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Cerebellar contributions to nonmotor behaviour

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Abbreviations

AMT	active motor threshold
BA	Brodmann Area
CCAS	cerebellar cognitive affective syndrome
cTBS	continuous theta burst stimulation
DCNs	deep cerebellar nuclei
DV	dependent variable
EEG	electroencephalogram
EF	emotional faces task
fMRI	functional magnetic resonance imaging
IAPS	international affective picture set
ISI	inter-stimulus interval
iTBS	intermittent theta burst stimulation
IV	independent variable
LD	lexical decision task
LTD	long term depression
MSO	maximum stimulator output
MT	motor threshold
PANAS	positive and negative affect scale
PICA	posterior inferior cerebellar artery
PET	positron emission tomography
RT	reaction time
rTMS	repetitive transcranial magnetic stimulation
SCA	spinocerebellar ataxia / superior cerebellar artery
sTMS	single-pulse transcranial magnetic stimulation
TBS	theta burst stimulation
tDCS	transcranial direct current stimulation
TMS	transcranial magnetic stimulation
TPJ	temporoparietal junction
VBM	voxel-based morphometry
VBSLM	voxel-based symptom lesion mapping
WM	working memory

Summary

The cerebellum's role in the co-ordination of motor behaviours is well-established. Evidence has been gathered that suggests that the cerebellum plays a role in a wider range of behaviours, but the nature and scope of this role remains controversial. Given the largely homogenous nature of the cerebellum's cytoarchitecture and the existence of discrete pathways linking motor and non-motor cerebral areas with the cerebellum the suggestion has been made that any cerebellar non-motor role is likely to be analogous to that played within motor behaviour. This thesis presents a series of experiments that sought to examine whether a cerebellar non-motor role can be placed within this explanatory framework.

Previous attempts to elucidate the cerebellum's role in non-motor behaviour have relied on clinical investigations or neuroimaging. Both of these methods present issues with either the limited availability of suitable subjects or the strength of the inferences that can be drawn from correlations. The experiments within this thesis instead used brain stimulation techniques to investigate the living, healthy cerebellum in a range of non-motor behaviours.

The experiments described in chapter 3 employed a Sternberg paradigm and transcranial direct current stimulation (tDCS) to investigate the cerebellar role in verbal and visual working memory (WM). No clear evidence for a cerebellar role in WM was obtained. These experiments highlighted the difficulties entailed in the use of a non-focal stimulation technique for cerebellar stimulation. From this point a rationale is advanced for the use of more-focal stimulation techniques for further research. An experiment is presented in Chapter 4 that used continuous theta burst stimulation (cTBS) targeting the posterolateral cerebellum (lobule VI/Crus I) to determine whether a lateralised cerebellar contribution to WM processes could be detected during the performance of visual and verbal Sternberg tasks. An impairment in the percentage of correct responses after cTBS to the right cerebellar hemisphere was noted. Chapter 5 presents two experiments that used cTBS targeting mid-hemispheric and lateral areas of the posterior cerebellum to determine whether a lateralised cerebellar role could be demonstrated in visuospatial WM. An impairment in the recall of the order of presented targets was seen after stimulation of the left cerebellar mid-hemisphere. An impairment in the speed of participants' responses was seen after stimulation of the more lateral areas of the left cerebellar hemisphere. The results were taken to indicate a preferential role for the cerebellar left hemisphere in spatial WM. Chapter 6 describes an experiment that examined the cerebellum's role in processing emotional stimuli in contrast to the proposed cerebellar function in verbal cognition. This experiment sought a dissociation between the effects of vermal and lateral cTBS in the performance of a 'masked emotional faces' colour-naming task, which incorporated emotionally-salient distractors, and a lexical decision task. Increased reaction times were seen on the emotional faces task after stimulation to both areas. No changes were indicated in participants' reported mood and post-stimulation differences were not specific to a single valence of emotional stimulus. These results were taken to indicate a cerebellar role in the orientation and shifting of attention, with particular emphasis on emotionally-salient stimuli.

The WM results lent support to the proposed cerebellar hemispheric specialisation that is similar, but opposite to that observed in the cerebral hemispheres. The results, as a whole, are discussed in the context of the wider literature and an argument is made that the cerebellum does indeed play a role in the efficient implementation of non-motor behaviours that is somewhat analogous to its role within motor activity.

Chapter 1 - Introduction

The human cerebellum presents a series of paradoxes. Smaller than the cerebrum, though holding many more neurons, it has been both one of the most intensively-researched and most neglected regions of the brain. The cerebellum has been dismissed as having yielded up its functional secrets, yet the scope and nature of its role remain the subject of fierce debate. Researchers from many disciplines have been drawn to the cerebellum as its well-described circuitry offers the prospect of being able to document the operation of a brain organ, within the context of human behaviour, in precise computational terms. Further to this, the homogenous nature of the cerebellum and the presence of discrete circuits that link diverse cerebellar and cerebral areas raise the possibility that the discovery of the nature of cerebellar computation would allow a general understanding to be gained of the role played by the cerebellum across multiple behaviours. An additional factor encouraging research into the *human* cerebellum is that its disproportionate development within our species hints at a wider significance within human behaviour than within that of other animals. The purpose of this thesis is to examine the possibilities that exist for the inference of a cerebellar role that extends beyond the support of motor behaviour and to determine if new evidence can be generated for a cerebellar role within these activities.

In the course of this thesis I consider previous research on the nature and role of the cerebellum and present a series of experiments aimed at furthering our understanding of cerebellar activity within non-motor behaviours.

In this chapter, I discuss how early views of the cerebellum as a motor organ shaped cerebellar research. I describe the fundamental structure of the cerebellum, compare the human cerebellum with those of other species and examine more recent cerebellar research to enable a discussion of how the understanding of cerebellar function has developed. I examine the methods used in cerebellar research and consider their merits. From this discussion I present a justification for the use of brain stimulation techniques for cerebellar research and describe the aims of this study.

Chapter 2 comprises a systematic review of the use of brain stimulation techniques to study the cerebellum's role in non-motor behaviours.

Chapter 3 describes two experiments that used transcranial direct current stimulation (tDCS) to manipulate cerebellar operation within a series of working memory tasks. No clear evidence emerged from these experiments of the nature of the cerebellar role in working memory.

Chapters 4 and 5 describe experiments that used theta-burst stimulation (TBS) to examine the cerebellar role in verbal, visual and spatial working memory. Evidence was gained for a role for the right cerebellar hemisphere in verbal working memory, though no clear indication was obtained of a role for either hemisphere in visual working memory. The results suggested a contribution of the left cerebellar hemisphere in spatial working memory with the possibility of a nonmotor functional topology present within the cerebellum.

Chapter 6 describes an experiment that sought to dissociate the activities of the cerebellar vermis in emotional processing from the role of the lateral cerebellum in cognition. A performance impairment was seen in emotion processing after the application of TBS to the cerebellum, but no difference was seen between vermal and hemispheric applications. No indication was given for a critical role for the cerebellum in performing lexical decisions.

Chapter 7 examines the findings of the preceding experiments and discusses what can be concluded from the results in relation to cerebellar activity within non-motor behaviours.

The developing view of cerebellar function

The role of the cerebellum in motor behaviours has been appreciated for several centuries. Early in the 19th century pioneers such as Rolando and Flourens noted the disturbance of motor behaviours resulting from cerebellar disease (Glickstein, Strata, & Voogd, 2009). Luciani observed that cerebellar disease or injury led to a triad of symptoms, namely, atonia, asthenia and astasia (Luciani, 1891) and resulted in the impairment rather than the elimination of motor behaviours. Atonia is defined as an absence of normal muscle tension; asthenia as muscular weakness; and astasia as an absence of postural stability. As a result of further observations, Luciani added ataxia to the set of cerebellar symptoms. Ataxia, which was later to become the symptom most strongly associated with cerebellar disorder, manifests as impaired control of voluntary movement and an inability to make timely corrections to the implementation of a motor action. The emerging theme of these findings was that the cerebellum was a structure of importance for skilled voluntary control of motor behaviour. Volition, as presumably supported by the cerebrum, remained intact after cerebellar damage, whereas the co-ordination of the activity of the muscles required to perform the behaviour seemed critically reliant on the cerebellum. The obvious motor deficits noted by 19th century researchers eclipsed contemporary reports of cognitive and emotional disturbances ascribed to cerebellar disease (Schmahmann, 1997) and the suggestion that the cerebellum had a role in non-motor behaviours would appear rarely in the literature for the next hundred years.

Major advances were made in the understanding of the structure and composition of the cerebellum through the work of Purkinje, Golgi and Ramón y Cajal (D’Angelo et al., 2010). Their work gave insights into the networks formed between the cellular components of the cerebellum and between the cerebellum and other structures. These discoveries began the process whereby hypotheses of the operation of the cerebellum could be informed by, and inspected against, the biological substrate of the organ. Of particular importance were the growing understanding of the interaction between the cells of the cerebellar cortex and the deep cerebellar nuclei, and the role that may be played by mossy and climbing fibres in providing information to the cerebellum (Ramón y Cajal, 1911).

Further progress in the understanding of the role of the cerebellum in motor behaviours was made by Babinski (1899), who observed the cerebellum's role in allowing control over the timing of the activity of antagonistic muscles and by Holmes who noted the cerebellum's provision of tonic support for posture and stability (Holmes, 1917, 1939). Babinski's work introduced the concepts of dysdiadochokinesia and dysmetria (being an inability to implement rapidly alternating movements and to manage accurately the extent of movements, respectively) and Holmes's observations provided further detail to the concept of ataxia.

The findings described above resulted in a view of the cerebellum as an organ whose primary purpose was to provide support to the cerebrum in the implementation of motor behaviour. The activity of the cerebellum as an integrator of sensory, particularly proprioceptive, information had been discussed by Sherrington (1906), though this function was seen as subserving motor behaviour.

Throughout the 20th century further understanding was gained into the cellular interactions that underlie the operation of the cerebellum and detail was added to knowledge of the relationship between the cerebellum and other brain structures. Pioneering electrophysiological work by Eccles (1967) and Ito (reviewed in Ito, 2006) increased understanding of the interactions between the cerebellum and spinal neurons and between the cerebellum and brainstem, and led to the development of the first models of cerebellar activity expressed in computational terms. The marked contrast between the mossy/parallel and climbing fibre systems' interaction with the cerebellar cortex led to the speculation that the former represented a contextual system providing a model of the agent's unfolding environment whilst the latter provided an error signal relaying the success or failure of current activity (Dow, 1942). This view was expressed computationally in the models of Marr (1969) and then Albus (1971), which provided a plausible explanation of the cerebellum's role in the development of motor skills and suggested a more general role in associative learning.

Developing from this point were increasingly sophisticated models of cerebellar activity that sought to unite observations of deficits resulting from cerebellar injury with increased knowledge of the interaction between cerebellar components into a single explanatory framework. Fujita enhanced the descriptions of cerebellar computation proposed by Marr and Albus through the adaptive filter model that placed emphasis on the interaction between Golgi and granule cells in providing the capability to process temporal patterns (Fujita, 1982). Further emphasis on the cerebellum's role as a timing device, particularly for short-interval processing, was derived from examination of the cerebellum's cytoarchitecture (Braitenberg, 1967). Observations drawn from animal experimentation on the cerebellum's role in the vestibule-ocular reflex led to the concepts of the cerebellum as a gain controller (Ito, 1982) and the provider of feedforward models of body components (Kawato, Furukawa, & Suzuki, 1987). Consideration of the observed operation of the cerebellum in the context of principles drawn from systems engineering led to proposals of the cerebellum as a provider of virtual feedback (Miall, Weir, Wolpert, & Stein, 1993) to allow the effect of an action to be estimated ahead of sensory feedback being received. In later years these models coalesced into a view of the cerebellum as being a prime component in the formation and manipulation of internal models: a symbolic representation within the brain of elements of the universe, which provide either the method of achieving a desired state or a timely prediction of the likely effects of an action (Ito, 2000; Wolpert, Miall, & Kawato, 1998).

By the end of the 20th century the view of the cerebellum as an organ of vital importance to the effective and efficient implementation of motor behaviours was thoroughly established and expressed in detailed operational terms. Several researchers noted the potential utility of cerebellar internal models for the manipulation of purely mental objects in addition to providing a representation of either objects in the world or components of the body (Bellebaum & Daum, 2007; Ito, 2008). Others noted the lack of a firm distinction between motor behaviour, motor or embodied cognition and more abstract modes of thought and contended that these behaviours represented elements on a continuum, with a cerebellar support role being highly plausible (Fuentes & Bastian, 2007; Koziol et al., 2014; Koziol, Budding, & Chidekel, 2011). In order to understand how these proposals for an augmented cerebellar role were developed it is instructive to consider how knowledge of the cerebellum as an organ has developed with the use of improved technology.

The cerebellum as an organ

The human cerebellum is the major component of the metencephalon and occupies the posterior fossa at the base of the skull. It is attached to the pons and medulla of the brainstem by the cerebellar peduncles, which convey the white matter tracts connecting the cerebellum to other brain regions, primarily via the thalamus. The surrounding area is rich in cerebro-spinal fluid due to the presence of the fourth ventricle and the cisterna magna, a fact significant for cerebellar stimulation as will be discussed.

The cerebellum is conventionally divided into 3 regions referred to as the archi-, paleo- and neo-cerebellum reflecting their perceived phylogenetic origin. The archicerebellum comprises the flocculonodular lobule located in the inferior region of the structure; the paleocerebellum consists primarily of the central cerebellar vermis; whilst the neocerebellum consists of the cerebellar hemispheres that extend laterally from the vermis. The archicerebellum is believed to be instrumental in both the adaptation of eye movements and the maintenance of balance due to reciprocal connections with the vestibular nuclei. The paleocerebellum has been shown to be essential for gait and truncal posture. The neocerebellum has been shown to be essential for the smooth implementation of fine motor movements, for speech and is the region that has been suggested as playing a role in the cerebellum's non-motor activity. Studies of comparative anatomy have noted that the human neocerebellum is expanded laterally to a disproportionate degree and contains features unique to our species (Baizer, 2014; Voogd & Glickstein, 1998). It has been proposed that the lateral cerebellum's expansion was accompanied in our species by the development of the prefrontal cerebral cortex (Balsters et al., 2010). It has been argued that the concomitant expansion of these cerebral and cerebellar areas in humans, when compared with other species, indicates a close functional relationship between these regions (Bellebaum & Daum, 2007). The observation that our motor repertoire is not necessarily more complex than that of other primates is a factor supporting the proposition that this expansion reflects a role for the most recently developed areas of the cerebellum in cognition and other nonmotor behaviours.

The paleo- and neocerebellum are also divided into anterior and posterior lobes that comprise both vermal and hemispheric regions of the superior and inferior cerebellum, respectively. A functional division between these areas has been suggested with proposed non-motor area being located primarily with the lateral areas of the posterior lobe, especially the cerebellar crura. The anterior and posterior lobes of the cerebellum are further divided into lobules consisting of largely transverse folia that may be observed at a gross level as forming the ridged surface of the cerebellum.

Within the folia of the cerebellum are the three layers of the cerebellar cortex that hold the vast majority of cells that comprise the organ. The cortex, from interior to surface, is divided into granular, Purkinje and molecular layers that hold different cell types as were first observed microscopically by Golgi and Ramón y Cajal (Glickstein et al., 2009). The deep granular layer holds inhibitory Golgi and Lugaro interneurons and a dense and numerous population of small granule cells that receive extracerebellar afferents from a wide range of brain and body sites via mossy fibres. Axons rising from the granule cells travel to the outermost molecular layer where they form parallel fibres that stretch for up to 1.5 mm (in each direction) along the axis of the folium (Eccles, 1967). The dense distribution of the parallel fibres allows many fibres to cross the flattened dendritic trees of the Purkinje cells that rise from the Purkinje layer. It is estimated that a single Purkinje cell forms synapses with approximately 80,000 parallel fibres. Additional synapses on Purkinje cell dendrites are formed by basket and stellate inhibitory interneurons of the molecular layer.

Additional input to each Purkinje cell is provided by a single climbing fibre – an input pathway that conveys information solely from the inferior olive of the medulla. Climbing fibre discharges generate the most powerful action potential within the brain, as discovered by the pioneering electrophysiological experiments conducted by Eccles (1967): the discharge of parallel fibres simultaneous to climbing fibre discharge results in the adjustment of the strength of parallel fibre – Purkinje cell dendrite synapses. This mechanism of 'long term depression' (LTD) results in the generation of complex spikes that reduce the likelihood of a Purkinje cell action potential being triggered by those parallel fibre synapses that were active during the discharge of the relevant climbing fibre. It is now understood that the generation of complex spikes is one of a range of processes that result in either LTD or, conversely, long term potentiation (Hansel, Linden, & D'Angelo, 2001). The processes that drive the adjustment of Purkinje cell action potential likelihoods are understood to be the mechanisms that underlie associative learning across species (Attwell, Rahman, & Yeo, 2001; Dittman & Regehr, 1997; Hoffland et al., 2011; Yeo & Hesslow, 1998).

All output from the cerebellar cortex travels via Purkinje cell axons that synapse on the cells of the deep cerebellar nuclei (DCNs) and the vestibular nucleus. The four pairs of DCNs, from medial to lateral: fastigial, globose, emboliform and dentate, receive input from Purkinje cells located in longitudinal bands from medial to lateral areas (Oscarsson, 1979). The DCNs receive inhibitory input from Purkinje cells and excitatory input from branching afferents of the mossy fibres. All output from the cerebellum is sent via the axons of the DCNs and vestibular nuclei. The availability of virus tracing (Middleton & Strick, 2000), functional neuroimaging (Thürling et al., 2012) and, more recently, diffusion tensor imaging (Kamali, Kramer, Frye, Butler, & Hasan, 2010) have allowed advances to be made in tracing the pathways emerging from the DCNs to other brain structures. The introduction of viruses and horseradish peroxidase into the cerebellar tissue of non-human primates allowed a trace to be made of pathways across multiple synapses (Middleton & Strick, 2001), for example from DCNs to the cerebral cortex via the thalamus. Further to this, the existence of reciprocal pathways has been confirmed in non-human primates – thus closing the loop between cerebrum and cerebellum (Middleton & Strick, 2000). Detailed study of the circuits formed by these pathways allowed a separation to be proposed between the circuits linking motor and non-motor areas of the cerebrum to the cerebellum (O'Reilly, Beckmann, Tomassini, Ramnani, & Johansen-Berg, 2010).

The majority of recent interest in DCN activity and the efferent pathways has focussed on the laterally-situated dentate nucleus. The dentate nucleus is the largest and phylogenetically most recent of the DCNs and a division between a motor dorsal and non-motor ventral region has been proposed (Leiner, Leiner, & Dow, 1986). The ventral region of the dentate nucleus receives input primarily from the most lateral regions of the posterior lobe: an area which has shown to be reciprocally connected to non-motor areas of the cerebrum (as per the review of imaging of the deep cerebellar nuclei conducted by Habas (2010)). The discovery of neural pathways linking areas of the posteriolateral cerebellum to regions of the prefrontal cerebrum strongly associated with cognition (Fuster, 2008; Strick, Dum, & Fiez, 2009) and the proposal that reciprocal connections between these areas formed discrete processing loops (Middleton & Strick, 2001) led to a re-examination of the possibility of a cerebellar role that extended beyond sensorimotor processing.

Oscarsson (1979) stated that the longitudinal cortical bands described above were divisible at a finer level into ‘microzones’ consisting of a group of adjacent Purkinje cells receiving innervation from, in the case of sensorimotor cerebellar regions, the same somatosensory field. Ito extending this finding by noting that discrete circuits are formed by sets of inferior olive, DCN or vestibular nuclei neurons and Purkinje cell populations within topologically-ordered regions of the brain areas in which they reside (Ito, 1984). This organisation of cells was described as the microcomplex and is held to the fundamental processing unit of the cerebellum and a structure that is replicated throughout the organ. The discovery of the microcomplex and its ubiquity across all regions of the cerebellum led to the suggestion that a ‘universal cerebellar transform’ may underlie all information processing activity within the organ. The proposal of a fundamental computational operation further led to the proposition that the cerebellum may provide a similar function within all behaviours in which it is involved (Schmahmann, 2001).

Emerging from the most recent physiological research into the cerebellum is a picture of an organ with a huge neuronal population that is connected via discrete circuits to a diverse range of extracerebellar structures. Improved understanding of the nature of the mossy/parallel and climbing fibre systems have led to a view of the cerebellum as a structure optimised for rapid learning and recalibration. The discovery of the ubiquity of the microcomplex has suggested that at a fundamental level the computation performed across the cerebellum may be similar in nature and therefore the organ as a whole may provide similar support to the other brain areas to which it connects. The discovery of the reciprocal links between ‘executive’ areas of the cerebrum and the posteriolateral cerebellum and the disproportionate expansion of these areas within our species have led to the suggestion that the role of the human cerebellum extends through a wider range of behaviours that that of other animals. Taken together, these factors have caused an increase of interest in the possibility of the human cerebellum having a role in non-motor behaviour and generated multiple strands of research.

The cerebellum in non-motor behaviour

As noted in the previous section, there are several factors that suggest the possibility of a cerebellar role in non-motor behaviour. Until recently, investigations into this possibility have primarily been either neuropsychological studies conducted on patients who have experienced cerebellar injury or disease, or examinations of the cerebellum using neuroimaging. The emergence of brain stimulation as a method for the study of the cerebellum has added to the range of research approaches and will be considered in detail in chapter 2: this section will consider the findings of clinical and imaging studies of the cerebellum in non-motor behaviour.

Clinical Investigations

Several early investigators into the effects of cerebellar abnormality suggested that a range of non-motor symptoms may arise after damage to the cerebellum (as reviewed in Schmahmann (1997). Given the technology available to earlier cerebellar researchers, it is difficult to exclude the possibility that the abnormalities investigated were not limited to the cerebellum: it is therefore understandable that later researchers viewed the suggested links between cerebellar damage and non-motor symptoms with caution. With the development of more advanced tools for the examination of pathology and more rigorous neuropsychological testing it has become possible to examine patients with damage limited to the cerebellum and give a clear definition of the nonmotor symptoms experienced. Later clinical studies have enabled not only the suggestion of a set of nonmotor symptoms that may arise from cerebellar damage, but also the development of a putative cerebellar functional topology.

Clinical data regarding the effects of cerebellar damage have been derived mainly from the study of patients who have experienced strokes or the resection of neoplasms; or have suffered from a degenerative disease. In recent decades neuroimaging has emerged as a powerful tool for the investigation of injury and particularly in mapping the location and extent of lesions. There is a degree of overlap between neuroimaging and the later clinical studies therefore I shall include clinical studies that have used neuroimaging within this section and consider neuroimaging of the healthy cerebellum separately.

It has been noted (Lalonde, 2000; Timmann et al., 2009) that the occurrence of a cerebellar stroke affords the opportunity to examine a patient who had experienced normal cerebellar development and function until the stroke event. This factor may allow clearer conclusions to be drawn from the examination of stroke patients than of patients who have chronic cerebellar disease and, to a lesser extent, those who have suffered a cerebellar neoplasm. In the case of chronic disease the possibility arises of functional adaptation, prior to examination, by the intact components of the brain to compensate for the damage experienced. The brain's adaptive response to damage is of particular concern for the research of cerebellar nonmotor functions as impairments may be mild and transitory (Alexander, Gillingham, Schweizer, & Stuss, 2012). Despite these concerns, efforts have been made to study the nonmotor effects of chronic cerebellar disease. As reviewed by Manto and Lorivel (2009), patients suffering from ataxia can exhibit disturbances of executive function, working memory, visuospatial processing and emotional stability, but the extent of the disturbances varies considerably both within and across patient subgroups. Within the common spinocerebellar ataxias (SCA), it has been noted that the condition that usually presents damage that is limited to the cerebellum (SCA6) has been shown to be least associated with cognitive disturbance (Globas et al., 2003; Klinke et al., 2010) and that these disturbances are more associated with extracerebellar damage (Bürk et al., 2003): though see also Orsi et al. (2011) who detected a uniform set of (frontal type) cognitive impairments across SCA groups.

More instructive insights have been gained into the possible nonmotor role of the cerebellum through the examination of stroke and tumour resection patients. The view of the cerebellum as purely a motor structure was challenged through the studies of cerebellar stroke conducted by Exner, Weniger and Irle (2004) and Schmahmann, Macmore and Vangel (2009). Exner et al. suggested a functional separation between the anterior and posterior cerebellum as they noted that lesions caused by posterior inferior cerebellar artery (PICA) stroke were associated with impairments to cognitive and affective functioning, whereas no impairments to these functions were observed after superior cerebellar artery (SCA) stroke. Schmahmann et al. further challenged the purely motoric view of the cerebellum by demonstrating that that even substantial cerebellar lesions arising from stroke do not necessarily result in motor deficits.

Further to this suggestion of a division between a motoric anterior and a multi-functional posterior cerebellum, lesion studies have also suggested both longitudinal functional divisions and lateralisation of function in the cerebellum. As will be recalled, the phylogenetic history of the cerebellum has suggested a role for the cerebellar vermis in the management of autonomic and emotional processing (Snider & Maiti, 1976). Support for this proposal was given by the study of cerebellar patients by Schmahmann and Sherman (1998), who found that patients who presented with affective alterations, such as blunting of affect, all had damage to vermal or paravermal areas. Riva and Giorgi (2000) noted that resection of vermal tumours resulted in behavioural disturbances to a greater degree than damage to other regions of the cerebellum. Turner, Paradiso and Marvel (2007) detected both a reduction in response by, primarily vermal and paravermal, stroke patients to pleasant emotional stimuli when compared to controls. Additionally, through the use of positron-emission tomography (PET) they noted that whilst the stroke patients' subjective experience of frightening emotional stimuli was reported as normal, scans revealed altered activity in extracerebellar networks suggesting a compensatory mechanism to offset cerebellar damage. A role for the cerebellar vermis in emotional learning was proposed by Maschke et al. (2002) who observed that lesions to the cerebellar vermis resulting from stroke have been associated with a failure to learn new fear associations, whilst baseline emotional response remains unaffected.

Studies of the effects of stroke and surgical resection on the posterolateral cerebellum have lent some support the idea of a lateralised cerebellum. The specialisation of the left cerebral hemisphere for language and the converse right cerebral hemisphere advantage for visuospatial processing is widely-accepted (Jonides, Smith, Koeppe, & Awh, 1993; Wada, Clarke, & Hamm, 1975). Given the largely crossed connectivity between the cerebral and cerebellar hemispheres (Krienen & Buckner, 2009; Middleton & Strick, 1994) it has been proposed that similar, but opposite specialisations may be present in the cerebellum. Several case studies of the aftermath of cerebellar stroke have observed that right-sided cerebellar lesions have impaired verbal short term memory (Gasparini & Piero, 1999; Silveri, Di Betta, Filippini, Leggio, & Molinari, 1998). Riva and Giorgi (2000) noted impairments to verbal and auditory sequential memory in children treated for lesions to the right cerebellar hemisphere, which contrasted with impairments to visual and spatial memory after left-sided lesions (2000). Scott et al. (2001) observed similar lateralisation effects with a ‘plateauing’ of children’s verbal or visual skills after surgical treatment for right- or left-sided cerebellar tumours, respectively. Gottwald, Wilde, Mihajlovic and Mehdorn (2004) found a suggestion of the proposed specialisations, but qualified their findings by noting that damage to the right posterolateral cerebellum was, in general, more disabling. Other studies, however, have indicated a cerebellar role in nonmotor behaviours, but have not shown a clear lateralisation. Neither de Ribaupierre, Ryser, Villemure, & Clarke (2008) nor Ravizza et al. (2006) observed a distinction between the effects of left- and right-sided cerebellar lesions on performance of visual and verbal working memory; Tedesco et al. (2011) observed that the size of the lesion and the involvement of the cerebellar nuclei is more predictive of the extent of nonmotor symptoms rather than the side of the injury; and Peterburs, Bellebaum, Koch, Schwarz, & Daum (2010) proposed that patient age at the time of cerebellar injury was a more important predictor of the cognitive effects of cerebellar damage than the hemisphere injured.

The observations gathered from clinical studies of cerebellar injuries have added detail to, and been informed by, the ‘Cerebellar Cognitive Affective Syndrome’ (CCAS) (Schmahmann, 1997), which has become the most widely-accepted view of the nonmotor symptoms that may result from cerebellar injury. Schmahmann noted that damage to the posterior lobe of the cerebellum was often associated with a stereotypical set of non-motor symptoms. These symptoms included impaired executive function elements such as set shifting, planning, abstract reasoning, control of working memory and visuospatial organisation. Additional impairments were observed in verbal fluency, with speech production becoming agrammatical and dysprosodic. Schmahmann also noted the frequent occurrence of emotional disturbances such as blunting of affect or the inappropriate expression of affect. In contrast to previous observations regarding the subtle nature of cerebellar non-motor disturbances Schmahmann stated that these symptoms were "clinically relevant and noted by family members and nursing and medical staff" (Schmahmann, 1998). Given the characteristic set of symptoms and the previous knowledge of the role of cerebellum in motor behaviours, the concept of the CCAS evolved from the underlying idea that non-motor symptoms represented a 'dysmetria of thought' (Schmahmann, 1991) that impaired rather than abolished affected non-motor behaviours in a manner analogous to that seen in motor behaviours after cerebellar damage.

In the years following the proposal of the CCAS, improvements in neuroimaging technology have allowed the addition of further detail to the concept: high resolution structural neuroimaging has enabled the construction of a clearer mapping between cerebellar damage and the resultant neuropsychological symptoms. As reviewed by Timmann et al. (2009), the application of high field strength magnetic resonance imaging and new analytical techniques has allowed a more accurate assessment to be made of the extent of cerebellar lesions and delineate the regions affected. An example of this approach being the application of voxel-based symptom lesion mapping (VBSLM) used by Richter et al. (2007) to demonstrate the correspondence of lesions to the right posterolateral cerebellum and impairments to verbal processing. The application of voxel-based morphometry (VBM) and the use of probabilistic atlases (Diedrichsen, Balsters, Flavell, Cussans, & Ramnani, 2009) have allowed detailed analysis to be conducted into the condition of the cerebellum in a range of chronic and developmental conditions. The most striking findings, as regards the cerebellar role in nonmotor function, have been the consistently-reported cerebellar abnormalities in autism (Fatemi et al., 2012; Stoodley, 2014). The consistent findings of an enlarged cerebellum that, however, is relatively sparse in Purkinje cells (Amaral, Schumann, & Nordahl, 2008; Palmen, van Engeland, Hof, & Schmitz, 2004) hints at a key role for the cerebellum in a condition that is primarily characterised by psychosocial rather than motoric disturbances.

The findings that emerged from clinical neuroimaging of the cerebellum have inspired a wide range of neuroimaging studies of the healthy cerebellum that have in turn allowed further insight into the cerebellar role in nonmotor behaviour.

Functional neuroimaging of the healthy cerebellum

Obtaining neuroimaging data from the cerebellum presents a number of challenges above those entailed in the scanning of other brain areas. Not only is the cerebellum smaller than the cerebrum, but its proximity to major blood vessels results in disturbances in the uniformity of the magnetic field and movement during the cardiac and respiratory cycles. In addition to these factors, the hypotheses regarding cerebellar involvement in nonmotor functions ascribe a potential role within these behaviours to specific regions of the cerebellum rather than the organ as a whole and therefore a high level of scanning precision is required. Despite these challenges, improved imaging and analytical techniques have allowed the extraction of usable functional data from both the cerebellar cortex and nuclei. Meta-analyses conducted by Stoodley & Schmahmann (2009) and E, Chen, Ho, & Desmond (2014) have gathered the findings of cerebellar imaging studies across multiple domains of nonmotor behaviours and have highlighted the cerebellar role in timing, emotional response, working memory, spatial processing and executive function. Emerging from these analyses is support for the view of a cerebellar functional topology with sensorimotor integration, supported by multiple somatotopic representations, in the anterior lobe and superior regions of the posterior lobe, and cognitive and emotional functions supported by posterolateral areas. Stoodley and Schmahmann noted that no activation peaks were observed for ‘higher’ (i.e. non-motor) functions in the anterior lobe of the cerebellum, whilst significant activations during performance of these behaviours were seen primarily within lobule VI and the cerebellar crura. Stoodley and Schmahmann’s analysis noted the presence of a vermal activation peak during emotional processing, but also activations in the most lateral regions of the cerebellar hemispheres, which does not support a strict division between emotional and cognitive functions between the vermis and the hemispheres. Stoodley and Schmahmann found a degree of support for the proposition of the lateralised cerebellum with verbal tasks more likely to activate the right hemisphere and spatial processing more associated with left hemisphere activity; however, it was noted that there was a degree of bilateral activation during the execution of both task sets, again suggesting that any functional lateralisation is less than complete. The findings of the meta-analysis conducted by E et al. were largely confirmatory of the earlier study: once again the cerebellar crura were found to be strongly activated during cognitive tasks such as language processing, working memory and tests of executive function. Strong activation for language and verbal tasks was found in the right cerebellar crura, though a strong lateralisation between spatial and verbal working memory was not observed.

Studies that have examined activation of the cerebellar nuclei have given support to the view of the cerebellum’s phylogenetically newer regions being the major loci of its involvement in non-motor behaviours. A review by Habas (2010), whilst noting the especial difficulties in obtaining functional data from the DCNs, confirmed preferential activation within the ventral dentate nucleus for cognitive tasks. This finding in accord with other work (such as Küper et al. (2011)) that has built on the theory of a functional division between the dorsal motoric and ventral cognitive regions within the dentate nucleus.

A theme emerging from recent neuroimaging studies of the healthy cerebellum is the investigation of the hypothesis that the cerebellum is the key structure in in encoding and employing internal models for use across motor and non-motor behaviours. Internal models have been classified as 'forward': a mental representation of either the anticipated sensory consequences of an action; or 'inverse': a representation of the action required to effect a desired change (Wolpert et al., 1998). Evidence for a cerebellar role in abstract encoding within the context of task automation was provided by Balsters and Ramnani (2011), whilst Moberget, Gullesen, Andersson, Ivry, & Endestad (2014) used semantic tasks to demonstrate cerebellar activity consistent with internal model use in prediction and reaction to violated expectations. Yang, Wu, Weng and Bandettini (2014) associated activity within lobule VI and Crus I with the implementation of internal models and practice-based improvements on verb generation tasks. Guediche, Holt, Laurent, Lim and Fiez (2014) reported cerebellar activity consistent with internal model adjustment in dealing with speech perception errors. These most recent findings have allowed the development of the idea that the cerebellum has a role in non-motor function towards an account of what is this role and how it is performed. These findings may be used to guide the formation of testable hypotheses to enable further detail to be uncovered of cerebellar operation within these behaviours.

Limitations of previous methods

The conclusion that the cerebellum plays a role in the implementation of non-motor behaviours has not been universally accepted. A contrasting view of both cerebellar evolutionary development and the activity observed via neuroimaging during non-motor tasks has been advanced by Glickstein and others. Those sceptical of a cerebellar role in non-motor behaviours have suggested that the posterolateral cerebellum's links to frontal areas of the brain may form a component of the ocular motor control system (Doron, Funk, & Glickstein, 2010; Haarmeier & Thier, 2007; Stein & Glickstein, 1992) and that the expansion of the cerebellum does in fact reflect the requirements of complex human manual behaviours (Glickstein, 2007). Scope for dissent as to the role of the cerebellum in non-motor behaviours is afforded by limitations associated the methods that have been most commonly used for its investigation. Functional neuroimaging requires inferences to be drawn from alterations in regional blood oxygen levels, which is an indirect measure of neural activity. Neuroimaging provides only a correlation to between neural activity and experimental task demands and therefore caution is required in the interpretation of results (Logothetis, 2008). Animal studies are of limited utility in the consideration of the contribution of the cerebellum to the human cognition given the structural differences between the brains of species and the existence of elements of abstract thought that are currently held to be unique to humans (Koziol et al., 2011). Clinical studies of the human cerebellum have, as noted previously, been impeded by the possibility of attendant damage to extracerebellar structures, plasticity and reorganisation in the aftermath of cerebellar damage and the deployment of compensatory strategies by patients to ameliorate cerebellar impairments.

The limitations associated with prior methods of investigation are a strong justification for the use of non-invasive brain stimulation techniques for cerebellar research. The dependency of the brain on electrochemical activity for its operation has been understood for many years. Evidence has accumulated that the operation of the brain can be temporarily altered by the application of electrical or magnetic fields: initially through direct application (Heath, 1977; Penfield & Boldrey, 1937) and then transcranially, i.e. through the intact skull (Barker, Jalinous, & Freeston, 1985). The use of transcranial magnetic and electrical stimulation renders practical the experimental manipulation of the healthy cerebellum. Transcranial Magnetic Stimulation (TMS) entails the induction of an electric current through brain tissue by the generation of a magnetic field by a rapidly changing electric current in a coil held on the scalp. The induced current can either produce action potentials that introduce temporary disorder to an affected area, or, when applied repetitively at a lower intensity, can be used to raise or lower the resting potential of affected neurons' membranes thus temporarily altering their excitability. In a similar manner transcranial current stimulation (tCS) creates a current flow between electrodes positioned on the scalp, which results in an amount of current flowing through brain tissue. The flow of current across neural tissue is believed to alter neuronal resting potentials and thus affect neuronal excitability in a manner similar to repetitive TMS (rTMS). The temporary disruption of brain activity by TMS has been described as creating 'virtual lesions' (Walsh & Rushworth, 1999) allowing inferences to be drawn to the function of an area by observing behaviour changes resulting from stimulation.

As will be reviewed in the next chapter, transcranial stimulation of the cerebellum presents a number of challenges. The presence of highly conductive tissue and cerebro-spinal fluid and the nature of the surrounding cranium raise issues for the selection of appropriate stimulation parameters. Despite these challenges, transcranial stimulation has proved a safe and effective method of cerebellar investigation and was therefore examined with a view to use within the studies described in this thesis.

The experiments described in this thesis examine aspects of working memory, lexical processing and emotion processing. The following sections provide a brief introduction to each of these elements in the context of the proposed cerebellar role within each behaviour; more comprehensive consideration of these elements is given in the relevant following chapters.

Working memory

Working memory has been defined as a "system that provides temporary storage and manipulation of the information necessary for such complex cognitive tasks as language comprehension, learning, and reasoning." (Baddeley, 1992b). In their widely-accepted model, Baddeley and Hitch (1974) characterised working memory as comprising two modality-specific support systems, the visuo-spatial sketchpad and the phonological loop, under the direction of a co-ordinating central executive. The central executive is responsible for the dispatch of information to the slave systems and plays a role in managing and sustaining attention whilst cognition is performed. The phonological loop comprises the phonological store, capable of holding several seconds of verbal information, and the articulatory control system which encodes phonological data and acts to refresh the phonological store using subvocal rehearsal. The visuo-spatial sketchpad plays an analogous role to the phonological loop for the short term storage of visual data during cognition. Baddeley augmented his model of working memory with the additional of a further slave system, the episodic buffer (Baddeley, 2000), which acts to bind the multimodal information associated with an event into a single episodic memory.

A supportive role for the cerebellum role in working memory has been proposed based on the discovery of pathways linking the cerebellum to areas of the cerebral cortex associated with executive, visuo-spatial and auditory processing. Evidence has been gathered from neuroimaging and clinical studies that suggests a cerebellar role in verbal, visual and spatial working memory, as will be reviewed in chapters 3, 4 and 5 respectively.

Language processing

Substantial evidence exists for a left cerebral hemispheric specialisation for language in the majority of right-handed humans (Wada et al., 1975). The majority of cerebro-cerebellar pathways connect contralateral hemispheres of the two structures (Ito, 1984). It has therefore been hypothesised that if the cerebellum supports language processing then it is probable that the right cerebellar hemisphere would be more active in this function. Evidence for right cerebellar activity during language processing has been obtained, primarily from neuroimaging (e.g. Jansen et al., 2005), though, as detailed above, linguistic disturbances following injury to the right cerebellum have also been reported. The experiment described in chapter 6 examines a possible role for the right cerebellum in making lexical decisions i.e. deciding whether a presented string of letters forms a valid word. It is believed that multiple, parallel cognitive processes are activated upon presentation of a stimulus as orthographic, morphological and semantic elements are combined into competing partially-active lexical representations (Barca & Pezzulo, 2012). Given the proposed view of the cerebellum as supporting time-critical processing a cerebellar role within this behaviour is plausible: further exploration of this possibility is presented in Chapter 6.

Emotion processing

The human emotional system has been conceptualised as a development from evolutionarily older mechanisms for the promotion of survival through homeostasis, i.e., the detection of a need within the organism and the reconfiguration of motivational parameters to incline the organism to seek satisfaction of the need (Panksepp, 1998). A phylogenetic pathway has been proposed within human evolution that traces the development of the emotional systems from the simple stimulus-response mechanisms of the ‘reptilian brain’ through primary and complex emotional behaviours. As will be recalled, the evolution of the human cerebellum has been characterised as an expansion from the central, phylogenetically older, flocculonodular and vermal regions to the more recent lateral areas of the neocerebellum. In addition to the pathways that have been found to link the posterolateral cerebellum to ‘cognitive’ areas of the cerebrum, circuits have been discovered linking the cerebellar vermis to core components of emotional/homeostatic structures such as the hypothalamus (Sacchetti, Scelfo, & Strata, 2009). A role for the cerebellum in emotion and homeostatic systems is highly plausible given the ‘homeostatic’ nature of the cerebellum’s well-documented role in motor behaviours, i.e., enabling the smooth implementation of motor actions through rapid adjustment following perturbation. The experiment described in chapter 6 investigates the cerebellar role in primary emotions to determine whether a topological specialisation can be inferred.

Current opportunities

This chapter has demonstrated how the view of the cerebellum as active solely in motor behaviours has been challenged through an accumulation of evidence indicative of a wider range of activity. The plausibility of a cerebellar role in non-motor behaviours has been outlined, as supported by the diverse cerebro-cerebellar pathways and the disproportionate expansion of the human cerebellum. Evidence from clinical, animal and neuroimaging studies has been presented with an indication given of the limitations associated with each of these methods for the investigation of the cerebellar role in non-motor behaviours. The presence of methodological limitations and the observation that the cerebellar role in non-motor behaviours is neither universally accepted nor fully understood is a solid justification for a new approach to its investigation. The availability of a safe and effective means of experimental manipulation in the form of transcranial stimulation of the cerebellum presents an opportunity to examine the cerebellar role in non-motor functions and provide causal rather than correlative evidence.

The experiments in this thesis describe an investigation into the cerebellar role in verbal, visual and spatial working memory, language and emotion processing. Based on the evidence that exists regarding a cerebellar role in these functions and the effects of transcranial stimulation techniques the following hypotheses will be explored within this thesis:

- Transcranial Stimulation applied to the right cerebellar hemisphere of right-handed participants will affect verbal working memory to a greater degree than applied to the left cerebellar hemisphere.
- Transcranial Stimulation applied to the left cerebellar hemisphere of right-handed participants will affect visual and spatial working memory to a greater degree that applied to the right cerebellar hemisphere
- Transcranial stimulation applied to the right posterolateral cerebellum will affect language functions to a greater extent than emotion processing
- Transcranial stimulation applied to the cerebellar vermis will affect emotion processing to a greater extent than language functions

Through the examination of these hypotheses an elucidation of the role of the cerebellum in non-motor behaviours is sought, thus providing an original contribution to knowledge in this field.

Chapter 2 - Brain stimulation studies of non-motor cerebellar function: A systematic review

A version of this chapter appeared as: Tomlinson, S. P., Davis, N., Bracewell, R. M. (2013) *Neuroscience and Biobehavioral Reviews* 37(5) 766-789.

Abstract

Evidence for a cerebellar role in non-motor functions has been demonstrated by clinical and neuroimaging research. These approaches do not allow causal relationships to be inferred though the experimental manipulation of the cerebellum. Transcranial magnetic and current stimulation may allow better understanding of the cerebellum via the temporary alteration of its operation in healthy volunteers. This review examined all studies of the cerebellar role in non-motor functions using non-invasive brain stimulation. Of 7585 papers captured by an initial search, 26 met specific selection criteria. Analysis revealed behavioural effects across learning, memory, cognition, emotional processing, perception and timing, though the results were not sufficiently similar as to offer a definitive statement of the cerebellum's role. The non-invasive application of stimulation to the cerebellum presents challenges due to surrounding anatomy and the relatively small target areas involved. This review analysed the methods used to address these challenges with a view to suggesting methodological improvements for the establishment of standards for the location of cerebellar stimulation targets and appropriate levels of stimulation.

Introduction

The cerebellum has traditionally been viewed as a brain structure involved in the implementation of motor behaviour. Early clinical studies e.g. (Luciani, 1891) suggested that damage to the cerebellum resulted in a loss of muscle tone, disorganisation of movement and loss of balance. Several early investigators also noted cognitive and psychiatric changes in patients who had suffered cerebellar injury (reviewed in Schmahmann, 2010). These suggestions of non-motor cerebellar function were largely ignored in subsequent investigations as the reported effects were often subtle, contradictory and overshadowed by the effects of cerebral damage. Consideration of cerebellar contributions to non-motor behaviour was not part of mainstream research for several decades. In recent years, however, there has been renewed interest in the possibility of the cerebellum playing a role in autonomic, affective and cognitive functions with findings derived from newly available technologies. It is the purpose of this systematic review to examine the use of several recently developed brain stimulation techniques in the investigation of cerebellar contributions to non-motor behaviour. This review will examine the methodology and findings of studies that have used transcranial current stimulation and transcranial magnetic stimulation of the cerebellum and discuss the contribution that brain stimulation techniques may make to cerebellar research.

Justification for current review

Cerebellar stimulation has been used in recent years in an attempt to corroborate evidence gained from imaging and clinical work as to cerebellar involvement in non-motor behaviour, to infer the nature of this role and to localise function within the cerebellum. A wide range of tasks, targets and techniques has been used in this research and it is therefore appropriate to review the approaches taken in order to determine which approaches have proved most successful, to summarise the information that has been gained and to highlight the difficulties encountered so that methodological improvements may be suggested.

A further motivation for this review is that the nature of any cerebellar contribution to non-motor behaviours remains somewhat controversial and therefore examination of the findings of relevant studies may be of use within this context.

This review will first discuss the parameters used and the methodological decisions taken across all studies and then examine groups of studies categorised according to the behavioural function targeted.

Methods

A PubMed search was performed using the following search terms without restriction of date or database field: ((cerebellum) OR (cerebellar)) AND ((stimulation) OR (transcranial) OR (theta burst)). This search returned **7585** papers, which were assessed according to the following inclusion criteria:

- Neurologically normal, human subjects
- Cerebellar stimulation target
- Magnetic or electrical stimulation
- Transcranial, rather than deep brain or cortical stimulation
- Non-motor
- Not purely physiological, neurological, histological etc.
- Empirical research, not review, methods or best practice paper

The PRISMA flow diagram is shown in Figure 1.

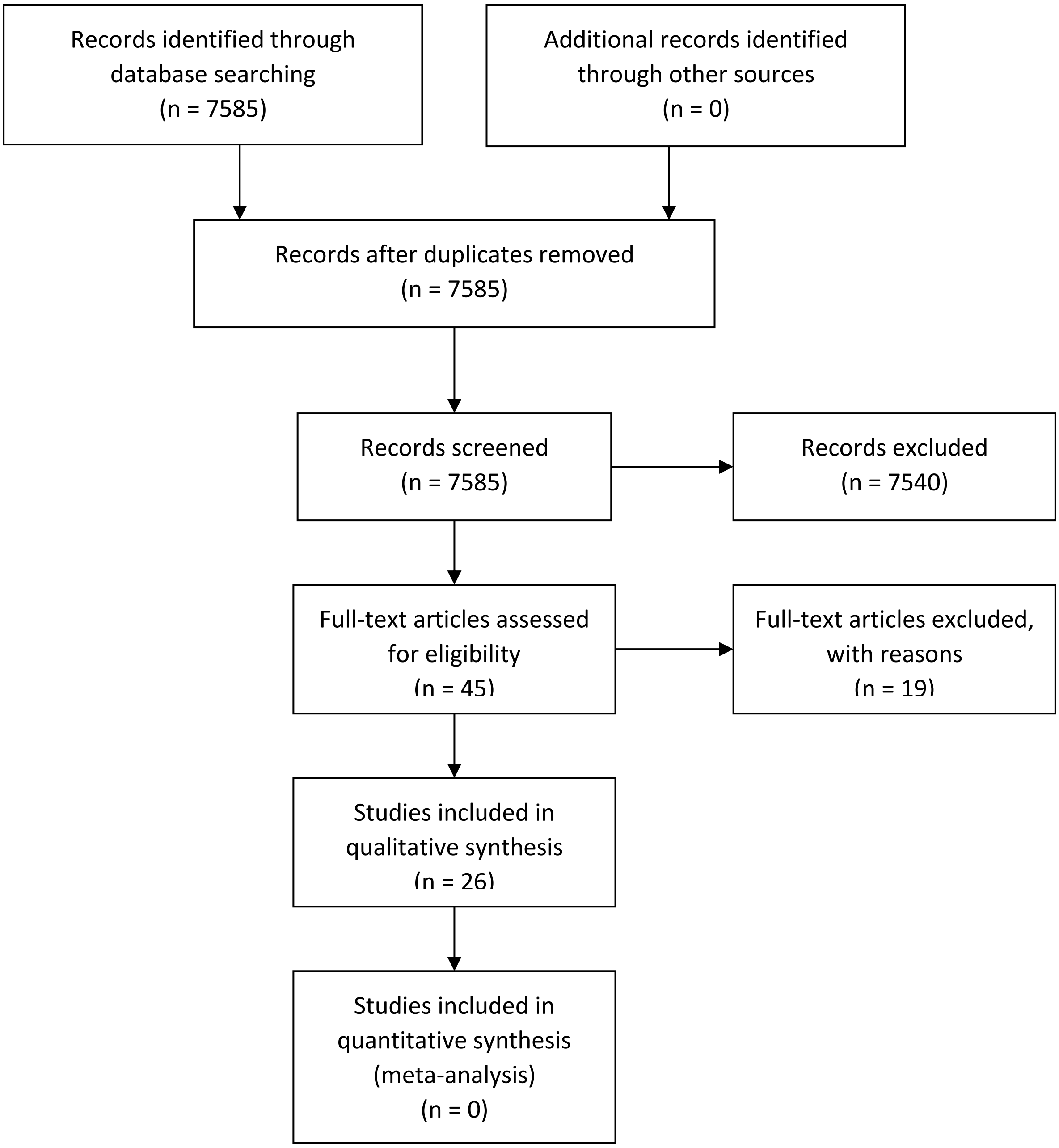

Figure 1. PRISMA flow diagram

The review of abstracts rejected **7540** papers and accepted **45** for full review. The reasons for rejection are detailed in Table 1:

Non-human	2817
No transcranial stimulation	2434
Clinical, Physiological or *in vitro*	1658
Review, methods or best practice	296
Motor	289
Not cerebellar	31
Modelling or simulation	14
Unobtainable	1

Table 1. Reasons for exclusion after review of abstracts

A full-text review of the remaining papers rejected **19** and accepted the remaining **26**. The reasons for rejection were as follows:

Motor	13
Physiological	3
Non-human	2
No transcranial stimulation	1

Table 2. Reasons for exclusion after full-text review

Studies included in the systematic review can be seen in Appendix A.

It was concluded that a meaningful quantitative synthesis of the results could not be accomplished given the relatively small number of studies in each category and their dissimilarities. This review should therefore not be considered to be a meta-analysis.

Discussion

The results of our review showed that several transcranial magnetic stimulation (TMS) paradigms have been employed for cerebellar non-motor research. The paradigms used can be divided into single pulse and repetitive TMS (see Walsh & Rushworth, 1999 for a discussion of their differences). Single pulse TMS is generally delivered at an intensity sufficient to generate action potentials in targeted brain regions: this externally-triggered discharge of neurons introduces temporary disorder into the activity of the targeted area and can be used to highlight the role played by a brain region within a behaviour through its disruption (Hallett, 2007). Repetitive TMS most commonly refers to the use of a number of magnetic pulses delivered at regular intervals and is generally described according to the frequency at which the pulses are delivered, typically from 1 Hz upwards. It has been demonstrated that low frequency (i.e. around 1 Hz) repetitive TMS produces a transient reduction in cortical excitability, whereas higher frequency stimulation (typically 5 Hz and above) produces a reduction in cortical inhibition (Fitzgerald, Fountain, & Daskalakis, 2006). A range of frequencies from 1 to 25 Hz were used within the reviewed studies therefore it is necessary to consider results from the use of cerebellar repetitive TMS within this context.

A more recently-described repetitive TMS paradigm is theta burst stimulation, which uses patterns of three 50 Hz pulses delivered at a frequency of 5 Hz and has been shown to produce behavioural effects after much shorter stimulation periods than previous methods (see Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005 for details). It has been demonstrated that the continuous application of TBS pulse trains has an inhibitory effect on cortical activity, whereas the incorporation of pauses between pulse trains increases cortical excitability. All except one of the studies that employed TBS within the scope of this review used a continuous TBS paradigm to inhibit cerebellar activity.

Within the following discussion we shall use the abbreviation TMS for transcranial magnetic stimulation in general, TBS exclusively for theta burst stimulation, and rTMS for any TMS paradigm other than TBS that uses multiple magnetic pulses.

No transcranial current stimulation techniques other than transcranial direct current stimulation were seen to have been used for cerebellar non-motor research. For clarity we use the abbreviation tDCS to refer to all transcranial current stimulation studies and techniques within the scope of the review. Several studies within the scope of the review made use of tDCS. It has been demonstrated that anodal tDCS has an excitatory effect on brain activity whereas cathodal tDCS increases inhibition. Both tDCS methods were employed within the studies reviewed allowing the contrast between the effects of facilitation and inhibition of cerebellar activity.

Stimulation Parameters and Procedure

Targets

The majority of relevant studies used distances measured from the inion to locate their target sites. Of interest was the diversity of co-ordinates selected when similar cerebellar regions were to be stimulated. The most commonly mentioned cerebellar regions were lobules VI and VII (within 15 of the studies) and the cerebellar crura. Scalp co-ordinates used for the stimulation of the crura were typically 1 cm below the inion and between 3 and 10 cm lateral. MRI was employed within three studies (Demirtas-Tatlidede, Freitas, Pascual-Leone, & Schmahmann, 2011; Desmond, Chen, & Shieh, 2005; Zunhammer et al., 2011) to locate cerebellar targets, either by within-task functional scanning or by use of structural scans and a cerebellar atlas. The approach taken by Demirtas-Tatlidede et al. compared individual structural scans with a cerebellar atlas to locate targets in each case then employed a neuro-navigation system to match cerebellar targets to appropriate coil positions on the scalp. This method offers the best assurance that the same physical (as opposed to functional) cerebellar location will be stimulated in each case. Where functional scanning was employed to locate cerebellar targets (as in Desmond et al.) a diverse range of target locations was observed: it is clear that there would have been discrepancies between these locations and any positions selected using scalp co-ordinates. The most interesting choice of target (Argyropoulos & Muggleton, 2013) was 10 cm to the right of the inion, which was based on co-ordinates obtained from the prior use of an individual's MRI and neuro-navigation software. Given the phylogenetic argument that the most lateral regions of the cerebellum are those most likely to participate in 'higher'-functions (e.g. Leiner, Leiner, & Dow, 1986) it is appropriate that more lateral regions be explored as targets for cerebellar stimulation within cognitive experiments. As the study's authors note, whilst *de facto* landmark-based co-ordinates have been generated it is an advantage to use neuro-navigation software where available to ensure uniform targeting of cerebellar regions. This consideration may be most apposite when targeting the more lateral regions of the cerebellum given increased scalp to cortex distance and the compounding of conformation differences from medial to lateral areas. It is interesting to note that the co-ordinates selected by a number of the studies could be traced back to those selected as part of the study conducted by Théoret, Haque, & Pascual-Leone (2001), though the rationale for the selection of these co-ordinates is not explained within the original study, excepting that a target over the lateral cerebellar hemisphere was required.

Non-stimulation studies have suggested a division in cerebellar function between vermal/medial areas involved in visceral and emotional processes and lateral areas involved in cognition (reviewed in Hu, Shen, & Zhou, 2008). This division was reflected in the selection of target sites for stimulation with the majority of cognitive studies selected lateral sites and all emotional/somatic studies targeted the vermis. With the exception of Argyropoulos, Kimiskidis, & Papagiannopoulos (2011) and Argyropoulos (2011), which anticipated a cognitive effect from paravermal stimulation, where vermal targets were included in cognitive studies they were employed for comparative or control purposes with the *a priori* suggestion that an effect would be seen after lateral stimulation: *vice versa* for lateral targets in studies of the cerebellar role in emotion.

The majority of studies examining cognition, learning or memory used sites on the right, lateral cerebellum: this reflects the crossed connections between the cerebellum and the cerebral hemispheres and the specialization of the left cerebral hemisphere for language (in the majority of right-handed subjects) and the use of words or letters within the tasks. As noted below, where assessed, all participants were right-handed.

Targets selected in the Perception and Timing categories were approximately equally divided both across hemispheres and between lateral and vermal targets. This perhaps reflects the situation in the literature where a clear functional localization has not been widely accepted.

Intensity, Duration and Stimulation Equipment

Transcranial Magnetic Stimulation:

Selecting the appropriate intensity for TMS of the cerebellum represents a challenge. The intensity of cerebellar stimulation must be set at a level sufficient to reach and affect cerebellar neurons, whilst not reaching brainstem structures and only causing activation in peripheral structures at a level which is tolerable to participants. Whilst tolerability can be assessed during an experimental session, it is difficult to be assured that an appropriately high level of stimulation is being delivered. The *de facto* standard for setting intensity within TMS studies is as a percentage of a subject's motor threshold. Within the studies covered by this review those employing repetitive TMS or continuous TBS typically selected either 80 or 90% of active or resting motor threshold; higher intensities were chosen for single-pulse TMS (120% AMT) or intermittent TBS (100% AMT), which were justified due to the lower seizure risk presented by these modes of stimulation. Reservations have been expressed as to the validity of motor thresholds as a measure of stimulation delivered to non-motor brain areas (e.g. Stewart, Walsh, & Rothwell, 2001). A recently published study (Stokes et al., 2013) suggests that some of these concerns may be unwarranted, given a robust demonstration of dose-dependent stimulation effects across motor and non-motor areas of the *cerebral* cortex, but caution remains appropriate as regards motor threshold applicability to the cerebellum. Stimulation of the cerebellum differs from that applied to cerebral areas due to factors such as the curvature of the base of the skull, the presence of the foramen magnum, increased distance from the scalp of lateral cerebellar structures, relative amounts of local cerebro-spinal fluid and a marked contrast in typical electrical activity (‘ultrafast’ waves dominating the cerebellar EEG profile (Niedermeyer, 2004)). The authors of several of papers within this review (Argyropoulos et al., 2011; Argyropoulos & Muggleton, 2013; Argyropoulos, 2011; Schutter & van Honk, 2006, 2009) showed an appreciation of the potential inapplicability of motor thresholds and elected to use a set percentage of maximum stimulator output (MSO), generally 45% MSO. MSO-based stimulation will necessarily be dependent on the individual stimulator and coil employed. Two different stimulation machines were used in the studies within the scope of this review and, in combination with the coils used, the authors quantified MSO as either exactly or approximately 2 T.

It is clear that further research is required to establish standards for the intensity levels of cerebellar stimulation since both methods described above are not wholly satisfactory. It is possible that modelling work may be able to give more information as to the amount of stimulation reaching cerebellar tissue, though it may also be the case that the observable effects of cerebellar stimulation itself may allow standards to be derived. A recent study (Mottolese et al., 2013) demonstrated that motor potentials could be evoked using direct electrical stimulation to cerebellar tissue. Whilst this study used direct rather than induced current within the cerebellum, it has identified cerebellar targets that can produce MEPs that may be used by future transcranial approaches.

The duration of stimulation ranged from 40 seconds in most of the continuous theta burst stimulation studies to a maximum duration of 20 minutes, wherein the highest number of TMS pulses were delivered (20,000 in this case).

Coil-orientation is a factor in the use of TMS since this will determine the direction of the current induced in brain tissue. Previous studies (e.g. Amassian, Eberle, Maccabee, & Cracco, 1992) have suggested that the effects of TMS are most marked when the current cuts across a neuron’s axon, whereas a current flowing in parallel to the axon is believed to have limited effect. Given the largely horizontal orientation of the parallel fibres, axons of the numerous cells of the granular layer and their being the axon system most accessible to stimulation, it seems appropriate that all of the studies used a vertical coil handle orientation, which induces an upward current cutting across the parallel fibres as this was shown to be the most effective at altering cerebellar function (Ugawa, Uesaka, Terao, Hanajima, & Kanazawa, 1995).

All but one of the studies used a figure-8 coil, which promotes stimulation focality (Ravazzani, Ruohonen, Grandori, & Tognola, 1996), though Desmond et al. (2005) used a double cone design, which is believed to increase the depth to which stimulation is effective (as discussed in Ugawa et al., 1995). The rationale for the selection of the double cone coil is not elaborated within the study, but this coil design is particularly suitable for delivering stimulation to brain regions at a greater distance from the scalp (Roth, Zangen, & Hallett, 2002) and, as noted in several studies (e.g. Argyropoulos et al., 2011; Argyropoulos & Muggleton, 2012), lateral cerebellar targets can be at a depth beneath the scalp of around 2 cm.

Transcranial Direct Current Stimulation:
All 3 studies used an intensity of 2 mA based on previously published parameters (Nitsche et al., 2003) and active electrode surface areas of between 21 and 42 cm² resulting in a maximum current density of 0.0095 mA/cm². These are well below the values believed to be capable of producing tissue damage, though more recently published work advises caution particularly in view of the use of inference from animal models (Bikson, Datta, & Elwassif, 2009).

Of particular interest was that all of the studies within this review employed an extra-cephalic reference electrode: concerns regarding the efficacy and safety of such montages have previously been expressed. It is known that a substantial amount of the current used in tDCS is shunted away from brain tissue by the skull and cerebro-spinal fluid (as illustrated in Miranda, Lomarev, & Hallett, 2006). This situation is compounded for cerebellar stimulation given the necessary positioning of the active electrode in proximity to the inion, which acts as the anchor point for the highly conductive muscle tissue of the neck. This raises the question of whether sufficient current will reach the cerebellum to affect its operation using a montage that strongly favours current flow away from this structure. Understanding the current flow within cerebellar tDCS is further complicated by the presence of the foramen magnum, which may have significant effects on current flow depending on the stimulation montage used. The presence of a large opening in the resistive material of the skull may either provide a conduit for the flow of current away from brain tissue (as modeled in Datta, Baker, Bikson, & Fridriksson, 2011) or may act to focus the flow of current (Mekonnen, Salvador, Ruffini, & Miranda, 2012; Nitsche et al., 2008) with possible implications for stimulation 'dosage' and the experimenter's ability to limit stimulation to structures of interest.. This concern is particularly salient for stimulation montages that incorporate extra-cephalic reference electrodes: Nitsche et al. (2003) noted that whilst the use of extra-cephalic electrodes avoids potential confounds arising from the activation of other brain structures outside the focus of a stimulation study, current flow in proximity to brainstem structures can produce adverse effects (Lippold & Redfearn, 1964). These cautions have led to the use of cephalic reference electrodes in the great majority of brain stimulation studies (outside the scope of this review), though a more recent physiological study (Vandermeeren, Jamart, & Ossemann, 2010) confirmed the absence of any adverse effects after a montage that employed an extracephalic electrode. Given the lack of evidence for adverse effects from the use of extra-cephalic electrodes and the positive results listed within the reviewed studies this arrangement may become standard for cerebellar tDCS, though further work to demonstrate the current flow entailed within the use of this technique would be highly beneficial.

The studies used stimulation periods of 15 or 20 minutes: these are above the durations found to induce changes in excitability in motor cortex lasting up to one hour (as reviewed in Nitsche et al., 2008), although limited data are available on the ratio between current delivered and the duration of altered cerebellar function. Galea, Jayaram, Ajagbe and Celnik (2009) demonstrated altered cerebellar function for up to 30 minutes after cathodal tDCS at the same level of current as the studies within this review, though with a longer stimulation period (25 minutes).

Stimulation to Test Delay:

The effect of brain stimulation decays at a rate governed by stimulation duration and intensity (Nitsche et al., 2008; Gilio et al., 2007). In the majority of studies post-stimulation testing started immediately, presumably to make use of the intervention at its level of highest effect. However two theta burst stimulation studies (Argyropoulos et al., 2011; Hoffland et al., 2011) incorporated a 5 minute delay before post-stimulation testing: this practice is justifiable given evidence (Huang et al., 2005) that the behavioural effects of theta burst stimulation can take between 5 and 10 minutes to reach their peak. Similar data do not exist for tDCS, which invites queries as to the selection of stimulation-to-test delays of 5 and 35 minutes in Ferrucci et al. (2008)and Ferrucci et al. (2012). Within Ferrucci et al. (2008) comparison of reaction times (RTs) on a modified Sternberg test before and 5-minutes after tDCS did not show a significant difference with respect to sham, whereas participants improved their RTs 35 minutes after sham stimulation, but not after tDCS. The authors conclude that both anodal and cathodal stimulation interfere with practice-based learning between the two post-stimulation test sessions. The authors note that it is not clear whether the cause of this result is the influence of the stimulation during the performance of the first post-stimulation test block (i.e. stimulation impaired the learning that took place during the first post-stimulation block) or the subsequent delay between blocks (for example by preventing the non-conscious consolidation of learning for more effective performance in subsequent blocks). Further research to elaborate the mechanism underlying this finding is warranted.

Participants:

Participants were healthy adults, typically aged between 20 and 35. In all studies where handedness was assessed (24 of 26) all participants were right-handed.

Tolerability and Side-Effects:

Several authors reported concerns about the tolerability of cerebellar stimulation, indeed Rami et al. (2003) elected to schedule the session comprising cerebellar stimulation after stimulation of all other sites to avoid participant withdrawal. It appears, however, that these fears were not well-founded as very few, mild side effects were reported. No adverse effects were reported in 17 studies, the reports within the remainder applied to very few of the participants and detailed mild, transitory conditions such as muscle twitching, headache, muscle pain and, on one occasion, transient concentration problems. One participant reported side effects after sham stimulation, which raises the possibility that *verum* stimulation may not have been responsible for all of the side effects reported above. In only one experiment (Desmond et al., 2005) were there (3 from 17) subject requests for the stimulation level (120% MT) to be reduced for tolerability. Only one participant requested to be excused from the studies due to discomfiture (Argyropoulos & Muggleton, 2013). One study (Demirtas-Tatlidede et al., 2011) collected subjective participant reports that lateral cerebellar repetitive TMS was less comfortable than stimulation at medial sites due to increased activation of neck muscles. Of interest were the findings of two studies (George et al., 1996; Rami et al., 2003) where direct comparisons were made in the tolerability of cerebellar and cerebral repetitive TMS that both showed less discomfort resulting from cerebellar stimulation.

It must be noted, however, that a meta-analysis conducted by Brunoni et al. (2011) suggested that adverse effects of tDCS may be under-reported therefore the lack of reported adverse effects should not be interpreted as an assurance of their absence. The stimulation parameters used within the TMS studies were within the ranges suggested by Wassermann (1998) therefore the risk of seizures from repetitive TMS was well-managed.

Sham:

Establishing an effective sham condition is challenging in brain stimulation studies. TMS generates a loud click as the unit’s capacitor is discharged, and can generate muscle twitches and other sensations. tDCS, at higher current densities, can cause a ‘tingling’ sensation under the electrodes particularly when the current is increased or decreased (Poreisz, Boros, Antal, & Paulus, 2007), though effective blinding to tDCS condition has been demonstrated (e.g. Gandiga, Hummel, & Cohen, 2006). Sham conditions were used in 12 of the 26 studies. 6 TMS studies used the method of bringing the stimulation coil into proximity to the subject’s head and then orienting through 90° ahead of stimulation to ensure that the magnetic field did not penetrate the subject’s skull to a significant degree. The 3 other TMS studies used stimulation coils fitted with a metal plate under their iron coil so that the coil could be positioned as in *verum* stimulation, without current induction within the brain. These methods ensure that the experience of sound and physical contact associated with TMS are similar between sham and *verum*, but do not address the difference in muscle activation than can exist between conditions. The 3 tDCS studies using sham used a ramping-up and fade-out of current over a short period to ensure that participants experienced the characteristic tingling sensations. One of the studies (Pope & Miall, 2012) also exploited the tDCS machine’s test function to send a low level of current to the electrodes at intervals throughout sham stimulation.

Control of Task Motor Confounds:

A charge commonly levelled at studies that claim to show cerebellar involvement in non-motor domains is that activity detected in the cerebellum can be attributed to motor elements within the task, for example eye movement, that have not been controlled (e.g. Glickstein, 2007). Within the reviewed studies 15 of 26 contained a motor component that could confound the conclusions unless controlled.

The most common method for addressing potential motor confounds was to use the same motor components across multiple conditions within the same task (Argyropoulos & Muggleton, 2013; Argyropoulos, 2011; Bijsterbosch et al., 2011; Ferrucci et al., 2012; Schutter, Enter, & Hoppenbrouwers, 2009) across tasks (Pope & Miall, 2012)or across times of measurement (Ferrucci et al., 2008). Pope and Miall described their approach as a ‘parametric method to vary the level of cognitive relative to motor demands required to perform two information processing tasks’. Other studies prevented the on-line error-corrective nature of cerebellar motor activity from being a factor within their experiments by removing the time-critical elements of providing motor responses (Arasanz, Staines, Roy, & Schweizer, 2012; Oliver, Opavsky, Vyslouzil, Greenwood, & Rothwell, 2011).

Other approaches were to perform a comparison between motor and cognitive tasks (Desmond et al., 2005) between stimulation sites (Arasanz et al., 2012; Argyropoulos et al., 2011; Argyropoulos, 2011; Bijsterbosch et al., 2011; Koch et al., 2007; Oliver et al., 2011; Théoret et al., 2001; Torriero, Oliveri, Koch, Caltagirone, & Petrosini, 2004), with a no-stimulation condition (Torriero et al., 2004) or to separately confirm that motor components of a task had been unaffected by stimulation (Hoffland et al., 2011).

It is known that the cerebellum is connected to the ipsilateral effectors therefore the idea of motor confounds is less applicable to those studies where a motor response e.g. finger tapping or a button press is performed with an effector contralateral to stimulation. Reference was made to this fact within a number of the studies requiring a time-critical motor response (Argyropoulos, 2011; Bijsterbosch et al., 2011; Koch et al., 2007; Torriero et al., 2004).

Task Analysis:

Language and Cognition:

The majority of cognitive tasks involved verbal processing, hence the preponderance of right lateral targets. Verbal processing tasks included traditional phonemic and semantic fluency and lexical decisions under a priming paradigm. The only non-linguistic cognitive tasks entailed mental arithmetic. One complexity in looking for behavioural effects of altered cerebellar performance is that, whilst fundamental brain reorganisation is unlikely during an experimental session, subjects can employ task strategies to offset the effects of intervention. It has been suggested (e.g. Ito, 1993) that the cerebellum may act, in the cognitive sphere, as a fast, automatic processor, whose operation may be elaborated and adjusted by the cerebrum. Taken together these factors may indicate that any behavioural effects resulting from cerebellar alteration may be subtle and short lasting. The authors of the majority of the cognitive and other studies appeared mindful of this by limiting the response times available and adjusting the difficulty of the task to the capabilities of individual subjects.

Continuous theta burst stimulation to the right paravermal cerebellum produced enhanced associative priming effects on lexical decision tasks (Argyropoulos, 2011), though a variant of TBS (trains of three 30 Hz bursts at 100 ms intervals) delivered to the same region prevented performance improvement on a similar paradigm (Argyropoulos et al., 2011). Given that continuous TBS to the lateral right cerebellar hemisphere enhanced associative priming by comparison to medial stimulation (Argyropoulos & Muggleton, 2013) it is challenging to suggest a mechanism which can accommodate these results, which may partially be due to disrupted activity within the cerebellum or the effects of disrupted cerebellar output releasing regions of the cerebrum from inhibition (Galea et al., 2009).

This potential explanation is also suggested and extended within Pope & Miall (2012), which interprets enhanced performance on a mental arithmetic task after cathodal tDCS as potentially representing augmented prefrontal processing after a reduction of cerebellar inhibition. Cathodal tDCS has been shown to temporarily hyperpolarise the neuronal membrane lowering overall activity. Given the parameters used within this study (2 mA via 25 cm^2 electrodes) and previous research on the current flow in tDCS (Miranda et al., 2006) it is reasonable to suggest that the effects on brain tissue would be greatest at cortical structures. If these effects are primarily manifest in decreased Purkinje cell activity then deep cerebellar nuclei would be released from inhibition from Purkinje cells and pass greater excitation to extra-cerebellar targets, possibly DLPFC in the case of the cerebellar crura. Whilst increased excitability in prefrontal areas may account for task improvement resulting from a general raising of alertness this is not taken to indicate a distinct role for the cerebellum in actual cognitive calculations.

Emotion:

One study reported altered theta wave activity after single pulse TMS to the cerebellar vermis (Schutter & van Honk, 2006). Whilst a direct change in emotional state was not reported by the participants, the authors discuss the role of theta wave activity in emotional activity particularly in the context of the links identified between the cerebellum and limbic structures.

Two repetitive TMS studies reported a direct change in mood state after brain stimulation: an unquantified increase in positive mood and alertness was reported after high frequency repetitive TMS to the vermis (Schutter, van Honk, D'Alfonso, Peper, & Panksepp, 2003) and increased negative emotion was reported during a task wherein subjects viewed images from the International Affective Picture Set (Lang, Bradley, & Cuthbert, 2008) and were required to either suppress or experience the resultant emotion after low frequency vermal repetitive TMS (Schutter & van Honk, 2009). Two other repetitive studies inferred implicit changes to emotional processing by examining reaction times to emotional face tasks: increased reaction times to positive expressions after high frequency repetitive TMS were taken to represent a processing bias resulting from enhanced implicit positive mood (Schutter et al., 2009); whereas increased reaction times after both positive and negative tDCS were taken to represent the results of impaired implicit mood (Ferrucci et al., 2012), although it must be noted that within (Schutter et al., 2009) the emotional valence of the faces was effectively a distractor from a colour naming task.

Learning and Memory:

Imaging studies (Balsters & Ramnani, 2011) have suggested that the cerebellum is particularly active during learning and that activity drops after successful performance has been achieved. If this is the case it is likely that the most marked effects would be seen in studies that interfere with cerebellar involvement in learning compared with interference with the cerebellum after skills had been acquired.

All except one of the studies within this domain reported impaired performance in working memory and procedural learning after stimulation: with all impairments recorded as increased reaction times rather than a reduction in accuracy. Increased reaction times were seen after single pulse TMS, low frequency rTMS and both anodal and cathodal tDCS, with no behavioural change being reported after the application of higher frequency rTMS (5 Hz) during task performance.

It is difficult to draw inferences from this set of results given that an increase in reaction times resulted from anodal tDCS, a technique understood to be excitatory, as well as the other disruptive (single pulse TMS) and inhibitory (low frequency rTMS and cathodal tDCS) paradigms. Since a polarity-specific effect of tDCS on the excitability of the cerebellum has been established (e.g. Galea et al., 2009) it may be the case that whilst anodal tDCS does increase cerebellar excitability this does not necessarily imply a resultant improvement in the performance of complex behaviours. The increase or decrease of cerebellar cortical excitation will alter the level of inhibition exerted by the cerebellar cortex on the deep cerebellar nuclei, though it does not necessarily follow that this will optimise performance of a task.

The alterations seen to reaction times within this task domain may suggest that either the cerebellum is required for efficient processing of learning and memory tasks, or that other brain areas are able to compensate for reduced cerebellar input to ensure that a correct answer is delivered, albeit after a longer time.

Eye-blink conditioning was impaired by cerebellar continuous theta burst stimulation (Hoffland et al., 2011), which gives a clear demonstration of the ability of stimulation to affect a task that has been shown to be critically reliant on cerebellar operation (Yeo & Hesslow, 1998).

Perception:

Oliver et al. (2011) conducted two experiments exploring hemispheric bias in real and abstract space, by using line and number-line bisection tasks respectively. After the application of low frequency rTMS to the left cerebellum, no difference in spatial judgement bias was found in the line bisection task, but a significant rightward (i.e. to higher numbers) bias was found in the number-line task. Perhaps a critical difference between in these results is that a 2 second response time limit was enforced for the number-line task whereas the subjects were under no time constraints in the line bisection task. Re-running the line bisection task with time pressure placed on the subjects may alter the result and give further evidence for the time-critical nature of cerebellar involvement in non-motor tasks (cf. Pope & Miall, 2012).

A mild alteration in heat, cold and pain detection thresholds was detected after the application of low frequency vermal repetitive TMS by (Zunhammer et al., 2011) supporting the suggestion that the vermis plays a role in the core homeostatic brain circuitry.

The most unusual result published was a single-case report of a subject who had an out-of-body experience after low frequency repetitive TMS (Schutter, Kammers, Enter, & van Honk, 2006). Whilst it has been suggested that the cerebellum may be responsible for the ongoing integration of sensorimotor information (Ito, 2000) there have been no other reports of perceptual alterations of this nature after cerebellar stimulation or injury. It has been reported that magnetic stimulation of the temporo-parietal junction (TPJ) can give rise to own-body illusions (Blanke, Ortigue, Landis, & Seeck, 2002), that both TPJ and cerebellar functional abnormalities can arise in autism (Gomot et al., 2006) and that functional connectivity has demonstrated coherent cerebellar and parietal activity. Taken together, this suggests the possibility of cerebellar and TPJ participation in a network supporting proprioception and sensory prediction. The physical connectivity between these areas awaits confirmation.

The single tDCS experiment within this task category (Ferrucci et al., 2012) reported results that suggest a cerebellar role in the perception and processing of specifically negative emotions. Within this study participants were significantly faster to react to negative emotional faces after both anodal and cathodal cerebellar tDCS. The authors relate this finding to known reciprocal connections between the cerebellum and the amygdala and suggest that this may be the neural substrate of a protective system that primes responses to threats in the environment. The authors do suggest a possible explanation for the lack of a polarity-specific effect, though it is clear that further physiological research is necessary to confirm whether this explanation is correct.

Timing:

Within the scope of this study only repetitive TMS and TBS were employed for the investigation of the cerebellar contribution to timing. Guided by prior work in this domain (e.g. Ivry & Keele, 1989) the majority of the cerebellar stimulation studies either examined subsecond timing functions or looked to draw a contrast between sub- and supra-second timing mechanisms within the brain (suggesting a distinction between cerebellar and cerebral timing mechanisms).

Timing tasks lie at the boundary of cerebellar motor and non-motor studies as tapping and interval reproduction necessarily have a motor component. The most motoric of the studies (Théoret et al., 2001) showed that low frequency rTMS to the superior vermis could produce increased variance in finger tapping, but this did not suggest the operation of a timing mechanism that applies to multiple domains.

Fierro et al. (2007) demonstrated an impairment in time perception in the subsecond range after right lateral low frequency rTMS and the responses were delivered by the subjects' right hands, but since the relevant measure was accuracy rather than reaction time it is reasonable to conclude this represents an impairment in perception rather than in performing a motor response. Two groups used low frequency repetitive TMS (Koch et al., 2007; Lee et al., 2007) and one used continuous TBS

(Grube, Lee, Griffiths, Barker, & Woodruff, 2010) to infer a role for the cerebellum in sub- rather than supra-second time perception by demonstrating impairments in performance after stimulation. It is interesting to note that in addition to increased answer variability, both of the studies using low-frequency repetitive TMS showed an overestimation of duration after stimulation. This is somewhat counterintuitive if one assumes an oscillator-accumulator model of cerebellar timing since it could be assumed that reducing cerebellar activity would lower the number of oscillations per time period and lead to an under-estimation of duration. Bijsterboch et al. (2011) examined the cerebellar role in timing by contrasting subjects' response in a tapping task where inter-stimulus intervals were perturbed by 'sub-' or 'supra-liminal' amounts (18 or 90ms respectively). A significant impairment was found in correcting supra-liminal errors after continuous TBS to the left lateral cerebellum, which, given the use of the right hand for responses, removes the suggestion that this may be a motor effect. This study agrees with the consensus as to the cerebellum's involvement in subsecond time perception, but also perhaps places a lower-level on the intervals were a behavioural change may be observed after manipulation.

Of further interest was Koch et al.'s (2007) finding that online high frequency (20 Hz) TMS interfered with time perception within the encoding rather than the reproduction phase of a temporal perception / working memory task, which agrees with the findings listed above that emphasise the importance of the cerebellum in learning and gives a demonstration of the potential of brain stimulation to provide temporal as well as spatial functional localization.

Conclusion

Emerging from this review is a clear picture of the challenges involved in cerebellar stimulation, both in terms of methods and the interpretation of results. The diversity of targets selected for the stimulation of similar cerebellar regions highlights the benefits of using neuronavigation where available. Skull landmarks can be unreliable indicators of the presence of larger, cerebral regions, such as the dorsolateral prefrontal cortex (e.g. Herwig, Padberg, Unger, Spitzer, & Schönfeldt-Lecuona, 2001); these issues may be even more important when attempting to locate smaller, motorically silent cerebellar areas. The placement of electrodes and the resulting current flow in tDCS requires further study as it is difficult to judge how much current reaches cerebellar tissue given the presence of the foramen magnum and substantial amounts of CSF and muscle fibres in its immediate environment. Modelling work (e. g. Miranda et al., 2006) may help illuminate this issue by demonstrating the current flow that results from the interaction of a stimulation montage and the environment of the cerebellum. It must be noted, however, that no studies have been published to date with a specific focus on modelling current flow within cerebellar tDCS therefore questions remain as to how this technique influences the operation of the cerebellum.

Another issue is the applicability of percentages of motor threshold in 'dosing' cerebellar stimulation: further physiological work is required in this area to describe the optimal parameters for cerebellar stimulation. Physiological work is also required to clarify the mechanism of action of stimulation techniques on the cerebellum. There are grounds for believing that stimulation interacts primarily with the cerebellar cortex rather than the deep cerebellar nuclei (DCNs). There are, however, multiple components within the three layers of the cortex that may be affected differently by stimulation and result in opposing effects. Inhibition of the Purkinje cells will result in a release from inhibition of the DCNs and greater cerebellar output, but inhibition of the Golgi cells may result in a relative excitation of granule cells and a commensurate excitation of the Purkinje cells. The studies reviewed suggested several mechanisms of action to account for their results, therefore clarity of the physiological effects would be beneficial, especially in the interpretation of results gained from less-focal techniques such as tDCS due to possible incidental stimulation of non-cerebellar structures. Clarification of the mechanism of action might help explain findings such as those of Ferrucci et al. (2008) in which an impairment to working memory processing was observed after both anodal and cathodal cerebellar stimulation when compared to sham. Given that it is believed that these modes of stimulation have opposite effects on affected tissue it is difficult to interpret this result except in viewing the effects of stimulation as introducing disorder to an otherwise optimal system. This may be plausible in that of the 16 studies that found a performance change after stimulation, 12 reported impairments whereas only four studies reported performance improvements (of which two demonstrated increased priming effects rather than improvements in absolute performance).

It was acknowledged that effects generated by stimulation were likely to be subtle and transitory and this was reflected in several elements of the studies. The temporal structure of experiments were tuned by either limiting the amount of time taken in testing to half the stimulation time or, in the case of tDCS, adding delays from stimulation to test for effects to develop. The analysis undertaken within several studies (e.g. Ferrucci et al., 2008; Pope & Miall, 2012; Torriero et al., 2004) reflected awareness of the transitory nature of the effects by separating testing into epochs rather than conducting an overall analysis of pre- versus post-stimulation performance. The different approaches taken to this issue, however, also argue for the benefits of further physiological work to determine how the effects of a period of stimulation vary with time after the stimulation ceases. The analysis of the results from the studies also acknowledged that 'brute effects' such as a drop in task accuracy would be not be detectable in all cases and therefore measures such as reaction time were taken despite potential motor complications. It was also clear that there was an awareness of the need to prevent the adoption of task strategy by subjects or allow extra-cerebellar compensatory effects to occur. Adjusting task difficulty to take into account individual ability (Pope & Miall, 2012) is also an appropriate measure.

The reviewed studies provide evidence for a cerebellar role in multiple non-motor functions, but it would not be reasonable to conclude that the exact nature of this role has been elaborated. In the absence of a definitive statement of the physiological effects of cerebellar stimulation it is difficult to place seemingly contradictory results (e.g. the effects of cathodal tDCS in Ferrucci et al.(2008) and Pope & Miall) within an explanatory framework. Across the task types and stimulation parameters sufficiently similar effects of intervention were not observed to enable a statement to be made as to the function being performed by the cerebellum. If, as suggested by Schmahmann and Caplan (2006), the goal of cerebellar research is to identity the fundamental computation common to each cerebellar operation then further research will be required. It is possible that improved stimulation techniques, such as the use of double-cone or 'H'-coils may give more readily interpretable results, but improved knowledge of the physiological effects of cerebellar stimulation is essential.

Chapter 3 - Investigating the cerebellar contributions to working memory using transcranial direct current stimulation

Abstract

This chapter describes two experiments that examine the cerebellar role in verbal and visual working memory using transcranial direct current stimulation (tDCS). A cerebellar hemispheric specialisation that is similar, but opposite, to the cerebral specialisations for visuospatial and verbal processing has been proposed. These experiments sought to demonstrate that tDCS to the right cerebellar hemisphere would have a greater effect on participants' performance than when applied to the left cerebellar hemisphere. A converse effect on participants' performance was hypothesised for visual working memory. No clear evidence for a cerebellar role in visual or verbal working memory was generated by these experiments. Limitations in the use of tDCS as a tool for cerebellar experimentation are considered and possible enhancements to experimental methodology are discussed.

General Introduction

As demonstrated in the previous chapter, there is not only a substantial amount of evidence for a cerebellar role in non-motor activity, but also a strong argument for the efficacy of transcranial stimulation of the healthy cerebellum in the inference of the nature of this role. This chapter will describe two experiments conducted using transcranial direct current stimulation (tDCS) to examine the role of the cerebellum within working memory.

tDCS is a method of temporarily altering activity within a targeted area of the brain, through alterations to the resting potential of neurons' membranes rather than the induction of action potentials. It has been demonstrated that anodal tDCS, i.e. stimulation with the positive electrode brought into proximity of the targeted brain region, raises the excitability of neurons and promotes activity within the region (Nitsche & Paulus, 2001). Conversely, it has been shown that cathodal tDCS lowers the neurons' resting potential and inhibits activity within the region (Stagg et al., 2011). This suggests that the application of tDCS to the cerebellum may temporarily alter its activity, which may lead to performance differences being observed in tasks that require cerebellar involvement. As shown in chapter 2 and in Reis and Fritsch (2011), tDCS has been applied to the cerebellum and behavioural differences have been observed in both motor and non-motor activities.

Neural pathways that link areas of the prefrontal cerebrum, strongly associated with cognition (Fuster, 2008), to the posterior-lateral cerebellum (Strick et al., 2009) have been described. Damage to these cerebral areas has been associated with lengthened performance times or increased error rates on appropriate neuropsychological tests (e.g. Goel, Grafman, Tajik, Gana, & Danto, 1997; van Asselen et al., 2006). To an extent, similar results have been observed in populations with damage to the posterior lobe of the cerebellum (Gottwald et al., 2004), though it must be noted that these results have on occasion been mild or transient in nature (Alexander et al., 2012). The detection of impaired performance on non-motor tasks in the aftermath of cerebellar injury suggests that areas of the cerebellum are making a contribution to their execution. Additional support for a cerebellar role in these functions comes from neuroimaging studies that have shown increased activation in these regions during executive and visuospatial tasks (reviewed in Stoodley, 2011).

A factor that has informed hypotheses regarding cerebellar non-motor contributions has been the contralateral connectivity of the majority of cerebro-cerebellar circuits (Krienen & Buckner, 2009; Middleton & Strick, 1994). It has been demonstrated extensively that in the majority of subjects the left cerebral hemisphere is dominant for language (Wada et al., 1975). If regions of the cerebellum actively contribute to the activities driven by the cerebral regions to which they are connected then it is plausible that cerebellar hemispheric specialisations converse to those seen in the cerebrum may also be observed, i.e., the right cerebellar hemisphere would be more active in verbal than visuospatial processing.

Working memory is a promising area of investigation for the elucidation of the cerebellum's role in non-motor behaviours since this function has been shown to place a demand on a number of the non-motor cerebral areas to which a cerebellar pathway has been identified (Wager & Smith, 2003). Working memory is defined as the cognitive system that allows the short-term storage and manipulation of information (Baddeley & Hitch, 1974). Baddeley and Hitch's model of working memory divides the system in to a modality-free central executive directing the activities of subsystems that process either visuospatial or phonological data, or provide access to longer-term memory stores. The activity of the working memory system has also been characterised as a series of operations that can be mapped to distinct temporal phases of activity (Smith & Jonides, 1997) namely encoding, maintenance and retrieval.

Given the proposed role of the cerebellum as a general-purpose support module providing similar computations to distinct cerebral systems (Ito, 1993), working memory processing presents several opportunities for cerebellar involvement and the prospect of being able to observe cerebellar contributions within different phases and across modalities.

It has been proposed that the cerebellum achieves its contribution to behaviour through the use of internal models representing either the predicted consequences of an action (forward models) or the steps necessary to effect an action (inverse models) (Wolpert et al., 1998). An argument has been made that the acquisition of cerebellar forward models enables the automatisation of elements of the encoding and maintenance phases of working memory tasks (Hayter, Langdon, & Ramnani, 2007) thus decreasing the amount of conscious control necessary over these stages and enhancing overall task performance. The use of tDCS enables an investigation to be made to whether the use of cerebellar internal models is essential to the efficient execution of working memory and whether their use can be disrupted.

The Sternberg task (Sternberg, 1966) is amongst the most widely-used paradigms for the investigation of working memory processing. This task entails the serial presentation of items, followed by a maintenance pause and the presentation of a probe item. Within the Sternberg task the participant is required to indicate whether the probe item appeared in the preceding list as quickly as possible. As noted above, Baddeley's model of working memory describes an amodal central executive that directs the operation of modality-specific slave systems that perform the encoding, maintenance and retrieval of relevant information. If the cerebellum plays a role in working memory processing then it would be expected that areas associated with the central executive would be equally likely to be found in either cerebellar hemisphere, whereas it may be expected that cerebellar areas associated with modality-specific processing would be associated to a greater degree with the cerebellar hemisphere contralateral to the cerebral hemisphere more specialised for processing within that modality. To an extent this suggestion has been supported by evidence from lesion (Marien, Engelborghs, Fabbro, & De Deyn, 2001) and neuroimaging studies (Hautzel, Mottaghy, Specht, Müller, & Krause, 2009). The Sternberg task is associated with placing a higher level of demand on the modality-specific maintenance subsystems than other well-researched working memory tasks such as n-back (Kirchner, 1958; Thürling et al., 2012) therefore I elected to examine the proposed laterality within cerebellar WM processing using a Sternberg paradigm in order to place a greater demand on modality-specific, lateralised subsystems.

The experiments described in this chapter used tDCS to manipulate the activity of the right cerebellar hemisphere during the performance of working memory tasks. It was hypothesised that a temporary alteration in the activity of the right cerebellar hemisphere would result in greater effects on working memory performance when participants processed verbal rather than visual material. It was further hypothesised that cathodal tDCS to the right cerebellar hemisphere would impair verbal working memory performance whilst anodal stimulation to this region would result in an improvement in performance.

Experiment 1: The effects of cathodal tDCS to the right cerebellar hemisphere on verbal and visual working memory

Introduction

The purpose of this experiment was to use tDCS to examine whether further evidence could be gathered for a specific role being performed by the right cerebellar hemisphere in verbal working memory processing. As explained above, a Sternberg paradigm was selected given the demands placed by this task on the modality-specific slave systems of working memory. I determined that a contrast would be made between verbal and visual working memory performance before and after stimulation to the right cerebellar hemisphere. To limit participants' ability to translate visual stimuli into a verbalised list I generated a stimulus set of complex non-nameable Attneave shapes (Arnoult & Attneave, 1956). Examples of the visual stimuli used are shown in Figure 2. Conversely, within the verbal task I sought to limit the effects of visual comparison by using capitalised stimuli and lower case probes.

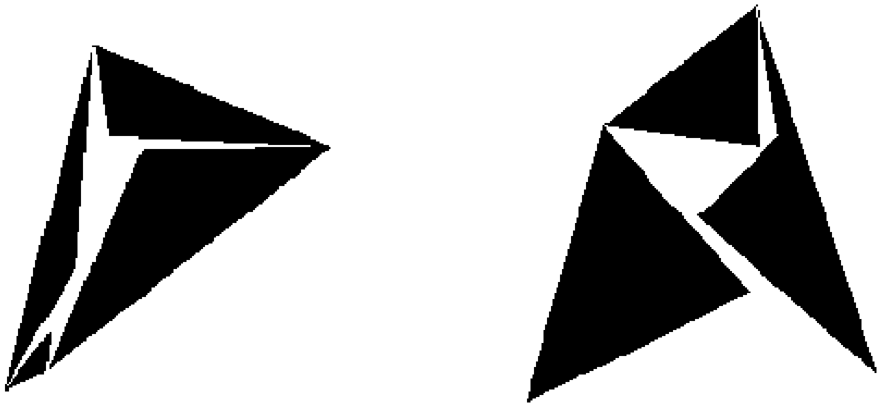

Figure 2. Examples of Attneave shapes used in the experiment

The systematic review (chapter 2) showed that in the studies where cerebellar tDCS had been used to investigate non-motor function cathodal tDCS had proved effective in twice the number of experiments than anodal therefore it was decided that cathodal stimulation would be employed.

I selected stimulation parameters of 2 mA for 15 minutes, which were within the safety limits described by Nitsche et al. (2003) and similar to those found to be effective by Ferrucci et al. (2008). I elected to site the reference electrode on ipsilateral masseter to reduce the possibility of current flow through brainstem structures and to avoid siting the reference at a location directly overlying the brain due to the possibility of incidental stimulation effects on other brain regions. To further control the flow of current I selected a smaller active electrode and a larger reference electrode as per Miranda, Lomarev and Hallett (2006).

Difficulties have been noted with the use of sham stimulation in experiments using tDCS (Davis, Gold, Pascual-Leone, & Bracewell, 2013), namely 'itching' or 'tingling' sensations in the skin under the electrodes. These issues have been particularly noted during the use of relatively high current densities (See chapter 2): given the proposed use of a stimulation of 2 mA in the experimental condition, a sham condition was excluded from this study.

With any cerebellar experiment it is important to ensure that any observed effects cannot be ascribed to post-treatment differences in motor performance. To address this issue it was decided to use 'decision tasks' as a control. The decision tasks were to be identical to the experimental tasks in their motor and attentional demands, but differ in the level of working memory activity required: an approach similar to the parametric method employed by Pope and Miall (2012). Any differences observed in pre- and post-treatment performance on experimental and control tasks could therefore be reasonably ascribed to treatment rather than motor effects.

As described in chapter 2, all previous studies that had reported performance alteration on learning or memory tasks after the application of cerebellar stimulation had documented differences in reaction time rather than accuracy. I hypothesised an increase in reaction times after tDCS to the right cerebellum that would be most pronounced on the verbal working memory task.

Methods

Participants:

Approval for the performance of this study was granted by Bangor University School of Psychology Ethics and Research Committee. Participants were recruited via advertisement on Bangor University's intranet and received £10 for the session. All participants completed a safety questionnaire prior to participation with exclusion criteria following the guidelines documented by (Nitsche et al., 2003). Informed consent was obtained from all the participants in accordance with Bangor University's School of Psychology ethical policy.

6 students (2 female) from Bangor University aged between 18 and 23 were recruited for this experiment. All participants were assessed as right-handed using the Edinburgh Handedness Inventory (Oldfield, 1971).

Tasks:

I used Sternberg tasks (Sternberg, 1966) with a similar control task to assess the cerebellar contributions to verbal and visual working memory. For verbal and visual experimental tasks, each trial consisted of the display of a fixation cross for one second followed by the serial display of a list of either 2, 4 or 6 items randomly drawn from the relevant stimulus set. Each item was displayed for one second then replaced by a blank screen. The last item was followed by a pause of 2 seconds and the display of a probe item. The participants' task was to press a key, within a one second response window, indicating whether the probe item had been a member of the previously displayed list.

The control tasks were similar except that the participants were required to respond as to whether the probe item matched the last item of the displayed list.

In each trial it was equally likely that a positive or negative answer would be required.

The timeline for the tasks is shown in Figure 3.

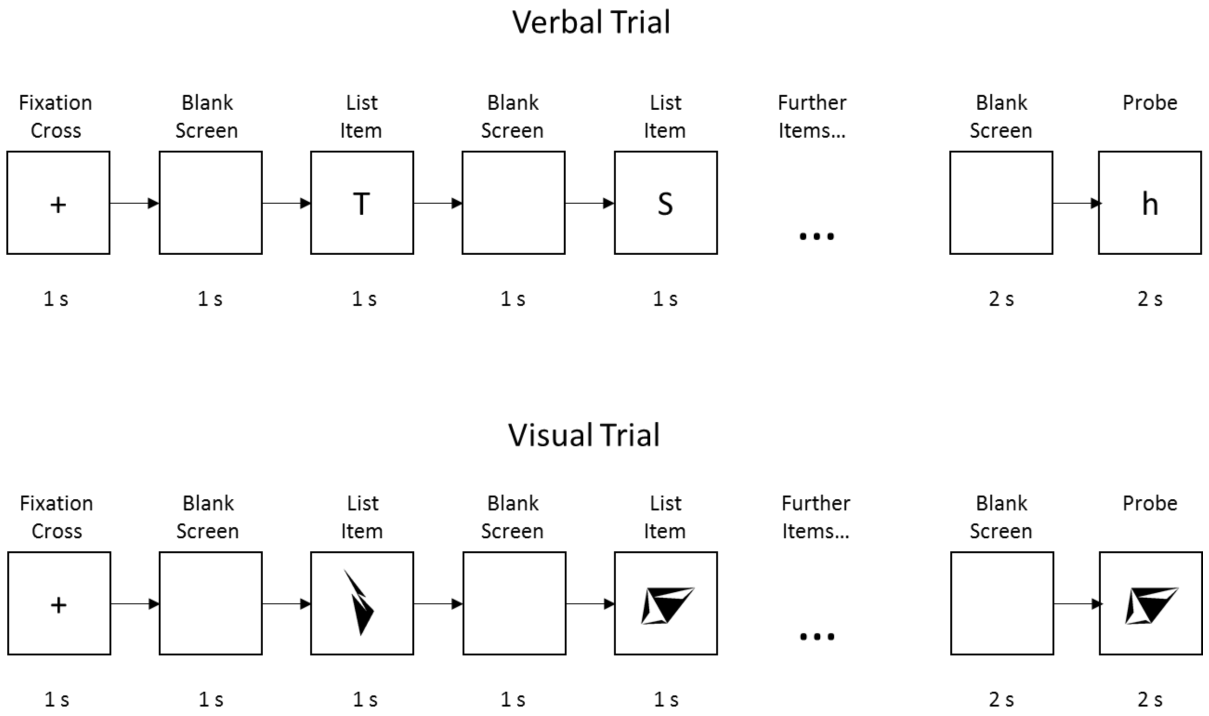

Figure 3. Timeline of the experimental tasks

Ahead of the experimental sessions a series of behavioural trials were held to ensure that participants' average performance would be above chance, but be unconstrained by ceiling effects.

Stimuli:

The verbal task employed capital consonants from the English alphabet displayed using a 24-point plain sans serif font. The consonants were randomly selected with the constraint that each letter may appear only once in each trial's list. The probes used in the verbal task were lower case consonants displayed using the same font.

The visual task employed 20 complex, non-nameable, Attneave shapes (Arnoult & Attneave, 1956) with at least 8 vertices, which were generated using the routines developed by Collin and McMullen (2002). The shapes were randomly selected from the available set with the constraint that each shape may appear only once per trial. The probes used in the visual task were Attneave shapes drawn from the same set and displayed identically. The stimuli were approximately 4cm in width, with an approximate angular subtense of 3.3 °

Experiment Structure:

The experiment consisted of 2 sets of tasks performed before and after the application of tDCS. Each set consisted of 6 blocks of 6 verbal and 6 visual trials: therefore a participant would perform 72 trials before and after tDCS. Equal numbers of memory and control trials were used and the trials were divided equally between stimulus list lengths (i.e. trials with 2, 4 and 6 item lists).

The experiment structure is illustrated in Figure 4.

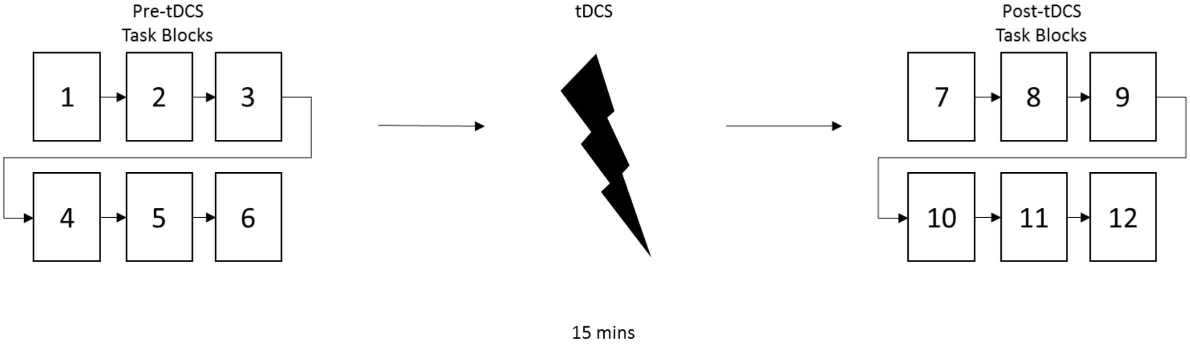

Figure 4. *Structure of Experiment 1.*

tDCS procedure

tDCS was applied to participants using a stimulating electrode of 25 cm² and a reference electrode of 35 cm². In accordance with the location selected by similar studies, as discussed in chapter 2,the stimulating electrode was positioned above the right cerebellar hemisphere 1 cm below and 3cm lateral to the inion. The reference electrode was positioned on the ipsilateral masseter. Participants received 15 minutes of 2 mA cathodal stimulation.

Data Analysis:

Participants' performance was assessed for accuracy (percentage of correct responses) and reaction time. Repeated measures ANOVAs with independent variables Stimuli (with conditions Verbal and

Visual), Task (with conditions Memory and Control), Length (with conditions 2, 4 and 6) and Time (with conditions Before- and After-tDCS) were performed on accuracy and for reaction times where correct responses had been made.

Results

Tolerance of tDCS:

None of the subjects reported any adverse effects from the stimulation.

Reaction Times:

Participants' mean reaction time was 0.84 +/- 0.24 s on the verbal task and 0.77 +/- 0.22 s on the visual task. No significant differences were seen between participants' reaction times on either task, with either set of stimuli, before or after the application of tDCS. Participants' reaction times on the memory and control tasks are shown in Figures 5 and 6.

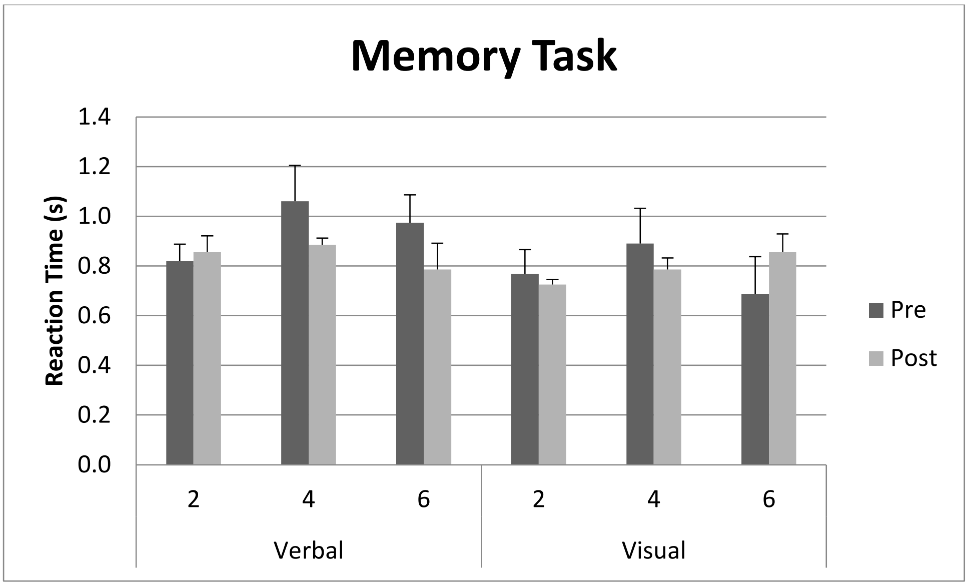

Figure 5. *Participants' Reaction Times on the Memory Task. Results are shown by stimulus type and by number of list items. Error bars represent standard error.*

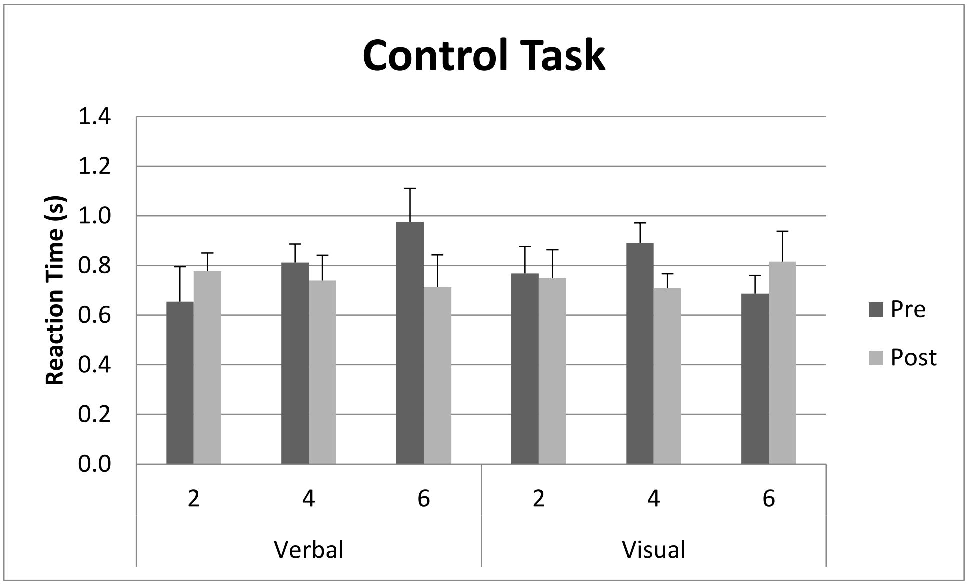

__Figure 6.__ Participants' Reaction Times on the Control Task. Results are shown by stimulus type and by number of list items. Error bars represent standard error.

Accuracy:

Participants' overall accuracy was above chance on both tasks (Verbal: 82.36 +/- 23.31%, Visual: 66.05 +/- 27.26%) and was significantly higher on the verbal task when compared to visual (F(1, 5) = 17.05, p < .01), though it was noted that two participants did not perform above chance on the visual tasks. Participants' recall accuracy on the memory and control tasks are shown in Figures 7 and 8.

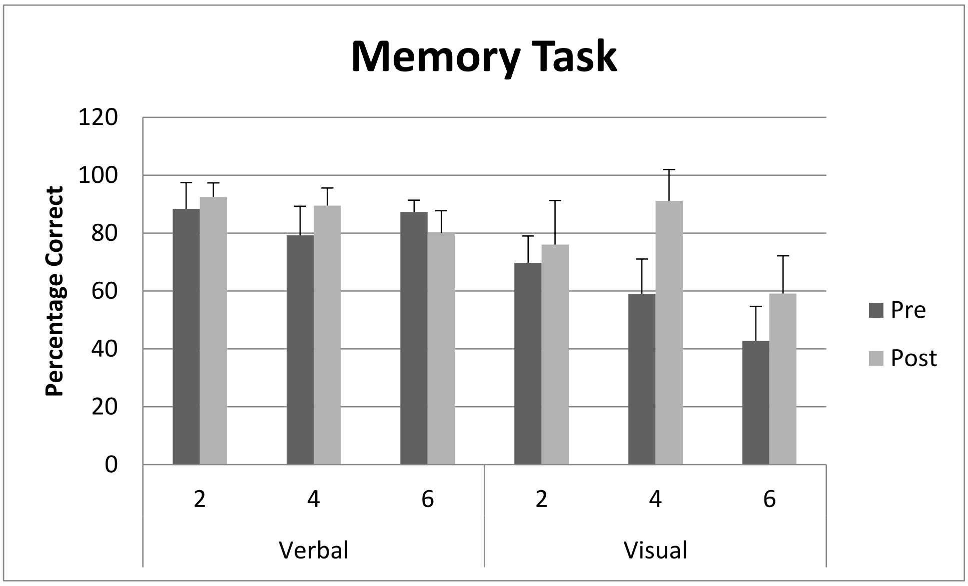

__Figure 7.__ Participants' Accuracy (%) on the Memory Task. Results are shown by stimulus type and by number of list items. Error bars represent standard error.

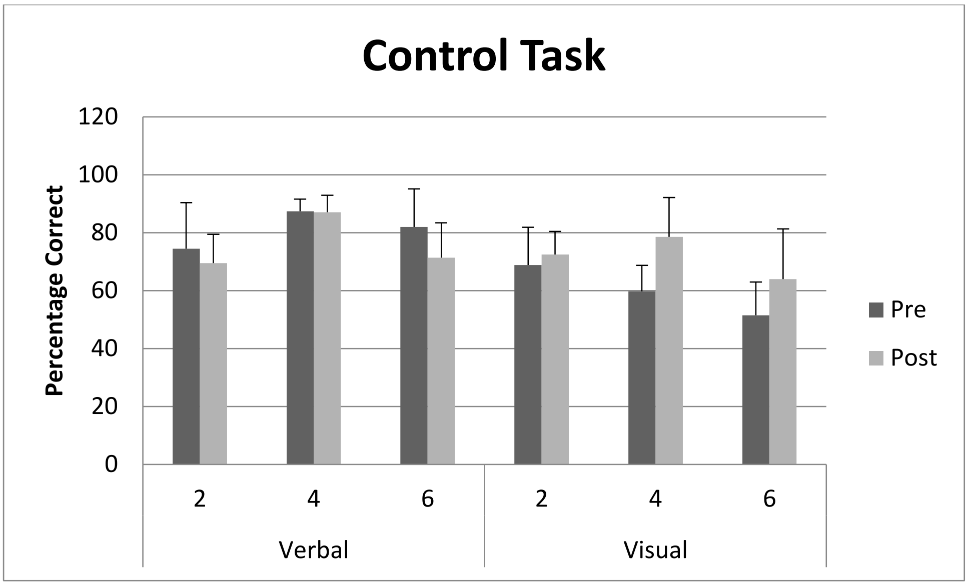

Figure 8. *Participants' Accuracy (%) on the Control Task. Results are shown by stimulus type and by number of list items. Error bars represent standard error.*

No significant interaction was seen between Time, Task, Length and Stimulus (F(2, 10) = 0.61, ns), nor was a significant interaction seen between Time, Task and Stimulus (F(1,5) = 0.02, ns). A significant interaction was seen between Stimulus and Time (F(1, 5) = 9.57, p = .03). No significant differences were seen between participants' performance on differing list lengths on either task.[1]

Discussion

The experimental hypothesis of an increase in reaction time following tDCS that was specific to the verbal memory task was not supported. A smaller increase in accuracy after tDCS to the right cerebellar hemisphere was seen in the processing of verbal rather than visual stimuli; however this was observed across both control and memory tasks and therefore could not be ascribed to an interaction between cerebellar tDCS and the operation of working memory.

It has been noted that the non-motor effects of cerebellar injury are often subtle and transitory (Alexander et al., 2012). By using cathodal tDCS I sought to induce a temporary, virtual lesion to the right cerebellar hemisphere that would affect participants' performance in a manner analogous to damage to this region. Given that the behavioural effects of this intervention were likely to be modest their appearance and detection were dependent on a number of factors and therefore there are several plausible causes for their absence.

[1] The data was subsequently examined for trends and interactions, but no reportable results were discovered.

tDCS is somewhat limited in its stimulation focality (Miranda et al., 2006; Parazzini et al., 2014): a situation that is exacerbated by the anatomical situation of the cerebellum. As noted, I sought to control current flow within our experiment through the use of unequally sized electrodes and the selection of a reference site that was on the surface of the head and ipsilateral to the active electrode. Despite these measures I cannot be wholly confident that a sufficient 'dosage' of stimulation reached our targeted area given the presence of highly conductive muscle tissue and an amount of cerebro-spinal fluid that is comparably greater than would be found in proximity to most cerebral targets. There have been, however, several studies that have achieved an observable effect on behaviour used a similar montage to that employed within our experiment (Galea, Vazquez, Pasricha, de Xivry, & Celnik, 2011; Jayaram, Galea, Bastian, & Celnik, 2011) therefore the failure to find support for our experimental hypothesis may have been due to other factors.

I sought to ensure that suitable tasks were employed within our study and that parameters were selected that allowed participants' to perform the tasks at a reasonable level. I was successful in that all participants' performances on the verbal tasks were at the expected level, but despite pre-session calibration, some participants did not reach this criterion on the visual tasks, which suggests that a refinement to these tasks would be beneficial.

Analysing the participants' level of accuracy across the tasks revealed a significant difference in performance following stimulation. Participants improved their performance on the visual tasks, but they did not improve to the same degree on both control and memory verbal tasks. Consideration of the elements that are shared and differ between the tasks may clarify the effects of tDCS in this case. Motor demands were equal across all four tasks and therefore cannot account for the differences in performance across stimulus modalities. A failure to improve performance applied to both control and memory verbal tasks therefore this difference cannot be ascribed to the effects of tDCS on working memory performance. The elements that were shared between both verbal tasks, but differed from the visual, were the stimuli themselves. It is possible that right cerebellar tDCS interfered with the participants' ability to accurately encode, maintain and retrieve the single letter required for the control task, but it must be noted that the participants failed to improve their performance on these tasks rather than demonstrate a decrease in accuracy. The most plausible explanation for this result is practice: before stimulation participants' accuracy was lower on the visual than the verbal tasks and therefore there was a greater opportunity for a performance increase without encountering a ceiling effect. This suggests a disparity in the relative difficulty of the tasks that may limit the visual tasks' efficacy as a comparator for verbal working memory processing, without further refinement.

Participants performed a single experimental session and their task results were aggregated. It is possible that the effects of treatment may have been overshadowed by the effects of confounding variables such as practice and fatigue. To control for the effects of practice and fatigue it was determined that a comparison would be made between performance on verbal and visual tasks, but as noted above a disparity in the relative difficulty of the tasks may have impaired the value of this comparison and therefore an alternative should be considered. Rather than introduce a sham stimulation condition it was considered appropriate to introduce anodal stimulation to determine whether the nature of the cerebellar role in working memory could be clarified through a comparison of performance after excitatory and inhibitory stimulation had been applied.

Alterations to cerebellar function are associated with subtle changes in behavioural performance on non-motor tasks both in clinical and experimental settings (Alexander et al., 2012; Tomlinson, Davis, & Bracewell, 2013). An explanation that has been advanced for this is the brain's ability to compensate for impaired function within its components: an example being increased frontocerebellar activity observed in the performance of a working memory test by alcoholic participants (Desmond et al., 2003). Whilst fundamental reorganisation of the brain is unlikely, and indeed undesirable, within the scope of this experiment, other studies (e.g. Desmond et al., 2003) have shown that the effects of impaired activity within a region of the brain can be offset by increased activity within others that may result in a lack of observable behavioural change.

Several researchers have noted that, in the case of neuroimaging, observable cerebellar activity only accompanies the performance of highly demanding non-motor tasks (Desmond, Gabrieli, Wagner, Ginier, & Glover, 1997; Salmi et al., 2010) . Additionally, clinical studies have shown that a high level of task demand is required if the non-motor effects of cerebellar injury are to be demonstrated (Ravizza et al., 2006). With this in mind it was concluded that our investigation would benefit from an increase in task difficulty to ensure that the demands of the tasks were sufficient to allow any treatment effect to be observed. To increase the resource demands associated with the experimental tasks it was determined that the list of presented stimuli would be lengthened and a longer maintenance period would be introduced. Given that questions had been raised over the suitability of the visual task as a comparator within our study, the possible influence on our results of practice and the level of task difficulty it was decided that the experimental hypothesis would be re-examined in a refined experiment.

Experiment 2: The effects of anodal and cathodal tDCS to the right cerebellar hemisphere on verbal working memory

Introduction

One of the primary issues to emerge from consideration of the previous experiment was that of the suitability of the complex shapes task as a comparator. In order to discourage the conversion of the visual stimuli into a verbal list, the shapes used were necessarily complex. The effect of this complexity was to render the visual task somewhat more difficult than the verbal task and therefore to threaten the validity of a comparison between participants' performance across these tasks. It was noted that calibration of the tasks' relative difficulties with each participant's ability may alleviate this issue, but given that the focus of this study was the investigation of laterality within the cerebellum with particular regard to verbal working memory, it was determined that the complex shapes tasks would be excluded from the second experiment and that an alternative method for comparison be used. As noted earlier, difficulties have been encountered within studies that have sought to use sham stimulation as a control. Some researchers have avoided these issues through the use of stimulation targeted at 'placebo locations' but since these targets have generally been in proximity to the brain the possibility remains that this stimulation may have a confounding effect. Within my study it was decided that a comparison would be made between anodal and cathodal stimulation to determine if excitation or inhibition of the cerebellum would lead to observable and contrasting behavioural effects on a verbal working memory task.

To address the issues of task sensitivity and to ensure that tasks were sufficiently demanding it was decided that the stimulus lists would be lengthened to 4, 6 and 8 items and that the maintenance period would be increased to 6 seconds, which is comparable to the parameters used successfully by Altamura et al. (2007).

As per my observation that Galea et al. and Jarayam et al. had successfully used a similar tDCS montage to our own, it was decided that no change to the montage would be made.

I hypothesised that the application of cathodal tDCS to the right cerebellum would impair performance on a working memory task, whereas anodal stimulation would result in improved performance.

Methods

Participants:

Approval for the performance of this study was granted by Bangor University School of Psychology Ethics and Research Committee. Participants were recruited via advertisement on Bangor University's intranet and received £10 for each session attended. All participants completed a safety questionnaire prior to participation with exclusion criteria following the guidelines documented by Nitsche et al. (2003). Informed consent was obtained from all the participants in accordance with Bangor University's School of Psychology ethical policy.

6 students (3 female) from Bangor University aged between 18 and 27 were recruited for this experiment. They had not taken part in experiment 1. All participants were assessed as right-handed using the Edinburgh Handedness Inventory (Oldfield, 1971).

Tasks:

I used a verbal Sternberg task with a similar control task to assess the cerebellar contributions to verbal working memory. For the experimental task each trial consisted of the display of a fixation cross for one second followed by the serial display of a list of either 4, 6 or 8 letters randomly drawn from the set of English consonants. Each letter was displayed for 0.5 seconds then replaced by a blank screen. The last item was followed by a pause of 6 seconds and the display of a probe item. The participants' task was to press a key, within a one second response window, indicating whether the probe item had been a member of the previously displayed list.

The control task was similar except that the participants were required to respond as to whether the probe item matched the last item of the displayed list.

In each trial it was equally likely that a positive or negative answer would be required.

The task timeline is illustrated in Figure 9.

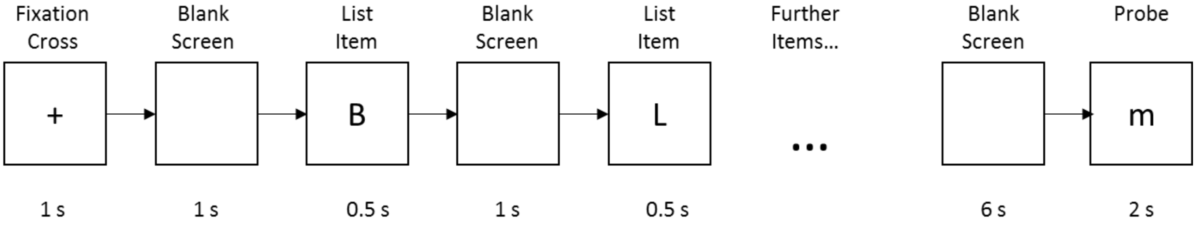

Figure 9. *Task Timeline*

Stimuli:

The verbal task employed capital consonants from the English alphabet displayed using a 24-point, plain, sans serif font. The consonants were randomly selected with the constraint that each letter may appear only once in each trial's list. The probes used were lower case consonants displayed using the same font. Participants were seated approximately 50 cm from the display and confirmed that they could perceive the stimuli clearly.

Experiment Structure:

The experiment consisted of two sessions separated by at least one week. Participants received either anodal or cathodal tDCS during each session, with the order of the sessions being randomly assigned. Each experimental session consisted of 2 task sets performed before and after the application of tDCS. A task set consisted of 6 blocks of 12 trials, therefore a participant would perform 72 trials before and after tDCS. The trials were divided equally between list lengths, but there were 56 memory trials and 18 control trials in each task set.

tDCS procedure

tDCS was applied to participants using a stimulating electrode of 25 cm^2 and a reference electrode of 35 cm^2. The stimulating electrode was positioned above the right cerebellar hemisphere 3cm lateral to the inion; the reference electrode was positioned on the ipsilateral masseter. Participants received 15 minutes of 2 mA cathodal or anodal stimulation.

Data Analysis:

Participants' performance was assessed for accuracy (percentage of correct responses) and reaction time. Repeated measures ANOVAs with independent variables Stimulation (with conditions Anodal and Cathodal), Task (with conditions Memory and Control), Length (with conditions 4, 6 and 8) and Time (with conditions Before- and After-tDCS) were performed on accuracy and for reaction times where correct responses had been made.

Results

Tolerance of tDCS:

None of the subjects reported any adverse effects from the stimulation.

Reaction Time:

Participants' mean reaction time was 0.70 +/- 0.06 s on the memory task and 0.59 +/- 0.05 s on the control task: a difference that was found to be significant ($t(5) = 3.73$, $p = .01$). Participants responded more slowly on both tasks with increasing list length (F(2, 10) = 11.65, p < .01). No significant differences were seen between participants' performance across any of the other factors. Participants' reaction times on the memory and control tasks are shown in Figures 10 and 11.

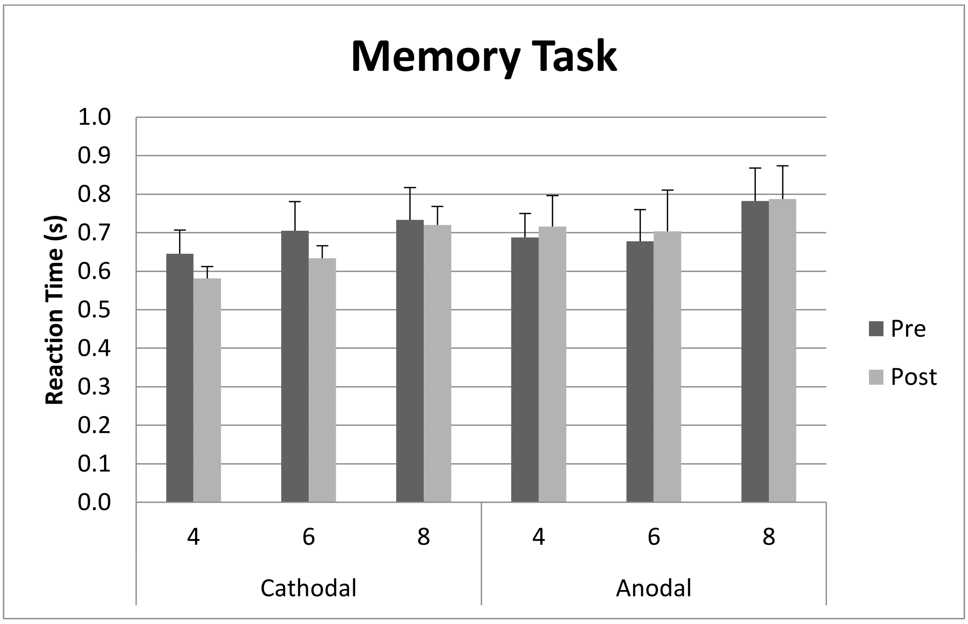

Figure 10. *Participants' Reaction Times on the Memory Task. Results are shown by tDCS polarity and by number of list items. Error bars represent standard error.*

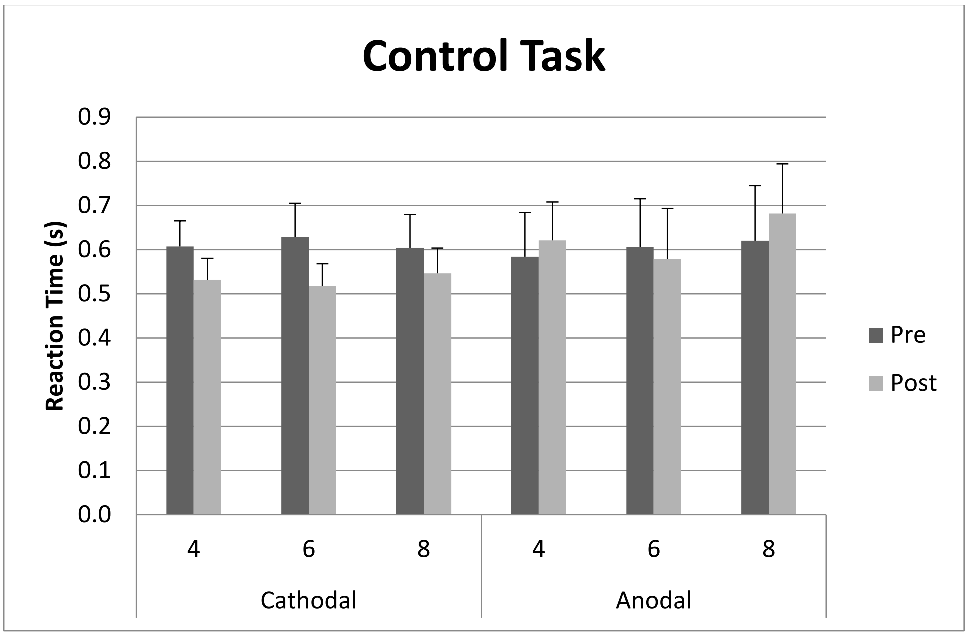

Figure 11. *Participants' Reaction Times on the Control Task. Results are shown by tDCS polarity and by number of list items. Error bars represent standard error.*

Accuracy:

Participants' accuracy was above chance on both experimental and control tasks (Experimental: 93.72 +/- 4.23%, Control: 97.40 +/- 2.44%). Participants were less accurate on both tasks with increasing list length (F(2, 10) = 6.51, p =.02). No significant differences were seen between participants' recall accuracy across any of the factors as shown in Figures 12 and 13.

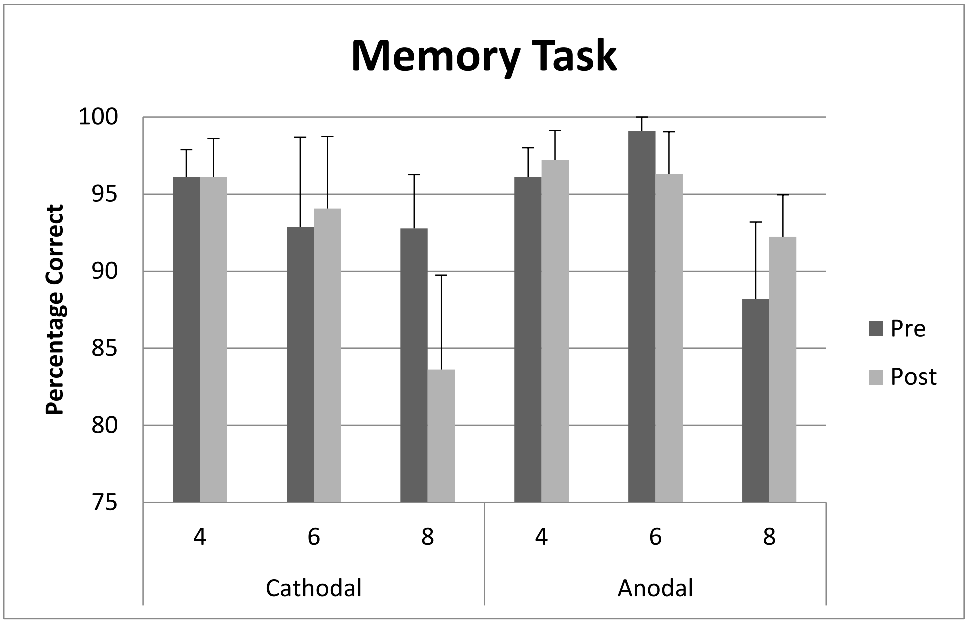

Figure 12. *Participants' recall accuracy on the Memory Task. Results are shown by tDCS polarity and by number of list items. Error bars represent standard error.*

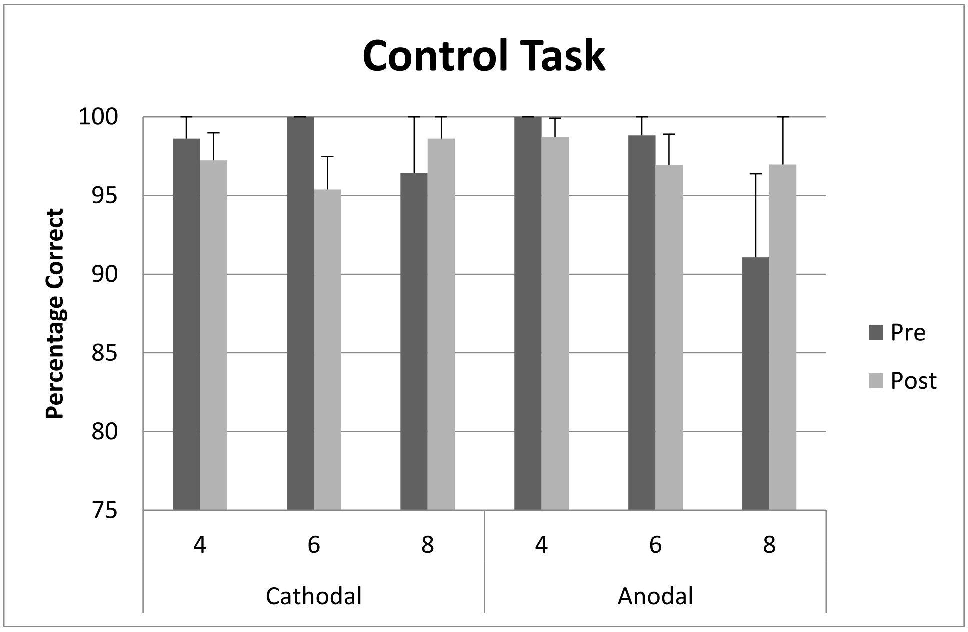

Figure 13. *Participants' recall accuracy on the Control Task. Results are shown by tDCS polarity and by number of list items. Error bars represent standard error.*

Discussion

The experimental hypothesis was not supported as no difference in participants' performance, either in terms of accuracy or reaction times, was noted after the application of anodal or cathodal tDCS. I attempted to address the issues identified in the previous experiment by eliminating the possibly unsuitable comparator task and increasing the demands associated with the verbal working memory task, but these measures did not lead to the anticipated results. I will consider the impact of each of these measures and indentify possible causes for the lack of support for the experimental hypothesis.

As shown by Altamura et al. (2007), increasing the number of items presented in a working memory task and lengthening the maintenance period increases the task's relative difficulty and has resulted in increased cerebellar activity as observed by functional imaging. The working memory task and the task's parameters that were selected for this experiment were similar to those used by Altamura et al. and therefore I believed these to be suitable for this experiment. It is interesting to note, however, that the group of participants selected for the second experiment performed marginally better on the more demanding version of the verbal working memory task than the previous participants had on the equivalent task. This change in peformance may be due to individual differences or may have been derived from the removal of the effects of switching between stimulus sets (Monsell, 2003). A ceiling effect may have affected our ability to observe a treatment effect as a subset of participants made no errors within a number of the task blocks. The high level of performance that was observed in the tasks within this experiment despite the measures taken to increase task difficulty suggest that this experiment may have benefitted from the use of parameters calibrated for each participant rather than those derived from pre-experiment calibration using different participants.

There also remain the possibilities that either the cerebellum is not critically involved in the processing required for a verbal Sterberg task, sufficient current was not directed to the critical areas of the cerebellum by our use of tDCS or testing the effects of tDCS immediately after the cessation of stimulation may not allow the time required for effects to develop. These elements will be considered in detail in the general discussion.

General Discussion

I conducted two experiments to examine the contribution of the cerebellum to working memory through the use of tDCS. My first experiment suggested that cathodal tDCS to the right cerebellar hemisphere reduced participants' improvement across a working memory and control task involving verbal stimuli in comparison to those that made use of non-nameable shapes. My second experiment sought to extend this finding to determine if a behavioural difference that was specific to a working memory task could be observed using a contrast between anodal and cathodal stimulation, but no significant differences between task conditions were observed.

As discussed above, there are multiple possibilities that may account for the results observed. The task refinements incorporated into the second experiments were intended to deal with the issues identified regarding task difficulty and the suitability of the visual task, but it is possible that the improved versions of the task were themselves not sufficiently sensitive to allow differences to be observed. In dealing with the subtle changes to non-motor performance that result from cerebellar differences (Grimaldi & Manto, 2011; Neau, Arroyo-Anllo, Bonnaud, Ingrand, & Gil, 2000) it is the case that task calibration for individual participants' performance would give the best chance of being able to observe any alterations.

The lack of certainty regarding the amount of current that interacts with the relevant areas of each participant's cerebellum is a challenge within tDCS experiments (Parazzini et al., 2014). The uncertainty of the effects of individual anatomical differences is exacerbated by the nature of the cerebellum's environs, which include the presence of muscle tissue, relatively large quantities of cerebrospinal fluid and varying skull depth. Despite the success of Galea and colleagues (Galea et al., 2009) I cannot be certain that a sufficient amount of current reached their intended targets within this study. To investigate this possibility I conducted a series of tests using variations of the montage used within this study (with an active electrode targeting more anterior areas of the cerebellum) to determine if behavioural differences could be observed on tasks with a well-documented cerebellar element. It is well-established that the cerebellum plays an important role in the management of rapid, alternating movements and that cerebellar disease or injury can cause a marked impairment in this ability (dysdiadochokinesia) (Holmes, 1939). I observed performance on a task requiring rapid, alternating movement of a rotating pointer between target areas before and after the application of cerebellar tDCS, but was unable to detect any differences in speed, accuracy or time at rest. With these results I was unable to exclude the possibility that my stimulation montage had been ineffective and therefore elected to consider alternative stimulation techniques for future investigations.

Prior to my experiments being conducted, one study involving cerebellar tDCS and working memory (Ferrucci et al., 2008) had been published. After completion of my experiments, another study entailing cerebellar tDCS and verbal working memory was published (Boehringer, Macher, Dukart, Villringer, & Pleger, 2013). Ferrucci et al. reported an impairment to participants' ability to improve performance on a modified Sternberg task after the application of either anodal or cathodal tDCS. Boehringer et al. reported an impairment of participants' ability to perform digit span working memory tasks after cathodal tDCS. It is informative to consider my experiments in the context of these studies.

The positive result reported by Ferrucci et al. suggested the suitability of cerebellar tDCS for the investigation of working memory and therefore similar stimulation parameters (2 mA, 15 min) were selected within my study, albeit with differences in electrode size and the selection of a cephalic location for the reference electrode. Boehringer et al. used a cephalic reference electrode (located on the ipsilateral buccinators), but delivered 2 mA cathodal tDCS for 25 minutes during the treatment condition, which represents a substantially greater amount of charge than was delivered during my experiments. It is possible that increasing the amount of charge delivered to a level comparable to that used by Boehringer et al. may have generated observable results, but it must be noted that both the other studies used substantially more participants than my experiments. Given the subtle differences that were sought by my study and reported within the others it is possible that my experiments lacked sufficient power to be able to give a clear demonstration of the effects of tDCS on cerebellar operation within working memory and would have benefitted from a larger set of participants. Given the broad similarity between the tasks and parameters used by Ferrucci et al. I performed an analysis of the effect size of their results. This analysis suggested that approximately twice the number of participants as were used in experiment 1 would be required to observe an effect of a comparable size. These results suggested that further experiments would benefit from the recruitment of larger participant groups to ensure sufficient statistical power.

It is interesting to note that Ferrucci et al. proceeded with a hypothesis that related to the cerebellum's role in practice-driven learning rather than suggesting its operation as a general-purpose support module (as per Ito) as were the case both within my study and that of Boehringer et al. Ferrucci et al. anticipated an impaired improvement in performance after tDCS that was due to interference with learning during practice whereas I anticipated an impairment that derived from a reduction in the effectiveness of operation of the cerebellum during actual task performance. In line with this hypothesis Ferrucci et al. observed no difference in participants' performance when tested 5 minutes after the completion of tDCS, whereas after 35 minutes their performance improved to a lesser degree after tDCS than after sham. I could find nothing in the literature to suggest that tDCS required a pause between application and testing to enable effects to be observed therefore I (and Boehringer et al.) elected to test immediately after stimulation.

Ferrucci et al. found a similar effect of both stimulation polarities, which is unusual given the polarity-specific effects seen within several other cerebellar stimulation studies (e.g. Galea et al., 2009; Jayaram et al., 2012). Ferrucci et al. interpreted this result as representing tDCS disrupting the equilibrium of cerebellar neurons during the performance of the first post-stimulation task block. Ferrucci et al. interpreted the performance of the first post-stimulation task block as representing practice in advance of subsequent testing. Given that the operation of the cerebellum was impaired during the performance of this task block any learning based on this set of trials would itself be impaired as would be evidenced subsequent tests. My experiments did not set out to examine a practice-driven learning paradigm therefore a delayed retest was not incorporated. Given the results derived from my experiments it may be informative, in future experiments, to incorporate both immediate and delayed testing to determine whether the learning-based hypothesis of Ferrucci et al. or the support-based hypothesis favoured by myself and Boehringer et al. is better-supported.

In conclusion, whilst I saw elements of an interaction between tDCS and the cerebellum's role in a working memory task in my first experiment, I was unable to extend this result in my second experiment despite refining the experimental task and conditions. My study may have benefitted from a greater number of participants and individual calibration of tasks therefore these factors will be considered in future work. There is substantial evidence for cerebellar involvement in the working memory operations that are entailed by the Sternberg task and therefore it is possible that further evidence will be derived from effective cerebellar stimulation used in conjunction with appropriately sensitive tasks.

Chapter 4 - Cerebellar Contributions to Verbal Working Memory

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Abstract

There is increasing evidence for a cerebellar role in working memory. Clinical research has shown working memory impairments after cerebellar damage and neuroimaging studies have revealed task-specific activation in the cerebellum during working memory processing. A lateralisation of cerebellar function within working memory has been proposed with the right hemisphere making the greater contribution to verbal processing and the left hemisphere for visuospatial tasks. I used continuous theta burst stimulation (cTBS) to examine whether differences in post-stimulation performance could be observed based on the cerebellar hemisphere stimulated and the type of data presented. I observed that participants were significantly less accurate on a verbal version of a Sternberg task after stimulation to the right cerebellar hemisphere when compared to left hemisphere stimulation. Performance on a visual Sternberg task was unaffected by stimulation of either hemisphere. I discuss my results in the context of prior studies that have used cerebellar stimulation to investigate working memory and highlight the cerebellar role in phonological encoding.

Introduction

The suggestion that the cerebellum may play a role within a diverse range of behaviours has gained popularity in recent years (see (O'Halloran, Kinsella, & Storey, 2011) for a review). Observations from clinical (Schmahmann, Weilburg, & Sherman, 2007) and neuroimaging studies (reviewed in Stoodley (2011)) have been considered in the context of the cerebellum's cytoarchitectural homogeneity (Bloedel, 1992) and widespread, closed-loop, connectivity to motor and non-motor cerebral areas (Middleton & Strick, 2000; Salmi et al., 2010; Strick et al., 2009). This has led to the proposal that the cerebellum may make a similar contribution to both motor and non-motor behaviours (Schmahmann, 2004). Within the motor domain the cerebellum is seen as supporting the efficient and effective implementation of behaviour rather than being responsible for its instigation. Dysmetria and ataxia are the common sequelae of cerebellar damage (Holmes, 1939; Luciani, 1891). In non-motor behaviours it has been proposed that a similar disorganisation, referred to as 'dysmetria of thought', may be the corresponding result of posterior-lateral cerebellar disease (Schmahmann, 1991), which may manifest as reduced accuracy or efficiency in the performance of tasks that utilise cerebellar resources.

The predominantly contralateral cerebro-cerebellar connectivity has informed hypotheses regarding possible cerebellar non-motor contributions (Krienen & Buckner, 2009; Middleton & Strick, 1994). In the majority of humans the left cerebral hemisphere is dominant for language (Wada et al., 1975) with a converse right hemisphere dominance for visuo-spatial tasks (Jonides et al., 1993). It has been proposed that similar, but opposite specialisations may be present within the cerebellar hemispheres (Jansen et al., 2005; Marien et al., 2001), which may be detectable in functional neuroimaging or inferred behavioural deficits in cerebellar patients.

Working memory (WM) tasks have received much attention in the investigation of cerebellar non-motor function. Working memory is the system that allows the temporary storage and manipulation of information during cognitive tasks (Baddeley, 1992a). Studies in this area have commonly interpreted their findings in the context of Baddeley and Hitch's model of working memory (Baddeley & Hitch, 1974), which describes a modality-free central executive that directs the operation of modality-specific subsystems. Baddeley and Hitch's model has been elaborated to describe different processes that are active during a working memory task. The successful completion of a working memory task requires the encoding, storage and retrieval of information (Jonides et al., 2008). Within the context of verbal working memory, Baddeley describes a phonological loop, which comprises a limited buffer for storage of phonological input and an articulatory control system, which acts to refresh memory traces whilst they are required. This framework has allowed researchers into the cerebellar role in working memory to structure their findings and draw conclusions about cerebellar activity during different stages of processing.

Evidence for a cerebellar role in working memory has been derived mainly from clinical or functional imaging studies. Neuropsychological investigations of patients with cerebellar damage have shown reduced accuracy in digit span tasks (Ravizza et al., 2006; Schmahmann & Sherman, 1998; Silveri et al., 1998) with reduced accuracy and marginally increased reaction times seen on *n-back* tasks (Peterburs et al., 2010). For information, the digit span task tests participants' ability to memorise lists of numbers of increasing length, whereas the *n-back* task examines participants' ability to react when a probe matches the stimulus that was displayed n items previously (e.g. *2-back* = 2 items previously).

Cerebellar patients have also shown reduced accuracy in tests specific to verbal working memory (Greve, Stanford, Sutton, & Foundas, 1999) particularly following damage to the right cerebellar hemisphere (Baillieux et al., 2010). Evidence for a cerebellar role in spatial memory is not as strong as for verbal, but mild deficits following cerebellar injury, particularly to the left cerebellar hemisphere have been noted (Gottwald et al., 2004). Neuroimaging studies have shown cerebellar activation during working memory performance: a meta-analysis by Stoodley and Schmahmann (Stoodley & Schmahmann, 2009) revealed bilateral peak activations in lobule VI/Crus I during verbal and a peak activation in left lobule VI during spatial memory processing. A later meta-analysis (E et al., 2014) investigated cerebellar working memory with a detailed focus on cerebellar activation during the phases of working memory tasks. Similar activation peaks were found, but with a greater hemispheric lateralisation of cerebellar working memory activity: the right hemisphere being more active for language and the left for visuospatial tasks. The analysis based on the phases of verbal working memory tasks revealed different clusters of cerebellar activation during each phase of the tasks, notably Crus I and lobule VI during encoding and lobule VIII during maintenance, supporting Chen and Desmond's (2005b) finding that the superior cerebellum is active during encoding, whilst the inferior cerebellum participates in maintenance.

In recent years transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have provided new opportunities for the *in vivo* investigation of cerebellar activity. Single pulse TMS can be used to induce action potentials within a brain area, whereas repetitive TMS and tDCS can temporarily alter the resting membrane potentials of affected neurons and thus alter their likelihood of firing (Cheeran, Koch, Stagg, Baig, & Teo, 2010). This approach can be used to induce temporary change to the functioning of a targeted area within a neurologically normal brain, which, in contrast to patient or imaging studies, allows direct causal inferences to be drawn. TMS and tDCS also have the advantage of avoiding the confounding effects of brain plasticity or the adoption of compensatory strategies in the aftermath of brain disease or injury. Brain stimulation techniques have been used in a number of previous investigations of cerebellar function, both motor and physiological (Koch et al., 2008; Lorenzo et al., 2013) and non-motor (see (Grimaldi et al., 2014) and chapter 2 for recent reviews).

Four published studies have used either tDCS (Boehringer et al., 2013; Ferrucci et al., 2008) or TMS (Desmond et al., 2005; Rami et al., 2003) to investigate the cerebellar role in working memory. Both tDCS studies found an impairment in working memory performance after the application of stimulation to the right cerebellar hemisphere either in terms of the increased reaction times or a reduction in digit span. Rami et al. used TMS to examine the effects of cerebellar stimulation on memory performance, but did not detect any effects when high frequency (5 Hz) repetitive stimulation was applied to the right cerebellar hemisphere (2 cm down, 3 cm right of inion) during a suite of memory tasks. Desmond, Chen and Shieh employed single-pulse TMS over the right superior cerebellar hemisphere (targeting lobule VI/Crus I using neuronavigation) immediately after the encoding phase of a verbal Sternberg task. The target and time of application of the TMS pulse were selected based the fMRI studies that had revealed specific activation of this area during stimulus encoding (Chein & Fiez, 2001; Chen & Desmond, 2005b). Desmond et al. found that, whilst there were no differences in accuracy when stimulation trials were compared with sham, participants were significantly slower to respond after TMS. They interpreted these results as representing the effects of disruption to the articulatory processing of incoming information whereby Broca’s area, the premotor cortex and the right superior cerebellum create an articulatory trajectory for the storage of phonological data. They concluded that increased reaction times after stimulation resulted from additional time being required to extract lower-quality memory data from the phonological store.

Taken together this evidence suggests that the right cerebellar hemisphere is involved in verbal working memory processing; that areas of this hemisphere participate to varying degrees throughout the phases of relevant tasks; and that processing can be impaired by non-invasive stimulation. However, given the lack of effects seen by Rami et al. there is also evidence that the effects of stimulation are sensitive to targeting and to the stimulation protocol selected.

A number of other studies have demonstrated the efficiency and effectiveness of continuous theta burst stimulation (cTBS) for temporary alteration of cerebellar functioning (Arasanz et al., 2012;

Argyropoulos et al., 2011; Argyropoulos, 2011; Bijsterbosch et al., 2011; Grube et al., 2010; Hoffland et al., 2011). cTBS is a form of repetitive TMS that delivers bursts of three 50 Hz TMS pulses at 200 ms intervals, which has proved to be efficient in inhibiting the operation of affected areas after only a short period of stimulation (see (Huang et al., 2005) for specifics). Studies using cerebellar cTBS have applied stimulation at a percentage of either participants' motor thresholds or as a percentage of stimulator output (see chapter 2 for consideration of these approaches). Within this study I elected to use a stimulation strength of 80% active motor threshold (AMT) based on the successful stimulation of cerebellar regions as reported by Hoffland et al. , from Arasanz, Staines, Roy and Schweizer and from similar work conducted within our own laboratory.

Desmond, Chen and Shieh demonstrated an impairment of memory efficiency after the application of single pulse TMS to the right cerebellar hemisphere, but they did not detect any change in participants' accuracy. Given the effectiveness of cTBS of cerebellar stimulation, as demonstrated by the above studies, I aimed to determine whether the conditioning effects of cTBS could be used to provide additional evidence for the nature of the contribution of the cerebellum for working memory processing by affecting the accuracy and efficiency of task performance.

I anticipated that right lateral cerebellar cTBS would cause a selective impairment of verbal working memory but would not affect visual working memory, and cTBS to the left cerebellar hemisphere would have no effect on verbal working memory but may affect visual working memory.

Methods

Participants:

Approval for the performance of this study was granted by Bangor University School of Psychology Ethics and Research Committee. Participants were recruited via advertisement on Bangor University's intranet and received £10 for each session attended. All participants completed a safety questionnaire prior to participation with exclusion criteria following the guidelines documented by Wassermann and Rossi, Hallett, Rossini and Pascual-Leone (Rossi, Hallett, Rossini, & Pascual-Leone, 2009; Wassermann, 1998). Informed consent was obtained from all the participants in accordance with Bangor University's School of Psychology ethical policy.

10 students (6 female) from Bangor University aged between 18 and 35 were recruited for this experiment. All participants were assessed as right-handed using the Edinburgh Handedness Inventory (Oldfield, 1971).

Tasks:

I used Sternberg tasks (Sternberg, 1966) to assess the cerebellar contributions to verbal and visual working memory. Test routines were used to establish appropriate difficulty settings for participants prior to performance of the experimental tasks. For both tasks, each trial consisted of the display of a fixation cross for one second followed by the serial display of a list of items randomly drawn from the relevant stimulus database (i.e. words or shapes). Each item was displayed for the stimulus interval as established in the previous test routine then replaced by a blank screen. The last item was followed by a pause of 2 seconds and the display of a probe item. The participants' task was to press a key indicating whether the probe item had been a member of the previously displayed list within a 1 second response window.

Stimuli:

The verbal task employed 50 English nouns drawn from the MRC Psycholinguistics Database (Coltheart, 1981) of between 4 and 6 letters and with both familiarity and concreteness ratings greater than 575 (of a maximum 700).

The visual task employed 50 complex, non-nameable, Attneave shapes (Arnoult & Attneave, 1956) with at least 8 vertices, which were generated using the routines developed by Collin and McMullen (Collin & McMullen, 2002).

Procedure:

Each experiment comprised two sessions: these were separated by at least one week to avoid the possibility of the stimulation during the first session affecting task performance during subsequent testing (Walsh & Pascual-Leone, 2003). During the first session each participant's active motor threshold (AMT) was obtained by applying single TMS pulses over the hand area of their motor cortex and determining the minimum stimulation intensity necessary to elicit a thumb twitch during voluntary contraction of the hand muscles.

Participants were provided with task instructions and asked to practice the experimental tasks. The practice routines varied list length and inter-stimulus interval (ISI), from a baseline length of 8 items and ISI of 0.5 s, by increasing difficulty on successful performance and decreasing on repeated error. The routines recorded the parameters in use when the user made their fifth error on the same level of difficulty and set these parameters for use during the experiment.

Each session comprised 12 task blocks: 6 verbal, 6 visual. Visual and verbal blocks alternated, with the start block being assigned in a pseudorandom manner. cTBS was applied upon completion of block 6. Each task block consisted of 10 Sternberg trials. Participants were requested to respond as quickly and as accurately as they could.

Stimulus display and response collection was performed on a standard PC with a 17-inch monitor using Psychtoolbox (Brainard, 1997) on MATLAB (The Math Works Inc., Natick, MA, 2010). The type of task block was displayed to the participant for 2 seconds ahead of its start. Participants were seated approximately 50 cm from the display and confirmed that they could see the stimuli clearly.

Participants received stimulation to a location over their left or right cerebellar hemisphere within each session in a pseudo-random counterbalanced order.

Theta Burst Stimulation:

cTBS was delivered using a Magstim Rapid (Magstim, Whitland, UK) and a figure-8 coil (ring diameter 70 mm) at 80% of AMT. The coil was placed tangentially to the scalp with the handle pointing upward: a position which induces downward current in the cerebellar cortex. This coil position has proved optimal for suppressing the contralateral motor cortex in single pulse TMS (e.g., (Oliveri, Koch, Torriero, & Caltagirone, 2005) and to interfere with cognitive processes such as procedural learning in 1 Hz rTMS paradigms (e.g., (Torriero et al., 2004) and lexical processing in cTBS paradigms (e.g. (Argyropoulos, 2011)). "Bursts" of three pulses at 50 Hz were repeated at intervals of 200 ms over a 40 s period (600 pulses in total). I used BrainSight (Rogue Research Inc., Montreal, Canada), to examine MRI scans taken from 3 participants and selected scalp co-ordinates of 1 cm below and 6 cm lateral to participants' inions to be appropriate for targets in the region of lobule VI/Crus I.

Data Analysis:

Participants' performance was assessed for accuracy (percentage of correct responses) and reaction time. Difference scores were calculated for participants' performance in pre- and post-stimulation task blocks. Repeated measures ANOVAs with independent variables Task (with conditions Verbal and Visual), Time (with conditions Before- and After-cTBS) and Stimulation Side (with conditions Left and Right) were performed on accuracy and for reaction times where correct responses had been made.

Results

Tolerance of cTBS:

None of the subjects reported any adverse effects from the stimulation. The mean subjects' AMT was measured as 59.7 +/- 8.45% of maximum stimulator output.

Task parameters:

For the verbal task the mean time between stimulus onset was 0.53 s +/- 0.21, with a mean stimulus list length of 11.47 items +/- 2.37. For the visual task the mean time between stimulus onset was 0.68 s +/- 0.32, with a mean stimulus list length of 9.89 items +/- 2.28.

Task Results:

Participants performed above chance on both tasks (Verbal correct: 76.92% +/- 9.26; Visual correct: 59.41% +/- 9.45) and delivered 98.4% of their responses within the allocated time window. The participants' reaction times were similar on both tasks (Verbal RT: 0.56 s +/- 0.08; Visual RT: 0.56 s +/- 0.13). There was no increase in the proportion of missing responses after stimulation.

Participants produced a significantly higher percentage of correct answers on the verbal task when compared with the visual (Task: $F(1, 9) = 91.45$, $p < .001$). A significant interaction was observed among task, time and site of stimulation (Task x Time x Site: $F(1, 9) = 13.18$, $p < .01$). Examining the differences between task performance before and after cTBS revealed that this effect was primarily driven by a decrease in performance on the verbal task after cTBS to the right cerebellum (i.e., comparing verbal task performance after left- and right-cerebellar stimulation revealed a significant difference ($t(9)=2.46$, $p =.04$), which contrasted with a non-significant difference in post-stimulation performance on the visual task). These results are illustrated in Figure 14.

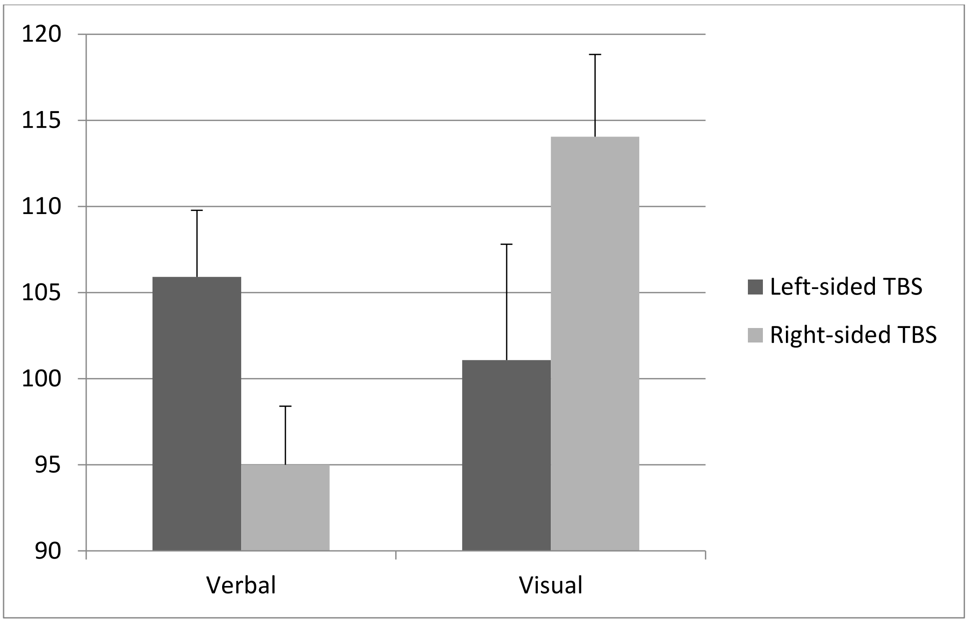

Figure 14. *Percentage difference between Pre- and Post-Stimulation Accuracy on Verbal and Visual Tasks. A value higher than 100% indicates an increase in the ratio of correct answers in the post-stimulation blocks compared with pre-stimulation. Error bars represent standard error.*

Participants were significantly quicker to produce correct results in both tasks following stimulation (Time: F(1, 9) = 22.48, p < .001). No other significant differences in reaction times were observed, other than the post hoc determination that participants were significantly slower in producing incorrect responses across all task conditions, site of stimulation and time (Correct v Incorrect: F(1, 9) = 14.39 p < .005). There was a slight, but non-significant increase in reaction times on the verbal task after stimulation to the right cerebellar hemisphere, as shown in Figure 15.

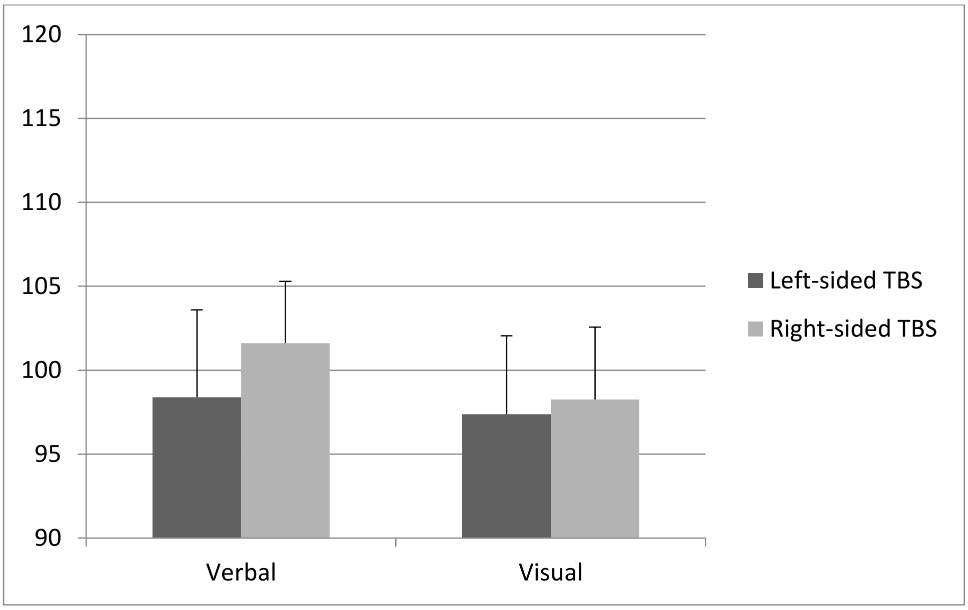

Figure 15. *Percentage difference between Pre- and Post-Stimulation Reaction Times on Verbal and Visual Tasks. A value lower than 100% indicates a decrease in reaction time between pre- and post-stimulation blocks. Error bars represent standard error.*

Having seen no overall impairment in reaction times, I conducted further analyses by examining both the effects of a present vs. absent probe, and the times taken to deliver correct vs. incorrect answers. No significant differences were seen resulting from the type of probe used. The participants took significantly longer to deliver an incorrect answer, but this was the case across all experimental conditions therefore cannot be attributed to the effects of stimulation.

Discussion

My results showed an impairment of verbal working memory performance after the application of continuous TBS (cTBS) to the superior right cerebellar hemisphere, which contrasted with a general post-stimulation performance improvement that was seen both on a visual memory task and after stimulation to the left cerebellar hemisphere. The impairment was manifested as a decrease in task accuracy without an increase in reaction times.

Given the well-documented cerebellar contribution to motoric behaviour it is essential to ensure that motor factors cannot account for these results. cTBS as used in my procedure is believed to promote inhibition (Koch et al., 2008) and prior studies using cTBS have shown impaired rather than enhanced performance after stimulation (Bijsterbosch et al., 2011; Grube et al., 2010; Hoffland et al., 2011; Picazio, Oliveri, Koch, Caltagirone, & Petrosini, 2013). A motor effect within my experiment resulting from impaired cerebellar operation would have been seen as an increase in reaction times across all conditions, whereas the participants in this experiment showed a significant decrease. The participants' general decrease in reaction times in the blocks following stimulation can most plausibly be ascribed to the effects of practice, as was found by Kirschen et al. (Kirschen, Chen, Schraedley-Desmond, & Desmond, 2005) using a similar procedure. There was, however, a non-significant increase in reaction times that was specific to performance on the verbal task after cTBS of the right cerebellar hemisphere. Given the prior result of Desmond et al., which showed a significant increase after rTMS to the superior right cerebellum, this suggests a similar effect that may warrant further investigation with more sensitive measures.

I targeted the region of the superior right cerebellum (lobule VI/crus I) that has been shown to be active during the encoding phase of a verbal memory task and has shown sensitivity to disruption by TMS. Given the reciprocal connections that have been demonstrated between the targeted region and areas of the prefrontal cortex (BA 9/46) (Dum & Strick, 2003), and the corresponding task-specific increases in activity observed in these areas (Stoodley & Schmahmann, 2009), I anticipated that TMS would interfere with the cerebellum's support of the cerebral areas' activity during performance of these tasks (as per Ito's suggestion of the cerebellum's role in cognitive function (Ito, 1993)). Using BrainSight neuronavigation software I determined that my stimulation targets were approximately 24 mm from the surface of the skull, which were similar to the 27 mm target depths found by Argyropoulos, Kimiskidis and Papagiannopoulos (Argyropoulos et al., 2011) and Argyopoulos (Argyropoulos, 2011) for cerebellar stimulation sites 1 cm below and 4.5 cm lateral to the inion. It has been demonstrated that the strength of the magnetic field induced by TMS drops rapidly with increasing distance from the stimulating coil (Barker, 2002) and therefore the primary interaction of TMS with cerebellar tissue in my study would be at the level of the cortex rather than the deep cerebellar nuclei (Hoffland et al., 2011). Within the cerebellar cortex the Purkinje cells are believed to have the primary role in processing information received from extra-cerebellar sites (Ito, 2006). These cells exert an inhibitory influence on the deep cerebellar nuclei, which in turn direct excitatory impulses to cerebral targets (by way of the thalamus) (Strick et al., 2009). If cTBS inhibits the activity of Purkinje cells then this may result in a release from inhibition of the deep cerebellar nuclei. In the context of this study's tasks one might expect that this alteration in the activity of the deep cerebellar nuclei would have a disruptive effect on cerebro-cerebellar interaction as manifest in a reduction of task performance. Using cTBS instead of single pulse TMS I expected to be able to demonstrate an impairment in verbal working memory performance that would result from a reduction in participants' ability to encode incoming verbal stimuli efficiently.

In contrast to Desmond et al.'s results the impairment resulting from cTBS over the superior right cerebellar was shown as reduced accuracy rather than an increase in reaction time. This difference in results may be considered in the context of the tasks used and the stimulation method.

Unlike Desmond et al. I selected the serial presentation of common words rather than the parallel presentation of an array of letters. As noted by Desmond et al., a previous imaging study had shown that the right superior cerebellum is most active when rapid articulation of verbal input is required (Wildgruber, Ackermann, & Grodd, 2001). The covert articulation of verbal input is believed to be integral to the initiation of the phonological loop that allows the short-term storage of verbal information (Baddeley, 2000). I selected a task requiring the rapid processing of lists of words to increase the level of articulatory requirements with a view to placing stress on the encoding function of the superior right cerebellum. My participants were required to encode lists of approximately 11 words containing an average of 4.81 letters every 0.53 seconds during the encoding phase. I propose that this represents a higher level of encoding demand than Desmond et al.'s array of 6 letters within 1.5 seconds and would be more vulnerable to the disruptive effects of TMS. My results suggest that participants were able to complete the encoding of verbal data successfully in fewer instances after the application of right cerebellar stimulation. The differences between my and Desmond et al.'s results may be indicative of participants having access to proportionally *less* rather than *worse* encoded data with which to make a comparison with the probe, and hence performing with less accuracy rather than reduced speed.

I used cTBS rather than single pulse TMS to alter cerebellar function during the working memory tasks. Offline application of cTBS between task sessions has the advantage of preventing participants being distracted by the application of stimulation, but lacks the temporal specificity of online single pulse TMS. Given the positioning of the stimulation site and evidence regarding the magnetic field generated by the coil employed (Thielscher & Kammer, 2004) I consider it unlikely that my stimulation interacted with the proposed inferior cerebellar locations that have been implicated in the maintenance and retrieval phases of working memory activity. However, a further experiment to contrast the effects of cTBS over the superior right cerebellum, with stimulation to lobule VIII would confirm the specificity of this result and give an indication of whether the maintenance phase of working memory processing can be impaired by the application of cTBS.

I did not observe a significant difference when performance on the visual task after stimulation to the left cerebellar hemisphere was compared to peformance following right cerebellar hemisphere stimulation. As per the meta-analysis by E and colleagues (E et al., 2014), there are fewer data available regarding the cerebellum's role in visuospatial working memory. Within the scope of this analysis, whilst a region of left lobule VI was the locus of peak activation during visuospatial working memory tasks, no areas were seen to be solely activated by visuospatial when compared to verbal working memory. The absence of an effect of stimulation on this task suggests that an element specific to the verbal working memory task was more vulnerable to impairment by cerebellar stimulation. As noted above, there is evidence that my use of cTBS disrupted the encoding phase of the verbal working memory task, which has been described as entailing the extraction of phonological data from visually presented stimuli to initiate storage within the phonological loop. To achieve a contrast between my task conditions I selected complex, non-nameable shapes, which would impair participants' ability to form and memorise a verbal description of each stimulus. Given that a phonological strategy was unavailable to participants during the visual task and that my stimulation interacted primarily with phonological encoding it is reasonable to suggest this would account for the lack of difference between pre- and post-stimulation performance on the visual task. The absence of a significant difference between the accuracy in performance on the visual task may, in part, have been due to the considerable variance in the participants' individual performances. It is possible that a further investigation of the cerebellar role in visual WM may be able to detect a significant effect of stimulation with the use of better-calibrated task conditions.

I employed a Sternberg task within this experiment and demonstrated an effect of right-lateralised stimulation that was specific to verbal memory. A previous fMRI study with the specific aim of comparing differences in activation across the cerebellar hemispheres during verbal and spatial working memory task performance did not detect any lateralisation of activity between modalities (Hautzel et al., 2009). This study did detect load-specific activation within a range of cerebellar regions including those targeted by this study. Hautzel et al. suggested that this may reflect their use of a *n-back* paradigm, which places greater emphasis on the central executive elements of working memory than Sternberg tasks. It would be informative to extend my investigation into cerebellar contributions to working memory through the use of an *n-back* paradigm. A comparison between the effects of cerebellar stimulation on Sternberg and *n-back* tasks would allow greater understanding of whether only phonological encoding can be impaired by stimulation to the cerebellar crura or whether executive tasks can also be manipulated, thus confirming the cerebellar contribution within this aspect of cognition.

I noted a sizeable range of accuracy in participants' overall task performance, which suggests that improvements may be made in the use of pre-test calibration routines. The purpose of these routines were to ensure that participants were able to adequately perform the tasks and to avoid floor and ceiling effects. Whilst this was successful, the task results suggest that participants found the visual task more difficult than the verbal and that the overall task difficulty varied for participants. I note, however, that the performance variance recorded is comparable to that observed in the most similar studies, viz., Hautzel et al.'s study of the cerebellum's role in verbal and visual memory (Hautzel et al., 2009) and Desmond et al's use of cerebellar TMS to examine working memory (Desmond et al., 2005).

The results of my study support the proposal that the cerebellum plays a role in the operation of verbal working memory and that cTBS represents a viable approach for the manipulation of cerebellar function. I believe that further studies using this technique will enable the elucidation of the role of the cerebellum in a wide range of non-motor behaviours.

Chapter 5 - Cerebellar Contributions to Spatial Memory

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Abstract

There is mounting evidence for a role for the cerebellum in working memory (WM). The majority of relevant studies has examined verbal WM and has suggested specialisation of the right cerebellar hemisphere for language processing. My study used theta burst stimulation (TBS) to examine whether there is a converse cerebellar hemispheric specialisation for spatial WM. I conducted two experiments to examine spatial WM performance before and after TBS had been applied to mid-hemispheric and lateral locations in the posterior cerebellum. Participants were required to recall the order of presentation of targets on a screen or the targets' order of presentation and their locations. I observed impaired recollection of target order after TBS to the mid left cerebellar hemisphere and reduced response speed after TBS to the left lateral cerebellum. I suggest that these results are evidence of the contributions of the left cerebellar cortex to the encoding and retrieval of spatial information

Introduction

There is growing evidence for cerebellar involvement in non-motor behaviours (O'Halloran et al., 2011). The suggestion has been made that distinct areas of the cerebellum may perform a similar role in diverse behaviours. This hypothesis is based on the cytoarchitectural homogeneity of the cerebellum (Bloedel, 1992) and the presence of separate circuits linking primarily anterior regions of the cerebellum with motor areas of the cerebrum and postero-lateral areas of the cerebellum with non-motor cerebral areas (Salmi et al., 2010).

Damage to posterior lobe of the cerebellum has been associated with lengthened performance times or increased error rates on cognitive tests (Goel et al., 1997; van Asselen et al., 2006). Neuroimaging studies have also demonstrated increased activation within this region during executive and spatial tasks (Stoodley, Valera, & Schmahmann, 2011).

A factor that has informed hypotheses regarding cerebellar non-motor contributions has been the contralateral connectivity of the majority of cerebro-cerebellar circuits (Krienen & Buckner, 2009; Middleton & Strick, 1994). Given the dominance, in most subjects, of the left cerebral hemisphere for language (Wada et al., 1975) and the converse dominance for spatial tasks (Jonides et al., 1993), it is plausible that similar, but opposite, specialisations may be observed in cerebellar activity.

Working memory (WM) is the system that allows the temporary storage and manipulation of information during cognitive tasks (Baddeley, 1992a). WM studies have given a demonstration of cerebellar involvement in non-motor activity (Tomlinson, Davis, Morgan, & Bracewell, 2013). The majority of studies of the cerebellar contribution to WM has focused on verbal processing (as demonstrated in chapter 2). A meta-analysis (E et al., 2014) reported that there had been 16 fMRI and PET studies of the cerebellum's role in verbal WM but only 4 that had examined spatial WM. This review revealed the hypothesised cerebellar hemispheric specialisations in that peak activation for spatial WM was found in left lobule VI, whereas right lobules VI and VIIIB (though also left crus I) showed peak activation for verbal WM tasks.

Together, these results suggest the possibility of hemispheric specialisation of the cerebellum within WM. The aim of this study was to determine if a more detailed account of the cerebellar role in spatial WM processing could be elucidated using continuous theta burst stimulation (cTBS) in combination with a spatial memory task. cTBS is a form of transcranial magnetic stimulation that is capable of temporarily inhibiting activity within a brain region (Huang et al., 2005) and has been used to alter the operation of the cerebellum in both motor/physiological and non-motor studies (Tomlinson, Davis, & Bracewell, 2013).

Taking into consideration the contralateral connectivity of cerebro-cerebellar circuits, the dominance of the right cerebral hemisphere in spatial processing and the disruptive effects of cTBS, I hypothesised that cTBS applied to the left postero-lateral cerebellum would impair performance on a test of spatial WM to a greater extent than would cTBS applied to the right cerebellar hemisphere.

Materials and methods

Participants:

Approval for the performance of this study was granted by Bangor University School of Psychology Ethics and Research Committee. Participants were recruited via advertisement on Bangor University's intranet and received £10 for each session attended. All participants completed a safety questionnaire prior to participation. Exclusion criteria were any neurological or psychiatric conditions requiring medication (Davis et al., 2013). Informed consent was obtained from all the participants in accordance with Bangor University's School of Psychology ethical policy.

Experiment 1: 10 students (7 female) from Bangor University aged between 19 and 35 were recruited for this experiment. All participants were assessed as right-handed using the Edinburgh Handedness Inventory (Oldfield, 1971)

Experiment 2: 13 students (9 female) from Bangor University aged between 18 and 29 were recruited for this experiment. All participants were assessed as right-handed using the Edinburgh Handedness Inventory.

Tasks:

I used two similar experimental tasks, 'aiming' and 'memory,' to investigate the cerebellar contribution to spatial WM.

An aiming trial consisted of the serial presentation of 5 unfilled red rings, 0.5 cm in diameter (an approximate angular subtense of 1.15 °), on a white background. The location of each ring was randomly generated, but constrained to be at least 2 cm from any other and 5.5 cm from the edge of the screen. Each ring appeared after a delay of 1 second and remained on the display until the end of the trial. 1 second after the appearance of the fifth ring a set of crosshairs appeared, which the participant would use to mark the order in which the rings had appeared by guiding the crosshairs to the centre of the rings and clicking on each in turn. After the participant's fifth click the display was cleared ahead of the next trial.

A memory trial consisted of the serial presentation of 5 red rings, again 0.5 cm diameter, on a white background using the same location method as before. Each ring appeared after a delay of 1 second and, in contrast to the aiming task, remained on the display for only 1 second before disappearing. Crosshairs were displayed immediately after the disappearance of the fifth ring. The participant used a mouse, operated with their dominant hand, to guide the crosshairs to mark the locations where the rings were previously displayed in the order that they had appeared. After the participant had marked the fifth location the display was cleared ahead of the next trial.

Procedure:

Each experiment comprised two sessions separated by at least one week. Each session comprised 12 task blocks, with TBS being applied after the completion of block 6. Each task block consisted of 20 trials: 15 memory trials and 5 aiming trials in a randomised order. The participants were requested to perform the tasks as quickly and as accurately as they could and to use the first 3 blocks as practice: results from these blocks were discarded.

Stimulus display and response collection was performed on a standard PC with a 17-inch monitor using Psychtoolbox (Brainard, 1997) on MATLAB (The Math Works Inc., Natick, MA, 2010). The type of trial was displayed to the participant for 2 seconds ahead of its start.

The active motor threshold (AMT) of each participant was obtained by applying single TMS pulses over the hand area of the motor cortex and determining the minimum stimulation intensity necessary to elicit a thumb twitch during voluntary contraction of the hand muscles. Participants attended a second session one week later and performed exactly the same tasks as before, with the exception of participating in the procedure to establish motor threshold.

Participants received stimulation to a location over their left or right cerebellar hemisphere within each session in a pseudo-random counterbalanced order.

Theta Burst Stimulation:

Previous studies of cerebellar contributions to non-motor tasks have demonstrated performance impairment after TMS had been delivered to scalp targets 1 cm below and 3 cm lateral to the participants’ inions (Arasanz et al., 2012; Hoffland et al., 2011; Torriero et al., 2004). Whilst this location has been demonstrated, using stereotactic registration software such as BrainSight (Rogue Research Inc., Montreal, Canada), to be above the hemispheric region of the cerebellum’s posterior lobe, it is clear that the cerebellar crura extend more laterally from this location. To inform my investigation I used BrainSight to locate this region on the MRI scans and scalps of 3 participants. It was determined that a scalp location of 1 cm below and 6 cm lateral to the participants’ inions was appropriate for targets within the cerebellar crura. From this information it was decided that two separate experiments would be conducted using these co-ordinates (-1,3 and -1,6) to determine whether further elements of a functional topology could be inferred from the differing effects of stimulation on these two regions (mid and lateral cerebellar hemispheres).

TBS was delivered using a Magstim Rapid (Magstim, Whitland, UK) and a figure-8 coil (ring diameter 70 mm) at 80% of AMT. The coil was placed tangentially to the scalp with the handle pointing upward. "Bursts" of three pulses at 50 Hz were repeated at intervals of 200 ms over a 40 s period

(600 pulses in total) similar to parameters used in other recent cerebellar studies that have employed continuous TBS (Arasanz et al., 2012; Grube et al., 2010). In experiment 1 TBS was delivered to points 1 cm below and 3 cm lateral to the left and right of participants' inions. In experiment 2 TBS was delivered to points 1 cm below and 6 cm lateral to the left and right of participants' inions.

Difficulties have been noted in achieving effective blinding between sham and experimental conditions within brain stimulation studies (Davis et al., 2013). Earlier experiments within my laboratory (Tomlinson, Davis, Morgan, et al., 2013) had shown that *verum* TBS generates a series of audible clicks and, when targeting the cerebellum, can result in the rhythmic contraction of neck muscle tissue. The likelihood of a marked difference between participants' experience of experimental and sham conditions within this study prompted my exclusion of a sham condition.

Data Analysis:

Participants performed 12 blocks of 20 tasks each (5 aiming and 15 memory tasks), 6 before and 6 after stimulation. As per the task instructions, the results from the first 3 blocks were discarded. Each block took approximately 6 minutes to perform. Several studies that have used continuous TBS have noted that its effects are subject to decay in the minutes after stimulation:(Gentner, Wankerl, Reinsberger, Zeller, & Classen, 2008; Mochizuki, Franca, Huang, & Rothwell, 2005; Stefan, Gentner, Zeller, Dang, & Classen, 2008). Based on these factors it was determined that the post-stimulation blocks would be split into two sets, hereafter referred to as 'Post1' (performed within the first 20 mins following stimulation) and 'Post2' (performed after Post1) for comparison with participants' pre-stimulation performance.

Participants' performance was assessed for correct recollection of target order, response accuracy and response speed.

Correct recollection of target order was assessed as a ratio of hits to misses on each task. A hit was scored when a participant placed their response mark closer to the correct ring than any of the others, e.g., his second response mark was closer to the second ring to appear than to any of the others. This measure was taken to reflect participants' ability to encode and recall the order in which the targets had appeared.

Response accuracy was measured as the distance (in mm) between targets displayed and the corresponding mark made by the participant, with a lower value indicating a more accurate response. Accuracy was measured only for those points recalled in the correct order.

Response speed was measured as the distance between the participants' response marks (in mm) divided by the time taken (in ms) for a participant to deliver her response. This measure was selected rather than response time to control for the effects of differing distances between sets of targets across trials. Only trials in which participants had placed their marks in the correct order were included within this calculation.

Repeated measures factorial ANOVAs with factors Task with conditions Aiming and Memory; Time with conditions Pre, Post1 and Post2; and Stimulation Side with conditions Left and Right, were performed on the results of each experiment.

Results

Tolerance of TBS:

None of the subjects reported any adverse effects from the stimulation. The mean subjects' AMT was measured as 57.6 +/- 7.6% of maximum stimulator output.

Experiment 1: The effect of TBS delivered 1cm below, 3 cm lateral to the inion (mid cerebellar hemisphere) on Spatial Working Memory

Participants' recollection of target order was impaired on both tasks after stimulation: the repeated-measures ANOVA revealed a main effect of Time F(2, 18) = 3.99, p = .037, $\eta^2 = .31$) and demonstrated that recollection of target order was significantly worse after left rather than right-sided stimulation (F(2, 18) = 4.88, p = .02, $\eta^2 = .35$). These findings are illustrated in Figure 16.

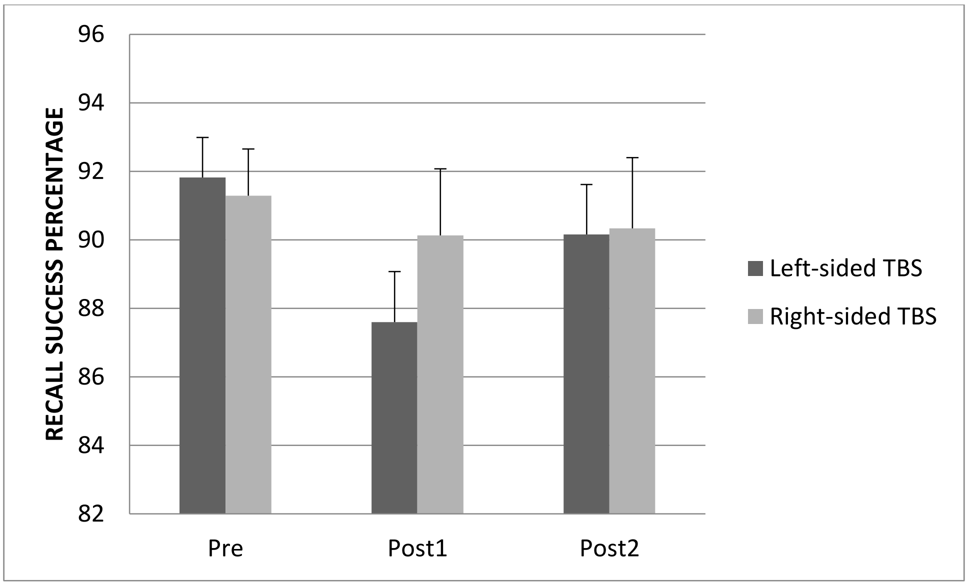

Figure 16. *Percent correct recollection of target order across both tasks before and after stimulation to the left and right cerebellar mid-hemisphere. 'Pre' are blocks performed before TBS, 'Post1' are blocks performed within 20 minutes of the application of TBS, 'Post2' are blocks performed after this*

time. Note the relative impairment in recollection evident after left-sided TBS in the task blocks immediately following stimulation ('Post1'). Error bars show standard error.

No significant differences were observed in response accuracy (i.e., the proximity of participants' responses to the displayed targets) before and after stimulation on either memory or aiming tasks.

The ANOVA demonstrated that participants had significantly lower response speeds on the aiming task than the memory task ($F(1, 9) = 41.65$, $p < .01$), $\eta^2 = .82$). Participants significantly improved their response speeds after stimulation ($F(2, 18) = 5.76$, $p = .01$, $\eta^2 = .43$). No significant differences were seen in response speeds when comparing the effects of left- and right-sided stimulation.

Experiment 2: The effect of TBS delivered 1cm below, 6 cm lateral to the inion (lateral cerebellar hemisphere) on Spatial Working Memory

No significant differences were observed in the participants' recollection of target order before and after stimulation.

No significant differences were observed in response accuracy before and after stimulation. Participants improved their response speed throughout the experiment ($F(2, 12) = 20.62$, $p < .001$, $\eta^2 = .63$), although were significantly slower at the aiming task than the memory task throughout (Task: $F(2, 12) = 103.85$, $p < .001$, $\eta^2 = .87$). Interactions were seen between the task and the side of stimulation ($F(2, 12) = 7.77$, $p = .02$, $\eta^2 = .39$) and task and session ($F(2, 12) = 3.81$, $p = .04$, $\eta^2 = .24$) as participants improved their response speeds to a greater extent after right-sided stimulation and to a greater extent on the memory task. Comparing the participants' pre-stimulation performance to the blocks performed within 20 minutes of stimulation revealed a significant interaction between task, side of stimulation and session (Task x Side x Time(Pre v Post1): $F(1, 12) = 5.91$, $p = .03$, $\eta^2 = .33$): further analysis revealed that this difference was due to a smaller improvement in speed on the memory task after left-sided stimulation compared to right ($t(12) = 2.61$, $p = .04$, Bonferroni corrected). The response speed results from the memory task are illustrated in Figure 17.

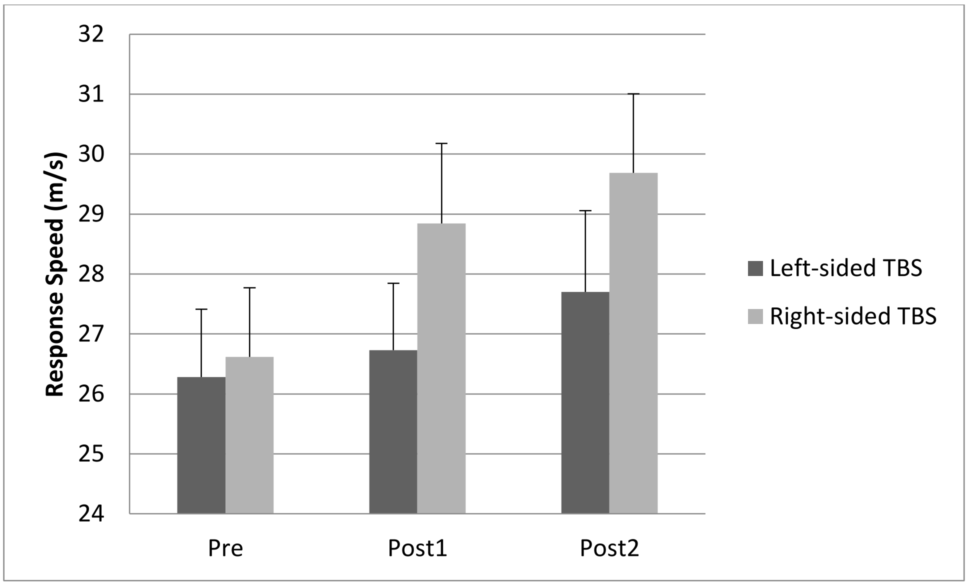

Figure 17. *Response Speed on the memory task before and after stimulation to the lateral left and right cerebellar hemisphere. 'Pre' are blocks performed before TBS, 'Post1' are blocks performed within 20 minutes of the application of TBS, 'Post2' are blocks performed after this time. Observe that impaired response speed improvement is evident in both Post1 and Post2 blocks after left-sided TBS. Error bars represent standard error.*

Summary

In summary, within experiment 1, I observed an impairment in the recollection of target order after the application of TBS that was significantly greater after left-sided cerebellar stimulation. I observed no differences in participants' response accuracy after stimulation. I observed a general improvement in participants' response speed after stimulation to both cerebellar hemispheres that was most likely due to practice.

In experiment 2, I observed no significant changes in either recollection of target order or response accuracy. I observed a reduction in the level of improvement in response speed after left-sided TBS, which was most marked in the task blocks performed immediately after stimulation.

Discussion

These results demonstrated a cerebellar contribution to spatial working memory. Experiment 1 showed that TBS to the left mid cerebellum impaired recollection of target order in both tasks. Experiment 2 showed that lateral cerebellar TBS reduced the expected increase in response speed (a likely practice effect) during memory trials.

Interpretation of these results requires consideration of which elements are shared and which differ between the experimental tasks. Both tasks require that the participant memorise the order in which the targets appeared, but the memory task further requires the encoding, storage and retrieval of the locations in order to generate the behavioural response.

I found that participants were less able to recall the order of the targets' appearance after stimulation of the left cerebellar mid but not lateral hemispheres. This impairment applied to both tasks as was expected due to the encoding and retrieval of target order being a component of both tasks. That the impairment was more marked after the stimulation of the left cerebellar hemisphere was also consistent with my hypothesis of this region acting in support of the spatially dominant right cerebral hemisphere.

After stimulation to more lateral regions of the left cerebellar hemisphere participants' response speeds were selectively impaired on the memory task, both by comparison to the aiming task and to the effects of right lateral stimulation.

That this effect was seen only on the memory task suggests that TBS interacted with a cerebellar region involved in the performance of an aspect of this task that is not shared with aiming task. The primary difference between the aiming and memory tasks is the latter's requirement that locations be memorised and recalled in the absence of persistent spatial information. There were no significant differences in response accuracy, nor were there differences in recall success rate before and after stimulation: this suggests that the encoding of target locations had been accomplished, but that processing these data during the retrieval phase was more difficult for participants. That the impairment was observed in terms of efficiency (speed of response) rather than accuracy may suggest that the information required for correct responses had been encoded in sufficient quality to allow success on the task and that performance impairment resulted from the effects of stimulation on the retrieval processes.

An alternative explanation is that a reduction of efficiency during the retrieval phase may result from increased processing required to compensate for impaired encoding of data. The latter interpretation was advanced by Desmond, Chen and Shieh (Desmond et al., 2005) in an investigation of verbal WM, though this study used a single pulse of TMS immediately after stimulus presentation with the specific goal of disrupting encoding. Further study is required to determine if the targeting of areas of the right cerebellum during encoding and retrieval phases can dissociate the effects of disrupting the encoding and retrieval of spatial data.

In considering evidence for a cerebellar contribution to any non-motor function it is essential to confirm that any observed effects cannot be accounted for by motoric factors. All responses were made with the right hand, which implies that primary control of the motoric implementation of responses lay with the right cerebellum and left cerebral hemisphere. Therefore, one might have expected effects of right rather than left cerebellar stimulation, *if* the main effect of my stimulation was on skeletomotor control, rather than memory as I have argued. TBS has been shown to be an inhibitory form of stimulation (Huang et al., 2005); one might therefore have expected impaired accuracy and/or reduced response speed after TBS. However, I observed no effect on accuracy and, across most conditions, an *improvement* in response speed. The improvement in response speed that was seen across all conditions apart from the memory task after left lateral stimulation.

My suggestion that the cerebellum plays a role in the efficiency of non-motor processing finds support from neuroimaging (Salmi et al., 2010), animal studies (Nixon & Passingham, 1999), clincial studies (Botez, Botez, Elie, & Attig, 1989; Gottwald et al., 2004; Townsend et al., 1999) and previous brain stimulation work (Desmond et al., 2005; Ferrucci et al., 2008, 2012; Pope & Miall, 2012; Tomlinson, Davis, & Bracewell, 2013). Salmi et al. (Salmi et al., 2010) demonstrated a negative correlation between reaction time on a WM task and activity levels within the cerebellar crura suggesting that a participant's ability to perform this task efficiently was related to their recruitment of cerebellar resources. Gottwald (Gottwald et al., 2004) noted that lateral cerebellar damage was consistent with an impaired ability to prepare responses within non-motor tasks. Desmond et al. (Desmond et al., 2005) suggested that impaired reaction times following disruptive cerebellar stimulation indicated an impaired ability to extract stored information from memory and use it efficiently. My results add to the view of the cerebellum as a support module, operating below the level of conciousness, that facilitates task execution by assisting in the preparation of response actions. Similar results from motor studies (Holmes, 1917; Stein & Glickstein, 1992) lend credence to the idea that this role generalises across motor and non-motor domains through the provision of similar operations to multiple regions of the cerebrum.

In conclusion, these results support the notion of cerebellar processing that is additional to, and separate from, pure sensorimotor action monitoring. These results are consistent with the emerging view that the cerebellum is involved in WM, and I have demonstrated a causal role for the left cerebellum in spatial WM. Furthermore, I found a topographic specialisation in function, suggesting that cerebellar areas closer to the midline were involved in encoding of serial position, while more lateral areas underpinned recall.

Chapter 6 - Cerebellar Contributions to Lexical and Emotion Processing

Abstract

Evidence has emerged for a cerebellar role in emotion processing. Patients with cerebellar damage have demonstrated emotional symptoms and increased activation has been seen in the cerebellum during emotional tasks using neuroimaging. The suggestion has been made that the cerebellar vermis is a critical structure for emotional processing, which contrasts to the proposal that more lateral areas of the cerebellar hemispheres are involved in cognitive tasks. This chapter describes an experiment that contrasts the effects of continuous theta burst stimulation (cTBS) to the vermis and to the lateral cerebellum on the performance of an emotional and a cognitive task. A previous study had suggested that excitatory cerebellar stimulation improves participants' implicit mood. This study used a 'masked emotional faces' task that entailed the brief presentation of an emotional face followed by a coloured mask: the participants' task was the identification of the colour of the mask as quickly as possible. An impaired reaction time, specific to happy faces, was taken to indicate that excitatory stimulation had improved participants' implicit mood and impaired their ability to shift attention from mood-congruent distractors. The experiment reported in this chapter sought to investigate whether an opposite effect could be induced through the use of inhibitory cTBS and to contrast this effect with that seen on a lexical decision task. The lexical decision task was selected as an exemplar of a cognitive task hypothesised to require support from the lateral cerebellum, which could be contrasted to the vermal role in emotional processing. Participants showed increased reaction times on the emotional faces task after stimulation to both the vermis and right lateral cerebellum. No changes were recorded in participants' explicit mood and no differences were indicated in implicit mood as similar increases were seen across emotional valences. No effects of stimulation were seen on the lexical decision task. The results were taken to indicate a cerebellar role in processing emotional stimuli, but a role that could not be exclusively ascribed to the cerebellar vermis. Consideration was given to the possibility that the results may indicate a more general role for the cerebellum in the process of shifting attention, particularly for survival-relevant stimuli.

Introduction

In addition to the evidence presented in previous chapters that the cerebellum plays a role in cognition, the suggestion has been made that the cerebellum contributes to emotional processing. As part of the 'Cerebellar Cognitive Affective Syndrome,' Schmahmann and Sherman (1998) reported blunting of affect, behavioural disinhibition and emotional dysregulation as sequelae of cerebellar damage, whilst noting the results of earlier studies (e.g. Levisohn, Cronin-Golomb, & Schmahmann, 1997) that suggested vermal involvement in affective symptoms. In the case of cerebellar stroke, alterations of emotional experience have been noted as manifested by pathological crying and laughter (Parvizi, Anderson, Martin, Damasio, & Damasio, 2001), increased aggression (Greve et al., 1999), reduced response to pleasant and increased response to unpleasant emotional stimuli (Turner et al., 2007), and flattening of affect (Baillieux et al., 2010). Baillieux et al. also noted that all patients within their study with vermal abnormalities displayed emotional dysregulation.

Many neuroimaging studies have shown increased activation within the cerebellum during emotional processing. Reviews conducted by Schutter and van Honk (2005), Stoodley, Valera and Schmahmann (2011) and a recent meta-analysis (E et al., 2014) have documented evidence of a cerebellar role in emotional processing. Amongst this evidence is a suggestion that the vermal areas of the cerebellum may be most strongly activated by emotional stimuli and that the cerebellum may be more strongly activated by negative emotions (e.g., Schraa-Tam et al. (2012)). A further suggestion has been made that cerebellar activation by emotional stimuli may be multi-faceted in that vermal and paravermal activations may be common to a range of primary emotions, whereas activations specific to particular emotions may spread to more lateral areas (Baumann & Mattingley, 2012).

Cerebellar abnormalities have also been associated with the affective symptoms of a number of psychiatric disorders. Studies of psychiatric patients (as reviewed in Schutter & van Honk, 2005) have shown a link between vermal disease and affective disturbance within schizophrenia, depression and bipolar disorder.

From this research, a consensus has formed that the cerebellum plays a role in affective processing, but the nature and scope of this role remains unclear. As discussed in earlier chapters, the homogeneity of the cerebellum's cytoarchitecture and the discrete connections that exist between specific cerebellar areas and a range of cerebral regions suggest that the cerebellum may play a similar role across diverse behaviours (Ito, 1993; Timmann & Daum, 2007). In motor behaviours the cerebellum has a well-documented role in allowing the efficient execution of actions in a timely and fluid manner (Holmes, 1939). This has led to the suggestion that the cerebellum may contribute to the efficient formulation and execution of appropriate responses to emotional stimuli and that cerebellar dysfunction may result as emotionally ‘dysmetric’ behaviour (Schmahmann, 2004) where responses are inappropriate in valence or magnitude.

Pathways have been discovered linking the cerebellum to brain areas that are integral to the processing of emotional stimuli: hypothalamus, amygdala, basal ganglia, substantia nigra and locus coeruleus (Sacchetti et al., 2009). If the cerebellum plays a role in emotional processing that is analogous to that in motor behaviour then it would be expected that interaction between the cerebellum and these areas would support efficient reaction to emotional stimuli and the management of affective response.

The primarily vermal activation that is characteristic of cerebellar emotional processing can be contrasted to the more lateral activation that has been associated with cognitive processing (Stoodley, 2012). As noted in earlier work, activation in the cerebellar crura has been associated with cognitive functions such as working memory and executive control (E et al., 2014). As shown in chapters 4 and 5, my earlier experiments demonstrated a role for the lateral cerebellum in cognition as evidenced by the temporary impairment of processing after the application of continuous theta burst stimulation (cTBS). Within these experiments cTBS was used to temporarily disrupt activity within postero-lateral areas of the cerebellum, which resulted in an impairment in verbal and in spatial working memory. Given that cTBS is a relatively focal technique (Thielscher & Kammer, 2004) and that a topological division has been proposed between the role of vermal areas in affective processing and more lateral regions in cognition, I sought to investigate whether a dissociation could be established between the effects of cTBS on a vermal and lateral cerebellar site and performance of a cognitive and an emotional task.

Several previous studies have used brain stimulation techniques to examine the cerebellum’s role in emotional processing (see chapter 2). Where participants’ explicit mood has been assessed, most studies have reported no change after stimulation, although an unquantified report of improved mood following vermal rTMS at 25 Hz was reported by Schutter, van Honk, D’Alfonso, Peper and Panksepp (2003). A combined EEG-TMS investigation revealed raised levels of frontal theta activity following vermal single pulse TMS, which was taken to indicate the cerebellum’s role in the processing of anxiety and fearful stimuli (Schutter & van Honk, 2006). Mixed results have been derived from the assessment of the effects of vermal brain stimulation on the processing of emotionally-salient stimuli: Demirtas-Tatlidede, Freitas, Pascual-Leone and Schmahmann (2010) found no change in participants’ reactions to images from International Affective Picture Set (Lang et al., 2008) after the application of intermittent TBS (600 pulses delivered in 20 trains of 10 bursts each separated by 8 s); Schutter, Enter and Hoppenbrouwers (2009) showed impaired reaction times following rTMS at 1 Hz, specifically for the processing of happy facial expressions; whereas Ferrucci et al. (2012) noted improved reaction times following both anodal and cathodal cerebellar 2 mA tDCS, specifically for faces conveying negative emotions. Ferrucci et al. interpreted their results as indicative of a specific cerebello-amygdalic role in the efficient processing of potential threats. Schutter et al. suggested that their results derived from an alteration in participants' implicit mood that had been caused by the stimulation. A distinction to be made between the studies of Schutter et al. and Ferrucci et al. is that the latter required the participants to identify the emotion of a displayed face as quickly as possible, whereas the former employed a 'masked emotional faces' task. The masked emotional faces task entails the brief presentation of a face displaying fear, happiness or a neutral expression followed by a coloured mask. The participant is required to identify the colour of the mask as quickly as possible. Differences in reaction times are taken to be indicative of the amount of non-conscious attention paid to the emotional stimulus. Schutter et al. suggested that participants attend more strongly to stimuli that are congruent with their current mood, therefore if their mood, albeit implicitly, were improved by TMS then this would account for impaired reaction times for coloured masks that follow a happy face. Their stimulation protocol used 5 second bursts of 20 Hz stimulation at 80% of participants' motor threshold. rTMS above 5 Hz has been taken to be an excitatory form of stimulation (Paulus, 2005); therefore it can be reasoned that Schutter et al.'s protocol would have enhanced cerebellar activity during the task sets following stimulation. I elected to use Schutter et al.'s masked emotional faces task to determine whether an opposite result would be produced with an inhibitory form of stimulation. I hypothesised that if cerebellar inhibition impaired participants' implicit mood then they would identify coloured masks more slowly when following the presentation of a face conveying a negative emotion. In contrast to Schutter et al. I elected to use faces conveying sadness rather than anger as the negative emotion within this experiment to avoid the possible confound of increased alertness to threatening stimuli (as per Ferrucci et al.). I further hypothesised that this effect would be limited to vermal rather than lateral stimulation, given the results from these experiments and the clinical and imaging data described above. I selected a vermal stimulation site of 1 cm below the inion in agreement with all previous studies (see chapter 2) with the location of a lateral stimulation site to be determined by the requirements of an appropriate cognitive task.

To enable a comparison with the hypothesised vermal emotional processing, I selected a lexical decision task as an example of a task that is reliant on verbal processing function for which the involvement of the right lateral cerebellum has been demonstrated (chapters 2 and 4). A lexical decision task entails the rapid presentation of a string of characters that may either be valid or invalid words within the specified language: the participant is required to respond with the appropriate category as quickly as possible. My previous experiment (chapter 4) had demonstrated that a target of 1 cm below and 6 cm to the right of the inion was appropriate for the impairment of verbal processing and therefore this site was selected for use in this study. Given the inhibitory nature of cTBS and the results derived from previous experiments (chapter 2), I hypothesised that lateral cTBS would disrupt performance on the lexical decision task to a greater extent than vermal stimulation thus enabling a dissociation to be observed in the effects of medial and lateral stimulation on emotional and cognitive tasks.

Methods

Participants:

Approval for the performance of this study was granted by Bangor University School of Psychology Ethics and Research Committee. Participants were recruited via advertisement on Bangor University's intranet and received £10 for each session attended. All participants completed a safety questionnaire prior to participation. Exclusion criteria were any neurological or psychiatric conditions requiring medication. Informed consent was obtained from all the participants in accordance with Bangor University's School of Psychology ethical policy.

12 students (5 female) from Bangor University aged between 18 and 32 were recruited for this experiment. All participants were assessed as right-handed using the Edinburgh Handedness Inventory (Oldfield, 1971) .

Tasks:

I used a masked emotional faces (EF) task and a lexical decision (LD) task for this experiment.

The EF used a similar paradigm to that employed by Schutter, Enter and Hoppenbrouwers (2009). A trial within this task consisted of the display of a fixation cross for a period of 750 ms followed by the presentation of a face with either a happy, neutral or sad expression for 14 ms at the point of fixation. The face was replaced by a coloured mask of an equal size that was red, blue or green and was displayed until either the participant responded or 1500 ms had elapsed. Participants were instructed to respond to the colour as quickly and as accurately as possible by pressing an appropriate button with their left hands. The assignment of colours to response buttons was randomised at the start of each session. The mapping of colour to response key was displayed throughout the trials. Each task run consisted of the display of 30 images. Images to be displayed were chosen at random from the set, with the condition that each image could appear no more than once per task run. The structure of the EF task is illustrated in Figure 18.

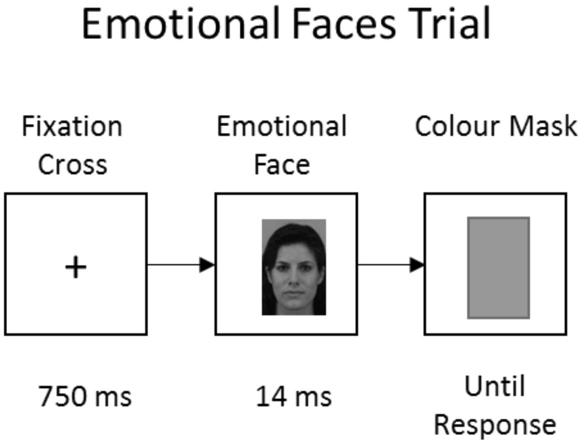

Figure 18. *Timeline of the Emotional Faces Task.*

Within the LD task participants were instructed to judge whether a displayed string of letters formed a valid English word and press an appropriate response key as quickly as possible. A trial within this task consisted of the display of a blank screen for 300 ms followed by a string of 4 characters displayed for 1000 ms. Each task run consisted of 30 trials. Stimuli were drawn at random from a list of words and a list of pseudohomophones, with the condition that each stimulus must appear no more than once per run. The structure of the LD task is illustrated in Figure 19.

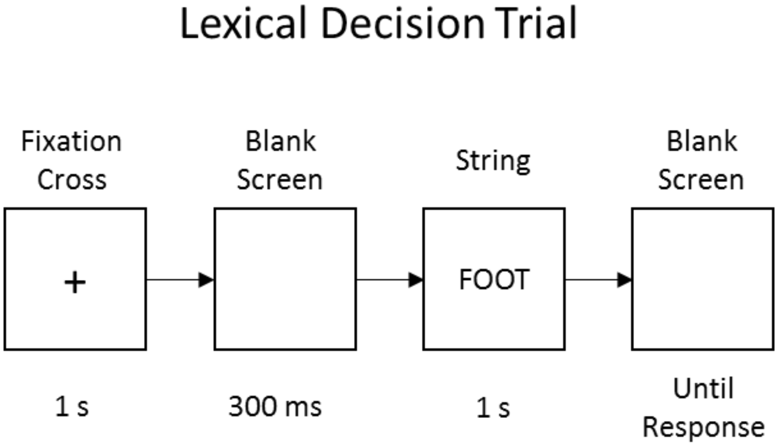

Figure 19. *Timeline of the Lexical Decision task.*

Stimuli:

The EF task used 210 images from the Karolinska Directed Emotional Faces (set ‘A’) (Lundqvist, Flykt, & Öhman, 1998). Each image selected consisted of a photograph of one of 35 men or 35 women directly facing the camera with either a happy, neutral or sad facial expression. Example stimuli are shown in Figure 20.

Figure 20. *Examples (from left to right) of faces expressing Happy, Neutral and Sad emotions.*

The LD task employed lists of 414 standard English nouns and 414 pseudohomophones drawn from the MRC Psycholinguistics Database (Coltheart, 1981) and the ARC Nonword Database (Rastle, Harrington, & Coltheart, 2002) respectively. The nouns had 4 letters and a familiarity rating greater than 575 (of a maximum 700). The pseudohomophones were specified to consist of legally-occurring onsets, bodies and bigrams (e.g. ‘bure’, ‘cadd’, ‘soal’).

Procedure:

Each experiment comprised two sessions separated by at least one week. At the start of each session participants were asked to complete a safety questionnaire and provide their consent. Participants were asked to complete the Positive And Negative Affect Schedule (PANAS) (Watson, Clark, & Tellegen, 1988) to give an indication of their current mood at the start and end of each session. During the first session each participant’s active motor threshold (AMT) was obtained by applying single TMS pulses over the hand area of their motor cortex and determining the minimum stimulation intensity necessary to elicit a thumb twitch during voluntary contraction of the hand muscles.

Each session comprised 12 task blocks: 6 EF and 6 LD. EF and LD blocks alternated, with the start block being assigned in a pseudorandom manner. TBS was applied upon completion of block 6. Each task block consisted of 30 trials. The participants were requested to respond as quickly and as accurately as they could. Participants were requested to use the first instance of each task to practice and informed that results from these blocks would be discarded. The structure of an experimental session is illustrated in Figure 21.

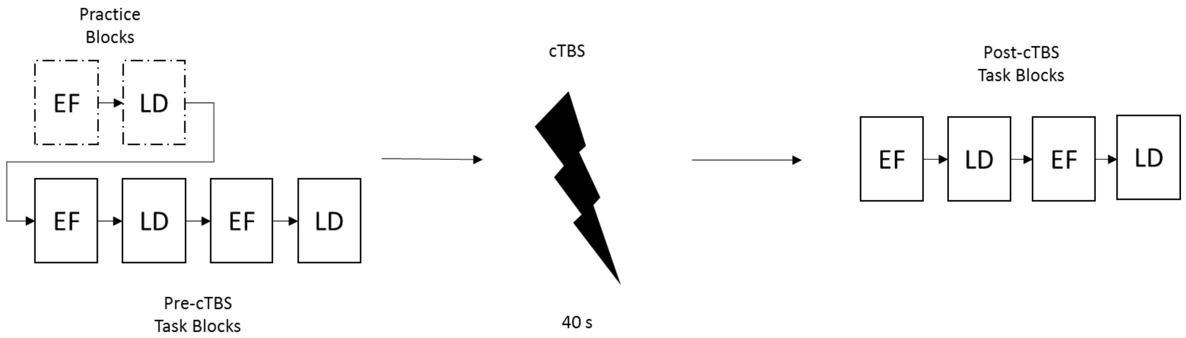

Figure 21. *An example of the structure of an experimental session (in this example it has been determined that the EF task will take place first)*

Stimulus display and response collection was performed on a standard PC with a 17-inch monitor using Psychtoolbox (Brainard, 1997) on MATLAB (The Math Works Inc., Natick, MA, 2010). The type of task block was displayed to the participant for 2 seconds ahead of its start.

The Participants received stimulation to a location over their cerebellar vermis or right cerebellar hemisphere within each session in a pseudo-random counterbalanced order.

Theta Burst Stimulation:

TBS was delivered using a Magstim Rapid (Magstim, Whitland, UK) and a figure-8 coil (ring diameter 70 mm) at 80% of AMT. The coil was placed tangentially to the scalp with the handle pointing upward. "Bursts" of three pulses at 50 Hz were repeated at intervals of 200 ms over a 40 s period (600 pulses in total). I wished to target the vermis and right hemisphere lobule VI/Crus I. I used BrainSight (Rogue Research Inc., Montreal, Canada), to examine MRI scans taken from 3 participants and selected scalp co-ordinates of 1 cm below participants' inions for the vermal site and 1 cm below the inion and 6 cm right for lateral stimulation.

Data Analysis:

Participants performed 10 task blocks: 5 verbal and 5 visual, with 3 of each type being performed before stimulation followed by 2 blocks of each type afterwards. Participants' performance was assessed for accuracy (percentage of correct responses) and reaction time.

To contrast the effects of stimulation on task performance I performed 2, 3-way ANOVAs (IVs: Task (EF, LD), Stimulation Site (vermal, lateral), Time (pre, post)) with dependent variables reaction time and accuracy.

To investigate the effects of stimulation on participants' processing of different categories of emotional stimuli I performed a 3-way ANOVA (IVs: Emotion (Happy, Sad, Neutral), Stimulation Site (vermal, lateral), Time (pre, post)) with dependent variables reaction time and accuracy.

Results

Tolerance of TBS:

None of the participants reported any adverse effects from the stimulation. The mean participants' AMT was measured as 61.42 +/- 5.44% of maximum stimulator output.

PANAS:

No significant changes in participants' reported mood were shown between sessions (F(1,11) = 0.10, ns)). Participants reported significantly higher positive than negative affect throughout the experiment (F(1,11) = 299.29, p < .001)). Participants' affect scores are shown in Figure 22.

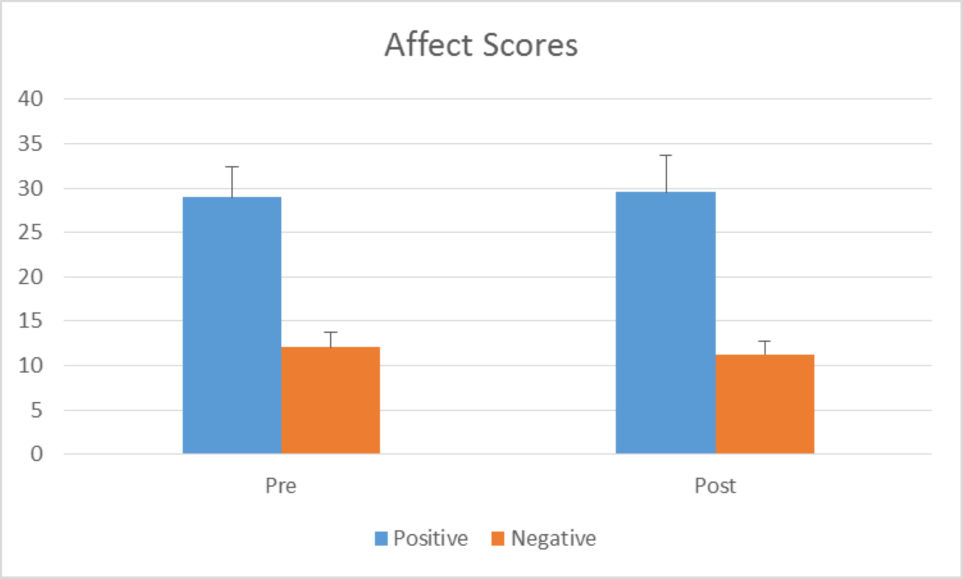

Figure 22. *Positive and Negative Affect Scores before and after cTBS. Error bars represent standard deviation.*

General Task Results:

Participants performed above chance in their accuracy on both tasks (LD correct: 93.07% +/- 2.73; EF correct: 84.74% +/- 12.83). The participants were significantly faster to respond on the LD task (LD: 0.25 s +/- 0.31; EF: 0.6 s +/- 0.07; F(1, 11) = 75.13, p < .01). The participants' correct responses precentages on each task are shown in Figure 23.

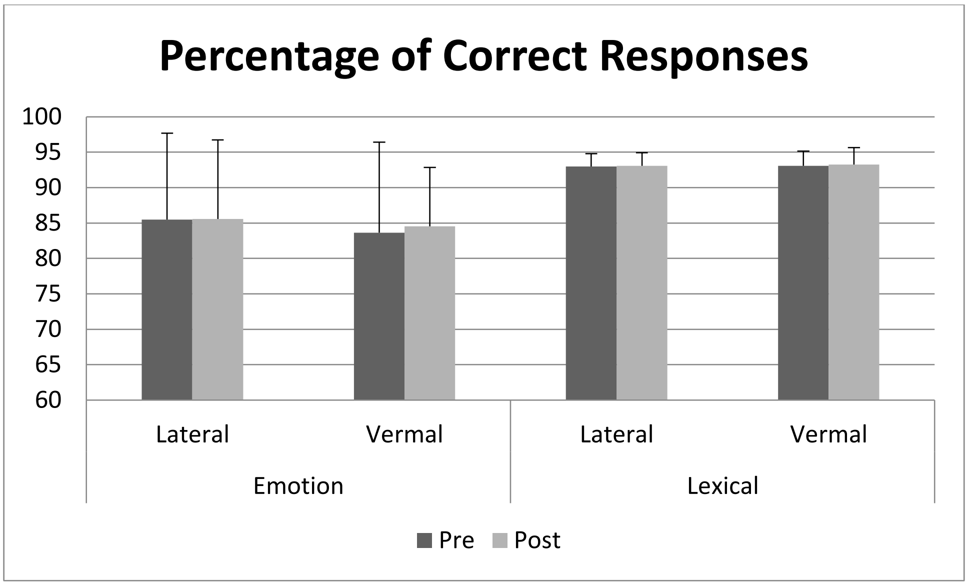

Figure 23. *Participants' percentage of correct responses on the EF and LD tasks. Error bars represent standard deviation.*

The participants were significantly slower on the EF task after stimulation compared to LD (Task x Time: F (1, 11) = 4.79, $p < .05$). No significant differences were seen in the effects of vermal vs. lateral stimulation across the tasks. Participants' response times on the tasks are shown in Figure 24.

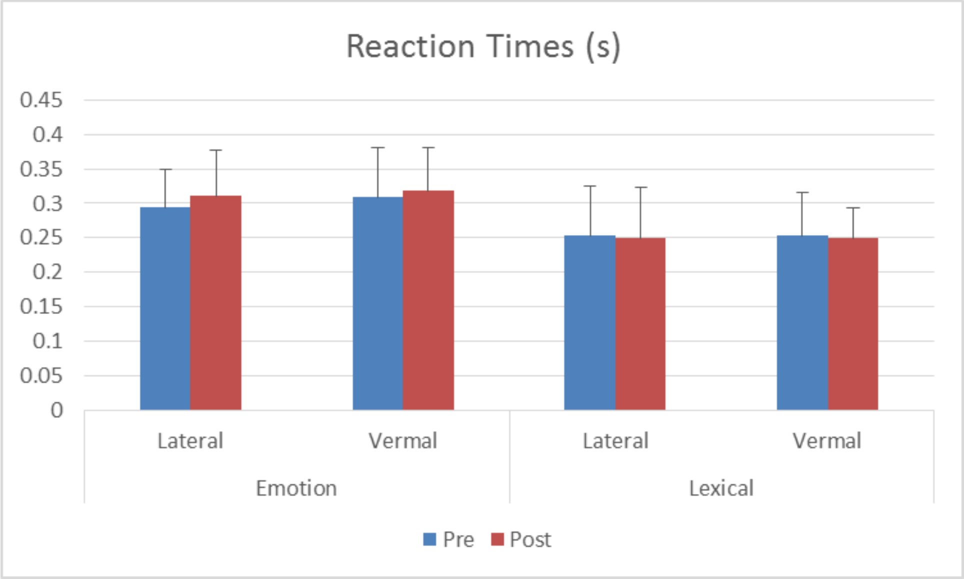

Figure 24. *Participants' response times on the EF and LD tasks. Error bars represent standard deviation.*

The effects of emotional valence:

The results were further analysed by examining accuracy and response times after the display of stimuli expressing differing emotional valences. The ANOVA on participants' reaction times (RTs) did not show a significant interaction between Time, Stimulation Site and Emotion nor an interaction between Time and the Stimulation Site. Participants' reaction times before and after stimulation across valences of emotional stimuli are shown in Figure25.

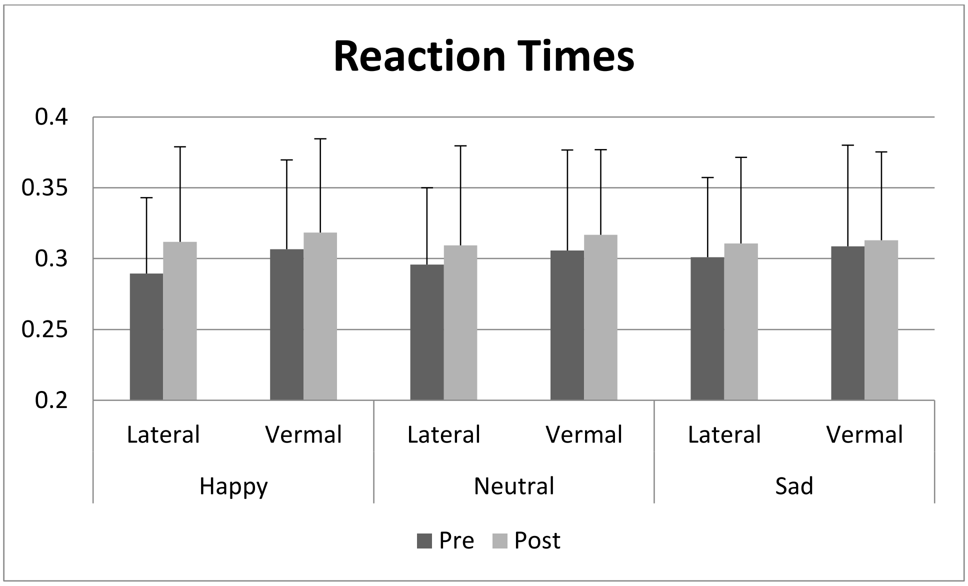

Figure 25. *Reaction Times before and after lateral and vermal stimulation across valences of the emotional stimuli. Error bars represent standard deviation.*

No significant differences were seen in reaction times across emotional valences nor was a correlation observed between participants' reported emotional state and their speed of response to congruent or incongruent emotional stimuli.

Discussion

The results demonstrated a general effect of cerebellar cTBS on the processing of emotional stimuli as shown by the increase of participants' reaction times on the emotional faces (EF) task when compared to the lexical decision (LD) task after stimulation. The slowing of participants' reaction times on the EF task was observed after both vermal and lateral stimulation.

The results are not consistent with the induction of an impairment to motor behaviour since the EF and LD tasks had similar motor demands and the observed effects were limited to the EF task.

These results do not suggest that cerebellar cTBS had an effect on the emotional state of the participants. There were no significant changes in participants' reported mood as reflected in their PANAS scores. Additionally, there was no evidence of an alteration in participants' implicit mood as the effects of TBS did not differ significantly across all valences of the emotional stimuli. If TBS had had a similar, but opposite, effect to the rTMS protocol employed by Schutter et al., one would expect to see an increase in reaction times that was limited to happy emotional stimuli within the EF task.

The possibilities that remain to account for these results are that TBS affected either the participants' ability to process task-irrelevant emotional faces or that stimulation impaired the speed with which participants had been able to correctly identify the colours of the presented stimuli.

No evidence has been found to suggest that colour information is directly projected to the cerebellum (Glickstein, 2000). There is limited evidence to suggest that the cerebellum plays a critical role in the processing of colour. Claeys et al. (2003) found bilateral regions of lobule VI were active during a colour discrimination task and Bird, Berens, Horner and Franklin (2014) reported that a medial posterior region of the left cerebellum showed specific activation for the categorical processing of colours. Gottwald, Wilde, Mihajlovic and Mehdorn (2004) observed a significant impairment in the ability of cerebellar patients to perform a colour naming task, when compared to controls, whereas Alexander, Gillingham, Schweizer and Stuss (2012) found no impairment on a similar task. This evidence does not give a strong indication of the involvement of the sites stimulated within my experiment in the processing of colour and therefore does not suggest that the effects of TBS were instrumental during the colour discrimination component of the EF task.

It is more plausible to suggest that my results indicate that inhibitory stimulation to the cerebellum impaired the efficiency with which participants were able to minimise the distraction caused by task-irrelevant emotional faces. It is interesting to note, however, that cTBS slowed participants' reaction times across all valences of the emotional faces. The suggestion that the participants' performance was affected by an impaired ability to dismiss *specifically emotional* distractors would have been lent greater support had this impairment been limited to emotionally-laden expressions (i.e., happy and sad) rather than also including emotionless faces (i.e., neutral). There is evidence that the presentation of a face is inherently emotionally-salient irrespective of its expression, given the survival relevance of extracting emotional information from a face as quickly as possible (Kanwisher & Yovel, 2006; Rellecke, Palazova, Sommer, & Schacht, 2011). However, further study is recommended to determine whether varying the mode of presentation of the faces and the emotions conveyed would allow confirmation of whether cerebellar cTBS affects specifically emotional elements of facial processing, whether the cerebellum plays a more general role in facial processing or if cTBS has, in this case, merely impaired a general attention shifting mechanism. Cerebellar damage has been associated with an impaired ability to process socially-relevant facial expressions (D'Agata et al., 2011) and with the ability to rapidly shift attention (Courchesne et al., 1994). Cerebellar abnormality has been associated with autism (Stoodley, 2014) and there is neuroimaging evidence to suggest that brain activity, including that of the cerebellum, differs in the processing of facial expressions between autistic and control subjects (Critchley et al., 2000). This evidence suggests that there is a cerebellar role that is relevant to both the processing of facial expressions and the control of attention to and away from emotionally-relevant stimuli: further experimentation is required to elucidate the specific functionality that can be affected by cerebellar cTBS.

The results of this experiment do not lend support to the hypothesis that vermal, rather than lateral, areas of the cerebellum are of greater importance to the processing of emotional stimuli since the similar results were observed after stimulation to both areas. This is perhaps not surprising as whilst the clinical and animal studies reviewed suggested a primacy of vermal areas in emotional processing it must be noted that the reviews of neuroimaging studies (E et al., 2014; Stoodley et al., 2011) identified foci of activity that were located both in the vermis and across lateral hemispheric regions.

In contrast to the experiment presented in chapter 4, no evidence was found for the role of the right lateral cerebellum in verbal processing. A similar stimulation protocol was used in both experiments, but there were clear differences in the elements of verbal processing that were employed in the experimental tasks. The current experimental task entailed the processing of a visually-presented verbal stimulus and its comparison with entries in participants' lexicons rather than the contents of their working memory. The use of a lexical decision for the investigation of cerebellar involvement in verbal processing is complicated, however, by the operation of complementary processes within the recognition and classification of verbal input. The conversion of visual information to abstract letter information and the grouping of letters to familiar word forms commence prior to the phonological encoding and analysis of the input (Warrington & Shallice, 1980). This evidence suggests that the effects of any manipulation of the cerebellum during a lexical decision task may be obscured by the operation of unaffected prior processes for which no evidence for a cerebellar role has been found. Detailed investigation of the stages of a lexical decision task (Coltheart, Besner, Jonasson, & Davelaar, 1979) suggests that, unlike the working memory task of chapter 4, the performance of this experiment's LD task does not necessarily entail the phonological encoding of stimuli. If, as was argued in chapter 4, the effects of cTBS applied to the right cerebellar hemisphere were the impairment of participants' ability to make an effective encoding of the presented stimuli then it is understandable that no effects of this stimulation were seen on the LD task since phonological encoding was not a critical component.

As shown in chapter 2, the lexical decision task has been successfully employed to investigate the cerebellar role in language using cTBS (Argyropoulos et al., 2011; Argyropoulos & Muggleton, 2013; Argyropoulos, 2011), but post-stimulation differences were seen on priming effects rather than on a simple lexical decision paradigm as was used in this experiment. Clinical case studies have presented mixed evidence of whether the cerebellum is a critical structure for the performance of lexical decision tasks with cerebellar patients showing normal (Fiez, Petersen, Cheney, & Raichle, 1992) and impaired (Mariën et al., 2009) performance. Taken together these factors suggest that the LD task was not an optimal selection for an exemplar of a cognitive task with clear involvement of the lateral cerebellum. Use of a verbal working memory task in conjunction with cTBS to the right cerebellar hemisphere would allow a better contrast to functions associated with other cerebellar areas.

The aim of the emotional faces aspect of this experiment was to investigate the cerebellum’s role in emotional processing by examining whether cTBS, as an inhibitory form of cerebellar stimulation, would produce an opposite effect to excitatory rTMS as used by Schutter et al. In order to expand on Schutter et al.’s findings a similar masked emotional faces task was employed, which used an indirect measure of emotional processing (i.e., reaction time on a colour naming task after the brief presentation of an emotional distractor). Unlike Schutter et al. I did not observe a change in reaction times that was specific to one valence of stimuli and therefore could not suggest that the stimulation had caused an alteration in participants’ implicit mood. The absence of any indication of a mood change in participants and the use of an indirect measure in the EF task admits alternate interpretations of the post-stimulation impairments in reaction times that were observed, as was discussed previously. Given that there is no evidence to suggest that cerebellar cTBS has an effect on participants’ explicit or implicit mood then the use of a more direct measure of emotional processing speed is recommended. A direct paradigm similar to that used by Ferrucci et al. may be more appropriate for future studies of the cerebellar role in the processing of emotional stimuli.

In conclusion, these results demonstrated an impairment in reaction times on a masked emotional faces task after cerebellar cTBS that contrasted with an improvement on a lexical decision task. The hypothesised dissociation between the effects of vermal and lateral stimulation on a cognitive and an emotional task was not observed. A degree of ambiguity was present in the interpretation of the results of this experiment’s emotional faces task: given the absence of any effects of cTBS on participants’ mood, more direct measure of performance are recommended for future studies of the cerebellar role in emotional processing.

Chapter 7 - General Discussion

In the research described in this thesis I sought to investigate the role of the cerebellum in nonmotor behaviours. I presented a series of experiments that used non-invasive brain stimulation techniques to enable the examination of the role of the cerebellum in cognitive and emotional processing. The results of the experiments are presented in Appendix B. This chapter will be used to summarise the experiments conducted and consider their results in the wider context of the existing literature. I will present a consideration of the cerebellum's role in cognition and emotional processing as informed by the results and then present observations on the use of cerebellar brain stimulation.

Summary of Experiments

Chapter 3 presented two experiments that sought to investigate the cerebellar role in verbal and visual working memory (WM) using transcranial direct current stimulation (tDCS). These experiments used versions of the Sternberg WM task using letters and non-nameable Attneave shapes to study WM performance before and after cerebellar tDCS. The experiments demonstrated the difficulties entailed in the use of a non-focal stimulation technique for cerebellar stimulation. No clear evidence for a cerebellar role in verbal or visual WM was obtained: a relatively-impaired performance improvement seen after tDCS to the right cerebellar hemisphere was taken to be indicative of the presence of a ceiling effect within one of the experimental tasks. The need for task calibration was discussed. Consideration was given to research conducted on the electric field strength produced by tDCS and the challenges faced in ensuring sufficient current reaches the intended cerebellar targets. Reference was made to further tests that failed to detect an effect of cerebellar tDCS on the performance of motor tasks that are known to be critically reliant on the cerebellum. From this point a rationale was advanced for the use of more-focal stimulation techniques for further research.

Chapter 4 presented an experiment that used continuous theta burst stimulation (cTBS) targeting the posterolateral cerebellum (lobule VI/Crus I) to determine whether a lateralised cerebellar contribution to WM processes could be detected during the performance of visual and verbal Sternberg tasks. The difficulty of the verbal WM task employed was increased through the use of words rather than letters, as had been used in the earlier experiments. This measure was taken to lower the possibility of a ceiling effect and to increase the demands on the cognitive systems responsible for encoding and rehearsing stimuli to be memorised. The visual Sternberg task used a new set of complex, non-nameable Attneave shapes. The results of this experiment demonstrated an impairment in verbal WM recall accuracy after cTBS to the right cerebellar hemisphere that contrasted to a performance increase, ascribed to practice, after left cerebellar cTBS. 'Recall accuracy' is defined here to be the percentage of correct responses given by the participants in the WM trials. The impairment to verbal WM additionally contrasted with improvements in recall accuracy that were seen on the visual WM task after cTBS to both left and right cerebellar hemispheres. No alterations were seen in reaction times after stimulation to either location on either task. Consideration was given to what this result indicated of the cerebellar role in WM in the context of what is known about the overall structure of WM processing.

Chapter 5 presented two experiments that used cTBS targeting mid-hemispheric and lateral areas of the posterior cerebellum to determine whether a lateralised cerebellar role could be demonstrated in visuospatial WM. An impairment in the recall of the order of presented targets was seen after stimulation of the left cerebellar mid-hemisphere. An impairment in the speed of participants' responses was seen after stimulation of the more lateral areas of the left cerebellar hemisphere. These results contrasted with an absence of change in performance after stimulation to either location on the right cerebellar hemisphere. The results were taken to indicate a preferential role for the cerebellar left hemisphere in spatial WM, which was contrasted to the null results seen in purely visual tests. It was noted, however, that these results provided insufficient evidence to strongly assert a clear functional topology for spatial WM function within the cerebellar left hemisphere.

Chapter 6 described an experiment that examined the cerebellum's role in processing emotional stimuli in contrast to the proposed cerebellar function in verbal cognition. This experiment sought a dissociation between the effects of vermal and lateral cTBS in the performance of a 'masked emotional faces' colour-naming task, which incorporated emotionally-salient distractors, and a lexical decision task. Increased reaction times were seen on the emotional faces task after stimulation to both areas, which contrasted with decreased post-stimulation reaction times on the lexical decision task. No changes were indicated in participants' reported mood and, in contrast to a previous, similar experiment, post-stimulation differences were not specific to a single valence of emotional stimulus. These results were taken to indicate a cerebellar role in the orientation and shifting of attention, with particular emphasis on emotionally-salient stimuli. Consideration was given to the suitability of the selected tasks for a comparison between vermal and lateral cerebellar functions and the advantage of using direct measures of emotional processing were discussed.

Consideration of main results

The most salient results for the elucidation of the role of the cerebellum in non-motor behaviour were derived from the experiments described in chapters 4 and 5. These results concerned the contribution of regions of the cerebellum to visual, spatial and verbal WM. Each of these experiments employed the offline application of continuous theta burst stimulation (cTBS) to allow a comparison to be made on the performance of WM tasks before and after stimulation. The experiments also entailed the stimulation of targets located in the cerebellar hemispheres contralateral and ipsilateral to the cerebral hemispheres that have been shown to be more instrumental in the performance of tasks using particular stimulus modalities. The inclusion of targets in both cerebellar hemispheres allows consideration of whether the experiments' results enable the inference of hemispheric specialisation in the cerebellum that is equivalent, but opposite, to that of the cerebrum.

It is useful, when considering the implications of the experiments' results, to recall the physiological effects of cTBS. As documented by Huang, Edwards, Rounis, Bhatia and Rothwell (2005), cTBS depresses the excitability of motor cortex (as measured by motor evoked potentials) for several minutes after its application. Later researchers have inferred a similar suppression of the activity of the cerebellar cortex after cTBS in both motor and non-motor studies (Koch et al., 2008; Picazio et al., 2013). A similar stimulation protocol, in terms of power, pulse pattern and duration, was used in my experiments to that used by Arasanz, Staines, Roy and Schweizer (2012) and Argyropoulos (2011). As applied to the cerebellum this stimulation is taken to partially supress the activity of the targeted area of the cerebellar cortex: modelling studies suggest that stimulation is not sufficiently powerful to directly affect the function of the cerebellar nuclei (Hoffland et al., 2011). The suppression induced by cTBS is believed to due to an induced hyperpolarisation of neuronal membranes that increases the level of input required to generate an action potential (Huang et al., 2005). If the view of the cerebellum as an organ that builds internal models that allow efficient task execution (Wolpert et al., 1998) is correct then the suppression of its activity may be manifest in the disruption of existing models for task execution; inefficiency in recalibrating existing models for the particular demands of a current task; or an inability to generate effective new models. An impairment in, or failure to improve, task performance after cerebellar cTBS may be taken to indicate the presence of a cerebellar contribution to task performance, provided that the impairment can be shown to be specific to the task in question (e.g., rather than representing a general impairment in attention). The nature of the impairment, by comparison to the results from other tasks and the stimulation of other locations, can be used to make inferences on the nature of the contributions being made by this region of the cerebellum to the task being performed.

The experiment described in chapter 4 used versions of the Sternberg task (Sternberg, 1966) to investigate WM functions. As was noted, the Sternberg task was preferred to other well-researched WM paradigms, such as *n*-back, for the emphasis it places on modality-specific elements of WM rather than on the modality-free central executive (Hautzel et al., 2009). Following from the literature on the specialisation of the cerebral hemispheres, the examination of modality-specific elements of WM was seen as increasing the possibility of being able to detect a cerebellar role in WM. The cerebellar contribution to the visuospatial sketchpad or the phonological loop could be examined by contrasting the effects of cTBS to the cerebellar hemisphere more strongly connected to the right or left cerebral hemisphere, respectively. It was hypothesised that the inhibitory effects of cTBS would produce either performance impairments, or a relative failure to improve performance, when applied to the right cerebellar hemisphere before verbal WM tasks and to the left cerebellar hemisphere before visuospatial tasks. The Sternberg task entails the serial or simultaneous presentation of a set of stimuli to be memorised; the provision of a period for scanning and encoding the stimuli; a maintenance period following the disappearance of the stimuli; and the display of a probe item to be compared against the previously displayed list. cTBS is an offline stimulation technique; therefore it is reasonable to suggest that any affected areas of the cerebellum will be in an equally-affected state throughout the phases of each trial after stimulation: analysis of the structure of each experimental task and its associated results is required to determine whether a stronger association can be made between the observed results and any of the task's phases.

The results from the verbal Sternberg task used in this experiment showed that participants' performance was impaired after the application of cTBS to a location 1 cm below and 6 cm right of the inion. The impairment was a decrease in the accuracy of participants' responses (i.e. the percentage of correct responses given) rather than an increase in reaction times. The stimuli employed were commonly-used English nouns of between 4 and 6 letters randomly selected from a list of 50 items. Stimulus presentation parameters were calibrated to each participant's ability with an average presentation rate of 0.53 s between items and an average list length of 11.47.

The stimulation site used in this experiment on the right cerebellar hemisphere was chosen to target the areas of the superior lateral cerebellum (lobule VI / Crus I) that had shown themselves to be active during verbal WM processing (Chen & Desmond, 2005a, 2005b) and to be affected by transcranial magnetic stimulation (TMS) (Desmond et al., 2005). A matching location on the left cerebellar hemisphere was also used to determine if a similar role in visuospatial processing could be inferred. Of importance for the interpretation of the results of this experiment were the neuroimaging findings that showed concurrent activation of both the right superior lateral cerebellum and Broca's area during the encoding phase of verbal Sternberg tasks though this activation was not sustained throughout the maintenance phase of the tasks. Chen and Desmond made a convincing argument that, in the case of verbal WM, this activation could be taken as being associated with the articulatory component of the phonological loop, i.e., representing the rapid conversion of visual stimuli to a phonological trace for preservation in WM. Further to this, Desmond and Fiez (Desmond & Fiez, 1998) argued that the concurrent activation of Broca's area and the supplementary motor area with the cerebellum during articulatory encoding indicates a system using motor encoding for the production of covert memory traces. Consideration of the cerebellum's role in non-motor activity as a development upon prior contributions to motoric behaviour will be given in the following sections. Of additional note regarding cerebellar activity during verbal WM tasks, was that an earlier study (Wildgruber et al., 2001) noted that activation in this region was most pronounced during trials where a high level of stimulus conversion was required.

The results from the verbal WM task in this experiment contrasted with those seen by Desmond et al. My results showed that application of cTBS to the right superior lateral cerebellum resulted in a decrease in response accuracy with no significant change in reaction time. Desmond et al. saw no change in accuracy with a significant increase in reaction time after the application of single-pulse TMS (sTMS) to the same area at the close of the encoding phase. In considering the contrast between these results it is useful to compare the effects of the stimulation techniques used. Desmond et al. applied sTMS at 120% of the participants' active motor threshold. It is reasonable to suggest that the effect of stimulation at this level of power was to introduce a burst of action potentials in cells within the targeted region, thus introducing momentary disorder to the encoding activity being supported by the cerebellum. The offline application of cTBS is not sufficient to produce action potentials, but is instead believed to reduce their likelihood, thus inhibiting the activity of the targeted region. Desmond et al., reasonably, interpreted the introduction of momentary disorder as resulting in the creation of a degraded articulatory trajectory, which in turn resulted in a 'noisy' memory trace being stored in the phonological buffer. Desmond et al. further suggested that the comparison of a probe against the degraded memory trace took longer to complete and therefore caused the increase in reaction times on the trials where sTMS was used. The absence of a change in reaction times in my experiment suggests that the retrieval and comparison process did not take longer following cTBS, but it was relatively less successful. Following Desmond et al.'s results, this would suggest that the memory traces that *were* encoded were encoded soundly, but encoding of all stimuli was not completed. This interpretation is lent credibility by my use of an experimental task that place a higher level of encoding demand on participants than that used by Desmond et al. The result of the high level of task demand coupled with an impaired articulatory control system was that participants had access to *less* rather than *worse* memory information and therefore were more prone to error after stimulation. In retrospect, further analysis of the errors made after stimulation would have been useful: the hypothesis that the participants' errors after stimulation were influenced by their inability to fully encode the stimuli would have been supported had there have been an increased rate of errors on positive trials, i.e., trials where the probe had appeared in the previous list. It would be beneficial for this aspect to be included in future experiments.

The visual Sternberg task that was run as part of the same experiment used complex non-nameable Attneave shapes as stimuli. Once again, the stimulation parameters were calibrated to each participant's ability with an average presentation rate of 0.68 s and an average list length of 9.87. A similar impairment to that seen on the verbal Sternberg task was anticipated after the application of cTBS to the left cerebellar hemisphere, but an impairment was not seen either in response accuracy or in reaction times. The absence of an impairment after stimulation of the left superior lateral cerebellum failed to provide evidence that this area may be involved in an analogous encoding function for visual stimuli to that provided by the opposite cerebellar hemisphere for verbal stimuli. Consideration of the literature on cerebellar contributions to visuospatial working memory suggested that the failure to detect an effect of left cerebellar TBS may have been due to the experimental task making insufficient spatial demands of the participants. Evidence has been provided to show a dissociation between the visual and spatial systems of working memory (Courtney, Ungerleider, Keil, & Haxby, 1996; Klauer & Zhao, 2004): visual working memory processes the form and identity of objects whereas spatial working memory operates on their locations and relative positions. It will be recalled that evidence has been presented for the specialisation of the right cerebral hemisphere for spatial tasks (Jonides et al., 1993), whereas no evidence has been presented for a right hemisphere advantage that is purely visual without spatial elements: in visual object-based studies activations have been seen to be primarily left hemispheric or bilateral (e.g. Haxby, Ungerleider, Horwitz, Rapoport, & Grady, 1995).

The previously-mentioned meta-analysis of cerebellar nonmotor neuroimaging studies conducted by E et al. (2012) showed a peak activation within the left cerebellar lobule VI (in a somewhat similar location to my 1cm inferior to the inion, 3 cm lateral scalp co-ordinates) during spatial working memory tasks, but did not show any areas within the hemisphere that were exclusively activated for visuospatial rather than verbal working memory tasks. Two of the studies included in the meta-analysis used Attneave shapes to investigate cerebellar lateralisation for WM and did not detect significant differences (Hautzel et al., 2009; Thürling et al., 2012). Clinical studies by Dimitrov et al. (1996) and Richter et al. (2007) failed to see any significant performance differences between cerebellar patients and the normal population on spatial working memory tasks. Examining the experimental tasks used within these studies reveals an emphasis on visual, rather than spatial demands: whilst there are elements of spatial analysis within the processing of an abstract shape, this is more a feature extraction (or 'what') task rather than an analysis of the spatial relationships (or 'where' task). Further to this a number of studies aimed at the study of the cerebellar role in visuospatial WM have employed tasks were such that the information required to successfully complete the task could be expressed as a single non-spatial concept, which allows the contamination of the task as an instrument for the examination of spatial WM through the introduction of strategic verbal labelling. Within this experiment previously unseen Attneave shapes were chosen for this task to prevent, as far as possible, participants from assigning the stimuli verbal labels and using a phonological encoding strategy to enhance their performance. The absence of a performance impairment after *right* cerebellar stimulation suggests that the participants were prevented from using phonological strategies. Subjective reports from the participants suggested that several of them expressed a desire to assign labels to the presented shapes (by comparing them to previously seen, similar items, e.g., an aeroplane), but were unable to use this strategy by the rapidity of the presentation of the stimuli.

The absence of any impairment to visuospatial WM performance after stimulation of a left cerebellar hemisphere prompted a search for a more demanding test of this ability. The experiments described in chapter 5 used tasks loosely based on the Corsi block task for spatial memory. The tasks entailed the serial display of a set of randomly placed rings on a blank background followed by the appearance of crosshairs, which were used by participants to mark the location of the stimuli in the order that they had appeared. The tasks were designated as ‘Memory’ and ‘Aiming’ with the difference being that each target would be removed after a short display period in the Memory trials and would remain visible during Aiming trials. For successful performance of both tasks the participant would be required to memorise the order of the targets’ appearance; however the Memory task also require the storage of the targets’ locations after their disappearance. The first experiment used cTBS to inhibit mid-hemispheric locations of the cerebellar posterior lobe and revealed an impairment in the participants’ recollection of the order of the targets’ appearance after stimulation of the left hemisphere. That this impairment applied to both Memory and Aiming trials was taken to be indicative of the disruption of a function common to both tasks, namely the encoding and retrieval of stimulus order. In this experiment the participants did not show any impairment in the speed with which they supplied their responses. The second experiment targeted more lateral locations: the same as were used in the experiment described in chapter 4. This experiment revealed a decrease in the speed of participants’ responses after stimulation that was present solely during Memory trials. Unlike the preceding experiment, no impairment in response accuracy was seen.

Since impairments were seen after left, rather than right, cerebellar stimulation these results provide support for the hypothesis that the left cerebellar hemisphere plays a role in visuospatial WM that is of greater importance than the role played by its counterpart. These results do, however, raise a number of questions and are open to contrasting interpretations. The experiments targeted locations in the superior posterior cerebellum: analysing the BrainSight data suggested that the targets for the first experiment lay within lobule VI, whereas the second experiment's more lateral targets lay at the VI/Crus I boundary. The proposed focality of TMS (Thielscher & Kammer, 2004) and Desmond et al.'s. description of a nonmotor functional topology in the posterior cerebellum suggested that targeting these areas and contrasting the results may allow further detail to be added to the cerebellar functional topology. Stimulation to both areas of the left cerebellum resulted in impairments, but the impairments were different in their expression and scope. It was observed that stimulation to the mid cerebellar hemisphere impaired the successful recollection of target order, whereas lateral stimulation impaired response speed. WM tasks are typically decomposed into encoding, maintenance and retrieval/response phases (Jonides et al., 2008). In the experiments described in chapter 5, however, it is perhaps more appropriate that these tasks be considered as consisting of only two phases: neither task incorporated a distinct maintenance phase, though maintenance of target data was required throughout encoding and response. Within the experimental tasks there is a difference in the nature of these task phases that may be of importance when considering their results. The time available for the encoding phase is set by the experiment (one second per target), whereas there is no time limit on the retrieval/response phase. If encoding of target details is not performed adequately within the available time then the task cannot be performed successfully and this would, presumably, be reflected in a decrease in the overall recall success rate. If, however, activity during the response phase is impaired then, in the case where adequate information has been encoded, given that no time limit is set for activity within this phase, it follows that whilst a correct response may still be produced, there is the opportunity for an impairment to be manifest as a reduction in processing speed, evidenced by a slower response. This interpretation accords with that advanced by Desmond et al. in suggesting that a degraded memory trace may manifest as slower recall performance. Taken together, this suggests a relative failure to complete encoding was seen in experiment 1, whilst encoding was completed in experiment 2, but of a relatively lower quality. An alternative explanation for the results derived from experiment 2 is that cTBS applied to the left lateral cerebellum has impaired the retrieval rather than the encoding phase of WM processing. As noted, the impairment applied only to the Memory rather than to both tasks. The Memory task requires the storage and retrieval of spatial information in the absence of persistent stimuli. The lack of an impaired success rate implies that sufficient data has been encoded to complete the task, but the impairment in response speed may indicate a slower process of retrieving the stored locations in order to provide a response. Further study is required, possibly with the use of an online stimulation technique such as sTMS, to determine if the targeting of areas of the right cerebellum during the encoding and, separately, the retrieval phases of a spatial WM task can dissociate the effects of disruption on the underlying processes.

Examining the results in chapter 5 together with the earlier results makes it difficult to advance an intra-hemispheric functional topology for spatial WM. In isolation, it may be suggested that inhibitory stimulation of the left cerebellar mid-hemisphere impairs encoding, whereas more lateral stimulation impairs retrieval, but it must be noted that the earlier experiment identified the same lateral area as being of importance for encoding: a suggestion with strong support in the literature. The seeming disagreement between the functionality of regions with the superior posterior elements of the left and right cerebellar hemispheres in the execution of verbal and spatial WM tasks is not necessarily surprising. Despite the case being made for a cerebellar functional homogeneity based on the ubiquity of the microcomplex, there is no reason to believe that the role played by the cerebellum in support of spatial WM must be exactly the same as that within verbal WM. Whilst the basic computational operations of the microcomplexes involved in the two processes may be the same, there is substantial evidence to suggest that there are fundamental differences in the cerebral areas associated with each function and the profile of their activations. Neuroimaging studies have demonstrated that, in most right-handed subjects, regions of the left cerebral hemisphere will be activated by verbal WM, whereas areas in the right cerebral hemisphere are more active during spatial WM tasks (Smith & Jonides, 1997). If the cerebro-cerebellar connectivity of both hemispheres is similar, and if active cerebral areas enlist the support of the cerebellar areas to which they connect, then it is reasonable to suggest that the cerebellar areas by the tasks across the hemispheres would not necessarily be the same.

A further reason for the suggestion that dissimilar cerebellar activations should be expected across verbal and spatial WM is derived from the differences in the cognitive operations involved, both generally and specifically with the experimental tasks used in chapters 4 and 5. The creation of a phonological encoding from the presented verbal stimuli is well established, whilst the process followed in the encoding of spatial data is less clear. Earlier studies have suggested that caution must be taken in the selection of stimuli for the assessment of spatial WM since different strategies can be employed by participants for the encoding of visual patterns rather than spatial paths (Pickering, Gathercole, Hall, & Lloyd, 2001). The experiments used in chapter 5 used a serial presentation of stimuli (i.e. the points that were used as stimuli were displayed serially) to encourage the treatment of stimuli as an ordered list, rather than a shape, and to emphasise the spatial nature of the task by requiring the participant to shift attention along a fixed path of points as the stimuli were displayed. Previous studies that have employed the serial presentation of points for the analysis of spatial working memory suggest that stimuli are encoded as a series of points located relative to the stimulus that preceded them, with the exception of the first point that is encoded as the ‘origin’ from which a path proceeds (Parmentier, Andrés, Elford, & Jones, 2006; Parmentier, Elford, & Mayberry, 2005). Eye-tracking experiments have demonstrated that, without instructions to fixate, participants move their eyes to the location of each stimulus and that these shifts of attention between points are relevant to the encoding of the required memory trace (Guérard, Tremblay, & Saint-Aubin, 2009). It is therefore clear that a WM representation of stimuli that are encoded and rehearsed in terms of imagined eye movements and attention shifts would require fundamentally different cognitive operations than a representation reliant on phonological encoding. With the marked difference in cognitive operations the absence of an exact similarity in cerebellar activity within both WM systems is not unexpected.

Emerging from these results is further evidence for a cerebellar role in the performance of both verbal and spatial WM. The role of the right superior posterior cerebellum in the encoding of the phonological memory trace in verbal WM has received support from the results described in chapter 4. Evidence for the involvement of the left cerebellar hemisphere in spatial WM has been generated by the results of the experiments described in chapter 5, but there remains a degree of ambiguity to the phase or phases within the process that are facilitated by cerebellar activity. The following section is intended to consider these results in the context of the wider literature of cerebellar involvement in nonmotor activity and propose an explanatory framework for the cerebellar role that extends across both motor and nonmotor behaviour.

The cerebellum’s role across behavioural domains

As has been noted, the expansion of the human cerebrum has been accompanied by a similar increase in cerebellar volume. The connections discovered between the phylogenetically most recent areas of both structures and the noted role of pre-frontal areas in cognitive behaviours have led researchers to investigate the possibility of a cerebellar role in nonmotor behaviour. Research into the pressures and processes driving evolution suggest a principle of parsimony: selection pressures favour brain expansions or increases in complexity where these developments serve a purpose advantageous to an organism’s survival (Aboitiz, 1996; Byrne, 2000; Finlay, Darlington, & Nicastro, 2001); and a principle of augmentation: behavioural solutions will emerge from the augmentation or repurposing of existing mechanisms rather than the development of new solutions from entirely novel components (Lemski, Offria, Pennock, & Adami, 2003). An example of the latter principle is believed to be the evolutionary development in humans of a multi-regional speech processing system comprising Wernicke’s, Broca’s and other areas of cortex from predecessor areas associated with basic communication, auditory processing and working memory (Aboitiz & García, 1997; Eccles, 1989). These factors are of relevance when considering the role and purpose of the human cerebellum. The cerebellum contains approximately half of the neurons in the human nervous system, which, given the principle of parsimony, would seem to imply their presence being required for survival-relevant behaviour. The cerebellum has expanded in parallel with the pre-frontal cortex: the noted cerebellar homogeneity taken with the discovery of circuits between the pre-frontal cortex and posterolateral cerebellum suggests that new multi-structure processing complexes have been formed, similar to those linking phylogenetically older areas. The principle of augmentation suggests that the requirements of new behavioural challenges will be adapted from pre-existing solutions – if this is the case then it is plausible that, at a fundamental level, common principles will have guided the development of solutions to both older, more basic, and newer, more complex, behavioural requirements.

Implied by these factors is a cerebellum, whose expansion has been driven by its role in survival-relevant behaviours and which has adapted existing solutions to fit the demands of new challenges. It is reasonable therefore, when considering a possible cerebellar role in complex behaviour (e.g., cognition), to take the cerebellar role in older behaviours (e.g., autonomic, motoric) as an instructive starting point. As discussed in chapter 1, the cerebellum's role in autonomic and motoric processing is not to instigate behaviour, but to contribute to its efficient and effective implementation. Research into the specific deficits resulting from cerebellar injury, augmented by findings from computer modelling and brain stimulation has developed a view of the cerebellum's ability to contribute to the execution of behaviour that derives from the development of internal models of task-relevant aspects of the universe. Evidence has been gathered that has led to the development of two classes of description applied to cerebellar internal models: as forward models that predict the sensory outcome of an action and as inverse models that provide mappings from intention to action (Ito, 2000; Wolpert et al., 1998). An example of inverse modelling is the conversion of a desired limb position to the muscle commands required to achieve this state as demonstrated in artificial systems by Kawato, Furukawa and Suzuki (1987). Evidence of cerebellar utilisation of forward models has been derived from neuroimaging and computer simulation and has suggested mechanisms of model development (e.g. Kawato et al., 2003). The work performed by Wolpert et al. highlighted the intimate association between forward and inverse models and suggested that it would be disadvantageous to consider either class in isolation: the development of 'forward' aspects of a cerebellar model, i.e. the likely sensory consequences, allows optimisation of 'inverse' aspects as the efficient achievement of desired sensory consequences enables a model to be preferred in similar future circumstances. It is clear that the instantiation of both classes of model enable the automatisation of behaviour through the acquisition of representations of the actions necessary to achieve a goal and their predicted consequences. I shall argue that through the use of internal models the cerebellum reduces the conscious demands of task performance and enables efficient execution.

The development of cerebellar models is held to be a component of the process by which a new motor skill is learnt (Ito, 2006). Skill acquisition can be characterised as the improvement in the execution of a behaviour through reduced error, reduced need for error-correction and a reduction in the level of conscious attention required during execution (Leiner, 2010). Practice in an activity is the process by which internal models can be tuned to maximise performance and minimise conscious load: a process which has been described as automation (Habas, 2012). It is known that cerebellar activity takes place below the level of consciousness (D'Angelo et al., 2010) and that the 'transfer' of activity load from cerebrum to cerebellum has been demonstrated during the learning process using neuroimaging, though it must be noted that activity within the cerebellar cortex may also be reduced after learning (Balsters & Ramnani, 2011). Analysis of the activity of learners during skill acquisition (Doyon, Penhune, & Ungerleider, 2003) and the replication of learning behaviour by computer models (Kawato & Gomi, 1992) suggest that internal models are a viable explanation of the process of motor learning. Taken together these facts provide strong support for the development and calibration of cerebellar internal models as being a critical component of motor learning. Key factors within the learning process are that a greater level of practice (in the sense of use or execution, rather than specifically training) correlates with a greater level of automation (Kelly & Garavan, 2005); that existing models can be recalibrated for the demands of novel tasks (Doyon & Benali, 2005) and that existing models can be recalibrated according to changing circumstances (e.g. Küper et al., 2014).

Given the factors outlined above I would argue that these processes are also instrumental in the acquisition and execution of skilled behaviours outside the motor domain. I suggest that cerebellar internal models are a factor in the automation and efficient execution of well-practiced cognitive behaviour. This process is analogous to that active within the motor domain where practice at a task or with the sub-operations than can be combined to provide a task solution is instrumental in building and calibrating the models that can be used for the automation of task execution. In the cognitive domain this would be expected to comprise the formulation of cerebrally-based operations schemata for task execution which would be converted into cerebellar internal models through practice. If this were the case one might expect to see an association between damage to the cerebellar regions active in the acquisition and use of cognitive internal models, and impairments in the efficient execution rather than the abolition of the ability to perform cognitive tasks. With the caveats noted regarding the study of the injured cerebellum (e.g., plasticity) this is indeed what it seen (Gottwald et al., 2004; Grimaldi & Manto, 2011). Developing this idea, the introduction of disorder to cerebellar operation through the application of transcranial stimulation should result in similar impairments, though milder and with a shorter duration. Examining the results from the experiments described in chapters 4 and 5 in this context will allow a consideration of whether this explanatory framework is congruent with empirical findings.

The model proposed suggests that the cerebellum's role in cognitive tasks should be most instrumental in those aspects of tasks that have well-developed internal models. Further to this, the evolutionary processes active in cerebellar development should predispose the cerebellum for the facilitation of the rapid acquisition of skills through the development of internal models that make use of operations that have, in themselves or in combination, relevance for survival. Internal models should be best developed and calibrated for cognitive operations that have been most extensively used; in this case, by experimental participants in their prior experience. Examining the experimental tasks described in chapters 4 and 5 suggests that the most commonly-employed of the cognitive operations required for the completion of the tasks are: extraction of task relevant information from presented stimuli (in this case the conversion of a word to a phonological trace and the encoding of a route between points), organising and maintaining a list of items, and comparing a presented object with items held in memory. It is therefore these operations that should be most reliant on cerebellar activity and therefore be most vulnerable to cerebellar disruption to an extent dictated by their level of automation. It has been shown (Shadmehr, Smith, & Krakauer, 2010) that cerebellar activity is of particular importance in rapid, time-critical activity such as gait, posture and error correction. A time-critical activity incorporated in the tasks above is stimulus feature extraction, i.e., the gathering of salient information as quickly and efficiently as possible: this is an attribute of obvious survival benefit and therefore it can be suggested that a cerebellar facilitation of the development of models employing this operation would be expected. There are good reasons to believe that the most highly automated of these operations in literate participants in the experimental tasks is the extraction of meaning from a presented verbal stimulus and its conversion into a phonological representation given their widespread prior use. If this model is correct then the encoding phase of the verbal WM experiment described in chapter 4 should be the most vulnerable to disruption via inhibitory cTBS: this is indeed what was seen. I would contend that disruptive cerebellar stimulation will manifest its effects either through the prevention of the effective recalibration of internal models to the demands of a current task (thus impairing practice-based improvement) or the disruption of existing models (thus resulting in a degradation of task performance). Evidence from other studies (e.g., Ravizza et al., 2006) supports the first aspect of this proposition; the results described in chapter 4 support the second.

Converting a visually-presented word or letter to a phonological trace is an efficient way of constructing a memory trace that is protected to an extent from decay (Silveri et al., 1998). It has been suggested that activity in the posterolateral cerebellum during this process may be merely an epiphenomenon, i.e., representing the muscle activity of the vocal apparatus that would happen if the verbal stimulus were articulated and incidental to the creation of the memory trace. However, it has been demonstrated that cerebellar activity during the creation of a phonological trace differs from that during the activation of the vocal apparatus (Shuster & Lemieux, 2005) and, more saliently, my results demonstrate an actual performance impairment from the disruption of this region of the cerebellum. A further factor for consideration in assessing whether cerebellar activity during the execution of the verbal WM task represents incidental 'inner speech' is that within the task the average presentation rate and size of the stimuli were such as to prevent an internal 'articulation' of the stimuli in a manner analogous to normal speech. Additionally, the use of a short maintenance period (2 seconds) prevented the explicit rehearsal of the presented stimuli through inner repetition, thus lessening the plausibility of the cerebellar role being restricted to the repeated representation of muscle activity in the vocal apparatus.

Phonological encoding is unlikely to have been a factor in the experiments described in chapter 5, although the rapid encoding of task-relevant information was still required. In accordance with the principles described above and the general description of cerebellar operation proposed, the task elements most vulnerable to cerebellar disruption were the encoding of the memory trace (as a sequential route between points) and the retrieval of the trace from working memory. The results were in accord with the proposed model, as applied to the left cerebellar hemisphere, but did not allow a clear distinction to be made to the areas involved in each of these operations. The results derived from these experiments add support to previous findings of a cerebellar role in sequence detection, organisation and usage (Leggio, Chiricozzi, Clausi, Tedesco, & Molinari, 2009; Molinari et al., 2008), which in turn are in accord with the suggestion of the cerebellum having a critical role in timing and timing-specific computation (Braitenberg, 1967; Ivry, 2000).

Methodological considerations

In conducting the experiments described in this thesis I gained an appreciation of the challenges presented by transcranial stimulation techniques both in general and particularly as apply to cerebellar stimulation. The experiments described in chapter 3 sought to use cerebellar tDCS to influence performance on WM tasks. Whilst the null results derived from the visual tasks are understandable in the context of the distinction between visual and spatial WM, the absence of a clear effect on verbal WM revealed difficulties in the interpretation of null results derived from cerebellar tDCS. tDCS has been used to demonstrate a cerebellar role in cognitive tasks (Ferrucci et al., 2008; Pope & Miall, 2012), but given the non-focality of the technique and the difficulties entailed in ascertaining what level of current reaches the targeted areas (Miranda et al., 2006; Parazzini, Rossi, Rossi, Priori, & Ravazzani, 2013); the small size of the targeted structures and the suspected subtle contributions of the cerebellum to cognitive tasks (Marvel & Desmond, 2010) it is difficult to suggest the most likely cause of any null result with any degree of confidence. Complexity in interpreting results from cerebellar tDCS is increased by the current lack of understanding of the exact physiological effects of stimulation on the cerebellum. It has been noted (Miranda et al., 2006) that the strength and flow of the applied current is such that the effects of stimulation would be limited to cortical elements rather than extending to the cerebellar nuclei. There are, however, multiple possibilities for the effects of stimulation on the cells within the three layers of the cerebellar cortex. Given the highly interdependent nature of their operation and, in cases, their antagonistic actions the exact effects of cerebellar tDCS will only be uncovered by further physiological research. It is true that the ambiguity of the effects of cerebellar stimulation also apply to those magnetic techniques that do not induce action potentials, but the increased focality of TMS reduces, to an extent, the interpretative difficulties. It is true that the use of TBS for cerebellar stimulation is still somewhat novel and a relatively small number of studies having been published. The results from the experiments described in chapter 5 suggest that further physiological research would also be beneficial in the interpretation of results derived from this method of stimulation. The effects of cerebellar cTBS on the performance of spatial WM tasks appeared to be strongest during the first 20 minutes after stimulation, though there is evidence that the effects of cerebral tDCS, using similar parameters, persisted for approximately one hour. Detailed physiological research is needed to determine whether the effects of cerebellar tDCS develop immediately and what are the factors that determine their persistence.

Considering all factors, cerebellar tDCS is a promising method for the investigation of cerebellar non-motor function as it appears to be sufficiently focal to target specific regions of the cerebellum, is effective in temporarily altering those regions' performance and is an efficient method of inducing these alterations when compared to older versions of rTMS. The briefer time required for stimulation using TBS when compared to standard rTMS is beneficial for cerebellar stimulation given these techniques' tendency for the induction of muscle contractions that can be unpleasant for participants.

In conducting the systematic review of cerebellar stimulation, and in reviewing the wider literature, I noted that the non-motor effects of either cerebellar experimental interventions or cerebellar damage are often subtle. The subtlety of the cerebellar contribution to non-motor behaviour increases the probability of type 2 errors, which may have been an issue within the experiments described in chapter 3. I sought to incorporate measures to reduce this possibility in the later experiments such as calibrating experimental parameters to individual participants' capabilities and by increasing sample sizes, but the possibility of a failure to detect existing differences cannot be excluded. For future cerebellar non-motor investigations it is recommended that all experimental routines are thoroughly calibrated and sample sizes are increased to the maximum practical size to ensure that subtle effects are not eclipsed by non-systematic variation.

Conclusion

In summary, these experiments demonstrated that the cerebellum does make a contribution to non-motor behaviour as evidenced by the alteration of performance on a series of working memory tasks after the application of continuous theta burst stimulation. The results give support to the hypothesis that the posterolateral cerebellum is active in the processing necessary to perform working memory tasks quickly and effectively, and additionally that hemispheric specialisation exists in the cerebellum that is equivalent, but opposite, to that of the cerebrum. Some support was given to an intra-hemispheric functional topology, but the possibility of alternative interpretations of the results from the spatial WM experiments reduce the confidence with which this topology may be asserted.

These results were discussed in the context of the wider literature that suggests the cerebellum as a key structure in the optimisation of behaviour through its incorporation into internal models that allow active cognitive control of well-practised operations to be minimised. The results derived from my empirical experiments were found to be in good accord with the explanatory framework described above and as such represent an original contribution to our understanding of the cerebellar role in non-motor behaviour.

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Appendix A: Studies included in systematic review of cerebellar nonmotor stimulation experiments

ID	Title	Authors	Details	Category	Stim	Intensity	Frqncy	Pattern	Duration	Time from Stim to Test	Coil / Electrode	Location	Task	n	Results
1	Changes in mood and hormone levels after rapid-rate transcranial magnetic stimulation (rTMS) of the prefrontal cortex.	George MS, Wassermann EM, Williams WA, Steppel J, Pascual-Leone A, Basser P, Hallett M, Post RM.	J Neuropsychiatry Clin Neurosci. 1996 Spring;8(2):172-80.	Emotion	rTMS	120% RMT	5 Hz for 10s	10 trains of 10 s, with 2 mins between trains	~20 mins	Tested through day	Fig-8 (coil diam 70mm per loop)	3 cm below inion	Report Mood	10	No change
2	Increased variability of paced finger tapping accuracy following repetitive magnetic stimulation of the cerebellum in humans.	Theoret H, Haque J, Pascual-Leone A.	Neurosci Lett. 2001 Jun 22;306(1-2):29-32.	Timing	rTMS	90% MT	1 Hz	300 pulses	5 mins	0 min	Fig-8 (coil diam 70mm per loop) handle "dorsally along midsagittal axis"	1 cm below inion	Replicate interval tapping	7	Higher variance than sham
2	Increased variability of paced finger tapping accuracy following repetitive magnetic stimulation of the cerebellum in humans.	Theoret H, Haque J, Pascual-Leone A.	Neurosci Lett. 2001 Jun 22;306(1-2):29-32.	Timing	rTMS	90% MT	1 Hz	300 pulses	5 min	0 min	Fig-8 (coil diam 70mm per loop) handle "dorsally along midsagittal axis"	1 cm below inion 3 cm left	Replicate interval tapping	7	No change
3	Effects of repetitive transcranial magnetic stimulation on memory subtypes: a controlled study.	Rami L, Gironell A, Kulisevsky J, Garcia-Sanchez C, Berthier M, Estavez-Gonzalez A.	Neuropsychologia. 2003;41(14):1877-83.	Learning / Memory	rTMS	90% MT	5 Hz	10 s, 30 s ISI	10 s online	0 min	Focal double 70mm butterfly coil oriented parallel to midline.	2 cm below the inion and 3 cm lateral to the right	Working memory, episodic memory	16	No change

4	Interference of left and right cerebellar rTMS with procedural learning.	Torriero S, Oliveri M, Koch G, Caltagirone C, Petrosini L.	J Cogn Neurosci. 2004 Nov;16(9):1605-11.	Learning / Memory	rTMS	90% MT	1 Hz	600 pulses	10 min	0 min	Fig-8 (coil diam 70mm per loop) handle up	1 cm below inion 3 cm left	Serial Reaction Time Test (SRTT)	13	Decrease in procedural learning effect on SRTT with ipsilateral hand
4	Interference of left and right cerebellar rTMS with procedural learning.	Torriero S, Oliveri M, Koch G, Caltagirone C, Petrosini L.	J Cogn Neurosci. 2004 Nov;16(9):1605-11.	Learning / Memory	rTMS	90% MT	1 Hz	600 pulses	10 min	0 min	Fig-8 (coil diam 70mm per loop) handle up	1 cm below inion 3 cm right	Serial Reaction Time Test	10	Decrease in procedural learning effect on SRTT with either hand
5	Cerebellar transcranial magnetic stimulation impairs verbal working memory.	Desmond JE, Chen SH, Shieh PB.	Ann Neurol. 2005 Oct;58(4):553-60.	Learning / Memory	sTMS	120% MT	N/A	1 pulse	N/A	0 min	Double cone 110mm - handle up	Right HVI/Crus I by scan	Working memory, which letter appeared in previous string	17	Increase in reaction times compared with sham
6	A case of illusory own-body perceptions after transcranial magnetic stimulation of the cerebellum.	Schutter DJ, Kammers MP, Enter D, van Honk J.	Cerebellum. 2006;5(3):238-40.	Perception	rTMS	90% MT (not specified)	1 Hz	1200 pulses	20 min	0 min	Fig-8 coil	1 cm below inion	Report Experience	1	Subjective reported of falling/drifting sidewards whilst motionless.
7	An electrophysiological link between the cerebellum, cognition and emotion: frontal theta EEG activity to single-pulse cerebellar TMS.	Schutter DJ, van Honk J.	Neuroimage. 2006 Dec;33(4):1227-31. Epub 2006 Oct 4.	Emotion, Language/ Cognition	sTMS	45% MSO (72% to 90% MT)	N/A	1 pulse	N/A	0 min	Bespoke – details not specified in paper	1 cm below inion	No task - EEG	8	Significantly higher theta band activity than sham
7	An electrophysiological link between the cerebellum, cognition and emotion: frontal theta EEG activity to single-pulse cerebellar TMS.	Schutter DJ, van Honk J.	Neuroimage. 2006 Dec;33(4):1227-31. Epub 2006 Oct 4.	Emotion, Language/ Cognition	sTMS	45% MSO (72% to 90% MT)	N/A	1 pulse	N/A	0 min	Bespoke	1 cm below inion, 3 cm right	No task - EEG	8	No change

8	Role of the cerebellum in time perception: a TMS study in normal subjects.	Fierro B, Palermo A, Puma A, Francolini M, Panetta ML, Daniele O, Brighina F.	J Neurol Sci. 2007 Dec 15;263(1-2):107-12. Epub 2007 Jul 25.	Timing	rTMS	90% MT	1 Hz	900 pulses	15 min	0 min	Fig-8 (coil diam 45mm per loop), handle up	2cm below inion, 2cm right	Compare intervals	10	Reduced accuracy v sham
8	Role of the cerebellum in time perception: a TMS study in normal subjects.	Fierro B, Palermo A, Puma A, Francolini M, Panetta ML, Daniele O, Brighina F.	J Neurol Sci. 2007 Dec 15;263(1-2):107-12. Epub 2007 Jul 25.	Timing	rTMS	90% MT	1 Hz	900 pulses	15 min	0 min	Fig-8 (coil diam 45mm per loop), handle up	2cm below inion, 2cm left	Compare intervals	10	No change
9	Repetitive TMS of cerebellum interferes with millisecond time processing.	Koch G, Oliveri M, Torriero S, Salerno S, Lo Gerfo E, Caltagirone C.	Exp Brain Res. 2007 May;179(2):291-9. Epub 2006 Dec 5.	Timing	rTMS	90% RMT	1 Hz	600 pulses	10 min	0 min	Fig-8 (coil diam 70mm per loop), handle up	1 cm below inion, 3 cm right	Encode and recall interval	9	No change
9	Repetitive TMS of cerebellum interferes with millisecond time processing.	Koch G, Oliveri M, Torriero S, Salerno S, Lo Gerfo E, Caltagirone C.	Exp Brain Res. 2007 May;179(2):291-9. Epub 2006 Dec 5.	Timing	rTMS	90% RMT	1 Hz	600 pulses	10 min	0 min	Fig-8 (coil diam 70mm per loop), handle up	1 cm below inion, 3 cm left	Encode and recall interval	9	Over-estimation of milisecond judgements, not seconds
9	Repetitive TMS of cerebellum interferes with millisecond time processing.	Koch G, Oliveri M, Torriero S, Salerno S, Lo Gerfo E, Caltagirone C.	Exp Brain Res. 2007 May;179(2):291-9. Epub 2006 Dec 5.	Timing	rTMS - online	90% RMT	4 x 20 Hz train	n/A	150 ms online	online	Fig-8 (coil diam 70mm per loop), handle up	1 cm below inion, 3 cm right	Encode and recall interval	8	Over-estimation of milisecond judgements if rTMS applied during encoding, not reproduction, phase.
9	Repetitive TMS of cerebellum interferes with millisecond time processing.	Koch G, Oliveri M, Torriero S, Salerno S, Lo Gerfo E, Caltagirone C.	Exp Brain Res. 2007 May;179(2):291-9. Epub 2006 Dec 5.	Timing	rTMS - online	90% RMT	4 x 20 Hz train	n/A	150 ms online	online	Fig-8 (coil diam 70mm per loop), handle up	1 cm below inion, 3 cm left	Encode and recall interval	8	Over-estimation of milisecond judgements if rTMS applied during encoding, not reproduction, phase.

10	The role of the cerebellum in subsecond time perception: evidence from repetitive transcranial magnetic stimulation.	Lee KH, Egleston PN, Brown WH, Gregory AN, Barker AT, Woodruff PW.	J Cogn Neurosci. 2007 Jan;19(1):147-57.	Timing	rTMS	90% MT	1 Hz	480 pulses	8 min	0 min	Fig-8 (coil diam 70mm per loop), handle up	1 cm below inion	Temporal bisection	11	Over-estimation of intervals
10	The role of the cerebellum in subsecond time perception: evidence from repetitive transcranial magnetic stimulation.	Lee KH, Egleston PN, Brown WH, Gregory AN, Barker AT, Woodruff PW.	J Cogn Neurosci. 2007 Jan;19(1):147-57.	Timing	rTMS	90% MT	1 Hz	480 pulses	8 min	0 min	Fig-8 (coil diam 70mm per loop), handle up	1 cm below inion, 3 cm right	Temporal bisection	11	Over-estimation of intervals
10	The role of the cerebellum in subsecond time perception: evidence from repetitive transcranial magnetic stimulation.	Lee KH, Egleston PN, Brown WH, Gregory AN, Barker AT, Woodruff PW.	J Cogn Neurosci. 2007 Jan;19(1):147-57.	Timing	rTMS	90% MT	1 Hz	480 pulses	8 min	0 min	Fig-8 (coil diam 70mm per loop), handle up	1 cm below inion, 3 cm left	Temporal bisection	11	No change
11	Cerebellar transcranial direct current stimulation impairs the practice-dependent proficiency increase in working memory.	Ferrucci R, Marceglia S, Vergari M, Cogiamanian F, Mrakic-Sposta S, Mameli F, Zago S, Barbieri S, Priori A.	J Cogn Neurosci. 2008 Sep;20(9):1687-97.	Learning / Memory	tDCS (anodal)	2 mA (0.095 mA/cm2)	N/A	n/A	15 min	5 min, 35 min	21 cm2 active, 64 cm2 ref	2 cm below inion, 1 cm behind mastoid process; right deltoid	Sternberg	13	No change in RT at 5, longer RTs at 35 mins compared with sham
11	Cerebellar transcranial direct current stimulation impairs the practice-dependent proficiency increase in working memory.	Ferrucci R, Marceglia S, Vergari M, Cogiamanian F, Mrakic-Sposta S, Mameli F, Zago S, Barbieri S, Priori A.	J Cogn Neurosci. 2008 Sep;20(9):1687-97.	Learning / Memory	tDCS (cathodal)	2 mA (0.095 mA/cm2)	N/A	n/A	15 min	5 min, 35 min	21 cm2 active, 64 cm2 ref	2 cm below inion, 1 cm behind mastoid process; right deltoid	Sternberg	13	No change in RT at 5, longer RTs at 35 mins compared with sham

12	High-frequency repetitive transcranial magnetic stimulation to the cerebellum and implicit processing of happy facial expressions.	Schutter DJ, Enter D, Hoppenbrouwers SS.	J Psychiatry Neurosci. 2009 Jan;34(1):60-5.	Perception	rTMS	80% MT	20 Hz	5 s on, 5 s off, 9000 pulses	15 min	0 min	Fig-8, handle up	1 cm below inion	Facial mood recognition, report own mood	15	Increased RT v sham for happy faces, no change in mood experienced
13	The cerebellum in emotion regulation: a repetitive transcranial magnetic stimulation study.	Schutter DJ, van Honk J.	Cerebellum. 2009 Mar;8(1):28-34.	Emotion	rTMS	45% MSO	1 Hz	1200 pulses	20 min	0 min onwards	Fig-8, handle up	1 cm below inion	Report Mood, EEG, Watch IAPS, regulate emotion	12	No change in mood immediately after rTMS, increased negative emotion in Emotion Regulation Task v sham, no change in EEG
14	Transcranial magnetic theta-burst stimulation of the human cerebellum distinguishes absolute, duration-based from relative, beat-based perception of subsecond time intervals.	Grube M, Lee KH, Griffiths TD, Barker AT, Woodruff PW.	Front Psychol. 2010;1:171. Epub 2010 Oct 25.	Timing	TBS	80% RMT	3 x 50 Hz, 5Hz	600 pulses	40 s	0 min	Fig-8 (coil diam 70mm per loop), handle up	1 cm below inion - targeting VI / VIIA	Duration discrimination	24	Impaired performance v Sham
14	Transcranial magnetic theta-burst stimulation of the human cerebellum distinguishes absolute, duration-based from relative, beat-based perception of subsecond time intervals.	Grube M, Lee KH, Griffiths TD, Barker AT, Woodruff PW.	Front Psychol. 2010;1:171. Epub 2010 Oct 25.	Timing	TBS	80% RMT	3 x 50 Hz, 5Hz	600 pulses	40 s	0 min	Fig-8 (coil diam 70mm per loop), handle up	1 cm below inion - targeting VI / VIIA	Regularity Detection	24	No change
14	Transcranial magnetic theta-burst stimulation of the human cerebellum distinguishes absolute, duration-	Grube M, Lee KH, Griffiths TD, Barker AT, Woodruff PW.	Front Psychol. 2010;1:171. Epub 2010 Oct 25.	Timing	TBS	80% RMT	3 x 50 Hz, 5Hz	600 pulses	40 s	0 min	Fig-8 (coil diam 70mm per loop), handle up	1 cm below inion - targeting VI / VIIA	Isochrony Deviation Identification	24	No change

	based from relative, beat-based perception of subsecond time intervals.														
14	Transcranial magnetic theta-burst stimulation of the human cerebellum distinguishes absolute, duration-based from relative, beat-based perception of subsecond time intervals.	Grube M, Lee KH, Griffiths TD, Barker AT, Woodruff PW.	Front Psychol. 2010;1:171. Epub 2010 Oct 25.	Timing	TBS	80% RMT	3 x 50 Hz, 5Hz	600 pulses	40 s	0 min	Fig-8 (coil diam 70mm per loop), handle up	1 cm below inion - targeting VI / VIIA	Intensity Discrimination	24	No change
15	The cerebellum and its role in word generation: A cTBS study.	Arasanz CP, Staines WR, Roy EA, Schweizer TA.	Cortex. 2011 Mar 30. [Epub ahead of print]	Cognition	TBS	80% AMT	3 x 50 Hz, 5Hz	600 pulses	40 s	0 min	Fig-8, handle up	1 cm below inion, 3 cm right	Phonemic Fluency	13	Significantly worse fluency compared to pre-TBS
15	The cerebellum and its role in word generation: A cTBS study.	Arasanz CP, Staines WR, Roy EA, Schweizer TA.	Cortex. 2011 Mar 30. [Epub ahead of print]	Cognition	TBS	80% AMT	3 x 50 Hz, 5Hz	600 pulses	40 s	0 min	Fig-8, handle up	1 cm below inion, 3 cm left	Phonemic Fluency	14	No change
15	The cerebellum and its role in word generation: A cTBS study.	Arasanz CP, Staines WR, Roy EA, Schweizer TA.	Cortex. 2011 Mar 30. [Epub ahead of print]	Cognition	TBS	80% AMT	3 x 50 Hz, 5Hz	600 pulses	40 s	0 min	Fig-8, handle up	1 cm below inion, 3 cm right	Semantic Fluency	13	No change
15	The cerebellum and its role in word generation: A cTBS study.	Arasanz CP, Staines WR, Roy EA, Schweizer TA.	Cortex. 2011 Mar 30. [Epub ahead of print]	Cognition	TBS	80% AMT	3 x 50 Hz, 5Hz	600 pulses	40 s	0 min	Fig-8, handle up	1 cm below inion, 3 cm left	Semantic Fluency	14	No change
16	Theta-burst stimulation of the right neocerebellar vermis selectively disrupts the practice-induced acceleration of lexical decisions.	Argyropoulos GP, Kimiskidis VK, Papagiannopoulos S.	Behav Neurosci. 2011 Oct;125(5):724-34.	Language/ Cognition	TBS	45% MSO	3 x 30Hz, 10 Hz	801 pulses (267 bursts)	~30 s	5 mins	Fig-8 (coil diam 70mm per loop), handle up	1 cm below inion, 1 cm right (VI, VII)	Lexical decision	24	No main effect, RTs didn't decrease from one to next session when medial delivered in second session

16	Theta-burst stimulation of the right neocerebellar vermis selectively disrupts the practice-induced acceleration of lexical decisions.	Argyropoulos GP, Kimiskidis VK, Papagiannopoulos S.	Behav Neurosci. 2011 Oct;125(5):724-34.	Language/ Cognition	TBS	45% MSO	3 x 30Hz, 10 Hz	801 pulses (267 bursts)	~30 s	5 mins	Fig-8 (coil diam 70mm per loop), handle up	1 cm below inion	Lexical decision	24	No change
17	Cerebellar theta-burst stimulation selectively enhances lexical associative priming.	Argyropoulos GP.	Cerebellum. 2011 Sep;10(3):540-50.	Language/ Cognition	TBS	45% MSO	3 x 50 Hz, 5Hz	600 pulses	40 s	0 min	Fig-8 (coil diam 70mm per loop), handle up	1 cm below inion, 1 cm right	Lexical decision	8	Enhanced associative priming pre- v post & v post medial v post lateral stimulation Drop in accuracy v pre and v lateral
17	Cerebellar theta-burst stimulation selectively enhances lexical associative priming.	Argyropoulos GP.	Cerebellum. 2011 Sep;10(3):540-50.	Language/ Cognition	TBS	45% MSO	3 x 50 Hz, 5Hz	600 pulses	40 s	0 min	Fig-8 (coil diam 70mm per loop), handle up	1 cm below inion, 4.5 cm right	Lexical decision	8	Enhanced associative priming pre- v post & v post medial v post lateral stimulation Drop in accuracy v pre and v lateral
18	The role of the cerebellum in sub- and supraliminal error correction during sensorimotor synchronization: evidence from fMRI and TMS.	Bijsterbosch JD, Lee KH, Hunter MD, Tsoi DT, Lankappa S, Wilkinson ID, Barker AT, Woodruff PW.	J Cogn Neurosci. 2011 May;23(5):1100-12. Epub 2010 May 13.	Perception	TBS	80% RMT	3 x 50 Hz, 5Hz	600 pulses	40 s	0 min	Fig-8 (coil diam 70mm per loop), handle up	1 cm below inion	Sensorimotor synchronisation	16	No change
18	The role of the cerebellum in sub- and supraliminal error correction during sensorimotor synchronization: evidence from fMRI and TMS.	Bijsterbosch JD, Lee KH, Hunter MD, Tsoi DT, Lankappa S, Wilkinson ID, Barker AT, Woodruff PW.	J Cogn Neurosci. 2011 May;23(5):1100-12. Epub 2010 May 13.	Perception	TBS	80% RMT	3 x 50 Hz, 5Hz	600 pulses	40 s	0 min	Fig-8 (coil diam 70mm per loop), handle up	1 cm below inion, 3cm right	Sensorimotor synchronisation	40	No change

18	The role of the cerebellum in sub- and supraliminal error correction during sensorimotor synchronization: evidence from fMRI and TMS.	Bijsterbosch JD, Lee KH, Hunter MD, Tsoi DT, Lankappa S, Wilkinson ID, Barker AT, Woodruff PW.	J Cogn Neurosci. 2011 May;23(5):1100-12. Epub 2010 May 13.	Perception	TBS	80% RMT	3 x 50 Hz, 5Hz	600 pulses	40 s	0 min	Fig-8 (coil diam 70mm per loop), handle up	1 cm below inion, 3cm left	Sensori-motor synchronisation	40	Decreased 'supraliminal' error correction performance
19	Modulatory effects of theta burst stimulation on cerebellar nonsomatic functions.	Demirtas-Tatlidede A, Freitas C, Pascual-Leone A, Schmahmann JD.	Cerebellum. 2011 Sep;10(3):495-503.	Emotion, Language/ Cognition	iTBS	100% AMT	20 x 10 50 Hz bursts at 8 s intervals	600 pulses	~3 min		Fig-8, handle up	Vermis VII (by scan)	Report	12	No difference in mood, blood pressure, lower heart rate v left (trend v right), no mood change, increased thirst v right (trend v left), trend to increased appetite
19	Modulatory effects of theta burst stimulation on cerebellar nonsomatic functions.	Demirtas-Tatlidede A, Freitas C, Pascual-Leone A, Schmahmann JD.	Cerebellum. 2011 Sep;10(3):495-503.	Emotion, Language/ Cognition	iTBS	100% AMT	20 x 10 50 Hz bursts at 8 s intervals	600 pulses	~3 min		Fig-8, handle up	Right Crus I (by scan)	Report	12	No change
19	Modulatory effects of theta burst stimulation on cerebellar nonsomatic functions.	Demirtas-Tatlidede A, Freitas C, Pascual-Leone A, Schmahmann JD.	Cerebellum. 2011 Sep;10(3):495-503.	Emotion, Language/ Cognition	iTBS	100% AMT	20 x 10 50 Hz bursts at 8 s intervals	600 pulses	~3 min		Fig-8, handle up	Left Crus I (by scan)	Report	12	No change

20	Cerebellum and processing of negative facial emotions: Cerebellar transcranial DC stimulation specifically enhances the emotional recognition of facial anger and sadness.	Ferrucci R, Giannicola G, Rosa M, Fumagalli M, Boggio PS, Hallett M, Zago S, Priori A.	Cogn Emot 2012 **26**(5):786-99.	Emotion	tDCS (anodal)	2 mA (0.06 mA/cm2)	n/A	n/A	20 min	35 mins	6 x 7 cm	2 cm below inion, reference on deltoid	Report Mood	21	No change to mood
20	Cerebellum and processing of negative facial emotions: Cerebellar transcranial DC stimulation specifically enhances the emotional recognition of facial anger and sadness.	Ferrucci R, Giannicola G, Rosa M, Fumagalli M, Boggio PS, Hallett M, Zago S, Priori A.	Cogn Emot 2012 **26**(5):786-99.	Perception	tDCS (anodal)	2 mA (0.06 mA/cm2)	n/A	n/A	20 min	35 mins	6 x 7 cm	2 cm below inion, reference on deltoid	Identify emotion from face	21	Improved RTs for negative emotional face recognition compared to sham
20	Cerebellum and processing of negative facial emotions: Cerebellar transcranial DC stimulation specifically enhances the emotional recognition of facial anger and sadness.	Ferrucci R, Giannicola G, Rosa M, Fumagalli M, Boggio PS, Hallett M, Zago S, Priori A.	Cogn Emot 2012 **26**(5):786-99.	Emotion	tDCS (cathodal)	2 mA (0.06 mA/cm2)	n/A	n/A	20 min	35 mins	6 x 7 cm	2 cm below inion, reference on deltoid	Report Mood	21	No change to mood
20	Cerebellum and processing of negative facial emotions: Cerebellar transcranial DC stimulation specifically enhances the emotional recognition of facial anger and sadness.	Ferrucci R, Giannicola G, Rosa M, Fumagalli M, Boggio PS, Hallett M, Zago S, Priori A.	Cogn Emot 2012 **26**(5):786-99.	Perception	tDCS (cathodal)	2 mA (0.06 mA/cm2)	n/A	n/A	20 min	35 mins	6 x 7 cm	2 cm below inion, reference on deltoid	Identify emotion from face	21	Improved RTs for negative emotional face recognition compared to sham
21	The role of the cerebellum in 'real' and 'imaginary' line bisection explored with 1-Hz repetitive transcranial magnetic stimulation.	Oliver R, Opavsky R, Vyslouzil M, Greenwood R, Rothwell JC.	Eur J Neurosci. 2011 May;33(9):1724-32..	Perception	rTMS	90% RMT	1 Hz	600 pulses	10 min	0 min	Fig-8, handle up	1 cm below inion, 3 cm right	Number line bisection	8	Non-significant change (slight bias toward smaller numbers)

21	The role of the cerebellum in 'real' and 'imaginary' line bisection explored with 1-Hz repetitive transcranial magnetic stimulation.	Oliver R, Opavsky R, Vyslouzil M, Greenwood R, Rothwell JC.	Eur J Neurosci. 2011 May;33(9):1724-32.	Perception	rTMS	90% RMT	1 Hz	600 pulses	10 min	0 min	Fig-8, handle up	1 cm below inion, 3 cm left	Number line bisection	8	Significant rightward bias (to higher numbers)
21	The role of the cerebellum in 'real' and 'imaginary' line bisection explored with 1-Hz repetitive transcranial magnetic stimulation.	Oliver R, Opavsky R, Vyslouzil M, Greenwood R, Rothwell JC.	Eur J Neurosci. 2011 May;33(9):1724-32.	Perception	rTMS	90% RMT	1 Hz	600 pulses	10 min	0 min	Fig-8, handle up	1 cm below inion, 3 cm right	Physical line bisection	8	No change
21	The role of the cerebellum in 'real' and 'imaginary' line bisection explored with 1-Hz repetitive transcranial magnetic stimulation.	Oliver R, Opavsky R, Vyslouzil M, Greenwood R, Rothwell JC.	Eur J Neurosci. 2011 May;33(9):1724-32.	Perception	rTMS	90% RMT	1 Hz	600 pulses	10 min	0 min	Fig-8, handle up	1 cm below inion, 3 cm left	Physical line bisection	8	No change
22	rTMS over the cerebellum modulates temperature detection and pain thresholds through peripheral mechanisms.	Zunhammer M, Busch V, Griesbach F, Landgrebe M, Hajak G, Langguth B.	Brain Stimul. 2011 Oct;4(4):210-7.e1. Epub 2010 Dec 17.	Perception	rTMS	120% RMT (Max 60% MSO)	10 Hz	20 x 50 pulses, 20 s inter-train	~8 min	0 min	Fig-8, handle up	Vermis VII (by scan)	Temperature and pain detection	10	Cold detection temp lower
22	rTMS over the cerebellum modulates temperature detection and pain thresholds through peripheral mechanisms.	Zunhammer M, Busch V, Griesbach F, Landgrebe M, Hajak G, Langguth B.	Brain Stimul. 2011 Oct;4(4):210-7.e1. Epub 2010 Dec 17.	Perception	rTMS	120% RMT (Max 60% MSO)	10 Hz	20 x 50 pulses, 20 s inter-train	~8 min	0 min	Fig-8, handle up	R Crus II (by scan)	Temperature and pain detection	10	Cold detection temp lower
22	rTMS over the cerebellum modulates temperature detection and pain thresholds through peripheral mechanisms.	Zunhammer M, Busch V, Griesbach F, Landgrebe M, Hajak G, Langguth B.	Brain Stimul. 2011 Oct;4(4):210-7.e1. Epub 2010 Dec 17.	Perception	rTMS	120% RMT (Max 60% MSO)	1 Hz	1000 pulses	~17 min	0 min	Fig-8, handle up	Vermis VII (by scan)	Temperature and pain detection	10	Cold detection and temp lower, Hot detection and pain threshold temp higher

22	rTMS over the cerebellum modulates temperature detection and pain thresholds through peripheral mechanisms.	Zunhammer M, Busch V, Griesbach F, Landgrebe M, Hajak G, Langguth B.	Brain Stimul. 2011 Oct;4(4):210-7.e1. Epub 2010 Dec 17.	Perception	rTMS	120% RMT (Max 60% MSO)	1 Hz	1000 pulses	~17 min	0 min	Fig-8, handle up	R Crus II (by scan)	Temperature and pain detection	10	Cold detection temp lower
22	rTMS over the cerebellum modulates temperature detection and pain thresholds through peripheral mechanisms.	Zunhammer M, Busch V, Griesbach F, Landgrebe M, Hajak G, Langguth B.	Brain Stimul. 2011 Oct;4(4):210-7.e1. Epub 2010 Dec 17.	Perception	rTMS	120% RMT (Max 60% MSO)	1 Hz	1000 pulses	~17 min	0 min	Fig-8, handle up	2cm below inion, 2cm right	Temperature and pain detection	9	Time x treatment interaction: hot pain threshold pre-post higher for true, lower for sham
23	Cerebellar theta burst stimulation impairs eyeblink classical conditioning.	Hoffland BS, Bologna M, Kassavetis P, Teo JT, Rothwell JC, Yeo CH, van de Warrenburg BP, Edwards MJ.	J Physiol. 2012 Feb 15;590(Pt 4):887-97. Epub 2011 Dec 23.	Learning / Memory	TBS	80% AMT	3 x 50 Hz, 5Hz	600 pulses	40 s	5 min	Fig-8, 9 cm external wing, handle up	1 cm below, 3 cm right	Eyeblink Conditioning	30	Fewer CRs v neck TBS & v control, Shorter CB stim CR peak latency
24	Task-specific facilitation of cognition by cathodal transcranial direct current stimulation of the cerebellum.	Pope PA, Miall RC.	Brain Stimul. 2012 Mar 31. [Epub ahead of print]	Language/ Cognition	tDCS (anodal)	2mA	N/A	N/A	20 min	0 min	25 cm2	1 cm under, and 4 cm lateral right of inion (targeting VII); right deltoid	Serial Addition	66	No change in accuracy
24	Task-specific facilitation of cognition by cathodal transcranial direct current stimulation of the cerebellum.	Pope PA, Miall RC.	Brain Stimul. 2012 Apr;5(2):84-94	Language/ Cognition	tDCS (anodal)	2mA	N/A	N/A	20 min	0 min	25 cm2	1 cm under, and 4 cm lateral right of inion (targeting VII); right deltoid	Serial Subtraction	66	No change in accuracy

24	Task-specific facilitation of cognition by cathodal transcranial direct current stimulation of the cerebellum.	Pope PA, Miall RC.	Brain Stimul. 2012 Apr;5(2):84-94	Language/ Cognition	tDCS (anodal)	2mA	N/A	N/A	20 min	21 min	25 cm2	1 cm under, and 4 cm lateral right of inion (targeting VII); right deltoid	Noun reading, verb generation, verb reading	66	No change
24	Task-specific facilitation of cognition by cathodal transcranial direct current stimulation of the cerebellum.	Pope PA, Miall RC.	Brain Stimul. 2012 Apr;5(2):84-94	Language/ Cognition	tDCS (cathodal)	2mA	N/A	N/A	20 min	0 min	25 cm2	1 cm under, and 4 cm lateral right of inion (targeting VII); right deltoid	Serial Addition	66	No change in accuracy
24	Task-specific facilitation of cognition by cathodal transcranial direct current stimulation of the cerebellum.	Pope PA, Miall RC.	Brain Stimul. 2012 Apr;5(2):84-94	Language/ Cognition	tDCS (cathodal)	2mA	N/A	N/A	20 min	0 min	25 cm2	1 cm under, and 4 cm lateral right of inion (targeting VII); right deltoid	Serial Subtraction	66	Better accuracy v sham & v anodal, significantly higher increase in accuracy v sham & v anodal, significantly higher response time difference pre-post, greater pre- post variability
24	Task-specific facilitation of cognition by cathodal transcranial direct current stimulation of the cerebellum.	Pope PA, Miall RC.	Brain Stimul. 2012 Apr;5(2):84-94	Language/ Cognition	tDCS (cathodal)	2mA	N/A	N/A	20 min	21 min	25 cm2	1 cm under, and 4 cm lateral right of inion (targeting VII); right deltoid	Serial Subtraction	66	Increased response speed
25	Effects of Cerebellar Stimulation on Processing Semantic Associations	Argyropoulos, GP & Muggleton NG	Cerebellum 10.1007/s12311-012-0398-y	Language/ Cognition	TBS	45% MSO	3 x 50 Hz, 5Hz	600 pulses	40 s	0 min	Fig-8 (coil diam 70mm per loop), handle up	1cm under, 1 cm right of inion	Lexical decision	50	No change

25	Effects of Cerebellar Stimulation on Processing Semantic Associations	Argyropoulos, GP & Muggleton NG	Cerebellum 10.1007/s12311-012-0398-y	Language/ Cognition	TBS	45% MSO	3 x 50 Hz, 5Hz	600 pulses	40 s	0 min	Fig-8 (coil diam 70mm per loop), handle up	10 cm right of inion	Lexical decision	50	Lateral cerebellar TMS selectively enhanced semantic associative noun-to-verb priming
26	High frequency repetitive transcranial magnetic over the medial cerebellum induces a shift in the prefrontal electroencephalography gamma spectrum: a pilot study in humans	Schutter, DJLG, van Honk, J, d'Alfonso, AAL, Peper, JS & Panksepp, J.	Neuroscience Letters 336 (2003) 73–76	Emotion	rTMS	80% MT	25 Hz (10 s on, 5 s off)	20000 pulses	20 min	0 min	Neotonus stimulator - coil not specified	0.5 cm under inion	Report mood, alertness	5	Elevated mood, alertness - not quantified
26	High frequency repetitive transcranial magnetic over the medial cerebellum induces a shift in the prefrontal electroencephalography gamma spectrum: a pilot study in humans	Schutter, DJLG, van Honk, J, d'Alfonso, AAL, Peper, JS & Panksepp, J.	Neuroscience Letters 336 (2003) 73–76	Emotion	rTMS	80% MT	25 Hz (10 s on, 5 s off)	20000 pulses	20 min	0 min	Neotonus stimulator - coil not specified	0.5 cm under inion, 2 cm right	Report mood, alertness	5	No change

Appendix B: Summary of Experimental Results

Chapter	Exp. Number	Experiment	Stim	Intensity	Duration	Coil / Electrode	Location	Task	n	Results
3	1	The effects of cathodal tDCS to the right cerebellar hemisphere on verbal and visual working memory	tDCS -ve	2mA	15 min	25 cm2 (active) 35cm2 (ref)	1 cm below inion, 3 cm right	Verbal Sternberg: 2, 4, 6 items	6	Reduction in improvement of accuracy (when combined with decision task and) compared to visual
							1 cm below inion, 3 cm right	Verbal Decision: 2, 4, 6 items		Reduction in improvement of accuracy (when combined with memory task and) compared to visual
							1 cm below inion, 3 cm right	Visual Sternberg: 2, 4, 6 items		No change
							1 cm below inion, 3 cm right	Visual Decision: 2, 4, 6 items		No change
3	2	The effects of anodal and cathodal tDCS to the right cerebellar hemisphere on verbal working memory	tDCS -ve	2mA	15 min	25 cm2 (active) 35cm2 (ref)	1 cm below inion, 3 cm right	Verbal Sternberg: 4, 6, 8 items	6	No change
							1 cm below inion, 3 cm right	Verbal Decision: 4, 6, 8 items		No change
			tDCS +ve				1 cm below inion, 3 cm right	Verbal Sternberg: 4, 6, 8 items		No change
							1 cm below inion, 3 cm right	Verbal Decision: 4, 6, 8 items		No change

4	1	The effects of cerebellar TBS on verbal and visual working memory	TBS	80% AMT	40 s	figure-8 coil (ring diameter 70 mm)	1 cm below inion, 6 cm right	Verbal Sternberg - Individualised parameters (8 items +/-)	10	Decrease in percentage answers correct verbal task compared to other conditions
							1 cm below inion, 6 cm right	Visual Sternberg - Individualised parameters (8 items +/-)		No change
							1 cm below inion, 6 cm left	Verbal Sternberg - Individualised parameters (8 items +/-)		No change
							1 cm below inion, 6 cm left	Visual Sternberg - Individualised parameters (8 items +/-)		No change
5	1	The effects of mid-cerebellar TBS on spatial working memory	TBS	80% AMT	40 s	figure-8 coil (ring diameter 70 mm)	1 cm below inion, 3 cm left	Order of spatial targets - memory	10	Decrease in percentage of correct recollection of target order after left cerebellar stimulation compared to right
							1 cm below inion, 3 cm left	Aiming at displayed targets		Decrease in percentage of correct recollection of target order after right cerebellar stimulation compared to left
							1 cm below inion, 3 cm right	Order of spatial targets - memory		No change
							1 cm below inion, 3 cm right	Aiming at displayed targets		No change
5	2	The effects of lateral-cerebellar TBS on spatial working memory	TBS	80% AMT	40 s	figure-8 coil (ring diameter 70 mm)	1 cm below inion, 6 cm left	Order of spatial targets - memory	13	Smaller improvement in response speed after left cerebellar stimulation compared to right
							1 cm below inion, 6 cm left	Aiming at displayed targets		Smaller improvement in response speed after left cerebellar stimulation compared to right

							1 cm below inion, 6 cm right	Order of spatial targets - memory		No change
							1 cm below inion, 6 cm right	Aiming at displayed targets		No change
6	1	The effects of cerebellar TBS on emotion processing and lexical decision performance	TBS	80% AMT	40 s	figure-8 coil (ring diameter 70 mm)	1 cm below inion, 6 cm right	Name colours after EF	12	No change
							1 cm below inion, 6 cm right	Lexical Decision		No change
							1 cm below inion, 6 cm left	Name colours after EF		No change
							1 cm below inion, 6 cm left	Lexical Decision		No change