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Modulations of cerebellar predictive language function through continuous theta burst stimulation

Allen-Walker, Louise

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Modulations of cerebellar predictive language function through continuous theta burst stimulation

Louise Allen-Walker

Bangor University

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Contents

Figures

Chapter 1: General introduction and thesis aims

Chapter 4: Continuous theta-burst stimulation modulates the role of the right cerebellum in associative priming

Chapter 5: Facilitation of fast backward priming after left cerebellar continuous theta-burst stimulation

Chapter 6: A combined continuous theta-burst stimulation and event-related brain potential investigation of right cerebellar involvement in lexico-semantic predictions

Tables

Chapter 2: The use of transcranial magnetic brain stimulation to study cerebellar language function

Chapter 4: Continuous theta-burst stimulation modulates the role of the right cerebellum in associative priming

Chapter 5: Facilitation of fast backward priming after left cerebellar continuous theta-burst stimulation

Chapter 6: A combined continuous theta-burst stimulation and event-related brain potential investigation of right cerebellar involvement in lexico-semantic predictions

Summary

Although the role of the cerebellum has historically been associated with motoric function, more recently it has become clear that the cerebellum also has a role in many cognitive functions, such as learning, perception, verbal working memory and emotion. Of particular interest to this thesis is how the cerebellum is involved in predictive language processing. Studies employing transcranial magnetic stimulation to examine the role of the cerebellum in language have primarily indicated that it is in some way associative or predictive, and have used methodologies that principally rely upon associative priming. The aims of this thesis are to: a) replicate previous findings as regards the role of the cerebellum in associative as compared to categorical priming, but with stimuli where the categorical relationship is controlled for across both types (namely, opposite pairs as compared to categorical pairs), and to determine whether these behavioural modulations are reflected in language specific event-related potentials that index language prediction, b) examine whether the role of the cerebellum in associative priming extends to backward priming, whose models imply a differing process as compared to forward priming, and c) examine whether the predictive or associative role of the cerebellum in language can be extended to more complex sentences and how modulation of this function affects later language specific event-related potentials that index language prediction. In Chapter 4, the opposite stimuli, and not the categorical, displayed a priming effect. This was reflected by the phonological mismatch negativity wave, implying that this task required only phonological access to be completed. There was no effect of the cTBS, possibly because this task did not require semantic access. This indirectly supports the literature that suggests the cerebellum plays a role in semantic prediction. In Chapter 5 I show for the first time, beyond fMRI activation, that the left cerebellar hemisphere is actively involved in backward priming. Modulation of the left cerebellar hemisphere through cTBS selectively enhanced backward as compared to forward priming,

indicating that the cerebellum has a role in backward priming that is localized to the left cerebellar hemisphere. Additionally, this finding provides a potential explanation for the presence and mechanism of short stimulus onset asynchrony backward priming. Finally, Chapter 6 shows that modulation of right cerebellar function through cTBS results in easier processing of incongruent endings of highly predictable sentences, as indexed by the N400 event-related potential. I hypothesise that the effect of cTBS exhibited here is caused by modulation of the process through which errors are fed back in order to update cerebellar internal models. For the first time, we have shown that modulation of cerebellar predictive language function impacts upon later electrophysiological measures, and that this method might be an effective way to further elucidate the role of the cerebellum in language. Overall, this thesis supports the evidence that the cerebellum is involved in predictive language function, and that it applies a similar set of computations or internal models here as it does in motoric function and other cognitive functions. Additionally, we have proposed mechanisms through which cTBS may be affecting these internal models attributed to the cerebellum.

Chapter 1

General introduction

General introduction

The cerebellum's role in cognitive functioning is not fully understood. The typical understanding of its function is that it is primarily involved in motor processing; however, there is emerging evidence that it is involved in language and a range of other cognitive and behavioural functions such as emotion, perception and verbal working memory. This thesis seeks to further examine the role of the cerebellum in language – specifically in terms of language prediction and association – using a type of transcranial magnetic stimulation (TMS) called continuous theta-burst stimulation (cTBS), a technique that has previously been shown to be useful in this field. cTBS uses bursts of low-intensity, high-frequency (50 Hz) TMS pulses, delivered at a 5 Hz rhythm for 40 seconds (600 pulses), eliciting a slightly stronger depression of activity than rTMS that lasts for several minutes after application (Huang, Edwards, Rounis, Bhatia & Rothwell, 2005).

This chapter discusses the structure of the cerebellum, at both an anatomical and cellular level, and how it is connected to other areas of the brain. I also describe the development of our understanding of cerebellar function, as well as more recent research on the cerebellum's role in both motor and non-motor functioning. This chapter was written by myself and developed in conjunction with my supervisors.

Chapter two is an edited and updated version of a published book chapter by Beaton, Allen-Walker and Bracewell (2015) reviewing the use of TMS to study language function in the cerebellum. I reviewed the literature and wrote the first draft of this chapter, which was then developed in conjunction with the co-authors.

Chapter three details the methodological considerations of the experiments presented here; I describe the tasks employed and their appropriateness for this type of research. This chapter also evaluates the suitability of cTBS and event-related potentials (ERPs) for examining these research questions. This chapter was written by myself and developed in conjunction with my supervisors.

Chapter four reports a study which aimed to replicate previous findings in the domain of associative priming as compared to categorical priming. We employed cerebellar cTBS to examine its effect on reaction times to pairs of words that were opposites, and therefore associatively related, as compared to categorically related pairs of words. Further, we employed EEG measures in order to examine the effect of cTBS in this task on the N400 ERP wave. There was no effect of cTBS either behaviourally or electrophysiologically. However, priming was present for the opposite rather than categorical stimuli and this was reflected in the ERPs, which displayed a phonological mismatch negativity, implying that semantic access was not required to complete this task. In this chapter, I developed the research question based on the literature and I designed the study and stimuli. I collected the data in collaboration with other members of the lab given the practicalities of the methodologies employed. I filtered and analysed the data. I then wrote up the first draft of this chapter which was then developed in conjunction with my supervisors.

Chapter five reports an experiment employing cTBS to examine the role of the cerebellum in backward and forward associative priming, specifically aiming to dissociate the two processes between the left and right cerebellar hemispheres. Although we found no effect of cerebellar cTBS over either hemisphere for forward priming, there was a significant increase in backward priming size as a result of left cerebellar cTBS. No studies have previously shown that backward priming can be modulated by cerebellar cTBS, nor have they shown that priming can be modulated via the left cerebellar hemisphere. In this chapter, I developed the research question based on the literature. I designed the study and the stimuli. I collected the data in collaboration with other members of the lab, given the practicalities of the methodologies employed. I filtered and analysed the data. I then wrote up the first draft of this chapter which was then developed in conjunction with my co-authors for publication.

Chapter six reports an experiment in which cTBS and ERPs are employed to study the associative predictive function of the cerebellum in the context of sentences, indexed by the N400 ERP waveform. A typical N400 protocol using semantic violations was employed, with the hypothesis that there would be modulation of the N400 component as a result of right cerebellar cTBS. We found no behavioural effects on processing of predictable sentences; however, there was a significant effect of right cerebellar cTBS on our right lateralised N400 effect. There was a significant reduction in the amplitude of the N400 to incongruent sentences, indicating a role for the cerebellum in later semantic processing. In this chapter, I developed the research question based on the literature; the combination of cTBS and ERPs was my idea. I designed the study and chose the stimuli from an existing set used in the lab. I collected the data in collaboration with other members of the lab given the practicalities of the methodologies employed. I filtered and analysed the data. I then wrote up the first draft of this chapter which was then developed in conjunction with my supervisors and co-authors for publication.

Chapter seven discusses the results of these experiments and explores the conclusions that can be made on the basis of these findings. This chapter also describes how this thesis contributes to the area and the implications both in terms of our understanding of the cerebellum and language function more generally. Strengths, limitations and future directions are also discussed. This chapter was written by myself and developed in conjunction with my supervisors.

Cerebellar structure

The cerebellum has approximately 400 million connections to the rest of the brain; this number is double the quantity of connections in the corpus callosum connecting the two cerebral hemispheres. This structure also has more neurons within it than in the rest of the brain itself.

There are two ways in which researchers have labelled sections of the cerebellum. First, it can be split it into medial, intermediate and lateral sections, the vermis, paravermis and cerebellar hemisphere respectively, this division is primarily in terms of function. Second, the cerebellum has been divided structurally into three lobes, the flocculonodular lobe (or vestibulocerebellum), anterior lobe and posterior lobe, also called the archicerebellum, paleocerebellum and the neocerebellum respectively. Deep fissures that run medial to lateral across the cerebellum separate these three lobes. These lobes are separated into lobules: there are ten lobules, lobules I-V are in the anterior lobe, lobules VI-VII and part of lobule IX are in the posterior lobe, and IX and X are in the vestibulocerebellum. These lobules in turn are split into folia, from the Latin for leaves, the gyri of the cerebellar cortex (Figure 1).

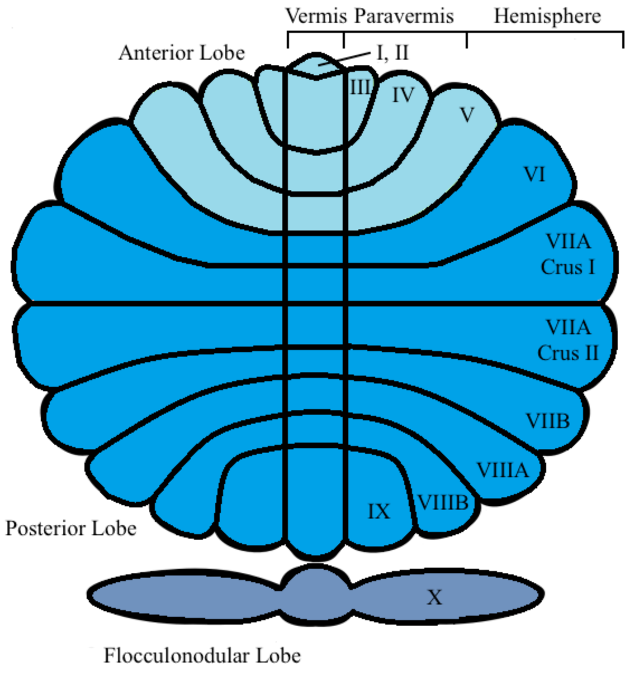

Figure 1. Structure of the cerebellum, figure displays lobes and lobules.

Generally, the anterior lobe containing lobules I-V and medial lobules VI and VIII are thought to be more associated with sensorimotor functioning, whereas lobules VI, VII and IX are more involved with cognition and emotion. The latter regions are also connected with limbic and association areas of the cortex whereas the former connect with sensorimotor areas of the frontal and parietal cortex (Stoodley & Schmahmann, 2015).

Cerebellar cytoarchitecture

There are three layers in the human cerebellar cortex: the granular layer is the deepest, then the Purkinje cell layer and the molecular layer on the surface. Within these three layers there are a number of cells that operate in a complex manner in order for the cerebellum to function (Figure 2). Mossy fibres connect to granule cells in the granular layer. The granule cells then extend through all three layers of the cerebellum; in the molecular layer they bifurcate at right angles. They are then named parallel fibres and they terminate on the dendritic tree of Purkinje cells. Mossy fibres excite Purkinje cells via this route. Each Purkinje cell also has input from one climbing fibre which originates in the inferior olive. Again, these climbing fibres extend through all three layers of the cerebellum. Basket cells (in the Purkinje cell layer) and stellate cells (in the molecular layer) receive input from the granule cells and inhibit Purkinje cells; basket and stellate cells also receive collaterals from climbing fibres. Finally, Golgi cells are inhibitory interneurons which terminate on the granule cells.

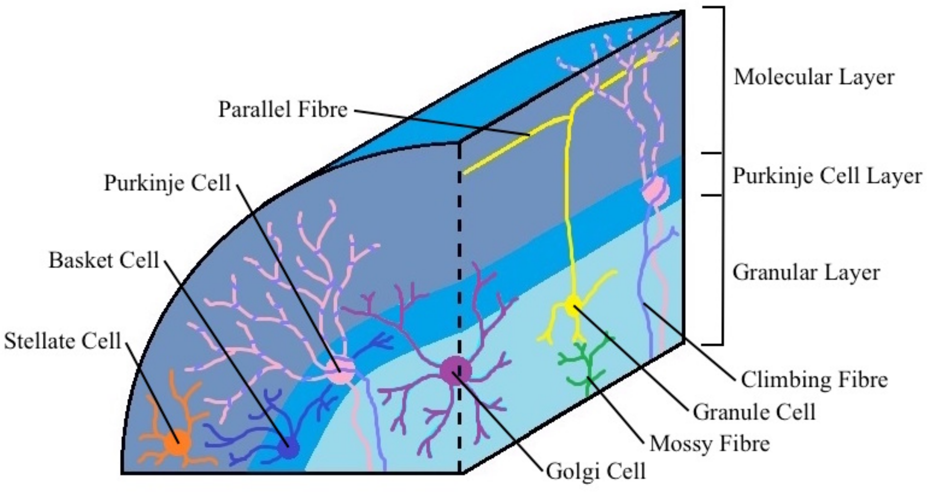

Figure 2. Cellular structure of the cerebellum, figure shows the layers of the cerebellar cortex and the cells within them.

Cerebellar connections to the cerebrum

The cerebellum receives information from the spinal cord and the vestibular system as well as the cerebral cortex. The cerebellar afferents received via the spinal cord deliver information regarding proprioception and mechanoreception. The cerebellum is connected to the brain via the pons and the medulla of the brainstem. The cerebellum is connected by the superior, middle and inferior cerebellar peduncles, these contain white matter tracts, with different tracts travelling through different sections of the peduncles to transfer different information to and from the cerebellum to other regions of the brain; principally via the thalamus. Of principal relevance to non-motor functioning are the feedforward projections (cortico-ponto-cerebellar) and the feedback projections (cerebello-thalamo-cortical) linking the cerebellum to the limbic and associative areas of the cortex (Stoodley & Schmahmann, 2015).

Historical literature examining animals

As the focus of this thesis is the role of the human cerebellum in language this chapter will predominantly cover literature concerning humans. However, it is important to note that there is a large body of literature that has examined the anatomy and functioning of the cerebellum in animals.

Very early literature focused on the phylogeny and anatomy of the cerebellum in animals, largely through lesion studies, these examined a range of animals such as fish, reptiles, amphibians, birds and mammals (for a review of this early literature see Dow, 1942). In mammals, early research examined cortico-nuclear fibres originating in the cerebellar cortex and projecting to its nuclei. For example, in animals such as rats, cats, rabbits and Rhesus monkeys (see e.g. Dow, 1936; Eager, 1963; Jansen, 1933; Jansen & Brodal, 1940; Jansen & Brodal, 1942).

Later, the functional roles of these projections in animals were examined, mostly using methods where electrodes record directly from the cerebellar cortex, in the context of, for example, posture (e.g. Chambers & Sprague, 1955), pressure and touch (e.g. Lundberg & Oscarsson, 1960) and arm movements (e.g. Thach, 1968).

Technological developments in this early period allowed for a more detailed understanding of the cellular processes in the cerebellum. Here cellular changes were recorded with electrodes applied to the cerebellar cortex during nerve stimulation (e.g. Precht & Llinás, 1969), and stimulation of the cerebellar folia themselves (e.g. Eccles, Llinás & Sasaki, 1966).

Some animal research also provides evidence of the role of the cerebellum in higher order functioning. For example, cerebellar lesions in cats cause changes in eating and grooming behaviours (Berntson, Potolicchio & Miller, 1973). Additionally, lesions to the cerebellum in cats has also been shown to produce a taming effect (Peters, 1969). This has been replicated in monkeys (Peters & Monjan, 1971; Berman, Berman & Prescott, 1974): lesions in the cerebellar vermis result in a decrease in aggressive behaviours. There are numerous studies in this domain which link the cerebellum to emotional functioning. For example, in dogs, stimulation of the paleocerebellum produced evoked potentials which indicated connections between the cerebellum and the limbic system (Anand, Malhotra, Singh & Dua, 1959); this has been supported by similar methods in Rhesus monkeys (Heath, 1972). Further, in cats, stimulation of the cerebellum has shown it to be important in emotional behaviours, for example eliciting cringe-like responses and occasionally pleasure-like responses (Clark, 1939) and cerebellar ablations have been shown to result in pleasure reactions such as kneading of claws and purring (Chambers & Sprague, 1955; Sprague & Chambers, 1959).

There is a great deal of animal research indicating a role for the cerebellum in motor learning. For example, in rabbits, researchers have shown that, in the context of eye blink conditioning, the neurons in the cerebellum and the cerebellar interpositus nucleus develop models of learned responses. These precede and predict the incidence of the conditioned response during and after training (Berthier & Moore, 1990; Foy, Steinmetz & Thompson, 1984; McCormick, Clark, Lavond & Thompson, 1982; McCormick & Thompson, 1984a,b; Steinmetz, 1990; Tracy, Weiss & Thompson, 1991). The role of the cerebellum in motor learning has also been examined in other mammalian species such as the Rhesus monkey. For example, Gilbert and Thach (1977) measured the activity of Purkinje cells during a learned motor task. Simple spike activity in these cells was related to the task; however, when the task was adjusted these cells exhibited complex spikes that persisted until the new task had been learned. They suggested that this is due to increases in the strength of parallel fibre activity which is then conveyed to the Purkinje cells via the climbing fibres. This finding supports a role for the cerebellum in motor learning.

I will refer to animal based research where useful in the following sections; however, the historical literature concerning humans that was occurring at this time and the research that occurred later is more relevant to this thesis and will therefore be the focus of subsequent sections.

The development of understanding of cerebellar function in humans

Only recently has the view that the cerebellum is more than an exclusively motoric organ become widely accepted. In this section I will review the historical research that has led to our current understanding of cerebellar function and structure.

In the early 1800’s Rolando and Flourens lesioned the cerebellum and discovered motor function impairments but no impairments in higher level cognitive functions

(Glickstein, Strata & Voogd, 2009). These theorists therefore proposed that the cerebellum is 'working as a whole' to aid motor control.

In the late 1800's Luciani identified a triad of symptoms that resulted from total and partial cerebellectomies (Glickstein, Strata & Voogd, 2009). First, atonia, which is defined as a loss of muscle resistance; second, asthenia, which is reduced muscle strength; and thirdly astasia, which is the defective stability of muscular contractions. He proposed that there was no localisation within the cerebellum outside of hemispheric localisation, i.e. that each side controlled the ipsilateral side of the body, and the role of the vermis as the trunk controller. Later, Luciani added ataxia to the list of symptoms associated with cerebellar lesions: this became the stereotypical symptom associated with these lesions. Ataxia refers to difficulties with the coordination of voluntary movement and the correction of actions.

These conceptions of the cerebellum as a purely motoric organ were further supported by other early work on cerebellar lesions, for example the work of Babinski in 1913 (Glickstein, Strata & Voogd, 2009) and Holmes (1917;1922), who also largely focused on the motoric symptoms exhibited by their patients. These reports of clear motor impairment due to cerebellar disease largely overshadowed evidence of deficits in cognitive and emotional abilities (Schmahmann, 1997); they were therefore largely ignored in the literature for the following century.

Bloedel and Bracha (1997) discuss the development of our understanding, from this point onwards, in terms of the different behaviours that were studied in association with various cerebellar lesions. First, researchers (such as: Brooks & Thach, 1981; Dow & Moruzzi, 1958; Goldberger & Growdon, 1973; Holmes, 1939) focussed on the role of the cerebellum in terms of voluntary motor behaviours, as well as posture and the orientation of the body in space. Second, researchers (such as: Amassian, Ross, Wertenbaker & Weiner, 1972; Amassian, Weiner & Rosenblum, 1972; Bloedel & Bracha, 1995; Chambers &

Sprague, 1951, 1955; Goldberger & Growdon, 1973; Rademaker, 1980) focussed on disruption to reflexes and postural responses relating to proprioceptive and cutaneomuscular sensory input and integration. In the 1970's the third behavioural focus became adaptive responses of vestibule-ocular and postural reflexes (Horak & Diener, 1994; Lisberger, Pavelko & Broussard, 1994; Robinson, 1976). This fed into the fourth behaviour, which was conditioned withdrawal reflexes (Kolb, Irwin, Winters, Bloedel & Bracha, 1994; McCormic et al., 1981; Supple & Kapp, 1993). Finally, the fifth group of behaviours examined were coined 'cognitive processes'. At this point researchers (such as: Akshoomoff & Courchesne, 1992; Botez, Botez, Elie & Attig, 1989; Fiez, Petersen, Cheney & Raichle, 1992; Leiner, Leiner & Dow, 1986; 1993; Schmahmann, 1991; Thach, 1996; Watson, 1978) began to see the cerebellum as an organ that contributed to many aspects of both motor and cognitive functioning.

Thus, in the 1980's and 1990's, the perception of the cerebellum began to change. This was largely due to the advances in technology, which allowed for methodological changes resulting in a better understanding of human neuroscience. Neuroimaging for example, gave us a better understanding of non-motor anatomy and functioning in the human cerebellum, as opposed to motor function in animals. This gave way to the idea that the cerebellum is involved in more than just motoric function but also language and other cognitive functions. In the thirty years since the introduction of neuroimaging techniques studies have revealed that the cerebellum is involved in a wide range of both motor and cognitive functioning, the roles for the cerebellum will be discussed more specifically in the following section.

Cerebellar functions: current understanding

This section will briefly review the functions currently associated with the cerebellum: first, motoric functions and second, those functions which are viewed as non-motor, namely, emotion, verbal working memory, perception and language. For a more detailed review of the motor as compared to non-motor functions of the cerebellum in the context of a topographic map see Stoodley and Schmahmann (2010).

Cerebellar motor function. As discussed above, the cerebellum has long been understood to be involved in motor function. Early researchers showed that within the cerebellar structure there are multiple maps of sensorimotor function in various areas of the cerebellum. Early studies by Snider (Snider, 1952; Snider & Stowell, 1944) mapped the tactile areas of the cerebellum in animals and reported an upside-down body map in the anterior lobe and bilateral maps in lobule VIII.

In addition to classic lesion-behaviour research and fMRI studies, researchers have used the behavioural deficits caused by cerebellar lesions in combination with imaging to examine the motoric aspects of cerebellar functioning. The development of detailed MRI techniques this has enabled researchers to use lesions to map the function of the cerebellum. For example, Timmann and colleagues (2008) reviewed papers examining the behavioural deficits caused by acute and chronic cerebellar lesions as well as cerebellar degeneration, in combination with MRI data mapping the lesions. Her findings supported the evidence that there are multiple somatotopic maps in the cerebellum. Further they showed that more medial regions are important for eye movements, stance and gait, whereas speech and limb movements were linked to more intermediate and lateral regions.

More recently, imaging techniques such as fMRI have been employed to map cerebellar motor function in healthy participants; for example, Stoodley and Schmahmann (2010) conducted a review examining research that either used clinical populations or employed imaging to map both motor and non-motor function across the cerebellum. They propose a functional divide between the sensorimotor anterior lobe and lobule VIII, the cognitive posterior lobe, specifically lobules VI and VII, and the limbic posterior vermis of the cerebellum.

Ocular motor control. One area of motor control that the cerebellum is particularly involved in is ocular motor control. The regions of the cerebellum thought to be involved in this function are the lobules VI and VII (also known as the oculomotor vermis), crus I-II of the ansiform lobule, flocculus, paraflocculus, uvula and nodulus. These structures contribute to multiple facets of ocular motor control, namely, steady gaze holding, smooth pursuit, vestibule-ocular reflex and the control of saccades. Overall this involvement can be summarised as ensuring the system is calibrated and to improve stability of gaze (Manto et al., 2012).

Grip forces. Another key aspect of motoric functioning that the cerebellum is involved in is the timing and coordination of grasping objects. This role is principally anticipatory (Manto, 2010). Cerebellar patients often show deficits in predictive grip control, but have unimpaired reactive control (Brandauer et al., 2008; Nowak, Hermsdorfer, Marquardt & Fuchs, 2002; Nowak, Topka, Timmann, Boeker & Hermsdorfer, 2007; Rost, Nowak, Timmann & Hermsdorfer, 2005). This control of grip forces has been most associated with damage to the dentate nucleus and Purkinje cells in the associated cerebellar cortex in the territories of the posterior inferior cerebellar artery and the superior cerebellar artery (Fellows, Ernst, Schwarz, Topper & Noth, 2001).

Sensorimotor integration. Another role for the cerebellum may be that it continuously integrates sensorimotor information (Ito, 2000). This role is principally in terms of sensory feedback during movement and the process is principally facilitated through climbing fibers (Ito, 2000). Research in this domain discusses this function in terms of internal models (Wolpert, Ghahramani & Jordan, 1995) which are attributed to the cerebellum, these are discussed in more detail below.

Motor learning. Early researchers posited that motor learning may take place in the cerebellum through the interactions between the cells (Albus, 1971; Marr, 1969). This theory particularly focussed on the interaction between climbing fibers, Purkinje cells and mossy fibers. Later, these theories were supported by recordings of cerebellar cellular activity (e.g. Ito & Karachot, 1989).

Both animal and human studies have indicated that the cerebellum is involved in conditioned responses (Woodruff-Pak & Steinmetz, 2000). Imaging studies have shown that cerebellar volume correlates with the acquisition of conditioned responses (Woodruff-Pak et al., 2001), particularly the volume of the posterior lobe (including lobule VI) grey matter (Gerwig, Kolb & Timmann, 2007).

For eye-blink conditioning to occur in animals, they must have an intact cerebellum for accurate timing (Thompson, 1990). In humans, patients with cerebellar cortical or olivopontocerebellar atrophy showed deficits in the acquisition, production and timing of conditioned eye-blink responses (Topka, Valls-Solé, Massaquoi & Hallett, 1993). Moreover, cerebellar cTBS impairs eye-blink conditioning (Hoffland et al., 2011).

Prism adaptation is another effective task for measuring motor learning. This involves the use of prisms to laterally displace the vision of participants while they point to a target. Once the glasses are removed the displacement remains for a short time afterwards. This is an excellent measure of adaptive motor learning. In patients with cerebellar damage this adaption is either very small or does not occur (Weiner, Hallett & Funkenstein, 1983).

Additionally, research shows that the cerebellum is likely to play a role in learning beyond motor function. PET studies have indicated that the right cerebellum is key in brain networks related to non-motor learning (Raichle et al., 1994), further supported by dysfunctional practice-related learning in a patient with a right cerebellar lesion (Fiez, Petersen, Cheney & Raichle, 1992). More recently, imaging studies have shown that the cerebellum is active during learning, but that there is a reduction in this activation after performance is reached (Balsters & Ramnani, 2011).

Gait, posture and limb movements. Research regarding the role of the cerebellum in posture, gait and limb movements comes principally from patient research. These deficits can largely be seen in those patients who develop cerebellar gait ataxia. This dysfunction of walking often results in a 'drunken gait' (Morton & Bastian, 2007) and recent studies have begun to tease apart the anatomical correlates of the various symptoms which characterise this issue.

First patients with cerebellar gait ataxia often have exaggerated postural sway (Dichgans & Diener, 1985; Diener, Dichgans, Bacher & Gompf, 1984; Mauritz, Dichgans & Hufschmidt, 1979). Damage to the anterior lobe of the cerebellum usually causes high velocity and low amplitude sway. Whereas, lesions to the vestibulocerebellum more often cause low frequency and high amplitude sway. Finally, lateral lesions usually produce only slight sway, very similar to that of healthy participants (Dichgans & Mauritz, 1983; Diener, Dichgans, Bacher & Gompf, 1984; Mauritz, Dichgans & Hufschmidt, 1979; Morton & Bastian, 2007).

The second principle cause of the drunken gait often reported with cerebellar gait ataxia is a dysfunction of limb movements. These patients often decompose limb movements (Earhart & Bastian, 2001; Hallett & Massaquoi, 1993; Palliyath, Hallett, Thomas & Lebiedowska, 1998); this refers to the separation of a movement requiring multiple joints (e.g. ankle, knee and hip) into a series individual movements (Holmes, 1917; 1939).

Motoric aspects of speech and language. In keeping with the traditional view of the role of the cerebellum in motor control is the role of the cerebellum in the motoric aspects of speech production. This involves sensorimotor control, management of the vocal tract, respiratory movements and laryngeal movements (Ackermann, 2008). This is reflected in the impairments related to lesions in the cerebellum, namely ataxic dysarthia (Kent et al., 2000). This is characterised by impairments in breathing during speech, voice quality, articulation, rate and rhythm; these impairments are often inconsistent but always present (Ziegler, 2015). Ataxic dysarthia is thought of as a purely ‘motor cerebellum’ disorder (Ziegler, 2015) and lesions that usually cause this disorder occur in hemispheric lobule VI, paravermal parts of the anterior cerebellum and in the dentate nucleus (Ackermann, Vogel, Petersen & Poremba, 1992; Amarenco, Chevrie-Muller, Roullet & Bousser, 1991; Lechtenberg & Gilman, 1978; Schoch, Dimitrova, Gizewski & Timmann, 2006; Urban, 2013; Urban et al., 2003; Ziegler, 2015). Lobule VI of the cerebellum is of particular importance to this topic as it is specific to the lips and tongue regions of the sensorimotor homunculus (Mottolese et al., 2013).

Timing. The cerebellum is key for behaviours requiring real-time prediction and this temporal encoding is thought to have its anatomical substrate in the granular layer (Manto et al., 2012). One of the principle symptoms of ataxia is the breakdown of timings associated with coordinated movement. These patients cannot generate rapid movements (Berardelli et al., 1996) or coordinate movements requiring multiple joints due to their inability to control timings (Bastian, Martin, Keating & Thach, 1996). Cerebellar pathology often includes deficits in timed movements (Ivry, 1997), particularly for those patients with lesions in the superior cerebellum (Harrington, Lee, Boyd, Rapcsak & Knight, 2004). This role of the cerebellum is reinforced by cerebellar dysarthia, a motoric problem thought to be due to difficulties in precisely timing articulation of the many muscles involved in speech (Ackermann, 2008; Kent, Netsell & Abbs, 1979). This timing issue may be the root cause of the deficits in precise motor control, given the need for accurate timing particularly for multi-joint movements.

Outside the motor domain, the role of the cerebellum in timing has been shown in perceptual tasks. For example, cerebellar degeneration can cause dysfunction in the perceptual judgement in temporal discrimination (Ackermann, Graber, Hertrich & Daum, 1997; Ivry, 1997). This role is also seen in the detection of temporal violations of expected sensory stimuli (Moberget et al., 2008; O'Reilly, Mesulam & Nobre, 2008)

Internal models of cerebellar motor function. In an effort to understand the mechanisms of motor function, researchers have invested much time in modelling motor function. These models, which help to explain the mechanisms of motor control, are often mapped to the cerebellum and fall broadly into two categories: forward and inverse models (Jordan & Rumelhart, 1992; Kawato, Furawaka & Suzuki, 1987). Forward models are the causal relationship between inputs to the system and the outputs; for example, a forward model of a limb will predict the next part of an action given the current position and motor command. Inverse models specify the motor command that will cause the change of state needed (Wolpert, Miall & Kawato, 1998). Recently, theorists have suggested multiple pairs of forward and inverse models may better explain motor function. This is the basis of the MOSAIC (modular selection and identification for control) model (Wolpert & Kawato, 1998), which has been supported using simulations (Haruno, Wolpert & Kawato, 2001) and may map onto the closed loop circuits between the cerebellum and the cortex (Haruno, Wolpert & Kawato, 2003). In this model, it is proposed that paired forward and inverse models, modules, are acquired and used together. In a specific context (e.g. a specific movement), the forward models predict the outcomes of a motor command, while the paired inverse models learn the appropriate motor commands for this context. Inverse models are selected based on prediction errors (discrepancies between the forward model predictions and actual events; Ito, 2008) from the forward models and sensory information. In this way, before a movement, the MOSIAC model can select appropriate controllers (Haruno, Wolpert & Kawato, 2001; Wolpert & Kawato, 1998).

The cerebellum is thought to be made from a series of modules, referred to as microcomplexes, each of which can learn a specific function (Ito, 2008); these microcomplexes are modified by climbing fibres and give rise to the cerebellum's ability to update internal models based on feedback (Ito, 2008).

More recently, authors have suggested that these cerebellar motor computations may be used more broadly in cerebellar function, particularly given that the cytoarchitecture of the cerebellum is homogenous across the organ (Eccles, Ito & Szentagothai, 1967). Some authors have therefore proposed that the cerebellum may perform a similar computation in non-motor and motor tasks, such as verbal working memory (Desmond, Gabrieli, Wagner, Ginier & Glover, 1997), language (Moberget, Gullesen, Anderson, Ivry & Endestad, 2014) and other types of higher order cognition (Ramnani, 2006; Schmahmann, 2004).

Cerebellar non-motor function. Until recently, the zeitgeist regarding the role of the cerebellum was principally that it plays a major role in motor function but little else, as discussed above. Although there was some evidence to support the idea that the cerebellum as involved in cognitive processes this was largely ignored. This section will briefly cover the evidence that the cerebellum is involved in emotion, verbal working memory, perception and language. Above, I have discussed its role in non-motor learning and timing in conjunction with the relevant motor sections.

Early clinical studies indicated that the cerebellum may be involved in a range of non-motor functions (for a review see Schmahmann, 1997). A review of patients suffering with ataxia demonstrated that symptoms included disturbances of emotional stability, executive function, visuospatial processing and working memory (Manto & Lorivel, 2009). Additionally, studies examining patients who have suffered cerebellar stroke have shown that the cerebellum has a functional divide between the anterior and posterior sections. Posterior inferior cerebellar artery stroke caused cognitive and affective functioning impairments; these impairments were not present after superior cerebellar artery stroke (Exner, Weniger & Irle, 2004).

For a review of the role of the cerebellum in non-motor function as studied through the use of brain stimulation see (Tomlinson, Davis & Bracewell, 2013).

Emotion. The emotional system in humans is thought to have evolved from older mechanisms for survival through homeostasis (Panksepp, 1998). The human cerebellum is understood to have developed from the phylogenetically older vermal and flocculonodular regions into the more lateral neocerebellar regions. Additionally, there are tracts connecting the cerebellar vermis to structures that are typically associated with homeostatic and emotional processing, for instance the hypothalamus (Sacchetti, Scelfo & Strata, 2009).

Clinical research has shown that patients with vermal or paravermal cerebellar damage showed affective disruptions, for example blunting of affect (Schmahmann & Sherman, 1998). Further, patients with damage to vermal and paravermal regions as a result of stroke show a reduction in response to pleasant stimuli and show PET activity consistent with a mechanism of compensation when presented with frightening stimuli (Turner et al., 2007).

Imaging studies have shown the cerebellum to be playing a role in emotional processing. For example, a meta-analysis of 105 fMRI studies showed the cerebellum to be activated during the presentation of many types of emotional faces. This lack of differentiation across types of emotional stimuli implies that the cerebellum's role is not specific to a type of emotional stimulus, rather that it is playing a more general role (Fusar-Poli, Placentino, Carletti, Landi & Abbamonte, 2009).

Brain stimulation studies have further explored the role of the cerebellum in emotional processing. For example, single pulse TMS over the midline of the cerebellum has been shown to alter theta-wave activity, which is commonly associated with the septo–

hippocampal complex. Theta-waves play a role in emotional activity, particularly in terms of the connections between the cerebellum and limbic structures (Schutter & van Honk, 2006). Additionally, high frequency vermal rTMS has been shown to increase positive mood and alertness (Schutter, van Honk, D'Alfonso, Peper & Panksepp, 2003). Further, high frequency rTMS has been shown to increase reaction times to positive emotional faces, which can be interpreted as a processing bias as a result of implicit improvements in positive mood (Schutter, Enter & Hoppenbrouwers, 2009).

Visual-spatial perception. Visual spatial deficits have been described after the removal of left cerebellar hemisphere tumours (Wallesch & Horn, 1990) as well as in the context of phenytoin intoxication (Botez, Gravel, Attig & Vezina, 1985). Additionally, deficits of this type present in patients with cerebellar cognitive affective syndrome (Schmahmann & Sherman, 1998).

Further, fMRI research has shown that the posterior lobe of the cerebellum shows increased activation during spatial tasks (Calhoun et al., 2001; Stoodley, Valera & Schmahmann, 2011).

Brain stimulation has been employed to further explore the role of the cerebellum in visual perception. For example, low frequency left cerebellar rTMS has been shown to cause a rightwards bias in a number-line task (Oliver, Opavsky, Vyslouzil, Greenwood & Rothwell, 2011).

Pain and temperature perception. Patients with cerebellar damage have been shown to have deficits in pain perception. For example, a group of 30 patients with cerebellar infarctions were shown to perceive pain caused by high temperature and pin-prick stimuli as more intense than controls (Ruscheweyh et al., 2014). Additionally, these patients also showed a reduced offset of this perceived pain as a result of analgesia or placebo analgesia, as compared to controls.

fMRI research has shown that at higher, noxious temperatures, as compared to non-noxious temperatures, there is cerebellar activation in the deep cerebellar nuclei, anterior vermis and lobule VI of the cerebellar hemisphere bilaterally (Helmchen, Mohr, Erdmann, Petersen & Nitschke, 2003). Of particular interest is that this activation was differentiated by the perceived intensity of the stimulus. More intense perceptions resulted in ipsilateral activation of lobule III-VI, the deep cerebellar nuclei and lobule III of the anterior vermis.

Finally, low frequency vermal rTMS has been shown to cause a small change in temperature and pain detection thresholds (Zunhammer et al., 2011), which supports the role for the cerebellar vermis in homeostatic systems.

Verbal working memory. Verbal working memory is a mechanism through which speech related information can be stored in short term memory using articulation. Baddeley's (1992) popular model argues that a phonological loop maintains verbal working memory. This model is comprised of two parts, a passive phonological store and an active articulatory control process, which refreshes the storage.

Clinical studies in this domain have shown that damage to the cerebellum causes reduced accuracy in working memory tasks such as the n-back task (Peterburs, Bellebaum, Koch, Schwarz & Daum, 2010) and digit span tasks (Ravizza et al., 2006; Schmahmann & Sherman, 1998; Silveri, Di Betta, Filippini, Leggio & Molinari, 1998), as well as in tasks specific to verbal working memory (Greve, Stanford, Sutton, & Foundas, 1999).

Neuroimaging research has suggested that the cerebellum is involved with the articulatory rehearsal of the speech information and with the phonological storage of the speech information (Marvel & Desmond, 2015). Additionally, research has shown that activation in the cerebellum increases when the number of items and length of maintenance period increases in a verbal working memory task (Altamura et al., 2007).

Brain stimulation has been effectively employed to further our understanding of this area. For example, the application of anodal or cathodal cerebellar tDCS has caused disruption in the ability to improve in a Sternberg task (Ferrucci et al., 2008) and the application of cathodal cerebellar tDCS has caused disruption to performance on a digit span task (Boehringer, Macher, Dukart, Villringer & Pleger, 2013). Further, right hemisphere cerebellar single-pulse TMS applied after encoding during a Sternberg task caused slower reaction times, thought to be disrupting articulatory processing during the formation of the phonological loop (Desmond, Chen & Shieh, 2005).

Language.

Hemispheric lateralisations. The majority of connections between the cerebellum and the cortex are between the contralateral hemispheres (Ito, 1984). Language is lateralised to the left cerebral hemisphere in the majority of right-handers (Wada, Clarke, & Hamm, 1975). It is therefore unsurprising that the right cerebellar hemisphere co-activates with the left cerebral hemisphere during language tasks (Jansen et al., 2005) indicating that language in the cerebellum is lateralised to the right hemisphere. Indeed, this asymmetry of cerebellar function is not uncommon in contexts were the cerebral function is highly lateralized. For example, in real and imagined motor movements there is activation in the cerebral hemisphere contralateral to the limb, and cerebellar activation in the hemisphere ipsilateral to the limb (Lotze et al., 1999). Further, this pattern is seen during brain activity to speech sounds, here the activation is left lateralized in the cerebral cortex and right lateralized in the cerebellar cortex (Johnsrude, Zatorre, Milner & Evans, 1997). This is also supported by studies of cerebellar lesions in children where those who experience right cerebellar lesions experience deficits in functions that are typically left lateralized in the cerebrum, namely verbal and literacy skills, whereas children with left cerebellar lesions have deficits in right cerebral hemispheric functioning, namely non-verbal and spatial skills (Scott et al., 2001).

Finally, evidence from a functional connectivity study has indicated that collections of regions in the cerebellar cortex that are highly lateralized activate with two networks that are highly lateralized in the cerebrum, and on an individual level that this lateralization in the cerebral cortex correlated with lateralization in the cerebellar cortex (Wang, Buckner & Liu, 2013). The implication of this finding is that these cerebrocerebellar networks may be the cause of this parallel lateralization in these two organs. Wang and colleagues (2013) argue that the lateralization in the cerebellum is not likely to be caused by cytoarchitectural differences but is rather due to the closed loop circuits connecting highly lateralized areas in the cerebrum to the contralateral cerebellum. This proposal is supported by clinical cases in which the cerebellar lateralization shifts after lesions in the cerebrum (Connor et al. 2006; Lidzba, Wilke, Staudt, Krägeloh-Mann & Grodd, 2008).

Links between the cerebellum and cortical language circuits. Until recently the cerebellum was generally believed to only be involved in the motoric aspects of speech production, with no role in language itself. However, research by Petersen et al. (1989) suggested that the cerebellum may functionally connect to language areas during a verb generation task. In this study, they employed PET to examine the areas that were involved in verb generation, as compared to reading nouns and repeating nouns. They found that there was activation in the left frontal cerebral cortex and the right cerebellum. This was the first indication that the right cerebellum may be functionally linked to cortical language areas.

The cerebellum is linked to the cortex via the thalamus, as discussed earlier in this chapter. There is abundant evidence that suggests there are reciprocal connections between the cerebellum and frontal areas in monkeys (see e.g. Middleton & Strick, 2001; Kelly & Strick, 2003). For example, Middleton and Strick (2000) used retrograde transneuronal transport of the herpes simplex virus to examine the connections between the cerebellum and the basal ganglia and the cortex. There were the expected reciprocal connections between the cerebellum and the motor and premotor cortices. In addition, they found that there were connections between the cerebellum and the prefrontal and inferiotemporal cortices. There are reciprocal cerebellar-thalamocortical pathways between ventral areas of the dentate nucleus and areas of the prefrontal cortex which are involved in working memory, specifically they guide behaviour using transiently stored information. This supports the theory that there are connections between the cerebellum and frontal areas that support cognitive functions.

In terms of human anatomy, there is not currently a technique that will supply the anatomical detail that is provided by the above technique. However, there are some early patient data that suggests that there are links between the cerebellum and Broca's area, and its homologue in the right hemisphere. For example, a case detailed by Stern (1942) in which a patient had an operation to remove skull fragments after a head injury, this damaged tissue in the right frontal lobe, specifically the right homologue of Broca's area. At post mortem, several years later there was degeneration of the medial region of the thalamic ventrolateral nucleus, this is the principle route through which projections from the cerebellum travel to reach the cortex. An early review of animal and patient literature by Leiner, Leiner and Dow (1989) suggested an anatomical model of communication between the cerebellum and the cortex; this model is still regarded as accurate (Murdoch, 2010). In this model information from the cerebellum travels to the cortex via the thalamus, additionally information from the cortex is looped back to the cerebellum via the pontine nuclei. There is also another route from the cortex to the cerebellum via the red nucleus and the inferior olive, both of which also receive inputs from the cerebellum.

Additionally, there have been findings that support the idea that there are reciprocal functional links between the cerebellum and cortical language areas using functional connectivity. A number of studies have shown that this is a viable method to examine relationships between the cerebellum and the cortex (e.g. Allen et al. 2005; Fransson 2005; Vincent et al. 2008). Krienen and Buckner (2009) used functional connectivity to examine the networks involving the cerebellum and frontal areas of the cerebral cortex. They found four dissociable networks which all showed the typical lateralisations described above, i.e. activity in the right cerebellar hemisphere was preferentially correlated with activity in the left cerebellar hemisphere, and vice versa. The four correlations between the cerebellum and frontal areas were between lobule V and the motor cortex, between Crus I and the dorsolateral prefrontal cortex, between Crus II and the medial prefrontal cortex, and between lobule VIIIA and the anterior prefrontal cortex. In two of the networks defined in this study there was activation in Broca's area (the dorsolateral prefrontal cortex and the medial prefrontal cortex), indicating that Crus I and II are functionally connected to this area, further supporting a role for the cerebellum in language and giving some indication that there are connections, direct or indirect, between these two areas.

Patient research. Patients with cerebellar cognitive affective syndrome display deficits in language function (Schmahmann & Sherman, 1998). Additionally, patients with cerebellar degeneration have shown deficits in language tasks such as phonemic and semantic verbal fluency, word stem completion and naming speed (Stoodley & Schmahmann, 2009).

Further, developmental dyslexia is associated with differences in the cerebellum. For example, deficits in reading are associated with functional and structural changes in the language network, including the right cerebellum (Richlan, 2012; Stoodley & Schmahmann, 2015; Turkeltaub, Eden, Jones & Zeffiro, 2002). Additionally, lobule VI in the right cerebellum has been shown to be a biomarker for dyslexia (Pernet, Poline, Demonet & Rousselet, 2009) and interventions for dyslexia in adults result in increased grey matter in the anterior lobe of the right cerebellum (Krafnick, Flowers, Napoliello & Eden, 2011).

Neuroimaging research. Neuroimaging research also supports this hypothesis; fMRI has shown activation in this cerebellar hemisphere during language processing (Keren-Happuch, Chen, Ho & Desmond, 2014; Stoodley & Schmahmann, 2009). Activation has been found during a variety of language tasks (that do not rely solely on articulation) such as: verbal fluency, phonological and semantic processing, word stem completion, reading and word/letter generation (see Stoodley, 2012; Stoodley & Schmahmann, 2009; Stoodley & Schmahmann, 2015 for reviews). This activation is principally found in lobules VI and VII (Crus I and II) of the right posterolateral cerebellum (Stoodley & Schmahmann, 2009).

Psycholinguistic theories

The focus of this thesis is to examine the role of the cerebellum in language. A related domain of research is psycholinguistics. This area attempts to model language function through complex linguistic tasks such as those used here. The tasks relevant to this thesis will be reviewed in Chapter 3. Psycholinguistic research has been largely ignored by researchers examining cerebellar function through brain stimulation. It may therefore be a useful adjunct to this thesis to consider the role of the cerebellum in language in the context of psycholinguistic models and theories. This section will therefore review some models that have been supported by the types of task used here and that may shed some light on the findings presented in the experimental chapters of this thesis. The models reviewed here will therefore be limited to those that relate to written word processing, as no tasks presented here use auditory language presentations or language production.

Lexical semantics. This section will describe theories relating to the recognition of words presented in the context of priming; this relates principally to chapters 4 and 5, which employ associative priming (this task, in relation to this thesis, will be outlined in chapter 3).

Spreading activation. This section will focus on studies that have used semantic or associative single word priming. This specifically refers to the reaction time advantage for targets presented after primes to which they are related (e.g. dog → BONE), as compared to unrelated ones (e.g. dog → ORANGE). Priming size is then calculated by subtracting reaction times to related pairs from the reaction times to unrelated pairs; this gives a value which indicates the size of the advantage. These two types of pairs are most often presented in the context of a lexical decision task (although there is a large body of literature that employs pronunciation of the target, Neely, 1991). In a lexical decision task participants are required to make judgements about whether or not the targets are real words or non-words, the latter tending to be pronounceable pseudowords.

The classic study that lead to the inception of this body of work is the paper by Meyer and Schvaneveldt (1971), who showed, for the first time, that there is a reaction time advantage when responding to associatively and semantically related words as compared to unrelated ones in a lexical decision task. This started a large body of literature relating to the contribution of the semantic context in terms of word recognition, and led to the spreading activation theory, which is the dominant theory in this domain for explaining this priming and reaction time advantage to related words.

The spreading activation theory was initially put forward by Collins and Loftus (1975). This theory describes the internal representations of individual words as nodes, which are activated when words are presented. When a prime is presented the semantic node relating to that word is activated; this activation spreads to related or associated nodes, which should include the target. The spread of activation is due to the organisation of the nodes in semantic memory. This process therefore reduces the time it takes for the activation of the target node to pass the threshold for recognition (Neely, 1991).

Posner and Snyder (1975) expanded on this theory: they describe this process as fast acting, and as not necessarily requiring the participants' awareness or intention to occur. This process is therefore automatic in nature. This idea is supported by the presence of associative and semantic priming at short SOAs (stimulus onset asynchronies, the time between presentation of the prime and the target; e.g. see Neely 1991 for a review), and by the presence of subliminal priming (e.g. Balota, 1983; Fischler & Goodman, 1978; Fowler, Wolford, Slade & Tassinary, 1981; Marcel, 1983). This theory is also strongly supported by Neely (1977), who found that the short SOA priming effect for targets related to the primes was independent of whether or not participants were instructed to expect related or unrelated targets.

Of additional relevance to this thesis is backward priming, a phenomenon whereby a priming effect occurs when highly asymmetrically associated pairs are presented in the reverse order (e.g. fly → FRUIT), causing facilitated responses to the targets as compared to unrelated pairs (Koriat, 1981). Typically, this effect has been attributed to post-lexical processes (Neely, 1991); however, these are slow and do not account for the backward priming effect that has been found at short SOAs (e.g. Kahan, Neely & Forsythe, 1991; Peterson & Simpson, 1989; Terrien et al., 2013). It has been suggested that the spreading activation theory might also account for this effect, although traditionally the spread of activation between the nodes was assumed to flow in only one direction. It has therefore been posited that feedback loops between the nodes could explain short SOA backward priming (Koriat, 1981).

The spreading activation theory might be pertinent to the questions addressed by this thesis. As has been described above and in the following chapter, the role of the cerebellum may be to aid prediction in the context of language, and other functions. Perhaps the cerebellum in some way contributes to this automatic spreading of activation process, particularly given its role in building models that enable motor prediction (Miall, Weir, Wolpert & Stein, 1993).

The principal alternatives to this explanation of priming are semantic integration and feature overlap. Semantic integration, tends to be used to explain backward priming and will be described in more detail in the following section. Feature overlap is more relevant to categorical priming: it suggests that the relationships between words that lead to priming are based on how many features overlap between two exemplars (Hutchison, 2003), for example, ‘apple’ and ‘cherry’, the features that overlap could include the features such as ‘round’ and the colour ‘red’. Further, this account has been used to explain backward priming, Hutchison (2003) suggested that feature overlap between primes and targets would produce priming regardless of the direction of presentation. This theory is not relevant to the priming tasks described in this thesis however, as the pairs of experimental interest are associatively related, i.e. the words are associated but not necessarily categorically related, and pairs have been chosen on the basis of associative strength.

Sentence-level semantics. This section reviews relevant theories in the domain of sentence-level semantics. This relates to experimental chapter 6, which employs a semantic prediction task, specifically a semantic violation task, which will be outlined in chapter 3. The dependent variable in this task is the N400 event-related potential (ERP), this section will therefore explore the semantic literature relating to this wave. The N400 is a negative deflection which occurs at about 400 milliseconds, with a maximum peak over central electrodes. Of relevance here, when a word is incongruent with the preceding sentence (e.g. I like coffee with cream and DOG), there is a more negative N400 than for sentences where the final word is congruent (e.g. I like coffee with cream and SUGAR). This wave can also be modulated in other modalities, for example in the context of linguistic stimuli the N400 has been seen during real words presented auditorially, and visually as written and signed words, and to stimuli that are similar to words such as pseudowords and acronyms (Federmeier & Laszlo, 2009; Holcomb & Neville, 1990; Kutas, Neville & Holcomb, 1987; Laszlo & Federmeier, 2008). The N400 is also present during environmental sounds (Chao, Nielsen-Bohlman & Knight, 1995; Van Petten & Rheinfelder, 1995), gestures (Kelly, Kravitz & Hopkins, 2004; Wu & Coulson, 2005), scenes and drawings (Ganis & Kutas, 2003; Ganis et al., 1996; Nigam, Hoffman & Simons, 1992), movies (Sitnikova, Kuperberg & Holcomb, 2003) and faces (Barrett & Rugg, 1989; Olivares, Bobes, Aubert & Valdes-Sosa). This wave is functionally specific to the processing of meaning and semantics, and is thought to be a marker of processing in the semantic memory system (Federmeier & Laszlo, 2009).

Semantic integration. The traditional explanation of the N400 wave was that it indexes semantic integration. In the context of sentence reading, semantic integration is the process whereby a presented word is integrated into the context of the previously presented words in the sentence and the semantic context these words have formed in working memory. The reduced amplitude for congruent sentences is thought to indicate increased ease of integration as compared to the incongruent sentences (Kutas & Federmeier, 2000). The semantic context here arising from sentence level information, or more globally, discourse level information (Kutas & Federmeier, 2011), and this representation is not already available in memory, but instead is constructed during on-line processing (Hagoort, Baggio & Willems 2009). Hagoort et al. (2009) describe this process as semantic ‘unification’, and explain that this process occurs for multi-word utterances and for information retrieved through other modalities, explaining the presence of N400 modulations in the wide range of modalities described above.

As mentioned above, this account has also been suggested as an explanation of backward priming. For example, Chwilla, Hagoort and Brown (1998) suggest that backward priming effects occur due to post lexical processes via a mechanism that uses semantic integration. However, as will be described in more detail in later chapters, this post lexical mechanism can only account for long SOA backward priming due to the time it takes for this process to occur (Neely, 1991), it cannot account for the short SOA backward priming described in the literature (Kahan, Neely & Forsythe, 1999; Peterson & Simpson, 1989; Terrien et al., 2013) and used in this thesis (Chapter 5).

However, evidence emerging over the last 20 years suggests that semantic integration is not driving the N400 wave. As the semantic integration explanation is post-lexical in nature it cannot explain data that indicate that this wave is modulated by stimuli that are presented prior to their point of recognition, nor can it explain data that show modulations of the N400 via manipulation of factors which are processed at the lexical and pre-lexical stages (e.g. orthography, frequency, phonology and repetition; Kutas & Federmeier, 2011). This has opened up the field and more recent theories suggest that the N400 may be more related to semantic memory rather than semantic integration.

Semantic memory. As discussed above, the N400 is present and can by modulated in a range of modalities. It has been proposed that the N400 therefore represents a process where these sensory modalities and stimuli types intersect, and that this process is related to processing in semantic memory (Kutas & Federmeier, 2011). Evidence for this comes from the sensitivity of the N400 to the established organization of semantic memory (Federmeier & Lazslo, 2009); for example, in sentence verification (e.g. ‘All dogs are animals/furniture’, ‘animals’ eliciting a smaller N400; Fischler, Bloom, Childers, Roucos & Perry, 1983), typicality of category membership (e.g. ‘DOG’ as a cue, N400s to ‘Collie’ are smaller than for ‘Bichon Frise’; Harbin, Marsh & Harvey, 1984; Heinze, Muente & Kutas, 1998; Polich, 1985; Stuss, Picton & Cerri, 1988), semantic similarity in various domains such as cognitive, affective, physical and functional characteristics (e.g. Barrett & Rugg, 1990a,b; Bentin, McCarthy & Wood, 1985; Holcomb & Neville, 1990; Kellenbach, Wijers & Mulder, 2000; Zhang, Lawson, Guo & Jiang, 2006).

This sensitivity to semantic category organisation is also present when the task is implicit; for example, in sentence reading the N400 is facilitated for final words which are similar to expected endings but still semantically incongruent (e.g. 'He caught the pass and scored another touchdown. There was nothing he enjoyed more than a good game of baseball'; Federmeier & Kutas, 1999; 2001). Further evidence in the domain of sentences is the negative correlation between the N400 amplitude and measures of contextual fit like cloze probability (when presented with a sentence missing the final word, the proportion of people who respond with a given ending; Federmeier & Laszlo, 2009).

The effects of semantic context on the N400 are also seen in other domains, when an item is being fit to verbal contexts, such as words, sentences and discourse (see Kutas & Federmeier, 2000 for a review), or non-verbal contexts such as pictures or movies (e.g. West & Holcomb, 2002; Sitnikova et al., 2003).

Additionally, evidence for the sensitivity of the N400 to semantic category organisation comes from N400 effects to exemplars of newly learned categories, with larger N400 effects for those exemplars that are more dissimilar to the training exemplars (Gratton, Evans & Federmeier, 2009).

Further evidence that the N400 is an index of processing in semantic memory systems comes from literature that indicates that the N400 is modulated by aspects of the stimuli which would fit with a system of semantic memory which is flexible and adapts with use (Federmeier & Laszlo, 2009). For example, the N400 is effected by repetition (Rugg, 1985; Van Petten, Kutas, Kluender, Mitchiner, & McIsaac, 1991), recognition memory (Chao et al., 1995; Friedman, 1990; Smith, Stapleton & Halgren, 1986), and word frequency (Münte et al., 2001; Rugg, 1990; Van Petten & Kutas, 1990).

As can be seen from the above, there is a vast literature that indicates that the N400 indexes processing in semantic memory, with smaller amplitudes indicating ease of processing; this ease is particularly facilitated when semantic context has indicated what the stimulus will be. The underlying mechanisms through which this processing might occur are a topic which has drawn debate from the pcyholinguistic community.

The N400 is sensitive to modulations during both semantic priming and sentence processing. As described above, semantic priming is explained through spreading activation and the N400 literature that employs this task supports this theory (Lau, Phillips & Poeppel, 2008). However, it has been suggested that different mechanisms may be involved in sentence and discourse level processing (e.g. Forster, 1981; Seidenberg, Waters, Sanders & Langer, 1984; Van Petten, 1993). In spreading activation theories, the representations of words are all held in memory and activation spreads between them automatically; however, representations of sentences and discourses cannot exist permanently in memory as there are infinite permutations of sentences. So, the alternative explanation for the facilitation of congruent sentences here is that this process occurs through semantic integration, described above, where processes, which are controlled by attention, integrate presented words into representations of previously presented information stored in working memory (Hagoort et al., 2009). This is supported by findings that show N400 effects in sentences and discourse before their completion which can be seen to incrementally increase with context (Van Petten & Kutas, 1990; 1991). However, the N400 can be modulated during semantic priming using parameters that diminish attentional and strategic processes (e.g. Brualla, Romero, Serrano & Valdizán, 1998; Deacon, Hewitt, Yang & Nagata, 2000; Vogel, Luck & Shapiro, 1998); this implies that the N400 could be elicited by automatic spreading activation (Federmeier & Laszlo, 2009).

The spreading activation account of the N400 to both word and sentence level contexts is supported by similarities in functional specificities (e.g. strength of context; Federmeier & Laszlo, 2009), and N400s to both types of stimuli have similar timings and scalp distributions (Kutas, 1993; Van Petten, 1993). Further, in a study where associative priming was embedded into predictable sentences, the joint effects of these contexts (word-level and sentence-level) have been seen (Van Petten, Weckerly, McIsaac & Kutas, 1997).

The spreading activation account of the N400 as a result of word-level contexts is compatible with the semantic memory account of sentence- and discourse-level contexts. Findings in this field can be argued to support the idea that the context presented, be that word-level or a higher mental representation of context based on a preceding sentence or discourse, pre-activates words that are related to the context. The words that are activated can be based on their relationships with specific words presented or the discourse context as a whole (Van Berkum, 2004, 2009).

As mentioned above and discussed in detail in the following chapter, there may be a role for the cerebellum in predictive language processing. Perhaps the processes to which the cerebellum contributes can be explained by the above theory of the N400.

Language models. Within the domain of psycholinguistics there are a number of models of language to which a role for the cerebellum could be ascribed. These may be useful in explaining the role of the cerebellum indicated in the experimental chapters of this thesis. The models described in this section will focus specifically on models of language that include the cerebellum, or could include the cerebellum, in a role that is related to semantic prediction. There are models of speech production that include a role for the cerebellum but in the context of motoric articulation, for example the model described by Hickok (2012a) and Poeppel, Emmorey, Hickok and Pylkkänen (2012). It includes a role for the cerebellum in feedback loops between the somatosensory and motor cortices in order to facilitate speech production. There are models of speech perception that conceivably could have a role for the cerebellum, for example the dual stream model, which suggests a dorsal, motoric, stream and a ventral, phonological and semantic, stream. When this was introduced by Hickok and Poeppel (2004) they criticized it as largely ignoring any contribution of the cerebellum and other regions not in the cortex. However, Hickok (2012b) discusses the role of motoric aspects of language in speech perception in the context of this model. Specifically, in terms of speech prediction they discuss the possibility that the dorsal stream is principally involved in motor control and may therefore play a role in the prediction of upcoming speech. Potentially the cerebellum may contribute to this function, there is some evidence that the cerebellum plays a role in phonological prediction (Runnqvist et al., 2016) and fits with the role of the cerebellum as a modeler of motoric outcomes (Miall, Weir, Wolpert & Stein, 1993). Models of speech production and speech perception are outside the remit of this thesis as all tasks employed use visual presentations of words, so this section will confine itself to models of reading. There are three principle types of computational models of reading, parallel distributed processing (PDP) models, dual-route cascade (DRC) models and hybrid models. These models attempt to model reading through computer simulations in which they teach a model to read words while matching the performance to behavioural and patient data.

PDP models. Models of this type are connectionist and argue that different components of reading (or other cognitive processes) are distributed into separable units that represent different aspects required in order to process a word. Although there are many PDP models of reading (see e.g. Bullinaria, 1996; Harm & Seidenberg 1999; 2004; Plaut, 1997; Plaut, McClelland, Seidenberg & Patterson, 1996; Plaut & Shallice, 1993; Seidenberg & McClelland, 1989; Zorzi, Houghton & Butterworth, 1998), arguably one of the most influential theories of this type is the Triangle model proposed by Seidenberg and McClelland (1989). In this model the units are Orthography, Phonology and Semantics.

There are two pathways from orthography to phonology, the first maps orthographic representations onto phonological representations, the second reaches phonological representations via semantic representations. In the initial model proposed by Seidenberg and McClelland (1989) they suggested only the former pathway.

This model was updated by Harm and Seidenberg (2004): here they introduced routes for mapping orthographic and phonological representations onto semantic representations. This addition meant they could simulate semantics related effects such as pseudohomophone and homophone effects seen in semantic priming and categorization studies (e.g., Lesch & Pollatsek, 1993; Van Orden, 1987). In the original model connections between orthographic and phonological representations were always mediated by hidden units; however, in the updated version (Harm & Seidenberg, 2004) additional direct connects between these units was added; this allowed for more effective non-word reading. It has also been suggested that there should be a fourth unit Context which interacts only with Semantic representations, this was to account for the usual presentation of words in a semantic context that may affect their meanings (e.g. ‘the rose’ as compared to ‘he rose’; Seidenberg, 2012).

DRC models. The second type of model are the DRC models which arose from the dual-route theory which existed prior to the introduction of computational models. The computational execution of the dual-route theory was developed by Coltheart and a number of colleagues (Coltheart, Curtis, Atkins & Haller, 1993; Coltheart, Rastle, Perry & Langdon, 2001; Coltheart & Rastle, 1994; Rastle & Coltheart, 1999; Ziegler, Perry, & Coltheart, 2000, 2003). As the name suggests, in this model there are two routes, a lexical route and a nonlexical route. These two routes are implemented as separate components and have independent representations. Further, each route operates differently, in the lexical route there is spreading activation that occurs in parallel, whereas in the nonlexical route there is serial processing.

The lexical route was based on two previously suggested models, the word recognition model (McClelland & Rumelhart, 1981; Rumelhart & McClelland, 1982) and the spoken word production model (Dell, 1986). This route employs interactive activation and cascaded processing which operates in parallel. The process that this route uses begins with letter features, activation then spreads to letters, then to word nodes in the orthographic lexicon, word nodes in the phonological lexicon and finally the phoneme system which facilitates phonological output. This route is used when the words are known, and is needed when the words are irregular (where one or more graphemes is pronounced differently to the most common grapheme-phoneme correspondence [GPC], e.g. PINT). The initial lexical route proposed by Coltheart and colleagues (1993) did not include a semantic unit, and although later versions have suggested that a semantic system would be present in this route and would interact with both the orthographic and phonological lexicons; however, as yet this system has not been included in the computational model (see e.g. Coltheart, 2011 for a discussion of the Lexical Semantic Route). This route can be linked to the spreading activation theory outlined above, although it refers to this type of processing in reference to the various units of this route outside of the semantic unit, it would be logical for this type of process to also occur in the semantic unit.

The nonlexical route operates differently; this route can be employed when reading any word or letter string, however is required when reading unknown words or non-words. This route uses only GPC rules in order to process words. Here the letter features and the letters are processed serially, left-to-right.

Hybrid models. These models attempt to include the best properties of both the above approaches. The first model of this type was a dual-route connectionist model called the connectionist dual process (CDP) model by Zorzi, Houghton & Butterworth (1998) which used connectionist aspects to link the orthographic and phonological units, with direct connections representing a sublexical route and the connections via hidden units represent a lexical route. However, this model does not process regular and irregular words separately via each pathway (Harm & Seidenberg, 2004).

There has however been a more recent hybrid model that has attempted to combine these two approaches, the CDP+ model (Perry, Ziegler & Zorzi, 2007). As with the previous hybrid model, this model retains the use of two routes, a lexical and a sublexical route; however, the sublexical route does not employ GPC but rather a process similar to that used in PDP models.

As with the DRC model, first letter features and then letters are processed, at this point the model splits into the two routes. The lexical route is similar to the DRC model with an orthographic and phonological lexicon, again semantic processing is suggested to occur in proximity to these components, however, they are not included in the model itself. The sublexical branch of the model employs grapheme nodes which then feed into a sublexical network. These two branches then both use a phonological output buffer.

Models of reading and the cerebellum. There have been attempts to map the components of the above models onto brain areas (see e.g. Fiez & Petersen, 1998; Jobard, Crivello & Tzourio-Mazoyer, 2003; Taylor, Rastle & Davis, 2013). However, as the cerebellum has only relatively recently become a focus in language research this area has been largely ignored in the domain of the application of neuroscience to models of reading (Jobard, Crivello & Tzourio-Mazoyer, 2003).

As the role of the cerebellum in language has become more established (see e.g. Marien & Manto, 2015 for a review) and the role of the cerebellum in reading has become better understood, both in terms of typical functioning and in dyslexia (e.g. Stoodley, 2015), some theorists have begun to consider a role for the cerebellum within models of reading. For example, Loritz (1991) considered models of language learning in the cerebral and cerebellar cortices. He makes comparisons between models of cerebellar cellular function and PDP models of processing, with granule cells as an input layer, Purkinje cells as an output layer, which are presented with input via the climbing fibers. Between these layers sit the other 'hidden' units which cannot be directly examined.

One language model, the declarative/procedural model (DP; Ullman, 2004), was designed with neuroscience evidence in mind; this included a role for the cerebellum. In this model, there are two memory systems, the declarative system and the procedural system, each with their own underlying brain areas.

The declarative system is the lexical part of this model, brain areas in this system, which are similar to those that support declarative memory in general, hold the mental lexicon. This system acquires and maintains representations of words, as well as knowledge regarding facts and events. In terms of words, this system contains word-specific information, such as, phonology, semantics and abstract information including word category. Information contained in these mental lexicons includes simple word representations (e.g. dog), irregular words, morphemes which are bound (e.g. past tense suffix –ed), idioms and verb complements. Some more complex forms that are regular, in a way which would also enable the procedural system to process them, can also be stored as part of this system, and the possibility of this occurring increases with factors such as frequency. This system also facilitates generalisations across representations using superpositional associative memory, for example in phonological terms the retention of similar past tense pairs that are irregular (e.g. sing → sang, spring → sprang), might aid in the processing of new irregular versions (e.g. bring → brang).

The anatomical substrates of these systems are those that support declarative memory: they play similar roles in both declarative memory in general and in lexical memory. New memories are encoded and consolidated in the medial temporal lobe where they can be accessed. Later, these memories are held instead in temporal and temporo-parietal regions. The temporal areas, specifically the inferior and ventral areas, are involved in conceptual representations and word meanings; there is also some evidence that abstract lexical representations may also be held here (Damasio el al., 1996). Phonological, syntactic and morphological representations are stored in the superior temporal cortex, making this area involved in both declarative and procedural systems.

The procedural system is involved in the mental grammar; it learns new rule-based processes and computes those that have previously been learned. These procedures direct those aspects of language that are in some way regular, particularly in terms of complex structures that are sequentially or hierarchically related. The procedural memory system is involved in all aspects of grammar that depend on this type of processing, this includes: morphology, syntax (Pinker, 1999; Ullman, 2001a,b), phonology, non-lexical semantics (specifically composing words into complex structures). These aspects likely utilise the same computations but this does not mean that they are in some respects independent processes.

The anatomical substrates for this system include: the basal ganglia (particularly the caudate nucleus), the frontal cortex (particularly Broca's area and pre-motor areas), the parietal cortex (particularly the supramarginal gyrus and superior parietal lobule), the superior temporal cortex and the cerebellum (hemispheres, vermis and dentate nucleus). These areas are functionally connected and interact with one another. Again, the language-related computations are thought to be similar to the non-language ones in these regions. Therefore, the basal ganglia are involved in learning the rules of and the maintenance of components of complex language related representations, which are either sequential or hierarchical in nature, in working memory. This process runs through the thalamus to the frontal cortex. In the frontal cortex, Broca's area is involved in very similar functions to the basal ganglia. The function of the remaining areas is a little less clear, attentional processes are possibly held in the supramarginal gyrus and the superior parietal lobule, the parietal cortex may also aid in the transformations of the representations from the superior temporal areas to Broca's area. Finally, the cerebellum's role is to search for lexical items and to aid in error-based learning of rules used in complex language structures. This model most closely resembles the dual-route models discussed above, although it differs in some respects. On the other hand, it is inconsistent with connectionist models.

Placing the role of the cerebellum into the context of these models of language may help to elucidate the role of the cerebellum in the larger language network, and may give us a better understanding of language functioning as a whole.

The present research

In order to examine my research questions, detailed in the following chapter, I will employ cTBS. The literature regarding the role of the cerebellum in language processing as examined through the application of TMS methodologies is reviewed in detail in the following chapter.

Chapter 2

The use of transcranial magnetic brain stimulation to study cerebellar language function

A literature review and thesis aims

Presented here is an updated version of a book chapter that appeared in:

Beaton, A. A., Allen-Walker, L., & Bracewell, R. M. (2015) The use of transcranial magnetic brain stimulation to study cerebellar language function. In P. Mariën & M. Manto (Eds.), *The Linguistic Cerebellum*, (pp. 355-376). San Diego, CA: Elsevier

There is now widespread agreement (but see Glickstein, 2007) that the role of the cerebellum is not confined to motor skills but extends to a wide range of cognitive functions (see Beaton & Mariën, 2010; Buckner, 2013; Stoodley, 2012). Studies of patients with cerebellar damage provide the classic source of information on functions of the cerebellum (Holmes, 1917; 1939; Schmahmann & Sherman, 1998) whereas positron emission tomography (PET), single-photon emission computerised tomography (SPECT) and functional magnetic resonance imaging (fMRI) are more recent investigative tools. The results of numerous investigations of cerebellar patients (e.g. Fabbro, Moretti & Bava, 2000; Mariën, Engelborghs, Fabbro & De Deyn, 2001) and neuroimaging studies with unimpaired participants (e.g. Frings et al., 2006; Petersen, Fox, Posner, Mintun & Raichle, 1988; Stoodley & Schmahmann, 2009) suggest that the right cerebellar hemisphere, in particular, is involved in various aspects of language processing and verbal working memory (Durisko & Fiez, 2010; Marvel & Desmond, 2010; Ravizza et al., 2006).

However, problems associated with injection of radioactive isotopes limit the applicability of PET (or SPECT) studies, whereas the need to restrict movement in the scanner and movement artefacts means that participants are often dropped from fMRI studies. They are also expensive and, importantly, do not allow direct causal relationships between cerebellar activation and function to be inferred (Tomlinson, Davis & Bracewell, 2013). Studying patients with cerebellar lesions potentially allows causal inferences to be made, but differences in aetiology, chronicity and location of lesion introduce unwanted variability in the data from such patients. An ideal method of investigation would bypass all these problems (see also Desmond, Chen & Shieh, 2005).

Transcranial magnetic stimulation (TMS) is a non-invasive, relatively inexpensive technique (for reviews see Sandrini, Umiltà & Rusconi, 2011; Walsh & Cowey, 2000) that can be applied safely to neurologically normal participants. It involves passing an electric current through a magnetic coil placed on the scalp. TMS uses a rapidly changing magnetic field in the coil to induce weak electric currents in the brain beneath the coil. Single pulse TMS has been used to evoke activity in the motor and visual cortices (excitatory effects). In cognitive neuroscience research, however, typically *repetitive* pulses are given in order to induce a reversible ‘virtual lesion’ (Walsh & Cowey, 1998). Repetitive low frequency stimulation (typically 1Hz) for about 15 minutes produces effects that outlast the period of stimulation by some minutes. This makes TMS a potentially valuable research tool for investigating the functions of the cerebellum (Grimaldi et al., 2014) although Fisher, Lai, Baker and Baker (2009) caution that stimulation over the posterior fossa probably does not selectively activate the cerebellum (which has contralateral projections to cerebral cortex) but also brain stem structures and corticospinal pathways.

Types of brain stimulation

There are two types of brain stimulation commonly used to investigate cognitive functions in healthy participants, tDCS (transcranial direct current stimulation) and TMS. Whilst most TMS studies to date have been directed at the cerebral cortex, there is growing interest in applying TMS to the investigation of cerebellar function. Although there are cerebellar tDCS studies of, for example, verbal working memory (e.g. Boehringer, Macher, Dukart, Villringer & Pleger, 2013; Ferrucci et al., 2008; Pope & Miall, 2012), we restrict ourselves in this chapter to consideration of TMS only (for tDCS see Argyropoulos, 2015). We present a brief review of the relatively few published studies which have used TMS to examine linguistic functions of the cerebellum.

For the purposes of research on the effects of cerebellar stimulation on language processing, the protocols chosen (from among many others that might have been adopted) have involved TMS being administered using (in the majority of studies) a figure of eight shaped coil in one of two ways. One way is repetitive TMS (rTMS) in which a train of pulses is delivered at 1 Hz over a period of about 10 minutes (600 pulses). The other way (see Huang, Edwards, Rounis, Bhatia & Rothwell, 2005) is continuous theta-burst stimulation (cTBS) in which a brief burst of three low-intensity, high-frequency (50 Hz) TMS pulses are delivered at a 5 Hz rhythm for 40 seconds (600 pulses). The latter type of stimulation (cTBS) elicits stronger effects as compared to rTMS and depresses the excitability of motor cortex (as measured by motor evoked potentials; MEPs) for several minutes after its application (Huang et al., 2005).

In order to look specifically at cerebellar language function, TMS has been administered over the right lateral cerebellum (lobule HVIIa/Crus I in the terminology of Larsell and Jansen, 1972), a region implicated in a range of language tasks by both lesion and imaging studies (De Smet, Paquier, Verhoeven & Mariën, 2013; Mariën et al., 2001; Murdoch, 2010). The test protocol entails comparison of baseline or control performance with performance after a repeated train of stimulation as outlined above. However, the locations stimulated have differed to some extent from study to study (see Table 1 below). The effects of rTMS versus zero (or sham) stimulation over the right lateral cerebellum have been compared with stimulation over the vertex and/or left cerebellum as control sites or with deeper sites within the right cerebellum.

In the context of lateral cerebellar stimulation, some researchers using single pulse TMS have claimed that it activates the inhibitory Purkinje cells causing increased inhibition of the disynaptic dentato-thalamo-cortical facilitatory connections; this results in the inhibition of the contralateral primary motor and pre-frontal cortex (Groiss & Ugawa, 2012; Iwata & Ugawa, 2005; Ugawa & Iwata, 2005). Other authors have inferred *suppression* of the activity of the cerebellar cortex after cTBS in both motor and non-motor studies (e.g. Koch et al., 2008; Picazio, Oliveri, Koch, Caltagirone & Petrosini, 2013). There is at present no consensus on the effects of rTMS and cTBS of the cerebellum on cerebral cortex function.

Both facilitation and inhibition of MEPs (a fairly direct measure of motor cortical activity) have been reported after cerebellar stimulation. It is likely that the protocol, duration and precise location of cerebellar stimulation are important parameters. The situation in cognitive studies, in which there is no direct physiological measure of cerebral cortical function such as an MEP, is even more complex; to date, cognitive studies have used behavioural measures. As we recommend below, using physiological measures of cortical function (in particular, electroencephalogram; EEG) may prove a useful adjunct.

What has been found?

In a relatively early study, Rami and colleagues used rTMS to determine the effects of high and low frequency of stimulation at various sites, including the right cerebellar hemisphere, on different aspects of verbal memory (Rami et al., 2003). No significant effect of stimulation of the cerebellum was found, nor was there an effect on phonemic fluency (number of words beginning with a given letter produced in one minute). Subsequently, in a combined fMRI and single pulse TMS study, Desmond et al. (2005) reported that stimulation over the superior right cerebellum (hemispheric lobule VI/Crus I as target) significantly increased response times to a letter probe in a verbal working memory task (Sternberg paradigm), as compared with a motor control task, but did not affect accuracy.

Both verbal and visual working memory tasks were employed by Tomlinson, Davis, Morgan and Bracewell (2014) who administered cTBS over the right and left cerebellar hemispheres to target the same area as Desmond et al. (2005). The expectation was that the right cerebellar stimulation would affect only verbal working memory and left cerebellar stimulation would affect only visual working memory. In the event, stimulation led to a non-lateralised improvement on the visual working memory task but on the verbal memory task, in contrast to the results of Desmond et al. (2005), right cerebellar stimulation impaired accuracy but not response times. Tomlinson et al. (2014) argued that, in comparison with the experiment by Desmond et al. (2005), their use of serial rather than parallel presentation of letters placed greater stress on the articulatory encoding function of the right cerebellum, whereby information is maintained through rehearsal in the phonological loop component of working memory.

In the first published study of repetitive TMS in relation to a specifically linguistic task, Argyropoulos (2011) used cerebellar cTBS to investigate its effect on lexical associative priming. Following a pilot study to establish the priming effects of interest, he used cTBS over the right lateral cerebellum and compared this with stimulation over the right medial cerebellum. Participants were presented visually with a prime word followed by a target and required to make a lexical decision in relation to the target letter string, that is, to decide whether it was a real word or not. Two types of real word pairs were used in this experiment: semantically related pairs in which the prime is a subordinate of the target, for example *apple* and FRUIT, and phrasal associates in which the prime and the target co-occur in speech but are not semantically related, for example *gift* and HORSE ("Don't look a gift horse in the mouth"). Argyropoulos (2011) reported that for associative but not semantically related word pairs there was a significant increase in the magnitude of the priming effect (measured as the difference in mean response time to unprimed words minus that to primed target words) after right medial stimulation as compared to right lateral stimulation. In short, cTBS over the right medial cerebellar hemisphere selectively enhanced associative priming. Argyropoulos proposed that these results suggest that the cerebellum is involved in making predictions that prepare cortical language areas for language processing.

In the Argyropoulos (2011) study described above, those individuals who had been given right medial stimulation first (i.e. before lateral stimulation) showed a significant drop in post-stimulation lexical decision accuracy as compared with their pre-stimulation performance. This effect was not shown when medial stimulation had been applied second;

this may have been due to practice effects. In a subsequent study, therefore, Argyropoulos, Kimiskidis and Papagiannopoulos (2011) looked at how right cerebellar cTBS disrupts "the practice induced acceleration of lexical decisions". The experimenters again used a visual lexical decision task, this time with native Greek speakers and Greek words. There were 100 word pairs in the associative condition (e.g. *wind-sails*; half unrelated) and 100 word pairs (e.g. *branch-leaf*; half unrelated) in the semantic condition. Right medial and right lateral cerebellar sites were stimulated using cTBS. In contrast to the results reported by Argyropoulos (2011) there was no significant effect on priming of either medial or lateral cerebellar stimulation. However, medial cTBS eliminated the practice effects on the lexical decision task seen in the control conditions (in which reaction times decreased on completion of the task a second time). The authors suggest that this effect arose because the cerebellum plays a role in the acquiring, storing and retrieving of associative memory traces of repeatedly co-occurring language events. Failure to find an effect of cTBS at the lateral site may have been because stimulation with the type of coil used did not penetrate to the region of the cerebellum involved in semantic priming (Théoret, Haque & Pascual-Leone, 2001). Absence of an effect of stimulation at a particular location should not necessarily be interpreted as lack of cerebellar involvement in the function in question.

Argyropoulos and Muggleton (2013) looked at the effects of cerebellar cTBS on the processing of semantic associations. Again, a lexical decision task was used. Participants were shown 500 word pairs, 250 of which were pairs with a non-word target; the other 250 contained 200 pairs that were of interest and 50 that were fillers. Half of the 200 word pairs of interest were categorically related (e.g. *applause-clapping*) and half were associatively related. There were four types of associated pairs. These involved a verb target denoting an action together with a noun prime denoting an agent (e.g. *butcher-carving*), patient (e.g. *lawn-mowing*), instrument (e.g. *scissors-cutting)* or location (e.g. *casino-gambling*) of that action. Argyropoulos and Muggleton (2013) used two stimulation sites, right medial and right lateral cerebellum, which were compared with a no-stimulation condition. The results showed that right lateral cerebellar cTBS, but not right medial cTBS, selectively enhanced associative priming as compared to categorical priming.

Argyropoulos (2011) had reported that cTBS over the right medial cerebellum enhanced associative priming whereas an effect of right lateral cerebellar stimulation was found by Argyropoulos and Muggleton (2013). This was attributed both to visual factors that differed in the two studies and to the fact that “immediately co-occurring nouns” (e.g. *gift-horse*) were used by Argyropoulos (2011) but “non-immediately co-occurring nouns and verbs” (e.g. *gift-accepting*) by Argyropoulos and Muggleton (2013). Whatever the merits of this argument, there were other differences between the two studies. The main difference is that Argyropoulos (2011) examined associative priming based on co-occurrence of words in idiomatic speech while Argyropoulos and Muggleton (2013) investigated thematic associative priming (script-based semantic associations). Thus, the level of association (phonological versus semantic) differed. The site of lateral stimulation relative to the inion also differed. Nonetheless, the combined results of the two studies suggest that the right cerebellum contributes in some way to lexical associative computations.

In a study by Lesage, Morgan, Olson, Meyer and Miall (2012) participants were asked to listen to sentences. On one half of the trials this noun could be predicted by the verb used. For example, *‘The man will sail the boat’*. While listening to these sentences, participants viewed pictures of four objects and the agent of the sentence. The four objects (three not mentioned in the sentence) were displayed at each corner of the screen and the agent of the sentence in the centre. Participants fixated on the agent until they could predict the final word, at which point they moved their fixation from the agent to the appropriate picture. Lesage et al. (2012) used rTMS over the right lateral cerebellum in the experimental condition with stimulation of the vertex and no-stimulation as control conditions. They found that after right cerebellar rTMS participants were significantly slower at predicting the final noun, when it could be predicted from the verb, as compared to before stimulation. There was no change in the onset latencies of fixation to the target object before and after right cerebellar rTMS for those sentences where the final word could *not* be predicted. Nor was there a significant change in fixation onset to the final word, in predictable sentences, between pre- and post- TMS in either the vertex stimulation condition or the no-stimulation condition. Thus, right lateral cerebellar rTMS selectively inhibited language prediction. Lesage and colleagues suggested that the right cerebellum, with input from cortical language areas such as Broca's area, provides an efferent copy of internalised speech, thus allowing the cerebellum to predict speech.

Oliveri et al. (2009) carried out two experiments to look at the linguistic and spatial linking of time and space in the cerebellum. In the first experiment, in which they did not use rTMS, they asked participants to respond to the tense of a group of Italian action verbs, state verbs and non-verbs. The verbs had previously been rated for motor imageability. The verbs were presented in two forms, future tense (e.g. *scriverai* – will write) and past tense (e.g. *scrivevi* – wrote). Participants were required to identify the tense of the stimuli. Within each main condition there were two sub-conditions, one in which the left hand responded to past tense and the right hand responded to future tense and vice versa in the second sub-condition. It was found that reaction times were faster to action verbs than to both state verbs and non-verbs and that reaction times to the future tense were significantly faster in right than left space. This pattern (which approached significance) was reversed for the past tense. For state verbs there were significantly faster reaction times to future tense on the right than left, but there was no lateral difference for past tense. There were no tense or spatial differences for the non-verbs. With regard to accuracy of performance, Oliveri et al. (2009) reported that there was a significant effect of the type of verb. Participants were less accurate in responding to action verbs, as compared to state and non-verbs, and were more accurate to future tense action verbs in the right as compared to left space but there was no lateral difference in responding to past tense action verbs. For both state verbs and non-verbs, participants were more accurate to the past tense in the left than the right side of space and to future tense in the right than the left side of space.

In a second experiment participants were split into two groups: left cerebellar stimulation and right cerebellar stimulation. Different words were used but the selection of the stimuli, presentation and procedure were the same as in the first experiment. Reaction time and accuracy were recorded in pre-rTMS and post-rTMS conditions. For action verbs, rTMS over the right cerebellum interfered with reaction times to the future tense significantly more than left cerebellar stimulation; there was no effect on performance with the past tense. There were no significant differences for accuracy with action verbs. For non-verbs, rTMS over the right cerebellar hemisphere increased reaction times but rTMS over the left cerebellar hemisphere was facilitatory. There was a significant tense-by-space interaction for accuracy with non-verbs. Repetitive TMS led to lower accuracy to past tense non-verbs in left as compared to right space and lower accuracy to future tense non-verbs in right as compared to left space. Finally, for state verbs there was no effect of rTMS on reaction times but in terms of accuracy there was an interaction between tense and space: rTMS resulted in lower accuracy to future tense in right as compared to left space. The findings were interpreted as indicating that the cerebellum has a role in "establishing the grammatical rules for verb conjugation" and as suggesting that the right cerebellum may be important in anticipating future events based on past experiences.

The suggestion that the right cerebellum anticipates future events is in accordance with the prediction hypothesis of cerebellar function, which holds that the cerebellum acts as a predictive device across different domains of function (Miall, Weir, Wolpert & Stein, 1993; Roth, Synofzik & Lindner, 2013). Arasanz, Staines, Roy and Schweizer (2012) used a between-groups design, one group having cTBS administered to the right cerebellar hemisphere, the other group receiving cTBS to the left cerebellar hemisphere. Before and after cTBS participants completed phonemic and semantic fluency tasks (giving as many words as possible beginning with a given letter or semantic category within a specified interval of time). Arasanz et al. (2012) were particularly interested in the number of category switches, that is, “the exhaustion of a phonemic or semantic cluster and the shifting to another”. They found no significant difference in performance in the semantic fluency task as a function of side of stimulation but did find a significant difference in the phonemic task. Specifically, participants in the right cerebellar stimulation group showed significantly fewer category switches during the early period (initial 15 seconds) as compared to the left cerebellar stimulation group. The authors argue that as the trials at the beginning of the experimental period are more demanding than subsequent trials, more neural tissue is recruited to cope; this idea is supported by the absence of an effect in the semantic fluency task as the latter is much easier than a phonemic fluency task.

A more recent study by Runnqvist et al. (2016) gave a differing explanation for their findings as a result of cerebellar rTMS as regards cerebellar prediction. They aimed to examine the internal modelling of speech via application of left and right cerebellar rTMS. They applied 15 minutes of MRI guided rTMS to the left and right cerebellum, specifically Crus I and II, after which participants completed three blocks of a priming task that encouraged errors. Prior to the presentation of target word pairs, which had to be read aloud, three word pairs were presented. The initial consonants of the first two pairs were the same as the target pair and the third word pair had an additional phonological overlap with the target pair, this primed errors (e.g. *sun mall – sand mouth – soap mate – mole sail*). They found that right cerebellar rTMS resulted in more errors and, in the first block, an increase in reaction time. They interpret these findings as evidence that the cerebellum employs internal models to ‘self-monitor’ speech production and that right cerebellar rTMS disrupts the updating of these internal models through disruption of verbal working memory and therefore the maintenance of a phonological goal.

Table 1. Provides a summary of the rTMS and cTBS experiments on cerebellar language function discussed above.

Authors	Stimulation	Site of stimulation	Experimental task	Participants	Main findings
Rami et al., 2003	rTMS at high (5 Hz) and low (1 Hz) for 10 s with ISI of 30 s 5 Hz, at 10% below motor threshold	3 cm below and 3 cm right of inion	Immediate and working verbal memory (digits forwards and backwards); phonemic fluency	N = 16 (males), 20-37 yrs; mean age 26.63 yrs	No effect of right cerebellar rTMS
Oliveri et al., 2009	1 Hz for 10 min; 90% of motor threshold	1 cm below inion and 3 cm L or R of inion	Expt 1: (Control) visual recognition of verb tense (Italian) Expt 2: (rTMS) Visual recognition of verb tense (Italian)	N=24; 20-30 yrs N=24; 20-35 yrs	Selective disruption of RTs to future tense of action verbs compared with state verbs and non-verbs when rTMS applied to R cerebellum
Argyropoulos, 2011	cTBS: 50 Hz pulses at 5 Hz rhythm for 40 s (600 pulses); 45% of maximum output	1 cm below and 1 cm R of inion (medial); 1 cm below and 4.5 cm R of inion (lateral)	Visual LDT with associative (gift-horse) or semantic (swan-chicken) prime (English)	N = 8; 19-43 yrs	cTBS over right medial site selectively enhanced associative priming; no effect of lateral stimulation

Argyropoulos et al., 2011	cTBS: 801 pulses in 267 bursts of 3 pulses at 30 Hz repeated at intervals of 100 ms; intensity 45% of maximum	1 cm below and 1 cm R of inion (medial); 1 cm below and 4.5 cm R of inion (lateral)	As above but with greater number of related pairs (i.e. more trials) of Greek words; R index finger response = yes (word); L index finger = No (non-word)	N=24; 18-52 yrs; mean = 26.42; N=12: lateral stimulation; N=12: medial stimulation	No effect of type of prime word; selective lack of decrease in RT for those receiving medial (compared with lateral) TMS second during first experimental session; significant decrease in RT after lateral stimulation
Arasanz et al., 2012	cTBS: 3 pulses at 50 Hz repeated at 5 Hz (theta frequency) for 40 s (total of 600 pulses)	1 cm below and 1 cm L or R of inion	Phonemic and semantic fluency tasks	N=14: L cTBS; N=13 R cTBS Mean age =23.8 yrs	Phonemic task – First 15 secs: number of words produced increased after R and L cTBS and number of category switches reduced after R cTBS but increased after L cTBS Last 45 secs: No effect on either number of words produced or on number of switches from one phonemic cluster to another Semantic fluency task – no significant effect of cTBS

Lesage et al., 2012	rTMS at 1 Hz for 10 min (total 600 pulses); 55% of maximum output	1 cm below and 3 cm to R of inion	Two types of sentence played over earphones: Predictive versus control. In predictive condition verb could refer to only one of four visually displayed objects; in control condition verb could apply to any of the four. Response measure was latency to fixate on target object from onset of verb	N=22: R rTMS; N=21: vertex; N=22: no stimulation Mean age = 20.5 yrs	rTMS to right cerebellum increased fixation latencies only for predictive condition.
Argyropoulos & Muggleton, 2013	As Argyropoulos, 2011	1 cm below and 1 cm R of inion (medial); 1 cm below and 10 cm R of inion (lateral)	Visual LDT: categorical (robbery-stealing) versus associative (casino-gambling) semantic priming	N=12: R lateral cTBS; N=11: R medial cTBS; N=23: no cTBS; Mean ages approx. 25, 22 and 21 yrs. respectively	Lateral rTMS selectively enhanced associative priming

Tomlinson et al., 2014	cTBS: 3 pulses at 50 Hz, repeated at 200 ms intervals for 40 s. (600 total) at 80% of motor threshold	1 cm below and 6m R or L of inion	Visual and verbal working memory (serial display of letters or shapes followed by probe)	N = 10; 18-35 yrs	Right cerebellar rTMS produced decreased accuracy on verbal working memory
Runnqvist et al., 2016	rTMS: 1 Hz at 60% of maximum output for 15 min (900 pulses), applied twice, once to each hemisphere	L and R cerebellar Crura I and II MRI guided application for all participants	Primed language task: three 5 min blocks. Target word pairs preceded by three word pairs. The first two shared initial consonants and the third pair had additional phonological overlap, priming errors (*sun mall – sand mouth – soap mate – mole sail*).	N = 16; Mean age 24 yrs	Right cerebellar rTMS elicited an increase in errors, in addition it produced an increase in reaction time in the first 5 min block

Note. L = Left, R = Right, LDT = Lexical decision task

Some outstanding questions

It is difficult to know exactly what to conclude from these studies, especially given their different sites of stimulation. In some experiments, rTMS or cTBS leads to enhanced performance of one kind or another (Argyropoulos, 2011; Argyropoulos & Muggleton, 2013; Oliveri et al., 2009) while in others there is a deleterious effect (Arasanz et al., 2012; Argyropoulos et al., 2011; Lesage et al., 2012; Runnqvist et al., 2016; Tomlinson et al., 2014). This may reflect the fact that the cerebellum itself has excitatory and inhibitory connections with the cerebrum. The effect of stimulation will obviously depend upon which pathways are stimulated and on their relative contribution to the behaviour or effect under investigation.

How does TMS produce the effects it does on linguistic functions? Are they direct or indirect, mediated through influences on and from frontal cortex? The cerebellum has reciprocal links through pontine and dentate nuclei and thalamus mainly to frontal and association areas of the cerebral cortex, including language-related areas such as Broca's area (Desmond et al., 2005; Mariën et al., 2001). When TMS is applied to the cerebellum there are changes in the glucose metabolism of this region as well as in Wernicke's area (posterior superior temporal cortex). Cho et al. (2012) used PET scanning after application of sham or rTMS to study the effect of left lateral cerebellar rTMS on the rest of the brain. The rTMS was applied for five minutes to the left lateral cerebellum (1 cm below and 3 cm to the left of the inion). The researchers looked not just at the whole brain in real versus sham rTMS conditions but also focused specifically on areas that they believed would be affected; of particular interest in the context of this review they looked at Broca's area, Wernicke's area and non-stimulated regions of the cerebellum. The following areas showed *decreased* glucose metabolism in the rTMS condition as compared to the sham condition: right cerebellum (tonsil) and left cerebellum/inferior semi-lunar lobule (lobule IX and lobule VIIb/Crus II in the terminology of Larsell and Jansen, 1972). Other regions of the brain showed *increased* glucose metabolism in the rTMS condition as compared to sham, namely left superior temporal gyrus (Wernicke's area), left inferior frontal gyrus (Broca's area) and left cerebellum (dentate nucleus). In a functional connectivity analysis using the rTMS target area as seed, Cho et al. (2012) found that the left inferior frontal gyrus (Broca's area) showed additional positive correlation with the cerebellar seed area in sham as compared to the rTMS condition. Thus, rTMS over the left lateral cerebellum affected glucose metabolism not only in the cerebellum but (*inter alia*) in key language areas as well. The clear implication is that the cerebellum has functional links to these areas and that when rTMS is used over the cerebellum it affects a cerebello-cerebral network rather than just the specific area being stimulated.

Although functional connectivity studies clearly show the cerebellum to be part of a distributed language network (Booth, Wood, Lu, Houk & Bitani, 2007; Londei et al., 2010; Wang, Buckner & Liu, 2013), the functional and temporal relationships between cerebral cortex and cerebellum (and basal ganglia) are unclear. A particular aim of future research should be to investigate precisely how TMS over the cerebellum affects this structure and the rest of the brain, and the interaction between them, both functionally and from a neurophysiological perspective. A significant step in this direction was recently made by Halko, Farzan, Eldaief, Schmahmann & Pascual-Leone (2014) who used intermittent theta-burst stimulation (iTBS) of sites within the cerebellum to explore the spatial specificity of the effects of stimulation of a default network node. Guided by individual resting-state fMRI scans from each of nine healthy volunteers, Halko et al. stimulated a lateral cerebellar target derived from the centre of largest connectivity in this region (always Crus I or Crus II) established in a previous study and, based on previous literature, lobule VII (lobules VIIAt/VIIB) of the cerebellar vermis (Schmahmann, Doyon, Toga, Petrides & Evans, 2000).

Stimulation was compared with sham stimulation. A double dissociation was found whereby lateral stimulation, but not midline or sham stimulation, increased connectivity of the cortical default network whereas midline cerebellar stimulation, but not lateral or sham stimulation, affected the cortical attention network. Stimulation of the motor network was not affected by stimulation of either cerebellar site (nor by sham stimulation). This research demonstrates that TMS applied to the cerebellum has sufficient specificity to influence connectivity between cerebral network nodes but further work will be necessary to determine the implications of network modulation for cognitive functions. It may be productive to use TMS over the cerebellum in conjunction with cortical EEG (difficult to obtain from the cerebellum owing to its anatomical position) to further investigate the functional and temporal relationships between cerebellum and cerebral cortex. Such an approach may help to elucidate the specific cerebellar contribution to linguistic functions.

A question that TMS methodologies have not answered is whether there is a specifically linguistic contribution by the cerebellum and, if so, whether it is involved in all or only some linguistic functions, or rather plays a purely supportive role. An alternative view is that the cerebellum applies one algorithm to all input, including linguistic. The remarkable cytoarchitectural homogeneity of the cerebellar cortex has led several authors (e.g. Schmahmann, 2004; Argyropoulos & Muggleton, 2013) to suggest that the cerebellum operates in terms of a single principle across different domains rather than in a domain-specific way. Consequently, theories developed to account for motor behaviour have been applied to linguistic behaviour. For example, Moberget and colleagues have proposed, on the basis of findings from their fMRI study with Norwegian participants, that the cerebellum has a predictive function that applies to language as to other domains (Moberget, Gullesen, Andersson, Ivry & Endestad, 2014), a theory supported by the findings of Lesage et al. (2012) outlined above. Others have suggested that temporal encoding is the critical property (e.g. Ivry & Keele, 1989; Oliveri et al., 2009; Szpunar, Watson & McDermott, 2007).

The view that the cerebellum has an essentially predictive role (see, for example, Miall & King, 2008) can be contrasted with the idea that it is primarily involved in associative learning (Timmann et al., 2010). However, in those rTMS studies that posit a 'predictive' role (Lesage et al., 2012) and those that posit an 'associative' role (Argyropoulos et al., 2011; Argyropoulos & Muggleton, 2013) the data can be interpreted so as to support either view. Lesage et al. (2012) manipulated the verb to make the final noun of the sentence predictable (e.g. the man will *sail* the *boat*). However, rather than being a prediction task this could instead be regarded as a verb-noun association task. It is therefore unclear from this experiment whether the cerebellum plays a predictive or associative role. Likewise, the results of Argyropoulos et al. (2011) and Argyropoulos and Muggleton (2013) indicate that the cerebellum undertakes an associative role for only those words that co-occur in speech. It is possible therefore that the results are a reflection of a cerebellar role in language prediction. A further logical possibility is that because the same stimulation sites were not used in the two sets of studies each of these roles may be accomplished by different cerebellar regions. Finally, it is conceivable that the two sets of results are reflections of the same predictive process and that the apparent difference between them is purely terminological. There is only a limited literature in this field with results being published by research groups from different laboratories. There is a need to establish an agreed terminology before significant theoretical advances can be made.

Methodological issues

In conducting or evaluating TMS research a number of methodological issues need to be borne in mind (see Tomlinson, Davis & Bracewell, 2013). One such issue concerns the type of coil used, since coil design affects the ability to stimulate the cerebellum.

Type of coil. The three principal types of coil are a figure of eight coil, a batwing coil and a double-cone coil. However, the efficacy of these different types of coils in stimulating the cerebellar cortex has not necessarily been taken into account when selecting the type of coil to use. Hardwick, Lesage and Miall (2014) systematically examined the effectiveness of these coil types over both the left primary motor cortex and the cerebellum, and from structural magnetic resonance (MR) images established the depth from the scalp of the cerebellar cortex at various locations relative to the inion which marks the boundary between the posterior cerebellum and the occipital cortex (Hashimoto & Ohtsuka, 1995). They found that resting motor threshold (RMT) was much higher over motor cortex with the figure of eight coil as compared to the other two and that RMT for the batwing coil was also significantly higher than for the double-cone coil. MEP recruitment curves were also less steep for the figure of eight coil as compared to the other two types. Lower RMTs and steeper recruitment curves imply more effective stimulation of the motor cortex.

Hardwick et al. (2014) quantified the effects of cerebellar stimulation applied 1 cm below the inion and 3 cm laterally, on the side contralateral to the participant’s dominant hand, by taking advantage of the phenomenon of cerebellar-brain inhibition (CBI). If a so-called conditioning pulse of TMS is first applied to the cerebellum, then amplitudes of MEPs evoked by stimulation of the primary motor cortex are typically reduced in comparison with stimulation of the motor cortex alone, reflecting an inhibitory influence from the cerebellum. Hardwick et al. (2014) found using the figure of eight coil that CBI was not consistently present (i.e. conditioned MEP amplitudes did not differ significantly from control MEP amplitudes). This was the case at all intensities used (from 65%-80% of maximum stimulator output; MSO). There were significant differences between control and conditioned MEPs at 75%-80% MSO with the batwing coil and significant differences at all intensities with the double-cone coil. This suggests that the figure of eight coil may be less effective in stimulating the cerebellum than the other two types of coil, particularly at low intensities. However, this was only in the context of motor activation; it may not be the case for the cognitive domain. In fact, the coil that has been most often used in cerebellar simulation studies of language is the figure of eight coil (Arasanz et al., 2012; Argyropoulos, 2011; Argyropoulos et al., 2011; Argyropoulos & Muggleton, 2013; Oliveri et al., 2009; Rami et al., 2003; Tomlinson et al., 2014), although the double-cone coil has also been used (Lesage et al., 2012). In any event, there is a need for the effects of different types of coil to be investigated within the context of cognitive studies of cerebellar function.

Intensity of stimulation. Another important issue concerns intensity of magnetic stimulation. A favoured procedure in deciding on the intensity of stimulation to use in cognitive studies is based on each participant's motor threshold, that is, the threshold required for stimulation of the motor cortex to elicit a twitch of the hand on the same side as cerebellar stimulation (given the crossed connections between cerebellum and motor cortex and from the latter to the hand) or a response (MEP) from a muscle or nerve on that side. However, as Argyropoulos (2011) points out, in the context of investigating cognitive function motor thresholds may not be appropriate, since there is no systematic relationship between thresholds for motor cortical stimulation and thresholds in non-motor, for example visual, cortex (Stewart, Walsh & Rothwell, 2001). Additionally, given the disparity in distance from the surface to the primary motor cortex on the one hand and, on the other, to the cerebellar cortex (Hardwick et al., 2014 – see below) this technique may not be a useful method for deciding on the intensity to use in studies of cerebellar function. An arbitrarily chosen intensity (such as percentage of maximum output, as used by some investigators) may be just as acceptable.

Localisation of stimulation. A further methodological issue is that of localisation of stimulation. Hardwick et al. (2014) looked at the shortest distance from the scalp to the cerebellar cortex at 20 locations in the structural MR images from 100 participants. Their locations were at one centimetre intervals from 0-3 cm below the inion and 0-4 cm lateral of the inion. The shortest distances to cerebellar grey matter tissue were found at 3 and 4 cm lateral to the inion and, for the same locations within the cerebellum, at 1 cm below the inion. At 3 and 4 cm lateral to the inion it was quite likely that the stimulation passed through the occipital cortex (31 of 100 participants) but this was not the case for those locations 1 cm below and 3-4 cm lateral to the inion.

The right lateral cerebellum has been labelled as such in relation to different distances from the inion: for example, 1 cm below the inion and 3 cm right of this anatomical landmark (Lesage et al., 2012; Oliveri et al., 2009) or 4.5 cm to the right (Argyropoulos, 2011; Argyropoulos et al., 2011). Even within the same research group, the measurements have not been consistent [4.5 cm right of the inion (Argyropoulos, 2011; Argyropoulos et al., 2011), 10 cm right of the inion (Argyropoulos & Muggleton, 2013)]. Rather than using the right lateral cerebellum, in two studies (Argyropoulos, 2011; Argyropoulos et al., 2011) this group used the right medial cerebellum as an experimental site (1 cm inferior and 1 cm lateral to the inion). Although, according to Hardwick et al. (2014), at this location the cerebellar surface is further away than at 1 cm below and 3 cm lateral to the inion, approximately 1 cm lateral and caudal to the inion was found to be the optimal site in studies of voluntary eye movements by Hashimoto and Ohtsuka (1995) and Ohtsuka and Enoki (1998). Furthermore, Théoret et al. (2001) found a greater effect on a paced finger-tapping task with a figure of eight coil over the medial cerebellum (in the midline and 1 cm below the inion) than with the coil placed 1 cm below and 3 cm to the right of the inion. As the former location is, according to Hardwick et al. (2014), even further from the cerebellar surface than 1 cm below and 1 cm lateral to the inion, it does not appear that this latter location cannot be effectively reached (at least with a figure of eight coil and suitable intensity of stimulation). The distance to the cerebellar surface of a coil placed 10 cm lateral to the inion, as was used by Argyropoulos & Muggleton (2013), was not examined by Hardwick et al. (2014) but it is an unusual choice of position and may have been less than ideal in so far as an extended distance from any landmark compromises localisation. Future work within the context of cognitive functions might usefully explore the effect not only of different coil types (see above) but of magnetic stimulation at different locations.

In any event, localisation of effects of stimulation can rarely be precise. Given individual differences in neuroanatomy, standard placement of the coil in relation to physical landmarks such as the inion will not ensure that each subject receives stimulation at exactly the same location in the cerebellum. Nor does coil placement on the basis of published neuroanatomical atlases allow precise location in individuals since they are based on data averaged across different brains. If stimulation affects the entire cerebellum, or even large parts of it (Fisher et al., 2009), then localising particular sites of stimulation as crucial, or identifying selective effects (e.g. lateral versus medial cerebellum), will only be approximate unless more accurate navigational techniques are adopted. An obvious remedy is to apply TMS in co-registration with MR images of the brain of individual participants as was done, for example, in the studies by Halko et al. (2014) and by Runnqvist et al. (2016) referred to earlier in this chapter.

Experimental design and artefacts. Yet another issue concerns the importance of designing experimental protocols that permit assessment of the role of the cerebellum in any particular linguistic task over and above its possible involvement in motor aspects of that task. The most straightforward way of doing this is to use control tasks that are equated for motor involvement but differ cognitively from the task in question. Establishing an effective sham stimulation condition controlling for effects such as noise (clicks), sensory effects and muscle activation constitutes a further challenge to experimenters' ingenuity (see Tomlinson et al., 2013).

Summary

The TMS studies of cerebellar linguistic function briefly reviewed in this chapter have produced some interesting and provocative results. However, there are several theoretical and methodical issues that workers in the field need to consider. In particular, we caution against the simplistic notion that rTMS or cTBS over the posterior fossa induces a simple 'virtual lesion' of the cerebellum. Future researchers should consider the physiological effects on the cerebellum of the precise pattern of TMS used, and the 'downstream' effects of such stimulation on the cerebral cortex. Conceivably, a combination of EEG recording (or fMRI) and TMS applied between sessions under scalp electrodes (or in the scanner) would prove informative as to relationships between cerebellum and supra-tentorial areas and the precise role played by the cerebellum in cognitive functions. Methodological questions that need to be considered in undertaking TMS research on the cerebellum include the type of coil that is to be used, the intensity and localisation of stimulation, and how to control for artefacts resulting from extraneous auditory and sensorimotor stimulation. With the caveat that such issues are successfully resolved, it is highly probable that TMS will prove to be an increasingly useful tool in the armamentarium of the cognitive neuroscientist interested in cerebellar contributions to linguistic behaviour.

Questions posed by this thesis

The aim of this thesis is to answer the following questions:

1. Are the findings that the right cerebellar hemisphere is involved in associative, as compared to categorical, priming reproducible when we control for categorical relationships across both types of stimuli, and does

the effect of stimulation also modulate ERP waveforms that index language prediction and semantic processing?

2. Is the cerebellum’s role in associative priming similar in backward priming as compared to its role in forward and symmetrical priming; and how does this relate to models of backward priming and models of cerebellar function?
3. Can the role of the cerebellum in associative priming, previously documented in tasks predominantly using pairs of words, be seen in a more complex language task employing sentences, and can the impact of this role be seen in ERP waveforms that index language prediction and semantic processing?

This thesis will outline ways in which I have used cTBS to examine the role of the cerebellum in language prediction through associative priming and sentence prediction, as detailed in experimental chapters 4, 5 and 6; and ERPs to assess cortical function as a result of modulation of the cerebellum, as detailed in chapters 4 and 6.

Chapter 3

Methodological Considerations

Methodological Considerations

The purpose of this chapter is to describe and justify the methodological choices that have been made in this thesis. First, I will outline the tasks used: associative priming, backward associative priming and semantic violations. I will then discuss the ways in which these have been previously employed in the literature, if they have been, and why they are appropriate for exploring the questions posed by this thesis. I will then describe the experimental methods used: event-related potentials (ERPs) and continuous theta-burst stimulation (cTBS), and their previous application in this research context.

As discussed in the previous chapters, the role of the cerebellum in language prediction and association is, as yet, unclear. It has been proposed that the computations utilized by cerebellum in motor prediction are similarly applied to the other predictive roles played by the cerebellum in various non-motor higher order cognitive functions (Ramnani, 2006; Schmahmann, 2004). This hypothesis is particularly compelling as the homogenous cerebellar structure makes it likely that the cerebellum applies very similar computations across all of its functions (Eccles, Ito & Szentagothai, 1967). In the motor domain, the cerebellum is thought to be associating two events that are temporally related, such as integrating sensory and motor information (Miall, Weir, Wolpert & Stein, 1993). Thus, the tasks employed to examine the role of the cerebellum in language have largely relied upon associatively related pairs of words. The methods used in this thesis will first aim to replicate the findings in this field using tasks of this nature and will then build on them by expanding on the tasks used previously.

Associative priming: as a means to examine associative prediction in language

The authors employing cTBS have often compared the effects of cerebellar stimulation on associative priming as compared to categorical priming, i.e. pairs of words that commonly co-occur in speech as compared to words that are semantically but not necessarily phrasally related. For example, Argyropoulos (2011) used cTBS to test both phrasal associative priming (e.g. gift → HORSE) and categorical priming, where the prime was a subordinate of the target (e.g. apple → FRUIT), in a lexical decision task. They compared medial (1 cm below and 1 cm to the right of the inion) and lateral (1 cm below and 4.5 cm to the right of the inion) stimulation of the right cerebellum. cTBS over the medial site selectively enhanced the phrasal associative priming effect as compared to the categorical effect, revealing the role of the right cerebellum in forward priming. Subsequent studies in that lab (Argyropoulos & Muggleton, 2013) also found increases in associated noun-to-verb associative priming (e.g. scissors → cutting), as compared to categorically related (e.g. applause → clapping), after stimulating other areas on the right of the cerebellum, although this time they were located in more distant lateral sites (1 cm below, 10 cm lateral of inion). These studies indicate that this type of task is effective for indexing changes in cerebellar associative function as a result of cTBS. However, there are some issues in these studies that have not been considered. Specifically, previous studies in this domain have not controlled for the semantic relationships between the two types of pairs, associative as compared to categorical. For example, in the case of Argyropoulos (2011) where there is no categorical relationship between the associative pairs. Further there are issues surrounding the stimulation sites used in the Argyropoulos (2011) and the Argyropoulos and Muggleton (2013) papers which will be addressed in the cTBS section of this chapter.

In the first experimental chapter (Chapter 4) we have employed a similar priming paradigm as Argyropoulos and colleagues (2011; 2013); however, we have attempted to use stimuli that are matched more closely and therefore better controlled than those that have been employed in previous research. We compared opposites (e.g. black → WHITE) to categorically related pairs using the same prime (e.g. black → BROWN). The associative strength for the opposite pairs was significantly higher than for the categorical (t(39)=15.36, p<.001). All of the pairs are therefore categorically related and we can interpret changes in behavioural measures as purely due to the manipulation in associative strength rather than a distinct difference in the type of relationship.

Backward associative priming: as a means to examine backward associations in language prediction

As outlined in the previous section, previous studies have examined associative priming by examining pairs of words that are associatively related (Argyropoulos, 2011; Argyropoulos & Muggleton, 2013). However, in these cases the association is predominantly symmetrical or has been forward in nature. It is likely that any associations that the cerebellum is making can be activated bi-directionally, particularly as the presence of feedback loops in models of cerebellar function within the motor domain have been well established, as described in Chapter 1.

Here we have chosen pairs that are highly associated but whose association is asymmetrical (e.g. pigeon → HOLE). This resulted in the use of both associated pairs of words and compound words. Overall, the pairs were predominantly compound words, which follows common practice in the backward priming literature as the two types of stimuli are comparable in terms of the backward priming effect (Chwilla, Hagoort & Brown, 1998; Franklin, Dien, Neely, Huber & Waterson, 2007; Kahan, Neely & Forsythe, 1999). The associative strength for the forward pairs was significantly higher than for the backward pairs (t(23)=2.70, p=.013).

Currently, there is no research, of which we are aware, that has employed backward priming and cTBS to examine the role of the cerebellum in this process. fMRI evidence has indicated that the left cerebellum is active during backward priming (Terrien et al., 2013), therefore left cerebellar cTBS may modulate backward priming, whereas right cerebellar cTBS should modulate forward priming as has been documented in the literature discussed in the previous section.

Semantic violations: as a means to examine language predictive functioning

The two tasks that are described above are designed to examine how the cerebellum is involved with relatively simple language associations. However, the final task employed in this thesis sought to examine the role of the cerebellum in more complex language stimuli, namely sentences.

A previous study using repetitive transcranial magnetic stimulation (rTMS) to examine the role of the cerebellum in language using highly predictable sentences (Lesage, Morgan, Olsen, Meyer & Miall, 2012) indicates a role of the cerebellum in more complex sentence prediction. However, these sentences relied upon verb-to-noun word pair associations in order to facilitate their predictability. Each sentence employed a verb that was strongly associated with an available target (e.g. '*The man will sail the boat.*') as compared to sentences with verbs that did not predict a specific final word target (e.g. *'The man will watch the boat.'*). This task cannot therefore be fully dissociated from the lexical decision tasks using associative priming outlined above. Additionally, participants were required to respond via changes in eye fixation. This is an unusual experimental protocol and is therefore a little difficult to reconcile with other literature, particularly given the significant role of the cerebellum in ocular motor control. Although, as the authors point out, modulations of ocular motor control do not explain their findings. However, it may still be beneficial to use a more direct physiological measure rather than indirect behavioural measures.

A useful extension of the above paradigm would be to discern the influence of the cerebellum on more complex sentences that do not explicitly rely on word pair associations alone but rather on a wider semantic context. A common task that can fulfil this brief is that of semantic violations. Here sentences, in which the semantic context makes the final word highly predicable, are presented and then either the correct, congruent, final word is presented or an unexpected word that is incongruent with the semantic context is presented: this is the sematic violation.

In order to create sentences in which the semantic context means that the final target word is highly predictable, often experimenters first measure the cloze probability of the sentences. Here the sentences are presented without a final target word to a large number of participants who are asked to complete the sentence with the first word that comes to mind. The cloze probability is the proportion of people who reported the target word (Kutas & Federmeier, 2000).

We asked 194 English native speakers (111 females, mean age = 39.6, SD = 17) to complete a questionnaire (11 participants in the lab, and the rest online) in which they were asked to type in the first noun that came to their mind to complete sentences in which the final word was missing. Only the sentences where the final word had a cloze probability score higher than .90 (90%) were retained in the analyses, the remaining were classed as fillers. This high cloze probability score indicated that the semantic context made the final word highly predictable and these sentences were therefore good candidates for a task examining predictive language function.

If the cerebellum is playing a role in more complex predictive computations then it is likely that cTBS to the right cerebellum would affect processing during this task. Here, we have employed behavioural measures – accuracy and reaction times – for identifying whether or not the final word was the correct (expected) final word. However, given the length of time available to read the sentence and the final word, the sentences were presented in increments over the course of 2300-3800 ms and participants had up to two seconds to respond, it is therefore likely that later cortical processes will have interfered with any behavioural effects of cTBS on the cerebellum. The purpose of this task is to therefore check that participants are maintaining their attention to the stimuli throughout the course of the experiment. The principle measure of the modulation of cerebellar function through brain stimulation will therefore be through direct electrophysiological measures.

Event-related potentials

Previous research in the domain of cerebellar language function has not employed ERPs. This is principally due to the fact that data collected using this method primarily gives information regarding functioning in the cerebrum rather than the cerebellum. However, a recent technique has been employed whereby ERPs are used in combination with TMS, thus producing data on how processes in the cerebrum are affected by brain stimulation in other areas. For example, recent research has employed this technique to examine motor function in the cortex (Kuipers, van Koningsbruggen & Thierry, 2013). Further, the effects of midline cerebellar stimulation on Theta-Wave activity, a type of wave linked to emotional processing, have also been documented (Schutter & Van Honk, 2006).

To the best of our knowledge there are currently no published papers that have employed EEG and cerebellar TMS to examine the role of the cerebellum in language. Given the breadth of research examining cerebral language function using ERPs it will be beneficial to glean information regarding the influence of the cerebellum on these later well documented ERPs.

As this research is focused on language associations and predictions, the logical choice of ERP waveform to index any changes in cerebral function as a result of cerebellar TMS is the N400. The N400 has previously been used to index semantic processing in a range of paradigms such as semantic, associative and categorical priming (see Kutas & van Petten, 1988 for a review). But, this component is commonly elicited by critical words that are semantic violations (Kutas & Van Petten, 1988). These have been described in detail above. These stimuli are effective when using ERPs as they reliably elicit the N400 waveform.

Literature has shown that the N400 event-related brain potential is an index of language prediction. For example, researchers have examined the processing of words that precede predictable targets. They have manipulated gender (van Berkum, Brown, Zwitserlood, Kooijman & Hagoort, 2005; Wicha, Bates, Moreno & Kutas, 2003) and form (e.g. a/an; DeLong, Urbach & Kutas, 2005) and found increases in the N400 amplitude when these aspects were incongruent with the predicted target as compared to when they were congruent. This indicates that the processes that the N400 reflects use contextual information early in the sentence in order to activate likely future words (Kutas & Federmeier, 2011).

Further, changes in the N400 to incongruent endings are thought to index difficulty of processing in this context. This is supported by findings that, when a final word is highly predictable, the N400 elicited by words that are semantically similar to the intended target have smaller amplitudes as compared to unrelated words and are therefore easier to process (see Kutas & Federmeier, 2000 for a review).

Here I will utilise this ERP to index changes in predictive function during a semantic violations task. Changes in this waveform as a result of right cerebellar cTBS will indicate that the cerebellum is not only involved in the early stages of associative prediction but that this has effects on cerebral language function in the later stages of language processing. Potentially by indicating directly whether the stimulation of the right cerebellum modulates the difficulty of the processing of these stimuli.

Continuous theta burst stimulation

Finally, the key methodology used in this thesis is that of cTBS. This technique has been effectively employed to examine cerebellar language function (Argyropoulos, 2011; Argyropoulos & Muggleton, 2013) as well as a range of other non-motor cerebellar functions (see Tomlinson, Davis & Bracewell, 2013 for a review). This is a particularly effective methodology as it reliably affects cerebellar function and modulations of these functions are easily measured using reaction time tasks. Additionally, this technique has been shown to have wide reaching effects in terms of connected language networks (Cho et al., 2012).

Protocol. This thesis specifically employed cTBS rather than rTMS. This is partially for practical reasons, as cTBS is much faster to administer (40 seconds) as compared to rTMS (10 minutes). Although there is some discomfort relating to cerebellar cTBS this is experienced for a shorter time period. Further, research has shown that this method is well tolerated and safe (Tomlinson, Davis, Morgan & Bracewell, 2014). Additionally, research has demonstrated that the effects of cTBS are slightly more intense than those of rTMS (Huang, Edwards, Rounis, Bhatia & Rothwell, 2005). This method of administrating TMS has also more recently become an industry standard for the above reasons.

Intensity. I used 55% of maximum stimulator output (MSO) during the cTBS employed in this thesis. Fixed intensities are arguably a more appropriate method for cerebellar stimulation as compared to calculating a percentage of motor threshold (Stewart, Walsh & Rothwell, 2001) due to the differences in skull and muscle structure surrounding the cerebral cortex as compared to the cerebellar cortex. Further, fixed intensities have previously been shown to elicit behavioural changes in the domain of language (Argyropoulos, 2011; Argyropoulos & Muggleton, 2013; Lesage, et al., 2012).

Location. In terms of choice of location for cerebellar stimulation, in all experiments presented here I have used the same stimulation sites, namely 1 cm below and 3cm laterally, to the left and right, of the cerebellum. One reason for this is that previous research has indicated that this site in the right cerebellum is effective in causing behavioural changes in tasks that relate to predictive function (Lesage et al., 2012). Additionally, MRI research has shown that these locations tend to be much closer to the cerebellar cortex than more medial sites (Hardwick, Lesage & Miall, 2014), making it more likely that stimulation will effectively reach the intended area of the cerebellum. Finally, these areas are thought to stimulate cerebellar Crus II (Grimaldi et al., 2014). Crus I and II in the right cerebellum are areas that have been consistently linked to language function in fMRI research (Keren-Happuch, Chen, Ho & Desmond, 2014; Stoodley, 2012; Stoodley & Schmahmann, 2009; Stoodley & Schmahmann, 2015).

The choice of the same site in the contralateral hemisphere of the cerebellum as a control site in chapters 4 and 6 was driven by the need to keep the sensation of the cTBS consistent across experimental and control conditions. It is very difficult to deliver true sham TMS, this has been discussed in the previous chapter. We therefore chose a site that was more distant from our experimental site than some that have been used in the literature (Argyropoulos, 2011, medial and lateral right cerebellar sites were 3.5 cm apart), and a control site that would give parity of experience for the participant so that behavioural differences could not be attributed to differing levels of discomfort. This has not always been present in the literature, for example Lesage et al. (2012) used a vertex control site. Further, both the Argyropoulos (2011) and the Argyropoulos and Muggleton (2013) papers used experimental and control cTBS sites that were in the same cerebellar hemisphere. A combined rTMS and positron emission tomography study indicated that stimulation to the cerebellum affects multiple lobules (Cho et al., 2012), it is possible therefore that stimulation to one site affected functioning at the other.

A further motivation for using a consistent site throughout this thesis is that consistency of stimulation site has been lacking in the literature thus far. Research in this domain has used a wide array of cerebellar stimulation sites, detailed in the previous chapter. By being consistent I can be sure that the effects of cTBS to this specific region are replicable. Further, this consistency allows us to make comparisons between the three experiments detailed in this thesis. Comparisons between the experiments currently published are difficult given the range of sites that have been used.

Coil type. Finally, in all experiments detailed in this thesis a figure of eight coil was used. This has become industry standard for studies in this domain, for example Argyropoulos (2011) and Argyropoulos and Muggleton (2013) both used a figure of eight coil. Although some research has indicated that cerebellar stimulation with this type of coil may not affect motor activation in the cortex as indicated through MEPs (Hardwick et al., 2014), there is a breadth of research that has found effects using this coil type in cognitive domains like language (Arasanz, Staines, Roy & Schweizer, 2012; Argyropoulos, 2011; Argyropoulos & Muggleton, 2013; Oliveri et al., 2009; Rami et al., 2003; Tomlinson, Davis, Morgan & Bracewell, 2014).

Summary

In this chapter I have described the key methodologies that have been employed in this thesis. The next three chapters will detail how I have employed cTBS in order to modulate cerebellar language function. Chapter 4 uses cTBS in conjunction with associative priming. Chapter 5 uses cTBS in conjunction with backward and forward associative priming, a version of this chapter has been published in *The Cerebellum*. Finally, Chapter 6, which is intended for publication, employs cTBS in conjunction with ERPs to measure the N400 elicited by semantic violations, a version of this paper has been submitted to *The Journal of Neuroscience*.

Chapter 4

Continuous theta-burst stimulation modulates the role of the right cerebellum in associative priming

Abstract

Previous research has indicated that the cerebellum plays a role in associative, but not categorical priming. Researchers have modulated the predictive function in the right cerebellum using continuous theta burst stimulation (cTBS) to induce enhanced associative priming. However, these studies have not explicitly controlled for categorical relatedness across the two types of stimuli, and have used stimulation sites that are proximal to one another. Here we aimed to replicate previous findings with regards to associative as compared to categorical stimuli, with the addition of EEG data, while controlling for categorical relationships across the stimuli types and using sites that are more distally placed. We employed pairs of words that are opposites (e.g. black → WHITE), thus these pairs are both categorically and associatively related, and compared them to categorical pairs (e.g. black → BROWN) in a lexical decision task, where we examined the N400 ERP component to index semantic processing. Participants completed this task before and after cTBS, which was applied to each cerebellar hemisphere in two separate sessions. We found a significant effect of relatedness for the opposite but not the categorical stimuli, indicating that priming had occurred. However, we found no N400 effect, and no effects indicating that the cTBS had affected predictive semantic processing. Although there was no N400 the EEG showed a phonological mismatch negativity: this indicates that the stimuli were processed at the phonological level. The implication is that these stimuli were not processed semantically; this may therefore explain the absence of an effect of the cTBS, and implies that cerebellar cTBS only affects semantic but not phonological processing in the context of priming.

Introduction

Within the domain of cerebellar research, an expanding area of interest is the role of the cerebellum in cognitive processes. Beyond the typical view that the cerebellum is principally involved in motor control (Stoodley & Schmahmann, 2010; Timmann et al., 2008), more recent research has indicated that the role of the cerebellum also extends to verbal working memory (Altamura et al., 2007; Boehringer, Macher, Dukart, Villringer & Pleger, 2013; Ferrucci et al., 2008; Greve, Stanford, Sutton, & Foundas, 1999; Marvel & Desmond, 2015; Peterburs, Bellebaum, Koch, Schwarz & Daum, 2010; Ravizza et al., 2006; Schmahmann & Sherman, 1998; Silveri, Di Betta, Filippini, Leggio & Molinari, 1998), emotion (Fusar-Poli, Placentino, Carletti, Landi & Abbamonte, 2009; Schmahmann & Sherman, 1998; Schutter, van Honk, D'Alfonso, Peper & Panksepp, 2003; Schutter, Enter & Hoppenbrouwers, 2009; Turner et al., 2007), learning (Balsters & Ramnani, 2011; Fiez, Petersen, Cheney & Raichle, 1992; Raichle et al., 1994), visuospatial perception (Botez, Gravel, Attig & Vezina, 1985; Calhoun et al., 2001; Oliver, Opavsky, Vyslouzil, Greenwood & Rothwell, 2011; Schmahmann & Sherman, 1998; Stoodley, Valera & Schmahmann, 2011; Wallesch & Horn, 1990) and language (Schmahmann & Sherman, 1998; Stoodley & Schmahmann, 2009). Functional imaging techniques have indicated that the right hemisphere of the cerebellum, specifically lobules VI and VII (Crus I and II), is selectively active during language tasks (Keren-Happuch, Chen, Ho & Desmond, 2014; Stoodley, 2012; Stoodley & Schmahmann, 2009; Stoodley & Schmahmann, 2015). This cerebellar hemispheric asymmetry is linked to the cortical asymmetry present in language, the left cerebral cortex and the right cerebellar cortex co-activate (Jansen et al., 2005) and these areas are preferentially connected to one another (Ito, 1984).

As was detailed in previous chapters (Chapters 1 & 2) transcranial magnetic stimulation (TMS) has become a commonly used tool in the domain of language research within the cerebellum (Beaton, Allen-Walker & Bracewell, 2015). Although the specific mechanisms of action of TMS on the cerebellar cortex remain a topic for debate, it is hypothesised that single-pulse TMS activates the inhibitory Purkinje cells, leading to inhibition of the disynaptic dentato-thalamo-cortical facilitatory connections, which, in turn, leads to inhibition of the primary motor areas and prefrontal cortex in the contralateral cerebral hemisphere (Groiss & Ugawa, 2012; Iwata & Ugawa, 2005; Ugawa & Iwata, 2005). Conversely, other investigators have suggested that facilitation in motor and non-motor domains would involve cerebellar suppression, rather than activation (e.g. Koch et al., 2008; Picazio, Oliveri, Koch, Caltagirone & Petrosini, 2013), perhaps by suppressing the inhibitory Purkinje cells. Within the context of cerebellar TMS and language association both facilitatory and inhibitory effects have been reported; repetitive TMS (rTMS) tends to have been inhibitory, whereas facilitatory effects have been reported in experiments employing cTBS.

Principally, within this domain, researchers have tended to rely upon stimuli that are associatively related (Argyropoulos, 2011; Argyropoulos, Kimiskidis & Papagiannopoulos, 2011; Argyropoulos & Muggleton, 2013) or contain words with associative relationships within the context of short sentences (Lesage, Morgan, Olson, Meyer & Miall, 2012). For example, Argyropoulos (2011) used continuous theta-burst stimulation (cTBS) to test both phrasal associative priming (e.g. gift → HORSE) and categorical priming, where the prime is a subordinate of the target (e.g. apple → FRUIT), in a lexical decision task. They compared medial (1 cm below and 1 cm to the right of the inion) and lateral (1 cm below and 4.5 cm to the right of the inion) stimulation of the right cerebellum. cTBS over the medial site selectively enhanced phrasal associative priming as compared to the categorical priming, demonstrating a role of the right cerebellum in forward priming. Subsequent studies (Argyropoulos & Muggleton, 2013) also found increases in noun-to-verb associative priming (e.g. scissors → cutting) after stimulating other areas of the right cerebellum, although this time they were located in more distant lateral sites (1 cm below, 10 cm lateral of inion). These two studies provide evidence for a role of the right cerebellum in associative priming. However, neither of these studies have explicitly controlled for categorical relationships across the two types of stimuli. Further, their stimulation sites are both in the right cerebellar hemisphere which may result in the stimulation of one site affecting the other, previous literature using rTMS and positron emission tomography have shown that stimulation to a cerebellar hemisphere causes changes in glucose metabolism in multiple lobules (Cho et al., 2012).

Functional connectivity studies have shown the cerebellum to be linked with language areas in the rest of the brain, such as Broca's area and Wernicke's area (Booth, Wood, Lu, Houk & Bitan, 2007; Londei et al., 2010). However, functional connectivity has relatively poor temporal resolution. The modulation of electrophysiological measures (EEG-ERP; electroencephalogram - event related potential) using cTBS may therefore provide useful additional information regarding cerebellar interactions with the rest of the language network. Previous research has successfully combined EEG and cortical TMS to examine motor functioning (Kuipers, van Koningsbruggen & Thierry, 2013), and EEG and cerebellar TMS to examine emotional functioning (Schutter & Van Honk, 2006), this technique has also been successfully employed to examine language function elsewhere in this thesis (Chapter 6; Allen-Walker, Barbet, Bracewell, Mari-Beffa & Thierry, Submitted).

The N400 brain potential manifests as an increased negativity over central regions around 400 ms after stimulus onset for incongruent/unexpected as compared to congruent/expected words in priming. Thus, the N400 is a likely candidate for examination of predictive function in combination with cTBS. It has previously been used to index semantic processing in a range of paradigms such as semantic, associative and categorical priming (see

Kutas & van Petten, 1988, Kutas & Federmeier, 2011 for reviews). Although it is traditionally elicited by critical words that are semantic violations in a sentence (Kutas & Van Petten, 1988), the presence of the N400 during associative priming and the use of associative priming in much of the literature in this domain mean that ERP measures, specifically the N400, might be a useful adjunct to a replication of previous associative priming results. The manipulation of predictive associative function in the cerebellum may modulate the N400 further clarifying the role of the cerebellum in associative priming and how it might interact with the larger language network.

The aim of the present study is to attempt to replicate the above findings regarding associative as compared to categorical stimuli by applying cTBS to the left and right cerebellar hemispheres, with the addition of ERP measures examining changes to the N400. We will measure the reaction times and priming size of responses to related and unrelated (priming size calculated as unrelated minus related) categorical and associative stimuli before and after stimulation. Based on the research conducted by Argyropoulos and colleagues (Argyropoulos, 2011; Argyropoulos & Muggleton, 2013), we hypothesise that there will be increased priming after right cerebellar cTBS for the associative stimuli but not for the categorical stimuli, while cTBS to the left cerebellar hemisphere will not affect priming size for either word type. Further, we expect that any changes in priming will be reflected in modulations of the N400.

Methods

Participants

Sample size was estimated *post hoc* using G*Power 3.1 (Heinrich Heine University, Düsseldorf, Germany) after analysis of the first 8 participants. Here the 3-way (2 x 2 x 2 analysis of variance; ANOVA) interaction of interest had resulted in an effect size of η_p^2=.47 (which converts to an f effect size of .92). This effect size in combination with an alpha of

0.05 was used to estimate the number of participants required. The minimum repeated measures correlation that we ever observed in this task across any pair of conditions was 0.62 producing a power of 1, where power should be above 0.90. Using the same parameters an *a priori* estimation of sample size produces a minimum required sample of 6 participants. However, in order to fully counterbalance the experiment a total of 20 participants were therefore collected.

Twenty undergraduate and graduate students at Bangor University (11 female) aged 21-32 (M=26.25; SD=3.81). Nineteen right-handed participants and one left-handed participant were all native speakers of English, with normal or corrected-to-normal vision. Standard exclusion criteria for TMS studies were applied: participants were not selected if they had an artificial heart valve, ever had metal fragments in their eyes, ever had any metal or shrapnel in their body, ever had any implanted electrical devices, had any heart problems, had participated in a brain stimulation experiment within the last seven days, or if they had been stimulated before with adverse effects, if they had ever suffered from a neurological or psychiatric illness, if anyone in their family had a history of seizures, had a history of fainting, suffer from migraines, had recently been binge drinking or taken recreational drugs, or if they were pregnant. The participants were tested following the safety guidelines established by Bangor University. The procedure and experiment were approved by the Ethics Committee of the School of Psychology at Bangor University and every participant gave their informed consent before taking part.

Stimuli

The stimuli comprised 40 pairs of words that were opposites, 40 categorically related pairs that used the same primes as for the opposites stimuli. The associative strength for the opposite pairs was significantly higher than for the categorical pairs (t(39)=15.36, p<.001), using the University of South Florida Word Association Norms (Nelson, McEvoy &

Schreiber, 1998). There were also 80 unrelated word pairs that again used the same primes, and with the same targets but reassigned to unrelated primes. Finally, there were 80 pairs of words with non-word targets. The non-word targets were pseudowords created either by changing a vowel to another vowel or by swapping two consonants ensuring all resulting stimuli were pronounceable but had no known meaning in either English or Welsh. Therefore, two-thirds of the stimuli were real-word targets and one third were non-word targets, see Table 2 for example stimuli.

Table 2. Example stimuli.

Stimulus Type	**Related**	**Unrelated**	**Non-word**
Opposite	black → WHITE	black → FALL	black → GERL
Categorical	black → BROWN	black → CLOSE	black → HEGH

Task

Participants were asked to respond as quickly and accurately as possible via button press in a lexical decision task (LDT). Left and right buttons on a response box were used, one for existing words and the other for non-words, response sides were fully counterbalanced by cTBS hemisphere and between participants i.e. in the first session (both pre and post cTBS) half of the participants responded to real words with the left button and non-words with the right, this was reversed in the second session, and half *vice versa*; while half of participants experienced right cTBS first and left second and half *vice versa*. In each trial a fixation cross was presented for 250 ms, then the prime for 150 ms, between the prime and the target there was an inter-stimulus interval of 25, 50 or 75 ms, then the target was presented until response. After the response had been made there was a 500 ms interval before the next trial began.

TMS Apparatus

Stimulation was delivered using a 70 mm figure of eight coil connected to a Magstim Super Rapid Transcranial Magnetic Stimulator (Magstim, Whitland, UK). The coil was positioned tangentially to the scalp with the handle pointing upwards, producing a downward current in the cerebellum. This coil position has proven optimal for suppressing the contralateral motor cortex in single-pulse TMS (e.g. Oliveri, Koch, Torriero & Caltagirone, 2005) and has been shown to successfully interfere with cognitive processes such as procedural learning in 1 Hz rTMS paradigms (e.g. Torriero, Oliveri, Koch, Caltagirone & Petrosini, 2004).

TMS Locations

cTBS was applied to the left and right cerebellum, 1 cm below and 3 cm lateral to the inion. This is thought to stimulate cerebellar Crus II (Grimaldi et al., 2014). This location has previously been shown to be an effective area to stimulate when trying to affect the right cerebellar hemisphere's predictive function (Lesage et al., 2012; Oliveri et al., 2009).

TMS Protocol

A cTBS protocol was used. A burst of three pulses was delivered at 50 Hz frequency; this burst was repeated at an interval of 200 ms; the whole run lasted for 40 seconds (given 600 pulses in total). This protocol has previously proven reliable for producing behavioural change (Arasanz, Staines, Roy & Schweizer, 2012; Argyropoulos, 2011; Argyropoulos & Muggleton, 2013) and has also been shown to be well tolerated and safe (Tomlinson, Davis, Morgan & Bracewell, 2014).

TMS Intensity

The stimulation intensity was set at 55% of maximum stimulator output for all participants. Although TMS experimenters often define their stimulation intensity on the basis of each participant's motor threshold, several recent cerebellar studies have used fixed intensities as this procedure is more appropriate for cerebellar stimulation (Argyropoulos, 2011; Argyropoulos & Muggleton, 2013; Lesage, et al., 2012).

Procedure

To begin with, participants were fully informed of the risks associated with TMS. They were given a brief explanation of the history of the method and how it acts on the brain. After screening and informed consent have been received, participants were given the opportunity to experience the sensation of TMS. Single pulses were delivered at the approximate site of stimulation beginning at 30% of MSO and rising in increments of 5% to 55% of MSO. At any point, the participants could choose to stop and withdraw if they found the sensation too uncomfortable. The first pre-stimulation session of the LDT was then completed, followed by the stimulation. After a seven-minute delay participants performed the LDT again, since a delay after the administration of cTBS has been shown to enhance behavioural effects (Huang, Edwards, Rounis, Bhatia & Rothwell, 2005). Throughout the session, the participants were asked to stay seated in the same chair to avoid disruption of the effect of the cTBS on the cerebellum. After a week, the participants returned and completed a second session structured in the same way as the first session but without the information and consent, which was designed to cover both sessions.

EEG Recording and Analysis

Electroencephalographic (EEG) data were recorded continuously at a rate of 1 kHz in reference to electrode Cz with an online bandpass filter set between 0.01- 200 Hz from 64 Ag/AgCl electrodes using SynAmp2 amplifiers (Neuroscan Inc., El Paso, TX, USA). Electrodes were attached to an elastic cap (Easycap^{TM}, Herrsching, Germany) and placed according to the extended 10-20 convention. The ground electrode was placed at FPz. Bipolar electrodes were placed to the left of the left eye and to the right of the right eye (HEOG) and above and below the right eye (VEOG) to record eye movement artefacts.

Impedances were kept below 5 kΩ for the 64 recording electrodes and below 10 kΩ for the eye electrodes.

Before segmentation, continuous EEG activity was low-pass filtered using a zero phase shift digital filter with a cut-off frequency of 20 Hz and high-pass filtered with a cut-off frequency of 0.1 Hz. Eye blinks were mathematically corrected based on the procedure advocated by Gratton, Coles and Donchin (1983). After correction, any trial with amplitude exceeding 75 μV at any point within an epoch and at any recording site except VEOG and HEOG was discarded from analysis. After visual inspection to dismiss major remaining artefacts, continuous EEG activity was segmented into epochs ranging from -100 to 1000 ms after stimulus onset. Baseline correction was performed in reference to pre-stimulus activity, and individual averages were digitally re-referenced to the global average reference. Nine individual datasets were discarded due to excessive noise and/or alpha contamination leading to undetectable early components (P1-N1 complex) in two or more sessions. Only correct trials were kept for the analyses.

Contrary to our expectation there was no N400 present for the unrelated as compared to the related stimuli; specifically, there was not a negative peak over central electrodes (Cz, C1, C2, CPz, CP1 and CP2) during the expected time window of 350 to 450 ms. However, there was an earlier negative peak present over right fronto-central electrodes, specifically Cz, FCz, C2, C4, FC2 and FC4. This pattern is typical of the PMN (phonological mismatch negativity; Connolly & Phillips, 1994; Vaughan-Evans, Kuipers, Thierry & Jones, 2014). We therefore measured amplitudes over these sites between 275 and 400 ms, where our PMN was maximal. Although the peak reported here is slightly later than the classical peak described in the literature, later peaks identified as the PMN have been described in experiments using visual, rather than auditory, word stimuli (e.g. Vaughan-Evans, Kuipers, Thierry & Jones, 2014).

Design and Analyses

First, we compared performance before and after each cTBS session (pre-post – from now on referred to as Phase). In addition, we compared the side of stimulation, left or right cerebellar hemispheres. Finally, priming effects for opposite and categorical pairs were calculated by comparing Related and Unrelated conditions.

Participants were presented with 240 trials, 160 featuring word targets (“Yes” responses) and 80 featuring non-word targets (“No” responses). From the “Yes” responses, 40 corresponded to associatively related targets (i.e. opposites) and 120 to associatively unrelated ones. Associative relatedness proportion was 0.17, which is low enough to prevent participants from engaging in top-down strategies (Neely, 1976; 1991). These trials were presented randomly for each participant and each phase.

For reaction times (RT) data the first 10 trials were discarded (as practice trials) as were all correct trials outside of 2 standard deviations from the mean for each participant from each condition; the remaining correct “Yes” responses were averaged. The resulting means were then submitted to a 2 Phase (Pre, Post) x 2 Hemisphere (Left, Right) x 2 Relatedness (Related, Unrelated) repeated measures ANOVA. This was followed up by the analysis of priming sizes using a 2 Phase (Pre, Post) x 2 Hemisphere (Left, Right) design, again for both Opposites and Categorical pairs. Priming sizes were calculated according to convention, RT for unrelated stimuli minus RT for related ones.

Accuracy data represent the proportion of correct “Yes” answers also excluding the first 10 trials as practice trials, and were analysed using the 2 x 2 x 2 design described above.

Finally, the mean amplitudes for the PMN were analysed using the same 2 x 2 x 2 design outlined above, with an additional 2 x 2 analysis of difference waves (unrelated minus related), in a similar analysis to the priming sizes described above.

Results

Table 3. **Mean** (standard deviation) reaction times and average accuracy rates per condition.

		Pre-Left	**Pre-Right**	**Post-Left**	**Post-Right**
Categorical	**Related**	**547.15** (181.17)	**520.00** (130.03)	**515.77** (185.23)	**482.58** (132.35)
		0.90	0.92	0.94	0.93
	Unrelated	**552.16** (204.97)	**513.80** (118.64)	**515.74** (184.11)	**490.71** (137.57)
		0.91	0.93	0.93	0.93
Opposite	**Related**	**517.50** (158.31)	**486.44** (121.25)	**472.93** (138.33)	**455.33** (130.62)
		0.95	0.97	0.98	0.98
	Unrelated	**525.89** (164.28)	**491.67** (113.36)	**483.65** (130.36)	**468.00** (123.72)
		0.95	0.96	0.97	0.96

Reaction Times

A 2 (Phase) x 2 (Hemisphere) x 2 (Relatedness) repeated measures ANOVA for the Categorical stimuli indicated that there was a significant main effect of Phase [F(1,19)= 11.19, p=.003, η_p^2=.37]. There were no other significant main effects or interactions (p>.132). However, the same analysis for the opposites stimuli indicated a significant main effect of Phase [F(1,19)=24.91, p<.001, η_p^2=.57] and a significant main effect of Relatedness [F(1,19)=12.76, p=.002, η_p^2=.40]. No other main effects or interactions were significant (p>.080; Table 3).

Priming Size

As the principle aim of this task was to elicit priming we therefore examined priming size (Figure 3). There were no main effects or interactions for priming size for the categorical stimuli (p>.359) or for the opposites stimuli (p>.581).

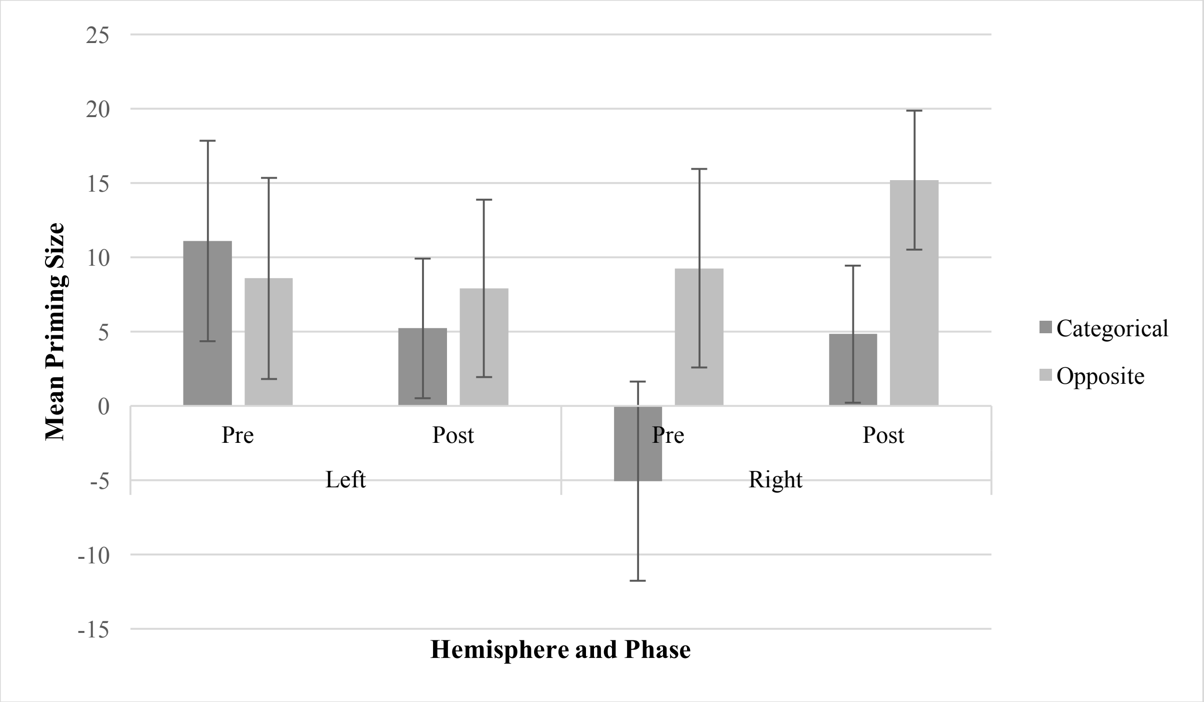

Figure 3. Mean priming size (unrelated reaction time minus related reaction time) for categorical and opposite word pairs, split by phase and hemisphere. Error bars depict standard error of the mean.

Accuracy

For the categorical stimuli there was a significant main effect of Phase [F(1,19)=6.87, p=.017, η_p^2=.27]. There were no other main effects or interactions (p>.100).

There was a main effect of Phase on the accuracy for opposites stimuli [F(1,19)=10.16, p=.005, η_p^2=.35]. There were no other main effects or interactions (p>.065; Table 3).

ERP Results

Table 4. **Mean** (standard deviation) of average amplidues of the PMN during the 275 to 400 ms time window.

		Pre-Left	Pre-Right	Post-Left	Post-Right
Categorical	**Related**	1.72 (0.72)	1.44 (1.32)	1.62 (1.05)	1.93 (1.57)
	Unrelated	1.11 (1.05)	1.47 (0.98)	1.80 (1.12)	1.95 (1.62)
Opposite	**Related**	1.37 (1.34)	2.16 (1.02)	2.28 (1.14)	2.32 (1.45)
	Unrelated	1.34 (1.01)	1.65 (0.93)	1.63 (0.90)	1.87 (1.06)

The ERP results (Table 4; Figures 4 & 5) indicated no significant main effects of interactions for the categorical stimuli (p>.085). This finding was also reflected in the difference waves, where mean amplitudes for the related pairs were subtracted from the unrelated pairs: again there were no main effects or interactions (p>.085).

However, for the opposites stimuli there was a marginal main effect of Phase [F(1,10)=4.17, p=.068, η_p^2=.29], a main effect of Relatedness [F(1,10)=4.89, p=.050, , η_p^2=.33], and a significant interaction between Phase and Relatedness [F(1,10)=8.47, p=.016, η_p^2=.46]. No other main effects or interactions were significant (p>.135). These effects were reflected in the difference waves where there was a main effect of Phase [F(1,10)=8.47, p=.016, η_p^2=.46]. No other main effects or interactions were significant (p>.166).

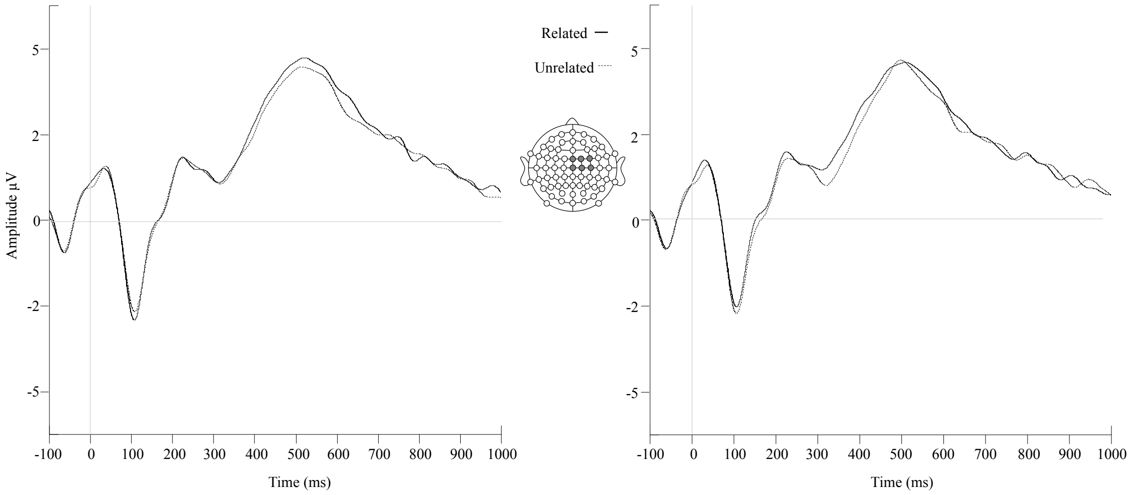

Figure 4. Grand average ERP waveforms showing the PMN for the categorical (left) and opposite (right) stimuli for six right fronto-central electodes (linear derivation of Cz, FCz, C2, C4, FC2 and FC4) for related (solid lines) and unrelated (dashed lines).

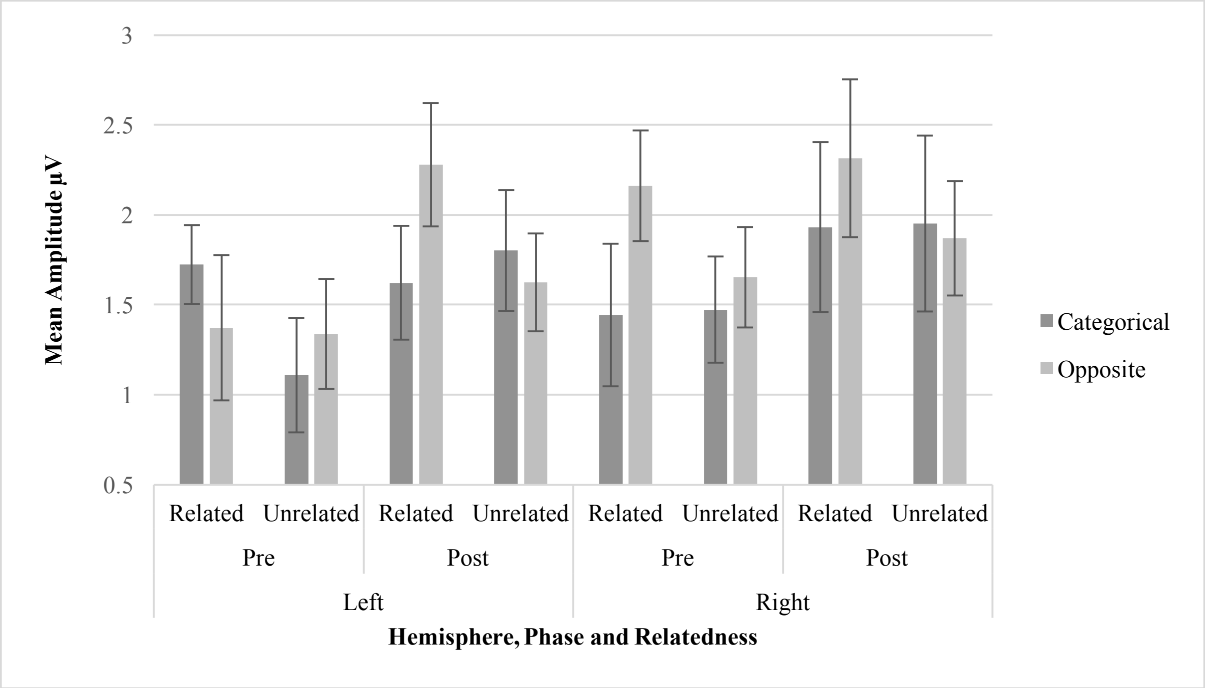

Figure 5. PMN mean amplitudes for each condition for categorical and opposite stimuli (275-400 ms, error bars represent SEM).

Discussion

Previous research using cTBS has indicated that the right cerebellum is involved in priming, specifically associative priming, i.e. words that are likely to co-occur in speech, rather than categorical priming, i.e. words that have a close relationship in terms of their semantic meaning. cTBS to the right cerebellar cortex causes associative, rather than categorical, priming size to be selectively enhanced (Argyropoulos, 2011; Argyropoulos & Muggleton, 2013). Here we sought to replicate these findings using pairs of words that were both associatively and categorically related as compared to categorically related only. Our stimuli therefore control for the categorical relationships between the words for both pairs – making any changes as a result of cTBS purely an effect of associative strength rather than of differences in type of stimulus. Additionally, we wished to replicate these findings using stimulation sites that were less proximal than those previously used in the literature, namely by stimulating sites in each cerebellar hemisphere, rather than using experimental and control sites that were both in the right cerebellar hemisphere (e.g. Argyropoulos, 2011; Argyropoulos & Muggleton, 2013). Finally, we aimed to replicate these findings with the addition of ERP data, specifically aiming to examine the N400, a wave often used to index semantic prediction (Kutas & Federmeier, 2011), and commonly found in associative priming tasks (Kutas & van Petten, 1988; Kutas & Federmeier, 2011). Cerebellar cTBS has previously been found to modulate EEG waves associated with emotion (Schutter & Van Honk, 2006) and language function (Allen-Walker, Barbet, Bracewell, Mari-Beffa & Thierry, Submitted, Chapter 6).

First, we found significant main effects of Phase on the reaction times and accuracy to both the opposite and categorical stimuli. This is likely due to practice effects, as a result of completing the same task twice. Additionally, we found a main effect of Relatedness for the reaction times to opposite stimuli, indicating that priming is present for these stimuli, participants were faster for the related than the unrelated stimuli. No such effect was present for categorical stimuli, indicating that the associative strength, and therefore the priming effect, is indeed higher for the opposite as compared to categorical stimuli. We were expecting to find a significant interaction between Phase and Hemisphere of stimulation for the opposites priming size; however, this effect was not present.

Additionally, we expected to find a similar effect for the N400; however, the N400 effect was not seen in our data. Instead, a PMN for the opposites stimuli was present. We therefore examined the PMN and found a main effect of relatedness, where there was a larger negativity for the unrelated as compared to the related stimuli. There was also a main effect of Phase on the PMN for the opposites, likely due to a practice effect. Finally, for the opposites stimuli there was a significant interaction between Phase and Relatedness, again this is likely due to a larger practice advantage for related as compared to unrelated stimuli, with a decreased, and therefore facilitated, PMN for the related stimuli in the post phase. There were no PMN effects for the categorical stimuli.

These results did not match our hypotheses. We did not find significant effects of cTBS on priming size for the opposite rather than the categorical stimuli; our results are therefore not in keeping with previous findings indicating that cTBS over the right cerebellar hemisphere selectively affects associative rather than categorical stimuli (Argyropoulos, 2011; Argyropoulos & Muggleton, 2013). However, the presence of a PMN rather than an N400 implies that in order to complete this task only phonological processing was required, whereas semantic processing was not required. The PMN is an index of phonological expectancy and presents as a larger negativity when the initial phoneme of the expected word does not occur (Connolly & Phillips, 1994), this wave is distinct and dissociable from the N400 wave (Newman & Connolly, 2009), and previous literature has suggested that the PMN is pre-lexical whereas the N400 is post-lexical (Connolly & Phillips, 1994; Newman &

Connolly, 2009), and therefore this could imply that the task completed did not require semantic processing (although this is not to say that semantic processing did not occur at all). This proposal is supported by the reaction times presented here, with the average for correct trials across all conditions being 502 ms. This time is within the time window that contains the N400 wave (200-600ms after stimulus onset; Kutas & Federmeier, 2011) and suggests that the response decisions were made without the input of the processing which produces the N400 wave. The lack of behavioural modulations as a result of cTBS presented here, in a task that has previously been shown to be behaviourally modulated, might be explained by the absence of the N400. As these stimuli were not processed semantically it may be that the role of the cereebullum is specifically semantic but as there is an absence of semantic processing no effect of cerebellar stimulation is observed. This would support the body of literature that argues that the cerebellum plays a predictive role in semantic language function (Lesage et al., 2012; Moberget, Gullesen, Andersson, Ivry & Endestad, 2014).

The results detailed in this chapter could be taken as support for models of reading, for example PDP models, such as the triangle model, a connectionist model that argue that the different components of reading are distributed across units which represent the different aspects of word processing (Seidenberg & McClelland, 1989), which contains three units, orthography, phonology and semantics. In this model, there are two pathways from orthography to phonology, the first is direct and the second travels via semantic representations. As cerebellar cTBS did not affect associative priming and the presence of a PMN but not an N400 can be taken as support for this model. Here, in order for participants to complete the task, they needed only to access phonological representations but not semantic representations; this suggests that this task used only the first pathway, rather than accessing semantic representations in the second pathway.

The difference between the present study and previous priming studies in this domain might be explained by the difference in stimulation sites we employed (3 cm lateral to the inion) as compared to those used previously (1 cm laterally in Argyropoulos, 2011; 10 cm laterally in Argyropoulos & Muggleton, 2013). It is therefore *possible* that the mechanisms affected in Argyropoulos' work that resulted in increased priming are localised to areas that remained unaffected by the stimulation used here. However, our choice of site was designed to maximize stimulation over areas of the cerebellum linked to predictive function (Lesage et al., 2012; Grimaldi et al., 2014), and to stimulate the areas active during language tasks (Crus I and II; Stoodley & Schmahmann, 2009). Furthermore, the other experiments presented in this thesis have shown successful changes in predictive function at this site.

Previous literature in the domain of language prediction has used rTMS and found an effect on phonological prediction. Runnqvist et al. (2016) aimed to examine the internal modelling of speech via application of left and right rTMS to cerebellar crura I and II, after which participants completed three blocks of a priming task that encouraged errors. Prior to the presentation of target word pairs, which had to be read aloud, three word pairs were presented. The initial consonants of the first two pairs were the same as the target pair and the third word pair had an additional phonological overlap with the target pair, this primed errors (e.g. *sun mall – sand mouth – soap mate – mole sail*). They found that right cerebellar rTMS resulted in more errors and, in the first block, an increase in reaction time. They interpret these findings as evidence that the cerebellum employs internal models to 'self-monitor' speech production and that right cerebellar rTMS disrupts the updating of these internal models through disruption of verbal working memory and therefore the maintenance of a phonological goal. Here however, we have indicated that these stimuli were processed at the phonological level with no effect of stimulation. Perhaps the key requirement for the cereebullum to become involved in phonological prediction is therefore speech production itself. This is supported by a large body of literature which indicates that the cerebellum is involved in language articulation (Ziegler, 2015).

A possible limitation of this study is that we did not employ MRI guided cTBS. This is a common issue across all three experiments described in this thesis and will therefore be examined in more detail in the general discussion.

The absence of an N400 effect and the presence of a PMN implies that here participants have not utilised semantic processing in order to complete this task. Future research aiming to examine the role of the cerebellum in priming might wish to employ a task which ensures some amount of semantic processing has occurred. For example, in this thesis we have employed a semantic judgement task, in Chapter 6 participants had to report whether or not the target fitted with the previously presented semantic context produced by the earlier sections of sentence. This task successfully elicited an N400 which was modulated by cTBS. Additionally, Lesage et al. (2012) employed a task in which participants we asked to select the appropriate ending of a auditorially presented sentence. Although there was no electrophysiological measure of semantic processing, as the task required understanding of the sentence in order to perform it we can assume that semantic access occurred, and again here cerebellar rTMS successfully modulated semantic predictions.

In conclusion, although we have not replicated findings that suggest the cerebellum plays a role in associative rather than categorical priming, this finding does not rule out a role for the cerebellum in this function. Here we have shown that these stimuli were processed at the level of phonology but not necessarily at the level of semantics, this therefore indirectly supports the hypothesis that the cerebellum plays a role in semantic language prediction.

Chapter 5

Facilitation of fast backward priming after left cerebellar continuous theta-burst stimulation

A version of this has been published in *The Cerebellum*:

Allen-Walker, L. S. T., Bracewell, R. M., Thierry, G., & Mari-Beffa, P. (2017). Facilitation of fast backward priming after left cerebellar continuous theta-burst stimulation. *The Cerebellum*. DOI: 10.1007/s12311-017-0881-6

Abstract

Traditional theories of backward priming account only for the priming effects found at long stimulus onset asynchronies (SOAs). Here, we suggest that the presence of backward priming at short SOAs may be related to the integrative role of the cerebellum. Previous research has shown that the right cerebellum is involved in forward associative priming. Functional magnetic resonance imaging reveals selective activation of the left cerebellar hemisphere during backward priming; but what this activation represents is unclear. This paper aims to further explore this issue using continuous theta-burst transcranial magnetic stimulation (cTBS) and associative priming in a lexical decision task. We tested the hypothesis that the left cerebellum plays a role in backward priming and that this is dissociated from the role of the right cerebellum in forward priming. Before and after cTBS was applied to their left and right cerebellar hemispheres, participants completed a lexical decision task. Although we did not replicate the forward priming effect reported in the literature, we did find a significant increase in backward priming after left relative to right cerebellar cTBS. The results are discussed in the context of theories of cerebellar motor function as regards language function and cognitive models of backward priming.

Introduction

In cognitive neuroscience, associative priming is often used to understand how the brain encodes two events taking place in a sequence. In the case of language, some words tend to appear in a particular order, such as DOG-BONE, while they are less frequent in the reversed one (BONE-DOG). When participants are presented with the first word of the pair, responses to the second are usually facilitated, producing a priming effect referred to as associative priming (Neely, 1991). It is commonly understood that words are represented through associative networks, and that the presentation of the prime word (DOG) automatically spreads its activation to those units most closely linked to it (e.g. BONE). When the second word appears, overall responses are facilitated due to its higher level of activation compared to unrelated ones (e.g. ORANGE). This spread of activation is automatic in nature and is considered *not* to be based on expectancies (Collins & Loftus, 1975), explaining why this effect appears even when the words appear with a very short interval between them, from a 50-360 ms stimulus onset asynchrony (SOA; Posner & Snyder, 1975; Neely, 1976). At long SOAs (>500 ms), priming effects are more commonly attributed to strategic, top-down activation of expected words in memory (Neely, 1991).

A rather puzzling priming phenomenon is what has been termed backward priming, i.e., the increase in performance observed when the associated words are presented in the reversed order. Traditional theories of backward priming explain this as a process involving memory retrieval, particularly in lexical decision tasks (LDT). Here participants need to decide whether the second word of a pair is known or not (Word–Non-Word decision). When the target appears (e.g. DOG), the decision can be helped by strategically retrieving the previous word from episodic memory (e.g. BONE). If they are related, then the target must be a word; but if they are not related, then it could be either a word or a non-word, a conflict that will increase reaction times to unrelated pairs. Being a strategic process, such post-lexical semantic integration takes time and can only account for backward priming with long SOAs (Neely, 1991). However, backward priming has been repeatedly observed with short SOAs also (Kahan, Neely & Forsythe, 1999; Peterson & Simpson, 1989; Terrien, et al., 2013), which is inconsistent with the semantic integration theory. Some researchers have suggested that backward priming at short SOAs is probably due to the same process of spreading activation described above (Koriat, 1981). One difficulty posed by these models is that activation normally spreads only in the forward direction, presuming that the prime needs to appear before its target. As Koriat (1981) acknowledged, if we assume that feedback loops connecting prime and target representations exist, then spreading activation could account for backward priming at short SOA. Here we explore the possibility that these feedback loops might be represented in the cerebellum, given its role as a temporal prediction modeller.

The cerebellum has a very important role in the creation of associations between events or representations that are in a temporal sequence, creating both forward and backward links between them to improve both fluency and accuracy. Historically, this function of the cerebellum has been widely studied in sensorimotor control by pairing motor actions to their expected sensorial outcomes and *vice versa* (see Miall, Weir, Wolpert & Stein, 1993 for a review of classic models and empirical evidence). However, recent studies show that the cerebellum is also involved in the creation of more abstract relations, such as those at play in verbal working memory (e.g. Desmond, Gabrieli, Wagner, Ginier & Glover, 1997; Fiez et al., 1996; Chen & Desmond, 2005a, 2005b), grammar processing (Justus, 2004; Silveri, Leggio & Molinari, 1994) or writing (Planton, Jucla, Roux & Demonet, 2013; see Marien & Manto, 2015, for a recent review of language functions in the cerebellum). Such a wide range of functions suggest that the cerebellum acts whenever the system needs to link two computational units into a sequence, extending its influence beyond motor control to potentially any representation, including those used in language processing. Importantly for our purpose, lexical access could be part of it, providing a substrate where forward and backward connections can automatically activate each other, and potentially explain backward priming at short SOAs.

When studying the role of the cerebellum in language processing researchers have employed various techniques; for example by assessing different language functions including lexical and morphological access in cerebellar patients (Mariën, Engelborghs, Fabbro & De Deyn, 2001, Fabbro, Moretti & Bava, 2000); using neuroimaging techniques to reveal the activation of the cerebellum elicited by language-based tasks (e.g. fMRI techniques, Frings et al., 2006; Stoodley & Schmahmann, 2009; or Positron Emission Topography, PET, Fiez, Petersen, Cheney, & Raichle, 1992), functional connectivity (Booth, Wood, Lu, Houk & Bitan, 2008; Buckner, Krienen, Castellanos, Diaz & Yeo, 2011; Tomasi & Volkow, 2012) and transcranial direct current stimulation (tDCS; see Argyropoulos, 2015, for a review). In particular, researchers have used transcranial magnetic stimulation (TMS) to investigate the role of the cerebellum in predictive or associative priming (for a review, see Beaton, Allen-Walker & Bracewell, 2015). Some authors suggest that single-pulse TMS activates the inhibitory Purkinje cells, leading to inhibition of the disynaptic dentato-thalamo-cortical facilitatory connections, which, in turn, leads to inhibition of the primary motor areas and prefrontal cortex in the contralateral cerebral hemisphere (Groiss & Ugawa, 2012; Iwata & Ugawa, 2005; Ugawa & Iwata, 2005). Conversely, other investigators have suggested that facilitation in motor and non-motor domains would involve cerebellar suppression, rather than activation (e.g. Koch et al., 2008; Picazio, Oliveri, Koch, Caltagirone & Petrosini, 2013), perhaps by suppressing the inhibitory Purkinje cells. Indeed, within the context of cerebellar TMS and language association, both inhibitory and facilitatory effects have been reported.

TMS studies have not explored the role of the cerebellum in backward priming, but have instead focused on forward priming. For example, Argyropoulos (2011) used continuous theta-burst stimulation (cTBS) to test both phrasal associative priming (e.g. gift → HORSE) and categorical priming, where the prime is a subordinate of the target (e.g. apple → FRUIT), in a lexical decision task. They compared medial (1 cm below and 1 cm to the right of the inion) and lateral (1 cm below and 4.5 cm to the right of the inion) stimulation of the right cerebellum. cTBS over the medial site selectively enhanced phrasal associative priming as compared to the categorical priming, demonstrating a role of the right cerebellum in forward priming. Subsequent studies (Argyropoulos & Muggleton, 2013) also found increases in noun-to-verb associative priming (scissors → cutting) after stimulating other areas of the right cerebellum, although this time they were located in more distant lateral sites (1 cm below, 10 cm lateral of inion). In this case, the direction of the associative relation was not described and they used a different list of associated pairs, potentially explaining the difference in relevant locations. In any case, these two studies provide evidence for a role of the right cerebellum in associative and forward priming, opening the possibility that it could also be involved in associative backward priming.

Argyropoulos (2011) posits that the role of the cerebellum in language is predictive, placing this role in the context of widely held theories of the predictive role of the cerebellum in motor control (Miall & Wolpert, 1996; Wolpert & Kawato, 1998; Wolpert, Miall & Kawato, 1998). The cerebellum is homogenous in its internal architecture (Eccles, Ito & Szentagothai, 1967), leading to speculations that it performs a similar computation in non-motor and motor domains, such as that of verbal working memory (Desmond et al., 1997), and other types of higher order cognitive processes (Ramnani, 2006; Schmahmann, 2004), in our case language (Moberget, Gullesen, Anderson, Ivry & Endestad, 2014).

Further support for the predictive model of motor function applied to language comes from Lesage, Morgan, Olson, Meyer and Miall (2012). The authors applied repetitive transcranial magnetic stimulation (rTMS) to the right cerebellar hemisphere (1 cm below and 3 cm lateral of the inion) with the vertex as a control site. Participants listened to sentences in which the final noun could be predicted on the basis of the verb (e.g. "The man will sail the boat") or not ("The man will watch the boat"). Simultaneously, four different pictures were displayed on the screen and participants had to fixate on the picture depicting the final noun. Thus, the latency of the eye movement could be taken as an index of the predictability of the noun. They found that eye movement latencies for the predictable sentences were affected only after stimulation of the right cerebellum but not the vertex, illustrating the predictive role of the cerebellum in the representation of these unidirectional associations. The authors inferred a cognitive effect of rTMS, not predictable by a simple saccadic latency effect of stimulation as the error rates were the same across conditions.

Although no TMS studies have yet been conducted to establish whether the cerebellum is involved in backward priming, there is some indirect evidence in the fMRI study by Terrien et al. (2013). They examined forward and backward priming with short SOAs using fMRI to determine their neural correlates. They found activation of the right cerebellum in forward and backward priming, and of the left cerebellum only in backward priming, combined with activation in the right middle temporal gyrus. More generally, this work suggests that forward and backward priming are supported by separate functional brain networks. Their asymmetrical distribution across the hemispheres makes them good candidates for cerebellar cTBS.

In the current study, we aimed to examine the role of the cerebellum in both backward and forward priming with a short SOA during a lexical decision task. Following the results obtained by Argyropoulos and colleagues (2011, 2013), we predicted that forward priming would be significantly greater after right as compared to left cerebellar cTBS. We also predicted, following Terrien et al. (2013), that this pattern would be reversed for backward priming.

Methods

Participants

Sample size was estimated *a priori* using G*Power 3.1 (Heinrich Heine University, Düsseldorf, Germany). For a desired power of 0.90 or above, an expected effect size of 0.25 or above and an alpha of 0.05 we estimated the required sample size for this 2 x 2 x 2 analysis of variance (ANOVA). The minimum repeated measures correlation that we ever observed in this task across any pair of conditions was 0.6 producing a minimum required sample of 16 participants.

Nineteen students from Bangor University participated; nine male, between the ages of 20 and 30 (M = 24.2, SD = 2.1). Due to overall poor performance on the task, the data from a twentieth participant were discarded. Eighteen right-handed participants and one left-handed participant were all native speakers of English, with normal or corrected-to-normal vision. Standard exclusion criteria for TMS studies were applied: Participants were not selected if they had an artificial heart valve, ever had metal fragments in their eyes, ever had any metal or shrapnel in their body, ever had any implanted electrical devices, had any heart problems, had participated in a brain stimulation experiment within the last seven days, or if they had been stimulated before with adverse effects, if they had ever suffered from a neurological or psychiatric illness, if anyone in their family had a history of seizures, had a history of fainting, suffer from migraines, had recently been binge drinking or taken recreational drugs, or if they were pregnant. The participants were tested following the safety guidelines established by Bangor University. The procedure and experiment were approved by the Ethics Committee of the School of Psychology at Bangor University and every participant gave their informed consent before taking part.

Stimuli

Participants were presented with 144 related word pairs: 24 pairs of forward associatively related words, 24 pairs of backward related words and 24 pairs of associatively unrelated filler words, all presented twice (Table 5). Associative pairs were predominantly compound words following common practice in the backward priming literature (Chwilla, Hagoort & Brown, 1998; Franklin, Dien, Neely, Huber & Waterson, 2007; Kahan, Neely & Forsythe, 1999). We used the University of South Florida Word Association Norms (Nelson, McEvoy & Schreiber, 1998) to select the asymmetrically associated pairs. From these, we chose those with the highest level of recognition in British English after piloting them with a sample of our postgraduate students. As a result, the associative strength was significantly higher for the forward pairs (0.1%) than for the backward pairs (0.008%; t(11) = 2.56, p = .026) with no overlap in associative strengths between the two directions. Unrelated pairs had zero associative strength in all cases, which was significantly different from the forward associative pairs (t(22) = 2.31; p = .031), but not different from the backward ones (t(22) = 1; p = .329). Associative (forward/backward) and unrelated pairs did not differ in terms of semantic similarity (Pedersen, Patwardhan & Michelizzi, 2004) (path length of 0.152 and 0.147 respectively, p = .864), demonstrating that potential differences should be free of categorical semantic confounds. Participants were also presented with 144 unrelated word pairs, the 72 related pairs with the targets reassigned to other primes within each type of stimuli and presented twice. The participants were also presented with 288 non-word pairs. These pairs used the same primes described above and the targets were changed into non-words and paired with different primes. The non-word targets were pseudowords created either by changing a vowel to another vowel or by swapping two consonants ensuring all resulting stimuli were pronounceable but had no known meaning in neither English nor Welsh. Therefore, half of the stimuli were real-word targets and half non-word targets.

Table 5. Example stimuli.

Stimulus Type	Related	Unrelated	Non-word
Forward	pigeon → HOLE	pigeon → BACK	pigeon → BOCK
Backward	hole → PIGEON	hole → BOOK	hole → BOEK

Lexical frequency was obtained for primes and targets from the CELEX lexical database (Baayen, Piepenbrock & van Rijn, 1995) using the N-Watch program (Davis, 2005). There was no significant difference in lexical frequency between the primes and targets, t(23)=-0.54, p=.59. There was also no significant difference in length between primes and targets, t(23)=1.64, p=.115 (Table 6).

Table 6. Means and standard deviations for frequency and length.

Stimulus Type	Prime Frequency	Target Frequency	Prime Length	Target Length
Forward	164.88 (257.69)	218.70 (394.89)	4.75 (1.57)	4.08 (1.06)
Backward	218.70 (394.89)	164.88 (257.69)	4.08 (1.06)	4.75 (1.57)

Task

Participants were asked to respond as quickly and accurately as possible via button press in a lexical decision task (LDT). Keys ‘M’ and ‘Z’ on a keyboard were used, one for existing words and the other for non-words, and response sides were counterbalanced by cTBS hemisphere and between participants i.e., for both pre- and post-right cTBS, ‘M’ corresponded to real words and for pre- and post-left cTBS ‘Z’ referred to a real word, or *vice versa*. In each trial a fixation cross was presented for 250 ms, then the prime for 150 ms, then the target was presented until response. After the response had been made there was a 500 ms interval before the next trial began.

TMS Apparatus

Stimulation was delivered using a 70 mm figure of eight coil connected to a Magstim Super Rapid Transcranial Magnetic Stimulator (Magstim, Whitland, UK). The coil was positioned tangentially to the scalp with the handle pointing upwards, producing a downward current in the cerebellum. This coil position has proven optimal for suppressing the contralateral motor cortex in single-pulse TMS (e.g. Oliveri, Koch, Torriero & Caltagirone, 2005) and has been shown to successfully interfere with cognitive processes such as procedural learning in 1 Hz rTMS paradigms (e.g. Torriero, Oliveri, Koch, Caltagirone & Petrosini, 2004).

TMS Locations

cTBS was applied to the left and right cerebellum, 1 cm below and 3 cm lateral to the inion. This is thought to stimulate cerebellar Crus II (Grimaldi et al., 2014). This location has previously been shown to be an effective area to stimulate when trying to affect the right cerebellar hemisphere’s predictive function (Lesage et al., 2012; Oliveri et al., 2009).

TMS Protocol

A cTBS protocol was used. A burst of three pulses was delivered at 50 Hz frequency; this burst was repeated at an interval of 200 ms; the whole run lasted for 40 seconds (given 600 pulses in total). This protocol has previously proven reliable for producing behavioural change (Arasanz, Staines, Roy & Schweizer, 2012; Argyropoulos, 2011; Argyropoulos & Muggleton, 2013) and has also been shown to be well tolerated and safe (Tomlinson, Davis, Morgan & Bracewell, 2014).

TMS Intensity

The stimulation intensity was set at 55% of maximum stimulator output (MSO) for all participants. Although TMS experimenters often define their stimulation intensity on the basis of each participant's motor threshold, several recent cerebellar studies have used fixed intensities as this procedure is more appropriate for cerebellar stimulation (Argyropoulos, 2011; Argyropoulos & Muggleton, 2013; Lesage, et al., 2012).

Procedure

To begin with, participants were fully informed of the risks associated with TMS. They were given a brief explanation of the history of the method and how it acts on the brain. After screening and informed consent have been received, participants were given the opportunity to experience the sensation of TMS. Single pulses were delivered at the approximate site of stimulation beginning at 30% of MSO and rising in increments of 5% to 55% of MSO. At any point, the participants could choose to stop and withdraw if they found the sensation too uncomfortable. The first pre-stimulation session of the LDT was then completed, followed by the stimulation. After a seven-minute delay participants performed the LDT again, since a delay after the administration of cTBS has been shown to enhance behavioural effects (Huang, Edwards, Rounis, Bhatia & Rothwell, 2005). Throughout the session, the participants were asked to stay seated in the same chair to avoid disruption of the effect of the cTBS on the cerebellum. After a week, the participants returned and completed a second session structured in the same way as the first session but without the information and consent, which was designed to cover both sessions.

Design and Analyses

First, we compared performance before and after each cTBS session (pre-post – from now on referred to as Phase). In addition, we compared the side of stimulation, left or right cerebellar hemispheres. The order of the stimulation site was fully counterbalanced across participants and order effects were compared between groups (Right-Left, Left-Right). Finally, priming effects for forward and backward pairs were calculated by comparing Related and Unrelated conditions, as described in the stimuli section.

Participants were presented with 576 trials, 288 featuring word targets ("Yes" responses) and 288 featuring non-word targets ("No" responses). From the "Yes" responses, 96 corresponded to associatively related targets and 168 to associatively unrelated ones. The former included 48 Forward Related and 48 Backward Related pairs. Associative relatedness proportion was 0.17, which is low enough to prevent participants from engaging in top-down strategies (Neely, 1976; 1991). These trials were presented randomly for each participant and each phase.

Reaction times (RT) data were extracted by first eliminating responses to the first 10 practice trials and then averaging all correct "Yes" responses with RTs less than 2 SD away from the mean for each participant and in each condition. This data filtering was applied separately to Forward and Backward conditions. The resulting means were then submitted to a 2 Phase (Pre, Post) x 2 Hemisphere (Left, Right) x 2 Relatedness (Related, Unrelated) repeated measures ANOVA. This was followed up by the analysis of priming sizes using a 2 Phase (Pre, Post) x 2 Hemisphere (Left, Right) design, again for both Forward and Backward pairs. Priming sizes were calculated according to convention, RT for unrelated stimuli minus RT for related ones.

Accuracy data represent the proportion of correct "Yes" answers also excluding the first 10 practice trials, and were analysed using the 2 x 2 x 2 design described above. Finally, order effects related to the hemisphere of stimulation were also analysed by including Stimulation order (Left-Right, Right-Left) as a between-group variable.

Results

Table 7. **Mean** (standard deviation) reaction times and average accuracy rates per condition.

		Pre-Left	**Pre-Right**	**Post-Left**	**Post-Right**
Backward	**Related**	**519** (63) 0.95	**516** (60) 0.96	**493** (60) 0.94	**498** (71) 0.95
	Unrelated	**527** (67) 0.93	**529** (61) 0.94	**513** (62) 0.92	**509** (60) 0.93
Forward	**Related**	**523** (59) 0.95	**526** (67) 0.94	**500** (63) 0.94	**498** (56) 0.94
	Unrelated	**533** (58) 0.91	**537** (62) 0.92	**508** (57) 0.91	**505** (50) 0.92

Results from participants who received cTBS on the right first were compared to those who received the stimulation in the reverse order. There was no order effect nor any interaction with the other variables in the design. Therefore, data were collapsed across groups for further analysis.

RT averages per participant per condition were analysed with a 2 (Phase) x 2 (Hemisphere) x 2 (Relatedness) repeated measures ANOVA separately for Backward and Forward trials. For Backward pairs participants were overall 20 ms faster after TMS than before [F(1, 18) = 34.72, p < .001, η_p^2 = .66]. They were also on average 13 ms faster in Related than in Unrelated trials [F(1, 18) = 58.09, p < .001, η_p^2 = .76]. No effect of hemisphere was found (F<1). Importantly, there was a significant interaction between Phase, Hemisphere and Relatedness [F(1, 18) = 4.05, p = .05, η_p^2 = .18]. No other interactions were significant.

To further investigate the three-way interaction we analysed changes in backward priming size across Phase (Pre-Post) and Hemisphere (Left-Right). Backward priming was increased exclusively after Left Hemisphere stimulation [15 ms larger, t(19)=3.44, p=.003], retaining virtually the same size when the Right Hemisphere was involved (-2 ms, Figure 6).

There was no significant effect on accuracy (Table 7).

Forward priming stimuli were analysed in the same manner. As with the backward pairs, overall RTs were 28 ms faster after cTBS than before [F(1, 18) = 59.14, $p < .001$, $\eta_p^2 = .77$]. Related targets were responded to 9 ms faster than unrelated ones [F(1, 18) = 8.91, p = .008, $\eta_p^2 = .33$]. No other effects nor interactions were significant.

Responses to related targets were 3% more accurate than unrelated ones [F(1, 18) = 6.40, p = .02, $\eta_p^2 = .26$]. There were no other significant effects on accuracy.

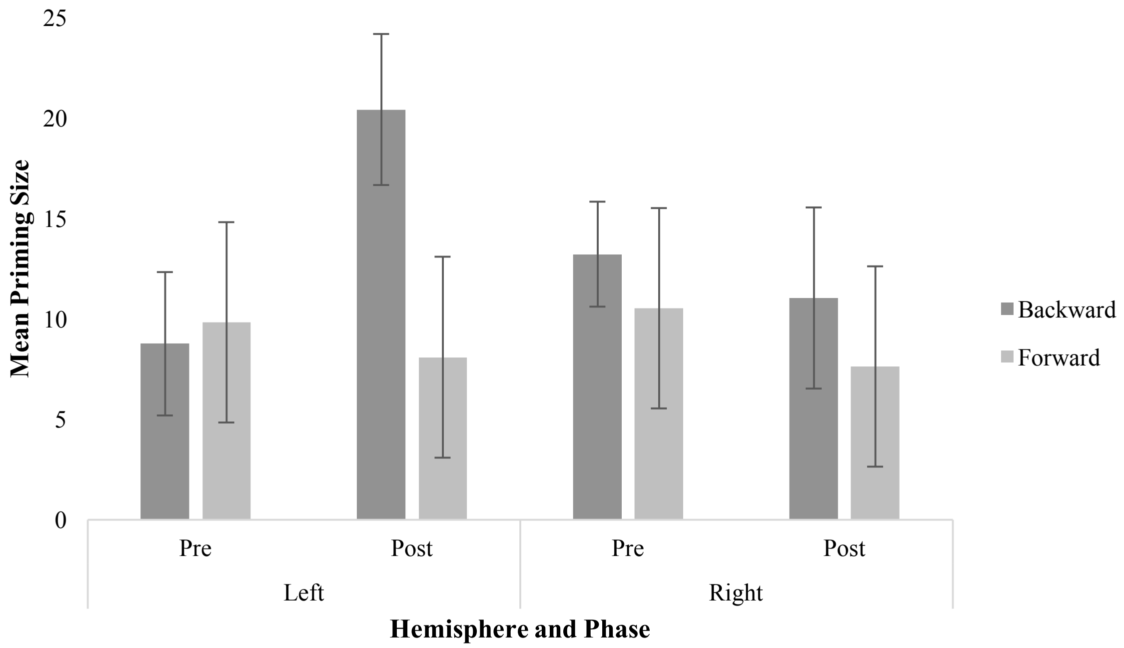

Figure 6. Mean priming size (unrelated reaction time minus related reaction time) for backward and forward word pairs, split by phase and hemisphere. Error bars depict standard error of the mean.

Discussion

In this study, we investigated the role of the cerebellum in backward associative priming at short SOAs in an LDT. Backward priming is commonly explained as a result of strategic processes of post-lexical integration (Neely, 1991) that are understood to take time and thus require long SOAs. Backward priming at short SOAs represents a challenge for this theoretical account (Chwilla, Hagoort & Brown, 1998), and has been attributed to the fast and automatic spread of activation in associative networks (Collins & Loftus, 1975, Koriat, 1981). Such networks are understood to be built on unidirectional connections, where the prime needs to appear before the target for priming to occur. Backward priming would thus need the inclusion of feedback loops in the associative network (Koriat, 1981). Some previous studies have pointed to the cerebellum as a likely locus for the representation of these associations both in forward (Argyropoulos, 2011; Argyropoulos & Muggleton, 2013) and backward priming (Terrien et al., 2013). Therefore, we examined the impact of right and left cerebellar cTBS on forward and backward associative priming with short SOAs.

Participants were generally faster after cTBS regardless of the stimulated hemisphere, probably due to practice effects. However, a significant reduction in reaction time and a significant increase in priming size were found only for backward related stimuli after left hemisphere stimulation, in the absence of any change for forward priming for either stimulation side. This validates our hypothesis that backward priming at short SOAs critically involves the left cerebellar hemisphere.

A role of the left cerebellar hemisphere in backward priming is consistent with previous fMRI research. Terrien et al. (2013), for instance, found specific activation for backward priming in the right inferior occipital gyrus and the middle temporal gyrus at short SOAs. These areas were interpreted as being responsible for mechanisms of post-lexical integration. In the same study, the authors found activation in the left cerebellum, but they did not hypothesise a role for this region in priming.

As discussed earlier, current theories of backward priming refer to mechanisms taking place strategically after lexical activation (Neely, 1991). These mechanisms include episodic retrieval of the prime in order to facilitate a lexical decision on the target, if it is related. This episodic retrieval is not automatic as it implies conscious post-lexical integration of both the items, and thus requires time. While these theories are a good fit for paradigms using long SOAs, they cannot account for the results obtained here. Here, we used an interval of 150 ms between prime and target onsets, making it unlikely that top-down mechanisms would account for the backward priming effect. Instead, our results are better explained by the spreading of activation from the prime to all units associatively connected to it (Collins & Loftus, 1975). This flow of activation is traditionally understood as being unidirectional needing the prime to appear *before* the target (e.g. pigeon → HOLE): this provides no system through which activation can travel backwards from target to prime when the prime appears *after* the target (e.g. hole → PIGEON). To account for this, the mechanism needs to include some form of feedback loop between the two units in the sequence (Koriat, 1981). In this research, we have found some initial evidence that such feedback loops can be dissociated from the forward connections and that they could critically involve the left cerebellar hemisphere.

Indeed, the presence of automatic and fast feedback loops in the left cerebellar hemisphere may explain why Terrien et al. (2013) found activation in the left cerebellum with backward priming at short SOAs. Given that the left cerebellum interacts preferentially with the contralateral cerebral hemisphere (Jansen et al., 2005), it could feed into a wider lexical processing system, possibly involving the right occipito-temporal network (O'Hare, Dien, Waterson & Savage, 2008). In any case, no activation in the left cerebellum was found in studies using long SOAs, suggesting that it has a more specific role in the formation of automatic associations rather than episodic ones.

Feedback loops in the cerebellum have long been used to explain the formation of automatic, predictive, sensory-motor associations, and becoming responsible for the fluency and accuracy of sensory-guided actions (Miall, Weir, Wolpert & Stein, 1993). For instance, Moberget et al. (2014) used fMRI to show that these models of cerebellar motor function are transferable to language. They presented sentences in which the final target was highly predictable, such that congruent sentences featured an expected word, whereas the incongruent sentences ended in an unexpected fashion. They found activation in the right cerebellar hemisphere when the target word was predictable and a higher level of activation when the prediction was violated. They proposed that this pattern of activation is consistent with models of sensorimotor control, supporting the idea that cerebellar computation may extend to the domain of abstract associations (including that of verbal working memory, Desmond et al., 1997). These studies, however, have focused mostly on the forward aspect of prediction within such models. Our study contributes to this area by showing that these models also apply to feedback loops in language processing.

One of these models which may be pertinent to this chapter is the MOSAIC (modular selection and identification for control) model (Wolpert & Kawato, 1998). This is a model of motor function which includes paired forward and inverse models which are acquired and used together. It has been suggested that this model may map onto the closed loop circuits known to exist between the cerebellum and the cortex (Haruno, Wolpert & Kawato, 2003). Forward models predict outcomes, whereas inverse models learn the appropriate commands for each context. Inverse models are selected based on prediction errors, i.e. inconsistencies between the forward model predictions and actual events (Ito, 2008). These inconsistencies arise from the forward models and sensory information. In this way, before a movement, the

MOSIAC model can select appropriate controllers (Haruno, Wolpert & Kawato, 2001; Wolpert & Kawato, 1998). As we have seen, models of motor function can be applied to language functioning in the cerebellum; this model may explain the findings presented here. The findings of this chapter indicate that there is a role for the cerebellum in backward priming and we have posited here that this role may involve feedback loops. These are relevant here where presumably prediction error has occurred, when the prime (e.g. BOX) is presented activation spreads to the words that would likely follow it (e.g. ROOM). In the context of backward priming these expected words are not presented and instead a word that is related to the prime but asymmetrically is presented (e.g. CARDBOARD). It may be that the inverse models, which are utilized as a result of prediction errors, are here causing the facilitation in backward priming. Our findings here could then support the MOSAIC model. However, this model describes multiple paired forward and inverse models, here we found no effects for forward priming, which would likely rely upon forward models. Our findings then could be argued in support of inverse models in the cerebellum but these models may not be paired in the way posited in this theory.

Our experiment was designed to test backward priming and thus substantially differs from the original studies by Argyropoulos and colleagues (Argyropoulos, 2011; Argyropoulos & Muggleton, 2013). Therefore, it is not entirely surprising that we did not find increases of forward priming at short SOA following right cerebellar cTBS. The inclusion of backward priming led us to include word pairs that were strongly asymmetric, including a mixture of compound and non-compound words unlike in the studies by Argyropoulos and colleagues. In addition, the stimulation sites were different across studies (3 cm laterally in the present study; 1 cm laterally in Argyropoulos, 2011; 10 cm laterally in Argyropoulos & Muggleton, 2013). Therefore, it is possible that forward priming is localised to areas that remained unaffected by the stimulation in our experiment. Our choice of site was driven by a need to maximize stimulation over areas of the cerebellum linked to predictive function (Lesage et al., 2012; Grimaldi et al., 2014), and other experiments presented in this thesis have shown successful changes in predictive function at this site (Chapters 4 and 6).

To conclude, we report evidence that the left hemisphere of the cerebellum is involved in backward associative priming at short SOAs. cTBS applied to the left cerebellum specifically reduced reaction times to related relative to unrelated stimuli inducing enhanced priming. It is thus likely that forward and backward priming critically involve different areas of the cerebellum. These results are important for current theories of backward priming, especially at short SOAs, since they point to a potential contribution of cerebellar feedback loops in predictive associative networks. It also extends the involvement of the cerebellum in predictive associations beyond sensory-motor control to the sphere of cognitive functioning.

Chapter 6

A combined continuous theta-burst stimulation and event-related brain potential investigation of right cerebellar involvement in lexico-semantic predictions.

A version of this is has been submitted to *The Journal of Neuroscience*

Abstract

Previous literature indicates that the right hemisphere of the cerebellum is involved in associative priming and prediction during language processing. In the present study, we aimed to examine this role further by taking advantage of event-related brain potentials (ERPs) to monitor cerebral cortical responses during sentence processing after right cerebellar continuous Theta-Burst Stimulation (cTBS). We examined the modulations in amplitude of the N400 effect, a reliable index of difficulty of lexico-semantic processing, before and after right, as compared to left, cerebellar cTBS. Participants read sentences with highly predictable endings (e.g. 'The jockey put the saddle on his…') in a semantic violation task: half of the sentences had a congruent final word (e.g. 'horse') and the other half an incongruent one (e.g. 'neck'). The results showed, beyond the typical N400 effect (increased negativity for incongruent as compared to congruent words), a significant reduction of this effect specifically after right cerebellar cTBS. This was driven by changes in the N400 to incongruent stimuli. We argue that this diminished N400 effect indicates that cTBS to the right cerebellum facilitated the error-related feedback loops in internal models in the cerebellum and therefore facilitated the processing of linguistic incongruences later in the cerebral language network. This further shows that the cerebellum applies similar computations across both motoric and language related cognitive domains, and that these computations are applicable not only to the processing of pairs of words but also complex sentences. For the first time, we also showed that the modulation of cerebellar language function can be effectively measured via EEG methodologies.

Introduction

Traditionally the cerebellum has been associated with motor function (Courchesne & Allen, 1997; Ito, 1984; Marr, 1969; Thach, Goodkin & Keating, 1992). However, emerging data suggest that the cerebellum also plays a role in higher-order cognitive domains such as emotion (Duggal, 2005; Liotti et al., 2000; Schutter & van Honk, 2006), verbal working memory (Schmahmann & Sherman, 1998; Stoodley & Schmahmann, 2009) and language (Desmond & Fiez, 1998; Fulbright et al., 1999; see Murdoch 2010 for a review). Traditional models of motor function suggest that the role of the cerebellum is to associate two events in a temporal sequence, particularly in terms of sensorimotor control by pairing motoric actions with expected sensory outcomes (see Miall, Weir, Wolpert & Stein, 1993 for a review; Miall & Wolpert, 1996; Wolpert & Kawato, 1998; Wolpert, Miall & Kawato, 1998). These associative computations are thought to be driven by internal models, that is, neural representations of specific objects (e.g. a body part) that facilitate prediction of contextual actions involving each object (Ito, 2008; Moberget, Gullesen, Anderson, Ivry & Endestad, 2014; Wolpert, Ghahramani & Jordan, 1995). More recently, researchers have suggested that these internal models may apply to the other cognitive domains in which the cerebellum plays a role (Schmahmann, 2004), such as verbal working memory (e.g. Desmond, Gabrieli, Wagner, Ginier & Glover, 1997; Fiez et al., 1996; Chen & Desmond, 2005a, 2005b) and language (Beaton, Allen-Walker & Bracewell, 2015; Moberget et al., 2014).

Language functioning in the cerebellum is lateralised to the right cerebellar hemisphere in the majority of individuals, and the right cerebellar hemisphere preferentially co-activates with the contralateral cerebral hemisphere (Jansen et al., 2005). Recently, fMRI has been employed in order to produce topographical maps of the linguistic function in the cerebellum (for reviews, see Stoodley & Schmahmann, 2010; 2015), which indicate that activation relating specifically to non-motor aspects of language, as compared to the motoric aspects of language, are localised in Crus I and II of the right postero-lateral cerebellum. For instance, fMRI studies showed activation in the right lateral cerebellum during noun-to-verb association tasks: Frings et al. (2006) asked participants to generate verbs in response to nouns, and compared this to participants reading the verbs that had previously been reported. They found that activation in Crus I was an indicator of verb generation specifically, whereas the articulation of verbs elicited activation in paravermal lobule VI in both hemispheres.

Furthermore, fMRI evidence linked this role of the cerebellum in language prediction to cerebellar internal models. Moberget and colleagues (2014) presented sentences in which the final critical word was highly predictable. The sentences ended with either a congruent (expected) or incongruent (unexpected) final word. They found activation in the right cerebellar hemisphere (Crus I/II) when the critical word was the predicted word as compared to a random word ending a random string of words, and furthermore that this activation was bilateral and more widespread when the prediction was violated (congruent vs. incongruent final word). They therefore suggested that the cerebellum may apply similar functional computations in multiple domains, and that these findings are consistent with internal models of sensorimotor control. They argued that the increased activation in the incongruent as compared with the congruent condition supports this view as internal models of motor control employ error-based learning in order to constantly update themselves. The application of cerebellar internal models to a range of domains is a particularly compelling theory given the homogeneity of cerebellar cellular structure (Eccles, Ito & Szentagothai, 1967).

In order to explore cerebellar functioning, researchers have employed transcranial magnetic stimulation (TMS) to examine the behavioural changes resulting from the modulation of cerebellar function. Some authors suggest that single-pulse TMS activates the inhibitory Purkinje cells, leading to inhibition of the disynaptic dentato-thalamo-cortical facilitatory connections, which, in turn, leads to inhibition of the primary motor areas and prefrontal cortex in the contralateral cerebral hemisphere (Groiss & Ugawa, 2012; Iwata & Ugawa, 2005; Ugawa & Iwata, 2005). Conversely, other investigators, using theta burst stimulation (TBS), a technique that uses a higher frequency of pulses over a shorter period eliciting slightly more intense effects than rTMS (Huang, Edwards, Rounis, Bhatia & Rothwell, 2005), have suggested that facilitation in motor and non-motor domains would involve cerebellar suppression, rather than activation, perhaps by suppressing the activity of inhibitory Purkinje cells (e.g. Koch et al., 2008; Picazio, Oliveri, Koch, Caltagirone & Petrosini, 2013). Indeed, within the context of cerebellar TMS and language association, both inhibitory and facilitatory effects have been reported.

The application of cerebellar TMS has further supported the role of the cerebellum in predictive language processing. Argyropoulos (2011) used cerebellar continuous theta-burst stimulation (cTBS) to study lexical associative priming. Argyropoulos performed cTBS over the right cerebellum (1 cm below and 4.5 cm to the right of the inion) and over the right medial cerebellum (1 cm below and 1 cm to the right of the inion). Before and after stimulation participants completed a lexical decision task employing semantically related pairs where the prime is a subordinate of the target (e.g. apple and FRUIT), and phrasal associates where the prime and the target co-occur in speech but are not semantically related (e.g. gift and HORSE). The results showed a selective increase in associative priming size after, as compared to before, right medial stimulation and as compared to right lateral stimulation. This effect was supported by later research from the same team. For instance, Argyropoulos and Muggleton (2013), who also employed a lexical decision task, used categorically related word pairs (e.g. applause-clapping) and associated word pairs (e.g. scissors-cutting), with two stimulation sites, a right medial site (1 cm below and 1 cm to the right of the inion) and a right lateral site (10 cm to the right of the inion). The results showed that right lateral cerebellar cTBS selectively enhanced associative priming as compared to categorical priming. In conjunction, these studies evidence a role for the cerebellum in associative priming rather categorical priming, and the authors posit that these results suggest that the cerebellum is making predictions that could prepare cortical language areas for language processing. Overall, results obtained using associative as compared to categorical priming demonstrate that the cerebellum is playing a role in priming specifically for word pairs that are likely to co-occur in speech. This may be a reflection of computations that are applied to more general predictive language processing.

Further support for the suggestion that the cerebellum applies a generalised model to all domains is found in Lesage, Morgan, Olson, Meyer and Miall (2012), who found that right lateral cerebellar repetitive TMS (rTMS) selectively inhibited language prediction. Participants listened to sentences with the final noun word missing. In half of the trials this noun could be predicted by the verb used: e.g. ‘The man will sail the boat’ as compared to ‘The man will watch the boat’. While listening to these sentences, participants viewed pictures of four objects and the agent of the sentence. Participants fixated on the agent until they could predict the final word at which point they fixated on the item that they were expecting to finish the sentence. rTMS over the right lateral cerebellum was used in the experimental condition (1 cm below and 3 cm to the right of the inion) and vertex stimulation and no stimulation in the control conditions. After right cerebellar rTMS, the participants were significantly slower at predicting the final noun when it could be predicted from the verb, as compared to before stimulation. This was not found for those sentences where the final word could not be predicted, or in the vertex stimulation and no stimulation control conditions. The authors posit that the right cerebellum, with input from cortical language areas such as Broca’s area, is providing an efferent copy of internalised speech, thus allowing the cerebellum to aid speech prediction, further supporting the application of sensorimotor models of cerebellar function to the cognitive domains.

Functional connectivity studies have shown the cerebellum to be linked with language areas in the rest of the brain, such as Broca's area and Wernicke's area (Booth, Wood, Lu, Houk & Bitan, 2007; Londei et al., 2010). However, fMRI has relatively poor temporal resolution. The moderation of electrophysiological measures (EEG-ERP; electroencephalogram - event related potential) via cTBS may therefore provide a more detailed picture of the cerebellum interactions with the rest of the language network. Previous research has successfully combined EEG and cortical TMS to examine motor functioning (Kuipers, van Koningsbruggen & Thierry, 2013), and EEG and cerebellar TMS to examine emotional functioning (Schutter & Van Honk, 2006).

The N400 brain potential manifests as an increased negativity over central regions around 400 ms after stimulus onset for incongruent/unexpected as compared to congruent/expected words in sentences. Thus, the N400 is a likely candidate for examination of predictive function in combination with cTBS, potentially resulting in modulation of the N400 effect resulting from changes in processing incongruent endings. It has previously been used to index semantic processing in a range of paradigms such as semantic, associative and categorical priming (see Kutas & van Petten, 1988, Kutas & Federmeier, 2011 for reviews). It is traditionally elicited by critical words that are semantic violations in a sentence (Kutas & Van Petten, 1988). Semantic violations occur when a word appears incongruent with the preceding sentential context. The N400 effect is especially sensitive to cloze probability, in other words, it is especially enhanced when a critical word is highly expected but not presented, for example, 'I take coffee with cream and *dog'* (Kutas & Hillyard, 1980). Moreover, literature has shown that the N400 event-related brain potential is an index of language prediction. For example, researchers have more recently examined the processing of words that precede predictable targets. In this context researchers have manipulated gender (van Berkum, Brown, Zwitserlood, Kooijman & Hagoort, 2005; Wicha, Bates, Moreno &

Kutas, 2003) and form (e.g. a/an; DeLong, Urbach & Kutas, 2005) and found increases in N400 amplitude when these aspects did not match the predicted target as compared to when they matched. This indicates that the processes that the N400 reflects use contextual information early in the sentence in order to activate likely future words (Kutas & Federmeier, 2011). This is supported by findings that when a final word is highly predictable, the N400 elicited by words that are semantically similar to the intended target have smaller amplitudes as compared to unrelated words and are therefore easier to process (see Kutas & Federmeier, 2000 for a review). Given the above evidence that the N400 is an index of semantic prediction it is therefore likely that the manipulation of predictive function in the cerebellum will modulate it, further clarifying the role of the cerebellum in language prediction and how this might interact with the larger language network.

Current literature has indicated that the cerebellum is involved in language (see e.g. Murdoch, 2010 for a review), and that it is functionally linked with other cerebral areas associated with the language network (see e.g. Cho et al., 2012; Booth et al., 2007; Londei et al., 2010). TMS evidence has further revealed that the role of the cerebellum in language may be predictive (Argyropoulos, 2011; Argyropoulos & Muggleton, 2013; Lesage et al., 2012); however, these studies have relied upon the associations between pairs of words, either on their own or in the context of a short sentence, and have employed only behavioural measures which cannot directly measure cerebral spontaneous responses. It would be beneficial to further examine this function in the context of longer and more complex sentences that are more representative of spontaneous speech. Furthermore, the relationship between the cerebellum and language has not yet been explored through the combined use of cTBS and EEG-ERP. This combination will reveal temporal information as regards interactions between the cerebellum and the cerebral language network. Additionally, it may further our understanding of the role of internal models of language processes in the cerebellum

(Moberget et al., 2014) with regards to more complex stimuli and how modulation of these cerebellar internal models may impact later language processing in the cortex.

In the present study, participants read sentences with congruent – and highly predictable – endings, or incongruent endings, and were requested to judge the semantic correctness of the critical final word. EEG recordings were taken during the task, which was completed before and after cTBS was applied to the one cerebellar hemisphere, and again around a week later, when cTBS was applied to the other cerebellar hemisphere. We expected accuracy in the judgement task to be very high overall, and reaction times to reflect mainly ease of response due to task repetition, and potential response bias resulting in a reduction in speed for the incongruent endings which required a negative answer. Principally, we were interested in changes in the EEG-ERP N400 effect resulting from cTBS. cTBS was applied to the right lateral cerebellum, and to the left lateral cerebellum as a control site. The N400 effect was taken as an index of changes in cerebellar functioning associated with language processing. We predicted that right lateral cTBS would modulate the N400 effect whereas left cerebellar cTBS would not. We hypothesised that this change would be a result of enhanced predictive processing in the cerebellum, resulting in easier processing of the incongruent stimuli.

Methods

Participants

Twenty-two native speakers of English (9 females; mean age = 23.32, SD = 3.58) gave written consent to take part in the experiment approved by the Ethics Committee of Bangor University, United Kingdom. All were undergraduate and graduate students from Bangor University. All were right handed and had normal or corrected-to-normal vision.

No data were recorded for one participant who withdrew before the experiment was complete. The data from two participants were discarded due to poor accuracy in at least one session (see below for details). The EEG data of four participants had to be dismissed due to excessive artefacts (see below for details). Therefore, statistical analyses of N400 mean amplitudes are based on 15 individual datasets and reaction times (RTs) on 19 individual datasets.

Standard exclusion criteria for TMS research were employed: no participant had an artificial heart valve, ever had metal fragments in their eyes, any metal or shrapnel in their body, any implanted electrical devices, any heart problems, participated in a brain stimulation experiment in the last seven days, ever suffered from a neurological or psychiatric illness, family history of seizures, suffered from migraines, recently been binge drinking or taken recreational drugs, and no participant was pregnant.

Stimuli

The participants were presented with 70 experimental sentences and 90 filler sentences. For 50% of the sentences the final words were semantically incongruent, see (1), given the semantic context of the sentence; the other 50% were semantically congruent and highly predictable, see (2):

1) To make coffee sweeter you can add tree.
2) To make coffee sweeter you can add sugar.

The same sentences were used for both congruent and incongruent trials. For the incongruent trials the final words were matched to different sentences, these pairings changed for each of the four times participants completed the task. The incongruent final words were rotated in each session in order to retain the N400 negativity to incongruent words over the course of the experiment. The same congruent sentences were used for all four sessions.

These sentences were chosen because they had a high cloze probability (mean = 0.97, SD = 0.02)[1].

TMS Apparatus

The stimulation was administered using a 70 mm figure of eight coil connected to a Magstim Super Rapid Transcranial Magnetic Stimulator (Magstim, Whitland, UK). The coil was positioned tangentially to the scalp with the handle pointing superiorly. This directs the current upwards, producing a downward current in the cerebellum. This has been found to be effective for suppressing the contralateral motor cortex when using single pulse TMS (Oliveri, Koch, Torriero & Caltagirone, 2005) and 1 Hz rTMS paradigms have previously been shown to interfere with cognitive processes such as procedural learning (e.g. Torriero, Oliveri, Koch, Caltagirone & Petrosini, 2004).

TMS Locations

cTBS was applied to the right lateral cerebellum, 1 cm below the inion and 3 cm to the right. This location has previously been shown to be an effective area to stimulate when trying to affect the cerebellum's predictive function (Lesage et al., 2012, Oliveri et al., 2009). This area is thought to be stimulating cerebellar Crus II (Grimaldi et al., 2014). The left lateral cerebellum was used as a control site, 1 cm below the inion and 3 cm laterally, so that the participants' experience of cTBS was consistent across sessions.

TMS Protocol

A cTBS protocol was used. Bursts of 3 pulses were delivered at a 50 Hz frequency, each set separated by an interval of 200 ms, the whole run lasted for 40 seconds (600 pulses in total). This protocol has proven to be reliable method for inducing behavioural changes (Arasanz, Staines, Roy & Schweizer, 2012; Argyropoulos, 2011; Argyropoulos &

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[1] 194 English native speakers (111 females, mean age = 39.6, SD = 17) answered to a questionnaire (11 participants in the lab, and the rest online) in which they were asked to type in the first noun that came to their mind to complete sentences in which the final word was missing. Only the sentences with a final word with a cloze probability score higher than .90 (see Appendix D for individual scores) were then kept for the ERP experiment.

Muggleton, 2013) and has also been shown to be well tolerated and safe (Tomlinson, Davis, Morgan & Bracewell, 2014).

TMS Intensity

The stimulation intensity was set at 55% of maximum stimulator output for all participants. Although studies often define their intensity on the basis of each participant's motor threshold, it has been posited that this method may not be appropriate for cerebellar research (Stewart, Walsh & Rothwell, 2001) and more recent studies have tended to use fixed intensities (Argyropoulos, 2011; Argyropoulos & Muggleton, 2013; Lesage et al., 2012) as motor threshold is not necessarily representative of the cerebellar depth etc.

Procedure

Prior to participation, participants were fully informed of the risks associated with, and exclusion criteria relating to, TMS experiments. They were also given a brief history of the use of TMS and an opportunity to experience the sensation of TMS on their wrist and head. Participants were given single pulses of TMS over the cerebellum starting at 30% of MSO and increasing in increments of 5% until 55% was reached. Throughout the participants were given the opportunity to withdraw.

There were two sessions, which all participants attended. In each session participants would complete the task twice, once before and once after the application of cTBS. In one session participants had cTBS to the right lateral cerebellum and in the other they were given cTBS over the control site. The order of these sessions was counterbalanced. The two sessions were held at least one week apart.

During the sentence reading and judgement task, participants were instructed to monitor stimuli presented in the centre of a 19" CRT monitor in bold Courier New font, size 18. The sentences were presented in white on a black background. A fixation cross was presented first for 1300 ms, followed by the beginning of the sentence, presented all at once for 1300 ms. The final 2 to 5 words were then presented one at a time, centrally on screen for 500 ms. The presentation of the final word was preceded by a randomly selected ISI of 250, 275, 300, 325 or 350 ms in order to reduce cross-trial ERP contamination. The final word was presented for 2000 ms or until a response was made. There was then a 500 ms ISI before the onset of the following trial. In order to ascertain that the participants were engaging with the sentences participants were required to indicate whether the final word of the sentence was the correct or incorrect ending. Responses were made on a keyboard with the left and right hands using the M and Z keys (Figure 7).

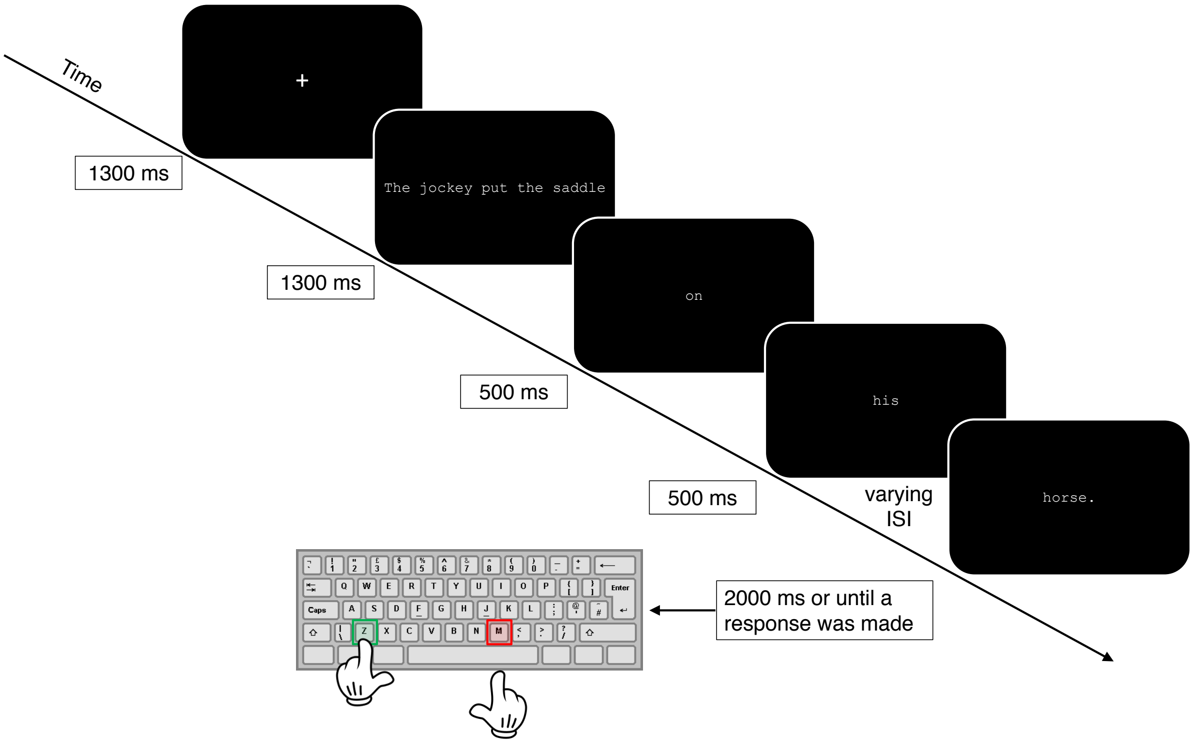

Figure 7. Example of stimulus sequence and expected response.

Response sides were counterbalanced, that is, for the first day, both pre and post cTBS, participants would use one orientation and then switch in the following day. This was so that any effects post-cTBS could be attributed to the TMS rather than to changes in response location. Participants needed around 20 minutes to complete the task.

EEG Recording and Analysis

Electroencephalographic (EEG) data were recorded continuously at a rate of 1 kHz in reference to electrode Cz with an online bandpass filter set between 0.01- 200 Hz from 64 Ag/AgCl electrodes using SynAmp2 amplifiers (Neuroscan Inc., El Paso, TX, USA). Electrodes were attached to an elastic cap (Easycap^{TM}, Herrsching, Germany) and placed according to the extended 10-20 convention. The ground electrode was placed at FPz. Bipolar electrodes were placed to the left of the left eye and to the right of the right eye (HEOG) and above and below the right eye (VEOG) to record eye movement artefacts. Impedances were kept below 5 kΩ for the 64 recording electrodes and below 10 kΩ for the eye electrodes.

Before segmentation, continuous EEG activity was low-pass filtered using a zero phase shift digital filter with a cut-off frequency of 20 Hz and high-pass filtered with a cut-off frequency of 0.1 Hz. Eye blinks were mathematically corrected based on the procedure advocated by Gratton, Coles and Donchin (1983). After correction, any trial with amplitude exceeding 75 μV at any point within an epoch and at any recording site except VEOG and HEOG was discarded from analysis. After visual inspection to dismiss major remaining artefacts, continuous EEG activity was segmented into epochs ranging from -200 to 1000 ms after stimulus onset. Baseline correction was performed in reference to pre-stimulus activity, and individual averages were digitally re-referenced to the global average reference. Four individual datasets were discarded due to excessive noise and/or alpha contamination leading to undetectable early components (P1-N1 complex) in two or more sessions, and two due to insufficient sweeps resulting from poor accuracy. Only correct trials were kept for the analyses. The average number of trials per congruence condition and per recording was 32.61 (SD = 2.43); there was no significant difference between the number of trials per condition [F(7, 112) = 0.64, p = .721); all comparisons p>.726].

N400 mean amplitudes were measured over 6 fronto-central sites: CZ, C1, C2, FCZ, FC1, FC2, between 350 and 450 ms, which is the 100 ms around the peak predicted by the literature, and indeed the grand average observed peak. We found that N400 amplitudes were larger over fronto-central sites. Previous literature has shown a more frontal N400 to be affected by semantic priming (Deacon, Mehta, Tinsley & Nousak, 1995). Furthermore, we observed that the N400 was right lateralised, with a larger negativity on the right as compared to left electrodes of interest. This has previously been referred to in the literature as ‘paradoxical lateralisation’ given the specialisation of the left hemisphere in language (Lau, Philips & Poeppel, 2008). Because of this observed lateralisation we added Electrode Location as an additional fourth factor in our experiment (Left, Midline and Right).

Design and Statistical Analysis

We examined the following three factors: before and after the administration of cTBS, hereafter referred to as Phase (Pre or Post cTBS), side of cerebellum stimulated, referred to as Hemisphere (Left or Right) and Congruence (Congruent or Incongruent final word), leading to a 2 x 2 x 2 experimental design.

Statistical analyses were performed using repeated measures analyses of variance (ANOVA) with the following factors, Phase (Pre or Post), Hemisphere (Left or Right) and Congruence (Congruent or Incongruent), and the interactions between them. In addition, for the analysis of the N400 mean amplitudes we added the fourth factor Electrode Location (Left, Midline or Right), as mentioned above.

For both RT and ERP analyses the data from two participants were discarded due to insufficient accuracy in at least one session (less than 60%), indicating that they were not engaging enough in the sentence reading and comprehension task. In addition, prior to the analysis of RTs incorrect trials from the remaining participants were removed (3.2% of trials), responses below 200 ms (see e.g. Baayen, 2008) were also removed (0.2% of trials) and the data were trimmed 2.5 SD around the mean for each participant in each condition (2.9% of trials). This procedure left a total of 5000 trials across all participants.

Results

Behavioural Results

Table 8. **Mean** reaction times (standard deviation) and mean accuracy.

	Pre-Left	**Post-Left**	**Pre-Right**	**Post-Right**
Congruent	**676.14** (260.93) 0.98	**613.00** (242.34) 0.98	**681.43** (283.83) 0.98	**587.32** (251.14) 0.97
Incongruent	**697.65** (240.48) 0.98	**633.14** (238.01) 0.98	**696.45** (252.94) 0.98	**625.12** (238.01) 0.98

Accuracy rates were overall very high (mean = .98, SD =0.03). Analysis of the accuracy data indicated no significant differences or interactions (p>.230) (Table 8).

Analysis of the RT data showed, as expected, a significant main effect of Phase [F(1,18)=49.54, p<.001, η_p^2=.73] and of Congruence [F(1,18)=8.98, p=.008, η_p^2=.33]. RTs were overall faster for congruent as compared with incongruent items, as well as in the post-cTBS vs. pre-cTBS phase (most probably a repetition effect). There were, however, no other significant main effects or interactions (p>.266) (Table 8). Mean reaction times are displayed in Figure 8.

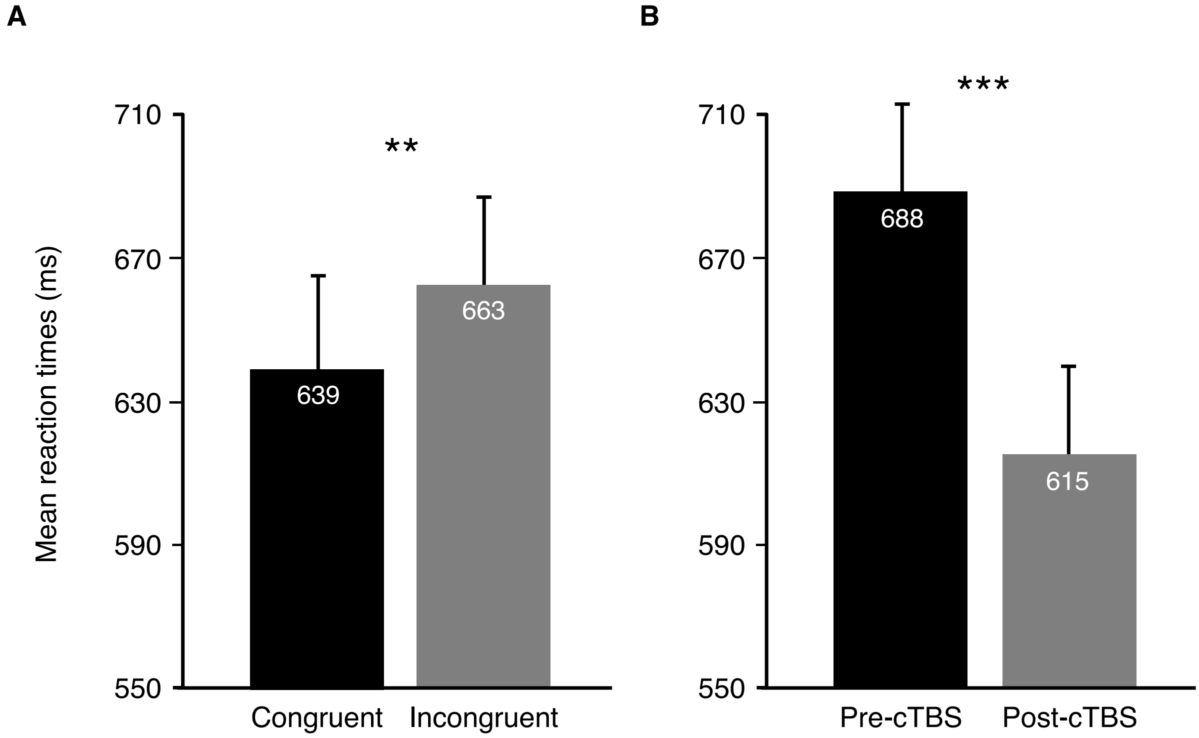

Figure 8. Mean reaction times as a function of A) *Congruence* and B) *Phase*. Error bars represent SEM, and integers in the bars show the mean reaction times for each condition.

ERP Results

The effect of cTBS on ERP modulations are displayed in Figures 9 and 10. Analysis of the mean amplitudes between 350 and 450 ms showed a main effect of Phase [F(1,14)=6.90, p=.020, η_p^2=.33], a main effect of Congruence [F(1,14)=53.65, p<.001, η_p^2=.79] and a main effect of Electrode Location [F(2,28)=4.20, p=.025, η_p^2=.23], and of interest here, a significant 4-way interaction between Phase, Hemisphere, Congruence, and Electrode Location [F(2,28)=8.46, p=.001, η_p^2=.38]. There were no other significant main effects or interactions (p>.059).

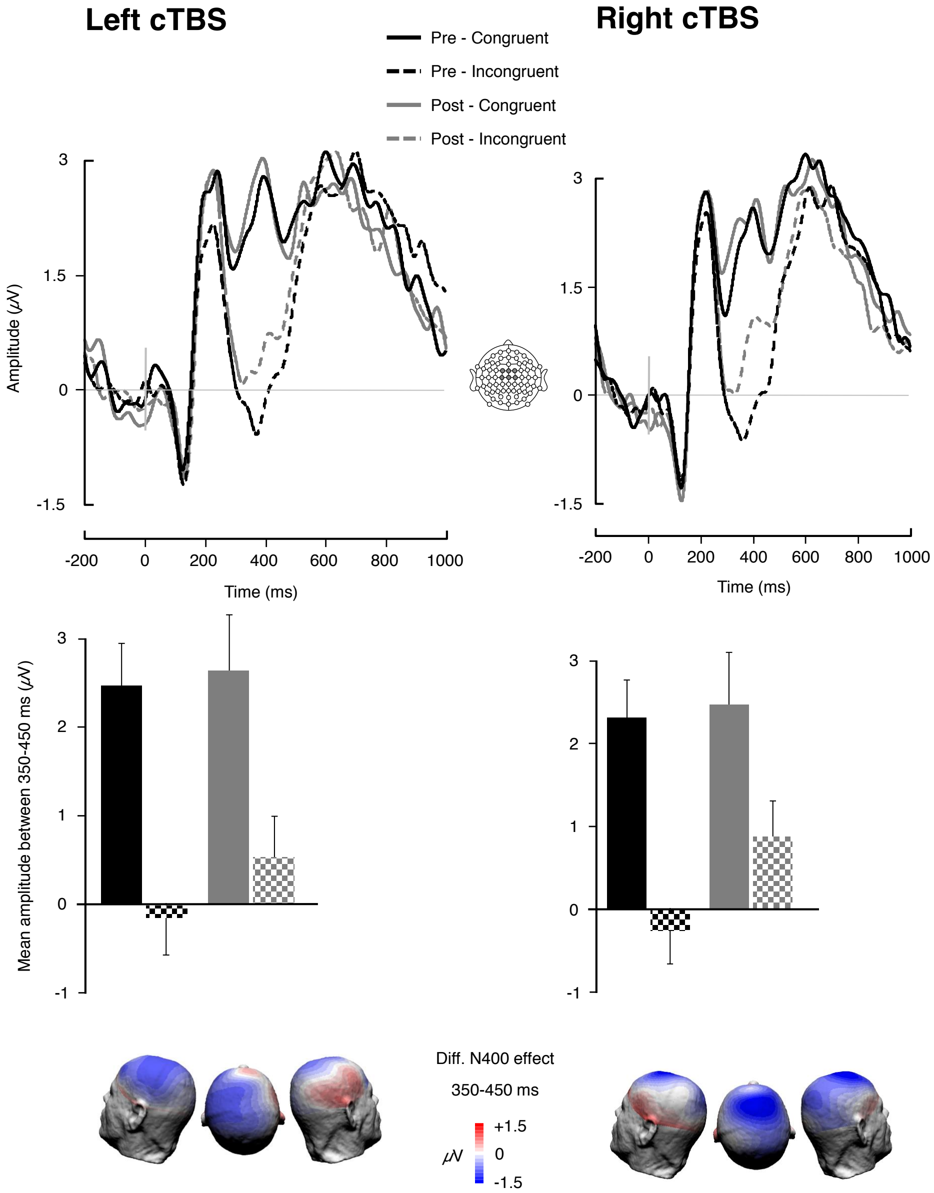

Figure 9. Effect of cTBS on ERP modulations. *Upper panel*, Grand-average ERP waveforms elicited over the fronto-central region (linear derivation of FC1, FCz, FC2, C1, Cz, C2) by congruent (solid lines) and incongruent (dashed lines) critical words before (black lines) and after (grey lines) left and right cerebellar cTBS. *Middle panel,* N400 mean amplitude as a function of *Congruence* and *Phase* between 350 and 450 ms in the fronto-central region (error bars represent SEM). *Lower panel*, Topography of the differential N400 effects (N400 effect, i.e. Incongruent minus Congruent, Pre-cTBS minus Post-cTBS to left and Right cerebellar hemisphere) in the N400 time-window (350-450 ms).

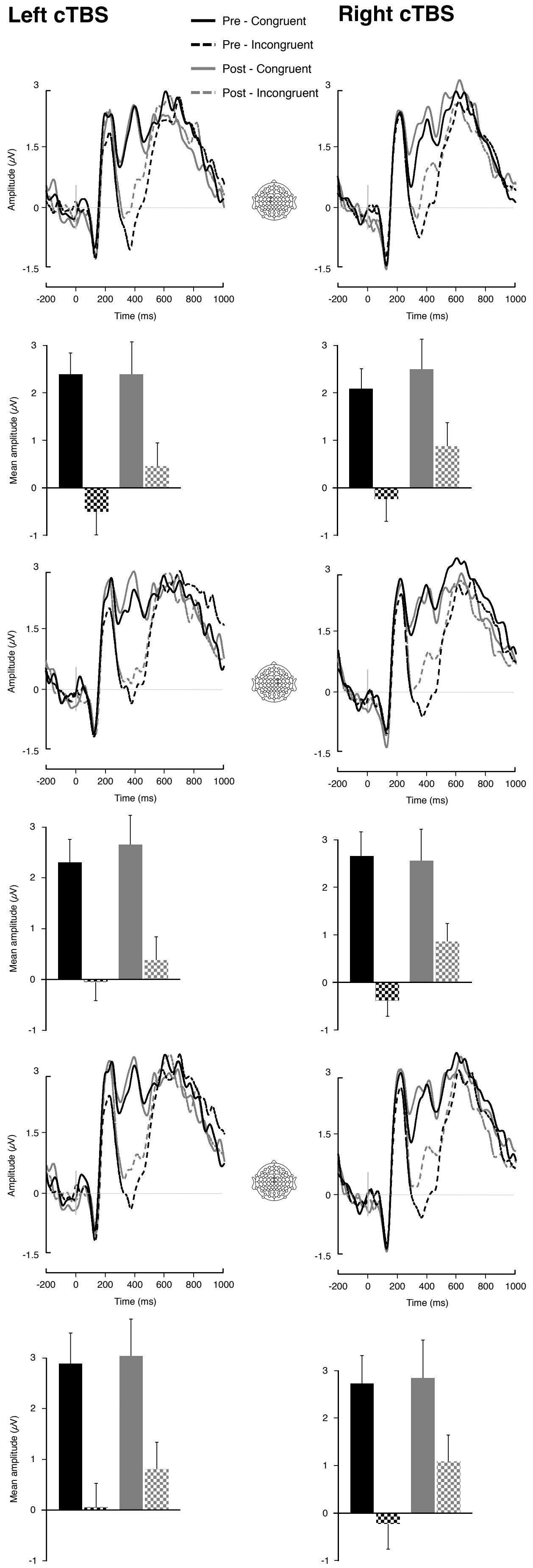

Figure 10. Effects of cTBS on ERP modulations according to *Electrode Location*. Grand-average ERP waveforms and N400 mean amplitudes (350-450 ms, error bars represent SEM) elicited by congruent (solid lines) and incongruent (dashed lines) critical words before (black lines) and after (grey lines) left and right cerebellar cTBS over the left electrodes of interest (linear derivation of FC1 and C1, *upper panel*), the midline electrodes (linear derivation of FCZ and CZ, *middle panel*), and right electrodes (linear derivation of FC2 and C2, *lower panel*).

To examine the 4-way interaction, we calculated the mean difference between the congruent and incongruent waves (Incongruent minus Congruent), that is, we examined the N400 effect (see Appendix E for the N400 effect graphs). Here there were no significant main effects or 2-way interactions (p>.063). However, there was, as expected, a significant 3-way interaction between Phase, Hemisphere and Electrode Location [F(2,28)=8.46, p=.001, η_p^2=.38]. We therefore conducted 2 way ANOVAs for the two cerebellar Hemispheres separately. In both Hemisphere analyses there were no main effects [Left Hemisphere stimulation (*ps* > .254); Right Hemisphere stimulation (*ps* > .079)], but in both there were significant interactions between Phase and Electrode Location [Left Hemisphere stimulation [F(2,28)=4.38, p= .022, η_p^2=.24]; Right Hemisphere stimulation [F(2,28)=5.40, p= .010, η_p^2=.28]. We therefore examined the effect of Phase for each Hemisphere and each Electrode Location. The only significant effect was the effect of Phase for Right Hemisphere stimulation in the Right Electrodes [F(1,14)=5.14, p= .040, η^2=.27], see lower panel Figure 10; there were no other significant differences (p>.058).

Discussion

The present study aimed to examine the role of the cerebellum in predictive processing of sentences and how this interacts with the wider language network as indexed by the N400 effect. Previous literature using functional connectivity and PET has shown that the cerebellum interacts with a wider language network (Booth et al., 2007; Cho et al., 2012; Londei et al., 2010); however, this gives little insight into the temporal relationship between the cerebellum and cortical language areas. The studies employing TMS methodologies to examine cerebellar associative language functioning have shown that this is an effective technique (Argyropoulos, 2011; Argyropoulos & Muggleton, 2013; Lesage et al., 2012). Furthermore, the N400 ERP has been consistently shown to be a reliable index of predictive semantic processing (see Kutas & Federmeier, 2000 for a review). The present study employed cTBS coupled with EEG in order to examine the specific role of the right cerebellum in predictive function in the context of sentence processing, as well as the interaction that this role has elsewhere in the language network as indexed by modulation of the N400 effect.

We found that participants were generally faster to respond after cTBS, likely due to a repetition effect. Additionally, we found that they were faster for congruent as compared to incongruent stimuli, thus showing the difference in difficulty/inhibition for these two types of stimuli as previously shown in literature employing semantic violations (Moberget et al., 2014), and more generally the cost of negative responses. However, the effect of cTBS can be seen in the ERP results, in the earlier time-window of the N400, which comes approximately 250 ms before the average reaction time. Overall, amplitudes of the N400 elicited by both congruent and incongruent final words were reduced in the post phase, as compared to pre, again likely due to task repetition. In addition, we report a significant effect of Congruence, indicating that our stimuli were effective for eliciting a typical N400 effect. We also observed a ‘paradoxical lateralisation’ of the N400 and therefore included Electrode Location in our analyses, leading to a 4-way interaction between Phase, Hemisphere, Congruence and Electrode Location. Examination of this interaction lead to the finding that the N400 effect size was reduced after right cerebellar cTBS specifically for the right fronto-central electrodes, where the N400 was maximal and that this effect was driven by a reduction in the amplitude of the N400 elicited by incongruent stimuli rather than congruent stimuli.

Previous research has shown that a reduction in the N400 amplitude for incongruent stimuli results from increased ease of processing (Kutas & Federmeier, 2000). We therefore posit that the reduction here may be due to facilitation of processing for the incongruent stimuli, i.e., the facilitation of cerebellar functioning, potentially through modulation of internal models of language, leads to easier processing of the incongruent stimuli later in the system. This proposal fits the finding that right cerebellar stimulation tends to facilitate associative language function (Argyropoulos, 2011, Argyropoulos & Muggleton, 2013). Our findings support our hypothesis that cTBS to the right cerebellar hemisphere enhances its predictive function and, for the first time, we show that this function has far reaching effects later in the language network.

These findings lend further credence to the theory that computations applied to motor function in the cerebellum are also applied to associative language function. Models of motor function use 'feedback loops' to explain predictive, sensorimotor associations, these are attributed to the cerebellum and are responsible for the accuracy and fluency of sensory-guided actions (Miall, Weir, Wolpert & Stein, 1993). More recently, Moberget et al. (2014) proposed that these models are applicable to language function. They used a semantic violations task, as we have done here, and found activation in the right cerebellar hemisphere (Crus I/II) which was more intense and widespread when the targets were semantic violations. Moberget and colleagues argue that this activation reflects the application of similar computations as used in sensorimotor control to the domain of language processing. Further, the more widespread activation for incongruent trials was argued to be a reflection of the processing of error signals caused by the unexpected sentence endings. Error-based learning through feedback loops is a well-documented element of the internal models attributed to the cerebellum (Miall & Wolpert, 1996; Wolpert & Kawato, 1998; Wolpert, Miall & Kawato, 1998) and cerebellar cTBS may be affecting these loops. The more widespread activation for incongruent trials reported by Moberget and colleagues in addition to our findings support this proposal. Here we have shown modulation of the N400 effect specifically for the incongruent trials, which may be due to the modulation of these feedback loops resulting in easier processing later in the language network. The processes through which internal models are updated are thought to rely upon microcomplexes in the cerebellum, each of which can learn a specific function (Ito, 2008). Within each microcomplex the role of climbing fibres is to update the model based on errors and this in turn causes long term depression (LTD) in the Purkinje cells which then relay information to the cortex (Ito, 2008). It has been proposed that cerebellar cTBS specifically affects Purkinje cells (Koch et al., 2008). This leads us to speculate that changes in the Purkinje cells caused by cerebellar cTBS may have led to faster or more effective updating of internal models. This in turn may have resulted in our finding that incongruent stimuli were easier to process later in the network, as indexed by the N400. This proposal is supported by the conclusions of Argyropoulos and Muggleton (2013), who also found a facilitatory effect and argued that it was caused by modulation of the Purkinje cells, leading to increased excitability in the cortex. This has also been reported as a result of cerebellar TMS in the motor (Oliveri et al., 2007) and motor learning domains (Torriero et al., 2011).

To further extrapolate the application of motor computations in the cerebellum to language functioning, the predictive functions in the motor domain interact with and support the cerebral cortex (Wolpert, Miall & Kawato, 1998). We have presented evidence here that this is also the case for language function. Although imaging and functional connectivity studies have consistently shown the cerebellum to be part of a wider language network (Booth et al., 2007; Cho et al., 2012; Londei et al., 2010), previously no research, that we are aware of, has examined the temporal role of the cerebellum in language processing. Here, for the first time, we have determined that the predictive function in the cerebellum previously documented in the literature interacts with cerebral predictive processing as indexed by the N400, supporting the hypothesis that the role of the cerebellum in language is occurring early and supports later processing (Lesage et al., 2012).

Further to this, we have shown that the role of the cerebellum in associative language processing can be applied to more complex sentence processing and that this functioning contributes to later predictive language processing in the cortex. This has not previously been demonstrated and we can interpret our findings here as evidence of the contribution of the cerebellum to more complex speech processing. We propose that this early processing could contribute to making the understanding of speech more fluent, and therefore improve the fluency of communication more generally. This proposal is supported by previous research examining patients with cerebellar degeneration have deficits in fluency tasks and naming speed (Stoodley & Schmahmann, 2009).

These findings can be interpreted in terms of psycholinguistic theories; for example, these findings support the theory that the N400 indexes semantic access. In the literature, this theory is supported by the presence of the N400 in different modalities, it has therefore been proposed that the N400 indexes processing in semantic memory, where these different modalities would intersect (Kutas & Federmeier, 2011). Further, modulations of the N400 indicate that it is sensitive to semantic memory organization (Federmeier & Lazslo, 2009). Here we have shown an N400 effect for incongruent as compared to congruent sentences which is modulated by right cerebellar stimulation. Previous literature has shown the right cerebellar hemisphere to be involved in associative priming (Argyropoulos, 2011; Argyropoulos & Muggleton, 2013), and it has been suggested that the process which supports backward priming in the left cerebellar hemisphere can be explained using the spreading activation theory of priming (Allen-Walker, Bracewell, Thierry & Mari-Beffa, 2017). Additionally, here (and elsewhere, see e.g. Lesage et al., 2012) we have seen evidence for the role of the right cerebellum in sentence prediction. Given that stimulation to the right cerebellum affects both sentence prediction and associative priming, one might infer that the cerebellum plays a similar role in both processes. This suggests that some of parts of these two processes could be similar. The spreading activation account of the N400 has previously been suggested as the N400 to both word and sentence level contexts is similar in functional specificities (e.g. strength of context; Federmeier & Laszlo, 2009), and N400s to both types of stimuli have similar timings and scalp distributions (Kutas, 1993; Van Petten, 1993). Further, in a study where associative priming was embedded into predictable sentences, the joint effects of these contexts (word-level and sentence-level) have been seen (Van Petten, Weckerly, McIsaac & Kutas, 1997).

The spreading activation account of the N400 as a result of word-level contexts is compatible with the semantic memory account of sentence- and discourse-level contexts. Findings in this field can be argued to support the idea that the context presented, be that word-level or a higher mental representation of context based on a preceding sentence or discourse, pre-activates words that are related to the context. The words that are activated can be based on their relationships with specific words presented or the discourse context as a whole (Van Berkum, 2004, 2009). Here we have shown that the cerebellum is involved in sentence level semantic prediction; this adds to a literature which has shown the cerebellum to be involved in associative priming. Given the proposal that the cerebellum applies similar computations to a range of functions it would be logical that this would also apply in this context, this is therefore some preliminary evidence that the cerebellum may play a role in a spreading activation like process which is applicable to both priming and sentence prediction, further implying that this theory is applicable in both contexts.

We did not replicate behavioural findings of previous research. We found no specific behavioural effect of right cerebellar cTBS on RTs. Although previous studies have found consistent effects after right cerebellar cTBS on associative function, when using lexical decision tasks (Argyropoulos 2011; Argyropoulos & Muggleton, 2013), here we have employed more complex stimuli. Argyropoulos and colleagues in both their studies utilised pairs of words rather than full sentences. Equally, although Lesage and colleagues (2012) employed sentences, these were very simple single clauses using verb to noun association to facilitate predictability. Our stimuli were more complex, some utilising multiple clauses. Additionally, we required the participants to make a semantic judgement, rather than a lexical decision, arguably requiring processes that occur later in the language system. The complexity of sentence processing and of the task presented here as compared to lexical decision tasks may have caused interference from more top-down processes making the differentiation of effects caused by cerebellar cTBS difficult. This is supported by our reaction time data: participants took an average of about 660 ms to respond, whereas in the lexical decision tasks reported in this thesis the slowest mean reaction times in any condition were under 460 ms (Chapter 4) and 540 ms (Chapter 5), further in Argyropoulos and Muggleton (2013) the slowest mean reaction time reported was less than 580 ms. This substantial difference may mean that processing of behavioural responses is occurring much later in this task, perhaps beyond the reach of the cerebellar modulations.

Another potential reason for the absence of an effect of cTBS on reaction times may be due to our choice of stimulation site. Behavioural effects have been found when stimulating 1 cm to the right of the inion (Argyropoulos, 2011), 3 cm to the right of the inion (Lesage et al., 2012; Oliveri et al., 2009) and 10 cm to the right of the inion (Argyropoulos & Muggleton, 2013). Previous research has shown that the cerebellum has a topographical map for motoric function (Stoodley & Schmahmann, 2009) as well as language function (Stoodley & Schmahmann, 2015). For example, language function is often associated with cerebellar Crus I and II. It may be that the areas of the cerebellum that drives these behavioural effects were not affected by our stimulation. Our location choice (1 cm below the inion and 3 cm to the right) was driven by a need to maximise the effect of stimulation to areas linked to predictive function (Lesage et al., 2012; Oliveri et al., 2009) and this location is believed to affect Crus II (Lesage et al., 2012; Grimaldi et al., 2014).

The present study used the N400 to examine the predictive function of the cerebellum using a semantic violations task, which reliably elicits this component (Kutas & Hillyard, 1980; Kutas & Van Petten, 1988). However, other common semantic tasks can also be indexed using this component, for example word priming (Kutas & Federmeier, 2011). Much of the previous literature surrounding the use of cTBS over the right cerebellum has employed associative priming to examine the function this region plays. The combination of associative priming and monitoring of the N400 may give further insight into the role the cerebellum is playing in predictive function beyond that of the cerebellum itself. It may further confirm that the associative and predictive functions that have been modulated by cTBS previously are in fact part of the same process, and therefore modulate the ERP component in the same way.

Future research could employ a combination of cTBS and fMRI. Here we show how the cerebellum is affecting an N400 component; however, this component is elicited by functioning in a range of language specific regions (Kutas & Federmeier, 2011). However, given the poor spatial resolution of EEG data it may be useful to employ a combination of cTBS and fMRI, perhaps similarly to the imaging protocol used here, during a predictive language task. Previous research has shown that rTMS over the cerebellum has effects on language specific regions of the cortex (Cho et al., 2012), and fMRI research has indicated regions including Broca's area and Wernicke's area in addition to the cerebellum are activated during incongruent trials (as compared to congruent and scrambled conditions) on semantic violation tasks (Moberget et al., 2014). However, the combination of fMRI and cTBS has not been carried out with a specific view to examine modulation of language prediction and later functional changes in the cortex.

By combining TMS and EEG-ERP techniques, we have shown that right cerebellar cTBS selectively enhances predictive processing as indexed by the N400 event related brain potential, and that this effect is specifically for targets that are semantic violations rather than congruent endings for the same sentences. This indicates that the cTBS is facilitating more effective use of feedback loops within the cerebellum. This further supports the application of cerebellar computational models to cognitive functions rather than exclusively motoric functioning. Additionally, we have shown that the role of the cerebellum has far reaching consequences later in language processing, possibly by providing support to late more complex processes.

Chapter 7

General discussion

General discussion

Summary of research aims

The aim of this thesis was to further examine the role of the cerebellum in associative and predictive language processing. To investigate this, continuous theta-burst stimulation (cTBS) and event-related potential (ERP) methodologies were employed.

The aim of this thesis was to answer the following questions:

1. Are the findings that the right cerebellar hemisphere is involved in associative, as compared to categorical, priming reproducible when we control for categorical relationships across both types of stimuli, and does the effect of stimulation also modulate ERP waveforms that index language prediction and semantic access?
2. Is the cerebellum's role in associative priming similar in backward priming as compared to its role in forward and symmetrical priming; and how does this relate to models of backward priming and models of cerebellar function?
3. Can the role of the cerebellum in associative priming, previously documented in tasks predominantly using pairs of words, be seen in a more complex language task employing sentences, and can the impact of this role be seen in ERP waveforms that index language prediction and semantic access?

Specifically, we first attempted to replicate previous findings as regards associative as compared to categorical priming while controlling for categorical relatedness across both types of pairs, specifically by comparing opposites (e.g. black → WHITE) to categorically related pairs (e.g. black → BROWN).

We also sought to expand on the previous literature by examining forward as compared to backward priming. Previous research has not specifically examined the directionality of priming modulated by cerebellar cTBS. Here we aimed to dissociate forward and backward priming in the cerebellar hemispheres, right and left respectively, by facilitating the predictive function in each cerebellar hemisphere.

Finally, we aimed to examine the effect cerebellar cTBS has on sentence prediction as indexed by the N400 ERP component. Previous literature in this domain has predominantly relied upon associative priming, either in the context of pairs of words or short sentences in which the final word is primed by an associatively related verb presented earlier. We used more complex sentences and to investigate the role of the cerebellum in more representative language functioning as well as to examine the consequences of cerebellar modulation in later language processing indexed via electrophysiological measures.

In this chapter I will summarise the key findings of this thesis and examine the contribution of the findings for each chapter as well as the more general implications for the areas built upon by the findings detailed here. Additionally, I will describe some limitations of this thesis, propose some possible directions for future research and outline some outstanding questions is this area.

Main findings and contribution

Chapter 4. The first experimental chapter aimed to replicate findings as regards the role of the cerebellum in associative as compared to categorical priming with the addition of electrophysiological measures. Previous literature has found that cerebellar cTBS selectively enhances priming size to associatively related word pairs such as nouns and verbs (e.g. scissors → cutting; Argyropoulos & Muggleton, 2013) and pairs that are associated through idiomatic phrases (e.g. gift → HORSE; Argyropoulos, 2011); however, previously this effect has not been shown for stimuli where the categorical relationship has been explicitly controlled for across stimuli types. Further, studies in this domain have used experimental and control stimulation sites within the same cerebellar hemisphere, potentially confounding the effects of stimulation. Further, no research in this domain has employed electrophysiological measures to examine the impact of cTBS on the N400, an index of semantic prediction. Here we attempted to replicate the findings of Argyropoulos and colleagues while controlling for both of the aforementioned issues, while examining the impact on the N400. We found a significant effect of relatedness on the reaction times for the opposite but not the categorical stimuli, indicating that there had been priming for the associative pairs, further, this priming was reflected in a phonological mismatch negativity (PMN) rather than an N400. There were no effects of stimulation on priming.

These findings suggest that this task may not have required semantic access, as we have found evidence of phonological but not semantic processing. As stimulation of the cerebellum has not modulated priming on this task it suggests that perhaps the area of the cerebellum stimulated is involved in semantic but not phonological prediction. Although this study did not replicate previous findings, it does indirectly support the wider literature that indicates that the right cerebellum has a role in semantic predictive language processing (Argyropoulos, 2011; Moberget, Gullesen, Andersson, Ivry & Endestad, 2014).

Our findings here showed no effect of cTBS on associative priming, whereas previous studies have successfully modulated priming in similar tasks (e.g. Argyropoulos, 2011; Argyropoulos & Muggleton, 2013). This might be explained by the difference in stimulation sites employed in this experiment (3 cm lateral to the inion) as compared to those detailed previously (1 cm laterally in Argyropoulos, 2011; 10 cm laterally in Argyropoulos & Muggleton, 2013). It is possible that the mechanisms affected in previous studies that resulted in increased priming are localised to areas that remained unaffected or were affected differently by the stimulation presented here.

Chapter 5. The second experimental chapter examined the role of the cerebellum in backward as compared to forward priming. Previous imaging literature indicated that there may be a dissociation between backward and forward priming in the cerebellum, with backward priming localised to the left hemisphere and forward priming in the right hemisphere (Terrien et al., 2013). Here we employed short stimulus onset asynchrony (SOA) priming as previous cTBS research has predominately used this technique (Argyropoulos, 2011; Argyropoulos & Muggleton, 2013). The results indicated that after left cerebellar cTBS there was a significant increase in backward priming size as compared to pre cTBS and post right cTBS. However, we did not replicate previous findings as regards forward priming in the right cerebellar hemisphere.

For the first time, we have shown that the left cerebellar hemisphere is actively involved in backward priming. Although previous research has shown that there is activation in the left cerebellar hemisphere during backward priming (Terrien et al., 2013), this has not been interpreted within the domain of cognitive cerebellar research. It is interesting to note that backward priming here is localised to the left cerebellar hemisphere as language in the cerebellum is predominantly located in the right hemisphere as this preferentially activates with the left cerebral hemisphere (Jansen et al., 2005). This leads us to believe that these two processes are in some way different. This is supported by the literature that indicates that backward priming is as a result of processing in the right rather than the left cerebral cortex (Koivisto, 1998; Franklin, Dien, Neely, Huber & Waterson, 2007; O'Hare, Dien, Waterson & Savage, 2008; Terrien et al., 2013).

Additionally, we have for the first time shown a potential mechanism through which we can explain short SOA backward priming. Previous explanations for backward priming involve episodic retrieval; this is a relatively slow process and therefore can only account for long SOA backward priming (Neely, 1991); but, as we have shown here and in other studies

(Kahan, Neely & Forsythe, 1999; Peterson & Simpson, 1989; Terrien, et al., 2013), backward priming also occurs at short SOAs. Internal models of cerebellar function typically use feedback loops, through which the models can be continuously updated if errors occur (Ito, 2008). This mechanism may help to explain how short SOA backward priming occurs. In order for fast automatic 'spreading of activation' theories to account for backward priming at short SOAs then there must be feedback loops present (Koriat, 1981). It may be that these feedback loops within the cerebellum are the mechanism through which this occurs.

Chapter 6. The final experimental chapter used a semantic violation task, which has traditionally been used to elicit this wave (Kutas & Van Petten, 1988), to examine the effect of cerebellar cTBS on the N400. We found a right lateralised N400, referred to in the literature as the 'paradoxical lateralisation' of the N400 wave (Lau, Philips & Poeppel, 2008). We found that right cerebellar cTBS caused enhanced predictive language function, indexed by a reduction in the N400 effect, specifically via a reduction in amplitude for incongruent stimuli in the right electrode sites. We interpreted the reduction in the N400 amplitude as an increase of ease of processing for the incongruent stimuli; this is the classic interpretation of a reduction in amplitude to incongruent stimuli for this component (Kutas & Federmeier, 2000).

We can infer that the cTBS specifically affected predictive function in the cerebellum, and seemed to allow for easier processing of incongruent stimuli. It is expected that this effect is only for the incongruent stimuli. The processing of expected congruent endings is already very easy, which may have resulted in a ceiling effect, meaning facilitation of the processing of congruent stimuli with cTBS is unlikely. Additionally, the principal changes documented in the N400 literature are as a result of task manipulations eliciting changes in the N400 to incongruent stimuli (see Kutas & Federmeier, 2011 for a review of the N400 literature).

This is the first experiment in which cTBS has been used modulate cerebellar language functioning and shown later differences in processing indexed by electrophysiological measures. It is particularly interesting that here we have shown that changes in cerebellar language function can modulate the later N400 ERP produced in the cerebral cortex. This indicates that the cerebellum is playing a very early role in language prediction that supports later language processing (Lesage, Morgan, Olsen, Meyer & Miall, 2012), and that it is part of a wider language network (Booth, Wood, Lu, Houk & Bitan, 2007; Cho et al., 2012; Londei et al., 2010).

Additionally, our findings here lend further credence to the application of internal models derived from cerebellar motor function to other domains. Replicating previous literature, cTBS to the cerebellum has facilitated predictive functioning. Here however, we have added further support as our effects are indexed via direct measures. Previous cTBS and rTMS studies in the domain of language have used only indirect behavioural measures (Argyropoulos, 2011; Argyropoulos & Muggleton, 2013; Lesage et al., 2012). Here we have supported their findings in terms of the role of the cerebellum in language but with the addition that these findings are still present when using an index that this not in some way conflated with motoric or ocular motor artefacts, a domain in which the cerebellum is much involved (Stoodley & Schmahmann, 2010; Timmann et al., 2008).

Contribution of thesis to cerebellar stimulation literature

Overall, these findings indicate that the cerebellum is involved in semantic prediction, in chapter 5 we found modulation of backward priming, and in chapter 6 we showed that cTBS resulted in modulations to the N400, a wave that indexes semantic prediction. Further, this is indirectly supported by the absence of an effect and the presence of the PMN and the absence of the N400 found in chapter 4. We have therefore shown that the area of the cerebellum stimulated in these experiments is specifically involved in semantic processing, but not phonological processing.

The use of the same stimulation sites across all three experiments means that we can contribute to a fragmented literature which has to date used a wide array of tasks and stimulation parameters. First, we have consistently not replicated findings that have indicated that the cerebellum is involved in forward associative priming. Argyropoulos (2011) and Argyropoulos and Muggleton (2013) both indicated that right cerebellar cTBS produces enhanced priming for associatively but not categorically related pairs. In chapter 4 we did not replicate this finding with our stimuli which controlled for categorical relationships; further, we found no modulations of forward priming in chapter 5. Taken together these results suggest that the cerebellum is not involved in this task; however, EEG data in chapter 4 showed a PMN rather than an N400, potentially indicating that this task did not require semantic access in order for its completion but rather it only reached the level of phonological processing. This suggests that in order to examine previous findings reported in the literature regarding associative priming it may be necessary to use a task which encourages or requires semantic processing, for example, a priming task with responses requiring semantic processing, such as a semantic matching task where participants report whether the target semantically relates to the prime. As we have seen in chapter 6 the location used does affect semantic predictive processing, in that chapter the task required participants to report whether or not the target matched the rest of the sentence. Further, it may be of interest to replicate the findings of Argyropoulos and colleagues using their stimulation parameters, given the presence of a PMN presented here in a similar task it may be that the areas affected in their experiments are involved in phonological rather than semantic prediction, and recent findings have shown cerebellar cTBS to affect phonological prediction (Runnqvist, 2016).

Additionally, the results presented in this thesis support previous findings which suggest that the cerebellum is involved in sentence prediction. Lesage et al. (2012) examined the role of the cerebellum in sentence prediction, and found that cerebellar rTMS significantly reduced fixation latency to visual targets; however, these stimuli were primarily built around verb to noun associations. In using more complex sentences we have therefore contributed to this area. Here we have shown that modulation of cerebellar predictive language function results in changes in the N400 wave. As these stimuli were more complex it supports the assertions made by Lesage and colleagues as regards the role of the cerebellum in sentence processing. Further, their stimulation site was the same as the site used here, supporting this location as an ideal place to stimulate when attempting to modulated cerebellar predictive language function.

Implications for understanding the role of the cerebellum in language

The findings presented here add to previous literature which has indicated that the cerebellum plays a role in language prediction (Chapter 6; Lesage et al., 2012) and association (Chapter 5; Argyropoulos, 2011; Argyropoulos & Muggleton, 2013). Beyond our support of the literature we have shown here that modulation of this function in the cerebellum has long lasting effects in the language system, as indexed through the N400. Further, we have shown that the role of the cerebellum in associative relationships between words extends to backward priming, but that this function is located in the left cerebellar hemisphere. Finally, we have shown that the predictive function of the cerebellum, which most likely encompasses the associative function (Beaton, Allen-Walker & Bracewell, 2015), extends to the processing of more complex sentence stimuli that are more representative of normal speech, thus lending further support to the proposal that these two effects stem from the same function. Finally, we have shown that when semantic processing is not required for the completion of the task, that stimulation of the cerebellum does not modulate behavioural or electrophysiological measures.

Our findings are consistent with the proposal that the cerebellum applies similar computations to those used in motor function to cognitive functions. As detailed above, the cerebellum is thought to use similar computations across both motor and non-motor domains (Ramnani, 2006; Schmahmann, 2004). These computations, or internal models, are predictive in nature and in the domain of motor control they help to predict motor outcomes to improve fluency of movements (Miall, Weir, Wolpert & Stein, 1993). It has been proposed that similar predictive models can be applied in the various cognitive domains to which the cerebellum contributes, for example verbal working memory (Desmond et al., 1997) and language (Moberget et al., 2014). This is a compelling theory given the homogenous cellular structure of the cerebellum (Eccles, Ito & Szentagothai, 1967).

The findings detailed in this thesis supported this theory. We have shown that the cerebellum plays a role in backward priming; this directionality of prediction in language has not been attributed to the cerebellum previously. This indicates that the predictive functioning in the cerebellum does not only apply to forward associations (Argyropoulos, 2011; Argyropoulos & Muggleton, 2013). Finally, we have shown through direct ERP measures that the predictive role of the cerebellum can be seen in complex sentences that are more representative of speech. This finding supports the proposal that the associative and predictive role of the cerebellum likely arise from the same computations (Beaton, Allen-Walker & Bracewell, 2015). The findings of chapter 6 also indicate that the predictive computations in the cerebellum contribute to later cortical predictive functioning, possibly in a supportive role as has been suggested previously (Lesage et al., 2012). Taken in conjunction these findings support the predictive role of the cerebellum in language, specifically in terms predicting upcoming words that typically occur with the previously presented word(s) and that this prediction supports later language processing. And our findings in chapter 4 confirm the proposal that this function in the cerebellum is specifically semantic in nature.

Implications for contribution to psycholinguistic theories

Much of the research on the role of the cerebellum in language function has ignored the implications of their findings for psycholinguistic theories. As I suggested in the general introduction these theories may make a useful addition to our understanding of the role of the cerebellum in language prediction and models of language function. In each chapter I have where relevant referred to the psycholinguistic theories reviewed in chapter 1; here I will discuss the overall contribution of the thesis to these theories.

Lexical semantics. Chapters 4 and 5 employed associative priming tasks and therefore may inform theories in this domain.

Spreading activation. This theory posits that in the context of priming, when a prime is presented, activation spreads to related words, or nodes, facilitating reaction times to related targets as compared to unrelated ones (Collins & Loftus, 1975). In both chapters examining associative priming there were significant effects of relatedness for the forward associative pairs, indicating that priming had occurred. As in both cases these pairs were associatively related rather than categorically related this supports the proposal that the spreading activation account rather than the feature overlap account can explain priming, given that, in chapter 5, the pairs and the targets had very little in common in a categorical sense, whereas in chapter 4 although both the categorical pairs and the associatively related pairs belonged to the same categories, the effect of relatedness was only present in the latter condition. Further, in chapter 5, we found a significant effect of relatedness for the backward stimuli, again implying that priming had occurred. In this condition, as well as in all conditions in both priming chapters, these stimuli were presented at short SOAs, this implies that spreading of activation is occurring in order to facilitate these pairs as compared to the unrelated ones (Koriat, 1981).

The contribution of the cerebellum to these processes remains unclear. In both chapters, there was no effect of cerebellar stimulation on forward priming. However, as discussed above, the presence of the PMN but not the N400 in chapter 4 implies that semantic access may not be required to complete this task. Given the assumption that the role of the cerebellum in these tasks is semantic in nature it would therefore follow that the cerebellum would not affect a task which does not require semantic access. Further, the presence of the PMN and not the N400 also suggests that the priming effects present here may not be as a result of spreading activation in semantic memory. However, in chapter 5 we found that there was a significant effect of left cerebellar stimulation on backward priming. We have therefore posited that the role of the cerebellum may therefore be to facilitate spreading of activation specifically in terms of the backwards connections between the nodes required for backward priming to be explicable using the spreading activation account (Koriat, 1981).

Sentence-level semantics. Chapter 6 of this thesis examined sentence prediction using the N400 wave and could therefore contribute to this area of psycholinguistics.

Semantic memory. The N400 wave is believed to index access to semantic memory, regardless of modality (Kutas & Federmeier, 2011). Larger amplitudes are seen with incongruent as compared to congruent stimuli, with lower amplitudes indicating increased ease of processing (Kutas & Federmeier, 2011). In chapter 6 we found a significant effect of congruence for the ERPs, with more negative amplitudes for the incongruent rather than the congruent stimuli, indicating that these stimuli produced an N400 effect. This effect supports the proposal that this effect indexes semantic access as the incongruent stimuli were more difficult to process that the congruent stimuli. The semantic context in which these targets were presented was very strong as we retained sentences with high cloze probabilities of .90 or above, which would result in a very clear prediction of the expected final word. However, on a superficial level these results could also be taken as support for the semantic integration theory of the N400, as presentation times of the stimuli are relatively slow, allowing for a representation of the sentence context to be formed and referred to in working memory (Hagoort et al., 2009).

The effects of cerebellar cTBS on the N400 indicate that there is a role of the cerebellum in the prediction of sentences. This is more in keeping with the former proposal given the role of the cerebellum in modelling upcoming motoric actions (Miall, Weir, Wolpert & Stein, 1993) and the proposal that the cerebellum applies similar computations across motor and non-motor domains (Ramnani, 2006; Schmahmann, 2004). The semantic access account suggests that the N400 is produced on the basis of context which builds as the sentences progresses (van Petten & Kutas, 1990; 1991). This is comparable to cerebellar models of motor prediction, it has been posited that the cerebellum predicts the outcomes of motor commands instigated by the cortex. These predictions prepare the motoric system for ongoing changes and are updated using prediction errors and feedback loops (Pisotta & Molinari, 2014).

As described in the general introduction, the semantic access account of the N400 is compatible with the spreading activation account of priming (Federmeier & Laszlo, 2009). However, here cerebellar stimulation presented in this thesis has affected only sentence-level predictive processing (Chapter 6) but not forward associative priming (Chapters 4 & 5). This may be because these two processes are distinct in the cerebellum which would lend support to the proposal that these two processes use differing mechanisms. However, as described previously, the lack of N400 and the presence of the PMN, implies that semantic processing was not required in order to complete this task. It may be that a priming task where responses require semantic processing, for example a semantic matching task, might then be open to modulation from cerebellar stimulation. This would help to elucidate the role of the cerebellum in priming as compared to sentence processing and therefore give a more detailed picture of the role of the cerebellum within spreading activation and semantic access accounts of the N400.

Language models. The findings described in this thesis may contribute to current models of reading. As detailed in the general introduction there are three principle types of theories of word reading: parallel distributed processing (PDP) models, dual-route cascade (DRC) models, and hybrid models. Here I will examine the findings presented in this thesis with regard to PDP and DRC models, and will also discuss these findings with regards to Ullman's (2004) declarative/procedural model, a model which specifically attributes some processes in reading to the cerebellum.

PDP models. PDP models are connectionist models that argue that the different components of reading are distributed across units which represent the different aspects of word processing; the most influential theory of this type is the triangle model (Seidenberg & McClelland, 1989), which contains three units, orthography, phonology and semantics. In this model, there are two pathways from orthography to phonology, the first is direct and the second travels via semantic representations. Our finding in chapters 4 and 5 that cerebellar cTBS did not affect associative priming and the finding in chapter 4 that there was a PMN but not an N400 can be taken as support for this model. Here, in order for participants to complete the task, they needed only to access phonological representations but not semantic representations; this suggests that this task used only the first pathway, rather than accessing semantic representations in the second pathway.

We found no effects of cTBS on forward priming. As the N400 was not present and the PMN was present we may infer, given the substantial evidence elsewhere, that the cerebellum in involved in semantic prediction. However, as Argyropoulos (2011) and Argyropoulos and Muggleton (2013) found effects of cerebellar cTBS on priming tasks using different stimulation sites it is possible that these sites are involved instead in phonological prediction, a role which has previously been suggested in a cerebellar cTBS study involving speech production (Runnqvist et al., 2016). In chapter 6 we have shown that cerebellar stimulation can affect the N400 and therefore semantic processing. This role of the cerebellum is widely accepted in the literature (REFS). The separability of phonological and semantic functions in the cerebellum supports this model.

DRC models. The dual route theory was developed by Coltheart and colleagues (1993). DRC models have two routes, a lexical route and a nonlexical route. The nonlexical route can be used to read any word, known or unknown, but is *required* for the latter. In contrast, the lexical route contains orthographic and phonological lexicons and is used for known words, and is *required* for irregular words. In this model processing is cascaded and occurs in parallel. Although the original version of this theory did not include a semantic unit it was later suggested that this unit would interact with both the orthographic and phonological units, although it has not yet been integrated into the computational model. Given that we did not find effects of cTBS on forward associative priming but that we found a PMN indicating that phonological processing occurred, and given the well-established role of the cerebellum in semantic processing (Chapter 6; Beaton, Allen-Walker & Bracewell, 2015; Lesage et al., 2012; Moberget et al., 2014), this suggests that the proposed interaction between phonological and semantic lexicons in this model is not required for reading to occur.

Declarative/Procedural model. The declarative/procedural (DP) model (Ullman, 2004), is a model of reading which is grounded in neuroscience rather than psycholinguistics. Within this model the role of the cerebellum was the procedural system; it was suggested to be key in the search for lexical items and to aid error-based learning of rules in complex language structures.

The results presented in this thesis support this theory. First, although we found no effect of cerebellar cTBS on forward priming in either chapter 4 or 5, there was an effect on backward priming in chapter 5. This suggests that in the context of backward connections between words the cerebellum may be aiding the spread of activation, and therefore the search for related nodes.

Additionally, the modulation of the N400 as a result of cerebellar cTBS, specifically the modulation of the N400 to incongruent sentences, suggests that in this context the cerebellum may be involved in error-based processing, arguably the incongruent trials in a semantic violation task can be viewed as errors. Additionally, the predictions made as a result of the sentential context would stem from rules learnt through experience of language use.

Implications for cerebellar research methodologies

An issue within this domain is the inconsistency of research practices in terms of the application of TMS methodologies to modulate language function in the cerebellum (Beaton, Allen-Walker & Bracewell, 2015). In this thesis, I have been consistent in my application of cTBS by using the same locations, protocol and intensity across all three of the studies reported here.

Location. Previous studies have employed a range of stimulation sites when examining cerebellar language function (Beaton, Allen-Walker & Bracewell, 2015). For example, effects have been found at 1 cm below and 1 cm laterally (Argyropoulos, 2011; Argyropoulos et al., 2011), 3 cm laterally (Lesage et al., 2012; Oliveri et al., 2009), and 10 cm laterally from the inion (Argyropoulos & Muggleton, 2013). This makes it is difficult to draw conclusions regarding the role of the cerebellum in language prediction; slightly different roles may be played by discrete regions. Previous studies have shown that there is a topographical map within the cerebellum (Stoodley & Schmahmann, 2010); it is unclear whether there may be a similar functional map of language processing.

Here we have employed the same stimulation sites across all three experiments (1 cm below and 3 cm to the left/right of the inion). In two of the three experiments presented here we have modulated cerebellar language function resulting in either behavioural (Chapter 5) or ERP (Chapters 6) changes. This area is thought to stimulate Crus II (Grimaldi et al., 2014); crura I and II of the right cerebellum are areas that are active for language function (Keren-Happuch, Chen, Ho & Desmond, 2014; Stoodley, 2012; Stoodley & Schmahmann, 2009; Stoodley & Schmahmann, 2015). As we have shown changes in language functioning, through either direct or indirect measures, it can be assumed that we are stimulating the appropriate area of the cerebellum, supporting the literature that used this site previously (Lesage et al., 2012). Further, although some authors employing TMS techniques over the cerebellum have used MRI guidance (Tomlinson, Davis, Morgan & Bracewell, 2013; Tomlinson, Davis, Morgan and Bracewell, 2014; Runnqvist et al., 2016), or suggested that not employing this technique is sub-optimal (Argyropoulos, 2011; Argyropoulos & Muggleton, 2013), we have shown in this thesis that the choice of location made here was appropriate and our effects have, as expected, modulated predictive language function, when the task employed has required semantic access.

We have also employed a left cerebellar cTBS site as a control site for the first and last experimental chapters detailed here. In chapter 5 this was an experimental site. The use of the left cerebellar homologue as a control site meant that the sensation was consistent across both sessions. Previous studies in this area have employed sites that are potentially very dissimilar in sensation as compared to cerebellar cTBS (e.g. vertex stimulation; Lesage et al., 2012) or they have employed sites that are proximal to the experimental stimulation site, for example Argyropoulos, (2011), whose sites were both over the right cerebellar hemisphere and were only 3.5 cm apart. The proximity of the two sites potentially resulted in the stimulation affecting both areas at the same time. Combined PET and rTMS research has shown that rTMS to the left cerebellum caused changes in glucose metabolism in multiple lobules in the ipsilateral hemisphere (Cho et al., 2012).

Protocol. The experiments presented in this thesis have all employed cTBS. As we have found changes as a result of the stimulation in two of the three experiments described here we can conclude that this is an effective method for stimulating the cerebellum. Studies have shown that cTBS can result in slightly more intense effects as compared to rTMS (Huang, Edwards, Rounis, Bhatia & Rothwell, 2005). Additionally, this method is practical, requiring only 40 seconds to apply rather than 10 minutes for rTMS. In the experiments presented here no participants withdrew as a result of the sensation of cTBS and previous research has shown that this technique is safe and well tolerated (Tomlinson, Davis, Morgan & Bracewell, 2014). The above indicates that this protocol is effective and practical for cerebellar stimulation and that it could be usefully applied in future research.

Intensity. Here we have used a fixed intensity of 55% of maximum stimulator output (MSO). Others have suggested that using fixed intensities might be an appropriate way to administer TMS methods over the cerebellum (Stewart, Walsh & Rothwell, 2001), whereas some researchers in this field have used a percentage of motor threshold, which gives an indication of the intensity required in order to produce effects in the cerebral cortex (Rami et al., 2003; Oliveri et al., 2009). However, anatomical differences between the cerebral and the cerebellar cortices (and overlying structures) mean that determining a cerebral cortical threshold may well give no indication of the intensity required for effective cerebellar stimulation. Here we have used 55% of MSO as previously used by Lesage et al. (2012); however, others in this field have utilised fixed intensities at differing intensities, for example Argyropoulos (2011) and Argyropoulos & Muggleton (2013) used 45% of MSO, whereas Runnqvist et al. (2016) used 60% of MSO. We have found effects using this technique, either through behavioural (Chapter 5) or electrophysiological (Chapter 6) measures. This indicates that we have been effectively stimulating the cerebellar cortex using this intensity and future research could employ this aspect of our stimulation parameters with the expectation of affecting the predictive role of the cerebellar cortex in language.

Combined cTBS and ERPs. An additional development presented in this thesis is that we have employed cerebellar cTBS in combination with ERPs. This technique has only been utilised in only one other domain, that of the role of the cerebellum in emotion (Schutter, Enter & Hoppenbrouwers, 2009; Schutter & van Honk, 2006); there have been no such studies in the domain of language. ERPs can be employed as effective measures of language processing and the research examining the N400, a wave that is related to language processing and prediction, is abundant (see Kutas & Federmeier, 2000; 2011 for reviews). Additionally, this technique has an excellent temporal resolution, giving a very detailed view of the timing of processes in the cortex. The combination of this methodology with cTBS means that direct changes in well documented waves associated with language processing give us a more detailed picture of the role of the cerebellum and how it contributes to cortical functioning. As we have shown here, this combination has yielded new and interesting data and could be employed in future research in this domain. Specifically, we have shown that when electrophysiological measures have indicated that the task employed required semantic access we have successfully modulated cerebellar predictive language function (Chapter 6), however, when the task requires only phonological processing behavioural and electrophysiological measures remain unaffected by cerebellar stimulation (Chapter 4).

Implications for understanding of language processing

Prediction. More generally this thesis has contributed to our overall understanding of language processing. The research presented here has expanded our understanding of cerebellar contributions to language and therefore our understanding of language functioning as a whole. As the role of the cerebellum in language is predictive and appears to be similar to the role that it plays in motoric functioning it is possible that the impact of the cerebellum in motor function is in some way similar to the impact of the cerebellum in language function.

For example, the cerebellum serves to in some way predict motoric outcomes through the integration of sensorimotor information (Miall, Weir, Wolpert & Stein, 1993) and therefore facilitates fluency of motor actions. It would follow that this is a possible role of the cerebellum in language. It may be, in some way, preparing the cortex during language processing allowing for more fluent functioning, be that the understanding of or delivering of speech. Lesage et al., (2012) made a similar assertion in their paper examining the role of the cerebellum in sentence prediction trough rTMS. They found that right rTMS resulted in slower prediction, measured via fixation latency to a target final object that was predictable based on a word placed earlier in the sentence. Based on these findings they proposed that the right cerebellum, with input from cortical language areas such as Broca's area, provides an efferent copy of internalised speech, therefore allowing the cerebellum to aid speech prediction. This is supported by the finding that cerebellar cTBS primarily effects associative rather than categorical priming, i.e. pairs of words that consistently co-occur in speech (Argyropoulos, 2011; Argyropoulos & Muggleton, 2013), and that when a task does not require semantic access, but only phonological processing, this prediction does not occur (Chapter 4).

Additionally, the finding that cerebellar cTBS modulates the N400 further supports this proposal (Chapter 6). We elicited this ERP using highly predictable sentences and this wave is believed to be driven by cortical language areas (Kutas & Federmeier, 2011). Modulation of this component, via right cerebellar stimulation, implies that there is an impact of the cerebellar functioning later in the processing of language.

Short SOA backward priming. The impact of the findings presented here reach also to the literature regarding cognitive models of priming. Forward priming occurs when the first word of a pair is presented (e.g. DOG) and responses to a second related word (e.g. BONE) are facilitated (Neely, 1991). This phenomenon has been modelled in terms of the automatic spreading of activation from the prime to related words that include the target (Collins & Loftus, 1975). This process is very fast and explains the presence of forward priming at short SOAs (Posner & Snyder, 1975; Neely, 1976), the presence of forward priming at long SOAs is more commonly attributed to top-down strategic activation of words in memory (Neely, 1991).

The presence of backward priming, the facilitation of the second word when the pair is presented in the reverse order (e.g. BONE → DOG) is typically explained as involving strategic memory retrieval; this is a longer process and can only account for long SOA backward priming (Neely, 1991). However, backward priming is also observed at short SOAs (Kahan, Neely & Forsythe, 1999; Petersen & Simpson, 1989). It has been suggested that the spreading of activation mentioned above can also account for this effect (Koriat, 1981), but this spreading of activation typically only spreads in the forward direction, meaning that in order for this model to account for backward priming feedback loops connecting the prime and target must also be present (Koriat, 1981).

As has been previously discussed, the role of the cerebellum seems to be to integrate information that is temporally linked, thus improving fluency. Further, models of cerebellar function often include feedback loops to constantly update these internal models (Miall, Weir, Wolpert & Stein, 1993). Our finding that left cerebellar stimulation modulates backward priming gives, for the first time, a potential indication of the location of mechanisms that could explain short SOA backward priming. Perhaps, the role of the cerebellum here is to employ these feedback loops in order to quickly facilitate the backward priming effect we observe at short SOAs.

This finding of backward priming localised to the left cerebellar hemisphere is inconsistent with general notion that the cerebellum is ‘right-lateralised’ for language. Imaging studies show activation in the right cerebellar hemisphere during language tasks (Keren-Happuch, Chen, Ho & Desmond, 2014; Stoodley & Schmahmann, 2009) and TMS evidence also points to a right cerebellar locus (Argyropoulos, 2011; Argyropoulos & Muggleton, 2013; Lesage et al., 2012). However, evidence from visual hemifield studies (Koivisto, 1998), ERP studies (Franklin et al., 2007) and fMRI studies (O’Hare et al., 2008; Terrien et al., 2013) suggest that the processes involved in backward priming are instead localised to the right cerebral hemisphere. It is therefore logical that we would find differences in backward priming as a result of left cerebellar cTBS as this hemisphere is primarily connected to the right cerebral cortex (Ito, 1984). The modulation of cerebellar backward priming function in the left hemisphere suggests that the cerebellum is supporting this function in the right cerebral cortex.

Implications for understanding the mechanisms of cTBS on the cerebellum

A much-debated issue within the domain of cerebellar cTBS is the effect that stimulation has on the cerebellum and how this modulates function in the cortex. Much of the research in this domain has been on motor functioning as this is relatively easy to measure using motor evoked potentials (for example, Koch et al., 2008; Oliveri, Koch, Torriero &

Caltagirone, 2005). However, these findings tell us only about the impact of the stimulation on later motor function rather than the specific cause of this change in the cerebellar cortex.

Further, mapping these findings onto cognitive functions is very difficult. Arguably, cognitive functioning is rather more complicated than motor function and involves a wider array of processes in order to be completed successfully. Research in the domain of language has found both facilitatory effects and inhibitory effects, and there is some evidence that this depends on the type of TMS used, cTBS tends to be facilitatory (Argyropoulos, 2011; Argyropoulos & Muggleton, 2013), whereas rTMS tends to be inhibitory (Lesage et al., 2012). However, there is room for varying interpretations, for example, increases in priming size could be driven by changes in the processing of either the related or unrelated stimuli and the effects would therefore be either facilitatory or inhibitory respectively. It is difficult to be certain about which of these is most likely without understanding the mechanisms of TMS on the cerebellum at a cellular level, which is not currently possible in humans (Ito, 2008).

The role of the cerebellum in the range of functions in which it is involved has tended to be explained in terms of internal models, which in the motor domain can be classified as either inverse or forward (Jordan & Rumelhart, 1992; Kawato, Furawaka & Suzuki, 1987). These models, which have been explained in more detail in the general introduction, are thought to be instantiated in the homogenous cellular structure of the cerebellum (Eccles et al., 1967). It is argued that the internal models rely on the homogenous cellular systems in the cerebellum, namely microcomplexes. Each microcomplex is able to learn a specific function (Ito, 2008) which, in the domain of language, could be one association. Within these modules, climbing fibres modify the models based on feedback from errors by causing long-term depression (LTD) in the Purkinje cells. The Purkinje cells are the principal output of the cerebellum to the cortex via the deep cerebellar nuclei (Koch et al., 2008). As detailed in previous chapters, cerebellar TMS is thought to suppress (Koch et al., 2008; Picazio, Oliveri, Koch, Caltagirone & Petrosini, 2013) or activate (Groiss & Ugawa, 2012; Iwata & Ugawa, 2005; Ugawa & Iwata, 2005) the Purkinje cells, resulting cortical and behavioural changes that are either facilitatory or inhibitory respectively.

In chapter 4 the results indicated that there were no effects of cTBS on the priming task. Therefore, the findings outlined in that chapter cannot be interpreted with regard to cTBS mechanisms in the cerebellum.

In chapter 5 we found a facilitatory effect of left cerebellar cTBS on backward priming but did not replicate findings in the right cerebellar hemisphere with respect to forward priming. This supports the previous literature in the domain of priming, which has principally pointed to a facilitatory effect of cerebellar cTBS on priming (Argyropoulos, 2011; Argyropoulos & Muggleton, 2013). As has been discussed above, one hypothesis for the presence of backward priming at short SOAs is the presence of feedback loops between the otherwise forward connections which make the spreading of activation theory in forward priming a possible explanation (Koriat, 1981). We hypothesise that it is the feedback loops present in the internal models attributed to the cerebellum that may be fulfilling this role. Here then, cTBS has facilitated these loops in order to improve backward priming. One possibility is that cTBS has modulated the Purkinje cells which, as mentioned above receive input from the climbing fibres. Climbing fibres are key in the updating of the internal models via feedback (Ito, 2008). These cells possibly represent the anatomical substrate of the aforementioned feedback loops required for backward priming (Koriat, 1981). It has previously been proposed that within the cerebellum there are paired forward and inverse models which are acquired and used together in the MOSAIC (modular selection and identification for control) model (Wolpert & Kawato, 1998). This model has been proposed to map onto the closed loop circuits between the cortex and the cerebellum (Haruno, Wolpert & Kawato, 2003). Backward priming in this context could be attributed to the inverse models, however, the modulation of backward priming, but not forward, through cerebellar stimulation implies that these models may not be paired, or are held in differing locations within the cerebellum. Although forward priming has not been modulated here, it has been affected by cTBS in other studies (Argyropoulos, 2011; Argyropoulos & Muggleton, 2013), however this has been in the right cerebellar hemisphere, whereas left cTBS here has affected backward priming. This suggests that if these paired models exist, and we have not affected them here with our stimulation parameters, they are held in contralateral cerebellar hemispheres.

In chapter 6 we found larger electrophysiological effects for the incongruent stimuli, which in this context could be viewed as prediction errors. Modulation of the Purkinje cells here may have changed the speed at which the models are updated as a result of error feedback and therefore modulate the processing of errors later in the system. I propose that as a result of the stimulation reported here we have perhaps modulated the functioning of the feedback loops in the cerebellum, as climbing fibres feed information regarding prediction errors to the Purkinje cells, modulation of the Purkinje cells might result in the facilitation or increased ease of the processing of the incongruent or error stimuli as exhibited here.

Overall, these studies in combination paint a convoluted picture of the potential mechanisms through which cTBS is affecting the cerebellar cortex and later related function. Further examination of the processes involved in cerebellar cTBS and the exploration of differences, if any, between the effect of cerebellar cTBS on areas that employ forward and inverse models should be examined in the future.

Limitations

Limitations for each individual experiment have been detailed in the relevant chapters. However, there is a methodological issue that applies to all three experiments. As discussed above, this thesis did not employ MRI-guided cTBS. This method has previously been employed in cerebellar research in domains such as verbal working memory (Tomlinson, Davis, Morgan & Bracewell, 2013) and language (Runnqvist et al., 2016). The principal benefit of using MRI-guided cTBS is that there is a much higher chance of accuracy in terms of stimulating the areas of interest, ensuring that effects of TMS are due to stimulation of the intended area. Additionally, the use of fMRI and MRI-guided TMS has been shown to result in larger effect sizes and therefore requires fewer participants to result in significant effects (Sack et al., 2008). However, despite not employing this technique we have found significant effects of cTBS on cerebellar predictive language function by using the inion as an anatomical landmark.

Future research and outstanding questions

In chapter 4 we showed that stimulation of the cerebellum did not modulate semantic prediction as this task did not require semantic processing to be completed. That chapter employed an associative priming task, performance on such a task has previously been modulated by right cerebellar cTBS (Argyropoulos, 2011; Argyropoulos & Muggleton, 2013). We showed here that this task required phonological but not semantic processing. Previous studies that have employed this task used different stimulation parameters to those used here, perhaps in these studies the functioning modulated by the cTBS was phonological prediction rather than semantic prediction. In future, it would be beneficial to examine the role of the cerebellum in specifically phonological processing using the stimulation parameters used by Argyropoulos and colleagues, and to perhaps dissociate these areas from the areas stimulated in this thesis for phonological and semantic prediction.

Further, teasing apart the role of the cerebellum in motoric, phonological and semantic processing would be useful in the future and could be examined using cerebellar cTBS and other types of task. For example, articulatory suppression, where participants verbally repeat irrelevant words (e.g. Letters, Emerson & Miyake, 2003; Words, Baddeley, Chincotta & Adlam, 2001; Bryck & Mayr, 2005; or Numbers, Baddeley, Lewis & Vallar, 1984), might help to suppress the use of subvocal rehearsal thereby minimizing the use of motoric and phonological processing allowing more detailed examination cognitive processing (Ullman, 2006) such as semantic processing. As described in the general introduction, the dual stream model includes a, motoric, dorsal stream and a, phonological and semantic, ventral stream (Hickok & Poeppel, 2004). Conceivably, given the evidence presented in this thesis, the cerebellum could contribute to both, in terms of motoric articulation, phonological prediction and semantic prediction. To some extent the findings that have indicated a role for the cerebellum in semantic prediction could be attributed to the role of the cerebellum in motoric functioning and therefore subvocal rehearsal. By removing this confound we may better understand the role of the cerebellum in semantics and be better able to place it within current theories of speech perception and word recognition.

Chapter 6 examined modulation of the N400, and therefore predictive function, resulting from cerebellar cTBS. We used a semantic violations task, which reliably elicits this component (Kutas & Hillyard, 1980; Kutas & Van Petten, 1988). However, the predictive processes present during other common semantic tasks can also be indexed using this component, for example word priming (Kutas & Federmeier, 2011). Two of the chapters detailed here (Chapters 4 & 5) in addition to the previous literature using cTBS over the right cerebellum have employed associative priming to examine cerebellar language function: however, in the context of a lexical decision task we were unable to replicate previous findings as regards right cerebellar stimulation. The combination of associative priming in a task which requires semantic processing and monitoring of the N400 may give further insight into the impact of the cerebellum on predictive function in later cortical processing. It may further confirm that the associative and predictive functions that have been modulated by cTBS previously are in fact part of the same process, which has been proposed previously in this domain (Beaton, Allen-Walker & Bracewell, 2015) and in the domain of psycholinguistics (Federmeier & Laszlo, 2009), and therefore modulate the ERP component in the same way. The combination of these two techniques has proven effective here in helping to examine the efficacy of tasks employed for eliciting semantic processing and may help to further elucidate the role of the cerebellum in language and how this role interacts with later language processing.

Additionally, future research could employ a combination of cTBS and fMRI. Here we show how processing in the cerebellum is affecting the cortically driven N400 component; however, this wave is elicited by the functioning in a range of language specific regions (Kutas & Federmeier, 2011). Further, given the poor spatial resolution of EEG it may be useful to also employ a combination of cTBS and fMRI, perhaps similarly to the protocol used here (Pre and Post cTBS), during a predictive language task. Previous research has shown that rTMS over the cerebellum has effects on language-specific regions of the cortex (Cho et al., 2012), and fMRI research has indicated regions including Broca's area and Wernicke's area in addition to the cerebellum are activated during incongruent trials on semantic violation tasks (Moberget et al., 2014). However, the combination of fMRI and cTBS has not been carried out with a specific view to examine modulation of language prediction and later functional changes in the cortex.

This combination of cTBS and fMRI may also help to account for some of the disparities in the location of stimulation. As has been detailed previously in this chapter, the literature has been inconsistent with the location choices of cTBS application. But these studies have often found effects that are broadly in agreement in terms of the role of the cerebellum in language. fMRI may help to reveal any topographical differences in locations of cerebellar activation/suppression as a result of cTBS. This is not possible with EEG as there is little to no coverage of cerebellar structures.

Another issue within the domain of language in the cerebellum is discovering specifically how cTBS is affecting the priming to pairs of words and sentences detailed here. As mentioned previously it is difficult to determine whether the effects of cTBS are on the congruent or incongruent pairs or sentences. The findings detailed in this thesis have provided evidence for both, detailed above. Further, given that a large part of the internal models that are attributed to the cerebellum rely upon feedback based on errors in order to update themselves (Miall & Wolpert, 1996; Wolpert & Kawato, 1998; Wolpert, Miall & Kawato, 1998) and that the climbing fibres, which fulfill this feedback role (Ito, 2008), link directly to the Purkinje cells which are a) the main output of the cerebellum and b) thought to be the cells which are specifically modulated via stimulation, there is a possibility that cTBS could affecting responses to errors, namely incongruent stimuli. Therefore, future research may want to differentiate this role by designing tasks that would likely require cerebellar involvement but without the reliance upon tasks that use a congruent vs incongruent manipulation. A task of this nature was employed by Lesage et al. (2012), who compared two types of congruent sentence. Their manipulation was instead the predictability of the final word based on words placed earlier, it was either predictable or not, the target was always congruent with the content of the sentence.

Conclusion

This thesis has investigated the role of the cerebellum in predictive language function by modulating this process through cerebellar cTBS and monitoring changes in performance on priming tasks and changes in electrophysiological measures. The three experiments detailed here support the role of the cerebellum in language prediction, and additionally support the hypothesis that the cerebellum applies similar computations across multiple domains, both motor and non-motor. Additionally, I have indicated that the role of the cerebellum in priming extends to backward priming, which may explain the mechanisms through which short SOA backward priming occurs. Finally, through combined cTBS and ERP methodology we have shown that modulation of the role of the cerebellum in language has later consequences in predictive processing which reinforces the proposal that it plays a supportive role in language prediction. Further, this combined methodology has proven an effective tool here and I have therefore outlined some future directions, employing this and other methods, to address some outstanding questions in this field.

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Appendices

Appendix A: Experimental word pair stimuli used in chapter 4

Related Pairs

Opposite Prime	Opposite Target	Categorical Prime	Categorical Target
husband	WIFE	husband	SPOUSE
good	BAD	good	FINE
boy	GIRL	boy	CHILD
yes	NO	yes	DEFINITELY
up	DOWN	up	HIGH
rich	POOR	rich	WEALTH
new	OLD	new	FRESH
above	BELOW	above	OVER
true	FALSE	true	RIGHT
now	THEN	now	PRESENT
near	FAR	near	CLOSE
black	WHITE	black	BROWN
day	NIGHT	day	SUN
fast	SLOW	fast	QUICK
win	LOSE	win	SUCCESS
first	LAST	first	INITIALLY
top	BOTTOM	top	PEAK
hit	MISS	hit	STRIKE
less	MORE	less	FEWER
strong	WEAK	strong	TOUGH
add	SUBTRACT	add	PLUS
major	MINOR	major	IMPORTANT
rise	FALL	rise	ASCEND
buy	SELL	buy	PURCHASE
war	PEACE	war	BATTLE
start	FINISH	start	BEGIN
early	LATE	early	PUNCTUAL
better	WORSE	better	IMPROVE
backward	FORWARD	backward	REVERSE
enemy	FRIEND	enemy	FOE
happy	SAD	happy	CONTENT
thin	THICK	thin	SLIM
awake	ASLEEP	awake	ALERT
love	HATE	love	AFFECTION
innocent	GUILTY	innocent	NAÏVE
for	AGAINST	for	PRO
big	SMALL	big	LARGE
laugh	CRY	laugh	SMILE
open	SHUT	open	AJAR
defend	ATTACK	defend	PROTECT

Unrelated opposite pairs

List 1		List 2		List 3		List 4	
Prime	**Target**	**Prime**	**Target**	**Prime**	**Target**	**Prime**	**Target**
husband	AGAINST	husband	WORSE	husband	OLD	husband	LATE
good	ASLEEP	good	LATE	good	MINOR	good	LOSE
boy	ATTACK	boy	WHITE	boy	LAST	boy	MISS
yes	BAD	yes	WEAK	yes	HATE	yes	MORE
up	CRY	up	THICK	up	GUILTY	up	NIGHT
rich	BOTTOM	rich	THEN	rich	GIRL	rich	NO
new	BELOW	new	SUBTRACT	new	FORWARD	new	PEACE
above	FALSE	above	SMALL	above	FRIEND	above	POOR
true	DOWN	true	SLOW	true	FINISH	true	SAD
now	FALL	now	SHUT	now	FAR	now	SELL
near	FRIEND	near	SELL	near	FALSE	near	SHUT
black	FAR	black	SAD	black	FALL	black	SLOW
day	GIRL	day	POOR	day	DOWN	day	SMALL
fast	GUILTY	fast	PEACE	fast	CRY	fast	BAD
win	FORWARD	win	OLD	win	BOTTOM	win	SUBTRACT
first	HATE	first	NO	first	BELOW	first	THICK
top	MINOR	top	NIGHT	top	BAD	top	GIRL
hit	FINISH	hit	MORE	hit	ASLEEP	hit	WHITE
less	OLD	less	MISS	less	AGAINST	less	WIFE
strong	LAST	strong	MINOR	strong	WIFE	strong	WORSE
add	NIGHT	add	LOSE	add	PEACE	add	AGAINST
major	LATE	major	CRY	major	WORSE	major	ASLEEP
rise	LOSE	rise	LAST	rise	WHITE	rise	FRIEND
buy	MISS	buy	HATE	buy	ATTACK	buy	FALSE
war	MORE	war	WIFE	war	NIGHT	war	BELOW
start	NO	start	GIRL	start	THICK	start	BOTTOM
early	PEACE	early	FRIEND	early	THEN	early	CRY
better	POOR	better	FORWARD	better	SUBTRACT	better	DOWN
backward	SAD	backward	FINISH	backward	SMALL	backward	ATTACK
enemy	SELL	enemy	FAR	enemy	SLOW	enemy	FORWARD
happy	SHUT	happy	FALSE	happy	WEAK	happy	FAR
thin	SLOW	thin	FALL	thin	SELL	thin	FINISH
awake	SMALL	awake	DOWN	awake	SAD	awake	WEAK
love	SUBTRACT	love	AGAINST	love	POOR	love	THEN
innocent	THEN	innocent	BOTTOM	innocent	SHUT	innocent	FALL
for	THICK	for	BELOW	for	NO	for	GUILTY
big	WIFE	big	GUILTY	big	MORE	big	HATE
laugh	WHITE	laugh	ATTACK	laugh	MISS	laugh	MINOR
open	WEAK	open	ASLEEP	open	LOSE	open	OLD
defend	WORSE	defend	BAD	defend	LATE	defend	LAST

Unrelated categorical pairs

List 1		**List 2**		**List 3**		**List 4**	
Prime	**Target**	**Prime**	**Target**	**Prime**	**Target**	**Prime**	**Target**
husband	SUCCESS	husband	IMPORTANT	husband	NAÏVE	husband	LARGE
good	STRIKE	good	AJAR	good	BEGIN	good	INITIALLY
boy	WEALTH	boy	ALERT	boy	PEAK	boy	IMPROVE
yes	TOUGH	yes	ASCEND	yes	PLUS	yes	IMPORTANT
up	SPOUSE	up	LARGE	up	PRESENT	up	NAÏVE
rich	SUN	rich	BEGIN	rich	PRO	rich	STRIKE
new	SMILE	new	BROWN	new	PROTECT	new	FOE
above	SLIM	above	CHILD	above	PUNCTUAL	above	FINE
true	REVERSE	true	BATTLE	true	PURCHASE	true	FEWER
now	PURCHASE	now	CONTENT	now	SUCCESS	now	DEFINITELY
near	RIGHT	near	DEFINITELY	near	REVERSE	near	CONTENT
black	QUICK	black	FEWER	black	RIGHT	black	CLOSE
day	PUNCTUAL	day	SMILE	day	SLIM	day	CHILD
fast	PROTECT	fast	NAÏVE	fast	SMILE	fast	OVER
win	PEAK	win	FRESH	win	SPOUSE	win	BEGIN
first	NAIVE	first	HIGH	first	BATTLE	first	BROWN
top	AFFECTION	top	FINE	top	FOE	top	AFFECTION
hit	AJAR	hit	IMPROVE	hit	SUN	hit	ALERT
less	ASCEND	less	INITIALLY	less	TOUGH	less	AJAR
strong	ALERT	strong	CLOSE	strong	WEALTH	strong	ASCEND
add	BATTLE	add	FOE	add	CHILD	add	WEALTH
major	BROWN	major	OVER	major	AJAR	major	TOUGH
rise	CLOSE	rise	AFFECTION	rise	ALERT	rise	BATTLE
buy	DEFINITELY	buy	PLUS	buy	ASCEND	buy	SUCCESS
war	CONTENT	war	PRESENT	war	IMPORTANT	war	HIGH
start	FEWER	start	PRO	start	AFFECTION	start	PROTECT
early	FOE	early	PROTECT	early	BROWN	early	SMILE
better	CHILD	better	PUNCTUAL	better	OVER	better	SLIM
backward	FINE	backward	PURCHASE	backward	CLOSE	backward	RIGHT
enemy	BEGIN	enemy	QUICK	enemy	CONTENT	enemy	REVERSE
happy	IMPORTANT	happy	REVERSE	happy	DEFINITELY	happy	QUICK
thin	HIGH	thin	RIGHT	thin	FEWER	thin	PURCHASE
awake	LARGE	awake	SLIM	awake	FINE	awake	PUNCTUAL
love	IMPROVE	love	PEAK	love	STRIKE	love	PLUS
innocent	OVER	innocent	SPOUSE	innocent	FRESH	innocent	PRO
for	INITIALLY	for	STRIKE	for	HIGH	for	PRESENT
big	PRO	big	SUCCESS	big	QUICK	big	SPOUSE
laugh	PRESENT	laugh	SUN	laugh	IMPROVE	laugh	PEAK
open	PLUS	open	TOUGH	open	INITIALLY	open	SUN
defend	FRESH	defend	WEALTH	defend	LARGE	defend	FRESH

Non-word pairs

Opposite Prime	Opposite Target	Categorical Prime	Categorical Target
husband	ANAIGST	husband	AFFENTIOC
good	ASPEEL	good	ANCESD
boy	ATTECK	boy	ARAJ
yes	BEWOL	yes	ATERL
up	CEAPE	up	CHOLD
rich	DEB	rich	CLESE
new	DEWN	new	FENE
above	FASLE	above	FRASH
true	DRIENF	true	FUE
now	FER	now	GARLE
near	FOLL	near	GEBIN
black	GERL	black	HEGH
day	HETE	day	IMTORTANP
fast	ILD	fast	ITINIALLY
win	KEAW	win	IVPROME
first	LESE	first	KEAP
top	LETE	top	LATTBE
hit	MURE	hit	LEAWTH
less	MOTTOB	less	NAOVE
strong	NA	strong	NONTECT
add	NHET	add	NROWB
major	NIFISH	major	OREV
rise	RINOM	rise	PLES
buy	ROOP	buy	PRI
war	SALL	war	PUSCHARE
start	SED	start	QUECK
early	SHET	early	SECCESS
better	SISM	better	SEN
backward	SLIW	backward	SKRITE
enemy	SMILL	enemy	SLEM
happy	SORWE	happy	SMOLE
thin	TASL	thin	SPAUSE
awake	THACK	awake	TEFINIDELY
love	THIWE	love	TEUGH
innocent	TIGHN	innocent	TIGHR
for	TUBTRACS	for	TRESENP
big	TUILGY	big	TROPECT
laugh	WEFE	laugh	TUNCPUAL
open	WORFARD	open	VERERSE
defend	YRC	defend	WEFER

Appendix B: Experimental word pair stimuli used in chapter 5

Related pairs

Forward		**Backward**		**Categorical**	
Prime	**Target**	**Prime**	**Target**	**Prime**	**Target**
cardboard	BOX	box	CARDBOARD	steel	METAL
pigeon	HOLE	hole	PIGEON	cotton	FABRIC
chain	REACTION	reaction	CHAIN	blue	COLOUR
corner	STONE	stone	CORNER	knife	UTENSIL
court	YARD	yard	COURT	chair	FURNITURE
cross	ROAD	road	CROSS	apple	FRUIT
book	WORM	worm	BOOK	gun	WEAPON
lip	STICK	stick	LIP	hammer	TOOL
chocolate	BAR	bar	CHOCOLATE	football	SPORT
fruit	FLY	fly	FRUIT	eagle	BIRD
crack	DOWN	down	CRACK	car	VEHICLE
high	WAY	way	HIGH	doll	TOY
bus	BOY	boy	BUS	ballet	DANCE
hatch	BACK	back	HATCH	carrot	VEGETABLE
bed	PAN	pan	BED	fly	INSECT
foot	NOTE	note	FOOT	rose	FLOWER
head	LINE	line	HEAD	water	LIQUID
back	PACK	pack	BACK	milk	DAIRY
space	SHIP	ship	SPACE	triangle	SHAPE
coat	RACK	rack	COAT	ring	JEWELLERY
eye	BALL	ball	EYE	sergeant	RANK
fire	TRUCK	truck	FIRE	diamond	GEM
hard	CORE	core	HARD	summer	SEASON
score	BOARD	board	SCORE	oak	WOOD

Unrelated word pairs

Forward		**Backward**		**Categorical**	
Prime	**Target**	**Prime**	**Target**	**Prime**	**Target**
bus	HOLE	rack	CARDBOARD	ballet	METAL
hatch	BOX	ball	PIGEON	carrot	FABRIC
bed	REACTION	truck	CHAIN	fly	COLOUR
foot	STONE	down	CORNER	rose	UTENSIL
head	YARD	board	COURT	water	FURNITURE
fire	ROAD	box	CROSS	milk	FRUIT
space	WORM	hole	BOOK	triangle	WEAPON
court	STICK	reaction	LIP	ring	TOOL
eye	BAR	stone	CHOCOLATE	sergeant	SPORT
back	FLY	yard	FRUIT	diamond	BIRD
hard	DOWN	line	CRACK	summer	VEHICLE
score	WAY	worm	HIGH	oak	TOY
cardboard	BOY	stick	BUS	steel	DANCE
pigeon	BACK	way	HATCH	cotton	VEGETABLE
chain	PAN	fly	BED	blue	INSECT
corner	NOTE	core	FOOT	knife	FLOWER
coat	LINE	bar	HEAD	chair	LIQUID
cross	PACK	boy	BACK	apple	DAIRY
book	SHIP	back	SPACE	gun	SHAPE
lip	RACK	pan	COAT	hammer	JEWELLERY
chocolate	BALL	pack	EYE	football	RANK
fruit	TRUCK	note	FIRE	eagle	GEM
crack	CORE	road	HARD	car	SEASON
high	BOARD	ship	SCORE	doll	WOOD

Non-word pairs

Forward		Backward		Categorical	
Prime	**Target**	**Prime**	**Target**	**Prime**	**Target**
bus	HULE	rack	CARDDOARB	ballet	MATAL
hatch	BIX	ball	PAGEON	carrot	FEBRIC
bed	TEACRION	truck	CHOIN	fly	CALOUR
foot	SNOTE	down	CARNER	rose	UTANSIL
head	YURD	board	CAURT	water	FURTINURE
fire	DOAR	box	CRISS	milk	FRAIT
space	WERM	hole	BOEK	triangle	WEIPON
court	STECK	reaction	LEP	ring	TOEL
eye	BER	stone	CHOTOLACE	sergeant	SPART
back	FYL	yard	FRUAT	diamond	BERD
hard	DUWN	line	CRECK	summer	VAHICLE
score	WIY	worm	HAGH	oak	TEY
cardboard	BEY	stick	BAS	steel	DONCE
pigeon	BOCK	way	HETCH	cotton	VETEGABLE
chain	PON	fly	DEB	blue	INSACT
corner	NUTE	core	FOET	knife	FLEWER
coat	LINI	bar	HEOD	chair	LAQUID
cross	CAPK	boy	CABK	apple	DEIRY
book	SHUP	back	SPUCE	gun	SHUPE
lip	RECK	pan	COUT	hammer	JERELLEWY
chocolate	LALB	pack	EYA	football	RONK
fruit	TROCK	note	FERE	eagle	GOM
crack	CERE	road	HIRD	car	SOASON
high	DOARB	ship	SCERE	doll	WOED

Appendix C: Experimental sentence stimuli used in chapter 6

Congruent experimental sentences

Sentence	**Word1**	**Word2**	**Word3**	**Word4**	**Target**
To make coffee sweeter	you	can	add		sugar.
A pigeon is one of many	types	of			bird.
Midwives help deliver	your				baby.
We needed a ladder as the cat was	stuck	up	the		tree.
Iron, copper and tin	are	all	types	of	metal.
A saxophone is a	musical				instrument.
I bought a brand new TV	that	had	a	42"	screen.
A moat usually surrounds	a				castle.
I cut up my food with a	knife	and			fork.
An eagle is a	bird	of			prey.
In front of the hotel is a	beautiful	sandy			beach.
The jockey put the saddle	on	his			horse.
Emily combed Sylvia's	beautiful				hair.
The moon shines	at				night.
Rob looked at his watch	to	check	the		time.
To write a letter one needs	a	pen	and		paper.
The weaker army	had	to	admit		defeat.
Bob had many good resolutions	for	the	new		year.
Clark ran to the platform,	but	still	missed	the	train.
The hungry man shovelled the food	into	his			mouth.
A giraffe	has	a	very	long	neck.
At the bakery Clare bought	a	loaf	of		bread.
The bird couldn't fly;	it	had	a	broken	wing.
Billy took his savings	to	the			bank.
The farmer milked	his	only			cow.
Steve washed the dishes	in	the	kitchen		sink.
Tanya went to the bank	to	open	an		account.
Cut flowers are put	in	a			vase.
A rose is a	very	beautiful			flower.
Tina was blind	in	one			eye.
The loosing team didn't	stand	a			chance.
Kate put the roast	in	the			oven.
Vegetarians	don't	eat			meat.
Helen looked at herself	in	the			mirror.
To eat soup	one	uses	a		spoon.

Incongruent experimental sentences – List 1

Sentence	Word1	Word2	Word3	Word4	Target
To make coffee sweeter	you	can	add		tree.
A pigeon is one of many	types	of			screen.
Midwives help deliver	your				metal.
We needed a ladder as the cat was	stuck	up	the		sugar.
Iron, copper and tin	are	all	types	of	baby.
I bought a brand new TV	that	had	a	42"	bird.
A moat usually surrounds	a				fork.
A female sheep	is	a			beach.
Noah loaded all the animals	into	his			mouth.
A stack of hay	is	called	a		train.
An eagle is a	bird	of			paper.
In front of the hotel is a	beautiful	sandy			bread.
The jockey put the saddle	on	his			neck.
Emily combed Sylvia's	beautiful				wing.
The moon shines	at				year.
Rob looked at his watch	to	check	the		castle.
To write a letter one needs	a	pen	and		oven.
The weaker army	had	to	admit		prey.
Bob had many good resolutions	for	the	new		defeat.
Clark ran to the platform,	but	still	missed	the	bank.
The hungry man shovelled the food	into	his			sink.
At the bakery Clare bought	a	loaf	of		time.
The bird couldn't fly;	it	had	a	broken	horse.
Billy took his savings	to	the			vase.
The farmer milked	his	only			account.
Steve washed the dishes	in	the	kitchen		instrument.
Tanya went to the bank	to	open	an		eye.
Cut flowers are put	in	a			meat.
A rose is a	very	beautiful			mirror.
Tina was blind	in	one			chance.
The loosing team didn't	stand	a			night.
Kate put the roast	in	the			flower.
Vegetarians	don't	eat			spoon.
Helen looked at herself	in	the			cow.
To eat soup	one	uses	a		hair.

Incongruent experimental sentences – List 2

Sentence	Word1	Word2	Word3	Word4	Target
To make coffee sweeter	you	can	add		paper.
A pigeon is one of many	types	of			castle.
We needed a ladder as the cat was	stuck	up	the		bank.
A saxophone is a	musical				tree.
A ships sails are held up	by	the			bread.
I bought a brand new TV	that	had	a	42"	wing.
A moat usually surrounds	a				mouth.
Most baths have a	hot	and	cold		mirror.
I cut up my food with a	knife	and			neck.
A female sheep	is	a			screen.
Noah loaded all the animals	into	his			year.
A stack of hay	is	called	a		chance.
An eagle is a	bird	of			baby.
In front of the hotel is a	beautiful	sandy			bird.
The moon shines	at				defeat.
Rob looked at his watch	to	check	the		fork.
To write a letter one needs	a	pen	and		sugar.
The weaker army	had	to	admit		night.
Clark ran to the platform,	but	still	missed	the	eye.
The hungry man shovelled the food	into	his			meat.
A giraffe	has	a	very	long	vase.
At the bakery Clare bought	a	loaf	of		metal.
The bird couldn't fly;	it	had	a	broken	sink.
Billy took his savings	to	the			beach.
The farmer milked	his	only			hair.
Steve washed the dishes	in	the	kitchen		flower.
Tanya went to the bank	to	open	an		oven.
Cut flowers are put	in	a			spoon.
A rose is a	very	beautiful			horse.
Tina was blind	in	one			instrument.
The loosing team didn't	stand	a			prey.
Kate put the roast	in	the			cow.
Vegetarians	don't	eat			time.
Helen looked at herself	in	the			account.
To eat soup	one	uses	a		train.

Incongruent experimental sentences – List 3

Sentence	Word1	Word2	Word3	Word4	Target
To make coffee sweeter	you	can	add		bread.
A pigeon is one of many	types	of			year.
Midwives help deliver	your				sink.
We needed a ladder as the cat was	stuck	up	the		oven.
Iron, copper and tin	are	all	types	of	prey.
A saxophone is a	musical				horse.
A ships sails are held up	by	the			night.
I bought a brand new TV	that	had	a	42"	spoon.
A moat usually surrounds	a				bank.
Most baths have a	hot	and	cold		tree.
A female sheep	is	a			flower.
Noah loaded all the animals	into	his			vase.
A stack of hay	is	called	a		wing.
An eagle is a	bird	of			defeat.
In front of the hotel is a	beautiful	sandy			account.
The jockey put the saddle	on	his			screen.
Emily combed Sylvia's	beautiful				neck.
The moon shines	at				eye.
To write a letter one needs	a	pen	and		hair.
The weaker army	had	to	admit		cow.
Bob had many good resolutions	for	the	new		time.
Clark ran to the platform,	but	still	missed	the	bird.
The hungry man shovelled the food	into	his			paper.
A giraffe	has	a	very	long	fork.
At the bakery Clare bought	a	loaf	of		mirror.
The bird couldn't fly;	it	had	a	broken	instrument.
Billy took his savings	to	the			baby.
The farmer milked	his	only			train.
Steve washed the dishes	in	the	kitchen		castle.
A rose is a	very	beautiful			metal.
Tina was blind	in	one			mouth.
The loosing team didn't	stand	a			meat.
Kate put the roast	in	the			beach.
Vegetarians	don't	eat			chance.
Helen looked at herself	in	the			sugar.

Incongruent experimental sentences – List 4

Sentence	Word1	Word2	Word3	Word4	Target
To make coffee sweeter	you	can	add		hair.
A pigeon is one of many	types	of			beach.
Midwives help deliver	your				horse.
We needed a ladder as the cat was	stuck	up	the		cow.
Iron, copper and tin	are	all	types	of	castle.
A saxophone is a	musical				time.
A ships sails are held up	by	the			train.
I bought a brand new TV	that	had	a	42"	sink.
A moat usually surrounds	a				bird.
Most baths have a	hot	and	cold		bread.
I cut up my food with a	knife	and			flower.
A female sheep	is	a			vase.
Noah loaded all the animals	into	his			sugar.
A stack of hay	is	called	a		mirror.
An eagle is a	bird	of			night.
The jockey put the saddle	on	his			wing.
Emily combed Sylvia's	beautiful				metal.
The moon shines	at				account.
To write a letter one needs	a	pen	and		defeat.
The weaker army	had	to	admit		year.
Bob had many good resolutions	for	the	new		bank.
Clark ran to the platform,	but	still	missed	the	neck.
The hungry man shovelled the food	into	his			tree.
A giraffe	has	a	very	long	screen.
At the bakery Clare bought	a	loaf	of		chance.
The bird couldn't fly;	it	had	a	broken	oven.
Billy took his savings	to	the			meat.
The farmer milked	his	only			fork.
Steve washed the dishes	in	the	kitchen		eye.
Tanya went to the bank	to	open	an		instrument.
A rose is a	very	beautiful			mouth.
The loosing team didn't	stand	a			spoon.
Kate put the roast	in	the			baby.
Vegetarians	don't	eat			paper.
To eat soup	one	uses	a		prey.

Congruent filler sentences

Sentence	Word1	Word2	Word3	Word4	Target
When it rains outside you should	put	on	your		coat.
Children under 16	should	normally	attend		school.
He rarely mowed the lawn	in	his	back		garden.
You would go to a cash point	to	take	out	some	money.
At a BBQ you put your food	on	a	paper		plate.
If you are ill your doctor can	prescribe	you			medicine.
The Canadian flag features	a	maple			leaf.
As a kid I spent days learning	to	ride	a		bike.
The shop did not have the shoes	in	Anne's			size.
She left the church after singing	the	last			hymn.
As soon as the crew had boarded,	the	boat	set		sail.
Anti-war activists want	world				peace.
William was unsure whether he was	wrong	or			right.
Dan didn't want a bath,	but	took	a		shower.
I don't know; I simply cannot	make	up	my		mind.
Everyone has a biological	mother	and			father.
He resigned last year to the	best	of	my		knowledge.
Don't ask me where he is,	I	haven't	got	a	clue.
The mother baked her daughter	a	birthday			cake.
Stephen wanted to play	a	board			game.
A fork is usually held	in	one's	left		hand.
In the 50s miniskirts were	the	height	of		fashion.
One's nose is in the middle	of	one's			face.
Ed likes listening	to	pop			music.
Jim needed some fresh air	so	he	opened	the	window.
The party took place	in	the	living		room.
The King's son	is	called	a		prince.
An apple is a fruit,	a	cabbage	is	a	vegetable.
As Matt had no chairs he had to	sit	on	the		floor.
I asked Ian what to do,	but	he	had	no	idea.
The game was very simple;	it	had	only	one	rule.
One man's gain	is	another	man's		loss.
Natalie washed her hair	with	a	mild		shampoo.
A person one hasn't met before	is	a			stranger.
Will went to sea	in	a	little	sailing	boat.
After spring	comes				summer.
The stalker watched	Vicki's	every			move.
A married woman's title is missis,	a	man's	is		mister.
The police told Kevin that	he	was	in	serious	trouble.
Fin was thirsty, so	he	got	himself	a	drink.
A ships sails are held up	by	the			mast.
Most baths have a	hot	and	cold		tap.

A female sheep	is	a		ewe.
Noah loaded all the animals	into	his		ark.
A stack of hay	is	called	a	bale.

Incongruent filler sentences – List 1

Sentence	**Word1**	**Word2**	**Word3**	**Word4**	**Target**
When it rains outside you should	put	on	your		window.
Children under 16	should	normally	attend		vegetable.
He rarely mowed the lawn	in	his	back		stranger.
You would go to a cash point	to	take	out	some	summer.
At a BBQ you put your food	on	a	paper		shampoo.
If you are ill your doctor can	prescribe	you			size.
The Canadian flag features	a	maple			shower.
As a kid I spent days learning	to	ride	a		trouble.
The shop did not have the shoes	in	Anne's			prince.
She left the church after singing	the	last			sail.
As soon as the crew had boarded,	the	boat	set		rule.
Anti-war activists want	world				room.
William was unsure whether he was	wrong	or			medicine.
Dan didn't want a bath,	but	took	a		school.
I don't know; I simply cannot	make	up	my		plate.
Everyone has a biological	mother	and			peace.
He resigned last year to the	best	of	my		music.
Don't ask me where he is,	I	haven't	got	a	hymn.
The mother baked her daughter	a	birthday			money.
Stephen wanted to play	a	board			mister.
A fork is usually held	in	one's	left		leaf.
In the 50s miniskirts were	the	height	of		right.
One's nose is in the middle	of	one's			loss.
Ed likes listening	to	pop			mind.
Jim needed some fresh air	so	he	opened	the	knowledge.
The party took place	in	the	living		idea.
The King's son	is	called	a		move.
An apple is a fruit,	a	cabbage	is	a	hand.
As Matt had no chairs he had to	sit	on	the		father.
I asked Ian what to do,	but	he	had	no	game.
The game was very simple;	it	had	only	one	floor.
One man's gain	is	another	man's		garden.
Natalie washed her hair	with	a	mild		coat.
A person one hasn't met before	is	a			face.
Will went to sea	in	a	little	sailing	drink.
After spring	comes				boat.
The stalker watched	Vicki's	every			coat.
A married woman's title is missis,	a	man's	is		clue.
The police told Kevin that	he	was	in	serious	fashion.
Fin was thirsty, so	he	got	himself	a	bike.
A saxophone is a	musical				ewe.
A ships sails are held up	by	the			tap.

Most baths have a	hot	and	cold		bale.
I cut up my food with a	knife	and			mast.
A giraffe	has	a	very	long	ark.

Incongruent filler sentences – List 2

Sentence	Word1	Word2	Word3	Word4	Target
When it rains outside you should	put	on	your		floor.
Children under 16	should	normally	attend		bike.
He rarely mowed the lawn	in	his	back		boat.
You would go to a cash point	to	take	out	some	cake.
At a BBQ you put your food	on	a	paper		clue.
If you are ill your doctor can	prescribe	you			fashion.
The Canadian flag features	a	maple			face.
As a kid I spent days learning	to	ride	a		father.
The shop did not have the shoes	in	Anne's			drink.
She left the church after singing	the	last			coat.
As soon as the crew had boarded,	the	boat	set		game.
Anti-war activists want	world				garden.
William was unsure whether he was	wrong	or			hand.
Dan didn't want a bath,	but	took	a		hymn.
I don't know; I simply cannot	make	up	my		idea.
Everyone has a biological	mother	and			knowledge.
He resigned last year to the	best	of	my		leaf.
Don't ask me where he is,	I	haven't	got	a	loss.
The mother baked her daughter	a	birthday			medicine.
Stephen wanted to play	a	board			mind.
A fork is usually held	in	one's	left		mister.
In the 50s miniskirts were	the	height	of		money.
One's nose is in the middle	of	one's			move.
Ed likes listening	to	pop			rule.
Jim needed some fresh air	so	he	opened	the	peace.
The party took place	in	the	living		plate.
The King's son	is	called	a		shower.
An apple is a fruit,	a	cabbage	is	a	right.
As Matt had no chairs he had to	sit	on	the		shampoo.
I asked Ian what to do,	but	he	had	no	music.
The game was very simple;	it	had	only	one	sail.
One man's gain	is	another	man's		school.
Natalie washed her hair	with	a	mild		room.
A person one hasn't met before	is	a			prince.
Will went to sea	in	a	little	sailing	size.
After spring	comes				stranger.
The stalker watched	Vicki's	every			summer.
A married woman's title is missis,	a	man's	is		trouble.
The police told Kevin that	he	was	in	serious	vegetable.
Fin was thirsty, so	he	got	himself	a	window.
Midwives help deliver	your				ark.
Emily combed Sylvia's	beautiful				ewe.

Bob had many good resolutions	for	the	new		mast.
The jockey put the saddle	on	his			tap.
Iron, copper and tin	are	all	types	of	bale.

Incongruent filler sentences – List 3

Sentence	**Word1**	**Word2**	**Word3**	**Word4**	**Target**
When it rains outside you should	put	on	your		mind.
Children under 16	should	normally	attend		medicine.
He rarely mowed the lawn	in	his	back		loss.
You would go to a cash point	to	take	out	some	leaf.
At a BBQ you put your food	on	a	paper		knowledge.
If you are ill your doctor can	prescribe	you			summer.
The Canadian flag features	a	maple			hymn.
As a kid I spent days learning	to	ride	a		hand.
The shop did not have the shoes	in	Anne's			garden.
She left the church after singing	the	last			game.
As soon as the crew had boarded,	the	boat	set		floor.
Anti-war activists want	world				father.
William was unsure whether he was	wrong	or			fashion.
Dan didn't want a bath,	but	took	a		face.
I don't know; I simply cannot	make	up	my		drink.
Everyone has a biological	mother	and			coat.
He resigned last year to the	best	of	my		window.
Don't ask me where he is,	I	haven't	got	a	cake.
The mother baked her daughter	a	birthday			boat.
Stephen wanted to play	a	board			bike.
A fork is usually held	in	one's	left		clue.
In the 50s miniskirts were	the	height	of		vegetable.
One's nose is in the middle	of	one's			trouble.
Ed likes listening	to	pop			idea.
Jim needed some fresh air	so	he	opened	the	stranger.
The party took place	in	the	living		size.
The King's son	is	called	a		plate.
An apple is a fruit,	a	cabbage	is	a	shampoo.
As Matt had no chairs he had to	sit	on	the		school.
I asked Ian what to do,	but	he	had	no	sail.
The game was very simple;	it	had	only	one	mister.
One man's gain	is	another	man's		room.
Natalie washed her hair	with	a	mild		right.
A person one hasn't met before	is	a			shower.
Will went to sea	in	a	little	sailing	prince.
After spring	comes				peace.
The stalker watched	Vicki's	every			music.
A married woman's title is missis,	a	man's	is		move.
The police told Kevin that	he	was	in	serious	money.
Fin was thirsty, so	he	got	himself	a	rule.
I cut up my food with a	knife	and			bale.
Rob looked at his watch	to	check	the		tap.

To eat soup	one	uses	a	mast.
Tanya went to the bank	to	open	an	ark.
Cut flowers are put	in	a		ewe.

Incongruent filler sentences – List 4

Sentence	Word1	Word2	Word3	Word4	Target
When it rains outside you should	put	on	your		mister.
Children under 16	should	normally	attend		money.
He rarely mowed the lawn	in	his	back		move.
You would go to a cash point	to	take	out	some	music.
At a BBQ you put your food	on	a	paper		peace.
If you are ill your doctor can	prescribe	you			shampoo.
The Canadian flag features	a	maple			prince.
As a kid I spent days learning	to	ride	a		room.
The shop did not have the shoes	in	Anne's			bike.
She left the church after singing	the	last			rule.
As soon as the crew had boarded,	the	boat	set		vegetable.
Anti-war activists want	world				school.
William was unsure whether he was	wrong	or			plate.
Dan didn't want a bath,	but	took	a		stranger.
I don't know; I simply cannot	make	up	my		size.
Everyone has a biological	mother	and			shower.
He resigned last year to the	best	of	my		summer.
Don't ask me where he is,	I	haven't	got	a	trouble.
The mother baked her daughter	a	birthday			sail.
Stephen wanted to play	a	board			window.
A fork is usually held	in	one's	left		coat.
In the 50s miniskirts were	the	height	of		loss.
One's nose is in the middle	of	one's			boat.
Ed likes listening	to	pop			cake.
Jim needed some fresh air	so	he	opened	the	clue.
The party took place	in	the	living		drink.
The King's son	is	called	a		face.
An apple is a fruit,	a	cabbage	is	a	fashion.
As Matt had no chairs he had to	sit	on	the		leaf.
I asked Ian what to do,	but	he	had	no	floor.
The game was very simple;	it	had	only	one	father.
One man's gain	is	another	man's		medicine.
Natalie washed her hair	with	a	mild		garden.
A person one hasn't met before	is	a			hymn.
Will went to sea	in	a	little	sailing	idea.
After spring	comes				knowledge.
The stalker watched	Vicki's	every			game.
A married woman's title is missis,	a	man's	is		right.
The police told Kevin that	he	was	in	serious	hand.
Fin was thirsty, so	he	got	himself	a	mind.
In front of the hotel is a	beautiful	sandy			bale.
Rob looked at his watch	to	check	the		ark.

Cut flowers are put	in	a	mast.
Tina was blind	in	one	tap.
Helen looked at herself	in	the	ewe.

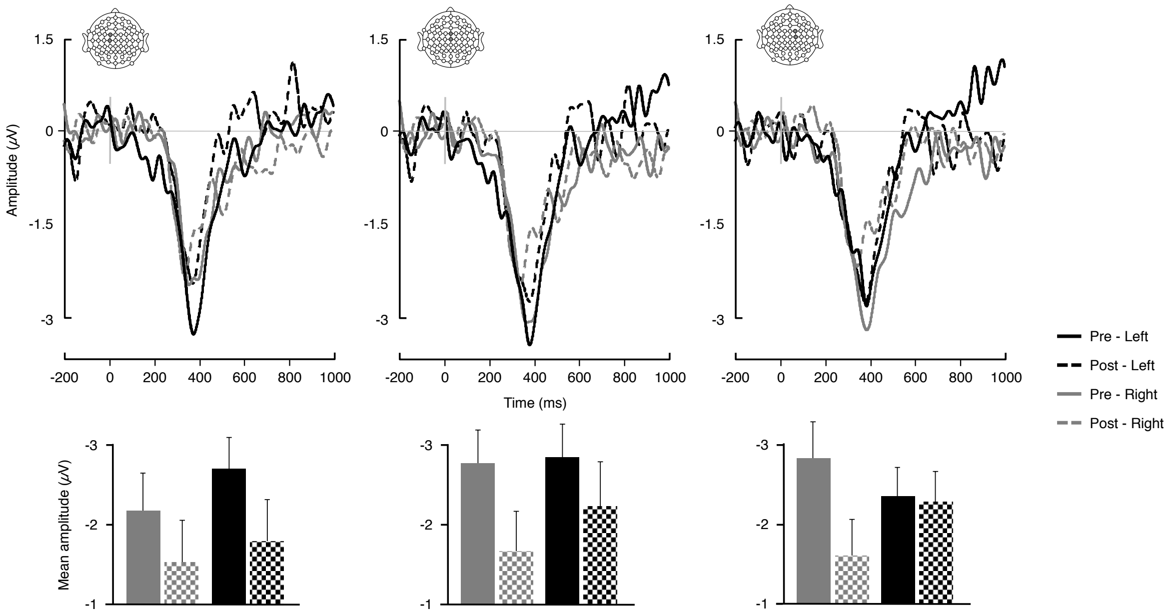
Appendix D: Cloze probability of sentence stimuli used in chapter 6

Sentences, predictable targets and Cloze probability scores for the 35 sentences analysed in chapter 6

Sentence	**Target**	**Cloze Probability Score**
Tanya went to the bank to open an ...	ACCOUNT	0.984615385
Midwives help deliver your ...	BABY	0.958974359
Billy took his savings to the ...	BANK	0.98974359
In front of the hotel is a beautiful sandy ...	BEACH	0.974358974
A pigeon is one of many types of ...	BIRD	0.994871795
At the bakery Clare bought a loaf of ...	BREAD	0.98974359
A moat usually surrounds a ...	CASTLE	0.928205128
The losing team didn't stand a ...	CHANCE	0.974358974
The farmer milked his only ...	COW	0.969230769
The weaker army had to admit ...	DEFEAT	0.984615385
Tina was blind in one ...	EYE	0.979487179
A rose is a very beautiful ...	FLOWER	0.964102564
I cut up my food with a knife and ...	FORK	0.974358974
Emily combed Sylvia's beautiful ...	HAIR	0.974358974
The jockey put the saddle on his ...	HORSE	0.938461538
A saxophone is a musical ...	INSTRUMENT	0.98974359
Vegetarians don't eat ...	MEAT	0.969230769
Iron, copper and tin are all types of ...	METAL	0.928205128
Helen looked at herself in the ...	MIRROR	0.98974359
The hungry man shovelled the food into his ...	MOUTH	0.964102564
A giraffe has a very long ...	NECK	0.98974359
The moon shines at ...	NIGHT	0.930769231
Kate put the roast in the ...	OVEN	0.979487179
To write a letter one needs a pen and ...	PAPER	0.979487179
An eagle is a bird of ...	PREY	0.923076923
I bought a brand new TV that had a 42” ...	SCREEN	0.953846154
Steve washed the dishes in the kitchen ...	SINK	0.938461538
To eat soup one uses a ...	SPOON	0.98974359
To make coffee sweeter you can add ...	SUGAR	0.964102564
Rob looked at his watch to check the ...	TIME	0.98974359
Clark ran to the platform, but still missed the ...	TRAIN	0.948717949
We needed a ladder as the cat was stuck up the ...	TREE	0.917948718
Cut flowers are put in a ...	VASE	0.943589744
The bird couldn't fly; it had a broken ...	WING	0.984615385
Bob had many good resolutions for the new ...	YEAR	0.964102564

Appendix E: Graphs showing the N400 effect described in chapter 6

Figure 11. Difference waves (incongruent-congruent) showing the N400 effect.



Top panel shows the difference waves for the left (C1 and FC1), midline (CZ and FCZ) and right (C2 and FC2) electrodes. Bottom panel shows mean amplitude of difference waves for the same electrodes.