 persists within the concurrent distractor condition. Given that in Study 2, there was a decrease in this peak post cTBS to the right cerebellum, it was discussed that this could be due to an impaired ability of the cerebellum to detect the conflict present between the two stimuli; within this study, it appears that the ability to distinguish between the two stimuli remains uncompromised.

The lack of modulation of the cortical peaks following left cerebellar cTBS is also supported by the minimal behavioural changes observed. While the cost of the distractor appeared to increase following left cTBS, this change was very minimal in comparison to the distractor costs observed following stimulation of the right cerebellum in Study 2. A comparison of the accuracy cost between the two studies can be seen in Figure 6.5. As with Study 2, the cost of a visual stimulus is larger than the cost of a tactile stimulus which is, as previously mentioned, potentially due to the nature of the stimulus presentation and the saliency of the visual stimulus.

The contrasting electrophysiological and behavioural data between Study 2 and 3 strengthen the potential role of the cerebellum as a modulator not only for the sole purpose of movement but also higher order functions. It is hypothesized that within the cerebellum, actual input and preceding stimuli are compared and discordances are identified. Should the incoming stimulus correspond to the predicted stimulus, cerebellar output is minimal; however, if a discrepancy is detected the activity in the cerebellum increases and diffuse areas of the cerebral cortex are alerted by enhancing its excitability by means of its widespread connections (Leggio

et al., 2011; Leggio and Molinari, 2015). This notion is well explained in the motor domain, however cerebellar lesion studies have demonstrated impairments in visuospatial learning sequences, working memory, and cognitive sequencing task such as the picture arrangement (PA) subtest of the Wachsler Adult Intelligence Scale Revised (WAIS-R) (Molinari et al., 1997; Orsini and Laicardi, 2000; Timmann et al., 2004; Chen and Desmond, 2005a). Although these tasks spread wide domains, each of them requires individuals to select and maintain relevant information in order to successfully complete, suggesting that the cerebellum is a common modulator of each.

This work further narrows the specificity of the cerebellum's function with regards to the functional role of the right side cerebellum and left side, higher-order cortical areas. However, given the unique anatomy and circuitry of the cerebellum, it is not possible to confirm whether the same lack of modulation would be observed if the side of somatosensory stimulation was altered to be presented on the left side as this has yet to be tested. Future work which changes the orientation of the sensory stimulation would allow for a more comprehensive view of the cerebellum's connections to these cognitive processes and how we can optimize its potential use as a therapeutic target.

6.6 Conclusion

This study was designed to build off of the previous study in an effort to add precision to the role of the cerebellum in higher order functioning. While there are various processes that may contribute to this, using the conduit of attention allowed for the easy manipulation of stimulus relevance, thus creating the aspect of expectancy which is central to the hypothesized cerebellar prediction function. This study replicated previous results in that prior to cerebellar stimulation, cortical peak responses from somatosensory areas are largest in response to relevant information.

These same peaks become attenuated when individuals are presented with irrelevant or distractor stimuli. However, unlike Study 2 where following right side cerebellar stimulation resulted in a dedifferentiation in cortical responses between all three conditions, Study 3 demonstrated a lack of change in the three conditions following left side cerebellar stimulation such that the post condition peak amplitudes mimicked what was observed pre-cTBS. The minimal change in grading accuracy following left sided stimulation supports the specific flow of input from the right side cerebellum to the left side cortical areas involved in higher-order processing given that the left sided stimulation produced a lack of modulation. While this evidence provides support for the cerebellum's involvement in processing sensory information for higher-order goals, follow up studies which modify the side that sensory stimulation is delivered will help in determining if there is a true lateralization pattern of attention within the cerebellum or whether this modulation is specific to the contralateral cerebellar-thalamo-cortical pathways in both directions.

Chapter 7: General Discussion

The overall objective of this thesis was to examine the nature of the cerebellum's influence on predominantly non-motor aspects of behaviour. The complex circuitry of the cerebellum, its widespread projections and the extensive range of higher-order strategies make it difficult to discern which facets of the process the cerebellum directly influences. Within the scope of this thesis, the aspect of attention was a common factor utilized throughout in an effort to narrow in on the cerebellum's influence given its known reciprocal connections with prefrontal and parietal areas and the involvement these cortical areas have within attention. The findings of these studies suggest that the cerebellum modulates attentional processes and disruption of its activity in a healthy population results in a characteristic impairment of adequate stimuli detection, as indexed by the changes observed in both neurophysiological and behavioural measures. Together, these studies form a basis for understanding how the cerebellum mediates sensory integration beyond the scope of simple movements given the sensory nature of the first study and the manipulation of attention instruction that was present within the second and third studies.

The first study sought to characterize the influence of cerebellar input within sensory processing without the need for overt and directed movement. The discrepancy between the copious amounts of sensory input that project to the cerebellum and the lack of observation of large sensory deficits in comparison to the gross motor deficits that accompany cerebellar lesions has framed the cerebellum as responsible for tuning voluntary movement only. Past studies examining cerebellar lesion patients have observed impaired change detection mechanisms whereby the presence of deviant stimuli amongst frequent stimuli did not elicit the expected cortical response. This impairment supports the cerebellum's role in the comparison of what is

expected and what is actually occurring. Given the variability of lesion studies, it is difficult to know what aspects of the stimulus itself the cerebellum is comparing and which anatomical areas of the cerebellum are contributing to this. Activation in the right-lateral cerebellum has been shown to be highly active during higher-order attentional tasks, as observed through imaging studies. In order to further confirm this relationship between cerebellar influence and pure sensory processing, Study 1 utilizes continuous theta burst stimulation (cTBS) to transiently decrease the right lateral cerebellum as it is hypothesized influence on higher order processes given its connectivity with the left cortical associative attentional networks. Performing this technique at a standardized location on a group of healthy participants allowed for a clearer view of the communication between the cerebellum and these broad networks.

It was hypothesized that cTBS to the right lateral cerebellum would impair identification of pertinent changes in the presentation of sensory stimuli without having to perform a movement task. Prior to cTBS, cortical responses to deviant somatosensory stimuli interspersed amongst frequent stimuli elicits a large negativity, known as the mismatch negativity (MMN), thought to be governed by a change-detection mechanism. This mechanism is thought to be heavily influenced by the cerebellum and is a main proponent of the comparison role that the cerebellum is hypothesized to be responsible for. In order for this comparison or estimation to occur, the cerebellum must integrate, as previously mentioned, what is expected with what is actually occurring. In this scenario, the expected stimulus would be considered the frequent stimulus presentation where the unexpected would be the deviant stimulus presentation. Prior to cTBS, the large MMN occurs due to an unexpected stimulus being presented. However, following cTBS, this large negativity in response to deviant stimuli becomes attenuated and appears to be comparable with the responses following the presentation of the frequent stimuli.

These findings demonstrated that the cerebellum does in fact contribute to the differentiation of sensory stimuli by means of comparison given the nature of the oddball paradigm context.

However, when discussing these higher-order natured tasks that the cerebellum contributes to it is critical to consider the requirement of multiple processes and cortical networks together.

Within the oddball paradigm of Study 1, although the presentation of the frequent and deviant stimuli creates a differential factor for comparison, the aspect of attention cannot be ignored within this task. Given the cerebellar connections with prefrontal areas heavily implicated in attentive processes, adding attention manipulation as another layer within a task will help to distinguish what the comparison process within the cerebellum may be guided by when it comes to higher order functioning.

The goal of Study 2 was to determine whether the cerebellum's evaluation of sensory stimuli was related to a change in attentional constraints. While the results of Study 1 demonstrate the role of the cerebellum in evaluating sensory stimuli without the need for overt movement, implementing a sensory task in which the aspect of attention is manipulated gives a means for determining the aspects of the tasks which the cerebellum directly utilizes to subserve the coordination of behaviour. In Study 2, participants were required to perform a graded sensory conflict task where they were presented with both visual (V) and tactile stimuli (T) and asked to respond using a pressure sensitive bulb by applying a proportional amount of pressure of the amplitude of the stimulus to the bulb. Participants were asked to grade the amplitude of unimodal V or T stimuli that were presented either individually or simultaneously (VT), while their attention was randomly oriented to specific stimuli during each trial block. This created two attention response conditions that were either attend to V or attend to T and three stimulus

presentations conditions where each stimulus would be relevant, irrelevant, or a concurrent distractor.

It was hypothesized that if the cerebellum contributes to the comparison of stimuli by the means of placing importance based on attentional goals, then following its transient inhibition, participants would be less likely to ignore irrelevant stimuli and will perform with decreased accuracy. Prior to cTBS, cortical somatosensory peaks, namely the N70, were found to be largest in response to relevant stimuli (ex. asked to attend to T and receiving T stimuli) in comparison to irrelevant or concurrent distractor stimuli, where the cortical peaks were seen to be attenuated (ex. asked to attend to T and receiving V stimuli or asked to attend to T and receiving T and V stimuli at the same time). Following cTBS, this differentiation of conditions, as indexed by the attenuation of cortical peaks in response to irrelevant and distractor stimuli is no longer present. Therefore, the cortical peaks in response to the irrelevant and distractor stimuli are not attenuated and are of similar amplitude to the cortical peaks in response to relevant stimuli. Although the presentation of this task is very different from that of Study 1, this pattern of change is very comparable to the findings observed where there was a loss of differentiation between the frequent and deviant stimuli following cTBS to the right lateral cerebellum. The results of Study 2 provide strong support for the role of the cerebellum in the evaluation of sensory stimuli for higher order functioning and more specifically, with regards to the manipulation of attention instruction and how these instructions are utilized to prioritize stimuli to perform accurate and meaningful behaviour. This is further supported by the behavioural findings in which the cost of a distractor following cerebellar cTBS was larger such that accuracy decreased.

Study 3 is an extension of the previous study in that it utilized an identical task set up with the graded sensory conflict task. With the complex connectivity of the cerebellum and the

vast amount of overlap between sensory, motor and cognitive domains when it comes to performing any task, only stimulating over the right side cerebellum and observing the resulting effects without a comparison group does not provide a complete picture of the nature and potential directionality of the cerebellar influence. Therefore, the aim of this study was to perform an identical protocol to that of Study 2 but with cTBS stimulation being applied over the left lateral cerebellum in comparison to the first two studies, which stimulated over the right lateral side. It was hypothesized that should the cerebellum's influence be more focused on general sensorimotor adaptation, then the stimulation of the left side cerebellum would result in similar cortical peak changes and behavioural changes as observed in Study 2. If the cerebellum is directly influencing higher-order processes through its contralateral prefrontal connections, then differential results would be expected when stimulation is applied over the opposite side cerebellum. Prior to cTBS, the results of Study 3 replicated what was observed pre-cTBS in Study 2 with cortical responses being largest to relevant stimuli and attenuated in response to irrelevant and distractor stimuli. However, following cTBS to the left cerebellum, instead of seeing the loss of differentiation of the condition as seen in Study 2, this same pattern of differentiation is maintained such that the post cTBS cortical peak amplitudes are very similar to the pre-cTBS cortical peak amplitudes. The behavioural results demonstrated a very similar pattern in that there was minimal change to the cost of the distractor post cTBS. This contrast between Study 2 and 3 which is driven by the change of stimulation side show the specificity of the cerebellum's influence within the broader attentional network.

Together, these three studies provide evidence that the cerebellum does play an influential role in the processing of sensory stimuli for more cognitively driven tasks. While many studies have demonstrated the importance of the role of the cerebellum for coordination,

these studies have focused explicitly on motor aspects with simple reaching movements. Decades of research surrounding the cerebellum have narrowly focused on this motor dominant role because of the motor deficits that have been so principally observable in cerebellar lesion patients. Due to the prominent nature of these motor symptoms and the fact that there is not a complete loss of sensory function in these patients, the loss of sensory and perceptual processing such as motion perceptions and the recognisance of perceptual sequences have been overlooked (Baumann et al., 2015). Within the motor domain, the cerebellar role has been largely discussed as one that is involved with prediction. This is well known in the context of motor skill learning where individuals are able to gradually adapt and perform a movement more accurately over time. The use of forward models to drive this prediction has been employed to describe this function (Ito, 2008; Friston, 2010). Within forward models, the cerebellum is hypothesized to operate as a state estimator using efferent copies of motor commands to predict the sensory consequences of actions. The difference between this predicted consequence and the actual outcome is referred to as the sensory prediction error (Ito, 2008; Sokolov et al., 2017). When relating this to more cognitively driven functions, the cerebellum may be predicting changes in perceptual states and communicate these updates to widespread associative cortical areas. What is unclear about this more cognitive approach is what would constitute a cognitive or higher-order based error which would form the basis for the comparison of predicted and actual consequences.

Higher-order or perceptual processes can still be thought of as interactions in time between an individual and an environment that are both dynamic; in order to synchronize these aspects, we must constantly tune ourselves to an ever-changing environment. As mentioned, past studies have demonstrated that cerebellar activity is enhanced after an unpredictable omission is

inserted into a regular train of somatosensory stimuli (Teschke and Karhu, 2000). Furthermore, individuals with cerebellar lesions demonstrate an impaired ability to differentiate somatosensory stimuli (Restuccia et al., 2006). These responses can be understood as an indication that something that is expected does not appear and when one of the critical areas responsible for this is lesioned, this response is weakened (Ivry, 2000; Sokolov et al., 2017). This is corroborated by Study 1 in which transient inhibition of the cerebellum resulted in a diminished mis-match negativity (MMN), which as mentioned is believed to be generated by an automatic cortical change-detection process which is activated by differences between current and prior inputs; which could be thought as synonymous with the comparator function of the cerebellum (Ito, 2006). Within the cognitive domain, pattern or sequence detections have the potential to be the substrate for the continued influence of cerebellar control. Within the sensory conflict tasks, assigning importance to specific stimuli to be attended to provides the basis for detection of what is expected and an individual's response will be attuned to this relationship. The loss of this comparative relationship following transient inhibition of the cerebellum serves as an extension of the pure sensory processing seen in Study 1, as there is now a layer of judgement as to which stimuli are relevant or irrelevant.

Chapter 8: Concluding Remarks

8.6 Conclusion

The studies within this thesis contribute to the growing literature that surrounds the role of the cerebellum in higher-order processing. While continued investigation of the mechanism of the prediction function is needed, this work provides a means for narrowing in on the cerebellum's influence specifically within the broader attentional network. The goal of the thesis was to extend the view of the cerebellum and strengthen the implications for its role as a widespread support structure through the comparison of predicted and actual consequences. It also explores the potential for attention to be a conduit of this prediction process for determining what types of input the cerebellum would utilize as a basis for comparison. The findings of Study 1 support this given that transient inhibition of the cerebellum resulted in a diminished MMN in response to deviant stimuli, which is thought to be activated by differences between current and prior inputs. Given that the differences in the stimulus presentation for Study 1 may be representative of attentional capture, Study 2 altered attended stimuli and demonstrated that following transient inhibition of the right lateral cerebellum, participants were less likely to ignore irrelevant or distractor information. Study 3 confirmed the laterality of the cerebellum's modulatory effects in that left sided cerebellar stimulation did not result in the same alterations seen in Study 2. The communication between the right side cerebellum and contralateral prefrontal cortex was therefore not affected since somatosensory stimulation was being applied to the right side, the processing of stimuli was not compromised.

Recent studies investigating cerebellar lesion-behaviour relationships have shown much overlap in symptomology with various mental health and developmental disorders (Riva and Giorgi, 2000; Tavano et al., 2007; Argyropoulos et al., 2019). Given the unique role that the

cerebellum plays within attentional tasks, further investigation of these cerebellar-associative cortex connections should be performed in order to determine the efficacy of this node in the potential treatment of various behavioural and developmental disorders.

8.7 Limitations

Within the studies of this thesis, although the use of cTBS provides an excellent tool for investigating the influence of a specific cortical area over a specific process, it still presents limitations. Firstly, although a standardized measurement was utilized over the cerebellum to localize Crus II, without individual imaging, it is not possible to claim with absolute certainty that the intended areas was always stimulated given the variability of each individual's anatomy.

While the use of cTBS has been widely studied and utilized, this has been mainly in the context of use over the motor cortex (M1). While the mechanisms of its efficacy are well understood over M1, there is continued debate of the technique being administered over the cerebellar cortex given its difference in both macro and micro architecture in comparison. Furthermore, given the individual anatomical variability, there is some debate as to the direction of the effect the stimulation has with regards to potential higher intensities directly influencing Purkinje cells whereas lower intensities acting upon interneurons in the outermost layer of the cerebellum (Koch et al., 2008). This may contribute further to the variability observed within the participants post cTBS. It is also important to acknowledge that given the unique structure of the cerebellum in comparison to M1, we are unable to rule out potential effects from the spread of the stimulation to areas in proximity to the stimulation site (e.g. adjacent cerebellar lobules, midbrain structures, inferior olivary effects). Distributed circuitry across the cerebellum, associative cortices, midbrain and subcortical areas are critical for the convergence of sensory processing for a multitude of behaviours. The overlap in such circuitry can be a cause of

confusion when determining where exactly is being affected with the stimulation (e.g. altered sensory input to the cerebellum or decreased communication of sensory input from cerebellum to widespread areas).

In order to be able to reliably measure cortical peaks, the averages of many trials are compiled together. Within Study 1, there are a total of three blocks of nerve stimulation following the administration of cTBS which spans over 30 minutes which each block containing a total of 240 stimuli. While there could be the potential for a habituation effect that could drive part of the decrease observed in the mean difference between peaks, the lack of change observed within the sham group would suggest otherwise. Within Study 2 and 3, each block of the sensory conflict task consisted of 54 stimuli with 10 blocks occurring both pre and post cerebellar stimulation. Similarly, the changes observed post cTBS could be due to a learning effect given the amount of trials that are performed. It is important to note that the lack of use of feedback within the sensory conflict task was done in an effort to avoid a learned reliance on the feedback and to keep participants engaged in the task.

Given that the studies include both behavioural and neurophysiological data however, we can be more confident in our findings and the association that cTBS highlights between the cerebellum and higher-order functions.

8.6 Future Directions

In order to further understand the specificity of the cerebellum's role in these broader higher-order networks, there is a need for a few follow up studies to be performed. While Study 3 demonstrated a specificity of the right side cerebellum and contralateral attentional network connectivity, the somatosensory stimuli was still delivered on the right side. Performing a study in which the somatosensory stimulation is delivered to the left side and two groups receive cTBS

stimulation on either left or right sides would lend itself to confirming a) the specificity of the contralateral connectivity and b) whether this higher-order attentional focus is specific to the hypothesized attentional nodes within the right lateral cerebellum.

The cerebellum's role in prediction is thought to be heavily influenced by a timing mechanism, performing similar sensory conflict tasks in which the stimuli are presented at differing time intervals pre and post cerebellar stimulation would clarify this function. As discussed, the mechanism of stimulation is not fully understood. Paired-pulse TMS paradigms are used to investigate intracortical circuits, using a paradigm such as this over non-motor areas is not as well established as there is no measurable muscle effectors, however using TMS evoked potentials (TEPs) over areas such as the prefrontal or parietal cortices following cTBS administration would allow for a better understanding of these complex networks. Furthermore, identifying individualized responses on a case by case basis could allow for the potential identification of response patterns and greater feasibility of therapeutic use.

Secondary analyses would also greatly supplement this work, for example, to address potential learning and timing effects, dividing EEG and task blocks into early and late blocks (first five blocks and last five blocks) to narrow in on whether there is a specific time that is driving the changes observed. Due to the aforementioned variability in individual responses to cTBS, a secondary analysis which groups differences in responses and correlate this with intensity may be useful in determining the efficacy of the stimulation over the cerebellar cortex for future consideration as a rehabilitative strategy.

8.7 References

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