The contribution of the fronto-cerebellar system in cognitive processing

by

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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 revisions, as accepted by my examiners.

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Abstract

Over two decades of patient and neuroimaging data have provided increasing support for a role of the posterior cerebellum in cognition, particularly attention. Contralateral connections between the prefrontal cortex and the cerebellum are a probable basis for this effect. It is the purpose of this thesis to understand the contribution of the fronto-cerebellar system to cognitive and attentional processes. The first aim of this thesis was to localize areas of the cerebellum that participate in non-motor behaviour. After transient disruption of cerebellar activity using continuous theta burst stimulation (cTBS), a form of transcranial magnetic stimulation, Study 1 and 2 identified the right posterior-lateral cerebellum as a contributor to a network involved in two non-motor tasks; word generation and the attentional blink. The aim of Study 3 was to investigate if manipulating task demands increased fronto-cerebellar recruitment. The final study of this thesis employed electroencephalography (EEG) and cTBS to probe the neural events disrupted during the attentional blink task when the left frontal- right cerebellar system was transiently disrupted. Understanding the manner in which these neural events are affected by transient perturbation is integral to the understanding of the fronto-cerebellar contribution to cognitive and attentional processes. Together these studies help elucidate the role of the fronto-cerebellar system in non-motor functions.

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List of abbreviations

AB	Attentional Blink
AIP	Anterior intraparietal area
cTBS	continuous theta burst stimulation
DCN	Deep cerebellar nuclei
DLPFC	Dorsolateral prefrontal cortex
dw-MRI	Diffusion weighted magnetic resonance imaging
EEG	Electroencephaloghraphy
ERN	Error-related negativity
ERP	Event-related potential
FEF	Frontal eye field
fMRI	Functional magnetic resonance imaging
M1	Primary motor area
PASAT	Paced auditory serial addition task
PASST	Paced auditory serial subtraction task
SMA	Supplementary motor area
SOA	Stimulus onset asynchrony
STN	Subthalamic nucleus
T1	Target 1
T2	Target 2
tDCS	Transcranial direct current stimulation
TMS	Transcranial Magnetic Stimulation
VGP	Video game players

Chapter 1 – Introduction

1.1. Overview of thesis

Chapter 1 outlines the general objectives of the thesis, followed by a review of relevant literature pertaining to the anatomy and physiology of the cerebellum and its role in non-motor functions. Chapters 2-5 detail the rationale, hypotheses, methods, results and discussion of the research studies contributing to the thesis. Chapter 6 includes a general discussion of the findings of the thesis, its limitations, and future directions for study.

1.2 General objective of thesis

The general objective of this thesis is to understand the contribution of the fronto-cerebellar system in non-motor functions. The cerebellum is traditionally viewed as a motor structure, involved in motor control, coordination, and balance. Trauma to the cerebellum does not lead to loss of motor function, but rather lack of coordination of motor function (Holmes, 1939). This suggests that the contribution of the cerebellum is to refine our movements and modulate function. However, the cerebellum does not communicate to the motor cortex alone, it forms reciprocal loops with prefrontal, parietal, and temporal cortices as well (Middleton and Strick, 2000). These loops are formed contralaterally between the cortex and cerebellum, and are functionally segregated (Schmahmann 2009). The lateral hemispheres of the posterior cerebellum (specifically Crus I, II) have projections to the dorsolateral prefrontal cortex (Kelly and Strick, 2003) and are associated with higher-level functions. Thus, the cerebellum is not restricted to motor coordination; it is involved in modulating function in the motor and cognitive domain alike. The fronto-cerebellar circuitry serves as the anatomical substrate for regulating neural signals in the prefrontal cortex (Koziol and Budding, 2009). Little is known, however, about when the cerebellum is recruited by the frontal cortex to modulate behaviour. During what tasks is this network necessary? And is its contribution hemisphere specific? In this thesis we use two different types of tasks to probe the fronto-cerebellar involvement in non-motor function. We hypothesize that that fronto-cerebellar system is integral to efficient and optimal performance during non-motor tasks.

1.3 Background Research

There are two organized brain systems that connect cortical and subcortical structures: the cortico-basal ganglia system and the cortico-cerebellar system. It was previously believed that 1) the basal ganglia and cerebellum strictly targeted areas of the cortex involved in motor control, and 2) these regions would integrate and convert incoming information from widespread cortical areas for motor output (Allen and Tsukahara, 1974; Kemp and Powell, 1971). This hypothesis of the subcortical areas forming loops to funnel information to the primary motor cortex was challenged after systematic mapping studies, using transneural tracers, identified reciprocal connections between subcortical nuclei and diverse regions of the cerebral cortex (Middleton and Strick, 2000;

Kelly and Strick, 2003). The observation of feedforward projections from frontal, parietal, and temporal cortices that are matched by basal ganglia and cerebellar feedback projections provide anatomical evidence that subcortical output is not restricted to the motor domain. Thus, what purpose might cerebro-subcortical circuits serve? While cortical input to the cerebellum and basal ganglia is excitatory, the effect of their output back to the cortex is largely inhibitory. Cortical-subcortical-cortical loops therefore serve a modulatory function, where subcortical structures regulate the amount of information to be returned to the cortex. This thesis will focus strictly on the cerebro-cerebellar system.

The cerebellum physically sits outside the cortex; its name literally means "little brain" yet it is composed of more than half of the neurons in the central nervous system (Ito, 1984). The purpose of these neurons is to fine-tune the behaviours that have been selected by the cerebro-striatal system (Booth et al., 2007). This is achieved via the dense interconnections between the cerebral cortex and the cerebellum. The pontine nuclei are the input stage of the cerebellum that receives afferents from layer V of the cortex. The axons of the pontine nuclei project to the cerebellar cortex via the middle cerebellar peduncle and these afferents are excitatory. After synapse occurs with cerebellar interneurons, which pass on information to GABAergic Purkinje cells, the resultant output of the cerebellar cortex is inhibitory. Purkinje cells inhibit the deep cerebellar nuclei (DCN), which tonically excite the thalamus. The cerebellum thus serves to regulate cortical excitation. Refining behaviour during environmental changes is such a specialized process that it requires its own system, housed outside the cerebral cortex (Koziol and Budding, 2009). Communication between the cortex and cerebellum is integral to all domains of behaviour. Regardless of what functions are being subserved by the region of origin in the circuit (language, memory, motor), the cortico-cererebellar system shares the same purpose of modulating these functions.

1.3.1 Circuitry of the cerebellum

The cerebellar cortex is composed of three distinct layers, the molecular layer, Purkinje cell layer, and granule cell layer (GCL). The GCL is the innermost layer, and houses granule cells, which are the most numerous cells in the brain, with about 5×10^{10} granule cells in the cerebellum alone (Llinas et al., 1990). Granule cells are excitatory, exciting all other cell types in the cerebellar cortex (Ito, 1984). Axons of the excitatory granule cells pass through the Purkinje cell layer and bifurcate in the molecular layer, forming parallel fibers. Both the ascending axons of the granule cells and the parallel fibers form many synaptic connections with Purkinje cells. Parallel fibers run along the transverse axis, perpendicular to inhibitory Purkinje and Golgi cells, which run sagittally (Ito, 1984).

There are two classical excitatory afferent systems that project to the cerebellar cortex: the mossy fiber and climbing fiber systems. These two systems are anatomically different. Mossy fibers run primarily sagittally and originate from (1) the cerebral cortex (via pontine nuclei), and (2) the spinal cord (via spinocerebellar afference). Mossy fibers project to the cerebellar cortex where they synapse on granule cells and also innervate the deep cerebellar nuclei (DCN). The parallel fibers of the granule cells activate wide array of Purkinje cells. This activation is soon inhibited by basket and stellate interneurons that run parallel to Purkinje cells (Llinas et al., 1990). While such inhibition is taking place in the Purkinje cell layer, mossy and parallel fibers excite Golgi cells that are in the granule cell layer. Here, Golgi cells inhibit granule cells to prevent further activity of parallel fibers. This inhibition is a feedback system that sets the threshold for granule cell firing.

Climbing fibers on the other hand originate from strictly one source, the inferior olive, and branch into fibers once inside the cerebellar cortex. Here they bypass granule cells and synapse directly onto one Purkinje cell each (Llinas et al., 1990). Climbing fibers fire simultaneously along Purkinje cells, which are aligned parasagittally in the cerebellar cortex (Lang et al., 1999). Climbing fibers generate complex spikes due to the branching pattern of the olivocerebellar axons, which run in straight narrow lines along the rostrocaudal axis from the brainstem to the cerebellar cortex. Climbing fibers also activate inhibitory interneurons and Golgi cells; they therefore inhibit the input coming from the mossy fibers and dominate Purkinje cells when they fire. Purkinje cell axons terminate by synapsing on one of the DCN. The DCN is where feedback from the cerebellum to the cerebral cortex originates. There are four DCN, and each receives input from different regions of the cerebellum. The most lateral nuclei (from midline) are the dentate, which receives input from the cerebellar hemispheres. Both have increased the most in size along with the posterior cerebellar hemispheres (Middleton and Strick, 2000). Next are the emboliform and globus nuclei, which together are referred to as the interpositus nuclei and receive input from intermediate zones of the cerebellum. The most medial nuclei are the fastigial nuclei, which receive input from the vermis.

1.3.2 Cerebellar connections and functional organization

The cerebellum forms parallel loops with many different cortical areas. These connections form the anatomical substrates of cerebellar involvement in motor and non-motor functions however the topography of the connections is still not completely mapped. It has been hypothesized that a functional dichotomy exists in the cerebellar cortex, such that the anterior portion (lobules I-V) and lobule VIII are involved in sensorimotor processing due to cerebral projections originating from motor and somatosensory cortices. Lobules VI and VIIA/B contribute to higher level processing as a result of projections from prefrontal regions (Stoodley and Schmahmann, 2010), such as the dorsolateral prefrontal cortex (DLPFC) which have been described as being essential for functions such as attention, organization, planning, and working memory. The vermis and fastigial nucleus are linked with limbic regions, such as the anterior cingulated cortex, for affective behaviour (Stoodley and Schmahmann, 2010).

Somatotopic maps have also been identified within the cerebellum. Using animal stimulation and human neuroimaging studies, two body representations have been found in the cerebellum, one in the anterior lobe and the other mainly in lobule VIIB and VIII of the posterior lobe (Manni and Petrosini, 2004; Thickbroom, 2003). Somatic maps have also recently been found in the neocortex of the cerebellum (lateral aspect of lobule VI and VIA) especially during complex movement tasks (Schlerf et al., 2010). Interestingly Crus II (lateral VIIA) had no significant somatotopic representation, supporting the functional hypothesis that the posterior-lateral cerebellum is involved in non-motor functions (Schlerf et al., 2010).

Functional organization is fairly consistent within the cerebellum, even at the level of the DCN. With retrograde transneuronal tracers it was found that distinct output channels exist within the DCN for specific functional purposes and that these output channels do not overlap (Middleton and Strick, 2000). Motor output channels for example can be found in the dorsal dentate and anterior interpositus nucleus and project to the primary motor area (M1); the lateral dentate projects to the premotor cortex (PMC); mid-dorsal dentate to supplementary motor area (SMA); and caudal dentate to the frontal eye field (FEF). Cognitive and affective output channels are organized predominately in the ventral dentate: ventromedially for Brodmann area 9 and pre-SMA, and ventrolaterally for Brodmann area 46 (Middleton and Strick, 2000; Akkal et al., 2007). The anterior intraparietal area (AIP) also projects to the cerebellum however its output channels are dispersed within the dentate (Purzner et al., 2007).

Apart from the cerebellum forming multiple closed-loop circuits with the cerebral cortex, reciprocal connections have recently been discovered between the cerebellum and the basal ganglia (Bostan et al., 2010). Hoshi and colleagues (2004) using transneuronal transport of rabies virus in primates found that the dentate nucleus is linked to the striatum via a disynaptic pathway. This communication between the output stage of the cerebellum and the input stage of the basal ganglia implies an influence of one structure over the other. A comparable relationship is reciprocated by the basal ganglia, as the subthalamic nucleus (STN) is linked to the pontine nuclei, enabling an influence of the basal ganglia on cerebellar function. The STN has functional divisions (sensorimotor, associative or limbic) and these divisions remain exclusive in the cerebellar cortex, as sensorimotor and associative regions of the STN linked with lateral VIII and Crus II respectively (Bostan et al., 2010). Thus the connection between the cerebellum and STN is involved in integrating motor and non-motor functions of basal ganglia and cerebellum, which is improved by two-way communication.

1.3.3 The cerebellum and non-motor functions

The identification of multiple segregated fronto-cerebellar loops has challenged the traditional view that the cerebellum is strictly involved in motor control. Reports of cerebellar patients with cognitive deficits without motor impairments also suggest the posterior cerebellum is involved in non-motor functions (Schmahmann 2004; Schmahmann et al., 2007). The cerebellar cognitive affective syndrome (CCAS) occurs following lesions of the cerebellar posterior lobe (Schmahmann and Pandya, 2008). The CCAS is defined by impairments of executive functioning, linguistic processing, visuospatial performance, and affective dysregulation. Lesions to the right posterior cerebellar hemisphere are associated with verbal fluency (Leggio et al., 2000; Akshoomoff et al., 1992; Appollonio et al., 1993; Silveri et al., 1994; Molinari et al., 1997; Richter et al., 2007; Schweizer et al., 2010) and working memory deficits (Hokkanen et al., 2006; Ziemus et al., 2007). These cognitive deficits resemble those seen after lesions to prefrontal areas (46 and 9) and would likely be seen after damage to the ventral dentate, as it too is part of the cerebellar loop with the prefrontal cortex. Visuospatial deficits are associated with left posterior cerebellar damage (Gottwald et al., 2004) although this finding is less consistent in the literature.

The dysregulation of affect is caused by disruption of the posterior vermis and includes negative (diminished) symptoms such as emotional blunting, passivity, and withdrawal, as well as positive (exaggerated) symptoms such as disinhibition and inappropriate behaviour (Stoodley and Schmahmann, 2010). Cerebellar affective disorders can be categorized into one of five neuropsychiatric manifestations: Attentional control, Emotional control, Autism spectrum, Psychosis spectrum, and Social skill set (Schmahmann and Pandya, 2008).

Many neuroimaging studies suggest the cerebellum is involved in non-motor functions, as cerebellar activation has been found within the posterior lobe during tasks that require cognitive processing such as working memory, language, spatial attention, executive functioning, and decision-making (Desmond and Fiez, 1998; Hayter et al., 2007; Chen and Desmond, 2005; Kirschen et al., 2005; Allen et al., 1997; Schlosser et al., 1998; Stoodley and Schmahmann, 2009). What these studies have in common is three fold: 1) Cerebellar activity was found independent of motor involvement, 2) Activity was confined to the posterior cerebellum, 3) Cerebellar activity was task specific. For example, Schlosser et al. (1998) found right, posterior cerebellar and left prefrontal activity during a verbal fluency task that was performed silently (without articulation/verbalization) but not during baseline, when participants were asked to silently count. The demands of a task thus play a crucial role in recruiting the cerebellum. If the cerebellum does indeed refine behaviour, then a fronto-cerebellar circuit may mediate increased cognitive control required for complex tasks. In tasks that are learned or 'automatic' however, readjustment of behaviour is no longer necessary. Cerebellar activity is found during the initial acquisition of learning (Doyon et al., 2003), when executive control is needed to guide the task. The same is true for the DLPFC, which also shows a practice related decrease in activity (see Meta-analysis by Chein and Schneider, 2005).

1.3.4 Fronto-cerebellar system and dual-task performance

Sometimes no matter how learned a task is, error is unavoidable. Task performance is often impaired when two or more tasks are performed concurrently. Limitations of dual-task performance can be studied using the attentional blink paradigm (Broadbent and Broadbent, 1987; Raymond et al. 1992) where two targets are presented within a trial with varying delays between them. When the second target (T2) occurs within 200-500 ms of the first (T1), the detection of T2 frequently fails. This temporal impairment has been coined by Raymond et al. (1992) as the attentional blink. The attentional blink paradigm manipulates the interference between two tasks by varying the delay between targets. This interference reflects a cost of selectively attending to T1, which results in a failure of late stage information processing (Chun and Potter, 1995; Vogel et al., 1998). Cognitive control is a late stage process, and responsible for inhibiting distracting information (Olivers and Meeters, 2008). One claim is that the cognitive control mechanisms required to inhibit task irrelevant information are taxed during the AB, implicating a decrease in selective attention efficiency. It is possible that the cerebellum may be necessary for the fast and efficient visuotemporal attention required during the AB. Marcantoni et al. (2003) reported increased activity in the lateral prefrontal cortex and cerebellum during the AB, but only during short delays and not during the detection of T1 alone. If the function of the cerebellum is to ensure efficient online adaptation to a changing environment, then it is no surprise that cerebellar activity is seen during tasks like the AB that require dual tasking. Schweizer et al. (2007) found that cerebellar patients performed significantly worse than aged matched controls during the same condition Marcantoni et al. (2003) found cerebellar activation. Thus although the AB is a universal phenomenon, performance inaccuracy is even greater in cerebellar patients. Therefore, the fronto-cerebellar system may be an important network for successful dual task performance.

1.3.5 Locus of the Attentional Blink

While animal behaviour is strictly stimulus driven, human behaviour is goal directed, and multiple goals can coexist at any given moment to bias behaviour. The maintenance of optimal goal-directed behaviour requires a control system to prioritize processing of information, planning and execution of actions. Two major components of this control, or executive system, are attention and working memory. Attention, when voluntary, is selective, and able to filter inputs that are irrelevant to a task goal. Working memory allows for the maintenance of a goal across time, as well as the relevant information necessary to achieve it. At what point during information processing does attentional selection take place? If selection is early, then it is required before the identification of stimuli, to control which stimuli will be processed more than others. If however voluntary attention occurs at a later stage, after stimuli have been fully perceived, then executive control gates information once all stimuli have been processed and categorized.

Event related potentials (ERPs) are voltage deflections recorded off the scalp using electroencephalography (EEG) and can provide an online measure of stimuli processing during cognitive tasks. ERPs have the temporal resolution to measure the influence the executive system has on the different stages of information processing and provide evidence in support of either an early or late selective attention. In support of early selection, P1 and N1 (which occur within 100 ms of stimulus onset) are modulated by attention. The amplitude of both of these potentials increase when visual stimuli are presented at attended spatial locations (Mangun and Hillyard, 1987) as well as for target and non-target stimuli alike (Hillyard et al. 1998). ERPs have been used to study why subjects fail to detect T2 during the AB. Seminal studies have shown that P1 and N1 waves, which are sensory evoked and represent a preset sensory gain control mechanism (Hillyard et al., 1998), are not suppressed during the attentional blink (Luck et al., 1996; Vogel et al. 1998). This led to the idea that unlike spatial attention, which requires early sensory processing, attention to rapid serial visual presentations (RSVP) requires a later perceptual process.

To assess how impaired performance during the AB arises at a later stage, researchers have investigated an ERP related to semantic processing, the N400 mismatch potential (Luck et al., 1996; Vogel et al., 1998). To elicit an N400, a word is given before the RSVP and T2 is either a word that is semantically related/expected or unrelated/unexpected. Expected stimuli that match the initial word will evoke a large N400 and unexpected stimuli elicit a small N400 if T2 is fully identified. The logic of using the mismatch potential is that since a stimulus needs to be identified before it is matched; the presence of the N400 during the AB would be evidence of semantic processing. The conclusion of the studies was such. Regardless of whether or not T2 was inside or outside of the AB, the N400 component was equally large (Vogel et al., 1998). Thus the results of the studies provide evidence that the T2 is fully identified during the AB and not a consequence of sensory suppression during either the early or late stage of selective attention.

There are many models that attempt to explain why the AB phenomenon exists. The majority of these models focus on cognitive capacity limitations (Chun and Potter, 1995; Jolicoeur and Dell'Acqua, 2000; Shapiro et al., 1994), other models assume that the cause of the blink is the result of an attention filter losing control and becoming vulnerable to distractor stimuli (Di Lollo et al., 2005). Regardless of the current theories of the AB, all models would predict that impairment in T2 accuracy does not reflect a failure to perceive T2, but a failure to store T2 into working memory.

1.3.6 Neuroimaging techniques

There has been a recent focus on the connections between prefrontal and cerebellar areas during cognitive functions. Salmi et al. (2009) combined measures of brain activity during a working memory and sensorimotor control task using functional magnetic resonance imaging (fMRI) with diffusion-weighted imaging (dw-MRI) data to investigate the circuitry between the different areas activated during the two tasks. Tractography results indicated segregated loops for cognitive and motor functions. The cognitive circuit linked Crus I/II of the posterior cerebellum with parietal, dorsal premotor, and lateral prefrontal cortices, and when task load increased, connections between Crus I/II and lateral prefrontal cortex were enhanced. Tractography studies are not only useful for mapping out how fronto-cerebellar information processing occurs (Kirschen and Buckner, 2009, O'Reilly et al., 2010), but also for how it malfunctions. Studies using dw-MRI in the autism spectrum population have found pathology of cerebellar feedback projections to the prefrontal cortex in adults with Asperger's syndrome (Catani et al., 2008) as well as altered integrity of feedforward and feedback loops in children with Autism (Sivaswamy et al. 2010). Thus, fronto-cerebellar circuits are poorly engaged in autistic individuals, and recruited when task demands increase.

Although anatomical connectivity is difficult to assess in humans, probing the transynaptic effect of one brain region over the other can be performed using another neuroimaging tool, transcranial magnetic stimulation (TMS). Mottaghy et al. (2003) combined repetitive TMS with positron emission tomography (PET) to map the effect of repetitive TMS (rTMS) following the performance of a verbal working memory task. They found cerebellar activity after rTMS to the right middle frontal gyrus, which supports functional connectivity of the cerebellum with the prefrontal cortex. This increased cerebellar activity after rTMS can be interpreted as a compensatory upregulation to offset a lack of prefrontal input in the fronto-cerebellar network (Mottaghy et al., 2003).

TMS is a non-invasive technique that can be used for mapping neurological functions. It involves passing an electric current through a magnetic coil placed on the scalp to induce a secondary electric current that disrupts the excitability of a focal population of neurons. The temporal precision of TMS is superior to functional imaging techniques and the spatial accuracy of induced inhibition allows for clearer interpretation than patient studies with inconsistent etiologies. As a result, TMS can provide unique support to imaging and lesion studies by transiently inhibiting focal areas of the cortex in healthy participants.

TMS can be used to investigate cerebello-thalamo-cortical pathway integrity (Ugawa et al., 1995). Repetitive application of the current to the cerebellum has induced significant behavioural changes in healthy participants, such as decreasing performance accuracy during a paced-finger-tapping-task (Theoret et al., 2001), and disrupted performance of cognitive tasks such as time perception (Koch et al., 2007, Oliveri et al., 2007). A relatively new form of TMS, continuous theta burst stimulation (cTBS), uses a very low current to transiently decrease cortical excitability for several minutes following stimulation. In the motor cortex inhibitory effects can last up to an hour in healthy participants (Huang et al., 2005). This effect has recently come into question, as the response to cTBS over the motor cortex is highly variable between individuals (Hamada et al., 2012). When cTBS is applied to the contralateral, posterior-lateral cerebellum, it has been found to modulate intracortical circuits of the human motor cortex, and depress motor cortical excitability (Koch et al., 2008; Popa et al., 2010). It is feasible then, that cTBS to the cerebellar cortex can also induce focal, transient cortical changes that influence the activity of the prefrontal cortex during tasks that require cognitive processing.

EEG is another neuroimaging tool useful for understanding functional connectivity within the brain. ERPs that are recorded from EEG and can provide an online measure of stimuli processing during cognitive tasks. The advantages to ERP recordings are its temporal resolution and ability to provide a continuous measure of cortical activity. ERPs can be extracted using signalaveraging procedures, where segments of EEG recordings that are stimulus/event locked are averaged together so that any random EEG activity is cancelled out and stimulus relevant neural activity can be observed (Luck and Vogel, 2001). The averaged wave that is formed consists of a sequence of voltage deflections; each deflection or 'peak' is named after its polarity and ordinal position in the sequence (i.e. P1, N1, P2, N2) or named after its latency from stimulus/event onset (i.e. P300 is a positive peak at 300 ms post-stimulus/event). Initial peaks (within 200 ms) reflect exogenous processes, and later peaks reflect endogenous processes (Eimer, 2001). Studies of spatial attention demonstrate that P1 and N1 waves are larger when stimuli are presented at attended locations compared to unattended locations (Mangun and Hillyard 1987). This modulation reflects a sensory gain control mechanism (Hillyard et al.1998) that has the same effect when searching for targets among non-targets. Even if a target is not consciously perceived, it will still evoke early sensory components (Vogel et al., 1998). ERPs have been used to study why subjects fail to detect T2 during the AB. Together TMS and ERPs can be used to probe the contribution of the fronto-cerebellar system to non-motor functions, by elucidating the neural events and behaviour that are modulated by disrupting this network.

1.4 Specific research objectives

1.4.1 Research Objective 1

To probe whether perturbing function in the posterior-lateral cerebellum using TMS will disrupt behaviour during non-motor tasks that require the fronto-cerebellar system.

Previous research has shown that there are intimate connections between the prefrontal cortex and the contralateral cerebellum (Middleton and Strick, 2000; Kelly and Strick, 2003). These connections serve as the anatomical substrate for a cerebellar involvement in cognitive and attentional operations, as they are thought to regulate the neural signals in the prefrontal cortex (Koziol and Budding, 2009). The cerebellum is also functionally organized (Stoodley and Schmahmann, 2010), and posterior-lateral regions of the cerebellar hemisphere have been associated with cognitive functions (Stoodley and Schmahmann, 2010, Salmi et al., 2010, Allen et al., 2005). Research Objective 1 set out to determine if functions that are lateralized in the cerebral cortex are also lateralized in the cerebellum. While word generation tasks and the Attentional Blink task probe cognitive and attentional control, they both involve letter stimuli. Given that language is highly lateralized to the left cerebral cortex, it was hypothesized that disrupting left frontal-right cerebellar connectivity would degrade performance during a task when optimal and efficient performance is at highest demand. Study 1 tests this hypothesis using word generation tasks and Study 2 using the Attentional Blink task. Both studies deliver cTBS over the posterior-lateral cerebellum to perturb frontal-cerebellar connections.

1.4.2 Research Objective 2

To determine if load influences the recruitment of the fronto-cerebellar system during the Attentional Blink.

All cognitive operations have a capacity limitation whereby increasing demands results in weakened performance (Kahneman, 1973). The load of a task is dictated by the magnitude and amount of its demands, and can be manipulated perceptually and cognitively. With increased cognitive load there is greater brain activation particularly in brain regions involved in the control and regulation of attention, particularly the dorsal frontal-parietal network (Corbetta and Shulmann, 2002). However, cerebellar activity also increases with increased cognitive load, particularly the posterior-lateral cerebellum (Salmi et al., 2010). Research Objective 2 set out to determine if increasing the cognitive load of detecting the first target (T1) influenced the recruitment of the fronto-cerebellar system during the Attentional Blink. In Study 3 the set size of T1 was increased from two to four. Since the magnitude of the blink in Study 2 was relatively low compared to other studies using similar parameters (Shapiro et al., 1994; Schweizer et al., 2007), it was hypothesized that increasing the set size of the T1 stimuli would increase the magnitude of the blink.

1.4.3 Research Objective 3

To probe the contribution of the fronto-cerebellar system to the Attentional Blink.

In Study 2 and 3 there was a lateralized Attentional Blink (AB) deficit that was specific to right cerebellar stimulation and only occurred when the delay between the two targets was less than 500 ms. Research Objective 3 set out to investigate the left frontal-right cerebellar contribution to the AB. It is possible that the cerebellum may be recruited during the AB to efficiently modulate the attentional resources dedicated to T1 to readily detect T2, when the time required to switch between targets is a constraint. In Study 4 electroencephalography (EEG) was used following cTBS to record the P300 component of event-related potentials time locked to T1 and T2. The P300 is characterized by a positive deflection distributed over the scalp with a latency of 300-500 ms and is related to target processing. It was hypothesized that cTBS to the right cerebellum would disrupt the frontal-cerebellar network and increase the latency of the P300 related to T2. An increase in latency would implicate a delay in processing T1 and a disruption in reengaging attentional resources to process T2.

Chapter 2 – Study 1: The cerebellum and its role in word generation: A cTBS study

Adapted from:

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2.1 Overview:

The purpose of this study was to investigate the role of the cerebellum in the executive control of word generation using a phonemic and semantic fluency task. Phonemic fluency tasks require novel strategy to organize verbal output, and are more effortful than semantic fluency tasks. The number of category switches made between subcategories of words is a measure of mental flexibility, and is greatest during the early phase of the task (first 15 sec). Both tasks were tested on healthy participants, before and after the application of transcranial magnetic stimulation using continuous theta burst stimulation (cTBS) applied over the left or the right posterior-lateral cerebellar cortex in separate groups. We hypothesized that the number of category switches and number of words produced within the first 15 sec would be reduced after cTBS to the right, posterior-lateral cerebellum during phonemic fluency tasks. The results from the study were consistent with the hypothesis. Within the first 15 sec of each trial, right cTBS participants displayed significantly lower switching scores ($p = .05$) after stimulation. Previous studies have illustrated similar impairments in switching between categories during phonemic fluency performance in patients with damage to the left frontal cortex. Our findings support the general hypothesis of cerebellar involvement in executive control through connections to the frontal cortex.

2.2 Introduction

Clinicians typically assess lexical access using standardized language tests such as word generation tasks. These tests measure the ability to generate as many words as possible within specific parameters and time constraints. Semantic and phonemic fluency tests are word generation tasks with a pre-determined word retrieval cue. Semantic fluency cues are category based and provide a template for the list of words that can be generated. For example, an appropriate response to the semantic cue “Animals” would be “dog”, “cat” or “bear”. Phonemic fluency tasks demand more executive control than semantic tasks, as they require novel strategic organization of words for correct output (Lezak, 1983). For example, the phonemic cue “F” can generate a far more exhaustive list of words then the semantic cue “Animals” and the task itself has more restrictions, such as no proper nouns and no sequential derivations.

Maximizing performance requires the ability to strategically organize words into meaningful groups (clusters), and the flexibility to make quick shifts (switches) to search and retrieve new clusters. Category switching, in this context, reflects executive and strategic mental processes (Troyer et al., 1998). The more category switches that occur within a trial, the higher the likelihood of increasing the total number of words generated. Typically most words are generated during the early phase (first 15 sec) of a trial, which includes the greatest scope of subcategories (Troyer et al., 1998). During this phase search and retrieval strategies are most flexible. As the time for the test elapses however, the number of correct selections begins to decline, strategic flexibility weakens, and words are produced less frequently (Troyer et al., 1998). Words generated within the early phase reflect an increased facilitation of a neuronal network to optimize speed of information processing (Stuss and Alexander, 2007). Based on this phenomenon, performance in the early phase of semantic and phonemic (verbal) fluency trials (e.g. first 15 sec) can be scored separately from performance in the late phase (e.g. last 45 sec).

Word generation deficits have been reported in cerebellar patients (Leggio et al., 1995; Ackschoomoff et al., 1992; Appollonio et al., 1993; Silveri et al., 1994; Molinari et al., 1997; Richter et al., 2007). A probable basis for such effects is the reciprocal connections between the cerebellum and contralateral regions of the frontal lobes (Middleton and Strick, 2000). For example, verb generation tasks require the linguistic ability to generate a verb in response to a cue that is always a concrete noun. Although linguistic functioning is left lateralized, the right lateral cerebellum is activated during verb generation (Petersen et al., 1989). This contralateral connection is supported by Fiez et al. (1992) in a case study of a patient with an infarct to the right posterior inferior cerebellar artery who performed significantly worse then healthy controls at a verb generation task. Debate however does exist over whether the right lateral cerebellum is involved in verb generation, as studies using cerebellar degenerative patients report no deficit in linguistic functions (Helmuth et al., 1997; Richter et al., 2004).

Verb and word generation tasks are both heavily lateralized because of their language component. Not surprisingly, impaired switching and reduced word output during phonemic (Lezak 1995; Troyer et al., 1998) and semantic (Troyer et al., 1998; Henry and Crawford, 2004) fluency tests are found in left frontal patients. Cerebellar patient studies however have conflicting results concerning laterality (left or right, both) and specificity (phonemic or semantic fluency, both) as they are based on patients with varying etiologies - cerebellar tumors, degeneration and lesions. Studies that restricted patients to one etiology, such as focal vascular lesions, had more consistent results and narrowed word generation deficits to Crus II of the right cerebellum (Richter et al., 2007; Schweizer et al., (2010)). Schweizer and colleagues (2010) reported reduced word output and a decreased number of category switches during phonemic fluency trials in patients with right unilateral lesions of the cerebellum. The greatest impairment occurred during the early phase of the task (first 15 sec), compared to patients with left, unilateral cerebellar lesions, and age-matched controls. Because of the specificity of the fluency impairment, it is likely that the deficits in the cerebellar population are not attributed to disturbed motor performance, but may be caused by impaired executive processes necessary for organizing and monitoring word output. A meta-analysis of neuroimaging studies also revealed that the cerebellar regions most identified during word generation tasks were the posterior-lateral areas of the right cerebellar hemisphere - lobule VI, Crus I/II (Stoodley and Schmahmann, 2008). Lacking from these studies is the separation of the early and late phase of the word generation tasks, thus neuroimaging studies have yet to disentangle the contribution of the cerebellum to word generation.

There is converging evidence from patient and neuroimaging studies that the left prefrontal cortex and right cerebellum are both involved in word generation tasks. Together these different methodologies elucidate the potential role of the cerebellum during non-motor functions. Another potentially useful technique, transcranial magnetic stimulation (TMS), may also prove effective in revealing the role of fronto-cerebellar connections in verbal fluency. TMS is a non-invasive technique that can be used for mapping neurological functions. It involves passing an electric current through a magnetic coil placed on the scalp to induce a secondary electric current that disrupts the excitability of a focal population of neurons. The temporal precision of TMS is superior to functional imaging techniques and the spatial accuracy of induced inhibition allows for clearer interpretation than patient studies with inconsistent etiologies. As a result, TMS can provide unique support to imaging and lesion studies by transiently inhibiting focal areas of the cortex in healthy participants. TMS can be used to investigate cerebello-thalamo-cortical pathway integrity (Ugawa et al., 1995). Repetitive application of the current to the cerebellum has induced significant behavioural changes in healthy participants, such as decreasing performance accuracy during a paced-finger-tapping-tasks (Theoret et al., 2001), and disrupted performance of cognitive tasks, such as time perception (Koch et al., 2007, Oliveri et al., 2007). A relatively new form of TMS, continuous theta burst stimulation (cTBS), uses a very low current to transiently decrease cortical excitability for several minutes following stimulation. In the motor cortex inhibitory effects can last up to an hour in healthy participants (Huang et al., 2005) and when this protocol is applied to the contralateral, posterior-lateral cerebellum, it can modulate intracortical circuits of the human motor cortex (Koch et al., 2008). It is feasible then, that cTBS to the cerebellar cortex can also induce focal, transient cortical changes that influence the activity of the prefrontal cortex during tasks that require cognitive processing. In the current study we address whether the cerebellum is critical in the executive control processes involved in word generation and whether there is a laterality effect following cTBS. Based on lesion and imaging studies that suggest involvement of the right, posterior-lateral cerebellar cortex (Crus I/II) during word generation tasks (Stoodley and Schmahmann, 2009), we hypothesized that cTBS would have an effect on verbal fluency performance. This effect will be specific to phonemic fluency as phonemic cues demand greater executive control and rely more heavily on the frontal lobes than semantic cues, which require semantic memory (Baldo et al., 2006). Behavioural changes from cTBS will be specific to the right cerebellar hemisphere, contralateral to the left prefrontal cortex, and represented by a decrease in the number of category switches and number of words produced, during the early phase of the task (first 15 s), as this time period demands the greatest strategic organization for executing the task. We also hypothesized that cTBS would have little effect on performance when applied over the left cerebellar hemisphere.

2.3 Methods

2.3.1 Participants

Twenty-seven (18 female) healthy, self reported right-handed participants (age range 20-35 years, mean = 23.85; education range 15-21 years, mean = 16.59) screened for neurological disease and psychological disorders were recruited for this study. All participants were fluent in English. Participants were randomly assigned to one of two groups for application of cTBS to the posterior-lateral cerebellum, Left or right hemisphere. There were 14 participants for the left hemisphere and 13 participants for the right hemisphere group. All participants provided written informed consent prior to testing. Experimental procedures were approved by the Office of Research Ethics at the University of Waterloo.

2.3.2 Stimulus and Apparatus

Prior to application of cTBS over the cerebellum, motor-evoked potentials (MEPs) were recorded from the right first dorsal interosseous (FDI) muscle using electromyography (EMG) with Ag-AgCl surface cup electrodes (9 mm diameter). The active electrode was placed over the muscle belly and the reference electrode over the metacarpophalangeal joint of the right index finger. EMG signals were amplified (1000x) and sampled at 1000 Hz using a custom program written in LabVIEW software (version 7.1, National Instruments). Participants were seated with their hands resting on the chair arms and instructed to remain relaxed while a figure eight TMS coil (MCF-B65) of a Medtronic stimulator (Model: MagPro x100, Medtronic, Minneapolis), was placed against the upper left surface of the participant's scalp at the optimal position for eliciting MEPs from the contralateral FDI muscle. Single pulse stimulations were applied with increasing intensity until a MEP of 200 µV peak-to-peak was elicited in the right FDI during an isometric contraction at 10% of their maximum voluntary contraction on 5 out of 10 trials. This intensity was taken as the active motor threshold (AMT).

Once the AMT was established, participants completed the "pre-stimulus" condition as described below. After this condition, participants were instructed to rest their forehead on a stability cushion so that their head is supported and comfortably positioned in a forward flexed posture. TMS was then applied at 80% of AMT using a continuous theta burst stimulation (cTBS) pattern in which three stimuli are presented at 50 Hz and repeated at 5 Hz (theta frequency) for 40 s (a total of 600 pulses). Stimulation over the lateral (left or right) cerebellum was positioned using predetermined coordinates with the handle pointing superiorly (Koch et al., 2008). The intended target for these coordinates were lobules Crus I and Crus II of the cerebellum. For stimulation of the left cerebellar hemisphere the centre of the coil was placed 1 cm below and 3 cm to the left of the inion. For the right hemisphere the coil was placed 1 cm below and 3 cm to the right of the inion (Theoret 2001). After the cTBS, the “post-stimulation” condition followed.

2.3.3 Procedure

Fluency tasks are designed such that a participant is given a minute to generate as many words as they can in response to a verbal cue. In our study, participants performed this task before and after cTBS application to the posterior-lateral cerebellum. The pre-stimulation condition consisted of 4 trials that took place before cTBS was applied to the cerebellum. The first three trials pertained to letter category, *phonemic fluency*. Subjects were instructed to generate as many words as possible that start with a particular letter. For the last trial, participants were instructed to generate a list of words that belong to a semantic category, *semantic fluency*. The semantic fluency trials always followed the phonetic trials. Trials were each one-minute in duration, except for the last phonetic category trial, which was two minutes – this was to test the time constraints of the task (Lezak, 1984). The post-stimulation conditions followed the same standardized procedure, however with different phonemic and semantic categories.

Phonetic categories were always paired as F, A, S or P, R, W. These sets of letters are well matched in the literature, reducing the influence of task difficulty (Ross et al., 2006). Semantic categories were either 'animals' or 'groceries'. There were less semantic trials than phonemic because there are less semantic categories that are equivalent in terms of task difficulty. However both 'animals' and 'groceries' are often used clinically and have normative data (Troyer, 2000). Phonemic and semantic categories chosen for test and retest were counterbalanced across groups (half of each group started with letters F, A, S and 'animals' first, the other half started with P, R, W and 'groceries') to ensure there was no difference in performance due to the phonemic and semantic categories chosen. For this study we used the same scoring criteria previously reported by Troyer et al. (1997). In brief, category switches were defined as the exhaustion of a phonemic or semantic cluster and the shifting to another. Phonemic clusters consisted of specific characteristics. Words could rhyme, begin with the same first letter, have the same first sound (i.e. school and skate), or be homonyms. Errors for phonemic fluency trials consisted of proper nouns, sequential derivations (i.e. feel, feeling), intrusions (words that do not begin with the appropriate letter cue) and word repetitions. For semantic fluency, successful clusters consisted of words within the same subcategory. For example, subcategories for "animals" consisted of farm animals, zoo animals, and domestic pets, and some subcategories for "groceries" encompassed fruits, dairy, and non-perishables, Semantic words that deviated from the semantic category or repeated words were considered errors and corrected for. All trials in the pre-stimulus and post-stimulus conditions were audio-recorded on computer for offline scoring. A standardized script was read at the beginning of each condition, explaining the specifics of the task.

2.3.4 Statistical Analysis

The initial analysis used a 2x2 ANOVA with a within-subject factor of condition (pre-cTBS, post-cTBS) and a between group factor of hemisphere (left, right), for both the number of switches and words generated during the first 15 s and last 45 s of the phonemic fluency task. Specific *a priori* hypotheses that performance would be affected were then tested by using one-tailed, t-tests.

Specifically for the first 15 s of the phonemic fluency task, baseline values for category switches and words generated pre-cTBS were compared to ensure that there were no between group differences prior to cTBS. The baseline means acted as a control to test the specific hypothesis that these measures during the first 15 s of the task would decrease following cTBS to the right hemisphere but not the left hemisphere. Post-cTBS means of the left hemisphere were also compared to the control, and to the post-cTBS means of the right hemisphere group. Comparisons between groups were made using one-tailed independent t-tests.

In order to control for possible individual differences, change scores were calculated by taking the mean difference of the scores between the within-subject factor of condition (pre-cTBS, and post-cTBS). The number of category switches and the number of words generated were the dependent measures of the phonemic and semantic fluency tasks. Scores for each measure were summed across trials. Separate comparisons were made for phonemic and semantic fluency tasks with two-way analysis of variance (ANOVA) using the between-subject factor of hemisphere (left and right), and within-subject factor of time period (First 15 s, and Last 45 s of the trial). ANOVAs were performed with an α level of 0.05. Where a significant interaction occurred between Hemisphere and time period, two-tailed independent t-tests were used to test *a priori* hypotheses comparing the two groups at each time period. Demographic differences between hemisphere groups were compared using one-way ANOVAs with age and education as between-subject factors.

2.4 Results

Analyses of the demographic data for the participants revealed no significant differences between groups on age [F(1,26)=.08, p=.078], or education [F(1,26)=0.06, p=.82].

2.4.1 Phonetic Fluency

For the number of switches produced in the first 15 s, there was no interaction between condition and hemisphere [F(1,54)= 0.36, p=0.55]. While there was no effect of condition [F(1,54)=0.78, p=0.38], a main effect of hemisphere approached significance [F(1,54)=3.77, p=0.06]. For the number of switches generated in the last 45 s of the phonemic fluency trial, there was also no interaction between condition and hemisphere [F(1,54)=1.33, p=0.26]. There was however a main effect of condition [F(1,54)=4.32, p=0.04], and hemisphere [F(1,54)=3.94, p=0.05].

For the number of words generated within the first 15 s of the phonemic fluency task, there was no interaction between condition and hemisphere [F(1,54)=0.29, p=0.60], nor was there an effect of condition [F(1,54)=0.82, p=0.37], or hemisphere[F(1,54)=3.77, p=0.08], this value did however approach significance. In the last 45 seconds of the phonemic fluency task, there was no interaction between factors [F(1,54)=2.04, p=0.16]. There was an effect of condition [F(1,54)=6.60 p=0.01] but not of hemisphere [F(1,54)=1.86, p=0.18].

A priori comparisons revealed no significant difference for the number of category switches (t(25)=1.12, p=0.14), and for the number of words generated (t(25)=0.93, p=0 .18) pre-cTBS for the first 15 s of the task. As a result, pre-cTBS scores of the left and right hemisphere groups were used as a control group for comparing the mean number of category switches generated after cTBS. These values can be seen in Figure 2,1. There was no significant difference between post-cTBS scores of the left hemisphere (LH) group and the pre-cTBS scores of the control. (t(38)=-0.35, p=0.36). There was however a significant difference between the post-cTBS scores of the right hemisphere (RH) group and the pre-cTBS scores of the control (t(39)=1.84, p=0.04). There was also a difference between the LH and RH groups, however it only approached significance (t(25)=1.58, p=0.06).

For the number of words produced within the first 15 s of the phonemic fluency task there was a significant difference between the LH group and control (t(38)=-1.71, p=0.04) but not between the RH and control (t(39)=0.20, p=0.4). The difference between LH and RH groups also only approached significance (t(25)=1.59, p=0.06).

Change scores analysis revealed a significant interaction between hemisphere group and time period for the differences in the mean number of category switches produced post cTBS relative to pre cTBS [F(1,27)=4.34, p=0.01]. Driving this interaction is the difference of the mean number of category switches made by the LH and RH groups during the first 15 s of the trials. We found that the number of category switches was reduced for the RH group and increased for the LH group and this difference was significant in the first 15 s of the trial (t(25) = 2.03, p=0.05) (Fig. 2.2). There was no significant difference between the RH and LH groups in the number of category switches produced in the last 45 seconds of the trial (t(25) = -1.64, p =0.12).

The ANOVA for the number of words generated also revealed a significant interaction between hemisphere and time period [F(1,27)=4.7, p=0.01]. Figure 2.3

summarizes the change scores for word generation during the phonemic fluency task. Participants within each hemisphere group increased their word output during the last 45 seconds of the task, the RH group statistically more than the LH (t(25) = -2.44, p = 0.02).

2.4.2 Semantic Fluency

There were no significant effects for semantic fluency trials. No significant effects between hemisphere and time period were found on the change score of the number category switches [F(1,27) = 2.26; p = 0.14], and no main effect of hemisphere [F(1,27) = 3.35; p = 0.07] or time period [F(1,27) = 0.38; p = 0.54]. For the measure of number of words produced, there was no significant interaction between factors [F(1,27) = 0.83; p = 0.37] and no main effect of hemisphere [F(1,27) = 3.02; p = 0.09] or time period [F (1,27) = 2.26; p = 0.14].

2.5 Discussion

The behavioural effects of cTBS over the posterior-lateral cerebellum on word generation were hemisphere and task specific. For the RH group, the number of category switches was reduced during word generation tasks. This effect was specific to phonemic fluency, and restricted to the early phase. These findings are consistent with those reported by Schweizer et al. (2010) with focal, unilateral cerebellar lesion patients. In that study, right hemisphere patients produced significantly fewer category switches compared to the left hemisphere patients during the first 15 s of phonemic fluency. Thus, the main results of this study support our hypothesis. The transient inhibitory effects of cTBS reduced the number of category switches during the early phase of phonemic fluency in only the RH group. This suggests the putative role the right cerebellum plays at the early phase of phonemic fluency tasks, when executive processes are required to optimize performance.

Recent clinical studies support the hypothesis that focal cerebellar injury disrupts some aspects of attention and executive functioning (Schweizer et al., 2008; Schweizer et al., 2007a; Schweizer et al., 2007b). In the current study, we posit that the cerebellum is recruited during the early phase of phonemic fluency when the novelty of the task requires a larger neural network to maximize performance. It is possible that when cerebellar excitation is modulated; it may disrupt tonic facilitation to cortical areas and consequently reduce category switches; this however is purely speculative. During the late phase, executive control is in less demand and does not require as large of a network to perform the task. Thus it is possible that distinct neural networks may be performing the same collective task.

Maximizing word output is the ultimate goal of phonemic fluency task, but not the main measure of executive processing. We did not find a reduction in the overall number of words generated by the RH group during the early phase of the phonemic fluency task after cTBS. One possible explanation for the discrepancy between our study and patient data that have reported word generation deficits during the initial 15 s phase (Schweizer et al., 2010), may be the difference between cTBS inhibition and structural damage as they affect cerebellar function. The transient, inhibitory effect of cTBS is much less and this may reflect the sensitivity of the category switch measure. While we did not have an a priori hypothesis as to what the effects of cTBS would be on the late phase of the task, we did find a difference in the number of phonemic words produced by each hemisphere group in the late phase of the task. The RH group had a larger change in word output, however in the same direction as the LH group. The difference between groups remains unclear. We speculate that for the RH group the change in the late phase of the phonemic fluency task is a result of the neural manipulation from cTBS over the early phase. The negative change in category switches may have influenced the positive change in word output, as more words were likely generated once the task goal was sustained. Future studies are required to investigate the difference in performance during the late phase of the task, perhaps by applying cTBS to the PFC and probing whether the disruption is specific to a time period of the task or is generalized.

This is the first TMS study using cTBS to probe the effects of cerebellar stimulation on the executive control of word generation. Results of this study are consistent with cerebellar focal lesion patient and imaging studies, suggesting it as a potentially powerful tool for mapping cognitive functions. Like all methodologies, cTBS has its limitations. Between-subject variability is difficult to control and direct output measures are limited. For example, the output measure for this study was strictly behavioural, making our findings less concrete since no physiological data was recorded. Using standard measurements for localizing the site of stimulation may have been a limitation to the study due to variability in head size. The efficacy of cTBS over the cerebellum as a non-invasive assessment of cerebellar function has been recently questioned. It is possible that stimulation to the posterior-lateral cerebellum could have directly activated corticospinal neurons (Fisher et al., 2009), however if such activation occurred it is not likely that it contributed to the results of our study. Activation of corticospinal neurons would have influenced the motor component of the task, specifically the initiation of speech, however; neither group showed any deficit for generating word output. Since cTBS modulation was hemisphere and task specific, it is more likely that the cerebello-thalomo-cortical pathway was activated or interrupted, as cTBS influenced the executive control of word generation.

The converging evidence from studies using different methodologies makes an argument for the benefits of using cTBS in future studies, as it is a technique that on its own can provide the spatial acuity necessary for mapping the functional organization of the cerebellum via noninvasive, transient interneuronal inhibition. Our results map onto previous findings implicating the involvement of the cerebellum during tasks that require attention and executive control.

2.6 Conclusion

The behavioural effects of cTBS over the posterior-lateral cerebellum on word generation were hemisphere and task specific. For the RH group, the number of category switches was reduced during word generation tasks. This effect was specific to phonemic fluency, and restricted to the early phase of the task.

Figures

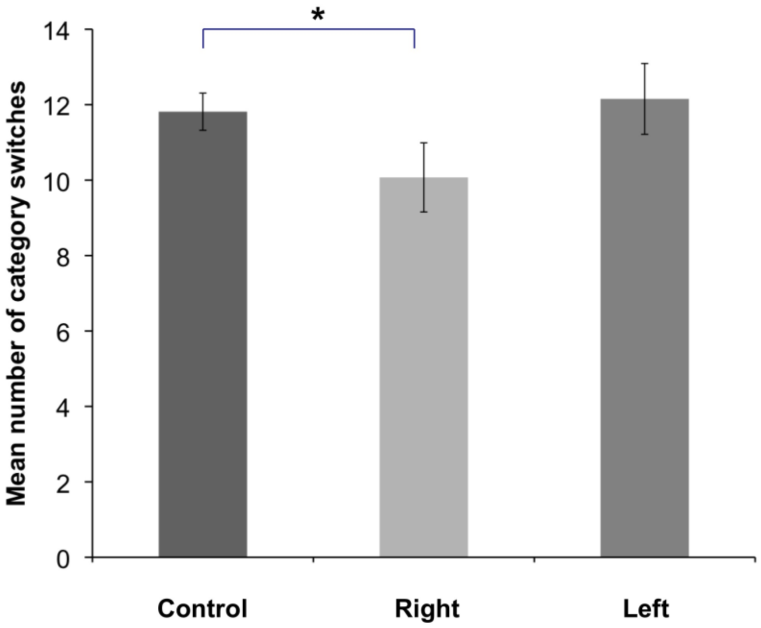

Figure 2.1
Group difference in the mean number of category switches produced post cTBS for the left and right hemisphere groups compared to the control for the first 15 s of the phonemic fluency task. There was a significant difference between the right hemisphere group and the control (p =0.04) and the difference between left and right hemisphere groups approached significance (p=0.06). Error bars indicate standard error of the mean.

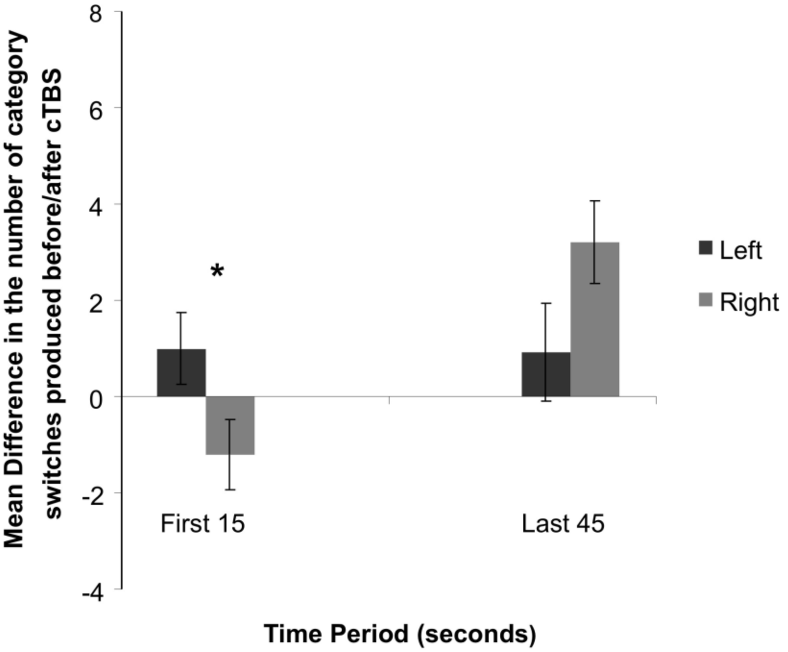

Figure 2.2
Change scores of the mean number of category switches for the phonemic fluency task. Change scores represent the difference between post-cTBS and pre-cTBS condition within each hemisphere. There was a significant difference between the left and right hemisphere groups for first 15 s of the task (p = 0.05). Error bars indicate standard error of the mean.

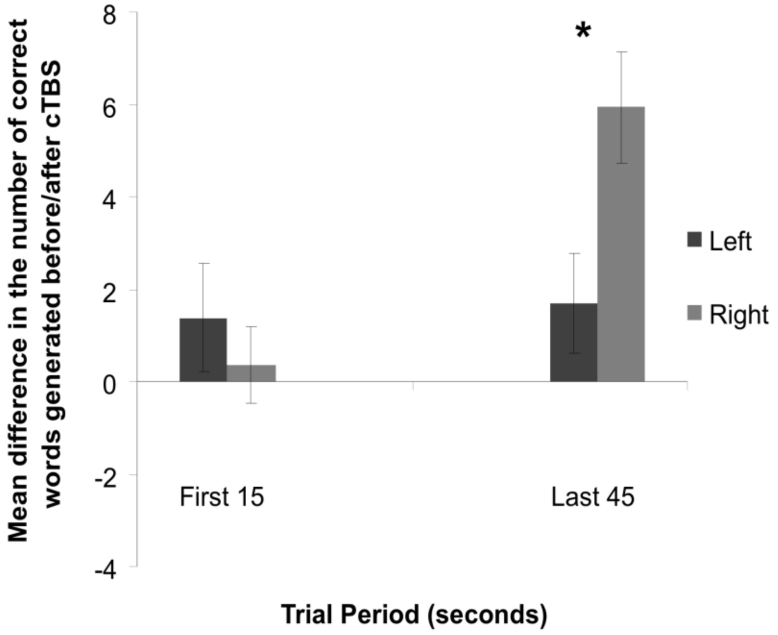

Figure 2.3
Change scores of the mean number of correct words generated for the phonemic fluency task. Change scores represent the difference between post-cTBS and pre-cTBS condition within each hemisphere. There was a significant difference between the left and right hemisphere groups for the last 45 s of the task ($p = 0.05$). Error bars indicate standard error of the mean.

Chapter 3 – Study 2: Isolating a cerebellar contribution to rapid visual attention using transcranial magnetic stimulation

Adapted from:

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3.1 Overview:

Patient and neuroimaging research have provided increasing support for a role of the posterior-lateral cerebellum in cognition, particularly attention. During rapid serial visual presentation, when two targets are presented in close temporal proximity (<500ms), accuracy at detecting the second target (T2) suffers. This phenomenon is known as the Attentional Blink (AB), and in cerebellar lesion patients this effect is exaggerated. Damage to the cerebellum may thus disrupt the use of attentional resources during stimulus processing conditions that are temporally demanding. There are reciprocal connections between the cerebral cortex and the contralateral cerebellum, these connections allow for the possibility that lateralized functions in the cerebral cortex (such as language) remain lateralized in the cerebellum. The purpose of this study was to investigate the temporal characteristics of the cerebellar contribution to the AB and to functionally localize the contribution of the cerebellum to the AB using transcranial magnetic stimulation (TMS). We hypothesized that T2 accuracy would decrease after right cerebellar stimulation when the delay between the first and second target was short (120-400 ms) compared to long (720-960 ms). We used continuous theta burst stimulation (cTBS), a form of TMS, to transiently inhibit a focal population of

neurons in the left and right posterior-lateral cerebellum of healthy participants (n=45). Three groups of participants (n=15) performed the AB before and after either sham, left, or right cerebellar stimulation. The results of this cTBS study support our hypothesis. During the short delay, participants in the right cTBS group showed a greater AB magnitude compared to both the left and sham cTBS groups ($p < 0.05$). No difference in T2 detection was found over long delays. The results provide further support for a cerebellar contribution to an integrated neural network recruited during temporally demanding attention-based tasks.

3.2 Introduction

The attentional blink (AB), coined by Raymond et al. (1992), is a phenomenon that occurs when two targets are presented in rapid succession (200-500 ms) and the accuracy of detecting the second target is impaired at the cost of detecting the first (Broadbent and Broadbent, 1987, Raymond et al., 1992). There are many theoretical accounts for this phenomenon (for review see Dux and Marois, 2009); a common claim is that if two targets that require attention are presented too closely together, attending to the first target (T1) can delay the processing of the second (T2). This leaves T2 susceptible to interference and increases the chance of it going undetected. If, however, the stimulus onset asynchrony (SOA) between T1 and T2 is long, T1 is processed before the presentation of T2, and accuracy is high for both targets. Thus, the deterioration of T2 accuracy when the SOA is short is the result of interference that occurs between stimuli during preliminary conceptual processing. At this stage, stimuli are vulnerable to being overwritten by subsequent stimuli. In order for a target to be encoded, it must enter a second stage of processing so that it can be consolidated into working memory. This stage, however, is capacity-limited, and consequently when T2 is presented in close temporal proximity to T1, it must wait to be encoded until T1 consolidation into working memory is complete (Chun and Potter, 1995; Vogel et al., 1998).

In support of this claim, recent neuroimaging studies have found that the magnitude of the AB is predicted by how much an individual devotes their attentional resources to T1 processing (Shapiro et al., 2006). A number of AB studies have used event-related potentials (ERPs) to target the amplitude and latency of the P300 component, which is characterized by a positive deflection distributed over the scalp with a latency of 300-500 ms. It is proposed that the P300 is related to post-perceptual processing, such as the updating of working memory and the conscious report of a target stimulus (Del Cul et al., 2007; Sergent et al., 2005). Kranczioch and colleagues (2007) found an inverse relationship between the P300 amplitudes time locked to T1 and T2, such that when T1's P300 was bigger, T2's P300 was smaller. This suggests that the more attention allocated to T1, the larger its neural response, and the less attentional resources are available for the processing of T2. Furthermore, an fMRI study of the AB that activated specific brain areas for T1 and T2 stimuli found that the level of activity in T1 visual object-encoding areas predicted detection of T2 (Slagter et al., 2010). These observations suggest that the AB does not necessarily reflect a bottleneck in information processing, but rather a processing strategy for how attentional resources are managed and allocated (Hommel et al., 2006).

Recent brain imaging and clinical studies have implicated a network of lateral frontal and posterior parietal areas involved in the conscious detection of targets in the AB. Functional MRI studies have shown greater activity in this network when T2 is detected compared to when T2 is missed, suggesting a highly distributed network is involved in attentional control (Marois et al., 2004; Kranczioch et al., 2005). The cerebellum, for example, forms a network with the lateral prefrontal cortex (Middleton and Strick, 2001; Schmahmann et al 2004; Allen et al., 2005) and its activation has been associated with the AB (Marcantoni et al., 2003; Slagter et al., 2010; Hesselmann et al., 2011). Clinical lesion studies have also provided support for a cerebellar contribution in the AB (Schweizer et al., 2007). In this study patients with focal cerebellar lesions performed equivalently to controls when detecting T1, and the duration of the AB effect was the same. There was, however, an increased AB magnitude specific to short SOAs, when T2 occurred within 500 ms of T1. This data provides evidence supporting the cerebellum as a critical node in the AB network.

For decades cerebellar patient studies have been documenting impairments that extend beyond the motor domain. Damage to the posterior-lateral cerebellum can result in purely cognitive deficits, such as those seen after lesions to prefrontal areas (Schweizer et al., 2008). Contralateral connections between the prefrontal cortex and the cerebellum allow for the possibility that lateralized functions in the cerebral cortex remain lateralized in the cerebellum. Language, for example, is heavily lateralized to the left cerebral cortex, and lesions to the right cerebellar hemisphere are associated with deficits in word generation tasks (Leggio et al., 2000; Akshoomoff et al., 1992; Appollonio et al., 1993; Silveri et al., 1994; Molinari et al., 1997; Richter et al., 2007; Schweizer et al., 2010) and verbal working memory (Hokkanen et al., 2006). AB paradigms predominantly use letter stimuli; it is therefore possible that the contribution of the cerebellum is right hemisphere specific.

The pattern of connectivity between the cerebellum and the contralateral cerebral cortex can be better understood using transcranial magnetic stimulation (TMS). Repetitive TMS (rTMS) delivers trains of stimuli at different frequencies, and has been shown to disrupt function of cerebellar circuits during cognitive tasks (Oliveri et al., 2007). The strength of rTMS is that it is a technique that can transiently alter the function of the brain region directly targeted, and can effectively change the activity of an associated distributed network (Mottaghy et al., 2002). In a previous study we used continuous theta burst stimulation (cTBS), a form of rTMS, to investigate hemispheric specificity of the cerebellum during word generation tasks. We found that cTBS to the right posterior-lateral cerebellum decreased performance during a word generation task, specifically during the early phase of the task, by diminishing the ability to efficiently organize word output (Arasanz et al., 2012a). Our previous finding is the first evidence that the effects of cTBS on word generation are lateralized to the right cerebellar hemisphere, and supports patient and imaging data for the role of the cerebellum in non-motor behavioural tasks, specifically when time is a constraint.

The purpose of this study is to investigate the temporal characteristics of the cerebellar contribution to the AB and to functionally localize the contribution of the cerebellum to the AB using cTBS. We hypothesize that T2 accuracy will decrease after right cerebellar stimulation, and have no effect after left cerebellar and sham stimulation, when the delay between the first and second target is short (120-480 ms) compared to long (720-960 ms).

3.3 Material and Methods

3.3.1 Participants

Forty-five healthy, right-handed participants (age range 20-35 years, mean = 23.3) with no reported history of neurological problems were recruited for this study. Participants were randomly assigned to one of three groups; Left, Right or Sham stimulation of cTBS to the posterior-lateral cerebellum. There were 15 participants in each group. All participants provided written informed consent prior to testing. Experimental procedures were approved by the Office of Research Ethics at the University of Waterloo.

3.3.2 Experimental task and stimuli

Participants were seated in a sound attenuating booth (Industrial Acoustics, 120A, NY), facing a computer screen at a viewing distance of 30 cm. Using EPrime software (Psychology Software Tools Inc, USA) stimuli were presented in black on a grey background as uppercase letters (9.1 cd/m^2), which subtended a visual angle of

16.3° by 12.5°. Letters were presented in RSVP (120 ms/letter) where each letter appeared for 120 ms with no blank interstimulus interval. Within each trial two targets were embedded among a string of distractors. The first target (T1) was either a white H or S and the second target (T2) was a black X or Y. No letter was ever repeated within the letter stream and distractors were any letter of the alphabet excluding defined target letters. T1 occurred 7 – 15 letters after the central fixation cue. T2 was always one of eight letters that followed T1. T2 occurred with no (lag 1), one (lag 2), two (lag 3), three (lag 4), five (lag 6) or seven (lag 8) distractors after T1. Lags 1-4 were short lags occurring within 480 ms of T1 and lags 6 and 8 were classified as long lags occurring at least 720 ms after T1. A distractor replaced T1 on trials where no T1 was presented. This occurred for approximately one-third of all trials and served as a control condition where no AB effect should be present.

3.3.3 Procedure

Participants were instructed to direct their attention to the center of the screen. Each trial began with the presentation of a small, white dot at center fixation that lasted 180 ms in duration. Letter stimuli succeeded the cue and the first task of the participants was to detect a white target letter presented among black letter distractors. The white target (T1) was either an H or S or did not occur at all. In every trial there was always a black X or Y target (T2) and participants were to also identify which target was presented. Manual responses to T1 and T2 were made after the RSVP of letters and were prompted by separate screens of instructions. For T1, participants were to press 'H' on the keyboard if they saw H, 'S' if they saw S, or 'N' if no T1 occurred. For T2, participants were instructed to press "1" if they saw X and '2' if they saw Y (See Figure 3.1). Importance was placed on accuracy and participants were encouraged to guess on trials when they were unsure. Target accuracy was recorded using Eprime software; no reaction time was recorded or emphasized. Participants performed 5 blocks of 72 trials before and after cTBS stimulation.

3.3.4 Theta burst stimulation procedure

Application of cTBS was performed with a MagPro x100 stimulation unit (Medtronic, Minneapolis, MN, USA) using a figure 8 coil (MCF-B65). For stimulation of the left cerebellar hemisphere the centre of the coil was placed 1 cm below and 3 cm to the left of the inion. For the right hemisphere the coil was placed 1 cm below and 3 cm to the right of the inion (Theoret et al., 2001). Stimulation intensity was set at 80% of active motor threshold (AMT) for the right first dorsal interosseous (FDI) muscle. To determine AMT, the stimulation coil was placed against the upper left surface of the participant's scalp at the optimal position for eliciting motor-evoked potentials (MEPs) from the contralateral FDI muscle. AMT was defined as the lowest stimulator output required to produce a MEP of > 200 μV peak-to-peak for 5 out of 10 trials during a 10% maximum voluntary isometric contraction of the right FDI. For sham stimulation, the TMS unit was set to 6% of maximum output so that participants could hear the stimulus pulses, however the coil was oriented up and outward from the scalp over either the left or right cerebellar target. This was done to simulate stimulation in naïve participants. Stimulation settings consisted of 600 pulses delivered over 40 seconds, applied in a theta burst pattern consisting of three pulses at 50 Hz repeated at 5 Hz. This pattern replicated that used by Huang et al. (2005).

3.3.5 Data analysis

To assess whether all three stimulation groups performed similarly pre cTBS, T2 detection accuracies were submitted to analyses of variance (ANOVAs) in which lag (six positions) was a within-subject factor and group (left, right, sham) was a between-subject variable. ANOVAs were also performed to test T1 detection accuracy across groups as well as to test T2 detection accuracy when it occurred in trials without the presentation of T1 (control condition). For T2 detection accuracy, only trials with a correct response for T1 were used for analysis. The same analyses were performed post cTBS, including paired contrasts to test the specific *a priori* hypothesis that there would be poorer performance in T2 accuracy during short lags after cTBS for the right cerebellar hemisphere group compared to the left cerebellar hemisphere and sham group.

3.4 Results

Analyses of the demographic data for the participants revealed no significant difference between groups on age [F(2,42)=3.09, p=0.06]. Means for the left, right and sham group were 23.5 (sd=3.34), 24.8 (sd=3.82), 21.8 (sd=2.68) respectively.

3.4.1 Pre-stimulation

3.4.1.1 Accuracy

3.4.1.2 T2 Detection (AB condition)

A 3 group x 6 lag ANOVA of T2 accuracy was performed. The test revealed no significant interaction (p=0.99) or main effect of group [F(2,42)=0.56, p=0.57], but a main effect of lag [F(5,39)=23.58, p=0.001] (Figure 3.2A). Thus while all groups responded similarly to the position of T2 with respect to T1, there was no difference amongst the groups at each lag.

3.4.1.3 T1 Detection

All groups were actively engaged in identifying T1 (99% for left, 99% for right, 99% sham). There was no significant difference in T1 accuracy between groups (p=0.64).

3.4.1.4 T2 Alone (control condition)

Accuracy at detecting T2 is virtually unimpaired when it is not preceded by another target. There was no difference between groups in detecting T2 in the absence of T1 (94% for left, 94% for right, 94% sham), (p=0.99).

3.4.2 Post-stimulation

3.4.2.1 Accuracy

3.4.2.2 T2 Detection (AB condition)

A 3 group x 6 lag ANOVA revealed no significant interaction (p=0.91) but a main effect of group [F(2,42)=5.27, p=0.006], and a main effect of lag [F(5,43)=25.44, p=0.001]. To probe at what lags the groups differed; a planned contrast was performed to test our a priori hypothesis, that the right cerebellar group would have a greater AB magnitude during short lags compared to the left and sham group. Group means for the planned contrasts revealed a significant difference between the right and both the left and sham (p=0.004) but no difference between left and sham (p=0.38) during the short lags (Figure 3.2B). There were no differences between the right and both left and sham groups (p=0.15), or between the left and sham groups (p=0.18) for the long lags.

3.4.2.3 T1 Detection

CTBS had no effect on the accuracy of detecting T1. There was no significant difference in T1 accuracy between groups (p=0.67). Group means were 99% for left, 99% for right, 99% for sham.

3.4.2.4 T2 Alone (control condition)

There was no difference in detecting T2 in the absence of T1 between groups (96% for left, 94% for right, 95% sham), (p=0.28).

3.4 Discussion:

The cerebellum is best known for its role in coordinating our movements to perform smooth and efficient actions. However, the cerebellum also modulates behaviour outside the motor domain and is involved in rapid visual attention.

We found that the right posterior-lateral cerebellum is an essential node in AB performance. While there was no difference in performance across groups in the pre-cTBS condition, a main effect of group was found after stimulation. Post-cTBS, there was a larger magnitude of the AB in the short lags for the right cerebellar group compared to left and sham stimulation. This supports our main hypothesis, that the right cerebellum is recruited in the AB network when the temporal constraints of the AB task are high. Also, performance at detecting T1 or T2 alone was not influenced by cTBS, suggesting that the right cerebellum is not involved in the general detection of a target, and is specific to the accurate detection of a target stimulus when it occurs within half a second of another target stimulus. Thus, disrupting the posterior-lateral cerebellum in healthy participants provides evidence that parallels previous cerebellar patient data (Schweizer et al., 2007), and for the first time provides specificity to the contribution of the cerebellum to the AB. The role of the right posterior-lateral cerebellum in the AB task is not surprising, as other cognitive tasks that use language based stimuli are associated with this area (Schweizer et al., 2010; Richter et al., 2007; Desmond et al 1997).

There has been recent evidence that the contralateral connections between the cerebral cortex and cerebellum are functionally segregated (Schmahmann et al., 2009).   Anterograde transneural virus tracers have identified projections from the dorsolateral prefrontal cortex (area 46) to the lateral cerebellar cortex (Crus II) that had no overlap with arm area projections from the primary motor cortex to cerebellar lobules IV-VI (Kelly and Strick, 2003). Thus, the role of the cerebellum is not restricted to motor coordination, and may be involved in modulating function in the motor and cognitive domain alike. We have evidence that supports a role for the cerebellum in the AB, however, understanding its precise role remains elusive. Contributing to this is the fact that there are many interpretations of how the AB phenomenon occurs. Most common is the idea that the AB reflects the inefficiency of managing attentional resources, where if too many attentional resources are allocated to T1, it increases susceptibility to distractor interference and performance on T2 suffers if it is presented before consolidation of T1 can occur (Geisbrecht and Di Lollo, 1998). Based on this account, it is possible that the cerebellum is involved in the efficient allocation or coordination of attentional resources to T1, so that the likelihood of distractor interference is decreased and the opportunity for T2 detection is increased. However, according to Lavie's load theory (2005), if the perceptual load of a target is low, the likelihood of distractors disrupting performance is high. This is because less attentional resources are required to process the target, and more are left open and vulnerable to distractors. In the case of the attentional blink, T1 is always quite salient and easily detected. Therefore, the increased AB magnitude at shorter lags may be a result of too few resources being attended to T1, and too many being susceptible to distractors, decreasing the prospect of T2 detection. The cerebellum may thus be recruited to efficiently modulate the attentional resources dedicated to T1 to readily detect T2. This would also account for why T2 accuracy is decreased after right cerebellar stimulation even at Lag 1, where no distractor occurs between the two targets. Regardless of how the cerebellum is involved in the AB, we speculate that the involvement of the cerebellum is driven by a left frontal-right cerebellar network, recruited during the early lags to rapidly detect both targets. More time is able to elapse between targets at later lags and therefore the demand for readily available attentional resources is decreased. Disruption to this same network decreased performance in a word generation task that required fast and efficient mental flexibility (Arasanz et al., 2012a). Kornysheva and colleagues (2011) reported that rTMS to the ventral premotor cortex increased activity in the cerebellum particularly in subjects that showed the smallest reduction in performance during an auditory-motor timing task. Cerebellar activity served as a predictor of task accuracy, with highest activity in less impaired subjects. Thus, the cerebellum may be recruited when additional or a reorganization of resources is required.

This study also provides further support for the use of cTBS as a neuroimaging tool to explore the causal relationship between the cerebellum and cognitive functioning. While a somatotopic organization of a sensorimotor map within the cerebellum has previously been identified in animals (Snider and Eldred, 1951) and humans (Grodd et al., 2005), it has recently been proposed that this functional topography extends to higher-order brain areas (Stoodley and Schmahmann, 2010; Stoodley et al., 2012). Using cTBS, we targeted the posterior-lateral cerebellar cortex, which topographically corresponds to a cerebellar subregion involved in cognitive functioning. By transiently disrupting this focal area, cTBS can provide a cleaner, more precise functional map of the cerebellum. This technique has an advantage over fMRI, as the BOLD response is simply correlational and does not provide a causal relationship between brain and behaviour. Continuous TBS also has an advantage over lesion studies, as it can provide local specificity; while the location of cerebellar damage can vary patient to patient.

The use of letters as stimuli during the AB task is commonly accepted in the literature, and was specifically chosen for its localization in the right cerebellar hemisphere. However, to support our finding that the cerebellum's contribution to the AB is hemisphere specific, future studies using other stimulus features may be beneficial. A limitation to the design of this study is that when T2 occurred at lag 8, no other stimuli in the letter stream followed T2, leaving it unmasked and easier to detect (Vogel and Luck, 2002). This may have contributed to the high accuracy performance at the long lags, however at lag 8 T2 occurs 960 ms after T1, which is far outside the boundaries of the attentional blink (Raymond et al., 1992). Another potential limitation to this study is the fact that it is strictly behavioural. Future studies are needed that combine TMS and EEG to elucidate how the cerebellum contributes to the AB network by comparing neural markers such as the P300, which is correlated to the AB phenomenon.

3.5 Conclusion

Based on our results, the network recruited for fast and efficient control of attentional resources during the AB involves the cerebellum. The role of the cerebellum in this network is hemisphere specific, localized to the right posterior-lateral cerebellar cortex. The goal of our future studies is to determine how the cerebellum contributes to the AB network.

Figures

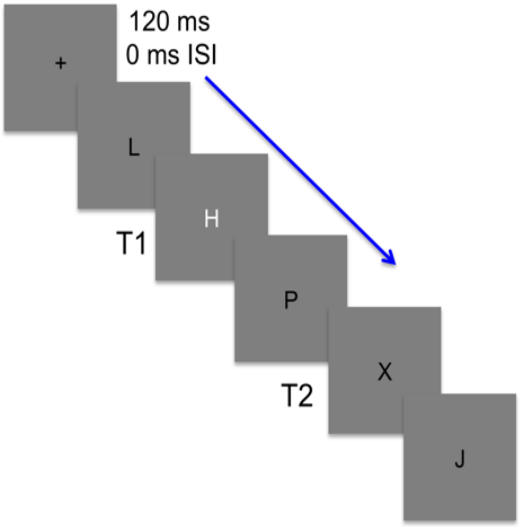

Figure 3.1
An illustration of the stimuli used in the attentional blink task. Stimuli were presented at a rate of 120 ms with no inter-stimulus interval (ISI). Participants were to first detect whether a white target (T1) was embedded among black distractors. T1 was either an H or S and on one-third of the trials was replaced by a black distractor. Participants then needed to detect a second target (T2) that randomly occurred 1-8 lags after T1 and was black like the distractors. T2 was present in every trial and was either an X or Y.

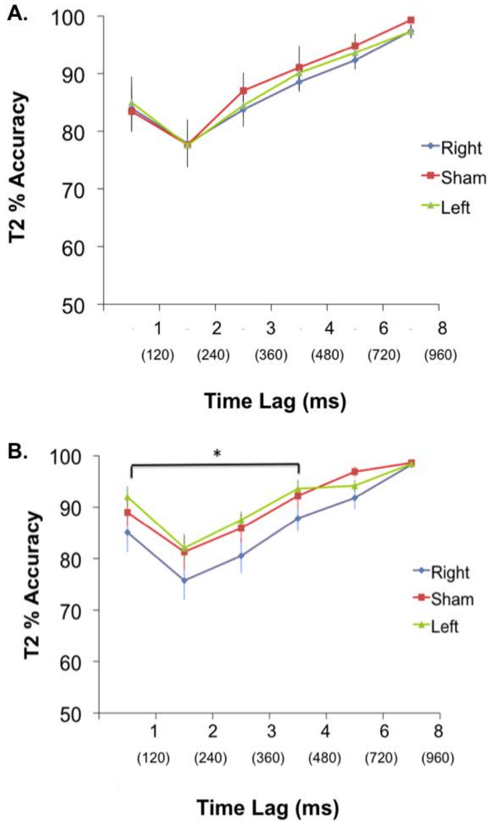

Figure 3.2
A. PRE: Performance (Mean % accuracy +/- S.E.M) in detecting T2 for the Left, Right and Sham group during pre cTBS condition. There was no significant difference in performance between groups at any lag. Time between each lag was 120 ms. B. POST: Performance (Mean % accuracy +/- S.E.M) in detecting T2 for the Left, Right and Sham group during post cTBS condition. Paired contrasts reveal a significant difference between the right group and both the left and sham group for lags 1-4, $*p < 0.05$. Time between each lag was 120 ms, and T2 at lags 1-4 occurred within 480 ms of T1.

Chapter 4 – Study 3: The influence of cognitive load on the recruitment of the fronto-cerebellar system in the Attentional Blink

4.1 Overview

All cognitive operations have a capacity limitation whereby increasing demands results in weakened performance (Kahneman, 1973). The load of a task is dictated by the magnitude and amount of its demands, and can be manipulated perceptually and cognitively. With increased cognitive load there is greater brain activation particularly in brain regions involved in the control and regulation of attention, particularly the dorsal frontal-parietal network (Corbetta and Shulmann, 2002). However, cerebellar activity also increases with increased cognitive load, particularly the posterior-lateral cerebellum (Salmi et al., 2010). In this study we attempted to increase the cognitive load of the Attentional Blink task by increasing the set size of the first target. Set size was increased from two to four. Since the magnitude of the blink in Study 2 was relatively low compared to other studies using similar parameters (Shapiro et al., 1994; Schweizer et al., 2007), it was hypothesized that increasing the set size of the T1 stimuli would increase the magnitude of the blink. A group of 13 participants performed the AB task with a set size of 4 before and after cTBS to the right cerebellum (Right SS4). When comparing this group to the right cerebellar stimulation group in Study 2, who performed the AB task with a T1 set size of 2 (Right SS2), there was no difference in behaviour between the groups. However, a secondary analysis revealed that the Right SS4 group had a greater AB magnitude during early lags compared to the Left and Sham group from Study 2. Thus, while the manipulation of set size to increase cognitive load was not successful, this study's results corroborate what we found in Study 2; disruption of the left frontal-right cerebellum network using cTBS increases the magnitude of the Attentional Blink specifically during early lags.

4.2 Introduction

One's ability to efficiently attend to relevant stimuli and ignore irrelevant information can dictate performance on a novel task. Performance however is also influenced by the particular demands of the task, such that increasing the demands diminishes performance (Kahneman, 1973). Task demands are usually manipulated in two distinct ways: perceptually and cognitively. Increasing perceptual load involves degrading a sensory signal (i.e., reducing the size of a target stimulus or the contrast so that it is barely detectable) to the point where the identification of the target stimulus is being subjected to its sensory 'data limits'. Increasing cognitive load (i.e., working memory) on the other hand increases task difficulty by subjecting target stimuli to attentional 'resource limits' (Lavie 2005). While the load theory posits that perceptual load strictly influences the perceptual processing stage and cognitive load the cognitive control stage, there has been recent evidence that working memory load can also modulate the early selection stage (Bollinger et al., 2009; Gazzaley 2010; Akyürek et al., 2010). Thus cognitive load can influence the consolidation of task relevant stimuli, but can also influence early attentional processing.

Although the outcome of increasing load is the same, the manner in which perceptual and cognitive load effect behaviour is different. Increasing perceptual load reduces distractor interference while cognitive load increases distractor interference (Lavie 2005). According to the load theory of selective attention (Lavie, 2005; Lavie et al., 2004; Lavie and Tsal 1994) there are two stages of information processing; a sensory, 'data limited' perceptual processing stage and an attentional, 'resource limited' cognitive control stage. At the first stage, attentional resources are allocated automatically to task relevant information. If all resources are occupied by relevant information (high perceptual load), capacity for irrelevant information is unavailable, and distractor interference is reduced. If however there are spare resources available (low perceptual load) then task irrelevant information is processed, and distractor interference increases. The cognitive control stage thus is responsible for inhibiting the processed irrelevant information. If however this stage is taxed by increased load on cognitive control processes, then distractors cannot be inhibited, and interference increases.

The effects of perceptual and cognitive load have been investigated in the attentional blink paradigm (Marois et al., 2000; Jolicoeur et al., 2006; Akyürek et al., 2007; Elliot and Giesbrecht, 2010; Visser 2010). While the increase in perceptual load has been found to increase the magnitude of the attentional blink (Marois et al., 2000; Shore et al. 2001, Jonston et al., 2007), there has also been evidence of it decreasing the magnitude of the attentional blink (Elliot and Giesbrecht, 2010). In Elliot and Giesbrecht's (2010) study, perceptual load of the targets was manipulated using flankers that were either congruent (low load) or incongruent (high load).

Under conditions of high perceptual load, the magnitude of the AB decreased with respect to the low perceptual conditions. Interestingly, increasing working memory load during the AB has solely been found to increase the AB magnitude (Akyürek et al., 2007; Akyürek et al., 2010).

Based on the results of Completed Study 2, it was decided that an increased attentional blink magnitude at baseline was necessary to tease out the effect of cTBS on the AB. Thus, to increase the cognitive load of the task without manipulating too many different parameters, we chose to increase the set size of T1 from 2 to 4. Increasing the set size has been shown to increase AB magnitude by increasing the difficulty of the task (Chun and Potter 1995; Shore 2001). Manipulations of cognitive load have been found to increase PFC activity while increasing perceptual load found no such relationship (Han and Marois, 2010). Increasing working memory load has also increased cerebellar activation (Salmi 2010). We hypothesized that increasing the set size of T1 will increase the difficulty of T1 and increase AB magnitude during early lags. This load manipulation will create a more robust effect of cTBS to the right cerebellum during the attentional blink task.

4.3 Methods

4.3.1 Subjects

Fifty-eight healthy, right-handed participants (age range 18-35 years, mean = 21.6), with no reported history of neurological problems were recruited for this study. Participants were assigned to one of four groups; Left, Sham, Right SS2, Right

SS4 stimulation of cTBS to the posterior-lateral cerebellum. Participants in the Left, Sham, and Right SS2 group, and Right SS4 had 13 participants. All participants provided written informed consent prior to testing. Experimental procedures were approved by the Office of Research Ethics at the University of Waterloo.

4.3.2 Behavioural task

For the Left, Sham and Right SS2 groups, task parameters were the same as in Study 2. For the Right SS4 group, each trial began with the presentation of a small, white dot at center fixation that lasts 180 ms in duration. Letter stimuli follow the cue and the first task of the participants was to detect a white letter presented among black letter distractors. The white target (T1) was a B, F, S, or H or was sometimes not present. In every trial there was always a black X or Y target (T2) and participants were to indicate the identity of T2. Manual responses to T1 and T2 were made after the RSVP of letters and were prompted by separate screens of instructions. For T1, participants were instructed to identify the white letter by pressing the corresponding keyboard tile, or to press ‘N’ if no T1 occurred. For T2, participants were instructed to press “1” if they saw ‘X’ and ‘2’ if they saw ‘Y’. No reaction time was recorded and participants were encouraged to guess on trials for which they were unsure.

4.3.3 Stimuli

Target and distractor stimuli were presented at central fixation of a grey field where each letter appeared for 120 ms with no blank interstimulus interval. All distractors were black capital letters (excluding B, F, H, S). The first target (T1) was a white capital B, F, H, or S, and occurred 7 – 12 letters after a central fixation cue. Eight letters always followed T1. A distractor replaced T1 on trials where no T1 was presented. The second target was a black capital X or Y and occurred with either no (lag 1), one (lag 2), two (lag 3), three (lag 4), five (lag 6) or seven (lag 8) distractors after T1.

4.3.4 Experimental design

A pre/post design was used with cTBS and sham stimulation delivered over the left or right posterior-lateral cerebellum within the separate experimental session. Each subject participated in 360 trials after 20 trials of training with verbal feedback. Trials were broken down into five blocks of 72 trials each.

4.3.5 Theta burst stimulation parameters

Application of cTBS was performed with a MagPro x100 stimulation unit (Medtronic, Minneapolis, MN, USA) using a figure 8 coil (MCF-B65). The centre of the coil was placed 1 cm below and 3 cm to the right of the inion (Theoret et al., 2001). Stimulation intensity was set at 80% of active motor threshold (AMT) for the right first dorsal interosseous (FDI) muscle. To determine AMT, the stimulation coil was placed against the upper left surface of the participant's scalp at the optimal position for eliciting motor-evoked potentials (MEPs) from the contralateral FDI muscle. AMT was defined as the lowest stimulator output required to produce a MEP of > 200 μV peak-to-peak for 5 out of 10 trials during a 10% maximum voluntary isometric contraction of the right FDI. Stimulation settings consisted of 600 pulses delivered over 40 seconds, applied in a theta burst pattern consisting of three pulses at 50 Hz repeated at 5 Hz. This pattern replicated that used by Huang et al. (2005).

4.3.6 Data Analysis

To assess whether increasing the set size of T1 would increase AB magnitude, T2 accuracy for the Right SS4 group during the pre cTBS condition was compared to participant performance of the Right SS2 group. T2 detection accuracies were submitted to analyses of variance (ANOVAs) in which lag (six positions) was a within-subject factor and group (SS4, SS2) was a between-subject variable. ANOVAs were also performed to test T1 detection accuracy across Right SS4 and Right SS2 groups as well. For T2 detection accuracy, only trials with a correct response for T1 were used for analysis. The same analyses were performed post cTBS; however, with the addition of a secondary analysis that was performed to test the hypothesis that transiently suppressing the right cerebellum using cTBS would disrupt T2 Accuracy during short lags. A 3 group x 6 lag ANOVA was performed using the Right SS4 group and Left and Sham group from Study 2. Next planned contrasts were performed to compare performance of the Right SS4 group for T2 accuracy during short and long lags with the Left and Sham group.

4.4 Results

4.4.1 Pre-stimulation

4.4.1.1 Accuracy

4.4.1.2 T2 Detection (AB condition)

A 2 group x 6 lag ANOVA of T2 accuracy was performed. The test revealed main effect of group [F(1,27)=0.23, p=0.63], but a main effect of lag [F(5,22)=18.93, p=0.001], and no significant interaction (p=0.74). Thus while all groups responded similarly to the position of T2 with respect to T1, there was no difference amongst the groups at each lag.

4.4.1.3 T1 Detection

Both groups were actively engaged in identifying T1 (99% for Right SS4, 99% for Right SS2). There was no significant difference in T1 accuracy between groups (p=0.67).

4.4.2 Post-stimulation

4.4.2.1 Accuracy

4.4.2.2 T2 Detection (AB condition)

A 2 group x 6 lag ANOVA revealed main effect of group [F(1,27)=0.47, p=0.83], but a main effect of lag [F(5,22)=18.36, p=0.001], and no significant interaction (p=0.97), (Figure 4.1). Although no significant difference between the Right SS2 and Right SS4 group revealed no effect of increasing T1 set size, it did not address whether stimulation was affecting performance during the AB task. As a secondary analysis, an ANOVA and a planned contrast between the Right SS4 group and the Left and Sham group from Study 2 was performed to determine if the groups differed post cTBS and specifically to see if Right SS4 group had a smaller AB magnitude after cTBS at early lags. A 3 group x 6 lag ANOVA revealed a significant effect of group [F(2,40) =4.31, p= 0.01] and lag [F(5,437) =27.78, p= 0.001], but no interaction (p=0.560). These results replicate the findings from Study 2. Group means for the planned contrasts revealed a significant difference between the Right SS4 and both the Left and Sham (p=0.004) but no difference between Left and Sham (p=0.38) during the short lags (Figure 4.2). There were also no differences between the Right SS4 and both Left and Sham groups (p=0.43), or between the Left and Sham groups (p=0.18) for the long lags.

4.4.2.3 T1 Detection

CTBS had no effect on the accuracy of detecting T1. There was no significant difference in T1 accuracy between groups (p=0.67). Group means were 99% for left, 99% for right, 99% for sham.

4.5 Discussion

The purpose of this study was to manipulate the attentional load of the AB task by increasing the number of letters T1 may appear as. The larger the set size of T1, the larger the room for error, as more letters crowd working memory capacity. When working memory is loaded, it reduces the ability to actively maintain the stimulus-processing priorities of the main task (Lavie 2005). Increasing set size of a target has been shown to amplify the AB magnitude by increasing the difficulty of the task (Chun and Potter 1995; Shore 2001). Unfortunately, our manipulation of T1 set size from two letters to four had no effect on the size of the AB before or after cTBS to the right posterior-lateral cerebellum. While for one of the early lags (Lag 2) T2 accuracy for the SS4 group appears lower then the SS2 group, the difference (about seven percent) was not significant. This may be due to the fact that increasing the set size to only four letters was not enough of a manipulation, as the average person can easily hold four items in working memory (Vogel et al., 2001). Also, after every trial participants were reminded of what the four potential letters T1 would be, making the task of identifying the target easier as it depended on recognition as oppose to recall. Perhaps increasing the set size of T1 to four letters that would change trial-to-trial and not prompting the participant with the letters after every trial would be a better manipulation and increase the working memory load of the AB task. This however requires further investigation.

While unable to answer the thesis objective of determining if load influences the recruitment of the fronto-cerebellar system during the AB, this study served an even greater purpose. Because the level of difficulty of the task was no different than that of Study 2, the performance of T2 Accuracy was comparable across studies. When comparing the accuracy of detecting T2 after cTBS, the Right SS4 group performed significantly worse then the Left and Sham cTBS groups from Study 2. Thus, the results from Study 2 are reproducible, which makes the validity of Study 2 even more reliable.

4.6 Conclusion

Manipulating the set size of T1 had no effect on AB performance. However, between group differences at early lags still hold after posterior-lateral cerebellar cTBS. This reaffirms the findings from Study 2 that left frontal-right cerebellar connections are part of an integrated network involved in the AB.

Figures

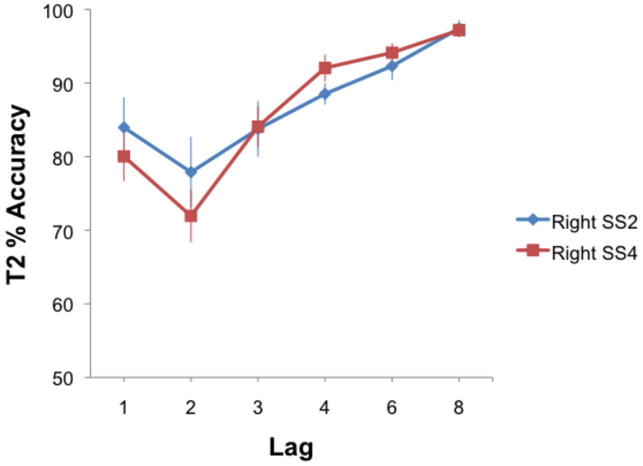

Figure 4.1
Performance (Mean % accuracy +/- S.E.M) in detecting T2 for the Right SS2 and Right SS4 group during pre cTBS condition. There was no significant difference in performance between groups at any lag. Time between each lag was 120 ms.

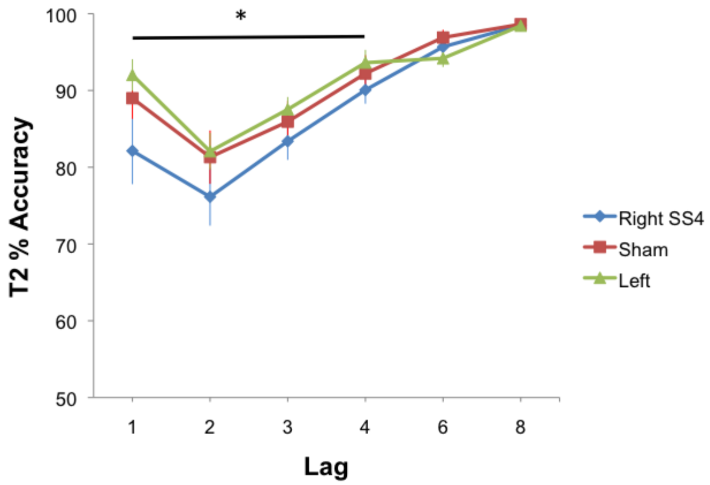

Figure 4.2
Performance (Mean % accuracy +/- S.E.M) in detecting T2 for the Right SS4, Left, and Sham group during post cTBS condition. Paired contrasts reveal a significant difference between the right group and both the left and sham group for lags 1-4, *p < 0.05. Time between each lag was 120 ms, and T2 at lags 1-4 occurred within 480 ms of T1.

Chapter 5 - Study 4: Probing the contribution of the fronto-cerebellar system to rapid visual attention: a TMS and EEG study

5.1 Overview

During rapid serial visual presentation, when two targets are presented in close temporal proximity (<500ms), accuracy at detecting the second target (T2) decreases. This phenomenon is known as the Attentional Blink (AB) and its magnitude is exaggerated in patients with focal lesions to the cerebellum, a structure classically involved in motor control. Reciprocal connections between the prefrontal cortex and the contralateral cerebellum may be accounting for this attentional control deficit as disrupting this system using continuous theta burst stimulation (cTBS), a form of repetitive transcranial magnetic stimulation associated with transient suppression of the targeted region, can impair performance in young, healthy adults. In a previous study we found a lateralized AB deficit specific to right cerebellar stimulation that only occurred when the delay between two targets was less than 500 ms. The purpose of the current study was to investigate the left frontal-right cerebellar contribution to the AB. Electroencephalography (EEG) was used following cTBS to record the P300 component of event-related potentials time locked to the first target (T1) and T2. The P300 is characterized by a positive deflection distributed over the scalp with a latency of 300-500 ms and is related to post-perceptual processing. It was hypothesized that cTBS to the right cerebellum would disrupt the fronto-cerebellar network and increase the latency of the P300 related to T2. An increase in latency would implicate a delay in processing T1 and readily reengaging attentional

resources to process the next target, T2. In the AB paradigm chosen, stimuli were letters presented at 10 Hz and targets were either separated by a short lag (200-300 ms), or a long lag (800 ms). Sixteen healthy subjects completed the AB task in two separate experimental sessions, which differed only in the type of stimulation delivered (cTBS to the right cerebellum or sham cTBS). Ordering of stimulation sessions were counterbalanced and a 64-channel EEG cap was used to record neural activity. Over central-parietal electrode sites there was an increased latency of the P300 peak that was found during the cTBS condition and was specific to the early lags. This suggests that the cerebellum may be recruited to efficiently modulate the attentional resources dedicated to T1 to readily detect T2, when the time required to switch between targets is a constraint. Our results suggest that the AB is driven by a left frontal-right cerebellar network recruited to rapidly detect both targets.

5.2. Introduction

Attentional limitations in information processing are evident when two target stimuli must be detected in rapid sequence. Accuracy at identifying the first target (T1) is unaffected but decreased for the second (T2) when targets are embedded in a stream of distractors and the inter-target lag is less than 500 ms (Broadbent and Broadbent 1987; Raymond et al., 1992). This phenomenon is known as the attentional blink (AB) and its effects are exacerbated in different patient populations, such as frontal, temporal, parietal and cerebellar lesion patients, and patients with schizophrenia (Husain et al. 1997; Richer and Lapage, 1996; Schweizer et al., 2007; Mathis et al., 2012). While most of these patient populations have an AB that is both larger in length and magnitude, the deficit in cerebellar patients is unique as they have a blink that is larger in magnitude only when targets occur in close succession; when the stimulus onset asynchrony (SOA) is larger than 500 ms, their performance is no different than aged-matched controls (Schweizer et al., 2007). In our lab we were able to support this patient data using continuous theta burst stimulation (cTBS), a form of transcranial magnetic stimulation that is used to temporarily suppress neural activity of a focal population of neurons. We found that when using letter stimuli, accuracy at detecting T2 during short SOA (under 500 ms) was significantly lower after right cerebellar stimulation compared to left cerebellar and sham stimulation, suggesting that the AB deficit is due to a specific left frontal-right cerebellar network disruption (Arasanz et al, 2012b). However, the mechanism and neural events related to this impairment have yet to be unveiled.

Many models attempt to explain the AB and the majority focus on cognitive capacity limitations, such that a bottleneck occurs during the late stage of processing in which only one item can be processed at a time (Chun and Potter, 1995; Jolicoeur and Dell'Acqua, 2000; Shapiro et al., 1994). Other models assume that the blink is the result of cognitive control limitations, where during the encoding of one target the attentional resources required to filter and select another relevant target are not readily available (Di Lollo et al., 2005). Regardless of the current theories, it appears that the AB is a consequence of the way in which selective information is temporally processed. However, the AB is not a universal phenomenon (Martens et al., 2006), some individuals have no blink at all, suggesting that speed and efficiency of information processing is crucial to task performance.

While T2 accuracy is the standard measure of the AB, electrophysiological measures such as event related potentials (ERPs) could provide temporal detail regarding the efficiency of detecting T2. The benefit to using ERPs is that they reveal the time course of information processing in the brain with high resolution. When ERPs are time locked to a visual stimulus, a positive deflection occurs around 300 ms (P300) after its presentation. The latency of this peak represents the timing of a cognitive process related to stimulus classification, such as detecting a target among distractors, and can be regarded as a measure for processing speed (Walhovd et al, 2005). The amplitude of the P300 is influenced by the probability of a target (Donchin, 1981), and therefore cannot occur before stimulus classification. The P300 component appears to reflect the updating of a stimulus into working memory (Donchin, 1981) and has been employed as an index of working memory consolidation and resource allocation within the AB (Luck, 1998; Kranczioch et al.; 2007, Craston et al., 2009). In a seminal study by Vogel and colleagues (1998), the P300 time-locked to T2 was abolished during the AB period while perceptual components (P1 and N1) of T2 remained unaffected. This only occurred when T1 and T2 required a response. For trials where T2 was the only target to be reported, T2 accuracy was unimpaired and the P300 wave was consistent across lags. This suggests that suppression of the P300 during the AB is directly linked to processing of a preceding target. In another experiment within the same study, the authors observed that even though T2 accuracy suffers during the AB period, the target has been fully identified. The N400, a late ERP component that is sensitive to semantic mismatch, was used to see if its amplitude when time-locked to T2 would be suppressed during the AB period. T2 was a target word embedded among strings of digit or letter distractors and immediately before each rapid serial visual presentation (RSVP) stream, a context word was presented that either matched or mismatched T2. The authors found that during the attentional blink period the N400 was unaffected on mismatch trials even if T2 was not correctly reported. Thus, while T1 is being processed, T2 is perceived normally and even interpreted at a semantic level (Vogel et al., 1998), but not properly stored into working memory (Chun and Potter, 1995; Shapiro et al., 1994).

The P300, however, is not the only component that is suppressed during the AB. Sergent and colleagues (2005) found a divergence between detected and non-detected T2s at around 270 ms after T2 presentation during their AB paradigm; with detected T2s evoking larger left lateralized posterior negativity, termed the N2, than non-detected T2s. Kranczioch et al. (2007) also compared detected versus non-detected T2 trials by subtracting them from trials where no T2 was presented. They found a similar negative deflection over left parietal-occipital regions with the largest amplitude for detected T2 trials between 260-300 ms. They also reported larger P300 waves time locked to T1 in non-detected T2 trials compared to detected. Thus, the attenuation of N2 for T2 of non-detected trials may be the result of the large P300 evoked by T1 (Sergent et al., 2005). Based on these findings, it is reasonable to hypothesize that the neural process underlying the generation of the P300 to T1 cause the attentional blink (Sergent et al., 2005). The amount of attentional resources available to encode targets in a RSVP is limited, and when allocated to T1, less is available for processing T2. This delays the encoding of T2, and leaves it susceptible to distractor interference (Geisbretch and Di Lollo, 1998). Findings from Vogel and Luck (2002) support this hypothesis, as they found a delayed (instead of abolished) P300 elicited by T2 when T2 was unmasked (not followed by distractors). The increased latency of the P300 when T2 is unmasked reflects the delay in the working memory encoding of T2. Therefore, the suppressed T2-P300 during the AB is the result of consolidation being postponed and T2 inevitably being overwritten by subsequent stimuli (Vogel and Luck, 2002).

The P300 latency in cerebellar degeneration patients has been found to be prolonged during visual discrimination tasks compared to age-matched controls suggesting that a slowing of cognitive information processing may be due to a fronto-cerebellar network disruption (Tachibana et al., 1999; Paulus et al., 2004; Hirata et al., 2006). While it is recently understood that the left frontal-right cerebellar network has a role in the AB (Arasanz et al., 2012b), how this network influences the amplitude and latency of the P300 elicited by T1 and T2 has not yet been studied. We hypothesize that the cerebellum during the AB may play a role in efficiently disengaging from T1 processing so that T2 can be properly encoded into working memory. Specifically, we hypothesize that transient inhibition to the right cerebellum will increase the latency of the P300 evoked by T2 when it occurs at short lags.

5.3 Methods

5.3.1 Subjects

16 healthy, right-handed participants were recruited from the university community (mean age +/- SD = 22.7 +/- 2.7). All participants provided informed written consent and were paid a nominal fee for their participation. The University of Waterloo Office of Research Ethics approved experimental procedures.

5.3.2 Behavioural task

Participants were seated in a sound attenuating booth (Industrial Acoustics, 120A, NY), facing a computer screen at a viewing distance of 30 cm. Participants were instructed to direct their attention to the center of the screen. Each trial began with the presentation of a small, white dot at center fixation that lasted 180 ms in duration. Letter stimuli succeeded the cue and the first task of the participants was to detect a white target letter presented among black letter distractors. The white target (T1) was either an H or S. In every trial there was always a black X or Y target (T2) and participants were to also identify which target was presented. Manual responses to T1 and T2 were made after the RSVP of letters and were prompted by separate screens of instructions. For T1, participants were to press the corresponding letter ('H' if they saw 'H', 'S' if they saw 'S'). For T2, participants were instructed to press '1' if they saw 'X' and '2' if they saw 'Y'. No reaction time was recorded or stressed and participants were forced to guess on trials when they were unsure. Participants were given 20 trials as training and performed 5 blocks of 80 trials during testing.

5.3.3 Stimuli

Stimuli were uppercase letters presented in black on a grey background (9.1 cd/m^2), which subtended a visual angle of 16.3° by 12.5°. Letters were presented in RSVP (100 ms/letter) where each letter appeared for 100 ms with no blank interstimulus interval. Within each trial two targets were embedded among a string of distractors. The first target (T1) was either a white H or S and the second target (T2) was a black X or Y. No letter was ever repeated within the letter stream and distractors were any letter of the alphabet excluding defined target letters. T1 occurred 7 – 15 letters after the central fixation cue. T2 was always one of ten letters that followed T1. T2 occurred one (lag 2), two (lag 3), or seven (lag 8) distractors after T1.

5.3.4 Experimental design

All participants entered a single-blind cross-over design where they performed the attentional blink task twice, each session a week apart. Immediately prior to performing the task participants received either cTBS to the right cerebellum or Sham stimulation (same location, stimulation coil at 90 degree angle away from the scalp). The order of stimulation was counterbalanced across participants. ERPs were recorded during both conditions (cTBS, Sham).

5.3.5 Stimulation parameters

5.3.5.1 cTBS

Application of cTBS was performed with a MagPro x100 stimulation unit (Medtronic, Minneapolis, MN, USA) using a figure 8 coil (MCF-B65). For stimulation of the left cerebellar hemisphere the centre of the coil was placed 1 cm below and 3 cm to the left of the inion. For the right hemisphere the coil was placed 1 cm below and 3 cm to the right of the inion (Theoret et al., 2001). Stimulation intensity was set at 80% of active motor threshold (AMT) for the right first dorsal interosseous (FDI) muscle. To determine AMT, the stimulation coil was placed against the upper left surface of the participant's scalp at the optimal position for eliciting motor-evoked potentials (MEPs) from the contralateral FDI muscle. AMT was defined as the lowest stimulator output required to produce a MEP of > 200 μV peak-to-peak for 5 out of 10 trials during a 10% maximum voluntary isometric contraction of the right FDI. For sham stimulation, the TMS unit was set to 6% of maximum output so that participants could hear the stimulus pulses, however the coil was oriented up and outward from the scalp over the right cerebellar target. This was done to simulate stimulation in naïve participants. Participants were told that they would be receiving two different types of stimulation, but no other detail was given. Stimulation settings consisted of 600 pulses delivered over 40 seconds, applied in a theta burst pattern consisting of three pulses at 50 Hz repeated at 5 Hz. This pattern replicated that used by Huang et al. (2005).

5.3.5.2 EEG recordings

EEG data was recorded from 64 electrode sites (64 channel cap, Neuroscan, Compumedics USA) using the international 10-20 system for electrode placement. Electrodes were referenced to the left and right mastoids (impedance < 5 kohms). EEG data was sampled at 500 Hz (Neuroscan, Compumedics USA), amplified (40

000x) and analog filtered (DC-200 Hz). Eye movement artifacts were removed by excluding components consistent with topographies for blinks and eye movements. For each trial, independent of performance, 1100 ms epochs were extracted from the data and time-locked to T1 and T2 of the RSVP. Each epoch began 200 ms pre-target onset; the 200 ms was used to baseline-correct the epochs. Epochs were then filtered (1-30 Hz) and removed if they displayed excessive peak-to-peak deflections (+/- 50 μV) or other artifacts. All trials within a given session were averaged to T1 onset (for T1 evoked ERPs), and averaged to T2 onset (separately for T2 evoked ERPs at Lag 2, 3, and 8). This enabled analysis of poststimulus T1-locked and T2-locked amplitude and latency effects in the centroparietal regions where the P3b typically shows its maximum amplitude (electrodes PZ, CPZ, CZ).

5.3.6 Data analysis

5.3.6.1 Behavioural data

Participant's responses were scored as correct if they correctly identified the target's identity. T2 accuracy always depended on T1 accuracy, so that trials were only analyzed on the condition that T1 was correctly reported. Data was analyzed offline and T2 accuracy was averaged for each lag. A two-way analysis of variance (ANOVA) was performed with Condition (cTBS, sham) and Lag (2,3,8) as within-subject factors.

5.3.6.2 Electrophysiological data

Neural dependent measures were peak amplitude and latencies of target-locked P300s. The P300 was identified as the largest positive peak between 300-

600 ms (Tachibana et al., 1995). Peak amplitude and latency values of the P300 were analyzed at electrodes of interest based on maximal amplitude of distribution (PZ, CPZ, CZ) for T1, T2_lag3, and T2_lag8. ANOVAs were performed for each target (T1 – one-way ANOVA with Stimulus Condition as a within-subject factor, T2 – two-way ANOVA for Stimulus Condition x Lag). Peak amplitude and latency values of the P300 were not entered into the ANOVA based on the difficulty of visually detecting the peak of the P300 was as this peak was often not distinct from T1 P300 (since the two targets were only presented within 200 ms of each other). Preplanned contrasts were performed to compare the effect of Stimulus Condition on Lag. This was done to test our *a priori* hypothesis, that cTBS would increase the latency of T2 P300 at early lags (Lag3) and not at late lags (Lag 8).

5.4 Results

5.4.1 Behavioural data

5.4.1.1 T1 Accuracy

All participants had no trouble detecting T1. In the Sham condition, participants performed at 99% accuracy and in the cTBS condition, 98.9%. There was no significant difference between Stimulus Conditions (p=0.62).

5.4.1.2 T2 Accuracy

ANOVA of T2 accuracy was performed with Lag and Stimulus Condition as within-subject factors. This analysis revealed no effect of Lag (F(2,14) 1.65, p=0.228), Condition (F(1,15) 0.01, p=0.93), or interaction (F(1,15) 0.07, p=0.93).

5.4.2 Electrophysiological data

5.4.2.1 T1-P300

A one-way ANOVA for Amplitude revealed no effect of Stimulus Condition on the T1-P300 at all three electrode sites: PZ (F(1,15) 0.706, p=0.414, CPZ (F(1,15) 3.06, p=0.101), CZ (F(1,15) 0.442, p=0.516). No effect of Stimulus Condition was found for Latency at any of the electrode sites (p>0.05).

5.4.2.2 T2-P300

A two-way ANOVA for PZ Amplitude revealed an effect of Lag (F(2,14) 4.46, p=0.032), but no effect of Condition (F(1,15) 0.309, p=0.586) and no interaction (p=0.453). ANOVAs for the Amplitude at CPZ and CZ also revealed an effect of Lag (p=0.001) and no effect of Stimulus Condition or significant interaction.

The same analysis for Latency however revealed a main effect of both Lag (F(1,15) 21.73, p=0.001), Stimulus Condition (F(1,15) 5.74, p=0.023), and an interaction that trended toward significant (p=0.088). The results were consistent at the other two electrode sites for Lag and Stimulus Condition, and the interaction between these factors was significant at CPZ. CPZ: Lag (F(1,15) 24.77, p=0.001), Stimulus Condition (F(1,15) 4.67, p=0.038), interaction (p=0.046); CZ: Lag (F(1,15) 21.66, p=0.001), Stimulus Condition (F(1,15) 5.85, p=0.021), interaction (p=0.12). For the three electrode sites, pre-planned comparisons revealed a statistical difference between cTBS and Sham condition for the Latency of the T2 P300 at Lag 3 ($p < 0.05$) but not for Lag 8 ($p > 0.05$). This suggests that cTBS increased the Latency of the T2 P300 when T2 occurred within the AB period and not outside, when T2 Accuracy is uninfluenced by T1. (Figure 2).

5.5 Discussion

Cerebellar patient (Schweizer et al., 2007) and neuroimaging data (Marcantoni et al., 2003; Slagter et al., 2010; Hesselmann et al., 2011) have provided a basis for the role of the cerebellum in the AB. In a recent study (Arasanz et al., 2012b) we found that the AB magnitude was highest after cTBS to the right cerebellum compared to left cerebellar and sham stimulation. The focus of this study was to extend our previous findings and understand how the cerebellum contributes to the AB phenomenon using ERPs time-locked to either T1, or T2 at early and late Lags. We found that cTBS to the right cerebellum increased the latency of the P300 time locked to T2 when it occurred at early Lags. When T2 fell outside of the AB period, cTBS had no effect on P300 latency. The results of this study are consistent with our previous finding that effects of right cerebellar stimulation are specific to early lags, when time to disengage from one target and reengage to the next is a constraint.

In our current study, T2 accuracy was not affected by right cerebellar stimulation. There are many variables that may account for this finding, the primary being a lack of power. In Arasanz et al. (2012b) there were 15 participants in each stimulation group (Right cTBS, Left cTBS and Sham), totaling 45 participants. This current study was designed so that all participants (n=16) underwent both Sham and Right cerebellar cTBS stimulation, and the ordering of each was counterbalanced. Behavioural data however was collapsed independent of stimulation order and as a result only half of the 16 participants performing the AB task under the cTBS condition were naïve to the task and the repeated session design likely subdued the effect of the cTBS intervention. The AB task also differed with respect to how often both targets were presented. In our previous study (Arasanz et al., 2012b) one-third of the trials had no T1, and participants had to first detect the presence of T1 and then identify it (if it occurred). The unpredictability of the presence of T1 may require additional resources and this may have had a down stream effect on T2 accuracy, as the mean accuracy of Lag 2 and Lag3 in our previous work was lower than in the present.

According to many theories the AB is caused by allocating too many resources to T1 and as a result not having enough to attend to T2 (For Review, Dux and Marios, 2009). On missed trials, the T1 P300 is bigger compared to detected trials (Kranczioch et al., 2007). In our AB paradigm, since T2 accuracy was quite high, we could not compare the effects of missed versus detected trials. There were not enough missed trials to average together to acquire a reliable signal (~ 20 trials per subject) creating a low signal to noise ratio. If however cTBS to the right cerebellum were to influence T1 processing, this would occur for missed and detected trials alike. We did not find a significant difference in either Amplitude or Latency of the T1 P300 between right cerebellar cTBS and sham cTBS. This suggests that the contribution of the cerebellum to the AB is not specific to the magnitude or speed of processing to T1, but the efficiency of disengaging from one target, to reengage to the next.

The findings of this study related to T2 processing are very clear-cut. Amplitude for the T2 P300 was affected by lag but not by condition. Smaller peaks at the early lag were expected as T2 P300 is reportedly suppressed during the AB

(Vogel et al. 1998; Vogel and Luck, 2002; Sessa et al., 2006; Kranczioch et al., 2007). For the latency of the T2 P300 it was hypothesized that cTBS would affect the latency of the T2 P300 during the AB, but not at longer lags. As expected, latency of the T2 P300 was influenced by Lag and Condition. We found that cTBS to the right cerebellum increased the latency of the T2 P300, but only when T2 occurred early and within the AB period (Lag 3). This is the first report of this finding and it sheds light on the role of the cerebellum during the AB, and on the general cause of the AB.

While many accounts strictly focus on the influence of distractors during the AB, our evidence supports a newer account of the AB, one that bases the AB primarily on the inability to reengage attentional resources to process the second target. Nieuwenstein and colleagues (2006) found that an AB can occur with just a blank screen in between the two targets, dismissing the capacity limit account that suggests that distractors are partly accountable for causing the AB. But with or without distractors, there still is an AB (Nieuwenstien et al., 2009). A computational model proposed by Bowman and Wyble (2007) best explain the AB. The stimulus type – serial token (STST) model proposes that feed forward models are used to recognize rapid visual stimuli to match corresponding visual representations, but when stimuli are brief and masked by one another they are easily forgotten. A relevant stimuli however (i.e. T1) activates an attentional enhancement mechanism – ''the blaster" – so that relevant stimuli can be selected and stored into working memory – "tokenization". During this time, other stimuli that may capture attention are inhibited. Once an item is encoded into working memory, the blaster is inhibited so that attention can be disengaged. It is possible that the ability to restart the blaster is what may be causing the AB. The blaster is inhibited once a target is consolidated, and reactivating it may take time. Thus the role of the cerebellum may be to efficiently reactivate this blaster. Even though we did not see this effect translate into behaviour, ERPs are a much more sensitive measure than behaviour, and a study that uses ERPs in patients during the AB may confirm our hypothesis.

5.6 Conclusion

This study probed the influence of the left frontal-right cerebellar system on the AB based off of a previous study that found an increase in AB magnitude after cTBS to the right cerebellum (Arasanz et al., 2012b). Other tasks that use letter stimuli have also found decreased performance after right cerebellar cTBS (Arasanz et al., 2012a), suggesting stronger network connectivity between the left frontal-right cerebellar system compared to its right frontal-left cerebellar counterpart. In conclusion, the results from this study suggest that T2 accuracy during the AB period is driven by a left frontal-right cerebellar network recruited to rapidly detect both letter targets. When this network is disrupted after cTBS to the right cerebellum, there is a delay in the encoding of T2 into working memory. The role of the cerebellum in the AB task may be to efficiently modulate the attentional resources dedicated to T1 to readily detect T2, when the time required to switch between targets is a constraint.

Figures

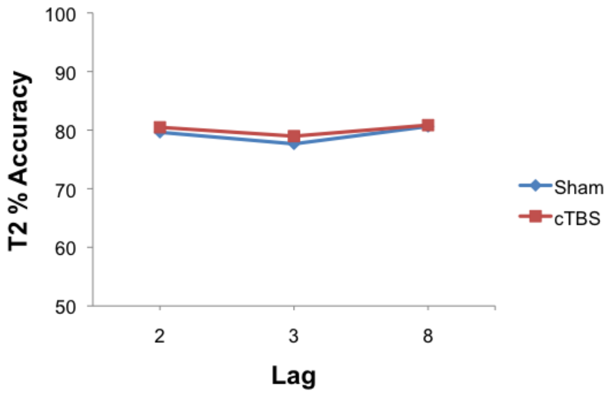

Figure 5.1
Performance (Mean % accuracy +/- S.E.M) in detecting T2 during the Sham and cTBS condition. There was no significant difference in performance between stimulation conditions at any lag.

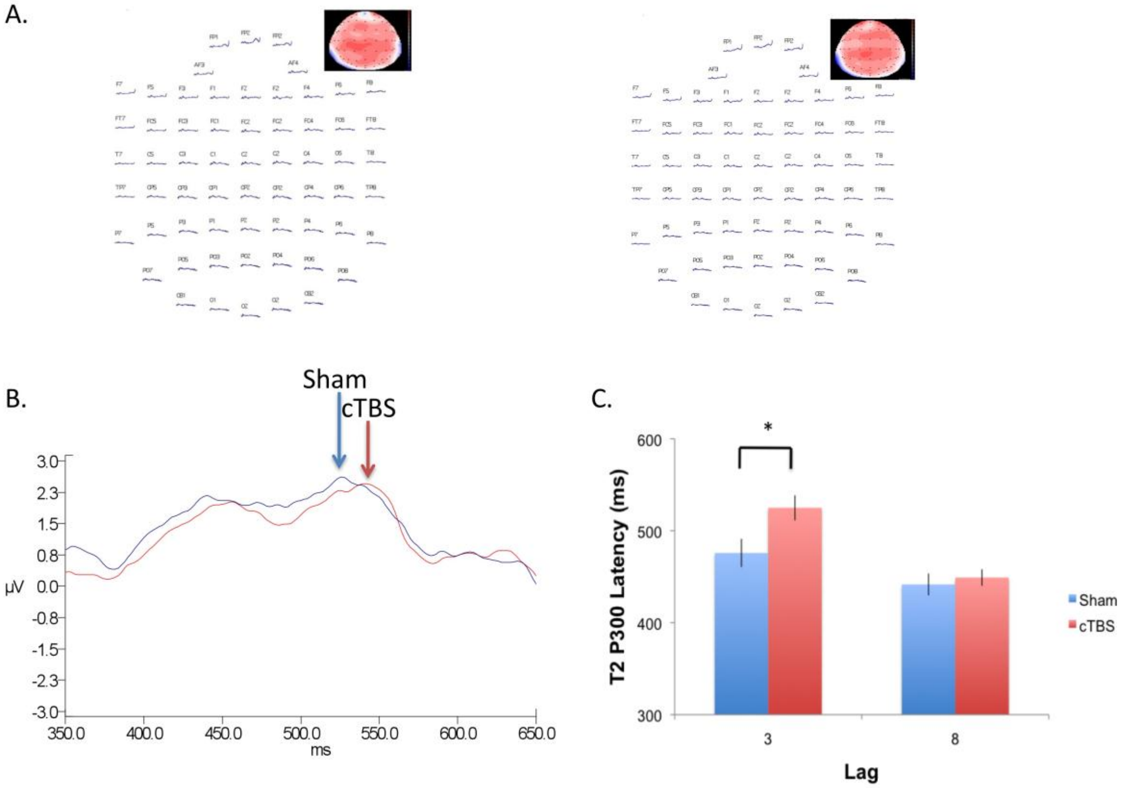

Figure 5.2

A: Multisite EEG trace and scalp topographies for the Sham and cTBS stimulation condition at Lag 3. B: Comparison of the T2 P300 timelocked to Lag3 for the Sham and cTBS stimulation condition at electrode site PZ. C: Latency (Mean +/- S.E.M) of the P300 related to T2 at electrode site PZ for early (3) and late (8) Lags during the Sham and cTBS stimulation condition. Paired contrasts reveal a significant difference between the two stimulation conditions at Lag 3, $^*p < 0.05$.

Chapter 6

6.1 General Discussion

The overall objective of this thesis was to probe the contribution of the fronto–cerebellar system during non-motor functions. The main findings of these studies suggest that the fronto–cerebellar system is involved in cognitive and attentional operations and that disrupting this network leads to behavioural and physiological changes that degrade performance during tasks that are temporally demanding. This finding is significant in that it contributes to our understanding of how the brain functions as an integrated network that involves frontal and cerebellar areas for fast and efficient cognitive processing.

The first study of this thesis sets out to localize areas of the cerebellum that participate in non-motor behaviours in the context of a word generation task. Given that word generation tasks, particularly those that use phonemic cues, demand executive control of word output to optimize performance, the speed at which one is able to organize and plan switches between subcategories during the initiation of the task is a measure of mental flexibility. Due to the fact that word generation tasks (because of their language component) are heavily lateralized to the left frontal cortex, it was hypothesized that transient perturbation of left frontal- right cerebellar connections would disrupt performance during the early phase of the task, when fast and efficient cognitive processing is necessary as executive functioning is at highest demand. Study 1 tested this hypothesis using continuous theta burst stimulation (cTBS), a form of transcranial magnetic stimulation used to transiently suppress a local population of neurons in either the left or right posterior-lateral cerebellar hemisphere, an area in the cerebellum that is known to have direct projections to the contralateral, dorsolateral prefrontal cortex (Middleton and Strick, 2000). The hypothesis that cTBS to the right posterior-lateral cerebellum would disrupt performance was supported by the decrease in the number of category switches made during the initial 15 seconds of the one-minute phonemic word generation task. The decrease in category switches suggests the putative role the right posterior-lateral cerebellum plays at the early phase of the task, when fast and efficient executive processes are required to optimize performance. This study provides evidence for left frontal-right cerebellar network involvement in cognitive processing and is the first to demonstrate that cTBS to the cerebellum can be used to probe this interaction.

The goal of Study 2 was to investigate if the strong connections between the left prefrontal cortex and right posterior-lateral cerebellum subserve rapid visual attention processes required during the attentional blink (AB) task. In this task, letter stimuli are presented serially and the goal is to detect two letters that can occur at various stimulus onset asynchronies (SOA). If the two target letters are presented with an SOA of less than 500 ms, accuracy at detecting the second target (T2) is impaired. In cerebellar lesion patients this impairment is exaggerated, but only during short SOAs of less than 500 ms. If T2 occurs at longer SOAs, accuracy levels do not significantly differ from age-matched controls. This pattern of impairment suggests that damage to the cerebellum may disrupt the use of attentional resources particularly during stimulus processing conditions that are temporally demanding. It was hypothesized that T2 accuracy would decrease after right cerebellar stimulation when the delay between the first and second target was short (120-400 ms) compared to long (720-960 ms). Three groups of participants performed the AB before and after either sham, left, or right cerebellar stimulation. During the short delay, participants in the right cTBS group showed a greater AB magnitude compared to both the left and sham cTBS groups. No difference in T2 was found over long delays. The results of Study 2 provide further support for a cerebellar contribution to an integrated neural network recruited during temporally demanding attention-based tasks.

Study 3 aimed to determine if manipulating the load of the first target (T1) would increase the magnitude of the AB. Increasing the load of a task has been associated with greater cerebellar recruitment (Salmi et al. 2010). According to the load theory of attention, increasing perceptual load decreases distractor interference while increasing cognitive load increases interference (Lavie 2005). It was hypothesized that increasing the set size of T1 would increase the working memory load of T1 and effectively increase the magnitude of the AB. Secondary to this, it was also hypothesized that cerebellar stimulation using cTBS would result in even greater deficit of T2 accuracy during early lags compared the right stimulation group in Study 2. The results of Study 3 did not support either hypothesis. The manipulation of load did not increase the AB magnitude before or after right cerebellar stimulation. Despite this however, these results reveal that even with the manipulation of load, T2 accuracy was still lower after right cerebellar stimulation compared to sham and left cerebellar stimulation when the temporal demands of the task were high (during early lags). The significance of this study was that it reproduced the findings from Study 2, strengthening a case for a left frontal-right cerebellar network involved in efficient attentional processing.

The first three studies provide evidence that different types of cognitive processing are sensitive to the perturbation of a left frontal-right cerebellar network in the context of tasks that are heavily lateralized to the left frontal cortex due to their language component. These studies are not arguing a role for this network in written language, it is simply that the strength of these frontal-cerebellar connections are reinforced because of how lateralized the nature of these tasks are. The focus instead was to understand the role of the frontal-cerebellar system in cognitive processing, and the study that got to the heart of this matter was the final study of this thesis. Study 4 sought to determine how the neural events that underlie the AB are affected by disrupting left frontal-right cerebellar connections using cTBS. This study used electroencephalographic (EEG) measurements in order to better understand which aspects of target processing are modulated in the AB after right cerebellar stimulation. The P300 event related potential (ERP) component is suggested to reflect the updating of working memory (Luck 2005), and occurs at a relatively late stage of processing, after perceptual and conceptual representations have been formed (Vogel et al., 1998). The P300 time locked to T2 is suppressed during the AB period if T2 goes undetected, likely due to not enough attentional resources being readily available to efficiently reengage to T2 (Bowman and Wyble, 2007; Nieuwenstien et al., 2009). The hypothesis of Study 4 was that cTBS to the right cerebellum would delay the peak latency of T2-P300 during the AB when T2 was presented at short lags (SOA less than 300 ms) compared to long lags (SOA of 800 ms). The results of the final study support that the role of the cerebellum during cognitive functioning is to provide fast and efficient information processing to optimize performance during tasks that are temporally demanding.

Little is known about how the cerebellum has a role in cognition. While there are many theories detailing how the cerebellum contributes to motor control, theoretical models underlying its cognitive role are less established. However, since the cytoarchitecture of the cerebellum is the same throughout, a similar computation can be performed upon the different information passing through it (Schmahmann, 2004; Ramnani, 2006). Therefore, models of information processing in the motor domain may apply to help understand how the cerebellum is involved in information processing in cognitive domains. Models of motor control processing are based upon error correction: cerebellar forward models. Forward models enable online performance monitoring by predicting the sensory consequences of actions by making use of efference copies – information exchanged across cortical networks that are transmitted to the cerebellum via fronto-cerebellar connections (Wolpert and Miall, 1996). With the use of these forward models the cerebellum can modulate cerebral processing via its feedback projections to the cerebral cortex (Ito, 2006). A recent study using combined tractography and magnetic resonance imaging provides strong evidence that the cerebellum generates predictions across different domains, including cognitive domains (Ramnani, 2006). In this study, participants performed an auditory-motor task where they were to press a button in response to a tone as quickly as possible. The task was then manipulated so that participants were to respond only if a tone matched a tone in a stream of sounds that had previously been presented (auditory memory task). While behavioural results were similar across the auditory-motor and auditory-memory task, the cerebro-ponto-cerebellar and cerebellar-thalamo-cerebral tracts for each task projected via different pontine and thalamic nuclei (Salmi et al., 2010). Results also revealed a functional segregation in the cerebellum, where the anterior cerebellum was activated during the auditory-motor task, and the posterior cerebellum (Crus I/II) was activated in the auditory-memory task. Thus the type of forward model necessary for optimal performance depends on the demands of the task. Increasing cognitive load with the auditory-memory task recruits a different area of the cerebellum compared to the auditory-motor task. The posterior-lateral cerebellum may be involved in optimization of response speed when cognitive load increases.

In humans, the expanded size of the cerebellum – particularly the dentate and lateral cerebellar cortex - parallels the development of the cerebral association areas (Weaver 2005; Stoodley and Schmahmann, 2010) and the corresponding capacity for goal-oriented behaviour. This suggests that the original predictive functions of the cerebellum to reduce motor variability naturally evolved to reduce variability for cognitive functions as well. Polysynaptic tracer studies have identified cortical targets of the cerebellum that go beyond primary and secondary motor areas. There are significant projections (via the thalamus) to prefrontal and parietal cortex (Middleton and Strick, 2001; Dum and Strick 2003). These intricate connections likely subserve a predictive brain state: a state in which anticipatory neural activity is generated to reduce performance variability (Ghajar and Ivry, 2009).

Interrupting fronto-cerebellar connections can cause performance degradation in a range of cognitive tasks, from word generation (Leggio et al., 2000; Akshoomoff et al., 1992; Appollonio et al., 1993; Silveri et al., 1994; Molinari et al., 1997; Richter et al., 2007; Schweizer et al., 2010; Arasanz et al., 2012a), time perception (Koch et al., 2007; Oliveri et al., 2007), mental rotation (Allen et al., 2005, Stoodley and Schmahmann, 2010), and working memory (Chen and Desmond, 2005; Hayter et al., 2007, Ferrucci et al., 2008). A combined cTBS and positron emission tomography (PET) study revealed increased cerebellar activity during a decision making task where participants were given three seconds to decide whether they wanted a smaller reward given immediately or a larger reward given after a time delay (i.e., one week). This activity decreased after delivering cTBS to the right dorsolateral prefrontal cortex (DLPFC), particularly in the left cerebellar cortex (Cho et al., 2012). cTBS also disrupted task performance, which is possibly the result of a right prefrontal-left cerebellar system disconnect. In much the same way that disrupting the fronto-cerebellar network can perturb behavioural performance, enhancing this system can have the opposite effect (Hope and Miall, 2012). Transcranial Direct Current Stimulation (tDCS) is a form of non-invasive neural stimulation that involves delivering low direct current through a pair of electrodes: a stimulation electrode and a reference electrode. The stimulation electrode is placed over the brain area of interest and the reference electrode is placed over a bony prominence, such as the shoulder. Current flow between the two electrodes modulates excitability in a focal population of neurons. Depending on the stimulation type, tDCS can either enhance (anodal) or decrease (cathodal) neuronal excitability in the region of interest. Although the cerebellum's output is excitatory, it has an inhibitory tone over the cerebral cortex. When tDCS is applied to the cerebellum, anodal tDCS has been found to increase the cerebellum's inhibitory influence on the cerebral cortex and cathodal stimulation has been found to decrease it (Galea et al., 2009). Decreasing the inhibitory effect of the cerebellum on a particular brain region can make that region more active. Based on these findings, Hope and Miall (2012) speculated that the cerebellum is capable of influencing cognitive functions by limiting its inhibitory effect on the dorsolateral prefrontal cortex and releasing cognitive resources in this working memory region of the brain. Supporting this, they found that cathodal stimulation enhancing performance during a cognitive task. Compared to anodal and sham stimulation, participants improved performance during a Paced Auditory Serial Subtraction task (PASST), a novel variant of a neuropsychological test to assess arithmetic aspects of working memory and attention. PASST is more difficult than its derivative, Paced Auditory Serial Addition task (PASAT), as it involves subtracting instead of adding a series of numbers as they are presented in a serial fashion every 2 to 3 seconds. Subtracting numbers is naturally more complicated to learn and perform as it, unlike adding, has two order-specific interpretations to consider (Fuson et al., 1984). Cathodal tDCS had a positive effect on participants' accuracy scores and on the response times during PASST, such that responses were more accurate, faster and less variable after stimulation. Thus the cerebellum is capable of influencing behaviour when cognitive tasks make high demands on working memory and attention resources, and facilitating this process can be done by manipulating fronto-cerebellar connections.

Attentional control is defined by the ability to focus on task relevant information and ignore irrelevant, potentially distracting sources of information. A sudden visual distraction can involuntarily capture attention and impact performance negatively, especially if the information it holds shares features with a specified target. The time needed to recuperate from the related item is increased in people with low working memory (Fukuda et al., 2011). Playing first person shooter games is associated with improvement in working memory (Colzato et al., 2012), and videogame players (VGPs) have better control over disengaging from distractions compared to non-videogame players (NVGP; Chisholm et al., 2010). This is likely because first person shooter games require fast and efficient visual selective attention, because they involve visual inputs that demand quick reaction time and precise timing. It is well established that the dorsal fronto-parietal network in the brain is involved in control and regulation of attention (Corbetta and Shulmann, 2002), and VGPs require less activation of this network during tasks that require ignoring irrelevant distractors (Bavelier et al., 2011). When load was manipulated in a visual search task, in NVGPs a frontal-parietal activation increased with load. The only regions however that increased in VGP were bilateral hemispheres of the cerebellar cortex (Bavelier et al., 2011). This is not to say that the cerebellum was not active in the NVGPs; cerebellar activity during the high load did not differ between groups. However, what can be said is that during training increasing task difficulty demanded increasing activity in frontal, parietal, and cerebellar regions in NVGP. Trained individuals on the other hand developed more efficient attentional processes. Thus, minimizing the amount of brain activity needed during a task is an adaptation of training that allows for more efficient allocation of attention. The reduced activity in the frontal-parietal regions and the increased activity in the cerebellum in VGPs suggest that these nodes work together as a network to allocate attentional resources more automatically, and possibly allow more efficient filtering of irrelevant information.

6.2 Conclusion

The findings from this thesis add to the collection of evidence that supports a role for the cerebellum in cognitive processing. While the exact mechanism is not clear, the intricate connections between the prefrontal cortex and the cerebellum make a case for cerebellar forward models. The temporal constraints of high order processes require that the brain adopt a predictive state. The frontal-cerebellar system is essential for the generation and utilization of real-time predictions. Without these predictions, responses would be too slow, as they would be based solely on sensory-perceptual feedback. Thus fronto-cerebellar connections assist in the accuracy and efficiency of goal directed behaviour when cognitive demands are high and time is a constraint.

6.3 Limitations

There are a number of limitations to this thesis, some of which are inherent to the neuroimaging tools chosen. Like all methodologies, cTBS has its limitations.

A limitation true to all the studies in this thesis was how the posterior-lateral cerebellum was localized. Because fMRI guided localization of the targeted Crus II lobules would be both cumbersome and expensive, standard measurements for localizing the site of stimulation were used instead, but this may have been a limitation to the study due to variability in head size of the participants. Between-subject variability is also difficult to control and direct output measures are limited. For example, the output measure for Study 1, 2, and 3 were strictly behavioural, making the findings less concrete since no physiological data was recorded. Despite the limitations in regional localization, between subject variability and output measure, region specific significant effects were attainable and reproducible. This suggests that a standardized method for localizing site of cerebellar stimulation, as well behavioural measures, can be used for assessing fronto-cerebellar disruption after cTBS.

The efficacy of cTBS over the cerebellum as a non-invasive assessment of cerebellar function has been recently questioned. It is possible that stimulation to the posterior-lateral cerebellum could have directly activated corticospinal neurons (Fisher et al., 2009), however if such activation occurred it is not likely that it contributed to the results of any of the studies of this thesis. In Study 1 for example, activation of corticospinal neurons would have influenced the motor component of the task, specifically the initiation of speech, however; neither group showed any deficit for generating word output. Since cTBS modulation was hemisphere and task specific, it is more likely that the cerebello-thalomo-cortical pathway was activated or interrupted.

A different set of limitations arises from the last study of the thesis, which used EEG as a measure of cortical activity. EEG measures electrical activity at the surface of the scalp and reflects the summated synaptic activity occurring in the underlying cortex. While this measure has the advantage of very precise temporal resolution, spatial resolution is poor as the EEG signal is attenuated and distorted by tissue and bone between the cortex and the electrodes, which makes it difficult to localize the generators of components of the EEG waveform. This is particularly true for the P300 as it has a broad topographical distribution.

6.4 Future Directions

While the studies of this thesis support the role of the cerebellum in executive and attentional control, the mechanism underlying its involvement is still largely in question. It is hypothesized that the cerebellum generates forward models in both the motor and cognitive domain to optimize performance; however, to date there is limited evidence that the cerebellum mimics cortical information processing to assist in flexible behavioural control. In the motor domain, patient data has shown that the cerebellum performs forward predictions to fine tune motor responses (Petersburs et al, 2012; Knolle et al., 2012). More studies are needed to show how this mechanism extends to cognitive processes. The error related negativity potential (ERN) is associated with unconscious error processing, which occurs approximately 150 ms after an erroneous response (Gehring et al., 1993). While the ERN originates in the anterior cingulated cortex (Dehaene et al., 1994), the error monitoring system it represents relies on efference copies of the motor command for the response (Gehring et al., 1994). During an anti-saccade task, cerebellar patients were impaired at detecting erroneous responses from correct responses (Petersburs et al., 2012). Although saccadic related efference copy processing is likely to involve anterior cerebellar regions (Salmi et al., 2010; Stoodley and Schmahmann, 2009), there is no evidence as of yet that permit clear conclusions with respect to the cerebellar regions particularly involved in error processing. Posterior-lateral regions of the cerebellum appear to be recruited for timing perception (Jueptner et al., 1995) and decision making (Blackwood et al., 2004); however, to understand if these regions are specifically involved in cognitive aspects of performance monitoring, future studies should use cTBS to measure the behavioural and physiological consequences of disrupting function in the posterior-lateral cerebellum. Because the cerebellum is intricately connected with the cerebral cortex, it can anticipate and adjust responsiveness in a variety of brain systems that extend beyond the motor domain. Understanding the role of the fronto-cerebellar system in cognitive and attentional functions is a preliminary but critical step toward informing rehabilitation strategies for patients with cerebellar damage, independent of their etiology.

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Appendix A

Statistical Approach

Study 1:

The initial analysis was a 2x2 ANOVA with condition as a within-subjects factor (pre-cTBS, post-cTBS) and stimulation site (left and right) as a between-subjects factor for the phonemic fluency task. The 2x2 ANOVA had a main effect of hemisphere (group) that approached significance. Subject variability due to the small sample size likely accounts for the lack of an interaction between condition and hemisphere; this is why change scores were performed as a secondary analysis. The change scores demonstrate that the right hemisphere indeed produced less switches after cTBS during the first 15 seconds of the phonemic fluency task.

The pre-cTBS data for each group were compared to confirm that there were no group differences prior to the application of cTBS. As expected there were no differences so the pre-cTBS trials for both stimulation sites were collapsed and used as a control group to compare the effect of group on the phonemic fluency task for the number of switches and words generated within the first 15 seconds of the task. The one-tailed t-tests were only performed on this early time period. The primary purpose of this was to ensure that the cTBS effects were isolated to the right hemisphere group.

Study 2:

For T2 detection accuracy, a 6x3 ANOVA with lag (six positions) as a within-subject factor and group (left, right, sham) as a between-subject factor was used to assess whether all three stimulation groups performed similarly pre cTBS. The same analyses were performed post cTBS, including paired contrasts to test the specific *a priori* hypothesis that there would be poorer performance in T2 accuracy during short lags after cTBS for the right cerebellar hemisphere group compared to the left cerebellar hemisphere and sham group. While the attentional blink magnitude is largest at lags 2 and 3, all short lags (1-4) were used in the paired contrast analysis as the timing of the 'blink' can shift between subjects.