ON THE CEREBELLUM AND LANGUAGE: NEUROSTIMULATION AND IMAGING STUDIES

by

ELISE LESAGE

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College of life and biosciences
University of Birmingham
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ABSTRACT

Mounting evidence suggests a cerebellar role in language, but to date few efforts have been made to characterise this role. A well-accepted model of cerebellar function in motor control posits that forward model prediction is the central function of the cerebellum, and the cerebellar architecture is suggestive of a single cerebellar computation. Recent accounts of linguistic function have proposed that forward model prediction is integral to receptive and productive language. The aim of this thesis was to explore cerebellar language function in the context of forward model prediction. In Chapter two, right cerebellar transcranial magnetic stimulation during an eye-tracking task affected a measure of online linguistic prediction. In Chapter three, the same linguistic prediction task was used in a group of cerebellar patients and control subjects. The deficit reported in Chapter two was not found in this chapter, but data-acquisition for the study is still ongoing. Chapter four describes a functional magnetic resonance imaging (fMRI) study where resting state connectivity before and after the acquisition of a new lexicon was compared. The right cerebellum was engaged in lexical learning. Chapter five reports posterolateral cerebellar and inferior frontal gyral activity related to online prediction using an event-related fMRI design where predictability is manipulated. Overall, findings are consistent with a cerebellar role in predictive language.

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LIST OF ABBREVIATIONS

BOLD	blood oxygenation dependent
DTI	diffusion tensor imaging
EEG	electroencephalography
ERP	event related potential
fMRI	functional magnetic resonance imaging
FWHM	full width at half maximum
FWE	family-wise error correction
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
PET	positron emission tomography
TMS	transcranial magnetic stimulation
rTMS	repetitive transcranial magnetic stimulation
RSFC	resting state functional connectivity
SCA6	spinocerebellar ataxia type 6

CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

In this introduction, a brief overview of the theoretical background of the thesis will be given. The first two sections will outline background on the neural basis of language processing and about prediction in language comprehension. The subsequent three sections will address the structure and connectivity of the cerebellum, a well-accepted theory about its function in motor control, and evidence for its implication in cognition and language. The final three sections outline the notion of forward models in language, the aims and hypothesis of the thesis, and finally give an overview of the experimental chapters. I have aimed to provide sufficient background to contextualise the work in this thesis, but the literature reviewed below should in no way be considered an exhaustive overview.

1.1. NEUROBIOLOGICAL MODELS OF LANGUAGE

1.1.1. A CORE LANGUAGE SYSTEM

We first turn to a simplified model of language structures in the brain. The literature on the neural basis of language is rich and varied, with very little in the way of a consensus view with respect to the relative contributions of different language regions. For the purposes of this introduction I have situated network of brain regions which has been consistently associated with language function. That is, areas which are consistently implicated in processing of meaningful spoken or written language regardless of the modality of the input. There is a reasonable degree of consensus that there exists a core left-lateralised cortical language system, which consists of inferior frontal gyrus, superior and middle temporal gyrus, inferior parietal regions and the fibre pathways that connect them (see Figure 1.1). This core cortical language system is left-lateralised in most right-handed persons, with contributions of homologous regions in the right hemisphere. Lateralisation in left-handed individuals is not as clear (Knecht et al., 2000). The specialisation of these regions was first described in the late 19th Century, in the works of Dax (Cubelli & Montagna, 1994), Broca (1861/2000), Wernicke, (1874/1977), Lichtheim (1885), and later on Geschwind (1970), and was based on neuropsychological findings in aphasic patients. While the Lichtheim-Broca-Wernicke model of language function has been criticised because it is anatomically and functionally poorly specified, it is still very influential as a framework used in textbooks, in clinical settings, and in research (Poeppel & Hickok, 2004). Moreover, while the functional description of the Lichtheim-Broca-Wernicke model has not stood the test of time, by and large it is agreed that these areas and their connecting pathways are specialised for language in humans.

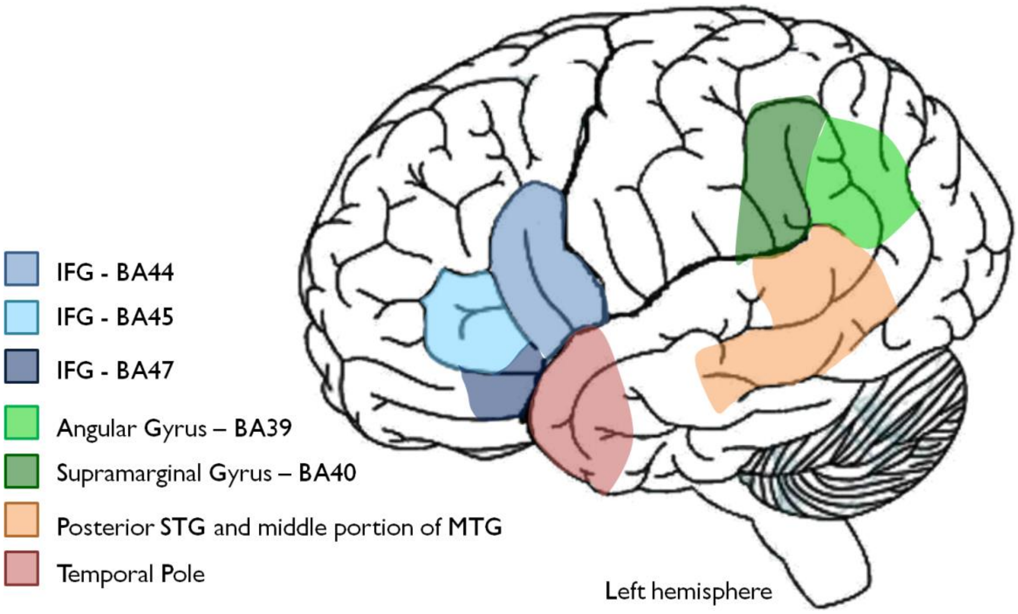

Figure 1.1. Core language regions (locations are approximate).

1.1.1.1. *Cortical language areas*

The inferior frontal gyrus was the first documented brain area which was found to be important in linguistic function(Broca, 1861; Cubelli & Montagna, 1994). Patients who were unable to produce speech even though language comprehension was intact, were found to have with lesions in the inferior frontal gyrus (IFG). There is no clear agreement on the exact location of Broca's area, but most authors agree that the area consists of left Brodmann area (BA) 44 (pars opercularis) and BA 45 (pars triangularis). A third language-selective region in the inferior gyrus is BA47 (pars orbitalis), which lies inferior to BA45 and covers the tissue extending ventrally into the frontal operculum. Finally, the frontal operculum (anterior insula) is sometimes included as an inferior prefrontal language region (Amunts et al., 2010; Anwander, Tittgemeyer, von Cramon, Friederici, & Knösche, 2007; Friederici, Bahlmann, Heim, Schubotz, & Anwander, 2006).

Language-selective areas in the temporal lobe centre around the posterior middle temporal gyrus, extending into the superior and inferior temporal gyrus, and anterior portions of the temporal lobe. In the Lichtheim-Wernicke-Geschwind model, the left posterior temporal cortex was thought to be the seat of language comprehension. Today, it is acknowledged that language comprehension is supported by a much larger network of regions, including those listed in this paragraph (Friederici, 2011). In the parietal lobe, angular gyrus (BA39) and supramarginal gyrus (BA40) are consistently implicated in language processing. While language function is considered to be one of the most lateralised brain functions, the right-lateral homologues of these regions are also engaged in language processing (Price, 2010).

1.1.1.2. *Connectivity and dual stream models of language comprehension*

In humans, the fibre tracts connecting the core language regions have been characterised using diffusion tensor imaging (DTI), a method that can estimate of the orientation and strength of white matter tracts based on water diffusion (Catani, Howard, Pajevic, & Jones, 2002). These tracts have also been identified between homologue areas of the primate brain (Petrides & Pandya, 2009). The inferior frontal gyrus and temporal cortex are connected via dorsal pathways and ventral pathways. Two dorsal pathways can be distinguished (Catani & Thiebaut de Schotten, 2008). First, the superior longitudinal fasciculus connects the temporal cortex to the inferior parietal lobule and premotor cortex (BA6 and BA44). Second, the arcuate fasciculus directly connects superior temporal cortex with inferior frontal cortex. Along the ventral pathway the temporal pole and ventral inferior frontal cortex (particularly BA47 and the frontal operculum) are connected through the uncinate fasciculus. In addition, the inferior fronto-occipital fasciculus connects occipital cortex with the frontal cortex via the temporal lobe (Catani & Thiebaut de Schotten, 2008). Inferior posterior portions of this fibre bundle reach occipitotemporal regions, including those implicated in visual word recognition, and frontal portions of the inferior fronto-occipital fasciculus extend into prefrontal cortex, including BA45, BA47, and BA46.

Analogous to the dual stream model in visual cognition (Mishkin, Ungerleider, & Kathleen, 1983), a dual stream model for language comprehension has been proposed (Friederici, 2011; Hickok & Poeppel, 2004; Saur et al., 2008). In the dual stream model of language, the ventral pathway is thought to convey sound-to-meaning mapping, and the dorsal pathway is thought to map sound to articulatory representations (Friederici, 2011). Like the visual dorsal and ventral pathways for vision, the major components of both streams are interconnected (Catani & Thiebaut de Schotten, 2008; Felleman & Van Essen, 1991; Verhoef, Vogels, & Janssen, 2011). This intricate connectivity pattern complicates attempts to functionally subdivide the core language system into action-based or meaning-based processing streams.

1.1.2. OTHER BRAIN REGIONS INVOLVED IN LANGUAGE

Imaging studies reveal that aside from the core language network, several other brain regions are also involved in language processing (Price, 2010, 2012). Broadly speaking, the core language areas are recruited in response to words, sentences, and stimuli with semantic content, regardless of their modality (see Figure 1.1.). Depending on whether overt speech is involved, and depending on the modality of the input, linguistic tasks can activate additional circuits involved in movement, vision and audition. For example, in spoken language the phonological word form is thought to be processed in the left superior temporal gyrus, just anterior of the primary auditory cortex (Dewitt & Rauschecker, 2012); in written language, the left inferior occipitotemporal cortex processes written word forms, and in overt articulation, brain structures governing motor control are implicated (Price, 2012; Wandell, 2011).

From this recent review by Price (2012), it is also apparent that there are two distinct cerebellar contributions to language. First, superior areas of the cerebellum (notably Lobule VI) respond to motor aspects of speech (Bohland & Guenther, 2006). These regions are thought to correspond to representations of the lips and tongue (Grodd, Hülsmann, Lotze, Wildgruber, & Erb, 2001) and are active in the same contrasts that bring out motor and premotor cortical structures. A second region in the right posterolateral cerebellum is recruited in semantic tasks, along with regions in the core language network (see Figure 1.2, see also Section 0). This thesis concerns itself with the latter, namely the higher-order linguistic contributions of the posterolateral cerebellum, which co-activates with the language regions outlined above (see also Section 0.)

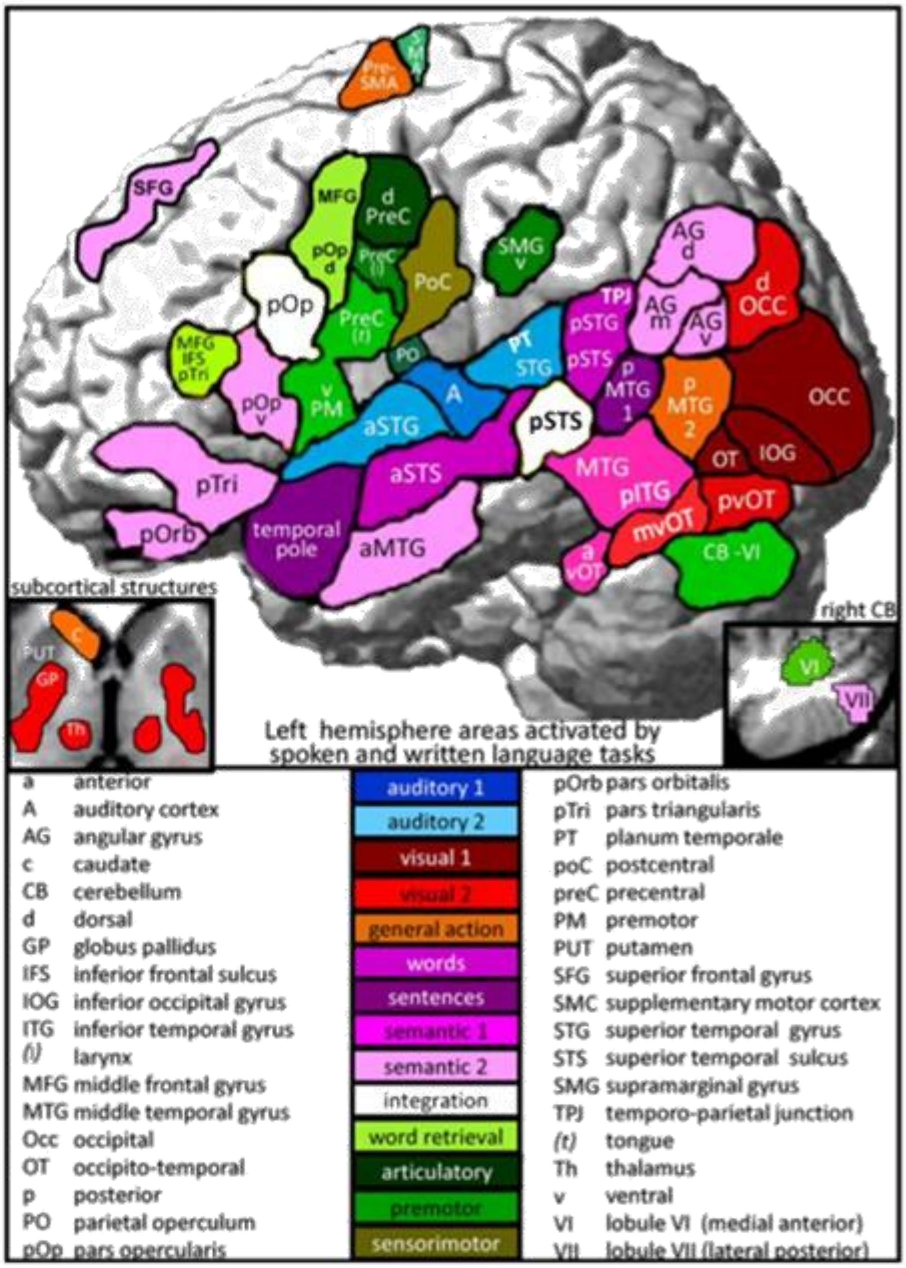

Figure 1.2. Brain regions activated by language contrasts as revealed with functional Magnetic Resonance Imaging (fMRI) and Positron Emission Tomography (PET) experiments. Figure from Price (2012).

1.2. LANGUAGE AND PREDICTION

During language comprehension, people actively predict upcoming content rather than interprete incoming information after stimuli have been presented. Supportive evidence for this notion comes from behavioural studies, eye-tracking paradigms, and electroencephalography (EEG) studies.

Reaction time experiments and eye-tracking experiments have supported the idea of incremental language processing, which posits that contextual information (linguistic or extra-linguistic) constrains expectancy during sentence comprehension (Hagoort, Hald, Bastiaansen, & Petersson, 2004). Throughout sentence processing, representations of presented stimuli are accessed at several levels (syntactic, semantic, phonological and lexical) and these representations interact to constrain and guide further sentence comprehension (Altmann & Steedman, 1988; Marslen-Wilson, 1975). For example, in a combined sentence completion and picture naming paradigm, participants were slower to name a syntactically incongruous word (Tyler & Marslen-Wilson, 1977).

An influential paradigm for prediction in language comprehension is the manipulation of the N400 response. In EEG, the N400 component is an event-related potential (ERP) component with a negative deflection that peaks around 400ms after stimulus onset (Lau, Almeida, Hines, & Poeppel, 2009). The N400 response was initially linked to semantic violations, as it is more pronounced when processing implausible sentence endings compared to plausible sentence endings (Kutas & Hillyard, 1980). However, subsequent research has made it clear that the component is modulated by the predictability of the stimulus given the preceding sentence, given the discourse context or given extra-linguistic world knowledge (Hagoort et al., 2004; van Berkum, Zwitserlood, Hagoort, & Brown, 2003). For example, the N400 response is smaller when the word is very predictable or likely (Kutas & Hillyard, 1984). The effect has also been observed with other meaningful stimuli, such as faces, pictures, and pronounceable non-words (Barrett & Rugg, 1989, 1990; Rugg & Nagy, 1987). As of yet, it is not clear which neural structures underlie the N400, but it has been suggested that it originates from a distributed network which underlies semantic processing, rather than from one single brain region (Lau, Phillips, & Poeppel, 2008).

One important point regarding the interpretation of these anticipatory and contextual effects is whether these effects necessarily imply an a priori expectation or prediction. That is, does a N400 effect simply reflect more effortful integration of the unexpected word into the sentence representation (integration view) or does it reflect a prediction error (prediction view). The crucial difference here is whether an expectation or prediction is generated before the word is encountered, or whether the word is integrated at the time of encounter. When an unexpected word is encountered, as in "Pete ordered his burger with a side of lipstick", an N400 response is elicited. This could be because the comprehender creates expectations of the upcoming content, which are violated upon encountering the word "lipstick". However, prediction is not necessary to explain this phenomenon. When the unexpected word "lipstick" is encountered, the comprehender needs to make an effort to integrate this word into his or her representation of the meaning of the sentence. Therefore, even if no predictions are made during sentence comprehension, the semantically anomalous item is more effortful to integrate into the sentence representation. There now is good evidence that predictions are in fact generated (Kutas & Federmeier, 2011; Pickering &

Garrod, 2007). DeLong, Urbach, and Kutas (2005) disambiguated the point where integration is difficult and the point at which a prediction is violated. In this experiment, highly constrained sentences ended either expectedly ("On windy days, the boy liked to go outside and fly a kite") or unexpectedly ("On windy days, the boy liked to go outside and fly an airplane"). Crucially, the expected noun was preceded by a different article ("a") than the unexpected noun (which was preceded by "an"). The integration viewpoint would predict that the N400 response should be elicited when the word airplane is encountered, as this is the point where the concept airplane is integrated into the sentence. Conversely, the prediction viewpoint would predict that the N400 is elicited when the article is encountered, because it is at this point that the input deviates from the expected input. Both articles are equally easy to integrate, so if integration drives the N400, there should be no response at that point. Results showed that the N400 effects was related to the presentation of the article "a" or "an" (DeLong, Urbach, & Kutas, 2005). Thus, this N400 response could constitute a prediction error, in support of the prediction view. In another EEG study, a very early ERP component related to syntactic anomalies was found when the context allowed a strongly constrained expectation of a noun, but not when a less constrained context preceded the same type of violation (Lau, Stroud, Plesch, & Phillips, 2006).

Eye-tracking has also been used to address linguistic prediction more directly, notably using the visual world paradigm (Cooper, 1974). This paradigm takes advantage of the tight link between attention and eye movements to investigate online processing (Tanenhaus, Spivey-Knowlton, Eberhard, & Sedivy, 1995). Here, participants look at a visual scene containing the agent and a number of objects while they hear a sentence about the depicted agent and one of the depicted objects. Participant's gaze fixates on the anticipated objects before the word is processed, providing strong evidence for semantic prediction during online sentence processing (Altmann & Kamide, 1999).

In sum, as language is processed, phonological, lexical, syntactic and semantic representations are activated in parallel, and these representations interact and constrain each other during online comprehension. Language comprehension is a process by which we make active predictions about likely upcoming input. People predict semantic, syntactic and orthographic features of upcoming content. These predictions can be based on linguistic constraints (such as syntax) or on real-world knowledge. This section has focussed on comprehension at the sentence level, but some of these effects have also been documented with other stimuli, for example lists of semantically related words (Lau, Holcomb, & Kuperberg, 2013).

1.3. CEREBELLAR STRUCTURE AND CONNECTIVITY

1.3.1. CEREBELLAR CYTOARCHITECTURE AND ITS IMPLICATIONS FOR FUNCTION

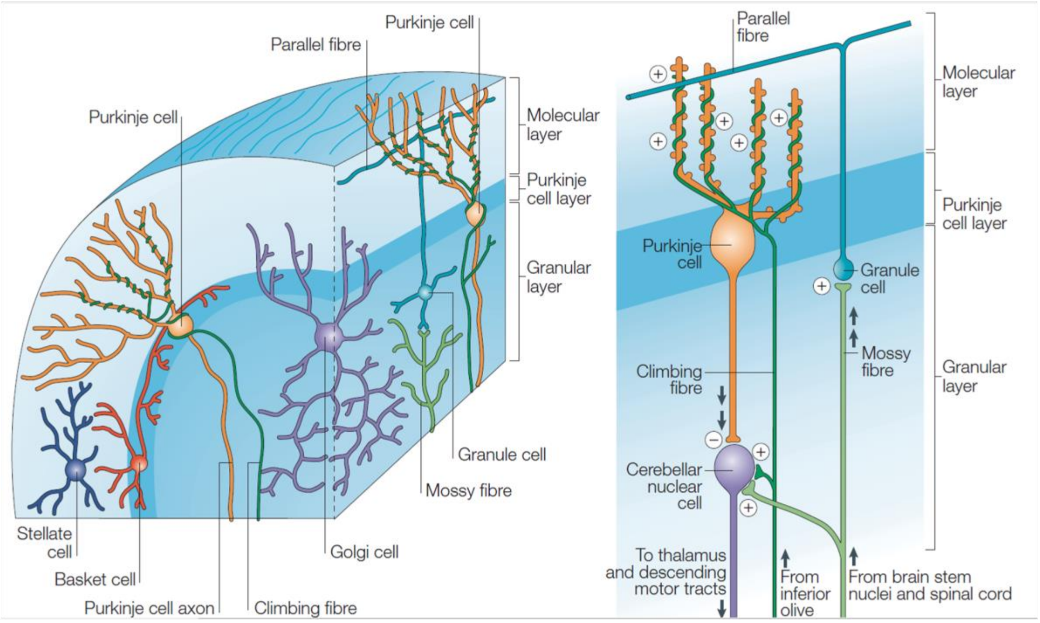

Figure 1.3. Cytoarchitectonic structure of the cerebellum. Figure from Apps and Garwicz (2005).

The cytoarchitecture of the cerebellum is relatively simple, and is homogenous throughout the structure (Eccles, Ito, & Szentagothai, 1967). The major computational unit of the cerebellum is the Purkinje cell, one of the largest neurons in our brain, which is characterised by its very large dentritic tree. Purkinje cells receive input via two main sources; parallel fibres which carry signals originating from the cerebrum via the pontine nuclei, and climbing fibres which originate from the inferior olive. Parallel fibres, lying parallel along the cortical surface, synapse onto multiple Purkinje cells, whereas climbing fibres make multiple synapses with a single Purkinje cell. A single Purkinje cell receives input from up to 200,000 parallel fibres, but only synapses onto about 40 neurons in the deep cerebellar nuclei (Eccles et al., 1967; Fox & Barnard, 1957). Its position is therefore ideal to integrate large amounts of information.

The cerebellum receives input from the periphery and from the cerebrum, and projects to the cerebrum, as well as to the brain stem and spinal cord (Apps & Garwicz, 2005). Information from the ipsilateral side of the body ascends through the spinocerebellar tracts (from the limbs) and through the trigeminocerebellar tract (from the head and face) and via the inferior cerebellar peduncle into the cerebellum. Climbing fibres originating from the olivary nucleus also ascend into the cerebellum via the inferior cerebellar peduncle. Projections from the cerebral cortex (see section below) descend via the pontine nuclei and enter the cerebellum through the middle cerebellar peduncle. Cerebellar output ascends through the superior cerebellar peduncle and via the thalamus to the cerebral cortex.

Larsell and Jansen (1970) proposed a nomenclature for the gross anatomy of the cerebellum which divides the cerebellum into 10 lobules, indicated with Roman numerals (see Figure 1.4). Lobules I-V comprise the anterior cerebellum, which is separated from the rest of the cerebellum by the primary fissure. Lobules VI-IX make up the posterior cerebellum and are separated from lobule X by the posterolateral fissure (Stoodley & Schmahmann, 2010). The lateral cerebellar hemispheres have expanded dramatically throughout evolution in primates (Larsell & Jansen, 1972), and most of this neocerebellar tissue is found in the lateral expansions of lobules VI and VII.

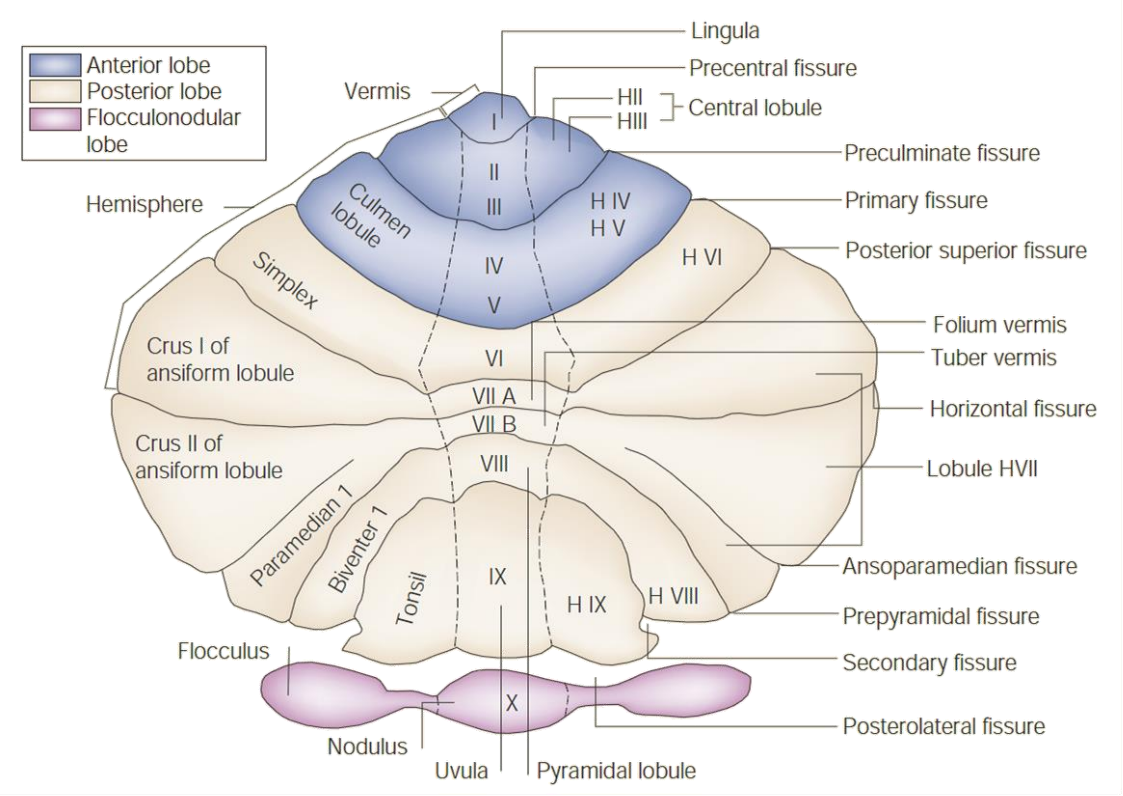

Figure 1.4. The cerebellum unfolded: lobular anatomy of the cerebellum. Organisation according to Larsell (Figure from Manni and Petrosini, 2004).

A striking feature of the cerebellar cortex is its uniform cytoarchitecture (Eccles et al., 1967). Given its structural homogeneity, it is likely that the entire cerebellum performs the same computational operations, and that functional differences arise from different inputs - the idea being that the cerebellum performs a uniform computation, but on different signals (Bloedel, 1992; Leiner, Leiner, & Dow, 1986). When we then want to functionally differentiate, we must turn to connectional topography, and consider the function of a cerebellar region as defined by its connections.

1.3.2. CORTICO-CEREBELLAR CONNECTIVITY

1.3.2.1. *Multiple parallel closed loops*

Corticocerebellar pathways have been characterised using transsynaptic viral tracers in non-human primates (Kelly & Strick, 2003). There is a bisynaptic pathway from cerebrum to cerebellum, via the cerebral peduncle and the pontine nuclei. Purkinje cell output returns to the neocortex via the deep cerebellar nuclei (i.e. dentate and interpositus nuclei) and the thalamus. These connections takes the form of multiple, parallel closed loops. That is, the cerebellar region which receives projections from a given part or the neocortex will project back to that area of the neocortex. Therefore, separate regions of the neocortex communicate with separate regions in the cerebellum. Different cerebellar regions do not directly project to one another (Leiner, Leiner, & Dow, 1991). Tracer studies have characterised projections between higher order cognitive cortical regions and the cerebellum (Kelly & Strick, 2003; Middleton & Strick, 1994, 1998, 2001). Specifically, posterior lateral portions of the cerebellum, particularly Crus II are densely connected with dorsolateral prefrontal cortex in the non-human primate (Middleton & Strick, 2001).

1.3.2.2. *Cerebro-cerebellar connectivity in humans*

Viral tracer studies, the gold standard of anatomical connectivity investigations, cannot be carried out in humans for obvious reasons. Because there is no language function in non-human primate (comparable to that in humans), these techniques are not suited to mapping the connections between cortical language regions and the cerebellum. In humans, DTI studies have been particularly influential in characterising important language pathways. Notably, the work of Catani and colleagues (Catani et al., 2002; Catani, Jones, & Ffytche, 2005) has characterised the connections between human language areas beautifully.

Unfortunately, the nature and location of the cerebro-cerebellar pathways make it very difficult to track from the cerebellar cortex to the cerebral cortex. Specifically, DTI tractography algorithms have not yet been able to reliably track the crossing fibre pathways in the pons (Mori, 2007; O'Reilly, personal communication). Recently, novel scanning techniques have made notable progress in the DTI imaging of cerebellar tissue (Takahashi, Song, Folkerth, Grant, & Schmahmann, 2013), but at present, cortico-cerebellar tractography based on DTI in vivo is not yet realistic. This notwithstanding, there are indications that the posterolateral prefrontal-projecting portions of the cerebellum are more pronounced in humans than in non-human primates. For example, the ventral portions of the dentate nucleus, which projects to prefrontal regions (Dum & Strick, 2003; Küper et al., 2011), are disproportionally expanded in humans compared to the medial portions, which are wired up to motor cortex (Leiner, Leiner, & Dow, 1989; Matano, 2001; Ramnani, 2006). Notably, not all regions of the cerebellum receive projections from the limbs or face (Stoodley & Schmahmann, 2010), suggesting nonmotor functionality. Efforts have been made to track from different areas in neocortex to the cerebellar peduncles. Different parts of the cerebral peduncles are known to be connected to distinct portions of the cerebellum, and the comparison of connectivity patterns in human and macaque, as assessed by DTI, showed a proportionally greater contribution of posterior parietal and prefrontal inputs into the cerebellum in humans (Ramnani et al., 2006; Ramnani, Behrens, Penny, & Matthews, 2004). Correspondingly, the volume of prefrontal cortex and prefrontal-projecting cerebellar lobules volumetric expansion has been shown to have selectively expanded throughout evolution when comparing three different species (Balsters et al., 2010), suggesting these regions have evolved as a functional system.

Another technique which can shed light on connectivity in the human brain is resting state functional connectivity (RSFC). Taking advantage of the fact that the Blood-Oxygen-Level Dependent (BOLD) signal in regions which form functional networks is correlated even in the absence of an overt task, this technique is able to map functional connections between brain regions, regardless of the number of synapses, or any crossing fibres between them (Fox & Raichle, 2007). An important limitation of this indirect measure of connectivity is that it does not take into account the fibre tracts between regions, but is solely based on their correlated haemodynamic response. However, the technique has been validated against tracer studies in primates and against DTI measures, and while resting state functional connectivity does not always map perfectly onto anatomical connectivity (Di Martino et al., 2008; Kelly et al., 2010; Uddin et al., 2008; Vincent et al., 2007), there is nevertheless a very good correspondence between the two (Damoiseaux & Greicius, 2009; Margulies et al., 2009; Vincent et al., 2007). With the advent of large-scale, freely available resting state datasets (Biswal et al., 2010) considerable steps have been taken towards mapping resting state functional connectivity in the human brain. Buckner, Krienen, Castellanos, Diaz, and Yeo (2011) investigated functional connectivity between the cerebellum and cerebrum in a large resting state dataset by performing seed-based correlation analyses. Analyses from cerebral seed regions to cerebellar cortex (based on Yeo et al., 2011) were made, as well as from cerebellar cortex to cerebral cortex. Results revealed a highly reliable set of connectivity patterns (see Figure 1.5). The data also showed a remarkable consistency with previous studies using resting-sate functional connectivity to probe cerebro-cerebellar connectivity (O'Reilly, Beckmann, Tomassini, Ramnani, & Johansen-Berg, 2010) and with known somatotopical organisations in the cerebellum (Snider & Sowell, 1944). Interestingly, a strong correlation between cerebellar volume and cerebral surface was found, such that regions with a larger surface in the cerebrum are functionally connected to larger volumes of cerebellar tissue. Indeed, cerebellar tissue connected to association cortex constituted the largest part of the cerebellum, a finding which seems to be in accordance with trends cross-species (Balsters et al., 2010; Ramnani et al., 2004). Two points are especially noteworthy with respect to this study. First, the correspondence with anatomical data demonstrates that resting state functional connectivity can be a powerful and reliable tool to investigate connectivity in the human brain. Second, results highlight not only that broad areas of the human cerebellum are connected to neocortical cognitive and language areas, but that this constitutes the largest portion of cerebellar cortex, mirroring the proportions of unimodal versus association cortex in the cerebrum.

Bernard et al. (2012) used resting state functional connectivity measures to investigate whether the structural division in the cerebellum into ten lobules also corresponds to its connectivity profile. It was found that while this was the case for the anterior ("motor") lobules, posterior ("cognitive") areas of the cerebellum could be subdivided beyond their lobular organisation. This is perhaps unsurprising given that these latter regions make up a larger portion of the cerebellar volume, and given that the association neocortex can be furter subdivided into functional units, the anatomical bounderies of which are not always clearly defined.

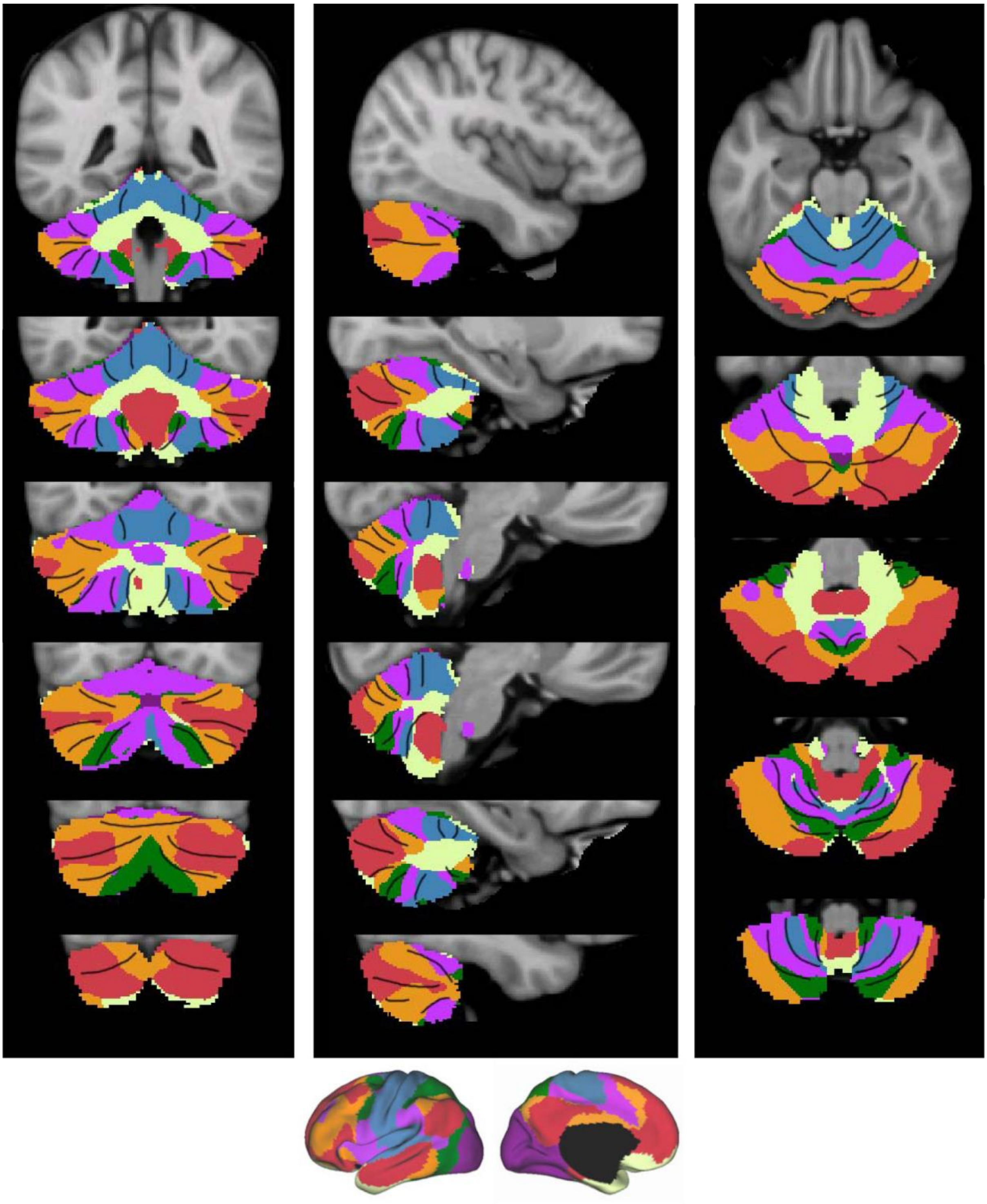

Figure 1.5. Organisation of the human cerebellum by means of functional connectivity (7 networks. (Figure from Buckner et al., 2011).

The notion that the cerebellum forms functional networks with association areas, and is implicated in functions beyond sensorimotor processing is now widely (though not unanimously, see Glickstein, 2007) accepted. The homogenous structure of the cerebellum suggests a uniform computation for the structure, such that functional differentiation within the cerebellum arises from different connectivity patterns (Bloedel, 1992; Leiner et al., 1991). Importantly, motor and nonmotor cerebellar regions can be distinguished on the basis of their anatomical location. Specifically, regions connected to higher cognitive and language regions are to be found in the lateral posterior cerebellum, most notably Crus I and Crus II (Lobule HVII). Therefore, the location of activations in PET, fMRI or magnetoencephalography (MEG) studies can be used to determine which cortico-cerebellar loops contribute to a given task (Stoodley & Schmahmann, 2009a; Stoodley, Valera, & Schmahmann, 2012).

1.4. THE CEREBELLUM, WORKING MEMORY, AND LANGUAGE

The notion of a cerebellar role in "nonmotor" functions - cognition, language and affective processing - is not new but has gained increasing support over the last couple of decades (Strick, Dum, & Fiez, 2009). Of course, these "non-motor" behaviours are inferred from actions; the cognitive or linguistic processes studied lead to measurable responses. In fact, one could question how meaningful the distinction between action and cognition is, considering that cognition generally is relevant to action. Best recognised are cerebellar contributions to language and to working memory, although there is also evidence for cerebellar contributions to affective processing (De Smet, Paquier, Verhoeven, & Mariën, 2013; Schmahmann & Sherman, 1998). Evidence for linguistic and cognitive functions is apparent from corticocerebellar connectivity patterns as well as clinical evidence and neuroimaging evidence. The former are outlined in Section 1.3.2, while the latter are the focus of this section. Below I have listed neuropsychological evidence from patients with cerebellar lesions and from dyslexia studies, and neuroimaging studies in healthy control participants.

1.4.1. CLINICAL EVIDENCE

Schmahmann and Sherman (1998) coined the term cerebellar cognitive affective syndrome (CCAS) to describe a group of cerebellar patients who presented with cognitive rather than motor deficits. These patients had lesions confined to the posterior lateral cerebellum and posterior vermis, and presented with a number of behavioural deficits unrelated to motor function. Affective disturbances tended to be linked with lesions in the cerebellar vermis, while executive, working-memory and linguistic deficits were associated with posterior lobe damage (Schmahmann & Sherman, 1998).

Patients with cerebellar lesions can present with problems with lexical access and syntactic problems (Fabbro, Moretti, & Bava, 2000) and speech production deficits (Silveri, Di Betta, Filippini, Leggio, & Molinari, 1998). Children with cerebellar tumours can develop learning difficulties, with damage to the right cerebellum associated with verbal and literacy problems in right-handed children (Scott et al., 2001). Deficits following cerebellar lesions can be interpreted as a failure of the cortico-cerebellar loop which includes frontal and cerebellar language areas (Mariën, Engelborghs, Fabbro, & De Deyn, 2001). Such accounts are consistent with the idea that these cortico-cerebellar loops support higher-level processes (Ito, 2008; Kelly & Strick, 2003; Ramnani, 2006).

Dyslexia has been linked to right cerebellar deficits (Bishop, 2002; Ivry & Justus, 2001; Nicolson, Fawcett, & Dean, 2001; Nicolson & Fawcett, 2011). While cerebellar grey matter volume is asymmetrical with a rightward bias in right-handed control subjects, cerebellar grey matter volume has been shown to be symmetrical in a group of dyslexic men (Rae et al., 2002), mirroring similar findings in left cerebral language regions (Larsen, Høien, Lundberg, & Odegaard, 1990). Similarly, using magnetic resonance spectroscopy Rae et al. (1998) found biochemical differences in the right cerebellum and left temporo-parietal cortex of dyslexic men and controls. Eckert (2003) analysed structural MRI scans of dyslexic children and controls, and found that the volume of the pars triangularis (BA45) and the right anterior cerebellum distinguished dyslexics from non-dyslexics. However, there is no apparent link between the posterolateral cerebellum and dyslexia. In fact, cerebellar abnormalities in dyslexia have been linked to processing deficits in sensory (visual and auditory) systems rather than higher-order language regions (Stein, 2001).

In sum, clinical evidence suggests that deficits following cerebellar lesions can be unrelated to motor control. In the case of cerebellar degeneration and stroke, the symptomatology can be interpreted in light of the connectional fingerprint of these regions. For example, cerebellar patients with posterolateral cerebellar lesions are more likely to present with cognitive or linguistic deficits than patients with damage in the anterior lobules (Schmahmann & Sherman, 1998).

1.4.2. NEUROIMAGING EVIDENCE

In whole-brain neuroimaging studies of language in healthy participants, right cerebellar activity is often found. PET and fMRI studies of word generation (Buckner et al., 1995; Frings et al., 2006; Herholz et al., 1996; Lurito, Kareken, Lowe, Chen, & Mathews, 2000), word stem completion (Ojemann et al., 1998), verbal fluency (Buckner, Koutstaal, Schacter, & Rosen, 2000; Gurd et al., 2002; Schlösser et al., 1998), and semantic judgment (McDermott, Petersen, Watson, & Ojemann, 2003; Seger, Desmond, Glover, & Gabrieli, 2000; Tieleman et al., 2005; Xiang et al., 2003) elicit activity in the right posterolateral cerebellum, along with cortical language areas such as the left inferior frontal gyrus and the left middle temporal gyrus. The lateralisation is such that verb generation in a left-hander elicits left-cerebellar activity and vice versa, in accordance with the crossing projections between cerebellum and cerebrum (Hubrich-Ungureanu, Kaemmerer, Henn, & Braus, 2002). Fedorenko, Hsieh, Nieto-Castañón, Whitfield-Gabrieli, and Kanwisher (2010) validated an fMRI language localiser, designed to be able to detect language areas in individual subjects. The right posterior cerebellum was amongst the regions which reliably (on an individual subject basis) responded to sentences versus non-word strings, whether there was a motor task component or not, and whether the stimuli were presented visually or aurally. While many of these studies cited here involve some type of motor response, these are controlled for in the contrasts used (i.e. there is an equal amount of covert speech or button presses in each condition). In a quantitative meta-analysis of various tasks that elicit cerebellar activation, language tasks were located to the right posterior lateral cerebellum (E, Chen, Ho, & Desmond, 2012; Stoodley & Schmahmann, 2009a; Stoodley, 2012). Therefore, a considerable body of imaging evidence supports right posterior lateral cerebellar contributions to language.

1.4.3. OBSCURE OR UNDERREPORTED?

In spite of the evidence for linguistic processes in the cerebellum, the structure receives little attention in the cognitive neuroscience of language. Most whole-brain neuroimaging articles will not mention cerebellar activation. Neurobiological models of language function (e.g. Friederici, 2012; Hickok & Poeppel, 2007) typically do not include the cerebellum. Reviews tend not to mention the cerebellum, and when they do, the cerebellar involvement is not interpreted. In part, this lack of evidence is due to methodological difficulties. First, because of its location, EEG signals from the cerebellum are particularly prone to artefact (Dien, Frishkoff, Cerbone, & Tucker, 2003). These problems can also affect signal in MEG measures. Second, brain mapping approaches do not always include the cerebellum in their field of view. A large portion of the evidence for a linguistic cerebellum comes from PET and fMRI data. In the earlier days of PET and fMRI, the standard approach was to scan the entire brain and look for global differences in activation. These older studies are more likely to report cerebellar activation in response to linguistic and semantic stimuli (Petersen, Fox, Posner, Mintun, & Raichle, 1989; Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996). As the field has progressed, there has been an evolution towards smaller fields of acquisition (often not including the cerebellum) and, particularly in language, towards surface-based approaches which only consider the neocortical sheet (Dale, Fischl, & Sereno, 1999). In fMRI language studies that do consider the entire brain, cerebellar activations are rarely reported and almost never discussed. Third, connectivity between language areas and the cerebellum is difficult to study using techniques such as anatomical tracer studies and DTI (see Section 1.3.2). The factors described above make it difficult to assess the prevalence of posterolateral cerebellar activations in language contrasts, and may go some way as to explain the lack of attention for the cerebellum in language processing literature. The absence of evidence for a cerebellar role in language processing should therefore not be taken as evidence for the absence of such a role.

1.5. CEREBELLAR MOTOR FUNCTION & FORWARD MODEL PREDICTION

The role of the cerebellum in motor control is extensively documented and much theoretical and empirical work has described its function. By far the most prolific models have applied concepts from control theory to this system and have conceived of the cerebellum as acquiring, storing and fine-tuning internal models of movements through error-based learning (Kawato, Furukawa, & Suzuki, 1987; Miall, Weir, Wolpert, & Stein, 1993; Paulin, 1989; Wolpert & Kawato, 1998). Internal models are representations that can simulate natural processes, in this case movements (Wolpert & Miall, 1996). A distinction is made between internal inverse models, which compute the motor command necessary to go from a current state to the desired state, and internal forward models, which compute the consequences of a motor command given the current state. Motor control is thought to be achieved by pairs of inverse and forward models (Wolpert & Kawato, 1998).

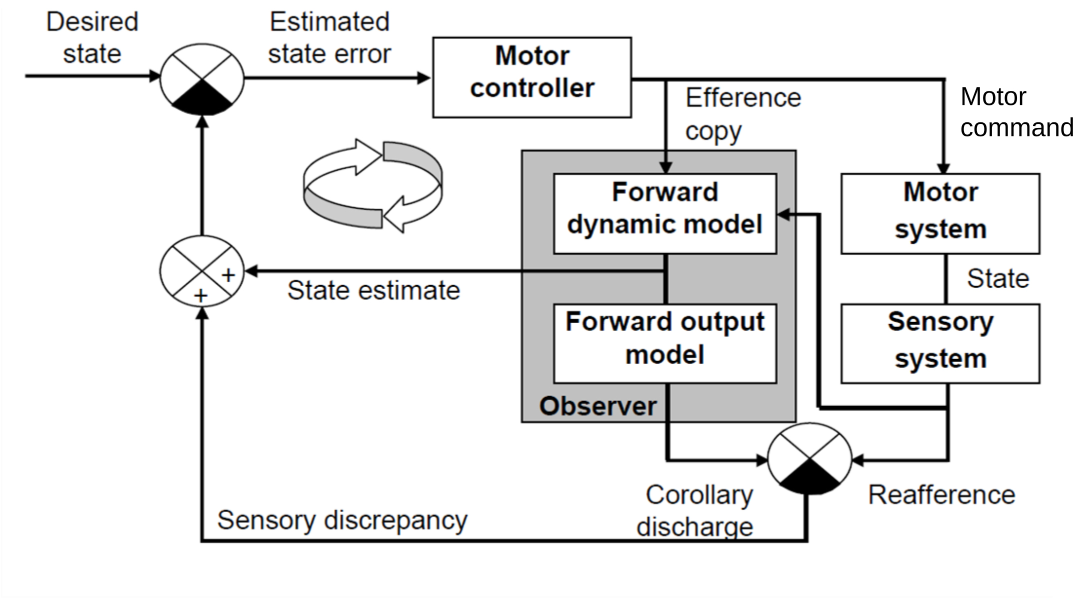

Figure 1.6. A schematic outlining the use of forward models in motor control. The entire system acts as an inverse model, which computes the appropriate action based on a discrepancy between the actual state (state estimate) and the desired state (this difference is the state estimate error). This motor command is executed by the motor system, and a copy of this motor command (an efference copy) is fed to the cerebellum. This efference copy is fed into a forward model of the movement. This forward model estimates the upcoming state (forward dynamic model), which can be compared with the desired state to estimate whether further motor commands are necessary to further decrease the estimated state error. Thus, corrections can be made during the movement, without relying on feedback signals (online correction). The forward model also computes the corollary discharge (expected sensory feedback) for the movement (forward output model). This predicted feedback is compared with the reafferent feedback, resulting in the sensory discrepancy (the difference between actual and predicted feedback). The sensory discrepancy is integrated into the state estimate, so that a more accurate state estimation can inform further motor commands. Figure from Miall (1998).

Figure 1.6 outlines the basics of the internal model approach to motor function. Importantly, forward models solve a number of problems in computational motor control (Wolpert, Ghahramani, & Jordan, 1995). First, they can account for the observed speed and fluency of movement control in the face of lengthy delays in the feedback loops. When people perform motor actions, such as reaching and grasping a familiar object in familiar surroundings, the forces that are exerted by the arm on the object are remarkably well-adjusted to the movement (Nowak, 2004). However, peripheral feedback alone cannot explain the observed fluency of everyday movements. It takes hundreds of milliseconds for a peripheral signal (proprioceptive or visual input) to make its way to the brain (Vercher et al., 1996). The signal itself needs to be converted and processed by the brain. Our ability to perform movements quickly and accurately therefore cannot be based on feedback control. . This problem is solved if one were to assume that an internal model is acquired through experience, and that this model can predict the upcoming state of the body and the corresponding sensory feedback. That is, the system does not have to wait for the feedback to make its way back to know the state of the motor system and react to this future state. Thus, in overlearned conditions, the system can rely on the internal forward model to accurately predict what will happen if the motor command is executed. Moreover, movements can be corrected online, based on the discrepancy between the estimated and the desired state. Cerebellar patients do not show this well-adjusted grasping behaviour seen in healthy participants; when a cerebellar patient lifts an object, he or she consistently uses a large force on the object (Nowak, 2004).

A forward model uses efference copies to predict the sensory outcomes of the movement (corollary discharge) and cancel out these effects (reafference cancellation). Compelling evidence from the electrosensory lobe in electric fish of the mormyrid family, which has a very similar structure to the mammalian cerebellum, suggests that the cerebellum could support this process (Ebner & Pasalar, 2008). Similar to the Purkinje cell layer in humans, these fish have a molecular layer with densely packed parallel fibers that synapse onto the principle cells. Like in the mammal cerebellum, the parallel fibers carry information from higher motor and sensory inputs. The principle cells also receive sensory input from the periphery, similar to projections from climbing fibers to Purkinje cells. Electrophysiological recordings from these cells have shown that these cerebellum-like structures encode predictions of the sensory outcomes of the fish's behavior on its electrosensory system (Bell, 1981). These predictive signals (corollary discharge) are then used to remove predictable signals from the sensory input (reafferent feedback). Thus, circuitry with the same architectural features as the cerebellum can function as a forward internal model that predicts the future state (Bell, Han, & Sawtell, 2008). In humans, a comparison between the sensation of being touched by someone else versus touching yourself (predictable sensation), was associated with less haemodynamic activity in the cerebellum, which could be interpreted as a result of reafference cancellation (Blakemore, Frith, & Wolpert, 2001).

The discrepancy between predicted outcome and the perceived outcome can serve as a teaching signal or an error signal to update the internal model (Shadmehr, Smith, & Krakauer, 2010). Such learning is called adaptation and it can keep these internal models calibrated throughout the lifespan (Bastian, 2008). Motor adaptation has been investigated in great detail and has been shown to be cerebellum-dependent. For example, in a paradigm where forces are applied to the arm during a reaching movement, healthy control subjects are able to systematically decrease their error over several trials, while cerebellar patients fail to learn from these errors (Smith & Shadmehr, 2005). Similar effects have been found in paradigms where cerebellar patient walk on a split-belt treadmill where the two halves have different speeds; here too did cerebellar patients show a deficit in adapting to these changed conditions (Morton & Bastian, 2006).

Indirect measures of neuronal activity such as fMRI, or patient studies do not distinguish between inverse or forward models in the cerebellum, because both inverse and forward models predict the same behavioural and learning patterns. Electrophysiogical studies can record the neural firing rates directly and can therefore distinguish between these types of internal models. If inverse models are present in the cerebellum, Purkinje cells should transform the state estimates into forces to be exerted, and the firing patterns should reflect these forces. Conversely, if forward models are present in the cerebellum, Purkinje cells should represent the upcoming state and/or the consequences of the future state. Electrophysiological studies recording from Purkinje cells in the cerebellum of monkeys while they are performing tracking tasks, suggest that the forces exerted are not represented by cell firing rates (Pasalar, Roitman, Durfee, & Ebner, 2006). Instead, the cell encoded the movement kinematics (the state of the arm). Further studies from this group demonstrated that these Purkinje cells' firing patterns reflect the future state (position, direction and speed of movement) of a limb during a movement task, with the cerebellar signals preceding the movement by about 250ms (Roitman, Pasalar, & Ebner, 2009; Roitman, Pasalar, Johnson, & Ebner, 2005). In sum, the electrophysiological evidence by this group is inconsistent with inverse models in the cerebellum and consistent with the notion of forward models that encode the upcoming state of the system. Liu, Robertson, and Miall

(2003) showed that Purkinje cells also encode the sensory consequences of a movement. These authors used a tracking task, in which primates made reaching movement and were able to see a cursor on the screen that represented their movement, but not their arm itself. In this study, sensory (visual) input was dissociated from arm movement by applying a right-left reversal between the arm movement and the cursor, or by applying a delay between the movement and the cursor. Results showed that the firing behavior of some of recorded cells corresponded the cursor position, rather than the arm position. This suggests that not only movement kinematics, but also their sensory correlates are encoded by cerebellar cells. There is a consensus that forward models exist in the cerebellum. Less agreement exists as to whether inverse models are also present in the cerebellum (Pasalar et al., 2006; Wolpert & Kawato, 1998), and whether or not prediction errors (the reafference cancellation) are computed in the cerebellum (van Broekhoven et al., 2009; Werner, Schorn, Bock, Theysohn, & Timmann, 2014)

The strength of the internal model theory is that it is well-supported by evidence from different methodologies, from single-cell recordings to patient data (Blakemore et al., 2001; Ebner & Pasalar, 2008; Liu et al., 2003; Nowak, Timmann, & Hermsdörfer, 2007; Roitman et al., 2005; Wolpert et al., 1995). As far as I know, there are no real competing models of cerebellar motor function. Other hypotheses of cerebellar function, which have largely developed from patient studies, emphasise different aspects of cerebellar function. For example, the cerebellar timing hypothesis highlights the importance of the cerebellum in perceiving timing and performing movements with a millisecond precision (Ivry, Spencer, Zelaznik, & Diedrichsen, 2002; Ivry, 1997). The cerebellar sequencing emphasises the role of the cerebellum in sequential movements (Leggio, Chiricozzi, Clausi, Tedesco, & Molinari, 2011). However, both of these models make explicit reference to forward models, feedforward control and the predictive role of the cerebellum.

As mentioned in Section 1.3, the notion of a single "cerebellar algorithm" has been proposed in the past (Bloedel, 1992; Dean, Porrill, Ekerot, & Jörntell, 2010; Leiner et al., 1989). It might therefore be that this forward model theory of cerebellar function could be extended beyond motor control. Specifically, it has been argued that, in parallel with motor forward models, "cognitive" forward models would be stored in the prefrontal-connecting cerebellum, which support cognitive and linguistic processing by means of predictive processes (Ben-Yehudah, Guediche, & Fiez, 2007; Imamizu & Kawato, 2009; M. Ito, 2008; Molinari, Restuccia, & have an important timing aspect to them. The simulated outcomes contain both what is predicted and when it is predicted (Miall, 1998). In the absence of a forward model, the behaviour is not expected to disappear. It is expected to become less coordinated and slower, and not to show adaptation in the face of a changing environment. This is exactly what is observed in cerebellar patients, who have difficulty making precise movements like reaching movements and do not show motor adaptation in the face of an abrupt change in the environment (Bastian, 2006). Third, there is the idea of internal models as additional representations of actions. While the operations outlined here happen in concert with motor cortex, representations of these motor operations exist in the cerebellar cortex. This implies that the action is represented in multiple locations in the central nervous system (Leggio, 2009; Ramnani, 2006). Hypotheses derived from this idea will form the theoretical backdrop for this thesis.

Three aspects of this model of cerebellar function are of note in the context of this introduction. A first point is the emphasis on feedforward prediction. The central process is continuous rapid prediction of sensory and proprioceptive signals. Second, these predictions have an important timing aspect to them. The simulated outcomes contain both what is predicted and when it is predicted (Miall, 1998). In the absence of a forward model, the behaviour is not expected to disappear. It is expected to become less coordinated and slower, and not to show adaptation in the face of a changing environment. This is exactly what is observed in cerebellar patients, who have difficulty making precise movements like reaching movements and do not show motor adaptation in the face of an abrupt change in the environment (Bastian, 2006). Third, there is the idea of internal models as additional representations of actions. While the operations outlined here happen in concert with motor cortex, representations of these motor operations exist in the cerebellar cortex. This implies that the action is represented in multiple locations in the central nervous system.

1.6. FORWARD MODELS IN LANGUAGE

Internal forward models are well-characterised in motor control (see Section1.5), and have been applied to several aspects of language function. At a articulatory and auditory level, the DIVA model (Golfinopoulos et al., 2011; Golfinopoulos, Tourville, & Guenther, 2010) uses forward and inverse models to capture and predict auditory feedback of speech in speech production. In recent years, several authors have proposed that internal forward models could also be applied to higher order linguistic function (Ito, 2008; Pickering & Garrod, 2007; Poeppel, Emmorey, Hickok, & Pylkkänen, 2012). Hickok (2012) proposed an account of language production which entails the use of forward models both at the articulatory level and the more abstract syllable level. In this account, the locus of the syllable-level forward model is placed in the temporoparietal junction, and that of the articulatory level in the cerebellum. The account proposes no forward models at the word or conceptual level, nor does it address prediction in language comprehension.

There is evidence for forward model prediction in speech production. Heinks-maldonado, Nagarajan, and Houde (2006) performed an MEG study where participants listened to their own speech as they were uttering it, either undistorted or distorted by a shift in pitch. A reduction in the M100 component was detected when participants listened to their own distorted speech. The M100 component in MEG (N100 in EEG) is detected 80-120ms after stimulus onset and is thought to reflect reafference cancellation. The speed of the effect (100ms) strongly suggests predictive processes, as a reaction which relied on the sensory apparatus would have been slower. In fMRI, Tourville, Reilly, and Guenther (2008) performed an experiment where auditory feedback was played back to participants distorted by shifting the first formant up or down. Participants corrected for this distortion by adjusting their speech in the opposite direction within 100ms of stimulus onset. Again the speed of this online correction implies predictive processes. These very early responses are also documented in the absence of overt speech. In an MEG experiment, Tian and Poeppel (2010) had participants either say or imagine saying a syllable, and they found the same response to both real and imagined speech about 170ms post stimulus onset over auditory cortex. This result suggests that a prediction of the auditory percept was created.

Pickering and Garrod (2013) have recently outlined a framework for language function which posits that forward models predict higher level representations of language, and play a pivotal role in both comprehension and production. The authors argue that the dichotomy between comprehension and production is false, and that linguistic representations are shared between production and comprehension systems (Menenti, Pickering, & Garrod, 2012; Pickering & Garrod, 2007). The authors treat language production as a form of action and language comprehension as a form of action perception. In this context, they apply ideas of internal models and forward model prediction from action control (Davidson & Wolpert, 2005; Wolpert, 1997) to language production and language comprehension.

According to this account, during speech production (see Figure 1.7), an utterance (specifying semantics, syntax and phonology) is planned by a production implementer, and a planned percept of this utterance will be created by the comprehension implementer. The production implementer and the comprehension implementer are the neural substrate or machinery which subserves language production and comprehension, but in the context of monitoring covert speech, the same implementers are used to plan the utterance. In parallel to this planning stage, an efference copy of the production command is sent to a forward production model. The forward production model creates a predicted utterance, with predictions regarding semantics, phonology and syntax. This predicted utterance is run through a forward comprehension model, which creates a predicted percept. The planned percept is compared to the predicted percept by a monitor on one or all of the levels of representation (semantics, syntax, phonology). If the production implementer has made an error, the monitor can pick this up by comparing the planned percept with the predicted percept created by the forward comprehension model. Depending on the relative confidence in the internal model and the production implementer, one or the other can be adjusted. If no errors occur, the utterance can be articulated.

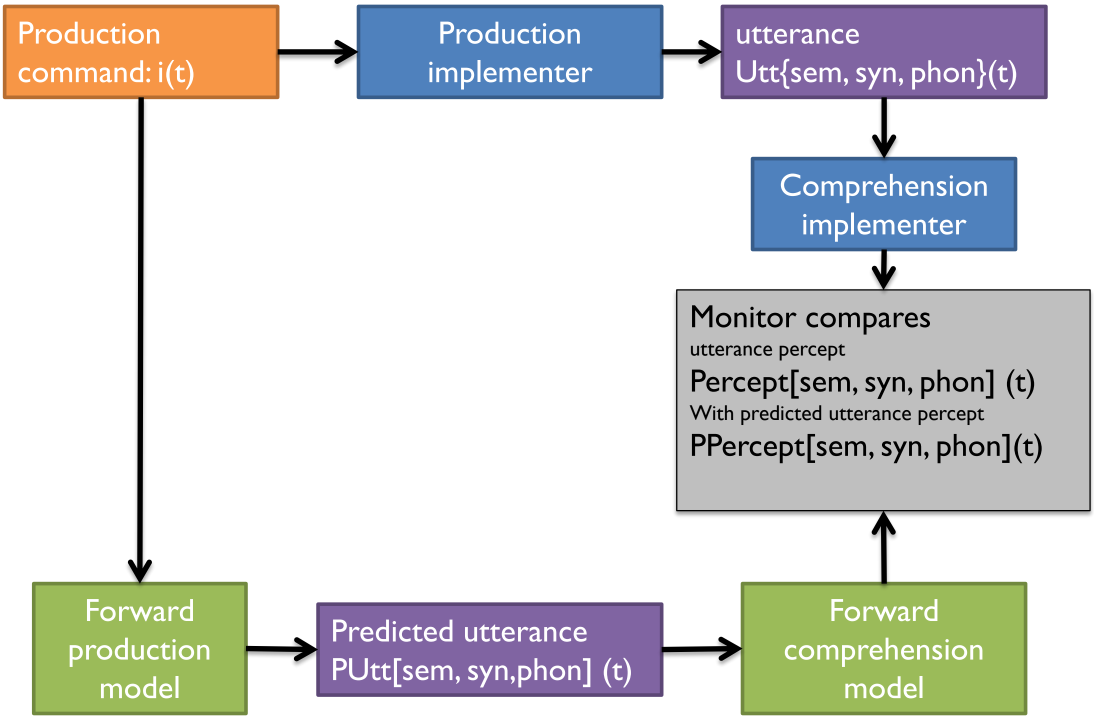

Figure 1.7. A model of language production. Figure adapted from Pickering and Garrod (2013).

In language comprehension, the perceived utterance is proposed to be understood via covert imitation. During this covert imitation, the comprehension implementer processes the utterance, and the perceived production command is derived from the perceived utterance via contextual information and an inverse model (see Figure 1.8). Then, the next production command is predicted on the basis of association or simulation. Linguistic features can be predicted via an association route (based on experience) or via a simulation route, depending on the situation. For example, simulation would be preferred if the speaker is very familiar to the listener, and association would be preferred in the case of written language (Pickering & Garrod, 2013). The predicted next production command is run through the forward production and comprehension models as in speech comprehension. The new perceived utterance is then compared with the predicted one.

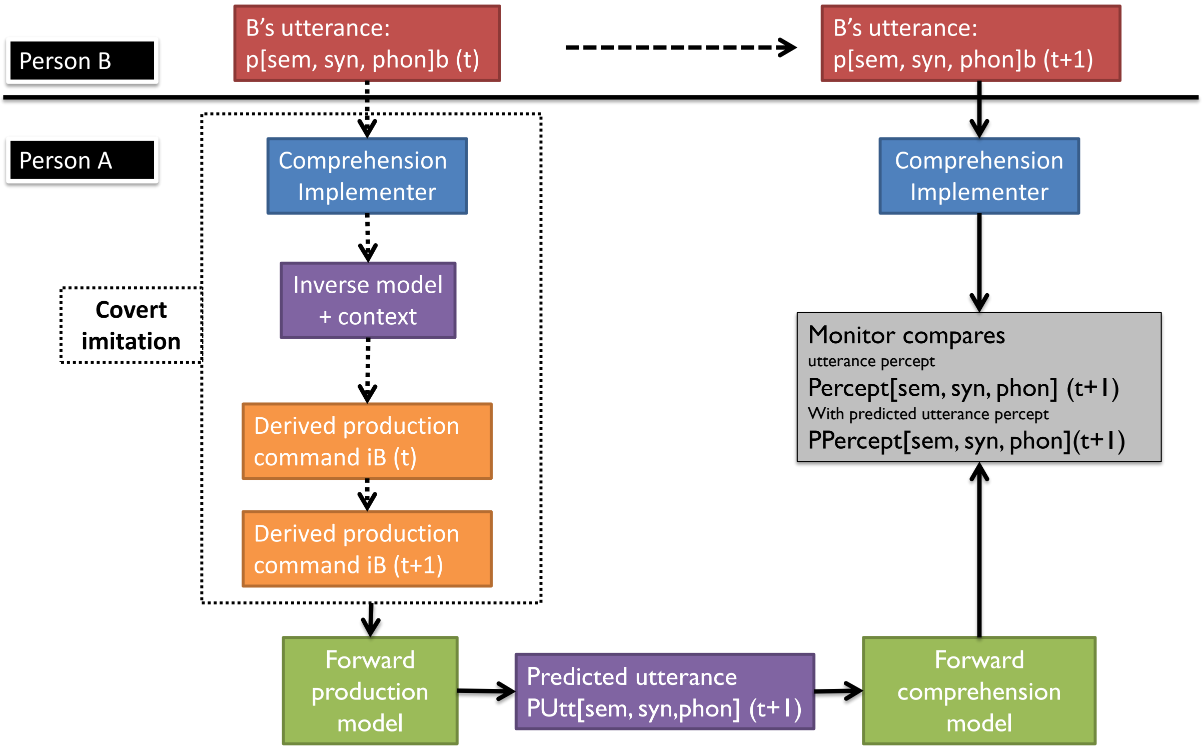

Figure 1.8. A model of speech comprehension. Figure adapted from Pickering and Garrod (2013).

A number of features of Pickering and Garrod's model stand out. First, in the model of comprehension, the specifics of the utterance are predicted by the forward model (i.e. how things are said), but the contents of what is coming next (the derived future production command in Figure 1.7) are still part of the covert imitation. In terms of levels of abstraction the forward production model is at the same level as the production implementer. Second, the forward model predictions here are proposed to be simplified, "easy-to-compute" impoverished version of the representation. The level and specificity of this specification is said to be flexible, depending on what is relevant in the specific context, or the specific task. Third, as in motor control the forward model represents rather than instantiates time. While the production and comprehension implementers take time, the forward models are fast.

Despite its potential explanatory power, forward model prediction in language comprehension has remained largely unexplored. Recently, Hosemann, Herrmann, Steinbach, Bornkessel-Schlesewsky, and Schlesewsky (2013) provide evidence for lexical prediction via forward models comprehension with an ERP study using German sign language. N400 effects were found in the (semantically empty) transition between two signs, indicating not just a violation at the time of the unexpected sign, but during the transition before the onset of the subsequent sign. This result indicates that comprehenders were covertly simulating signs, as would be predicted by a forward model prediction account.

Pickering and Garrod (2013) place a great emphasis on comprehension through imitation and the use of the production apparatus in comprehension. The notion that the language production apparatus is involved in language perception was proposed several decades ago in Liberman's motor theory of speech perception (Liberman, Cooper, Shankweiler, & Studdert-Kennedy, 1967). This theory posits that speech comprehension is achieved though the identification of the vocal tract sounds with which it is produced (Liberman & Mattingly, 1989; Liberman & Whalen, 2000). Some of the stronger claims of this theory, notably the position that a speech perception is achieved by a specialised language-specific module, have received criticism (Galantucci, Fowler, & Turvey, 2006). Nevertheless, a wealth of evidence from the embodied cognition literature implicates motor structures in language comprehension (Cappa & Pulvermüller, 2012; Carota, Moseley, & Pulvermüller, 2012). For example, specific parts of the motor system which underlie the production of certain phonemes are active during the comprehension of words with these phonemes (Pulvermüller & Fadiga, 2010). Covert imitation is associated with, and can facilitate comprehension, and the disruption of covert imitation can disrupt comprehension. For example, adapting to time-compressed speech is associated with increased recruitment of the ventral premotor cortex, suggesting that covert imitation may help adapt the motor speech apparatus by imitating the time-compressed speech (Adank & Devlin, 2010). Moreover, the comprehension of speech in a foreign accent is facilitated by the covert imitation of that accent (Adank, Hagoort, & Bekkering, 2010). Conversely, rTMS to the lip representation in motor cortex has been shown to disrupt the categorisation of phonemes which require lip movement, but not of other phonemes (Möttönen & Watkins, 2009). Similarly, an experiment where the position of participants' facial skin was manipulated in a speech-like pattern, biased the vowel they perceived accordingly (Ito, Tiede, & Ostry, 2009).

A strength of the Pickering and Garrod (2013) model is that it can account for much of the observed overlap between speech production and speech comprehension systems (Adank et al., 2010; Eickhoff, Heim, Zilles, & Amunts, 2009; Hickok & Poeppel, 2007; Pulvermüller & Fadiga, 2010; Vigneau et al., 2006; Wilson, Saygin, Sereno, & Iacoboni, 2004). Another strength is that this model can also account for the speed with which errors are detected (Dikker & Pylkkänen, 2012; Dikker, Rabagliati, Farmer, & Pylkkänen, 2010). However, there are also problems with this model. Importantly, the model is specified so generally and flexibly that it is difficult to falsify (Dick & Andric, 2013). For example, it is unclear under which circumstances predictions derived from internal loop models would differ from those based on Pickering and Garrod's model (Alario & Hamamé, 2013; Riès, Janssen, Dufau, Alario, & Burle, 2011). A second problem with this account is that in speech production, the predicted utterance is compared with the planned utterance rather than the actual utterance. This is necessary in order to account for the pre-articulatory monitoring and error correction (Levelt & Meyer, 1999). However, it is not immediately apparent why the planning and the prediction would generate differences useful for error detection, given that they are generated by the same person, on the basis of the same information (Meyer & Hagoort, 2013). If anything, the proposed "impoverished" representations generated by the forward models should yield less reliable plans than the production implementer (de Ruiter & Cummins, 2013).

In summary, several authors have proposed that internal forward model prediction exist in language. There is good evidence for forward model prediction in speech production, and there are indications that language comprehension too is served by forward models. Most accounts which argue for forward model prediction have not specified how internal forward model prediction relates to other linguistic processes (Heinks-maldonado et al., 2006; Tian & Poeppel, 2010). The framework proposed by Pickering and Garrod (2013) is the first to outline how forward model prediction in language might occur on a lexico-semantic and/or phonological level (rather than an articulatory level). However, this model remains largely untested and is not without problems. Nevertheless, it could be a useful starting point in the light of which the results gathered in this thesis can be assessed. Pickering and Garrod (2013) do not make reference to an anatomical substrate for the processes they describe. In models of speech production, the temporoparietal junction (Hickok, 2012) or the right-hemisphere homologues of the core language structures have been proposed to subserve forward model predictions (Federmeier, 2007). In this thesis, I will argue that the right lateral cerebellum is a plausible substrate for higher-order linguistic forward models.

1.7. A PREDICTIVE LINGUISTIC CEREBELLUM? HYPOTHESIS AND AIMS

A set of left-lateralised cortical regions is agreed to play a pivotal role in language processing. Efforts to disentangle the different contributions of these regions have been made (for example Friederici, 2012; Shalom & Poeppel, 2008), but no real consensus has arisen. Recently, the notion of forward model predictive processes in language has been proposed by several authors (Lau et al., 2009, 2013; Pickering & Garrod, 2013). As of yet, it is unclear which neural structures would underlie linguistic forward model predictive processes. The notion of a cerebellar role in language processing has gained more attention over the last three decades (De Smet et al., 2013), and a number of authors have proposed a cerebellar role in language, with some arguing that the cerebellar role in forward model prediction can be extended to language (Argyropoulos, 2010; Ito, 2008; Molinari et al., 2009).

The experiments in this thesis further explore the extent to which the cerebellum is recruited in language tasks, and whether this cerebellar recruitment is compatible with forward model prediction in language. I argue that the cerebellum is a plausible locus for forward model predictive language processes. First, its cytoarchitecture is well-suited for internal forward models, as has been demonstrated in the motor control literature. Second, the right posterolateral cerebellum is connected with higher order language areas such as the inferior frontal gyrus, and the angular gyrus. Finally, a cerebellar role in prediction in language is compatible with the patient and imaging literature. The aim of this thesis is to explore cerebellar involvement in a variety of linguistic tasks, with the overarching hypothesis that the right posterolateral cerebellum subserves prediction in language. However, the studies in this thesis are not designed to differentiate different types of prediction. Therefore, the hypothesis tested is whether the right posterolateral cerebellum is engaged in linguistic prediction, but not whether forward models are present in the right posterolateral cerebellum.

There are a number of closely related issues which are beyond the scope of the question at hand, and will not be addressed. These relate to the cerebellar role in overt articulation, to a possible cerebellar role in embodied forms of language comprehension, and to cerebellar involvement in verbal working memory. First, the cerebellar contribution to articulation, a motor aspect of language, will not be considered here. The cerebellum has a reasonably well-established role in articulation. Studies where overt spoken responses are required activate the superior regions of the cerebellum (Riecker et al., 2005). In addition, dysarthria is well-documented in cerebellar patients (Mariën et al., 2001). In disorders such as stuttering, a cerebellar role has also been proposed, such that it is conceived of as generating a motor prediction error (Golfinopoulos et al., 2010). Specific areas of the cerebellum are connected to specific areas of the neocortex by means of multiple parallel closed loops (Kelly & Strick, 2003), and articulation is associated with activity in motor portions of the cerebellum, notably lobule VI (Golfinopoulos et al., 2011; Riecker et al., 2005). These regions are separate from posterolateral regions of the cerebellum, which project to association cortex (Stoodley & Schmahmann, 2010).

A second specification relates to embodied cognition and the recruitment of motor structures in the comprehension process. The literature on embodied cognition has shown that motor structures are engaged when semantic content related to movements is processed. For example, arm representations in motor cortex are engaged when processing the word "throw" (Pulvermüller, 2005). Applied to the question of a cerebellar role in language comprehension, embodied language might mean that when someone processes linguistic stimuli about the foot (for example the word "football" or the word "kick"), motor areas of the cerebellum corresponding to representation for kicking footballs may be similarly engaged. While this is entirely possible, the present thesis is concerned with more abstract representations of language. If embodiment of language were to explain cerebellar activations in language, this activity would be present in motor-projecting cerebellar areas and not in prefrontal-projecting areas.

A third specification of the question is less straightforward, and relates to the cerebellar role in verbal working memory. Anatomically, the focus of this thesis is on the posterolateral, prefrontal-projecting areas of the cerebellum. These have been implicated in such processes as spatial and verbal working memory, executive function, and language (Stoodley & Schmahmann, 2009b). At present, the literature does not allow us to disentangle verbal working memory and linguistic contributions to the posterolateral cerebellum. Indeed, this is also not the case for Broca's area (Fedorenko, Duncan, & Kanwisher, 2012). From the imaging literature, it is apparent that activated cerebellar regions in language tasks overlap with those in verbal working memory tasks (E et al., 2012; Stoodley & Schmahmann, 2009b; Stoodley, 2012). In part, this could be due to the fact that many of the studies which investigate cerebellar language processing use contrasts where the experimental condition entails a heavier working memory load than the control condition. For example, this is the case in verb generation vs. word repetition (Frings et al., 2006) and semantic decision making vs. semantic association (Noppeney & Price, 2002). However, right posterior cerebellar activity is associated with semantic content, even when contrasted with a higher-load control condition. For example, in a task where participants read either a meaningful sentence or a series of nonwords and later had to indicate whether a probe words/nonword was part of the previous string, right posterior cerebellar regions responded more to more meaningful sentences than to strings of nonwords, even though the latter condition had a higher verbal working memory load (Fedorenko et al., 2010). Conversely, right cerebellar activity is associated with working memory tasks using nonverbal or abstract stimuli, such as an n-back task using abstract stimuli (Honey et al, 2000) or the paced serial addition task (Hayter, Langdon, & Ramnani, 2007). Therefore, working memory processing cannot account for all right cerebellar activation in semantic processing, nor can semantic processing account for all instances of working memory activation in the right cerebellum. It is possible that these processes are intrinsically linked, as any language processing entails a verbal working memory component. Conversely, verbal working memory, in particular phonological loop processes, entails internal speech. It is therefore difficult, and to some extent perhaps artificial to disentangle verbal working memory contributions from purely linguistic contributions. This thesis is not directly concerned with working memory processes, but the de facto link between working memory and language is a caveat for the interpretation of much of the literature as well as for the results presented in this thesis.

This thesis aims to explore the possibility of a cerebellar role in linguistic forward model prediction. However, the scope of the experiments described here is narrower. The focus will be on semantic prediction. Pickering and Garrod (2013) posit that all layers of representation (at least phonological, semantic and syntactic representations) are predicted by means of forward models. Their account also entails other nodes in the language production network which are not considered here. The work in this thesis is designed with internal forward models in mind, but cannot specifically address the distinction between forward model prediction and other types of prediction, like associative priming. Finally, the experiments outlined here engage language comprehension (as opposed to language production). This is done chiefly to minimise confounds with articulatory processes and speech motor control.

In summary, this thesis aims to test the hypothesis that the right posterolateral cerebellum, in connection with prefrontal and temporal language regions, supports semantic predictive language processing. The interaction of the hypothesised processes with and dependence on working memory will also be considered.

1.8. OVERVIEW OF THE EXPERIMENTAL CHAPTERS

In Chapter 2, the hypothesis that the right cerebellum is involved in linguistic prediction was tested. Participants received repetitive transcranial magnetic stimulation (rTMS) over the right cerebellum between two blocks of a visual world task. This is a psycholinguistic eye-tracking paradigm where sentences are presented aurally while a visual scene depicting the agent of the sentence, the object of the sentence and 3 distracter items is presented. Prediction sentences allow prediction of the object on the basis of the verb, while Control sentences do not. Typically, participants are much quicker to fixate their gaze upon the object in the Prediction condition, an effect which reflects online prediction. This eye-tracking protocol therefore captures online predictive language processing. Following cerebellar rTMS, participants were specifically impaired at making predictive saccades. Performance was not impaired in the Control condition. Two control groups, who either received no TMS or received TMS over a control site, showed no such effect. This study therefore demonstrated right cerebellar involvement in linguistic prediction processes.

In Chapter 3, the visual world paradigm described above was used in a patient study. Cerebellar degeneration patients and matched control participants performed the visual world task. The preliminary data analysis showed no overall group effect in the difference between Prediction and Control conditions. This study will be carried out further beyond this thesis using a larger number of participants, as at this stage the study is underpowered and cannot address the hypothesis sufficiently.

In Chapter 4, the effects of a language learning task on resting state functional connectivity were examined. Healthy young participants were scanned over two sessions; one in which they learnt the English translation of 25 Basque words, and one control session where they performed an identical task using 25 English synonym pairs. Resting state fMRI scans acquired before learning were compared with those after learning using seed-based correlation analyses. Results demonstrate altered functional connectivity between the left hippocampus and both right cerebellum and left inferior frontal gyrus. Task analysis revealed that a right cerebellar cluster (amongst other activations) was recruited more during the learning task than the control task. Interestingly, the activation in this cluster correlated with offline performance improvement following the learning task. These results demonstrate that functional connectivity patterns change following a language learning task. Results also indicate that the right cerebellum is part of the language network, and suggest a role in plasticity.

In Chapter 5, a series of fMRI experiments aims to capture semantic prediction in the cerebellum. An event-related linguistic prediction task tests the hypothesis that the right posterolateral cerebellum is differentially engaged in processing highly predictable versus neutral sentence stems. In addition, three control experiments are performed to characterise cerebellar recruitment during visual, semantic and phonological processing tasks. Results showed that the right cerebellum was recruited to a greater extent when processing a highly predictive sentence stem compared with a neutral sentence stem. Moreover, the site of this activation did not overlap entirely with cerebellar regions recruited during any of the three control tasks. Results indicate a cerebellar role in online linguistic prediction, and suggest that this role is separate from its role in attention to semantic, visual, and phonological processing.

Finally, Chapter 6 will summarise the main results reported in this thesis and will integrate and synthesise results into an updated description of the role of the posterior lateral cerebellum in linguistic prediction. Strengths and limitations of the considered empirical evidence presented will be considered and future directions will be outlined.

CHAPTER 2

CEREBELLAR RTMS DISRUPTS LINGUISTIC PREDICTION

The results from the experiment described in this chapter have been published (Lesage, Morgan, Meyer, Olson, & Miall, 2012).

Others' contributions: Blaire Morgan designed the stimuli for the visual world task used in this experiment.

2.1. INTRODUCTION

The cerebellum is traditionally viewed as a structure involved in the coordination of voluntary motor activity. Over the last decades however, it has become apparent that various tasks which are not motor in nature also rely on the cerebellum (Strick et al., 2009). Converging evidence from patient literature (De Smet et al., 2013), functional imaging studies (E et al., 2012; Stoodley & Schmahmann, 2009b), and connectivity studies (Kelly & Strick, 2003) supports a cerebellar role in higher-order functions, such as cognition and language. Specifically, the right posterolateral cerebellum is implicated in language function (Mariën et al., 2001; Price, 2012). However, to date there is very little in the way of a theoretical framework for this proposed cerebellar role in language.

By contrast, the cerebellar role in motor control is relatively well studied. In an well-supported model of motor control, the cerebellum is essentially seen as a predictive machine, which makes short-term estimations about the outcome of motor commands (Miall, Weir, Wolpert, & Stein, 1993; Wolpert & Miall, 1996, see also Chapter 1, Section 1.4.1). When a motor command is issued, an efference copy of this command is sent to the cerebellum, where an internal forward model of the command is activated. This forward model predicts the sensory and proprioceptive outcomes of the movement, and compares it with the actual signal coming from the system (body). If the predicted and actual signals do not match, online corrections can be made. This feedforward prediction system allows much quicker control and correction than if the comparison of the actual and preferred state would have to be compared on the basis of reafferent feedback (Wolpert & Miall, 1996). A cerebellar forward model prediction system therefore accounts well for the speed and efficiency observed in human motor control. The structural homogeneity of the cerebellum suggests that similar computations occur throughout the structure (Bloedel, 1992). Several authors have therefore argued that the models of cerebellar motor function may extend to cerebellar nonmotor functions (Bloedel, 1992; Miall et al., 1993; Ramnani, 2006), and that the cerebellum may support prediction in language processing (Ito, 2008). However, this hypothesis has never been directly tested.

In this study, the visual world paradigm (Cooper, 1974) is used to probe predictive language processing during online sentence comprehension. Eye-tracking paradigms can be used to "monitor the ongoing comprehension process on a millisecond time scale" (Tanenhaus et al., 1995, p1632). In a visual world task, eye-movements are recorded as participants listen to sentences whilst looking at a static visual scene that depicts the agent and object (the target) mentioned in the sentence, along with a number of distracters. In the Prediction condition, the object of the sentence can be inferred from the verb, whereas in the non-predictive (Control) condition the target object cannot be predicted on the basis of the verb. It has been observed that targets were fixated earlier in the Prediction condition than in the Control condition (Altmann & Kamide, 1999). In fact, in the Prediction condition, participants fixated the target before they were able to process the spoken target word. These findings demonstrate that people predict future content during language comprehension, and that eye movements can be used to study these predictive processes.

Given its predictive role in motor control and its involvement in language processing, the cerebellum is a plausible candidate for a role in predictive language processing. The predictive processes in the context of online language processing could be similar to the predictive processes the cerebellum performs in the context of online movement control. We hypothesise that the anticipatory eye-movements observed in visual world tasks are mediated by the right posterolateral cerebellum. If this is the case, these predictive eye-movements could be affected by transcranial magnetic stimulation (TMS) over the cerebellum. Here, repetitive transcranial magnetic stimulation (rTMS) was applied over the right lateral cerebellum, a region implicated in language processing (Mariën et al., 2001). We test the hypothesis that TMS will selectively affect target fixation in the Predictive condition. Hence, after TMS targets should be fixated later than before TMS in the Prediction condition, whereas TMS should not affect target fixation in the Control condition. In other words, we expect that the difference between the conditions reported in visual world experiments (Altmann & Kamide, 1999) will become smaller or disappear after rTMS to the right lateral cerebellum.

2.2. METHODS

2.2.1. PARTICIPANTS

Participants were 65 right-handed native English speakers (mean age = 20.5 years, 20 male) who had no contra-indications for TMS, as assessed by a standard screening questionnaire (http://prism.bham.ac.uk/downloads/TMS_screening_form.pdf). Participants were recruited from the University of Birmingham student population and received course credit or financial compensation for their time. Written informed consent was obtained for each participant. This study was approved by the local ethics committee at the University of Birmingham and was carried out in accordance with the guidelines set out in the Declaration of Helsinki (1964).

2.2.2. TASK AND PROCEDURE

Eye movements were recorded while participants listened to pre-recorded sentences and looked at static displays depicting the agent and the direct object (the target) of the sentence, as well as three distracter objects which were not mentioned in the sentence (see Figure 2.1). In half the trials, the target object could be predicted from the verb (Prediction condition), in the other half such prediction was not possible (Control condition). We measured the time it took listeners to look at the target object (the target fixation latency) from the onset of the verb.

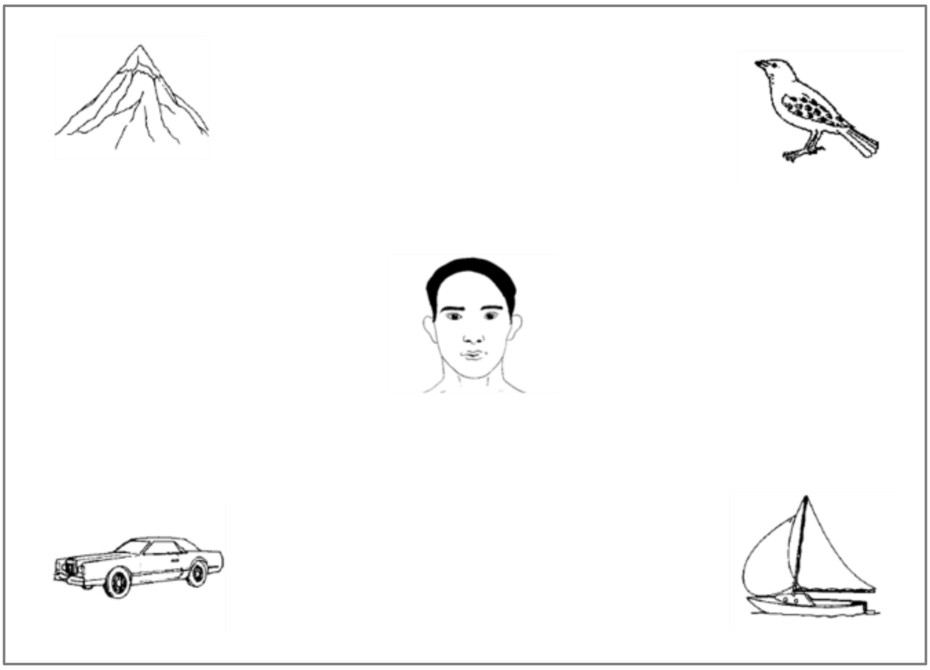

Figure 2.1. Example of a visual scene. In the Prediction condition (e.g. “The man will sail the boat”), the direct object of the sentence (the boat) can be predicted from the verb “sail” because it is the only object in the array plausibly related to that action. In the Control condition (e.g. “The man will watch the boat”), such prediction is not possible.

At the beginning of each visual world trial, four objects appeared, one in each corner of the screen. Participants were instructed to look at all objects, think about what they were and where they were on the screen. After 3000ms, the face of the agent (a man, woman, boy or girl) appeared in the middle of the screen, and as soon as the participant fixated the face of the agent, a pre-recorded sentence was played over headphones. Participants were instructed to look at what was mentioned in the sentence, but no time constraints were applied. Each visual world block lasted under 10 minutes.

In 22 participants, rTMS was applied to the right cerebellum between two blocks of visual world task trials. If the cerebellum is engaged in online linguistic prediction, the disruption of this mechanism should slow down target fixation when prediction is possible (Prediction trials). Conversely, when target prediction is not possible (Control trials) the disruption should not affect target fixation latency. To ensure that the slower fixation in the Prediction condition was not due to effects of fatigue, familiarity with the task, or an effect of rTMS not specific to the cerebellum, we performed two control experiments. One group of participants (n = 21) received rTMS over a control site, the vertex, and another group (n = 22) received no TMS stimulation at all.

2.2.3. STIMULI AND RANDOMISATION

Auditory stimuli were 64 spoken sentences, constituting 32 items. Sentences were spoken by an English native speaker with a neutral British accent. They were digitally recorded as .wav files and played over standard headphones. Eye movements were recorded using a desk-mounted Eyelink 1000 apparatus sampling the right eye at 1000 Hz. Each block was preceded by a 12 point eye tracker calibration. Drift correction was performed between trials. Of the 64 sentences, 28 were taken from Altmann and Kamide (1999). The remaining 36 sentences were newly created. Each item consisted of one sentence in the Prediction condition and one sentence in the Control condition. The only difference between Prediction and Control sentences was the verb, which could refer to only one of the objects in the display (Prediction condition), or to any of the four objects in the display (Control condition). The display was identical in both conditions. The two verbs were matched for frequency of occurrence using the CELEX data base (Baayen, Piepenbrock, & Gulikers, 1995).

The 32 items were divided across two blocks of 16 items. The Prediction and Control variant of each item appeared in the same block so that the eye movements before and after rTMS stimulation could be compared within participants and within items. The order of the blocks was counterbalanced between participants. Within each block, the presentation of the items was pseudorandom, such that the Prediction and the Control version of the sentence pair were never presented adjacently.

2.2.4. TMS PROTOCOL

TMS stimulation was delivered using a Magstim Rapid apparatus and lasted 10 minutes. There was less than two minutes between the end of the stimulation and the start of the next experimental block. In the two participant groups where TMS pulses were delivered, the stimulator intensity was set at a fixed level of 55% of maximum stimulator output (MSO). We opted to use a fixed intensity rather than an intensity proportional to motor threshold, as primary motor cortical excitability is uncorrelated to the excitability of tissue elsewhere in the brain (Boroojerdi et al., 2002; Stewart, Walsh, & Rothwell, 2001).

2.2.4.1. *Cerebellar rTMS*

The stimulation site was 1cm down and 3cm to the right from the inion. This is a site frequently used to stimulate lateral areas of the cerebellum (Théoret, Haque, & Pascual-

Leone, 2001) and data from our lab using a large number of structural MRI scans has shown that this location on the scalp is closest to cerebellar tissue. The target site was stimulated at a fixed 55% of maximum stimulator output intensity with a double-cone coil for 10 minutes at 1Hz (600 pulses). Low-frequency rTMS has been shown to produce LTD-like after-effects in the targeted tissue for a period lasting up to the length of the stimulation (Chen et al., 1997). Prior to the stimulation, one single pulse was delivered in order to familiarise the participant with the sensation, and to allow them the opportunity to withdraw their consent prior to the rTMS stimulation.

2.2.4.2. *Vertex rTMS control*

The control stimulation site was taken as the Cz (the vertex), measured as the mid-point between the two external auditory canals in the transverse plane and the mid-point between inion and nasion in the saggital plane. The target site was stimulated at a fixed 55% of maximum stimulator output intensity with a flat figure-of-eight coil for 10 minutes at 1Hz (600 pulses). Prior to the stimulation, one single pulse was delivered in order to familiarise the participant with the sensation, and to allow them the opportunity to withdraw their consent prior to the rTMS stimulation.

2.2.4.3. *No Stimulation control*

Participants in the No Stimulation group were given instructions and explanations as if they were going to receive cerebellar rTMS. After the first visual world block, they were informed that no TMS pulses would be delivered. However, the cerebellar stimulation site was determined and the double-cone coil was placed over this site for 10 minutes, without activation of the coil.

2.3. ANALYSIS

The dependent variable used was the target fixation latency; the time from the onset of the verb to the onset of the first fixation of the target object (the object of the sentence). We analysed fixations from 400ms after verb onset onwards, as it would take the participant at least 400 ms to understand the verb and initiate a saccade (Marslen-Wilson & Tyler, 1980; Matin, Shao, & Boff, 1993). The reported latencies are measured from verb onset. Trials where no target fixation was made before 3500ms after verb onset were discarded from the latency analysis. Repeated measures ANOVAs and mixed effect modelling were performed on the fixation latencies (see below). In addition to the analyses of fixation latencies, we also compared error rates and several eye-movement kinematic parameters before and after cerebellar rTMS using paired t-tests.

2.3.1. REPEATED-MEASURES ANOVA

Block-by-Condition interactions for each of the three groups were assessed using repeated-measures ANOVAs on the fixation latencies with Block (levels Pre- and Post TMS) and Condition (levels Prediction and Control) as fixed factors and Participant as a random variable. Subsequently, the data from the three groups was combined in a repeated-measured ANOVA to test for a three-way interaction between Group, Block and Condition. Finally, planned paired t-tests were conducted to tease apart this three-way interaction. These analyses were carried out using SPSS software.

2.3.2. EYE MOVEMENT KINEMATICS

The cerebellum has a well-documented role in oculomotor control (Ito, 2001). Therefore, in order to make inferences about target fixations prior to and after TMS, we need to ascertain that low level eye movement variables were not altered by cerebellar TMS. In order to do this, three saccade parameters (peak velocity, average velocity and duration) were compared before and after cerebellar rTMS using paired t-tests.

2.3.3. MIXED MODEL ANALYSIS

It has been proposed that a linear mixed model approach is a more appropriate analysis strategy for this type of psycholinguistic data than repeated-measures ANOVA (Baayen, Davidson, & Bates, 2008). The specific sentences and visual displays used in this study represent a subsection of a larger population of possible experimental items, and could therefore be treated as a random factor in addition to the random factor Participant. A repeated-measures ANOVA does not take this issue into account. Therefore, in addition to the analyses of variance we performed linear mixed effect modelling on the fixation latency data using the lme4 package in R. This allowed us to enter both Participant and Item simultaneously as random effects (Baayen et al., 2008; see also Bates, 2005), which is not possible in analyses of variance. Condition and Block were entered as fixed effects. For this analysis, Block was treated as a time-varying variable, with values 0 for the first block, and 1 for the second block. A model selection strategy using likelihood ratio tests was used to find the best fitting model with the least parameters (Baayen et al., 2008). When the most appropriate random effects structure was selected, models with different combinations of fixed effects were compared.

2.3.4. ERROR RATE COMPARISON

Finally, to ensure the fixation latency effects observed were not due to an inability to perform the task following cerebellar rTMS, we also analyzed error rates before and after rTMS, and between the two conditions after cerebellar rTMS. If the participants were unable to identify the spoken words, or if the information flow between language centres involved in sentence comprehension and oculomotor centres involved in object fixation was disrupted, this would be reflected in the fixation behaviour of participants. No-fixation trials were defined as trials in which the correct target object was not fixated within 3500ms; these trials have been excluded from the analysis of fixation latencies. We also determined the proportion of error trials: those in which the target was not the first object fixated, but where valid target fixation latency was measured within the trial duration; these trials have been included in the latency analyses.

2.4.

2.5. RESULTS

2.5.1. REPEATED-MEASURES ANOVA

The repeated-measures ANOVA revealed a main effect of Condition whereby participants were faster to fixate the target in the Predictive condition ($F(1,21) = 115.85$, $p<0.001$) as well as the hypothesised rTMS-by-Condition interaction. Participants were slower to fixate the target following cerebellar rTMS in the Prediction condition, but were not slowed in the Control condition (rTMS-by-Condition interaction: $F(1,21) = 8.848$, $p = 0.007$, repeated-measures ANOVA; see Figure 2.2). That is, disrupting function in the right cerebellum selectively impaired the prediction aspect of sentence processing in this task; performance was unaffected when sentences did not entail a prediction aspect. There were no other significant effects.

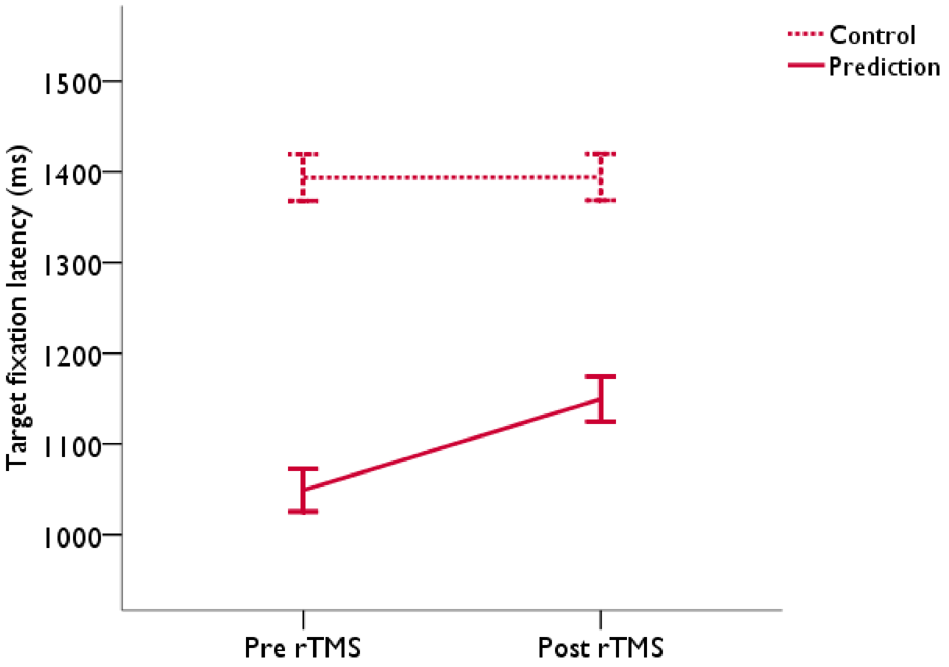

Figure 2.2. Target fixation latencies before and after rTMS to the right lateral cerebellum. Participants were slower to fixate the target in the Prediction condition (solid line), while fixation latency in the Control condition (dashed line) was unaffected. Error bars denote +/- 1 standard error of the mean.

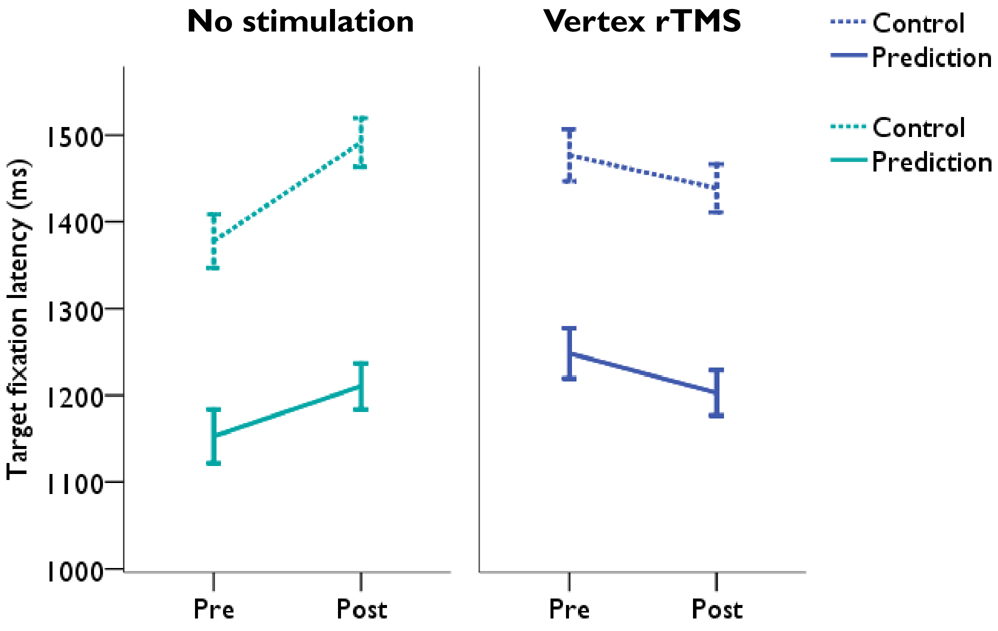

Figure 2.3. Target fixation latencies in the No Stimulation condition (left) and the Vertex rTMS condition (right). There was no interaction between Block and Condition in either group. Error bars denote +/- 1 standard error of the mean.

In both control groups, repeated-measures ANOVAs revealed a main effect of Condition, whereby targets were fixated faster in the Prediction condition (No Stimulation control group: F(1,21) = 264.00, p<0.001; Vertex rTMS control group: F(1,20) = 131.03, p<0.001). No other effects were present in either group. The Block-by-Condition interaction was absent in both the Vertex Stimulation control condition (F(1,20) = 0.064, p = 0.802) and the No Stimulation control condition (F(1,21) = 2.461, p = 0.132, See Figure 2.3). An analysis using data from all three groups revealed a significant three-way interaction (F(2,62) = 4.548, p = 0.014). Planned comparisons between the groups were carried out using t-tests and demonstrate that the Block-by-Condition interaction in the cerebellar rTMS group differed significantly from that in both the No Stimulation control group (t(1,41) = 0.875, p = 0.387) and the Vertex rTMS control group (t(1,42) = 3.111, p = 0.003), while the interaction did not differ significantly between the two control groups (t(1,41) = 0.875, p = 0.387; see Figures 2.3-4). We can therefore attribute the impaired performance in the Prediction condition to disruption of neural operations by rTMS over the right cerebellum. There is no reason to believe that rTMS effects on neighbouring structures, including the right occipital lobe, would be responsible for this selective deficit in predictive processing.

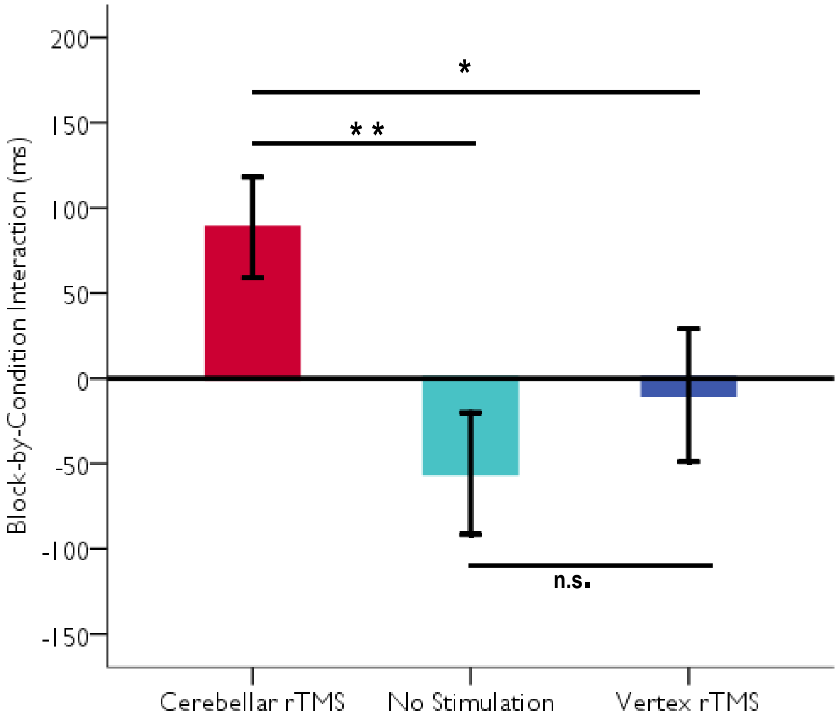

Figure 2.4. Block-by-Condition interactions for the three groups. The hypothesised positive interaction is only evident in the cerebellar group (red), and is significantly different from the two control groups (light and dark blue), which do not differ from each other. Error bars denote +/- 1 standard error of the mean.

2.5.2. EYE MOVEMENT KINEMATICS

None of the measured eye movement variables showed any difference after cerebellar rTMS (See Figure 1.5). Paired t-tests for average saccade velocity (t(21) = 1.26, p = 0.222), peak saccade velocity (t(21) = -0.04, p = 0.972), and saccade duration (t(21) = -1.64, p = 0.116) did not reach significance, indicating that there were no TMS-induced effects on eye movement kinematics, and ruling these out as a possible cause of post-TMS changes in target fixation latencies.

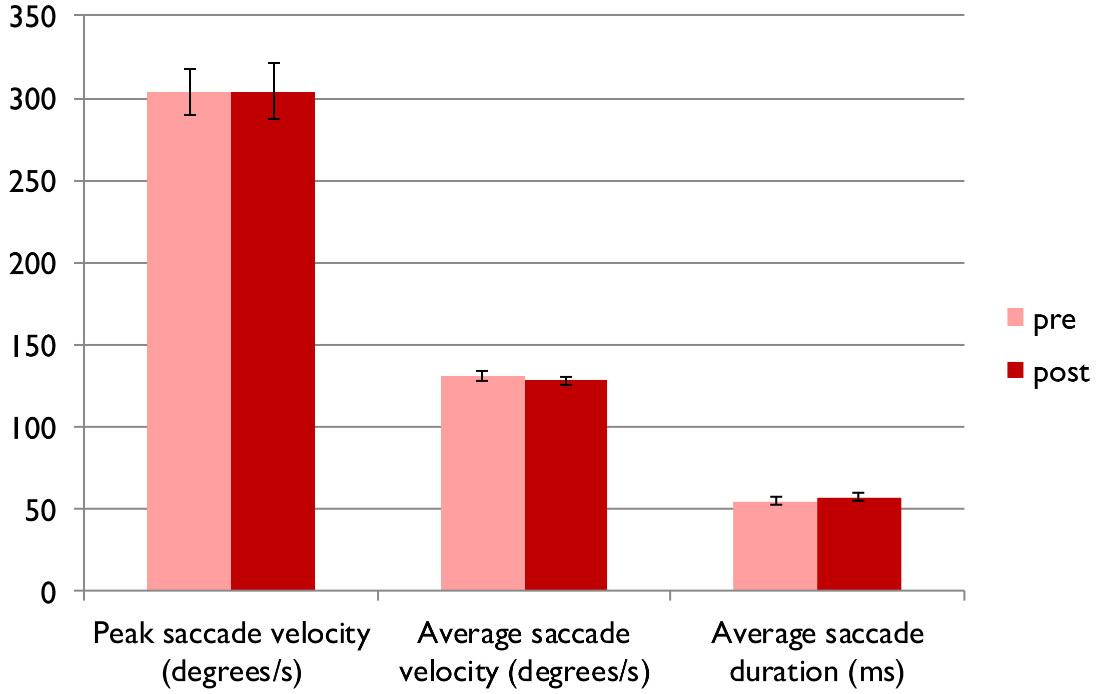

Figure 2.5. Eye movement kinematic measure before (pre) and after (post) cerebellar rTMS. Neither of the measure change significantly after rTMS. Error bars denote 1standard error of the mean.

2.5.3. MIXED MODEL ANALYSES

The additional linear mixed model analyses revealed the same pattern of results as the ANOVA approach reported above. In the Cerebellar Stimulation group, model comparison favoured a model with a Block-by-Condition interaction against the simpler model without an interaction ($\chi^2 = 4.100$, $p = 0.043$). In the Vertex Stimulation control group ($\chi^2 = 0.013$, $p = 0.908$) and in the No Stimulation control group ($\chi^2 = 1.044$, $p = 0.307$), the model with the interaction was not preferred, and therefore the simple, no interaction model should be assumed. The preferred random effects structure included Item as a random effect on the intercept, and Participant as a random effect on both intercept and slope.

2.5.4. ERROR RATE ANALYSIS

Pair-wise t-tests comparing the number of errors before and after cerebellar rTMS revealed no significant effect, with a trend towards fewer errors after rTMS, possibly due to greater familiarity with the task (Paired t-test: $t(21) = 1.916$, $p = 0.069$; see Figure 1.6, right column). Following rTMS, the error rates did not differ between the two predictive conditions (Paired t-test: $t(21) = -0.075$, $p = 0.941$, Figure 2.6). When comparing trials where no fixations to the target were made, no significant differences arose between blocks before and after cerebellar rTMS (Paired t-tests: $t(21) = -1.867$, $p = 0.076$), or between the two predictive conditions following cerebellar rTMS (Paired t-tests: $t(21) = -1.336$, $p = 0.196$; Figure2.6, left column). These results demonstrate that participants were equally able to identify the target words and make corresponding eye movements. Hence, cerebellar rTMS resulted in an equally accurate but delayed target fixation, consistent with the loss of the temporal advantage conferred by a short-term prediction.

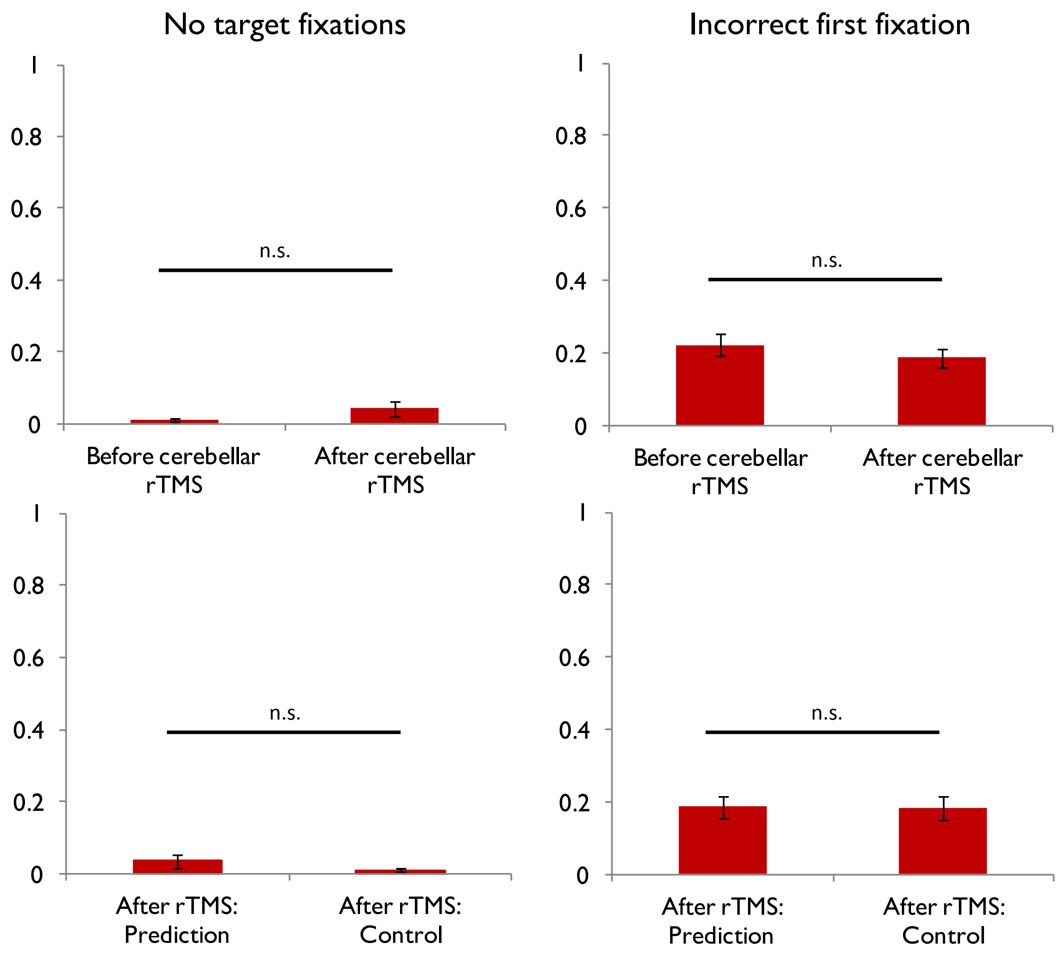

Figure 2.6. Error rate comparison. The amount of trials without a target fixation (left) and trials with an erroneous first fixation (right) did not differ between the two blocks, or between the two conditions after cerebellar rTMS. The results can therefore not be explained by a TMS-induced breakdown in sentence comprehension. Error bars denote +/- 1standard error of the mean.

2.6. DISCUSSION

In this experiment, we tested the hypothesis that the right cerebellum is implicated in predictive language processing. Repetitive TMS was applied to the right cerebellum between two blocks of a language task, where participants were asked to look at the object of a sentence with or without predictable content. Results show that after cerebellar rTMS, listeners showed delayed eye fixations on the target object predicted by sentence content, while there was no effect on eye fixations in sentences without predictable content. This effect cannot be explained by changes in eye movement kinematics, which were not altered by rTMS nor by a generalised blocking of language processing, as comprehension was not affected, nor by a general effect of rTMS, as stimulation of a control site did not produce the specific impairment. Therefore, it can be concluded that a cerebellar-dependent predictive process was perturbed.

Most of the literature on cerebellar language involvement stems from fMRI, PET and EEG experiments (Desmond, Gabrieli, Wagner, Ginier, & Glover, 1997; Petersen et al., 1989), and structural MRI comparisons (Eckert, 2003; Nicolson et al., 2001). The main limitation of these techniques is that they are essentially correlational; it is difficult to make the claim that the cerebellum is necessarily involved in the task used. A handful of neurostimulation studies have targeted nonmotor function in the cerebellum. TMS and transcranial direct current stimulation (tDCS) of the cerebellum have been reported to impact on verbal working memory (Desmond, Chen, & Shieh, 2005; Pope & Miall, 2012) and attention (Arasanz, Staines, & Schweizer, 2012). Two TMS experiments have used cerebellar theta-burst stimulation of the neocerebellum in lexical priming tasks (Argyropoulos & Muggleton, 2013;

Argyropoulos, 2011). Results of these studies showed selective effects on semantic associative priming. That is, cerebellar stimulation showed effects on phrasal associations (words that are temporally contiguous, e.g. "skeletons - closet") and lexical semantic associations (e.g. "cake - eat"), but not on associations related to semantic similarity (e.g. "storm - rain"), or to categorical associations (e.g. "horse - cow"). While these studies are in line with a specific cerebellar role in online prediction of upcoming content, the medial stimulation site and temporary nature of the effects found in these studies, leave some uncertainty as to whether lexical priming was genuinely affected (Grimaldi et al., 2013). The present experiment is one of the first to experimentally manipulate the cerebellum in a language task, and the first to do so at the sentence level.

Another strength of the current experiment is that the Predictive condition in the Visual World task used here is no more taxing in terms of working memory than the Control condition. Therefore, the impairment after TMS cannot be attributed to higher verbal working memory demands in the Predictive condition. Many of the language paradigms used in studies on the cerebellum tax verbal working memory more heavily in the experimental condition. For example, verb generation tasks entail a verbal working memory component which is greater in the experimental conditions (generate a verb) than the control condition (repeat a noun). This makes it is difficult to disentangle the contributions of executive load and language function selectively (e.g. Frings et al., 2006). While the visual world task is likely to recruit verbal working memory circuits, the Prediction condition is no more taxing than the Control condition. However, limitations of the methods include the unknown spatial specificity of TMS. It is unclear how much cerebellar tissue was stimulated with the cerebellar rTMS, but it is likely several square centimetres. Another limitation is that, unlike whole-brain imaging techniques, one can only use TMS to assess the involvement of one brain region at a time.

Despite the considerable and growing evidence for cerebellar involvement in language function, one point of controversy regarding cognitive and linguistic functions of the cerebellum concerns how "nonmotor" any task truly is (Timmann & Daum, 2007). For example, we cannot argue that the language comprehension task used here does not entail any motor aspects. Apart from the eye movements elicited by the task, there are at least two ways in which a "passive" language comprehension task could relate to activity in the motor system. First, there is a tight link between language comprehension and action. Action-related semantic content has been associated with activity in motor structures used to execute those actions (Pulvermüller & Fadiga, 2010; Pulvermüller, Kiff, & Shtyrov, 2012; Pulvermüller, 2005). For example, processing speed for leg-related words (e.g. "kick") was affected when the leg area of the left primary motor cortex was stimulated with TMS, while performance was unaffected when the right leg area, or the left arm area were targeted (Pulvermüller, Hauk, Nikulin, & Ilmoniemi, 2005). Similarly, an event-related fMRI study showed that BOLD activity elicited by action verbs was somatotopically organised in the primary motor cortex (Hauk, Johnsrude, & Pulvermüller, 2004). Considering its important role in motor control, cerebellar involvement in language processing could be interpreted in the context of action representation. As the visual world task used here did not differentiate between action-related and non-action related verbs, we were not able to test for possible specific effects of action verbs in motor areas of the cerebellum. It is therefore possible that motor areas of the cerebellum are more active when processing action-related verbs (e.g. move), and non-action related verbs (e.g. watch). However, if such mechanisms were present, they would not by themselves explain our results, as the observed deficit was specific to sentences with predictive verbs, whether these were action-related or not.

Second, there is a tight link between language comprehension and language production apart from this semantic link. The brain regions implicated in language production overlap to a large degree with those involved in language comprehension (Eickhoff et al., 2009; Vigneau et al., 2006). In fact, Pickering and Garrod (2013) propose that language production and comprehension require the same processes (see also Chapter 1, Section 1.6). In their model, speech comprehension is established by covertly imitating the speech production process of the speaker. Indeed, there is neuroimaging evidence that brain areas associated with language production are active during comprehension tasks (Scott & Johnsrude, 2003; Wilson et al., 2004). According to this theory, language comprehension might entail covert language production processes. Because cerebellar circuits are implicated in articulation (Blank, Scott, Murphy, Warburton, & Wise, 2002; Riecker et al., 2005), a language comprehension task could recruit (cerebellar) motor circuitry.

Following these arguments, it could be argued that language comprehension (perception) and language production (action) are too entangled to allow a clear, ecologically plausible anatomical distinction. However, these points should not be taken as evidence for a motor-only cerebellum. The effects observed in this study relate to semantic meaning (of the verbs and the presented objects), and it can reasonably be assumed that the motor demands in both conditions were equal, and therefore did not cause the observed effect. Therefore, regardless of any shared neural circuitry between comprehension and production, the present data support a cerebellar role in language processing, that cannot be explained by motor involvement.

It has long been hypothesised that the cerebellum serves a single computational function (Bloedel, 1992) and that this function may be prediction (Ito, 2008; Miall et al., 1993). Several authors have previously expanded the idea of forward and inverse internal models from the motor control domain to the cognitive and language domains (Imamizu & Kawato, 2009; Ito, 2008; Pickering & Garrod, 2013; Ramnani, 2006). In this experiment, we find evidence for such a predictive function in a language task. Indeed, there are some parallels between the two processes. Like motor control, language comprehension is highly time sensitive. Listeners must process the spoken input online, at a rate set by the speaker. In addition, successful language comprehension and production is highly practiced and largely automatic. Moreover, listeners can often predict future sentence content based on various contextual cues and previous experience (Altmann & Kamide, 1999). A predictive process similar to forward modelling in motor control (Miall et al., 1993) could therefore contribute to the speed and efficiency of language processing (Pickering & Garrod, 2007, 2013).

Our results indicate that the cerebellum is involved in linguistic prediction. However, the present data do not allow us to determine the computational processes by which these predictions are achieved, as of yet, is unclear how these predictions are made, which brain areas are involved and how they interact. It also remains to be determined whether the cerebellar activations found in other language tasks can be explained by predictive processes like the one we probed in this experiment. Below, we speculate on a possible mechanism of cerebellar forward models in language. An interesting account of language comprehension and production has been outlined by Pickering & Garrod (2013). In their model, language production is treated as a form of action, and language comprehension as a form of (action) perception. The authors then apply internal model-based theories of action and action perception (Wolpert & Miall, 1996) to language. Essentially, it is proposed that forward model prediction is central to language comprehension and production. Applied to sentence comprehension, the idea is that that listener will covertly imitate the speaker and predict future sentence content based on what they would likely say next, given the context. Pickering and Garrod (2013) do not discuss candidate brain areas for the processes they describe, but the right lateral cerebellum is plausible anatomical substrate for this forward modelling. First, there is evidence that the right lateral cerebellum (lobule HVII/Crus II) is part of the verbal working memory and language system (Desmond et al., 1997; Marvel & Desmond, 2010; Strick et al., 2009). Second, the right lateral cerebellum is connected with cortical language and higher cognitive areas such as Broca's area and the dorsolateral prefrontal cortex (Bloedel, 1992; Kelly & Strick, 2003; Mariën et al., 2001; Middleton & Strick, 2001). Third, the cerebellar cytoarchitecture strongly suggests that computations throughout the cerebellum are similar (Leiner et al., 1991). Finally, the present results implicate the cerebellum in a predictive role in language comprehension. Hence, we speculate that input to the right cerebellum from connected language structures, possibly the inferior frontal gyrus, would provide an ‘efferent copy’ of internalised speech, from which the lateral cerebellum would predict future linguistic visual or auditory input. These predictions then would feed back to frontal cortical language areas to facilitate processing. This proposed process is largely parallel to the cerebellar function in motor control (Wolpert & Miall, 1996). If we apply the Pickering and Garrod (2013) model to the conditions in this experiment, this means the participant actively predicts what was coming next at each point in the sentence. As s/he hears the utterance, s/he covertly imitates the heard sounds, a process which would recruit Broca's area (Friedman et al., 1998). An efferent copy of this internalised speech signal is sent to the cerebellum, and likely future input is predicted on the basis of contextual cues (in this case the visual scene). In the Control condition, this does not result in a noticeable advantage in the task, as each of the objects is equally plausibly the target. In the Prediction condition, this short-term prediction does allow the listener to decide faster what the target is. By perturbing the right cerebellum with TMS, the forward model prediction is disrupted. This is of little consequence in the Control condition, where the prediction was not useful in deciding between the potential targets. But in the Prediction condition, disruption of the predictive process results in a slower target fixation than if cerebellar function were intact.

At first glance, such a model does not seem to explain the existing literature describing cerebellar involvement in language. Indeed, many language tasks where cerebellar activations are found do not have an explicit predictive component. However, the model outlined above would not predict cerebellar activity to be absent in, for example, verb generation tasks (Frings et al., 2006; Lurito et al., 2000) or sentence reading tasks (Fedorenko et al., 2010). Instead, the proposed forward model prediction would be an unavoidable process during language comprehension and production. In other words, sentence reading may also trigger the predictive process, driven by internal vocalisation of the sentence. In verb generation, it is possible that the noun-verb associations also allow prediction of the verb from the single noun, without the full context of the sentence. This is supported by reports from cerebellar patient studies, where patient show deficits in verb generation (e.g. producing "kick" for the noun "football"), but are unimpaired at producing words in the same semantic category (e.g. naming several animals) (Drepper, Timmann, Kolb, & Diener, 1999; Gebhart, Petersen, & Thach, 2002). The former type of association provides information which could be predictive of upcoming sentences content ("kick" and "ball" are likely to occur in the same sentence), whereas the latter is not ("cow" and "horse" are not likely to co-occur in the same sentence).

Because the proposed model entails the continuous prediction of upcoming content, it may prove challenging to isolate this predictive component with whole brain imaging methods such as fMRI or EEG. The temporal resolution of fMRI is not well suited to pick up the timing of these short-term predictions, and it is difficult to get a reliable EEG measure from the cerebellum because of its anatomical position (Dien et al., 2003).

It should be clear that many aspects of this speculative model remain to be tested, and that the present data do not allow us to distinguish forward model prediction from other modes of prediction. There is evidence for anatomical connections between the cerebellum and higher order cortical areas (Ito, 2008; Kelly & Strick, 2003; Middleton & Strick, 2001), but how cortical and subcortical areas work together to achieve linguistic prediction remains to be investigated.

In summary, we have shown that disruption of the right cerebellum slows predictive language processing. These results further support a cerebellar role in language processing, and suggest that the predictive function of the cerebellum in motor control can be extended to the nonmotor cerebellum.

CHAPTER 3

PREDICTIVE LANGUAGE PROCESSING IN CEREBELLAR PATIENTS

Others' contributions: Dr. Marios Hadjivasilious at the Sheffield ataxia centre assisted with patient recruitment. Data acquisition for the Sheffield group was performed along with Dr. Paul Pope, who also acquired MoCA test scores for these participants. Dr. Ned Jenkinson and Dr. Muriel Panouilleres assisted in patient recruitment of the Oxford patient group and provided infrastructure at the Wolfson clinical neuroscience facility.

3.1. INTRODUCTION

In Chapter 2, rTMS to the right cerebellum of young healthy participants was applied between two blocks of a predictive language task, the visual world task. Results showed that predictive eye movements occurred later after right cerebellar TMS than before TMS, whereas no delay was present in a non-predictive control condition, or following TMS to a control site, or with no TMS applied. In this chapter, a group of patients with cerebellar degeneration and a group of age and education-matched controls performed the visual world task. We test whether predictive eye movements are also affected in cerebellar patients, hypothesising a small disadvantage in eye movement latencies in the predictive condition.

Symptoms as a result of cerebellar lesions are largely characterised by problems in the motor domain, notably with posture, gait, eye movements, articulation, and precise coordination of the limbs (Timmann et al., 2008). Occasionally, cerebellar patients present with cognitive, linguistic or affective symptoms (Schmahmann & Sherman, 1998; Schmahmann, 1998). Of these, linguistic deficits are amongst the most reported problems; these are apparent in verb generation, word stem completion, and verbal fluency tasks (De Smet et al., 2013; Fabbro et al., 2000; Fiez, Petersen, Cheney, & Raichle, 1992; Stoodley & Schmahmann, 2009b). Efforts have been made to specify the types of linguistic tasks associated with cerebellar lesions. For example, patients have been found to be impaired at phonemic fluency tasks (e.g. naming as many words beginning with the letter "L" as possible) but not at semantic fluency tasks (e.g. naming as many animals as possible; Leggio, Silveri, Petrosini, & Molinari, 2000). However, another study reports both semantic and phonemic fluency deficits (Stoodley & Schmahmann, 2009b).

Reductions in working memory capacity are not commonly reported in cerebellar patients, in stark contrast to the neuroimaging literature where the cerebellum is one of the more striking areas of activation in working memory contrasts (Justus, Ravizza, Fiez, & Ivry, 2005). Typically, cerebellar lesions do not affect the digit span, (Fabbro, 2004; Fiez et al., 1992), and when they do, only to a limited extent (Ravizza et al., 2006). When verbal working memory deficits are reported in cerebellar patients, these tend to be present in task variations using orthographic material rather than abstract material such as numbers (Ravizza et al., 2006). Cerebellar lesions have also been linked to cognitive associative learning, irrespective of motor deficits (Drepper et al., 1999). Finally, Leggio, Chiricozzi, Clausi, Tedesco, and Molinari (2011) reported impairment on a cognitive sequencing task, whereby participants were asked to order parts of a logical sequence. Cerebellar patients were impaired at a verbal, a pictorial and a visuospatial variant of the task, with right cerebellar damage more predictive of deficits in the verbal and pictorial versions, and left cerebellar damage associated with worse performance on the visuospatial variant. On the whole, compared to the motor deficits caused by cerebellar lesions, these cognitive and linguistic deficits are relatively mild and they tend not to be in the clinical range, emerging only in experimental testing sessions when contrasted with matched controls (Justus, 2004; Leggio et al., 2000; Silveri et al., 1998; Timmann & Daum, 2010).

Converging data from these patient studies indicate deficits in verbal fluency, semantic association, cognitive associative learning, and cognitive sequencing. The underlying cerebellar-dependent processes that underlie these various impairments are not yet clear. Early accounts argued that the process underlying these deficits is articulatory rehearsal (Ackermann, Wildgruber, Daum, & Grodd, 1998), but this has proved inconsistent with both clinical and imaging literature (Desmond et al., 1997; Ravizza et al., 2006). Another proposed explanation has been that phonological short-term memory may be cerebellar-dependent (Chiricozzi, Clausi, Molinari, & Leggio, 2008; Justus et al., 2005; Ravizza et al., 2006). Finally, deficits following cerebellar damage have also been interpreted in light of a uniform cerebellar role in state estimation and forward model prediction (Molinari et al., 2009). The latter perspective is taken in this chapter.

It has been argued that the pattern of cognitive as well as motor deficits in cerebellar patients could be explained by a cerebellar role in prediction (Ben-Yehudah et al., 2007; Molinari et al., 2009). The notion of linguistic internal forward models (see Chapter 1. Section 1.6) in the cerebellum is reasonably congruent with the patient literature outlined above. Argyropoulos and colleagues pointed out that the lexical retrieval deficits tend to occur only when the association in question could be informative with respect to co-occurrence in the sentence (Argyropoulos & Muggleton, 2013; Argyropoulos, 2011). This could explain the finding that patients can still name members of a semantic category, but are impaired at generating an appropriate verb for a noun. Similarly, word stem completion tasks and verbal fluency tasks entail phonological association which may be achieved by short-term linguistic prediction. Associative learning deficits may then be related to a deficit in acquiring or retrieving predictive relationships between linguistic items. The finding that cerebellar patients are impaired at cognitive sequencing is congruent with the notion that the cerebellum also subserves more abstract predictions, and has been linked to the idea of a universally predictive cerebellum (Molinari et al., 2009). We might therefore expect cerebellar patients to be impaired at online linguistic prediction. However, linguistic prediction deficits have not been directly addressed in the cerebellar patient literature to date.

The visual world paradigm used in the previous chapter captures online linguistic prediction by tracking subjects' eye movements (Altmann & Kamide, 1999). In this paradigm, participants listened to sentences while they look at a scene which depicts the subject of the sentence along with the direct object and three distracter objects. Typically, participants show anticipatory eye movements towards the object of the sentence if the object can be predicted on the basis of the verb. Thus, eye movements are used as a measure of online sentence processing, and anticipatory eye movements mark predictive language processing. In the previous chapter, right cerebellar rTMS delayed the fixations in the Predictive condition, but not in a non-predictive Control condition. This paradigm may provide insight into possible cerebellar-based linguistic deficits in prediction.

In this chapter, we test whether cerebellar patients are impaired at the visual world task. We test a group of cerebellar patients and a group of neurologically healthy control participants on a visual world task. We hypothesise that patients will be able to benefit less from the predictive context which will lead to a smaller differences between fixation latencies in the Predictive and non-predictive Control conditions. As of yet, due to difficulties in patient recruitment, we have not been able to test sufficiently large groups of patients and controls. The presented data are therefore incomplete, and do not allow firm conclusions to be drawn. Preliminary results and future directions will be discussed. Further data acquisition will take place beyond the scope of this thesis.

3.2. METHODS

3.2.1. PARTICIPANTS

3.2.1.1. *Participant recruitment*

Available patients with cerebellar lesions who had no extra-cerebellar damage and were not diagnosed with symptoms of nystagmus were recruited. One group of participants (N = 11) was recruited via the Sheffield ataxia centre (http://www.sth.nhs.uk/neurosciences/neurology/sheffield-ataxia-centre). Participants and their partners were contacted by their neurologist with an invitation to the study. If they indicated an interest in participating, they were contacted to arrange a testing session. A second group of participants (N = 8) was recruited from the Oxford ataxia clinic in collaboration with Dr. Ned Jenkinson and Dr. Muriel Panouilleres. These participants were contacted by their clinician with an invitation to the study. If they expressed an interest, they were contacted to schedule a testing session.

3.2.1.2. *Cerebellar disorders*

The primary group of interest was participants diagnosed with spinocerebellar ataxia type 6 (SCA6). SCA6 is an autosomal dominant disorder which leads to progressive cerebellar atrophy with little extra-cerebellar involvement. It is typically diagnosed in adulthood (4th or 5th decade), so patients have had a normal developmental trajectory, including normal language acquisition. The disease is characterised by ataxia, dysarthria, and nystagmus. In the Sheffield group, four patients were not diagnosed with SCA6, but all had lesions specific to the cerebellum and a similar symptomatic profile. All participants were diagnosed in adulthood.

3.2.1.3. *Participant characteristics and exclusion*

Data were acquired from eleven patients and eight control participants. One patient who developed ataxia as a result of alcoholism possibly had extra-cerebellar brain damage. A second patient was not a native English speaker. Data from these two participants were not analysed. A further three patients were excluded from the eye-tracking analysis. Eye-tracking data from one of these participants had to be discarded because his gaze showed abnormalities during testing, which caused a majority of trials to be unreliable (see below, Section 3.4.1.). Finally, two patients were excluded because they were outliers on some of the low level eye movement characteristics. Therefore, eye-tracking data was included for 6 patients and 8 control participants, and other behavioural data for 9 patients and 8 control participants (see Figure 3.1).

Table 3.1. Participant details. Participants excluded from eye-tracking analysis in grey italic.

ID code	Diagnosis	Gender	age	years of education
DM	idiopathic sporadic ataxia	male	74	10
LP	episodic ataxia type 2	female	41	10
WF	SCA6	female	60	12
KG	SCA6	female	59	10
LM	SCA6	female	57	15
LG	SCA6	female	54	12
RM	*SCA6*	*female*	*71*	*11*
AB	*episodic ataxia type 2*	*male*	*48*	*10*
BH	*hereditary ataxia (unspecified)*	*male*	*77*	*15*
CB	control	female	44	10
NM	control	female	72	10
MM	control	female	69	12
GP	control	male	40	10
RN	control	female	40	12
DP	control	female	64	18
JS	control	female	64	17
CJ	control	female	62	15

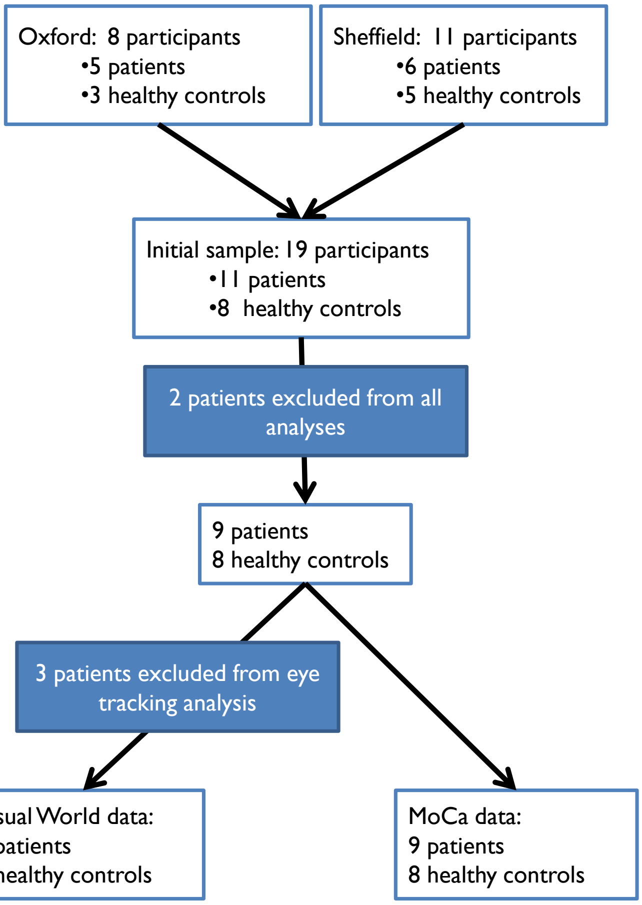

Figure 3.1. Participant exclusion. Exclusion criteria outlined in Section 3.2.1.3.

Ages for participants included in all analyses ranged from 40 to 74 years, and included one man (in the Patient group). Groups were reasonably well-matched for age (mean age controls 57 years, SE = 4.7 years, mean age patients 58 years, SE = 4.34 years) and showed only a slight difference in average educational background (mean number of years in formal education in Control group = 13 years, SE = 1.15 years; in Patient group = 11.5 years, SE = 0.81 years). See also Table 3.1 for participant characteristics.

3.2.2. APPARATUS AND LOCATION

The first group of participants was tested in their own homes. A portable head-mounted Eyelink II system was employed to acquire eye-tracking data. This part of the study was covered under University of Birmingham ethics. The second group was tested at the Wolfson Clinical Neuroscience Facility at the John Radcliffe hospital in Oxford, and was covered under Oxford University ethics. Informed consent was obtained from all participants prior to testing. Eye-tracking data for the second group was collected on a tower-mounted Eyelink 2000 system. The experiment was split into two blocks, so as to allow a break if desired. Participants also completed the Montreal Cognitive Assessment (MoCA) at the time of testing.

3.2.3. TASK

3.2.3.1. *The visual world task: changes to the task*

Nystagmus is a common symptom in cerebellar patients, but mild symptoms of nystagmus would not necessarily have repercussions for interpretation of eye movements with the design used. Because the eye-tracking experiment uses sizeable target interest areas, it is merely necessary to determine which corner of the screen the participant is looking at and when. Imprecise saccades and a small amount of "flutter" when in the target region is are therefore not necessarily problematic. Even mild symptoms of nystagmus could however cause difficulty during the calibration phase, when a series of small dots need to be fixated precisely and for an extended period of time. We therefore adjusted the calibration settings on the Eyelink apparatus from the design in Chapter 2 to allow less accurate and shorter fixations, and these settings were piloted with the help of a volunteer with a mild case of nystagmus. At the beginning of an eye-tracking block, the customary 9 point calibration was replaced by a 3 point calibration, and minimal period of fixed gaze to count as a fixation was reduced from 300 to 30 milliseconds. Similar adjustments are commonly made when testing patient populations (William Schmidt, SR Research, personal communication via email). These adjustments were made to the calibration phase, but not to the data acquisition phase. In the task proper, one adjustment to the trial timing was made, in that the initial scene was now presented for 5000ms of scene explorations, instead of the 3000ms in Chapter 2. In all other respects, the task design was identical to the one used in the previous chapter.

3.2.3.2. *Visual world task: procedure*

The procedure was identical to that described in Chapter 2 (see Section 2.2.2.) Eye movements were recorded while participants listened to pre-recorded sentences and looked at static displays depicting the agent and the direct object (the target) of the sentence, as well as three distracter objects which were not mentioned in the sentence In half the trials, the target object could be predicted from the verb (Prediction condition), in the other half such prediction was not possible (Non-predictive condition). We measured the time it took listeners to look at the target object (the target fixation latency) from the onset of the verb. At the beginning of each visual world trial, four objects appeared, one in each corner of the screen. Participants were instructed to look at all objects, think about what they were and where they were on the screen. After 5000ms, the face of the agent (a man, woman, boy or girl) appeared in the middle of the screen, and as soon as the participant fixated the face of the agent, a pre-recorded sentence was played over headphones. Participants were instructed to look at what was mentioned in the sentence. Each visual world block lasted under 10 minutes. Participants were offered a break between blocks.

3.2.3.3. *Items and randomisation*

The stimuli and randomisation protocol was identical to that in Chapter 2 (see Section 2.2.3).

3.2.3.4. *The Montreal Cognitive Assessment (MoCA)*

In addition to the visual world task, participants also performed the Montreal Cognitive Assessment (Charbonneau, Whitehead, & Collin, 2005). The MoCA is a short, standardised test which assesses cognitive functions across seven cognitive domains: visuoconstructional skills, naming, attention, language, abstraction, delayed recall and orientation. The MoCA has been designed as a screening tool for mild cognitive impairment (sensitivity 90%, specificity 100%) and mild symptoms of Alzheimer's disease (sensitivity 100%, specificity 78%). The maximum score is 30, with scores above 26 considered normal. Here, the scores on the language subscale, a phonemic fluency task and a sentence repetition task, were of particular interest. The test was administered and scored according to the MoCA instructions (http://www.mocatest.org/pdf_files/instructions/MoCA-Instructions-English_2010.pdf).

3.3. ANALYSIS

3.3.2. EYE MOVEMENT VARIABLES

Low level eye movement characteristics were analysed as in the previous chapter. Saccade duration, peak saccade velocity and average saccade velocity were processed in Matlab and average scores for each participant were further compared in SPSS. These saccade variables were used to ensure no low-level eye movement problems could underlie differences in the visual world performance, and to detect participants with atypical saccadic behaviour. For example, severe nystagmus could lead to differences in fixations unrelated to linguistic prediction and render task performance uninterpretable. An analysis of the saccade variables was therefore performed using boxplots to exclude participants with atypical low-level saccade variables. Independent samples t-test were carried out to detect group differences.

3.3.1. VISUAL WORLD TASK

3.3.1.1. *Correction for calibration problems*

Due to the more lenient calibration settings (see Section 3.2.3.1) systematic calibration errors were sometimes present in the data. In trials where this was the case, the recorded fixation pattern would typically be shifted systematically in one direction. This was especially the case for the head-mounted portable Eyelink II setup, where movement of the head set was an additional cause of systematic calibration errors. Small deviations in fixation were hand-corrected, and trials with larger deviations were excluded from analysis. Therefore, for each trial the fixation pattern was observed. If the fixation pattern for a trial indicated that a calibration error had occurred, the fixation record was shifted to better match the presented scene (see Appendix 2). If the deviations were too large or if not all fixations to the target object were evident in the record, the trial was discarded. Crucially, when making these adjustments, the experimenter was blind to the condition. Therefore, changes made could not consciously or subconsciously bias the data in any direction. Moreover, when the predictive trial of an item was excluded, the non-predictive counterpart was excluded also. Trials were therefore always excluded in pairs.

3.3.1.2. *Analysis of the target fixations*

Adjusted fixation reports were processed with a custom-made Matlab script, and timing of fixations to target were further analysed in SPSS. A repeated-measures ANOVA with within-subject factor Condition (2 levels: Predictive and Control) and between-subject factor Group (2 levels: Patients and Controls) was performed on the target fixation latencies. As in the previous chapter, fixation latencies from 400ms onwards were considered in the analysis.

3.3.2. MONTREAL COGNITIVE ASSESSMENT

Scores on the subscales of the MoCA, as well as on the total score were compared between groups using independent samples t-tests.

3.4. PRELIMINARY RESULTS

3.4.1. EYE MOVEMENT VARIABLES

After initial processing of the eye-movement data, one participant was excluded because more than half the trials yielded unreliable fixation data (see Table 3.2.). Low-level eye movement variables were compared through box plots. In the patient group, two outliers were detected and removed. After outlier removal, there were no significant group differences in peak saccade velocity (t(12) = 0.15, p = 0.871), average saccade velocity (t(12) = -0.46, p = 0.665), and saccade duration (t(12) = 0.11, p = 0.908; see Figure 3.2).

Table 3.2. MoCA scores and proportion of excluded trials per participant. Participants excluded from eye-tracking analysis in grey italic.

ID code	Group	MoCA score	Excluded trials (prop)
DM	patient	22	0.06
LP	patient	17	0.03
WF	patient	28	0.06
KG	patient	29	0.00
LM	patient	29	0.00
LG	patient	27	0.00
RM	*patient*	*26*	*0.00*
AB	*patient*	*15*	*0.59*
BH	*patient*	*23*	*0.16*
CB	control	30	0.22
NM	control	17	0.00
MM	control	23	0.06
GP	control	25	0.00
RN	control	28	0.00
DP	control	26	0.00
JS	control	28	0.00
CJ	control	27	0.00

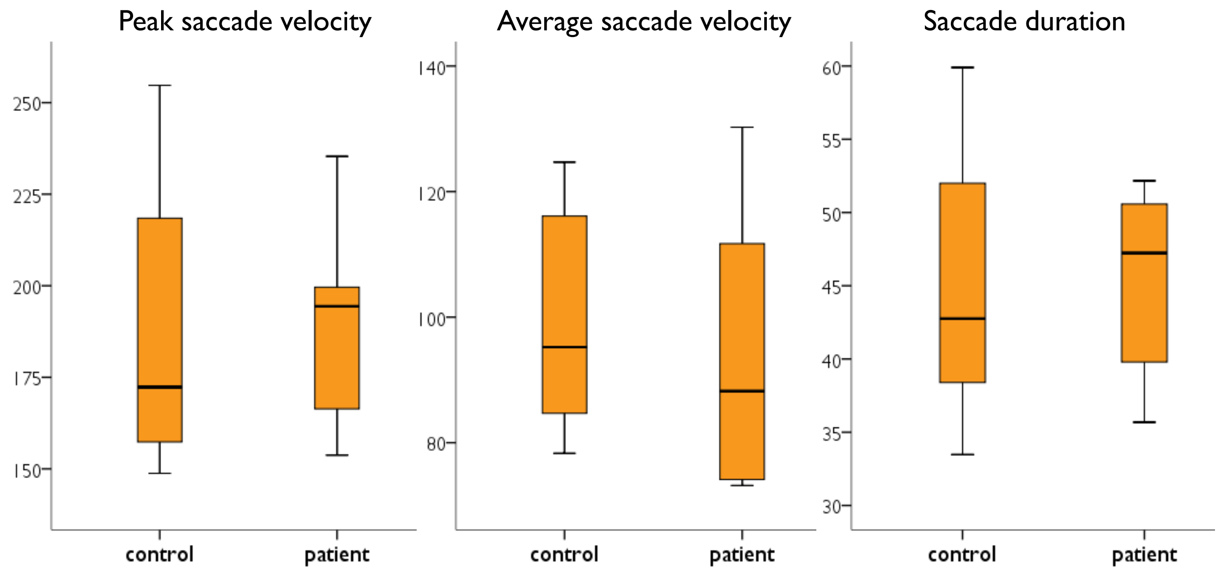

Figure 3.2. Box plots of low-level eye movement variables; peak saccade velocity (first column, degrees/s), average saccade velocity (second column, degrees/s), and saccade duration (third column, ms) after outlier-removal.

3.4.2. VISUAL WORLD TASK

The repeated-measures ANOVA revealed a main effect of Condition (F(1,12) = 54.69, p<0.001) with target fixations significantly earlier in the Predictive condition (mean = 1087.5 ms, SE = 37.9ms) than in the Control condition (mean = 1290, SE = 34.3ms). No Group-by-Condition interaction was observed (F(1,12) = 0.362, p = 0.559). Targets were fixated significantly earlier when the target could be predicted, but the advantage conferred by the predictive condition did not differ between the groups.

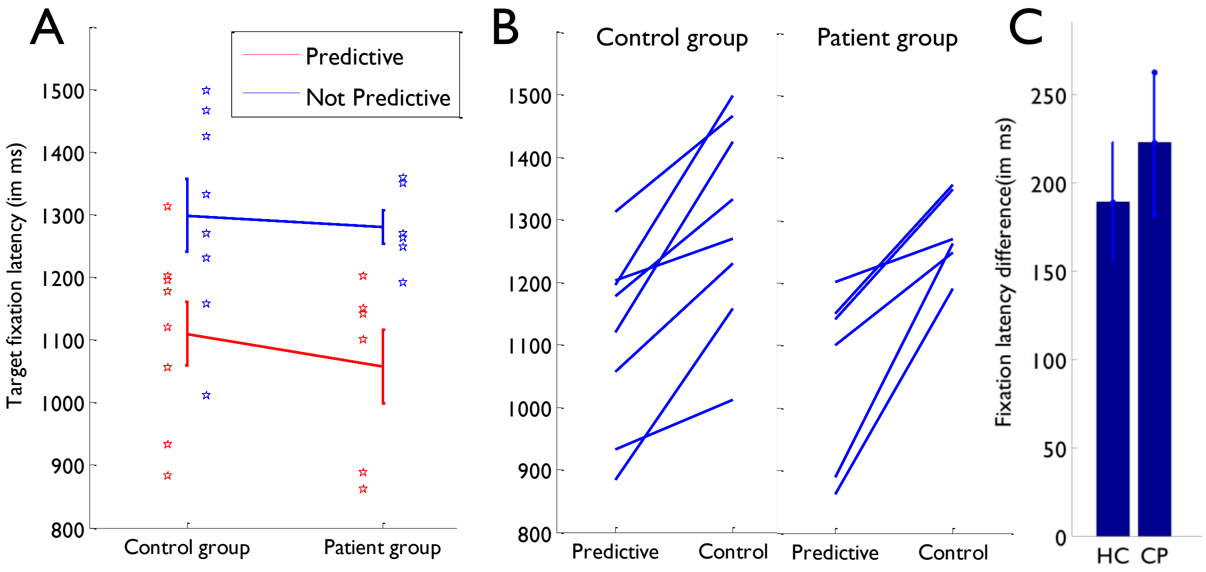

Figure 3.3. Visual world result. A. Mean fixation latency per group and condition. Asterisks represent individual data points. B. Individual differences between the predictive and the control condition for the control group (left) and the patient group (right). C. Mean fixation latency difference per group. Error bars denote +/- 1 standard error of the mean. HC: healthy controls, CP: cerebellar patients.

3.4.3. MONTREAL COGNITIVE ASSESSMENT

Scores for each subscale of the MoCA were compared by means of independent samples t-test. A composite measure of the two language subscales was also created and compared. Three patients were excluded from the visual world task analysis because of anomalies in their eye-tracking data, or because they were outliers on one of the low-level saccade variables. Those factors should have no influence on a participant's ability to perform the MoCA, so the behavioural scores of these participants were included. Patients tended to be worse at both language subscales (L-FL: $t(15) = -2.00$, $p = 0.066$; L-REP: $t(15) = -1.58$, $p = 0.140$), and the composite score of both language scales was significantly lower in patients than controls (LANG: t(15) = -2.22, $p < 0.05$). No other trends were observed (see Figure 3.3).

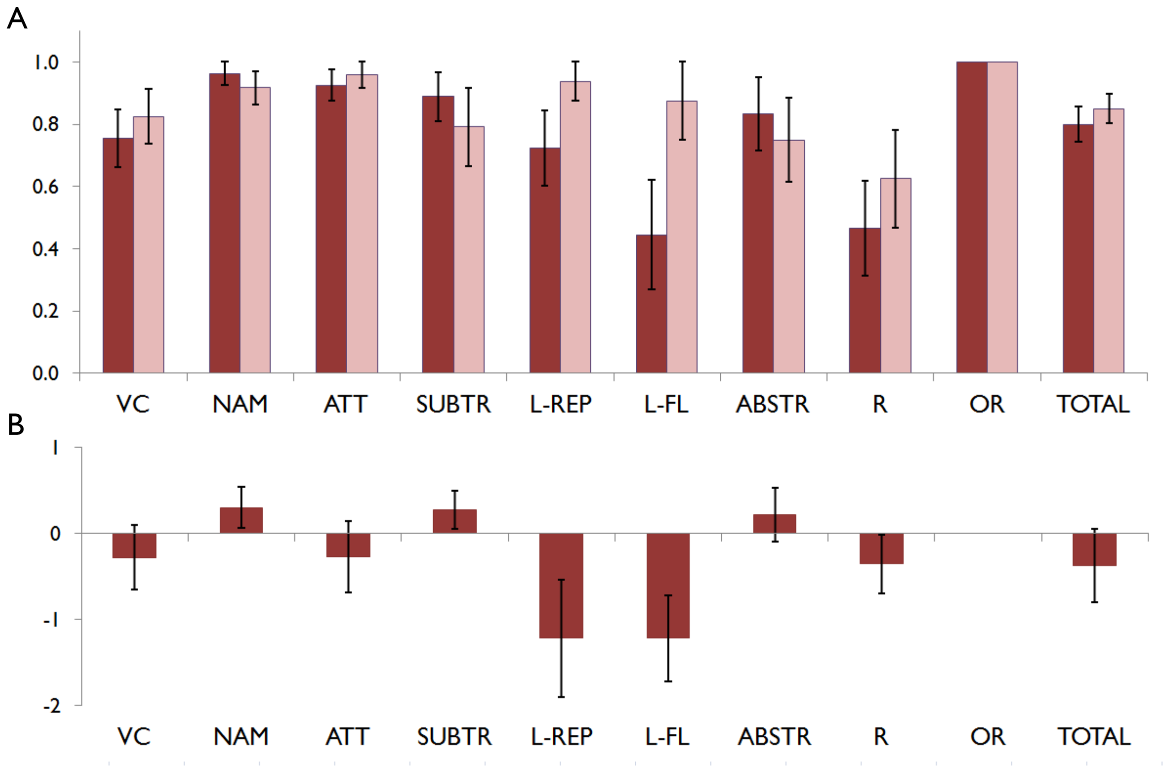

Figure 3.4. Performance on subscales of the MoCA. A. Average proportion correct for the subscales of the MoCA for Control group (light red) and Patient group (dark red), with higher scores indicating better performance. B. Patients' performance normalised with respect to Control participants' performance. VC: visuoconstructional skills; NAM: naming; ATT: attention; SUBSTR: subtraction; L-REP: language - repeat; L-FL: language - fluency; ABSTR: abstraction; R: delayed recall; OR: orientation. Error bars denote +/- 1 standard error of the mean (SE).

A separate set of comparisons was made including only the participants whose eye-tracking data was included. With 6 people in the Patient group and 8 in the Control group, there were no significant differences between the groups (see Figure 3.4). Trends were observed for the patient group to score lower on the fluency scale (L-FL; t(12) = -1.46, p = 0.181) and the composite language scale (LANG: t(12) = -1.80, p = 0.097) and for patients to score higher on the scales abstraction (ABS: t(12) = 1.87, p = 0.104) and naming (NAM: t(12) = 1.53, p = 0.170).

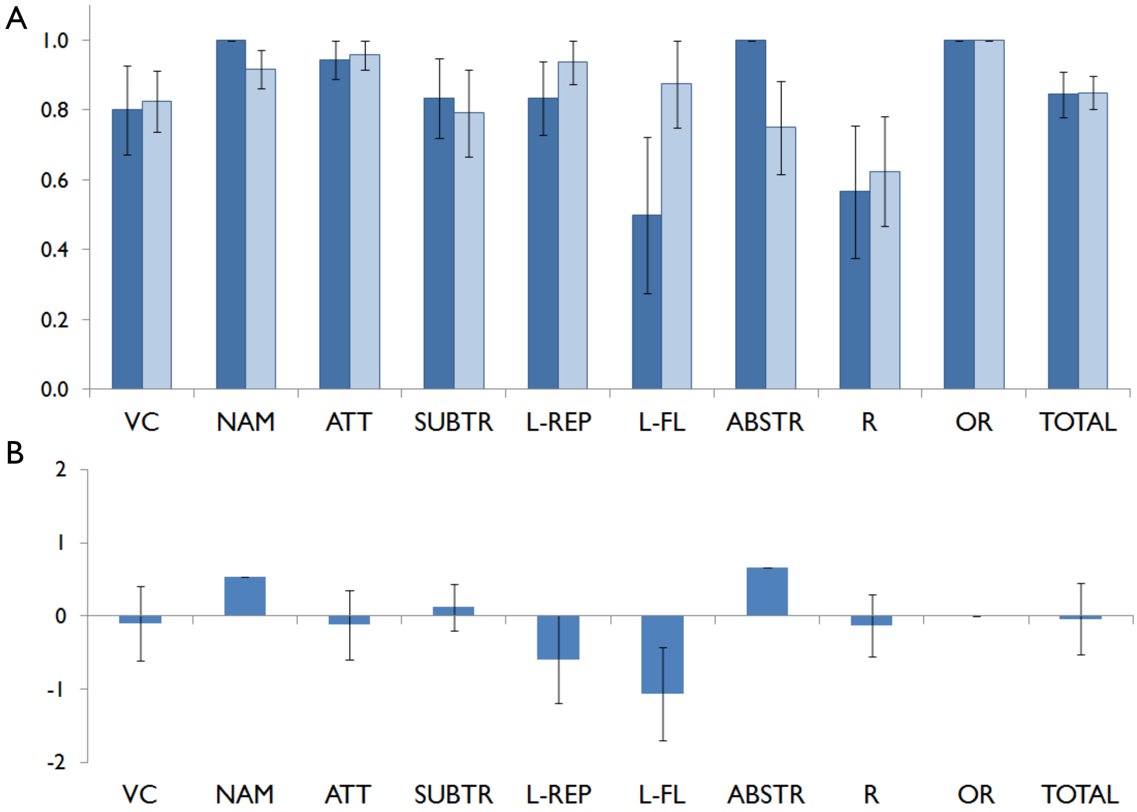

Figure 3.5. MoCA scores per group, only including participants in the eye-tracking analysis. A. Average proportion correct for the subscales of the MoCA for Control group (light blue) and Patient group (dark blue), with higher scores indicating better performance. B. Patients' performance normalised with respect to Control participants' performance. VC: visuoconstructional skills; NAM: naming; ATT: attention; SUBSTR: subtraction; L-REP: language - repeat; L-FL: language - fluency; ABSTR: abstraction; R: delayed recall; OR: orientation. Error bars denote +/- 1 standard error of the mean (SE).

3.5. DISCUSSION AND FUTURE DIRECTIONS

In this chapter, a group of cerebellar patients and group of age-matched controls performed a linguistic prediction task, as well as a standardised test which is sensitive to cognitive impairment across various domains. The aim was to determine whether cerebellar patients are impaired at making linguistic predictions, by studying eye movements under predictive and non-predictive conditions. Patient recruitment for this experiment is ongoing. No firm conclusions can be drawn from the preliminary results presented in this chapter, but the preliminary trends and future directions based on the present data will be discussed.

In the visual world paradigm, participants' fixations on target objects are typically 200-300ms faster under predictive conditions than when a prediction cannot be made. In Chapter 2, this prediction-specific advantage was reduced following rTMS-disruption of the right cerebellum. Here, we hypothesised that a similar prediction-specific deficit would be present in cerebellar patients. Specifically, we hypothesise that cerebellar patients' predictive target fixations would be delayed compared to those in neurologically healthy controls, whereas there should be no group difference under non-predictive conditions. In the small group tested thus far, the data provides no evidence for impaired linguistic prediction in the cerebellar patient group. In both groups, target fixations are faster when a prediction can be made, but no differences between the patient group and the control group were observed. Scores on various subscales of a cognitive screen were also compared between patients and control participants. Interestingly, the one subscale which separated patients from control participants was the language scale. Patients tended to be worse at a phonemic fluency task and at repeating sentences precisely. The composite score on these two tasks differed significantly between the groups. These observed patterns replicate previous reports of verbal fluency impairments following cerebellar damage (Leggio et al., 2000; Stoodley & Schmahmann, 2009b). Notably, when only the group of six patients who were included in the eye-tracking analysis were considered, these trends weakened considerably, and other trends appeared to indicate that patients scored better on abstraction and naming scales. The fact that interpretable differences emerge in a group of nine patients but not in a group of six further highlights the need to test a larger patient group.

A power analysis using an estimated effect size based on the data in Chapter 2 suggests that a minimum group of 34 subjects (17 in each group) is required to find group differences, if these are present. In this case, such a power analysis should be interpreted carefully, as the rTMS-induced experimental disruption in a consistent location is different from damage caused by cerebellar degeneration. Disease severity and lesion location in a patient group are expected to vary considerably, with only right hemispheric lesions expected to impact on predictive language processing. Moreover, the healthy group recruited in the previous chapter was much more homogenous with regards to age and educational background than either the patient or control group here.

Previous works have linked lesion location with symptomatology. Different areas of the cerebellum project to different areas of the cerebrum, forming multiple, separate corticocerebellar loops (Kelly & Strick, 2003; Middleton & Strick, 1998). Consistent with the proposed functional divisions in the cerebellum (Stoodley & Schmahmann, 2009b, 2010), lateral cerebellar rather than medial cerebellar lesions are associated with cognitive changes (Malm et al., 1998; Riva & Giorgi, 2000), and posterior inferior damage is linked to cognitive deficits, whereas anterior lesions tend to result in motor deficits (Exner, Weniger, & Irle, 2004; Schmahmann, Macmore, & Vangel, 2009). There is a tendency for verbal skills to be affected following right cerebellar damage, and visuospatial skills to be affected following left cerebellar damage, but this lateralisation is not as pronounced as in healthy individuals (Fabbro et al., 2000). Linguistic deficits are therefore likely to be associated with right hemisphere damage (in right-handed individuals). Moreover, damage to the cerebellar vermis is likely to result in impaired oculomotor control, which will render eye-tracking data unfit to assess linguistic symptoms. Patients with severe vermal lesions are therefore unlikely to yield interpretable eye-tracking data. These points indicate the need to incorporate lesion location data into the final analysis, and to ensure a sufficiently large group with right cerebellar hemispheric damage in the absence of oculomotor problems.

The visual world paradigm could contribute to the current patient literature in several ways. First, current tasks probing cerebellar deficits require the subject to overtly articulate a word, even if the deficit addressed is independent of productive speech. For example, a fluency task entails lexical retrieval, but also (brief) phonological storage and speech production. By contrast, the visual world task is a receptive language task where the measured eye movement responses are spontaneous (Cooper, 1974). In people with no oculomotor deficits, eye-tracking paradigms such as the visual world task can therefore provide a more direct window into comprehension. Second, the visual world paradigm can selectively address predictive language processing. Linguistic prediction has not been directly tested in cerebellar patients before.

This experiment will be extended further as cerebellar patients become available. Structural brain scans for the patients tested so far will be gathered, and further data collection will also include structural CT or MRI scans. An agreement to collaborate with group in the US and test a larger group of ataxic patients has been reached. However, this test is planned for mid-2014 and as such cannot form part of this thesis. Lesion location will be linked to visual world performance as well as cognitive test scores, which will also include verb generation and semantic fluency tests, in addition to phonemic fluency tests. Language fluency scores will also be linked to visual world performance, and this association may shed light on whether language deficits in cerebellar patients are linked to linguistic prediction. (This association has been tested for in the current data set, but the sample size is too small to allow any confidence in the results.) For example, if it emerges that verbal fluency scores are strongly linked to performance in the visual world task, this would provide evidence for the hypothesis that the observed linguistic impairments are fundamentally prediction problems. If, on the other hand both deficits are present in the patient population but are unrelated, this would argue for two separate systems.

In summary, in the preliminary dataset considered here, no predictive language deficits were detected in the patient group. Patients did perform worse on the language subscale of a cognitive screen. As this study is continued, lesion site information will be tied to performance measures on the visual world task as well as cognitive and language assessment. Further data acquisition should also balance the groups out in terms of educational background.

CHAPTER 4

THE ROLE OF THE CEREBELLUM IN LEARNING A NOVEL LEXICON: AN FMRI STUDY

Others' contributions: Emma Nailer contributed to the design, conducted a behavioural pilot study, and assisted in fMRI data acquisition of this experiment in the context of her Masters project.

4.1. INTRODUCTION

In the introduction (Section 1.4), evidence for a cerebellar role in linguistic processing was reviewed. Notable was the cerebellar involvement in processing semantic content, whether in the form of a single word, a sentence, or a picture (Fedorenko et al., 2010; Vandenberghe et al., 1996). A recent theoretical account by Pickering and Garrod (2013) proposed that forward model processes underlie language comprehension and production, and others have argued for cognitive and linguistic forward model processes in the right posterolateral cerebellum (Argyropoulos, 2010; Ito, 2008). In Chapter 2, we demonstrated a disruption of predictive eye movements in a semantic prediction task following right cerebellar rTMS, suggesting a role for the right posterolateral cerebellum in semantic prediction. Semantic forward model prediction may be subserved by semantic associations, representations of which could be stored in or processed by the right cerebellum (Argyropoulos, 2010). In the current chapter, a possible cerebellar role in the acquisition of a new lexicon is investigated.

Learning a new lexicon is a necessary and usually the first step in learning a new language. Near-instantaneous word learning has been studied in young children (Dollaghan, 1985), but such rapid vocabulary learning has also been documented in adults, where the EEG response to novel words matched that of familiar words after as little as 14 minutes of training (Shtyrov, Nikulin, & Pulvermüller, 2010). The acquisition of a novel lexicon depends on the hippocampus (Gabrieli, Cohen, & Corkin, 1988; Gooding, Mayes, & van Eijk, 2000), and it is thought that after an initial hippocampus-dependent encoding phase, representations are transferred to various cortical regions which store the semantic long-term memory (Battaglia, Benchenane, Sirota, Pennartz, & Wiener, 2011). The latter process is thought to be at least partially sleep-dependent (Battaglia et al., 2011). However, neuroimaging studies of early verbal memory encoding have shown the recruitment of neocortical areas during verbal encoding, consistently involving the inferior frontal gyrus (Buckner, Kelley, & Petersen, 1999; Kapur et al., 1994, 1996) but also the left dorsolateral prefrontal cortex, left temporal cortex, left angular gyrus, and the right cerebellum (Breitenstein et al., 2005; Davis, Maria, Betta, Macdonald, & Gaskell, 2009; Dolan & Fletcher, 1997). The cerebellum is a highly plastic structure, with its role in motor learning well-established (Jenkins, Brooks, Frackowiak, & Passingham, 1994; Raymond, Lisberger, & Mauk, 1996). Moreover, neocerebellar structures have been shown to be activated when participants acquire more abstract, rule-based associations (Balsters & Ramnani, 2011). Argyropoulos (2010) proposed that linguistic prediction is subserved by semantic associations in the cerebellum. If these semantic associations have some representation in the right posterolateral cerebellum, this region could be engaged during the mapping of a novel word onto an existing semantic concept. In support of this notion, the right lateral cerebellum has been reported in studies of word learning. These studies report right cerebellar in implicit learning tasks (Breitenstein et al., 2005), in comparing the familiarity of novel versus previously learned words (Davis et al., 2009), or related to vocabulary training over several weeks (Raboyeau et al., 2004). To date, no study has addressed whether the right posterolateral cerebellum is engaged during a vocabulary learning task where novel words are explicitly paired with their translation.

Relatively few studies have looked at the early stages of vocabulary learning prior to sleep-dependent consolidation (Shtyrov, 2012). Here, we combine task-based fMRI during a fast vocabulary learning task with resting state fMRI before and after learning. Resting state fMRI has proved a powerful and reliable tool to investigate functional connectivity, exposing functionally relevant, highly consistent networks, which are reproducible over subjects and sessions (Biswal et al., 2010; Damoiseaux et al., 2006; Fox & Raichle, 2007). Group differences in resting state functional connectivity (RSFC) have been linked a variety of disorders (Arbabshirani, Kiehl, Pearlson, & Calhoun, 2013; Buckner, Andrews-Hanna, & Schacter, 2008; Hong et al., 2010; Schneider et al., 2011) and intrasubject changes in RSFC have been reported in learning paradigms (Jolles, van Buchem, Crone, & Rombouts, 2011). Albert, Robertson, and Miall (2009) first reported RSFC changes following a motor learning task. Changes occurred in networks relevant to the learning task, and were particularly striking in a cerebellar component. In this chapter we investigate whether similar changes take place in a vocabulary learning task in which unfamiliar Basque words are linked to their English translation. Connectivity dynamics in the resting state phase immediately following learning may shed light on early offline processing (Albert et al., 2009). In light of the evidence that the right posterolateral cerebellum may be part of a "common semantic network" (Vandenberghe et al., 1996), and in light of the role of the cerebellum in cognitive learning (Balsters & Ramnani, 2011), we aimed to investigate the hypothesis that the right lateral cerebellum is involved in the acquisition of a new vocabulary.

In this study, participants learned 25 Basque translations for English works in a vocabulary learning (paired word association) task in an epoch-related fMRI task. Activations during this lexical learning task were compared with activations during a control task on a different day. Resting state scans were acquired before and after the learning task, as well as before and after the control task. We hypothesised that the right cerebellum, as a proposed integral part of the language network, and as a highly plastic structure, will be engaged in the learning task more than in the control task. We further tested whether resting state connectivity alters as a result of vocabulary learning, as it has been shown to do as a result of motor adaptation. Specifically, we hypothesise that areas which are engaged in paired-word association learning would show changes in their connectivity pattern following the learning task. To this end, seed ROIs were defined in left BA44, BA45, BA47 (inferior frontal gyrus), right cerebellum (Crus II) and in the left hippocampus (cornu ammunis, CA).

4.2. METHODS

4.2.1. PARTICIPANTS

Participants were 15 right-handed native English speakers (mean age 24 years, 5 male) and were compensated financially for their time. None of the participants spoke the Basque language or had spent time in the Basque country prior to the experiment. Participants were screened with a standard fMRI screening questionnaire (http://prism.bham.ac.uk/downloads/MRI_screening_form.pdf). This study was approved by the Birmingham University Imaging Centre (BUIC) Ethics Programme and written informed consent was obtained from each participant prior to the experiment.

4.2.2. DESIGN AND PROCEDURE

Each participant was scanned during two sessions; one session where a Basque vocabulary learning task was performed, the other where a control English synonym task was performed. The order of the sessions was counterbalanced between participants, with 7 participants performing the Control session prior to the Basque session. Sessions were at least one week apart. During each session, 25 Basque words or English synonyms were repeatedly presented (See Section 4.2.3).

Before scanning, a multiple choice questionnaire (pre-test) assessed prior knowledge of the words. The scanning session started with a 10 minute resting state block, followed by the learning task which lasted 12 minutes and by a second 10 minute resting state block. Immediately before both resting state blocks, there was 4 minute dummy task, where participants observed dynamic point light displays of human biological motion or scrambled version of these stimuli (Jastorff, Kourtzi, & Giese, 2006). This dummy task was used to avoid the participants perseverating on the learning task during the second resting state block. Moreover, it provided a better matched "cognitive baseline" for the resting state blocks (see also Albert, Robertson, & Miall, 2009). No images were acquired during the dummy tasks. Following the second resting state block, a T1 structural scan was acquired. One scanning session lasted about 50 minutes (see Figure 4.1). After scanning, subjects filled in a second multiple choice questionnaire (post-test). Participants who did the Control session first did not perform the post-test after the Synonym scanning session. This was done to ensure that participants were unaware that there would be a post-test after the Basque learning task and to thereby avoid that they would be 'studying' during the second resting state block. These 8 participants filled in both post-tests at the end of the second (Basque) session. Therefore, none of the participants had reason to expect a post-test after the MRI experiment in the Basque session.

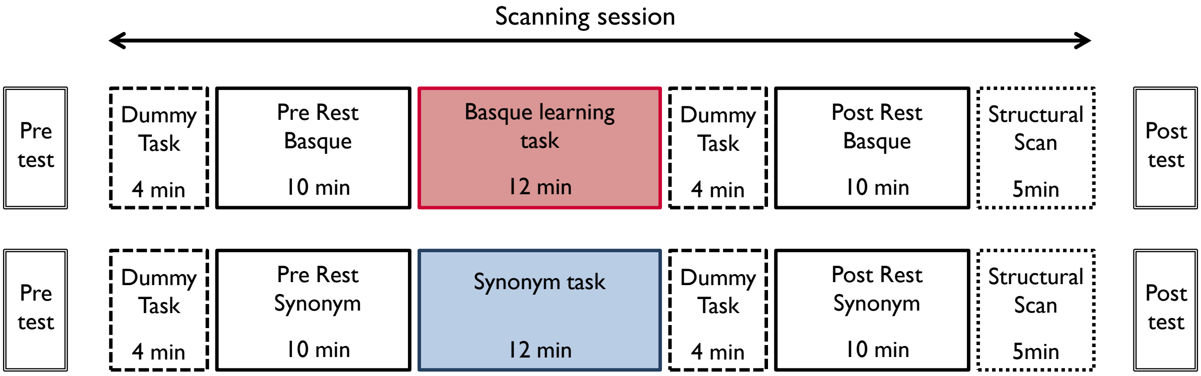

Figure 4.1. Structure of the scanning sessions. Each participant participated in both sessions, with a minimum of 1 week in between. The order of the sessions was counterbalanced between participants.

4.2.3. TASK

4.2.3.1. *Basque learning task*

The Basque learning task consisted of 5 Exposure blocks, followed by 15 Learning blocks. Each of the 5 Exposure blocks introduced 5 novel Basque words, so 25 Basque words were learnt in total (see Appendix 3 for the items used). An exposure block lasted 32s and consisted of two phases: 5 Presentation trials followed by 5 Recall trials. In a Presentation trial, a Basque word was presented alongside its English translation for 2700ms. During a Recall trial, a Basque word was presented for 1900ms, after which the translation appeared alongside the Basque word for 1000ms. This phase resembled a 'flashcard' type revision. For the different trial types see Figure 4.2.

After this Exposure phase, 15 Learning blocks, each lasting 18.2s were performed. Each Learning block consisted of 5 trials and was set up as a multiple choice test. During a Learning trial, a Basque word was presented on the left, along with 4 English words, one of which was the correct translation, on the right. Participants had 2300ms to press one of 4 buttons on an MR-compatible response box. As soon as participants had pressed a button, or after 2300ms if they had not, the correct translation was presented for the remainder of the trial (see Figure 4.2). The correct translation was presented in green, for a minimum of 500ms, regardless of the accuracy of the response, and was meant to provide a further learning opportunity rather than merely give feedback on the performance.

Each word was repeated 3 times over the course of the 15 Learning blocks. To avoid order effects in the learning, the order of the words was pseudorandom, ensuring that the same word was never repeated in the same block. The multiple choice alternatives were different at each presentation of a given word. The correct translations were presented at a different place amongst the alternatives (corresponding to a different button) at each repetition and were also used as distracters in trials with a different Basque word. All block onsets were temporally jittered with regards to the onset of the TRs (added delay from a uniform distribution ranging from 0ms to 3000ms). There was always at least 9s (3TRs) between blocks. Two null blocks were included to improve statistical efficiency. Over a session, 22.2% of time was spent on exposure blocks, 37.9% on Learning blocks, and 39.9% on rest moments between blocks. The time between blocks was used to estimate the implicit baseline in the first level analysis.

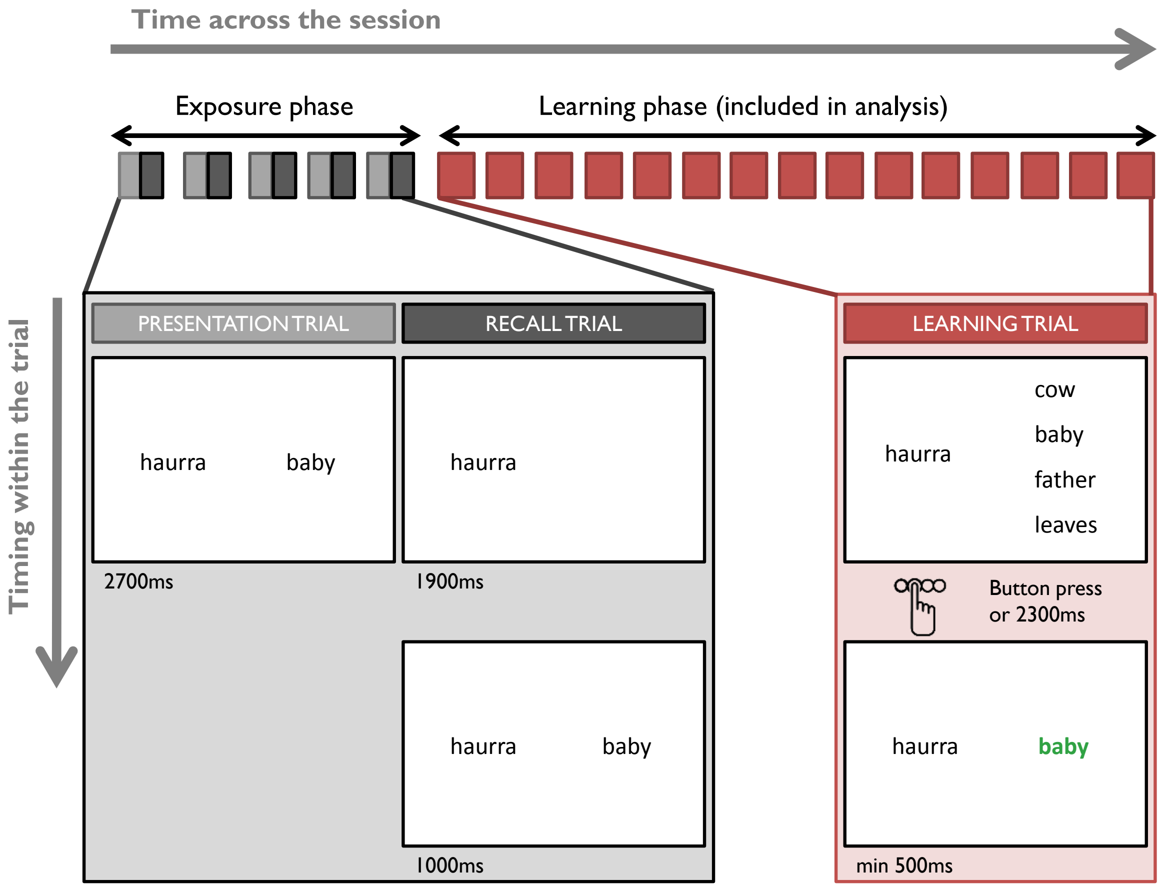

Figure 4.2. Different blocks, trial types and their timings. An exposure block (32s) consists of 5 Presentation trials (light grey) and 5 Recall trials (dark grey); a Learning Block (red, 18.2s) consists of 5 Learning trials. The bar it the top of the figure illustrates the occurrence of the various block types throughout the experiment. Null blocks are not shown.

4.2.3.2. *Synonym task.*

The synonym task was identical to the Basque task, except instead of Basque words, English words known to the participants were used (see Appendix 3 for the items used).

4.2.3.3. *Practice task*

Prior to the study, participants performed a laptop-based training version of the different blocks, to familiarise themselves with the task they would be performing inside the scanner. These training blocks used different stimuli from the ones in the main task.

4.2.4. MRI ACQUISITION

Images were acquired on a 3T Philips Achieve scanner with a 8-channel head coil at the Imaging Centre at the University of Birmingham (https://www.buic.bham.ac.uk/). Functional images were obtained with an ascending EPI sequence (TR=3s, TE=32ms, 52 axial slices (no gap), FOV 240x240, flip angle = 85°). A high-resolution T1-weighted structural scan was acquired with a standard MPRAGE sequence at the end of each session. Pulse oximetry and breathing traces were recorded using Philips-integrated systems for physiological monitoring.

4.3. ANALYSIS

4.3.1. BEHAVIOURAL ANALYSIS

Task performance was analysed to ensure that participants' performance increased during the Basque session, and that performance was at a very high level and did not increase in the Control session. For each word, performance was assessed at 5 time points: during the pre-test and the post-tests, and 3 times during the test phase of the fMRI task (see Section 4.2.3). It should be noted that the three testing points during the scanner session were not evenly spaced over the course of the task (stimulus presentation was randomised to avoid order effects in the learning). Due to a technical problem, the behavioural data of one subject during the scanning session were lost, and therefore are not included in the behavioural analysis. Because the behavioural data violate the assumptions of homogeneity of variances and of normality, parametric tests were inappropriate for this type of data. To test for a time-by-condition interaction, scores for the Basque words and the Synonyms were subtracted, and a Friedman's ANOVA was conducted on this difference to assess change over time. This analysis was followed by post-hoc Wilcoxon rank tests to test for differences between each pair of time points. Analyses were carried out using SPSS.

4.3.2. FMRI ANALYSIS: TASK BLOCKS

Preprocessing. Analyses were carried out in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). Raw images for each session were motion-corrected, slice-time corrected, and coregistered to the mean image before first level analysis. First level analysis was performed on images in subject-specific space. Further processing was performed on the contrast images created during the first level analysis. The analysis pipeline was segregated for the cerebellum and the rest of the brain. Standard normalisation as implemented in SPM8 is suboptimal for subcortical regions such as the cerebellum (Klein et al., 2009). To overcome this, the cerebellum was analysed separately using the SUIT toolbox (Diedrichsen, Balsters, Flavell, Cussans, & Ramnani, 2009) in SPM8. First, participants' cerebella were isolated from the T1 images and normalised to the SUIT template (Diedrichsen, 2006). Contrast images from the individual analysis were then normalised to the cerebellar template, as well as to the SPM8 EPI template for whole-brain analysis. Finally, images were smoothed with an 8mm full width at half maximum (FWHM) Gaussian smoothing kernel before entering second-level analysis.

BOLD signals around the brainstem and cerebellum can be vulnerable to confounding physiological signals, but these can be controlled for by regressing out heart rate and breathing traces in the GLM model (Schlerf, Ivry, & Diedrichsen, 2012). The PhLEM toolbox in SPM (Verstynen & Deshpande, 2011) was used to convert heart rate and breathing traces into SPM regressors with a CETROICOR method (Glover, Li, & Ress, 2000).

First level analysis. The first level general linear model of each session included two regressors of interest: one that modelled the Exposure blocks and one that modelled the Learning blocks. Eight regressors of no interest were included to model physiological artefacts, and 6 to model head movement. For each of the two sessions, two t-contrasts modelled the effects of the Exposure blocks and the Learning blocks against an implicit baseline. Over the two sessions, four contrast images were created and these were entered into the second level group analysis.

Second level analysis. At the second level, a 2x2 factorial ANOVA (Factor Session with levels Basque and Control, Factor Condition with levels Exposure and Learn) was carried out on the normalised t-contrasts. The contrast of interest was the subtraction of the Learning conditions in each session: t = [Learn Basque - Learn Control]. This contrast reveals areas more active during the Learning phase of the Basque task than during the Learning phase of the Synonym task. A conjunction analysis between t = [Learn Basque] and t = [Learn Control] was performed as well.

4.3.3. FMRI ANALYSIS: RESTING STATE ANALYSIS

Preprocessing. Images from the resting state sessions were preprocessed in SPM8. Raw images were realigned, slice-time corrected, coregistered to the mean image, normalised to the SPM8 EPI template and smoothed with an 8mm FWHM Gaussian kernel. Heart rate and breathing traces were processed using the PhLEM toolbox in SPM (Verstynen & Deshpande, 2011) as with the task data.

First level analysis. Statistical analysis was carried out with the functional connectivity toolbox conn (http://www.nitrc.org/projects/conn) in SPM8 (Whitfield-Gabrieli & Nieto-Castanon, 2012). Following our hypothesis, we used seed regions in Broca's area; left BA45, left BA45 and left BA47, as well as seeds in right posterolateral cerebellum (right Crus II) and left hippocampus (CA). Seed regions were defined using the Anatomy toolbox in the SPM8 (Eickhoff, Heim, Zilles, & Amunts, 2006) if these were available and from the AAL atlas (Tzourio-Mazoyer et al., 2002) if they were not. Average time courses were extracted from these masks for each subject and session, and correlated with the time course of every voxel in the brain. Eight regressors of no interest were included to model physiological artefacts, and 6 to model head movement. These seed-based correlation analysis were performed on the four resting state sessions per subject, and separately for each of the five source masks. This analysis yielded four connectivity maps per person and per seed (one for each resting state block).

Second-level analysis. The first-level connectivity maps were entered into second-level factorial ANOVAs in SPM8, with factors Session (levels Basque and Control) and Time (levels Pre and Post). Three contrasts were calculated per seed. The first aimed to identify a baseline connectivity map. To this end, a mean, t = [Pre Basque, Post Basque, Pre Synonym, Post Synonym], was calculated across the four sessions, and this contrast was inclusively masked with four t contrasts corresponding to the four sessions; t = [1 0 0 0], t = [0 1 0 0], t = [0 0 1 0], and t = [0 0 0 1]. The second contrast aimed to identify changes following the Basque task which had not occurred following the Synonym task. The interaction between t = [(Post Basque - Pre Basque) - (Post Synonym - Pre Synonym)] was carried out, and this contrast was masked inclusively with t = [Post Basque - Pre Basque], thereby restricting the result to voxels that showed a change in the Basque session. The opposite contrast (t = [(Pre Basque - Post Basque) - (Pre Synonym - Post Synonym)], inclusively masked with t = [Pre Basque - Post Basque]) was also tested. All contrasts were corrected for multiple comparisons by allowing a voxel-wise family-wise error rate of $p<0.05$ (FWE as implemented in SPM8). Given our cerebellar hypothesis, cerebellar clusters were small volume corrected with an anatomical mask of Crus II. Anatomical masks of left BA44, BA45, and left BA47 were also created for small volume correction. Masks were derived from maximum probability maps in SPM Anatomy toolbox (Eickhoff et al., 2006) if these were available and from the AAL atlas (Tzourio-Mazoyer et al., 2002) if they were not.

4.3.4. CORRELATIONS BETWEEN PERFORMANCE IMPROVEMENT AND TASK ACTIVATION

To determine whether the recruitment of areas identified during the learning task predicted offline performance improvement, task activation measures were correlated with improvements in performance after the task. Offline performance improvement was defined as the difference in performance (% correct) between the post test (after the scanning session) and the last test (third test) inside the scanner. Following our hypothesis, we tested for such a relation in any right cerebellar clusters found. To assess the specificity of these associations, task-related activations in other brain areas were also correlated with offline performance improvement. Note that that there is no risk of circular analyses here. Circularity arises when there is a dependence between the criterion for selecting a region of interest and the measure with which it is related (Kriegeskorte, Simmons, Bellgowan, & Baker, 2010; Vul, Harris, Winkielman, & Pashler, 2009). Here, the criterion for selecting the ROIs is whether they are more active in the Basque session than in the Control session. The activation level during the Basque task is then correlated with the performance improvement following the task.

4.4. RESULTS

4.4.1. BEHAVIOURAL RESULTS

The participants' behaviour demonstrates an increase in performance on the Basque task, and a consistently very high performance in the Synonym task (See Figure 4.3). Performance on the Synonym task was error-free in the pre-test and the post-test, and was very high and showed little variability in the scanner task. In the Basque task, performance increased from a level slightly above chance (mean = 29%, SE = 3.6%) in the pre-test to near-perfect performance on the post-test (mean = 94%, SE = 2.2%) in the post-test. In order to test for a time-by-condition interaction, non-parametric tests were carried out on the difference between the scores for the Synonym and Basque test. A Friedman's ANOVA showed that this differences changed significantly over time ($\chi^2(4) = 47.3$, $p<0.001$). Follow-up Wilcoxon rank tests show that performance increased significantly at each time point apart from the final one within the learning phase in the scanner (see Figure 4.4). These results confirm that learning occurred in the Basque, but not in the Synonym condition.

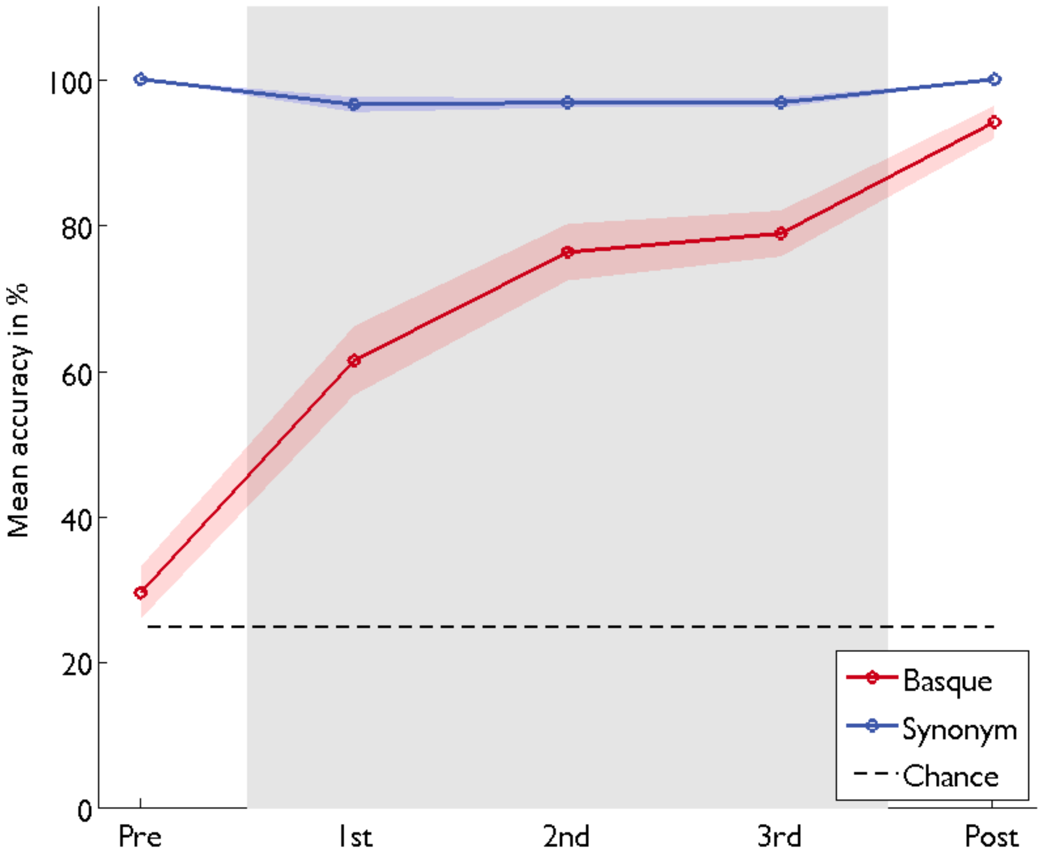

Figure 4.3. Mean task performance in the Basque (Red) and Synonym (Blue) tasks. Dashed line represents chance level (25%). Shaded regions around each line represent +/- 1 standard error of the mean. Grey shaded rectangle denotes performance in the scanner.

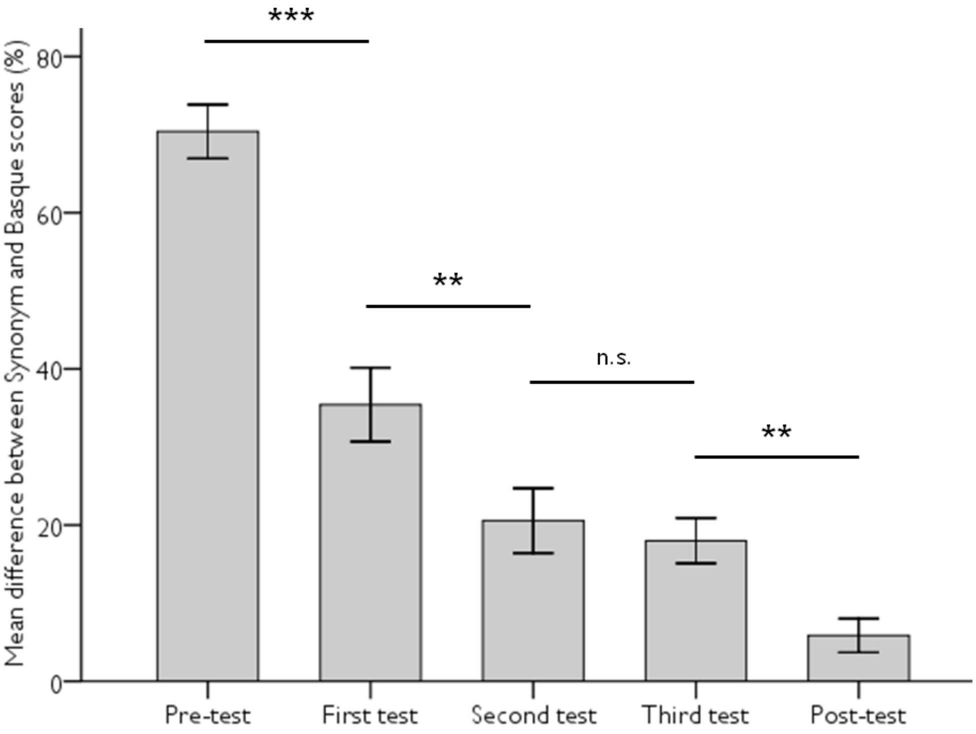

Figure 4.4. Difference between performance on the Synonym task and performance on the Basque task at different time points throughout the experiment. As learning progresses, the performance difference between the tasks becomes smaller. Error bars represent +/- 1 standard error of the mean. Stars denote significance levels of the Wilcoxon rank tests, with ***: p<0.001, **: p<0.01, and n.s.: no significant difference.

4.4.2. FMRI RESULTS: TASK

Two contrasts were carried out on the task-related components of the study: a conjunction between the Basque and Control tasks and a t-contrast exposing areas more active during the Basque task than the Control task. Note that these contrasts concern the Learning phase, and not the Exposure phase.

4.4.2.1. *Areas active in the Basque and Control tasks (Conjunction analysis)*

The conjunction analysis revealed areas commonly activated in Learning phases of both the Basque and the Synonym learning task. In both tasks, participants performed a multiple choice task and responded with finger presses of the right hand. Left-lateralised activity was found in motor and premotor cortex, with the activation extending into and covering most of the posterior parietal cortex. On the right, smaller activations were present in motor cortex and posterior parietal cortex. There was widespread activation bilaterally in ventral higher order visual areas. Other clusters were found in the supplementary motor area, the left anterior insula and left caudate nucleus. Cerebellar activity was noted bilaterally in the cerebellar vermis and lobule HVI, and on the right in lobule HVIII (See Figure 4.5. and Appendix 4 for a table of results).

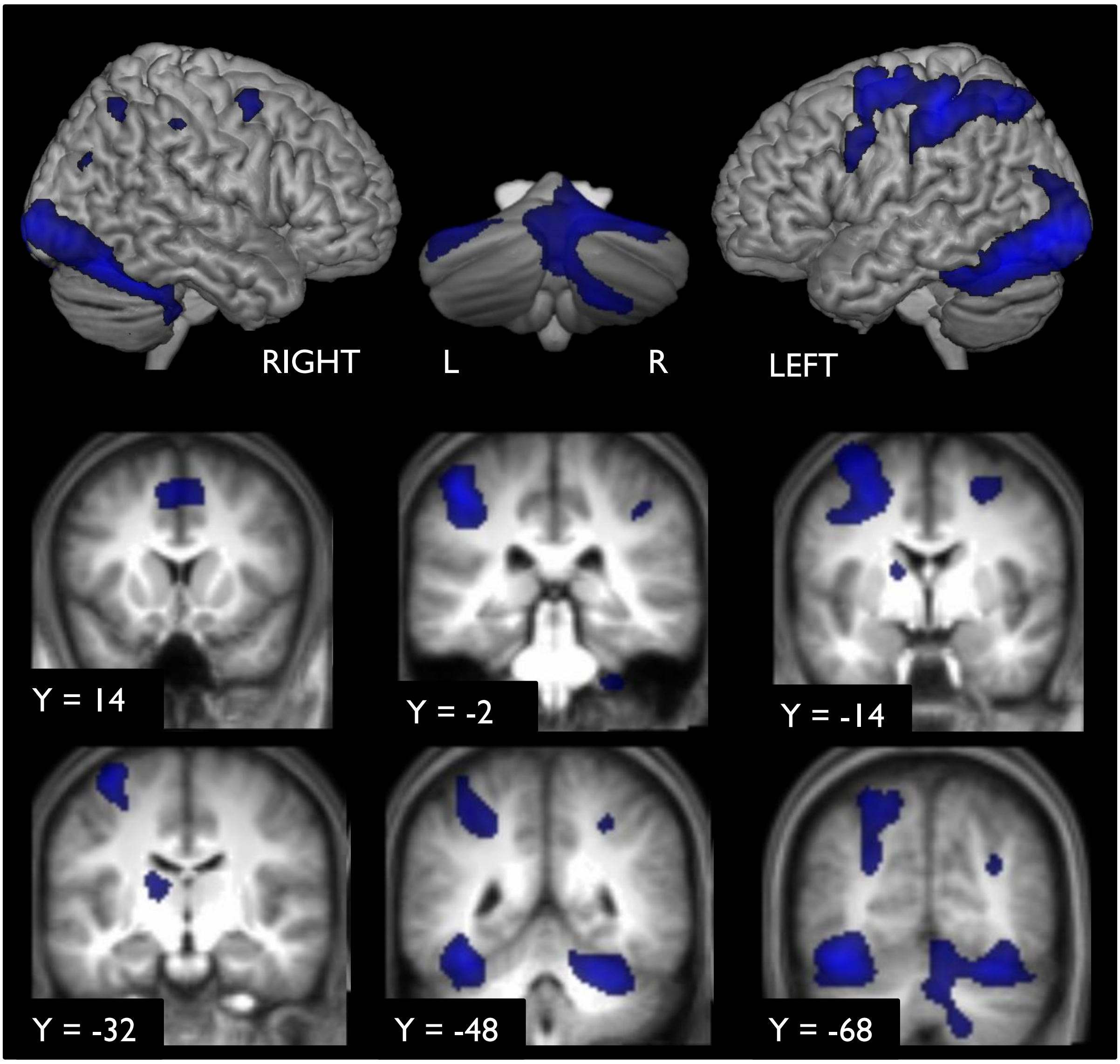

Figure 4.5. Results for the task-related conjunction analysis. Areas active both during the Basque learning task and the Control task. All clusters voxel-wise FWE corrected at $p<0.05$. Surface-rendered images are projected onto the Colin brain for whole brain, and SUIT template for cerebellum. Coronal slices are displayed on the average normalised structural images from the 15 participants. Left is displayed on the left.

4.4.2.2. *Areas more active during Basque learning than Control task (T-contrast)*

The contrast of interest compared the two Learning phases and exposed regions which were more active during Basque learning than during the control task with English synonyms (Figure 4.6, table 4.1). Bilateral activations were present in the anterior insula (frontal operculum), the thalamus and the cerebellar vermis. Left-lateralised activations were present in BA45, pre-SMA, superior parietal lobule and BA6. While premotor cortex is mainly concerned with the preparation of movements, it has also been implicated in the rule-based association of symbolic cues (Hanakawa et al., 2002). Additional clusters are present in the ventral occipital cortex, which has been shown to respond to written words (Price & Devlin, 2011; Price & Mechelli, 2005). Right-lateral activity was found in the caudate nucleus, which is implicated in semantic and phonological processing (Abdullaev, Bechtereva, & Melnichuk, 1998) and in right-cerebellar Crus II.

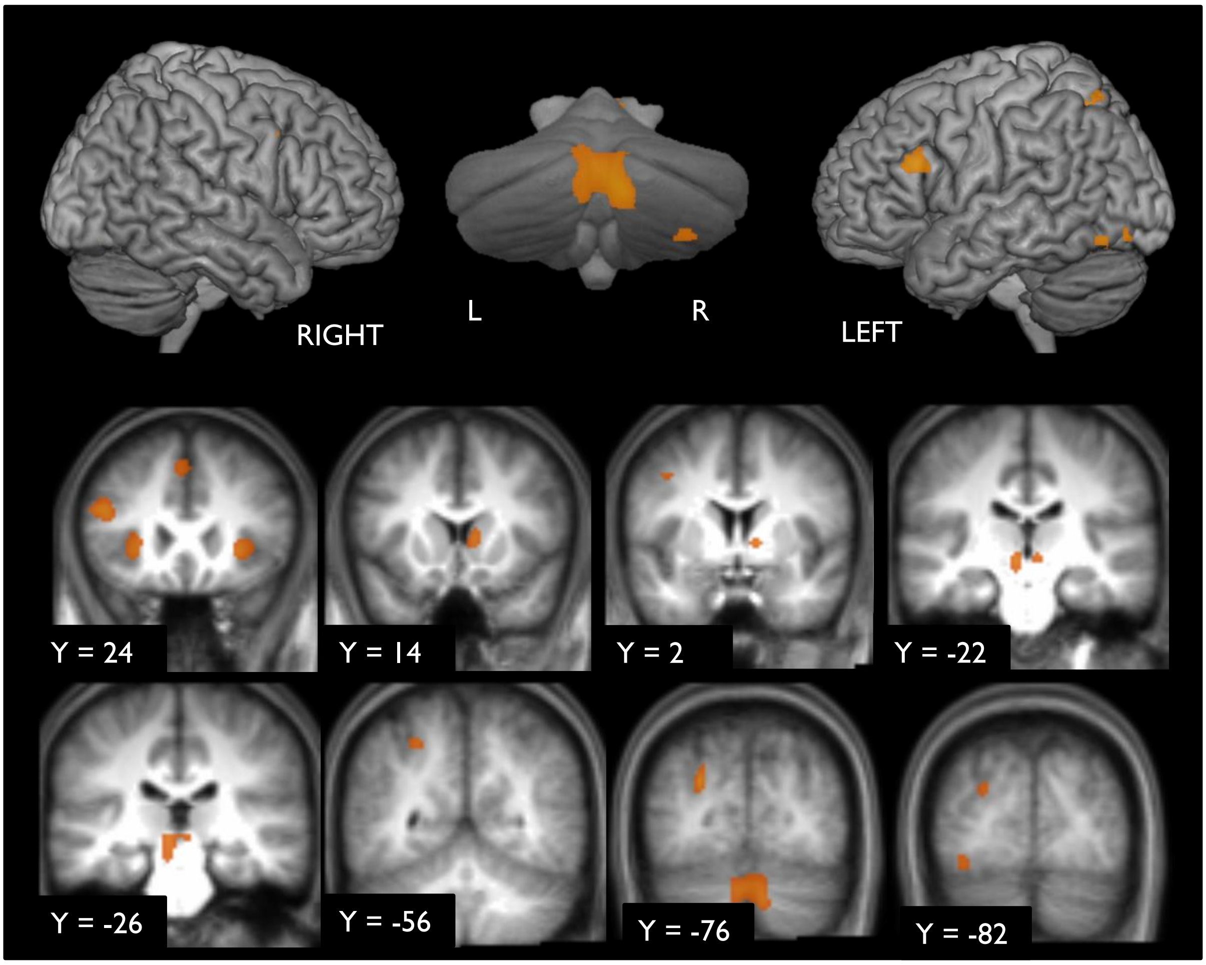

Figure 4.6. Areas more active during the Basque learning task than the synonym task. All clusters voxel-wise FWE corrected at $p<0.05$. Surface-rendered images projected onto the Colin brain for whole brain, and SUIT template for cerebellum. Coronal slices are displayed on the average normalised structural images from the 15 participants. Left is displayed on the left.

Table 4.1. Table of results: areas more active in Basque learning task than in Synonym task (FWE corrected; minimum cluster size 200mm^3 voxels). If a cluster spans several regions, the total cluster volume is reported and numbered according to the activation strength of the sub-cluster.

Gross anatomical location	Volume	T-value	MNI	coordinate		Cytoarchitectonic
	(mm^3)		x	y	z	region
Frontal						
Left Inferior Frontal Gyrus	2007	6.92	-48	22	24	BA45
Left pre-SMA	576	6.17	-2	22	48	BA6
Parietal						
Left Superior Parietal Lobule	3114 (2)	6.64	-24	-68	46	BA7
Occipital						
Left Middle Occipital Gyrus	3114 (1)	7.10	-26	-74	30	BA19
Left Inferior Occipital Gyrus	855	6.14	-48	-70	-14	BA19
Insula						
Right anterior insular cortex	1107	6.72	30	26	0	n/a
Left anterior insular cortex	756	6.59	-32	26	2	n/a
Cerebellum						
Right Cerebellum	5301	6.52	8	-74	-35	Lobule VII (vermis)
Right Cerebellum	423	5.82	32	-66	-53	Lobule HVII Crus II
Other subcortical						
Left thalamus	1341 (1)	6.52	-6	-24	-4	n/a
Right thalamus	1341 (2)	6.03	6	-22	-2	n/a
Right caudate Nucleus	1152	6.28	12	2	2	n/a

4.4.3. FMRI RESULTS: RESTING STATE

The primary question addressed in this experiment was whether resting state connectivity changes after learning a novel vocabulary. Seed-based correlation analyses were performed with seeds in left inferior frontal gyrus (left BA44, BA45, BA47), right cerebellar Crus II and the left hippocampus (CA).

4.4.3.1. *Left inferior frontal gyrus and right cerebellar seed regions*

Seed-based correlation analysis from ROIs in left BA44, left BA44, left BA47, and right Crus II were performed. The baseline connectivity maps over all four resting state sessions reveal connectivity unrelated to the session or learning conditions. These baseline maps from the three portion of the inferior frontal gyrus overlap considerably with the core language regions as outlined in Chapter 1 (see Section 1.1.1). Supramarginal gyrus, occipitotemporal junction and right cerebellum are functionally connected with each of these inferior frontal areas (see Figure 4.7). The seed in cerebellar Crus II showed a baseline activation pattern consisting of strictly left-lateralised neocortical areas, as well as contralateral cerebellum. The cortical areas functionally connected to right Crus II include left dorsolateral prefrontal cortex and left superior parietal cortex, an anterior portion of left inferior frontal gyrus, left anterior inferior temporal gyrus and left occipitotemporal junction. These regions are implicated in visual attention, working memory, executive and language tasks. None of these four areas showed significant increased or decreased connectivity with these seed regions following vocabulary learning after FWE correction.

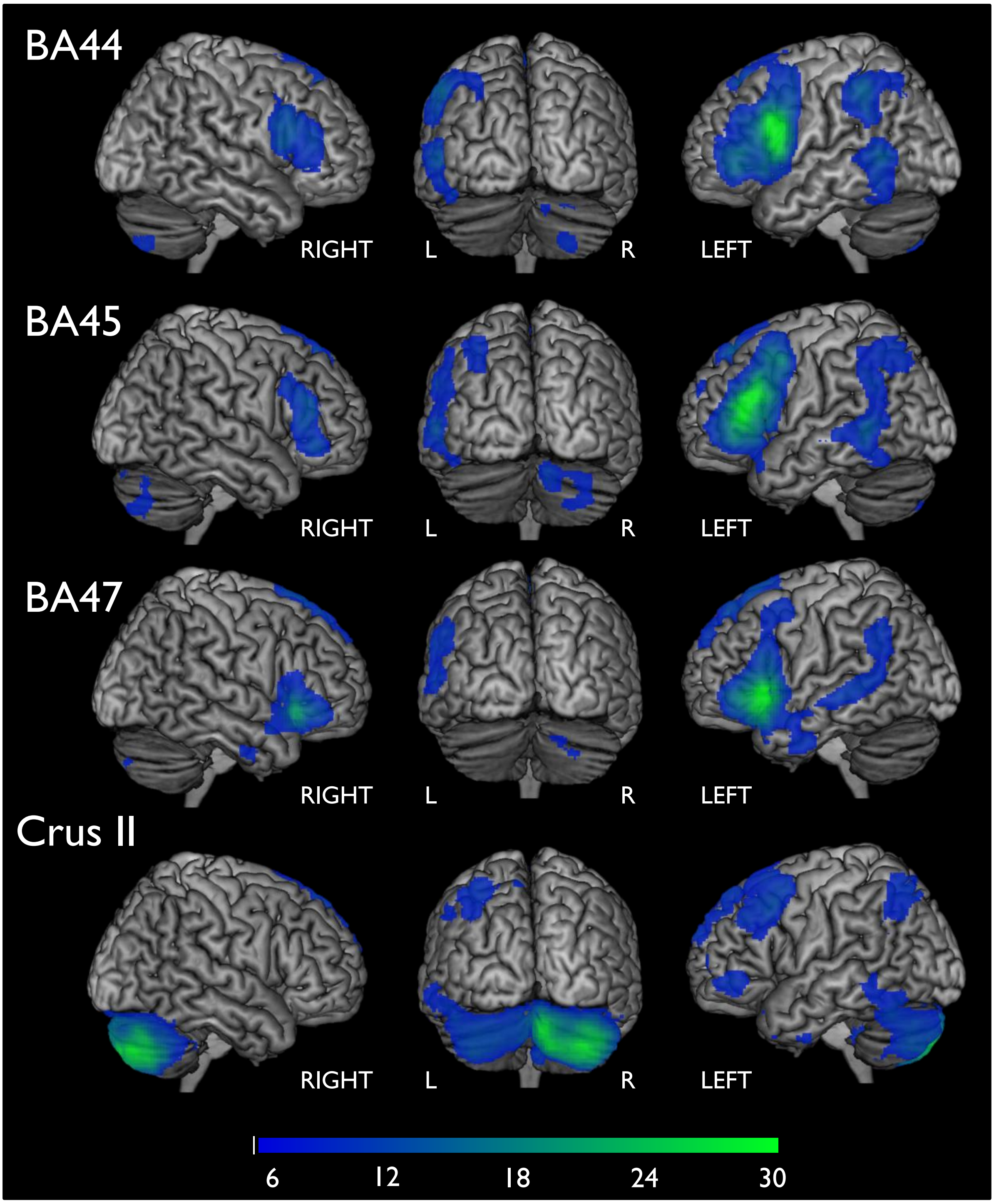

Figure 4.7. Baseline connectivity maps for the left inferior frontal gyrus and right cerebellar seed ROIs. Activation maps represent the average connectivity from seed regions in left BA44, BA45, BA47, and right cerebellar Crus II that is present in each of the four sessions (all FWE corrected).

4.4.3.2. *Left hippocampus (CA) seed region*

The baseline connectivity pattern for the left hippocampus demonstrates a bilateral hippocampal network. No areas were more connected to the left hippocampus after the Basque learning task. In the reverse contrast, which sought out regions that showed decreased connectivity with left hippocampal CA, no clusters survived correction for multiple comparisons. In each of the volumes of interest, one cluster tended towards a decrease in connectivity with the left hippocampus. A cluster in right cerebellar Crus II (p(FWE) = 0.055, svc.) one in the left inferior frontal gyrus (BA47, pars orbitalis; p(FWE) = 0.089, svc.) and a third cluster in the left anterior temporal gyrus tended to become less connected to the hippocampus (see Figure 4.8 and Table 4.3).

Table 4.2. Connectivity decreases with left hippocampal CA (none survive small volume correction).

Gross anatomical location	Volume (mm^3)	T-value	MNI x	coordinate y	z	Cytoarchitectonic region
Cerebellum						
Right Cerebellum	1242	3.90	26	-78	-38	Lobule HVII Crus II
Frontal lobes						
Left Inferior Frontal Gyrus	270	3.61	-34	34	-6	BA47
Temporal lobes						
Left Inferior Temporal Gyrus	2079	4.59	-44	-2	-32	

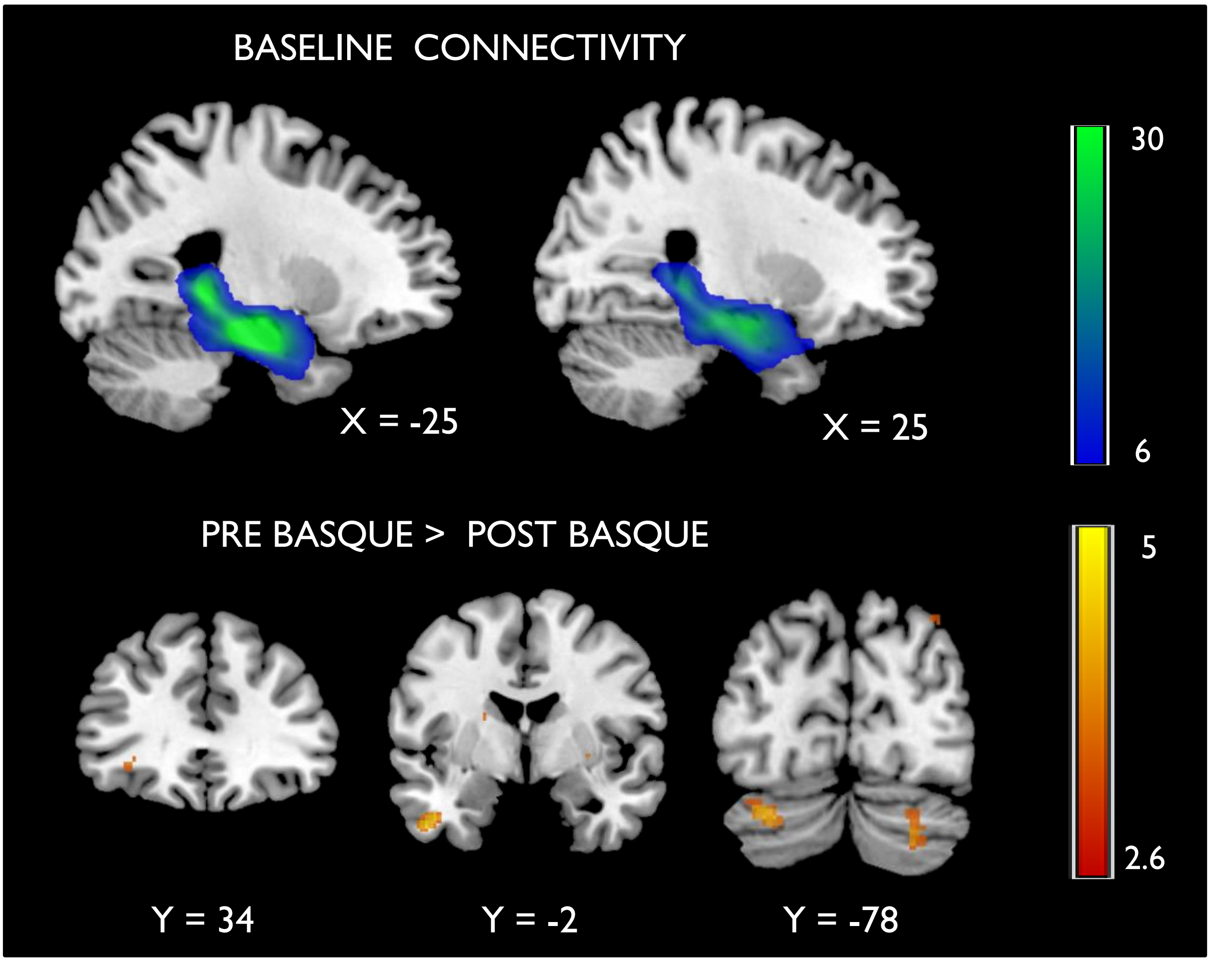

Figure 4.8. Connectivity results for left hippocampal CA. Top row: baseline connectivity (whole-brain p(PWE) < 0.05 corrected). Bottom row: connectivity decreases following vocabulary learning in left BA47, left inferior temporal gyrus, and right Crus II (uncorrected at p<0.001, none survive svc). Left is displayed on the left.

4.4.4. FMRI RESULTS: CORRELATIONS BETWEEN BRAIN AND BEHAVIOURAL MEASURES

Correlation analyses between task activations measured during the learning phase and offline improvement performance were carried out to assess whether recruitment of the lateral cerebellum was related to learning outcome. To address the specificity of this correlation, other activated regions were also correlated with improvement following the task (See figure 4.8). The right cerebellar cluster (Pearson's r = 0.657, p<0.011) as well as the cluster in the cerebellar vermis (Pearson's r = 0.656, p<0.011) significantly predicted performance improvement after the task. None of the other activated regions were correlated with offline improvements (see Table 4.3). Importantly, offline performance improvement (from 3rd test in-scan to Post-test, see Figure 4.3) was uncorrelated with the amount of learning during the task (Pearson's r = 0.21, p = 0.479), so these associations are not indirect correlations with learning during the task.

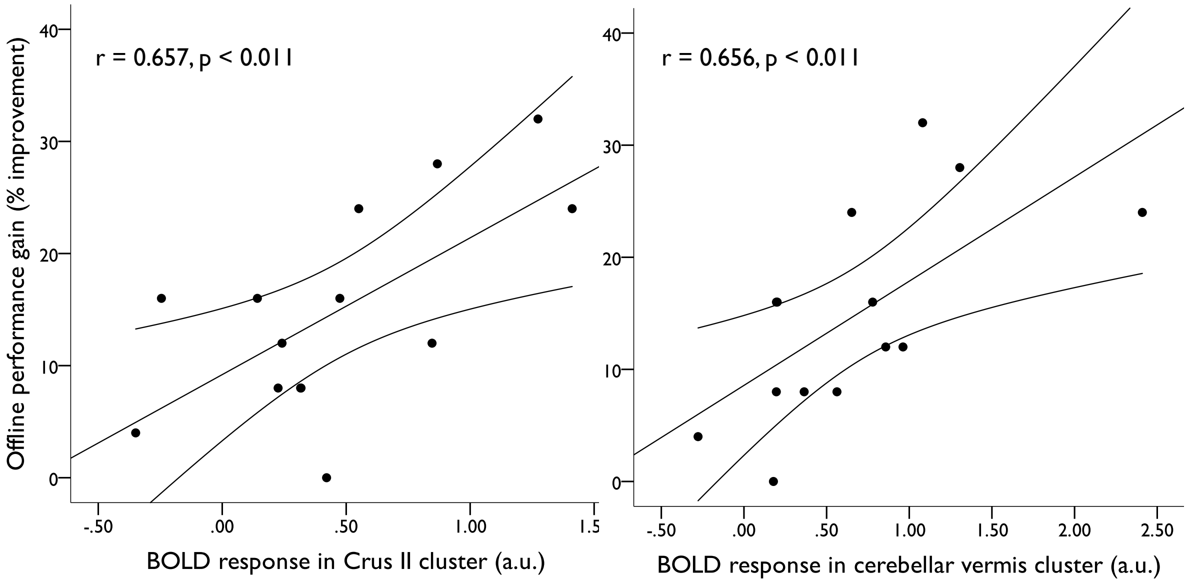

Figure 4.9. Scatter plot of offline performance improvement and haemodynamic response in the Basque task in a Crus II cluster (left panel) and a cluster in the posterior vermis (right panel). Lines show fitted linear regression and confidence intervals across the group of 14 participants (+/- 1SE).

Table 4.3. Correlation between task activations and offline performance improvement.

Anatomical location	T-value	MNI coordinate			Correlation	
		x	y	z	Pearson's r	p
Left Inferior Frontal Gyrus	6.92	-48	22	24	0.378	0.183
Left Superior Parietal Lobule	6.64	-24	-68	46	0.384	0.175
Left Inferior Occipital Gyrus	6.14	-48	-70	-14	0.046	0.875
Right frontal insular cortex	6.72	30	26	0	0.378	0.183
Left frontal insular cortex	6.59	-32	26	2	0.324	0.875
Right Cerebellum	6.52	8	-74	-35	0.657	0.011
Right Cerebellum	5.82	32	-66	-53	0.656	0.011
Right Caudate Nucleus	6.28	10	14	6	0.385	0.175

4.5. DISCUSSION

In this chapter, short-term vocabulary learning and its effects on resting state connectivity were investigated. Given the recruitment of the right posterolateral cerebellum in semantic association tasks (De Smet et al., 2013) and its documented involvement in motor and cognitive learning (Balsters & Ramnani, 2011; Jenkins et al., 1994), we hypothesised that the right lateral cerebellum would be engaged in the acquisition of novel lexical-semantic relations. Results indeed showed right neocerebellar activation during the learning task with significantly greater activity during the Basque learning session than during the control session. Moreover, activity in these two cerebellar clusters during vocabulary acquisition predicted offline performance improvements measured shortly after the task. However, connectivity analyses demonstrated no altered connectivity with seeds in left inferior frontal gyrus, left hippocampus or right cerebellar Crus II. Connectivity analysis with the three sub-domains of Broca's area and with right Crus II as seed regions did reveal connectivity with core language regions and with the right cerebellum, but no significant connectivity changes were found following learning.

Together, these results firmly place the right cerebellum in connection with the core language network (Chapter 1, Section 1.1). This is apparent in the baseline connectivity maps from Broca's area, as well as from the right cerebellar activation during the learning task. First, right Crus II was significantly more active when learning novel Basque words than during a control task. On its own, this task activation could be due to processing novel articulatory features, stimulus-response mapping, co-activation with connected regions, or any number of other processes unrelated to lexical learning. However, activity in Crus II as well as the posterior vermis was positively related to offline performance improvement. The greater the extent to which the cerebellum was recruited during the task, the more performance increased between the task and the post-test 20 minutes later. Such associations were not found with any of the tested neocortical activations. This finding argues against a mere co-activation of the cerebellum with connected language regions, and against activations related to either articulatory processing or response preparation. In either of these cases, one would not expect cerebellar activity to be related to a measure of performance, or at least not more so than other (neocortical) recruited regions. The present data therefore suggest that whichever processes generate the increased haemodynamic response in the cerebellum, they are associated with the successful acquisition of new words.

Second, the connectivity analyses from the inferior frontal cortex seeds bring out a network consisting of regions implicated in language processing, including left occipitotemporal cortex, left supramarginal gyrus, right cerebellum, and left superior and middle temporal gyrus (only left BA47 map). From each of these connectivity maps, it is apparent that the right posterolateral cerebellum is functionally connected to left inferior frontal gyrus. These connectivity patterns are consistent with those shown in previous work (Buckner et al., 2011). A RSFC study using cortical seeds based on a reading network has revealed a similar cortical language network, but did not include the cerebellum (Koyama et al., 2010). The baseline connectivity map from right cerebellar Crus II consisted largely of left-lateral regions including left dorsolateral prefrontal cortex, frontal eye fields, inferior frontal gyrus and superior parietal cortex, left inferior posterior temporal cortex and left inferior temporal pole. Some of the areas overlap with the networks connected to the inferior frontal gyrus seed regions, but other areas are implicated in visual attention and executive function. The connectional pattern found here is consistent with the functional topography of the cerebellum proposed earlier (Stoodley et al., 2012) and with RSFC patterns reported previously (Buckner et al., 2011). This pattern indicates that cerebellar Crus II is not exclusively engaged with the core language areas. It is possible that a more detailed subdivision of the cerebellar seed region might have pulled out separate maps related to executive function, language, and visual attention. Indeed, it has been suggested that neocerebellar areas can be divided into functionally separate regions beyond their lobular subdivisions (Bernard et al., 2012). We did not find connectivity changes from any of these four regions following the vocabulary learning task which survived correction for whole-brain comparison or small-volume correction. From our data, we cannot exclude that these may take place following vocabulary learning. It is possible such changes do take place over a longer time scale, or otherwise that the changes take place in much smaller, more specific regions of the language network than a coarse division into four regions could expose.

The network of regions found in the learning task is consistent with many of the areas found in previous studies of word learning. Previous PET and fMRI data into verbal encoding and explicit learning tasks consistently implicates inferior frontal cortex (Buckner et al., 1999; Kapur et al., 1994, 1996). Other areas are reported less consistently in word learning paradigms, which is likely due to the large variability in task, timescale and modality. In a study by Davis et al. (2009) novel words learned just prior to scanning elicited more activity in inferior frontal and premotor cortex, left superior temporal gyrus and right cerebellum than familiar words. Breitenstein et al. (2005) looked at change over time in a picture-word associative learning task and report declining activity in the hippocampus and fusiform gyrus, and increasing activity in angular gyrus. Activations in anterior insula and SMA, and may be associated with the phonological processing of new words (Paulesu, Frith, & Frackowiak, 1993). The right caudate nucleus, which was more active during the learning task, is implicated in various semantic and phonological tasks (Abdullaev et al., 1998). Activation of the left ventral occipital cortex is commonly found in tasks using written verbal material (Price & Devlin, 2011; Price & Mechelli, 2005).

Seemingly at odds with previous findings, our results for the learning task show no activations in either hippocampus, or left temporal neocortical regions, while the former structure is deemed critical for semantic learning and the latter regions are thought to store lexical and semantic knowledge (Binder, Desai, Graves, & Conant, 2009; Patterson, Nestor, & Rogers, 2007; Price, 2012). However, imaging studies of word learning do not consistently find hippocampal activity, and there are indications that hippocampal activity is only evident when stimuli are entirely novel to the participant (Dolan & Fletcher, 1997). This was not the case in the present study, where an exposure phase had preceded the learning phase. Moreover, reported activity in superior and middle temporal gyrus is typically found in paradigms using auditory stimuli, and may therefore reflect audition-specific learning (Breitenstein et al., 2005; Davis et al., 2009; Dobel et al., 2010; Shtyrov et al., 2010). With regards to the central hypothesis of this thesis, right cerebellar activity is reported in some of these studies, that span a variety of designs with different modalities and time scales (Breitenstein et al., 2005; Davis et al., 2009; Raboyeau et al., 2004). The present study is the first to specifically address a cerebellar contribution during a short-term explicit vocabulary learning paradigm.

A limitation of the task used is that it does not address the type of associations learnt. The vocabulary task used here is likely to induce the acquisition of semantic, orthographic, phonological and articulatory components of the words presented. We therefore cannot conclude that the activation found is specifically due to the acquisition of a semantic association. In this thesis, the focus is on semantic representations, but forward model prediction has been proposed to involve all levels of representation, including semantics, phonology, and syntax (Pickering & Garrod, 2013). When listening to or reading language, the proposed predictive role of the posterolateral cerebellum may very well include orthographic and phonological representations as well as semantic ones. One clue to interpretation could then be that the neuroimaging evidence indicates a right posterior cerebellar role in processing meaningful language, regardless of modality (Fedorenko et al., 2010; Price, 2012).

A striking finding was the extensive activity in the posterior cerebellar vermis, spanning lobules VI to VIII and extending into the hemispheres on both sides. Vermal lobule VII, also named the oculomotor vermis, is chiefly implicated in saccadic and smooth-pursuit eye movements (Thier, Dicke, Haas, Thielert, & Catz, 2002). Attentional effects could to some extent explain the increased metabolic demands on the oculomotor vermis during the processing of novel words, as top-down modulation has been linked to the modulation of the response in cortical visual areas (Twomey, Kawabata Duncan, Price, & Devlin, 2011). However, the correlation of the activity in the cerebellar vermis with offline performance improvement seems to argue against this interpretation, especially since neither the left inferior occipital cluster nor the left superior parietal cluster showed this link with performance improvement (see Table 4.4 and Figure 4.7). In patient and imaging studies activity in the vermis has been linked to emotional processing rather than language or working memory tasks (E et al., 2012; Schmahmann & Sherman, 1998; Stoodley & Schmahmann, 2009a; Timmann et al., 2010). However, it is not uncommon for children to develop linguistic problems, such as mutism and agrammatic symptoms, following the resection of a tumour in the vermis (Riva & Giorgi, 2000). Also, a voxel-based morphometry (VBM) study found that grey matter in the vermis correlated with working memory measures (Ding, Qin, Jiang, Zhang, & Yu, 2012). The portion of posterior right cerebellum adjacent to the vermis is often activated in semantic contrasts (Devlin et al., 2000; Fedorenko et al., 2010), and in a RSFC study into the cerebellar contributions of existing resting state networks, a Crus II cluster with the medial portions bordering the vermis was connected to the left executive control network (Habas et al., 2009). However, the latter linguistic and working memory studies (Devlin et al., 2000; Fedorenko et al., 2010; Habas et al., 2009) showing activations of the vermis and paravermis tend not to have the peak in the vermis. In the longer-term lexical training study by Raboyeau et al. (2004) increased activity was found in the cerebellar vermis and Crus II after lexical training, with the vermal increase predicting retention two months later. Although the timescale those authors considered vastly differs from the one in the present chapter, they too found that the vermis was more active during word learning and that its activity predicted future performance.

This study leaves many questions open for future investigations. At present the temporal progression of new word learning is unclear. This study did not address overnight consolidation, but it is striking that a longer-term study found learning-related increases in the same cerebellar regions found here in the task. Future investigations can elucidate the temporal progression of the effects observed. For example, it is an open question whether connectivity changes can be observed between left hippocampus, inferior frontal gyrus and right cerebellum beyond the 20 minute interval observed. With respect to the interpretation of the findings, several questions emerge. A first question concerns the nature of the representations which were acquired. While we set out to elicit the learning of semantic associations, the activation pattern in the learning task, notably the recruitment of SMA and anterior insula is suggestive of phonological encoding. An interesting outstanding issue is therefore whether lexicosemantic or phonological or orthographic representations, or all three, were acquired. Another finding that warrants further thought is the strong learning-related activity in the oculomotor vermis. Although this finding is not completely anomalous, it is difficult to marry with current ideas about cerebro-cerebellar connectivity and its relation to higher cognition (Kelly & Strick, 2003; Stoodley, 2012). However, the connectional fingerprint of the vermis is not yet completely known (Coffman, Dum, & Strick, 2011).

In conclusion, the present results provide further evidence for a right cerebellar role language, and more specifically in the acquisition of a novel lexicon, whereby cerebellar activity during the learning task is predictive of offline performance increases immediately following the task. Connectivity analyses from left inferior prefrontal seeds expose a network of regions implicated in language, which includes the right cerebellum. However, no significant changes in connectivity were detected in the resting state immediately following the vocabulary learning task. Together, these results support a right cerebellar role in association learning, but provide no evidence for the proposal that the right cerebellum may store linguistic semantic associations.

CHAPTER 5

CORTICO-CEREBELLAR CONTRIBUTIONS TO LINGUISTIC PREDICTION

Other's contributions: Dr Peter Hansen advised on fMRI design.

5.1. INTRODUCTION

In Chapter 2, cerebellar rTMS was shown to disrupt predictive language processing in an eye-tracking task. In this chapter, a set of fMRI experiments aims to further characterise the cerebellar contribution to predictive language processing.

Readers and listeners actively predict upcoming sentence content based on real-world and linguistic contextual factors. A wealth of evidence from EEG and eye-tracking literature has powerfully demonstrated that comprehenders actively predict upcoming language content (Altmann & Kamide, 1999), and are surprised when their predictions do not match the actual outcome (Kutas & Federmeier, 2011; Pickering & Garrod, 2007). Previous work (Chapter 2) has demonstrated that anticipatory eye movements to highly predictable targets are delayed following perturbation of the right lateral cerebellum (Lesage, Morgan, Olson, Meyer, & Miall, 2012). Therefore, these predictions may be supported by the cerebellum. The architecture of the cerebellum is suited to support rapid, online forward model predictions, as the structure is thought to do in motor control (Miall, 1998). Moreover, the right posterolateral cerebellum is functionally connected to left-lateralised cortical language regions such as the left inferior frontal gyrus, the left middle temporal gyrus and left angular gyrus (Buckner et al., 2011.; connectivity maps in Chapter 4, Section 4.4.3.1). Indeed, a considerable body of neuroimaging evidence supports a cerebellar role in semantic association and semantic processing (Fedorenko et al., 2010; Price, 2012).

To date, no fMRI study has looked at semantic prediction in the cerebellum. Here, the predictability of a sentence stem (i.e. a sentence without the final word; e.g. "He looked at the ...") was manipulated by varying its cloze probability. Cloze probability is the probability of a sentence ending with a particular word, and is therefore closely tied with predictability. High cloze sentences have one highly probable outcome (e.g. "It started to rain so the girl opened her [umbrella] "), whereas a low cloze sentence does not constrain the final word to a high degree (e.g. "As the airplane took off the man realised he forgot his ... [hiking boots]"). If the cerebellum is engaged in the prediction of upcoming linguistic content, it should be differentially engaged in processing highly predictive versus non-predictive (neutral) sentences. It is unclear whether a strongly predictive context should lead to an increase or a decrease in cerebellar activity. A stronger prediction could lead to a more refined representation and more cerebellar activity, or alternatively a non-predictive sentence could lead the cerebellum to process multiple alternatives, leading to higher activity. Thus we can only hypothesise that the level of cerebellar activity varies with linguistic predictability, but not specify the direction.

In this study, participants processed sentence stems where the final word was either predictable (highly constraining, high cloze) or neutral (not constraining, low cloze). The event-related design used here allowed us to manipulate semantic prediction independently from the contextual elements that make the sentences predictable, and independently from the outcome of the sentence. A complicating factor in this study is that written language comprehension is a complex task, which requires many concurrently operating functions. Under conditions where a comprehender makes a semantic prediction, other processes are occurring at the same time, and a number of these may recruit the cerebellum. So, in the context of a written sentence, participants are attending to the low-level visual stimuli with a certain complexity (attention to visual features), they are processing words with a certain meaning (attention to semantic features), and they are processing the phonological components of these words (attention to phonological features). The latter two have been shown to activate right lateral cerebellar regions in fMRI studies (E et al., 2012; Stoodley & Schmahmann, 2009a). To address these functional overlaps, three control experiments were designed to uncover the cerebral and cerebellar regions which were active in a visual, a semantic, and a phonological working memory task.

In summary, we hypothesise that the cerebellum is differentially recruited in processing the end of a strongly predictive sentence versus a non-predictive sentence ending. In addition, we aim to characterise and localise cerebellar recruitment in three matching tasks, designed to capture attention to semantics, to phonology, and to the visual features of the written words. These activation patterns will also be compared.

5.2. METHODS

5.2.1. PARTICIPANTS

Seventeen right-handed volunteers (3 male, average age 21 years, age range 18-27 years) participated in two fMRI sessions. All participants were native English speakers and were not fluent in any other language. None of the participants read, spoke or were familiar with the Punjabi language. Participants received monetary compensation for their time. An eighteenth subject was excluded from the second session and from the analysis due to severe signal dropout in the lateral cerebellum. Written informed consent was obtained for each participant. This study was approved by the local ethics committee at the University of

Birmingham and was carried out in accordance with the guidelines set out in the Declaration of Helsinki (1964).

5.2.2. SESSIONS AND ACQUISITION PARAMETERS

Each participant performed two fMRI scanning sessions on separate days. One session consisted of the prediction task, divided into 3 blocks of 10min 30s. A high-resolution structural image (T1 weighted image, MPRAGE sequence, voxels 1x1x1mm) was also collected during this session. During a second session, participants performed three matching tasks, designed to probe attention to semantics, phonology and visual features respectively. All three matching tasks were divided into an experimental block (1-back condition) and a control block (0-back condition), with each block lasting 8 mins. All images were acquired on a 3T Philips Achieva scanner using a 32-channel head coil. (Functional: ascending EPI sequence, TR=3s, TE=32ms, 52 axial slices (no gap), voxels 3x3x3 mm, FOV 240x240, flip angle = 85°.) Pulse oximetry and breathing measures were collected with a Philips-integrated physiological monitoring system.

5.2.3. PREDICTION TASK

The linguistic prediction task was an event-related task designed to capture semantic prediction. Participants processed sentences with varying degrees of predictability which were visually presented. The task was divided into three parts, with each part lasting 10mins, 30s.

5.2.3.1. *Items*

Participants performed a total of 78 trials. 30 of these were predictive trials, 30 were neutral trials, and 18 were of an intermediate level of predictability (semi-predictive trials). These semi-predictive items were added in order to make the distinction between the predictive and the neutral items less obvious to the participants. These items were modelled separately in the fMRI analysis but were not included in the contrasts of interest. 33 items were used from a study by Fitzsimmons and Drieghe (2013) and adapted to better suit this fMRI design. Items were altered to be matched for length. 45 new items were also constructed. A list of all items can be found in Appendix 5.

5.2.3.2. *Trial structure*

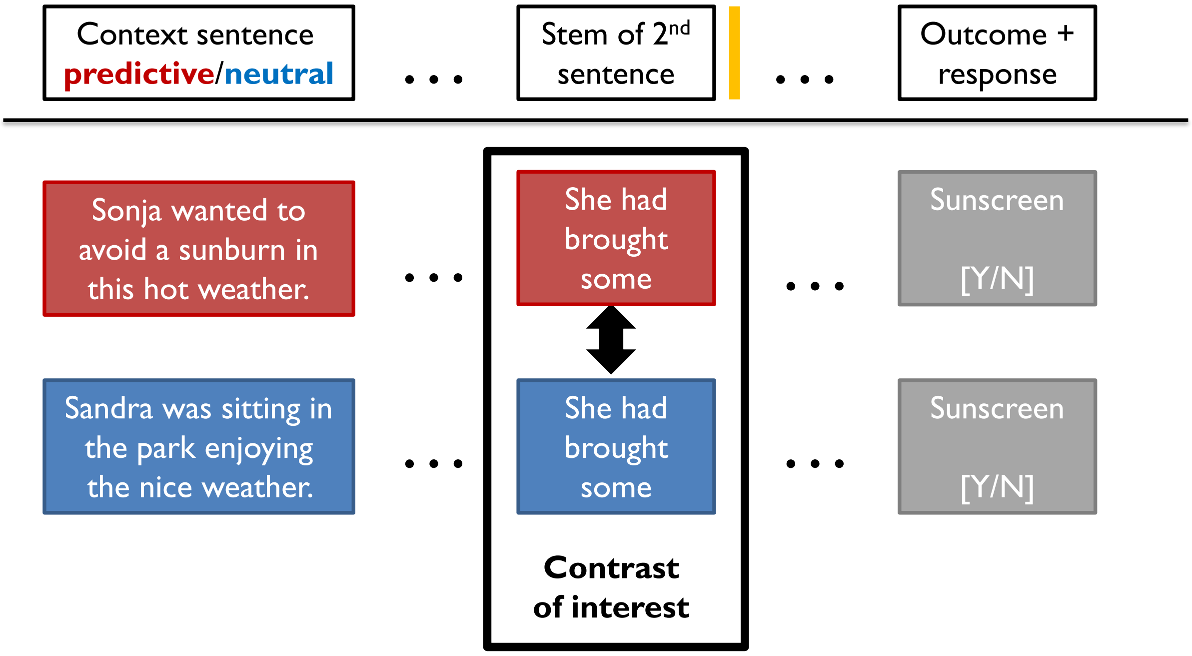

Figure 5.1. Trial structure of the prediction task. Three events are independently modelled: the context (3s), the second sentence stem (1s) and the outcome (1s). The comparison of interest is between the stem following a highly constraining context (red) and a stem in a less constraining context (blue). Ellipsis indicate variable delay/temporal jitter.

Three events per trial were independently modelled (see Figure 5.1). The first was the presentation of a context sentence, which appeared on the screen for 3 seconds (e.g. "Sonja wanted to avoid a sunburn in this hot weather."). The second was the presentation of the stem of a second sentence (e.g. "She had brought some"). The stem was displayed in 4 chunks, each displayed for 250ms in the centre of the screen to avoid eye movements. Typically, each chunk contained a single word, but occasionally it consisted of two short words. The stem sentence did not contain the last word of the sentence, and it is inferred that the participant would produce a semantic prediction (e.g. "sunscreen") in the predictive condition. The stem of the sentence, and the inferred prediction at the end, is the event of interest in this task. Item pairs therefore had a context sentence that was either predictive or neutral, and used the same sentence stem. The sentence stem was always shared between two or three sentences, and was therefore matched between conditions for all relevant parameters. Context sentences were controlled for the amount of syllables and words. The third event in the trial was the presentation of the final word of the sentence (probe), which was either plausible (50%) or implausible (50%) given the context. Participants made a response on a MRI-compatible response box to indicate plausibility. Presentation of the probe and the response were modelled as a single event (1s). Trials with erroneous responses were excluded from the analysis.

5.2.3.3. *Contrast of interest*

The effect of interest in this experiment is the difference between processing the end of a highly predictable sentence stem and processing the end of a neutral sentence stem (see Figure 5.1). Several features of this trial structure are relevant in terms of the interpretation of the results. First, as the wording of the sentence stem in each condition is controlled between the conditions, any differential activation cannot be attributed to differences related to the wording used. Second, no overt responses are made at this stage. Therefore, any differences in activation cannot be attributed to motor processes. Moreover, as the response at the outcome stage depends on the final word of the sentence, no motor response can be prepared.

5.2.3.4. *Temporal jittering*

A variable delay was introduced between the onsets of the context sentence and the sentence stem (4.5 - 10.5 seconds), between the sentence stem and the probe (3 - 7.5 seconds), and the between the probe and the context sentence of the following trial (4-10 seconds; see Figure 5.2A). This manipulation ensured that BOLD responses to one event were not contaminated with BOLD response to the previous stimulus (for another example of this technique, see Ramnani & Miall, 2004). The design orthogonality is illustrated in Figure 5.2B. Values of correlation between regressors (excluding diagonal) range from -0.086 to 0.105.

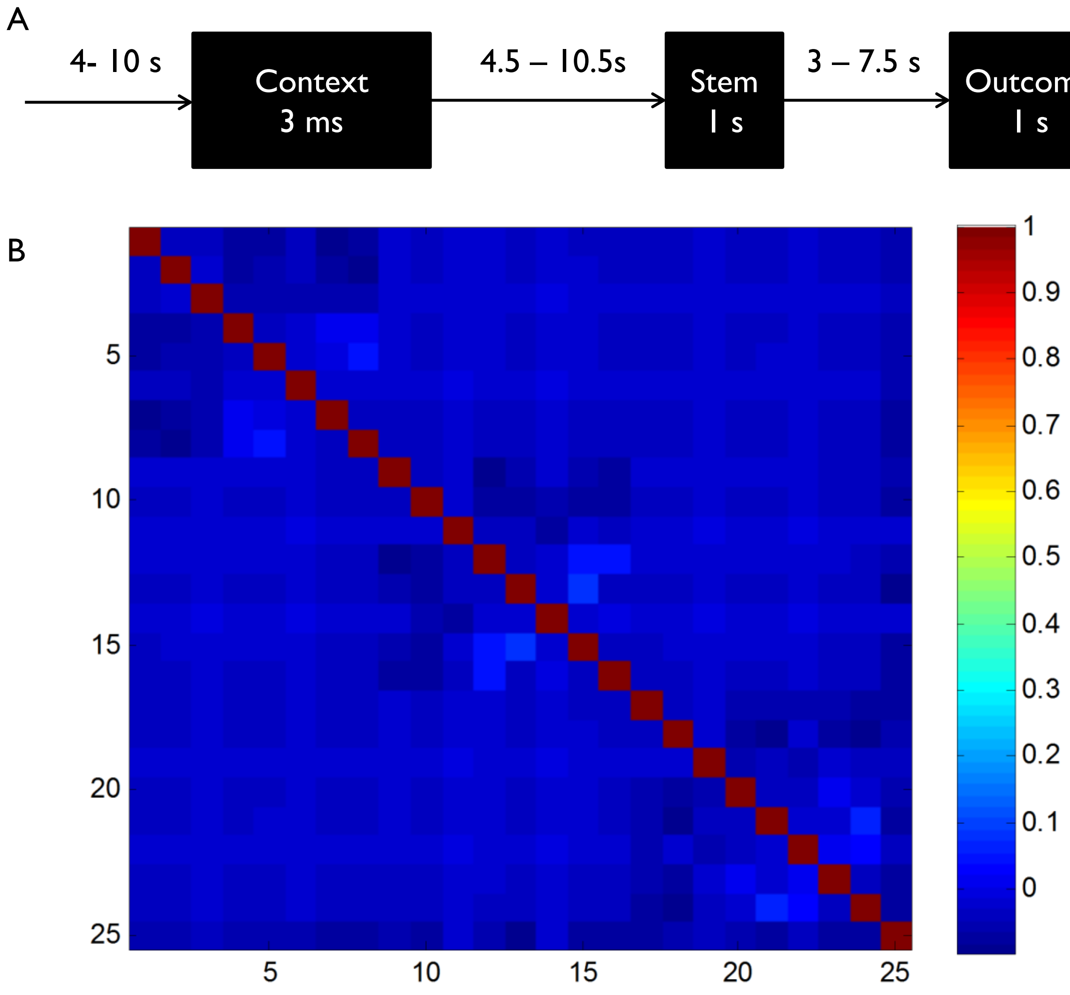

Figure 5.2 (A)Trial timing (B) Design orthogonality. Correlations between all 25 regressors of interest: context $^{\text{predictive}}$, context $^{\text{neutral}}$, context $^{\text{semi}}$, stem $^{\text{predictive}}$, stem $^{\text{neutral}}$, stem $^{\text{semi}}$, outcome $^{\text{likely}}$, and outcome $^{\text{unlikely}}$ for each of the three blocks, and one regressor that modelled trials with an erroneous response.

5.2.4. MATCHING TASKS

When reading a sentence (or for these purposes: a sentence stem), processes in addition to semantic prediction are taking place. When reading words, one is processing the meaning of these words (attention to semantics). When reading words or pronounceable non-words, one is processing phonological features of these words (attention to phonology). When looking at words or non-words, one is recognising and processing a visual stimulus with a certain configuration (attention to visual configuration). Three epoch-related one-back tasks (matching tasks) were designed to capture BOLD activity relating to these processes and to compare the activation pattern with that in the prediction task. Similar tasks have been used before to capture visual and phonological processing (Koyama, Stein, Stoodley, & Hansen, 2013; Paulesu et al., 1993). Two conditions of each task were performed in separate sessions: a 1-back task, where participants were required press a button if a stimulus matched the preceding stimulus and a 0-back task where participants were required to press the button when a known target stimulus appeared. Each of the six sessions lasted 8 minutes and contained 15 blocks. Each block consisted of 10 stimuli and lasted 15 seconds. Rest periods between blocks lasted 13 to 17 seconds. These rest periods took a total of 255s (53% of the scan) and were used as an implicit baseline in the analysis. Within a block, stimuli were presented for 500ms, 1000ms apart.

5.2.4.1. *Semantic task*

Prior to the scanning session, participants were familiarised with the ten stimulus categories and five members of each category. They were also shown the target stimulus (firework sparks, see Figure 5.2.), to which they had to respond in the 0-back session. During the 1-back task, participants pressed an MRI compatible response box with the index finger whenever the current stimulus was in the same stimulus category as the previous stimulus (e.g. if they were both boats; see Figure 5.3.). Please see Appendix 6, Figure 3 for the stimuli.

5.2.4.2. *Phonological task*

In the phonological 1-back task, participants were required to press a button when a stimulus rhymed with the preceding stimulus. Before the scanning session, participants were explained the task and shown some example stimuli, which were not used in the scanning task. They were also shown the target stimulus for the 0-back task (the word "press"; see Figure 5.3.). Stimuli were matched for length (five letters) and constructed such that a small minority of the rhyming pairs ended in the same syllable (see Appendix 6, Figure 3). This task could therefore not be performed to an acceptable standard by using a visual search strategy.

5.2.4.3. *Visual task*

In the visual 1-back task, participants were asked to press the button if a stimulus was identical to the previous stimulus (see Figure 5.3.). To the participants, the stimuli were meant to look like words, but hold no meaning and not be pronounceable. Stimuli consisted of a set of 10 five-letter Punjabi pseudo-words (see Appendix 6, Figure 2). Participants were familiarised with the 10 stimuli for the 1-back task as well as with the target stimulus for the 0-back task ("ਬੂਬੂਬੂਬੂਬੂ").

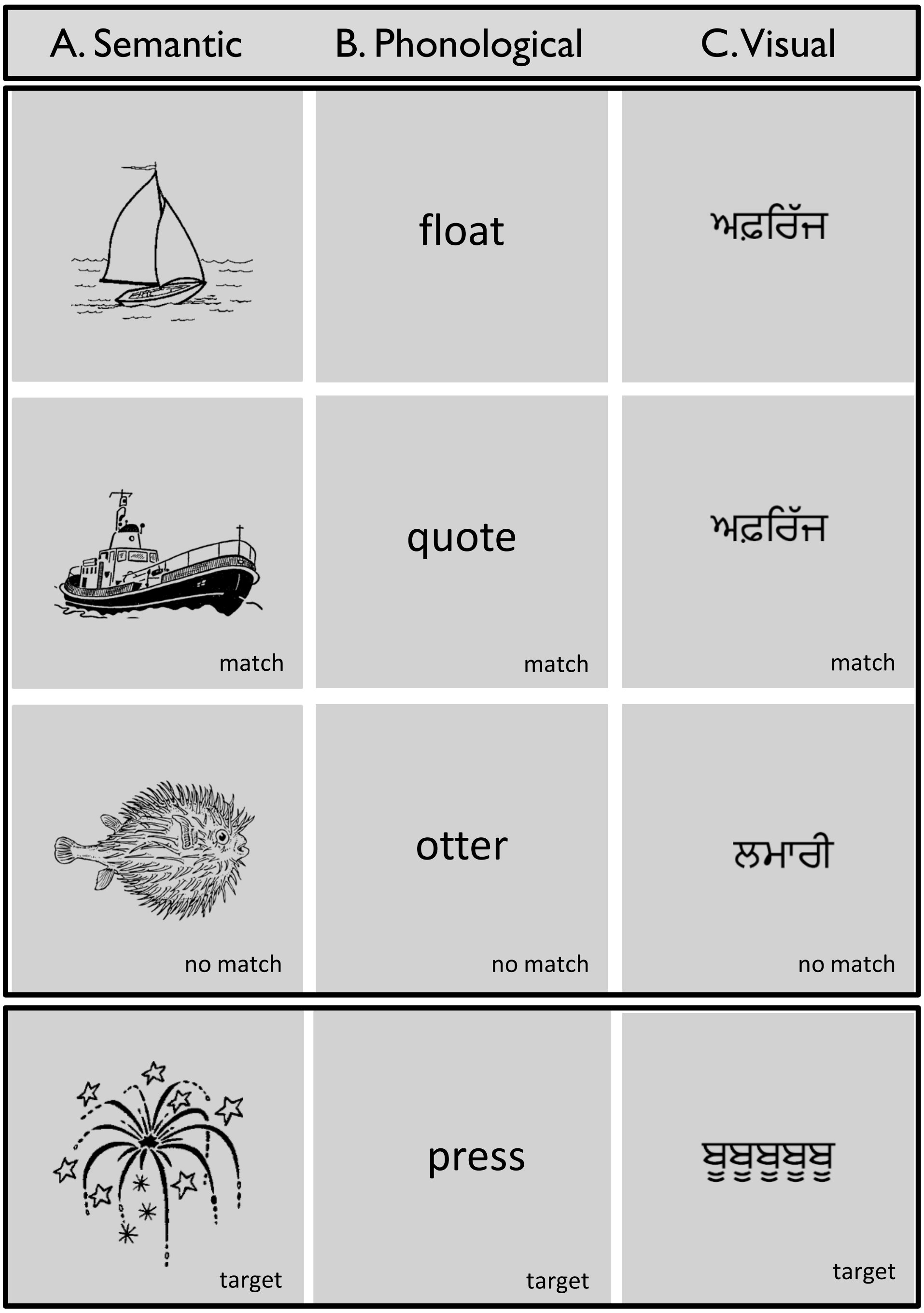

Figure 5.3. Example stimuli from the matching tasks. Matching stimulus (first and second row) and not-matching stimulus (second and third row) for the one-back sessions. Fourth row: target stimuli used in 0-back sessions.

5.3. ANALYSIS

5.3.1. PREDICTION TASK

5.3.1.1. *Behavioural analysis*

Behavioural data were processed using custom-made MATLAB code and SPSS software was used to analyse the performance in the outcome phase of the trials. A 3x3 repeated-measures ANOVA with factors Condition (levels Predictive, Semi-predictive, and Neutral) and Block (levels First, Second and Third block) was carried out on the number of correct responses.

5.3.1.2. *Imaging analysis*

Preprocessing. The preprocessing pipeline was the same as in Chapter 4 (see Section 4.3.2). All analyses were carried out in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). Prior to the first level analysis, raw images were realigned to correct for head motion, slice-time corrected, and coregisted to the mean image. First level analysis was performed on images in subject-specific space. Further processing was performed on the contrast images before entering second level analysis. For the cerebellum, data were further processed using the SUIT toolbox (Diedrichsen et al., 2009) in SPM8. Contrast images from the single subject analysis were normalised to the SUIT template (Diedrichsen, 2006) and smoothed with a 8mm FWHM Gaussian smoothing kernel. For the whole-brain analysis, contrast images were normalised to the SPM8 EPI template and smoothed with an 8mm FWHM Gaussian smoothing kernel. BOLD signals around the brainstem and cerebellum can be vulnerable to confounding physiological signals, but these can be accounted for by regressing out heart rate and breathing traces in the GLM model (Schlerf et al., 2012). The PhLEM toolbox in

SPM (Verstynen & Deshpande, 2011) was used to convert heart rate and breathing traces into SPM regressors with a CETROICOR method (Glover et al., 2000).

First level analysis. Eight events per block were modelled at the first level: context $^{\text{predictive}}$, context $^{\text{neutral}}$, context $^{\text{semi}}$, stem $^{\text{predictive}}$, stem $^{\text{neutral}}$, stem $^{\text{semi}}$, outcome $^{\text{likely}}$, and outcome $^{\text{unlikely}}$. The three blocks were concatenated, thus creating a single first level analysis per person with 24 regressors of interest. A 25th regressor modelled all trials where an erroneous response had taken place. All contrasts were estimated against the implicit baseline. Differences in performance could therefore not underlie differences in BOLD activation patterns. Eight regressors of no interest modelled physiological signals and a further 6 modelled head movement.

Second level analysis. Normalised first level contrast images were entered into a 3x8 level (3 Blocks, 8 Conditions) factorial design. One contrast directly tested our hypothesis and several others served to provide a view of the activated networks in various conditions and different events in the trial, and to ensure that any found clusters in our regions of interest were specific to the contrast of interest. The contrast of interest looked for areas which responded more to the predictive sentence stem than to the non-predictive sentence stem across the three blocks: t = [sentence stem $^{\text{predictive}}$ - sentence stem $^{\text{neutral}}$] across all three blocks. Results were small volume corrected (svc) for regions with an a priori hypothesis. These ROI masks were constructed using the Anatomy toolbox in SPM8 (Eickhoff et al., 2006) for right cerebellar Crus II and with the AAL atlas (Tzourio-Mazoyer et al., 2002) for left inferior frontal gyrus area (BA44, BA45, and BA47). Activations were family-wise error (FWE) corrected at $p<0.05$ (voxel-wise-level) within the anatomical volumes of interest. A number of additional contrasts were carried out to investigate activation patterns specific to the neutral condition, and in other phases of the trial. The inverse contrast t = [sentence stem $^{\text{neutral}}$ - sentence stem $^{\text{predictive}}$] revealed areas more active during the non-predictive condition. The conjunction between sentence t = [stem $^{\text{predictive}}$] and t = [sentence stem $^{\text{neutral}}$] against the implicit baseline captured areas that were active when participants processed the sentence stem, regardless of the predictability of the sentence ending. To see whether the hypothesised patterns of activation were specific to the stem sentence, and were not evoked by the predictive content at the time of the context sentence, we applied the t = [context $^{\text{predictive}}$ - context $^{\text{neutral}}$] and the inverse contrast to the time of the context sentence, as well as a conjunction between context $^{\text{predictive}}$ and context $^{\text{neutral}}$. Finally, t = [outcome $^{\text{unlikely}}$ - outcome $^{\text{likely}}$] and t = [outcome $^{\text{likely}}$ - outcome $^{\text{unlikely}}$] compared the BOLD response to unlikely versus likely outcomes, and a conjunction over outcome $^{\text{likely}}$ and outcome $^{\text{unlikely}}$ was also carried out. For the control contrasts, an uncorrected threshold at $p<0.001$ was applied to the contrasts that entail a subtraction, while the conjunction analyses were FWE corrected at $p<0.05$ (voxel-wise).

5.3.2. MATCHING TASKS

5.3.2.1. *Behavioural analysis*

Behavioural data were processed using custom-made MATLAB code and then further analysed in SPSS. Participants were required to press a button when the stimulus matched the previous stimulus (1-back tasks) or when a target was presented (0-back tasks). A button press when one was due was regarded a correct response. A 2x3 repeated-measures ANOVA was performed on the number of hits.

5.3.2.2. *Imaging analysis*

Imaging analysis was conducted in SPM8. Preprocessing was carried out as described in Section 5.3.1. At the first level, a single t-contrast was applied for each of the six sessions. At the second level, the normalised t-contrasts were entered into a 3x2 factorial group analysis (factor Task with levels Semantic, Phonological and Visual; factor Condition with levels 1-back and 0-back). For each of the three tasks, a t = [1-back - 0-back] contrast was calculated. A conjunction analysis between the three contrasts was also carried out. Contrasts were family-wise error (FWE) corrected at $p<0.05$.

5.4. RESULTS

5.4.1. PREDICTION TASK

5.4.1.1. *Behavioural results*

Overall performance was high (95% correct, SE = 0.6%). A 3x3 repeated-measures ANOVA showed a significant effect of Condition ($F(2,24.9) = 22.25$, $p<0.001$, partial eta squared = 0.582), whereby performance was higher for predictive trials (98% correct, SE = 0.9%) than for neutral trials (91% correct, SE = 1.1%, see Figure 5.3.). Neither the main effect for Block nor the interaction between Block and Condition was significant. These results are indicative of the fact that an implausible ending to a highly predicable sentence may stand out more than an implausible ending to a neutral sentence. On the whole, behavioural results indicate that participants were attentive and able to judge whether a sentence ending was likely or unlikely in the context of the trial. Trials with incorrect or missing responses were excluded from the analysis (Predictive: 2% (SE=1%) excluded; Neutral condition: 8% (SE=1%) excluded; overall 5% excluded, SE = 1%).

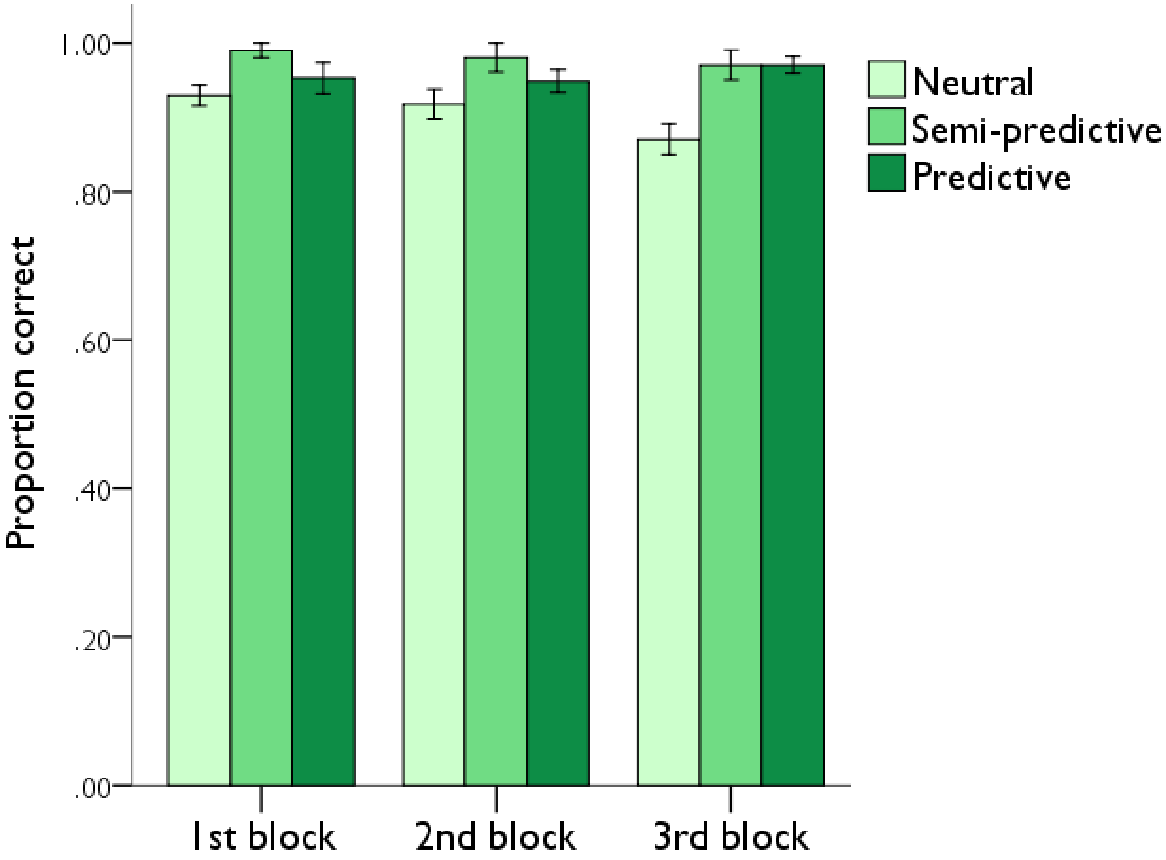

Figure 5.4. Average proportion correct per condition in the prediction task. Error bars denote 1 standard error of the mean.

5.4.1.2. *Imaging results*

Because of the a priori hypothesis about the right cerebellum and the left inferior frontal gyrus, small volume corrections (svc.) were applied using anatomical masks of these regions. When results were FWE corrected within the anatomical region of interest, clusters within both of the regions of interest emerged (see Table 5.1 and Figure 5.4: circled regions). In the right posterolateral cerebellum, a cluster at MNI (28, -84, -46) and a slightly more anterior one at MNI (36, -72, -54) survived correction for multiple comparisons ($p < 0.05$ svc.). In the inferior frontal gyrus interest areas two clusters survived; one in BA47 at MNI (-38 22 -4) and one in BA45 at MNI (-42 52 -12). The former cluster is part of a larger activated region which extends into the anterior insula. The latter is part of an activation which extends into BA10. Results therefore show that the right cerebellum and left inferior frontal gyrus are more active when an online prediction can be made than when such a prediction is not possible. When a whole-brain FWE correction was applied no suprathreshold clusters remained. At an uncorrected threshold ($p<0.001$) the whole-brain activation pattern includes left angular gyrus and bilateral middle temporal gyrus, as well as right dorsolateral prefrontal cortex and bilateral anterior insula, see Figure 5.5 and Appendix 7. While these uncorrected clusters should not be functionally interpreted, the location of the peaks is in regions consistent with semantic and phonological processing in other imaging studies. The inverse contrast (sentence stem $^{\text{neutral}}$ - sentence stem $^{\text{predictive}}$) revealed no significant clusters.

Table 5.1. Predictive stem > Neutral stem contrast (small volume corrected at voxel-wise $p(FWE)<0.05$).

Gross anatomical location	Volume	T-value	MNI	coordinate		Cytoarchitectonic
	(mm3)		x	y	z	region
Left Inferior Frontal Gyrus/insula	2187	404	-38	22	-4	BA47 / n/a
Left Inferior Frontal Gyrus	99	3.81	-42	52	-12	BA45
Right Cerebellum	252	3.44	28	-84	-46	Right Crus II
Right Cerebellum	117	3.55	36	-72	-54	Right Crus II

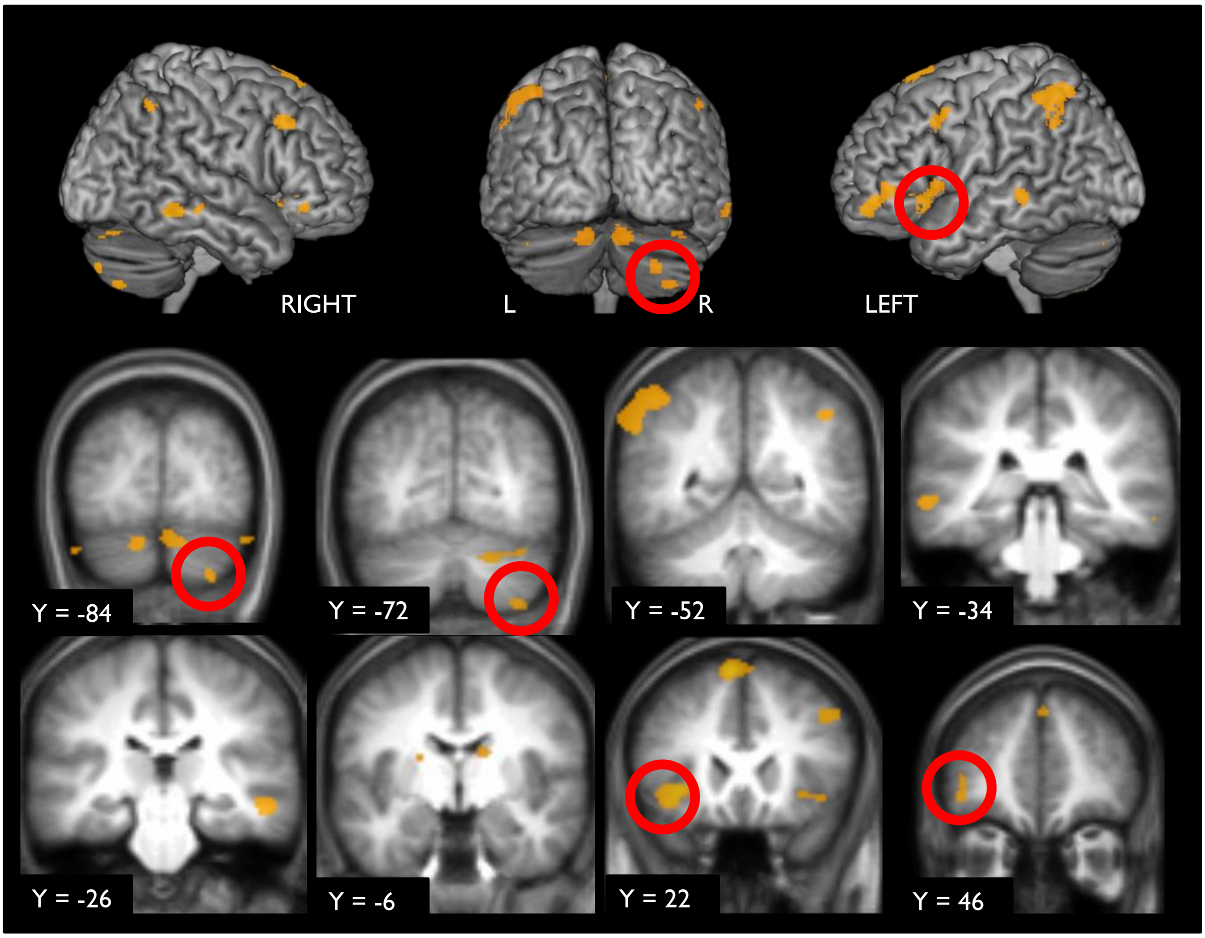

Figure 5.5. Results for contrast of interest: predictive versus non-predictive sentence stem ($p<0.001$, uncorrected). Circled clusters surpass threshold with an anatomical mask ($p(FWE) < 0.05$, svc.). Surface-rendered images projected onto the Colin brain, coronal slices displayed onto the mean of all 17 normalised T1 images. Left is displayed on the left.

5.4.2. MATCHING TASKS

5.4.2.1. *Behavioural results*

Participants performed well in all conditions (average hits 94%, SE = 0.84%, average number of false alarms 1.2%, SE = 1.1%; see also Figure 5.6.). The repeated-measures ANOVA revealed a significant effect of condition (F(1,16) = 20.07, p<0.001, partial eta squared=0.56) whereby performance was better in the 0-back condition, consistent with the less demanding nature of the 0-back tasks. There was no significant main effect of the factor Task (F(2,22.36) = 3.00, p=0.09, partial eta squared =0.16, Huyn-Feldt corrected for violations of the sphericity assumption).

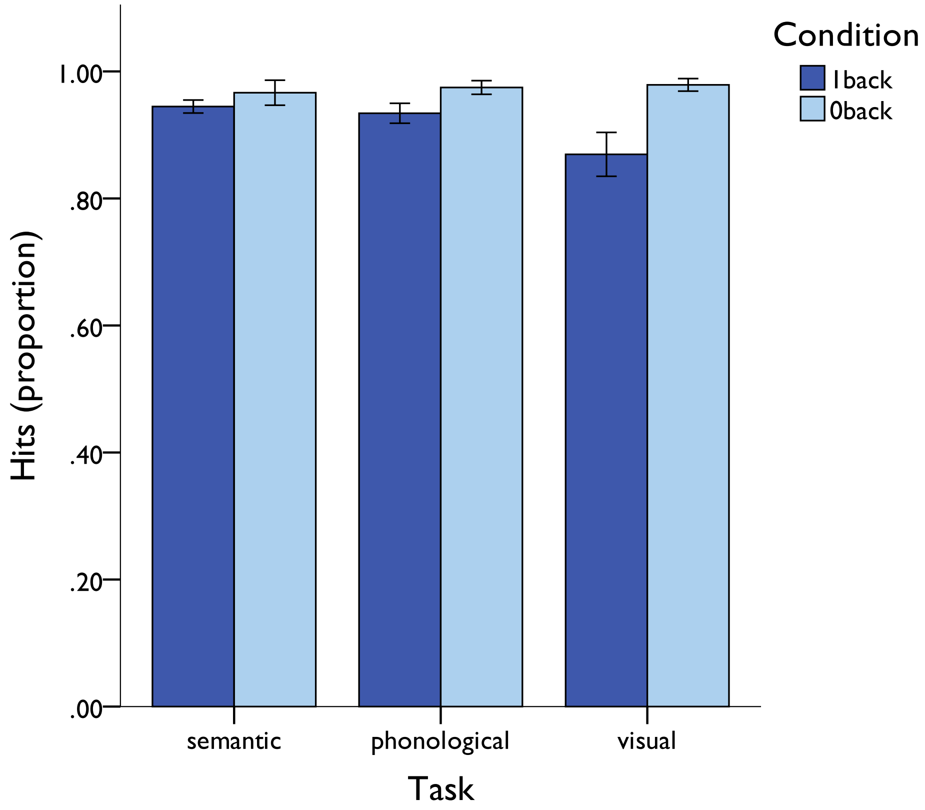

Figure 5.6. Average proportion of hits per condition. Error bars denote 1 standard error of the mean.

5.4.2.2. *Imaging results*

Semantic matching task. The semantic matching task activated a left-lateralised frontoparietal network, with clusters in pre-SMA, dorsolateral prefrontal cortex, BA44, the frontal operculum and the premotor cortex, see Figure 5.7. Prefrontal peaks were found bilaterally, but were much more extensive in the left hemisphere. Large bilateral activation was present in the superior parietal lobule. Strong higher order visual activations were also found, with peaks in bilateral posterior inferior temporal gyrus. Subcortical peaks were found in the left thalamus and hippocampus, and bilaterally in the caudate nucleus. In the cerebellum, large clusters were found in right Crus II and vermal areas of lobule VI.

Phonological matching task. The rhyming task revealed a strongly lateralised network comprised mostly of activations in left middle and inferior frontal gyrus, left inferior parietal lobule, and right cerebellar Crus II (see Figure 5.7). A cluster in the left frontal operculum and one in left occipitotemporal junction overlapped with activated regions in the semantic matching task.

Visual matching task. The visual matching task engaged areas bilaterally in supramarginal gyrus and superior parietal lobule, and at the occipitotemporal junction. In the frontal lobes clusters were present in premotor cortex, pre-SMA bilaterally, and in dorsolateral prefrontal cortex on the right. In the cerebellum, vermal regions of lobules VI and VII were activated, as well as bilateral Crus II, where the left cluster was more pronounced than the right.

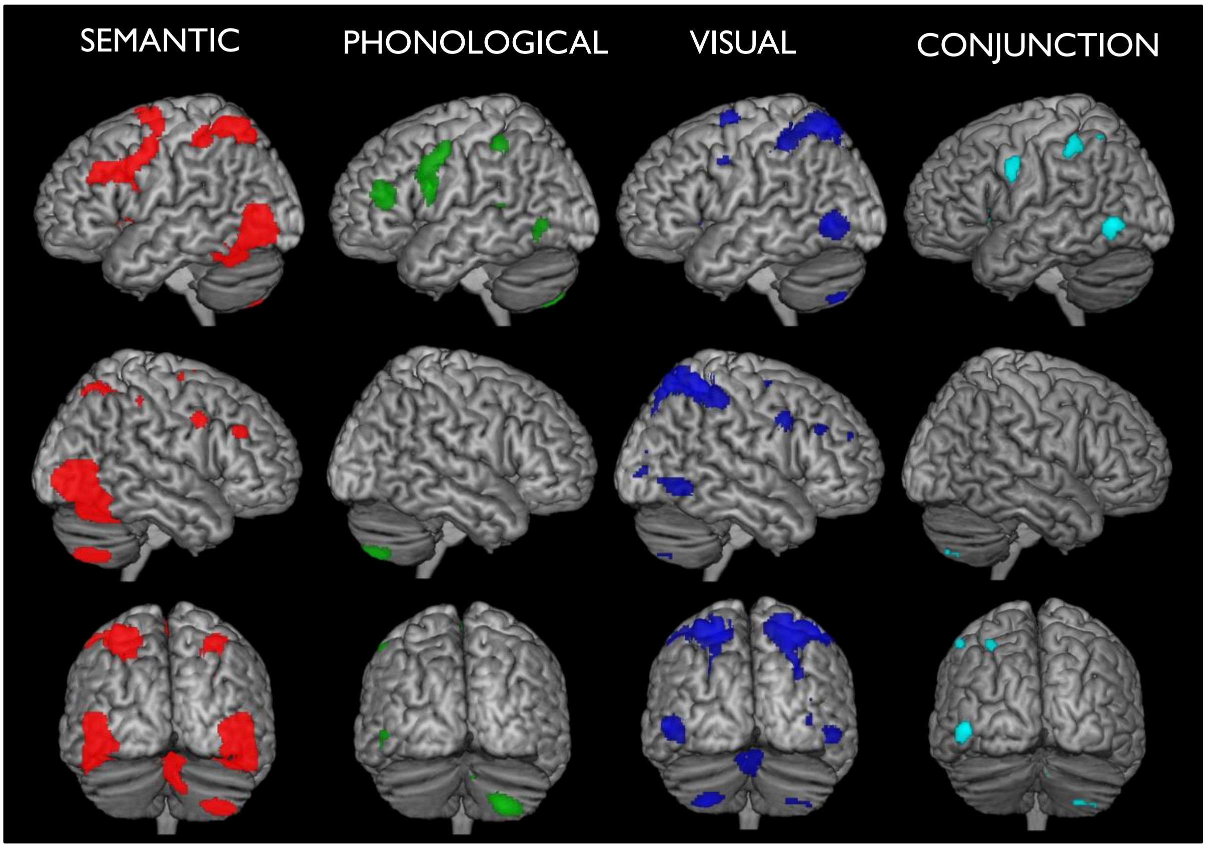

Figure 5.7. Areas activated in 1-back> 0-back contrast for the semantic (first column, red), phonological (second column, green), and visual (third column, blue) matching tasks, as well as the conjunction between the three (fourth column, cyan). All statistical maps thresholded at p(FWE) <0.05. Activations projected onto the Colin brain. Left is displayed on the left.

<u>Conjunction over all three matching tasks.</u> A conjunction analysis over these three contrasts demonstrated that all three matching tasks recruited the left BA44, left frontal operculum, left pre-SMA, left superior parietal cortex, left occipototemporal junction and right cerebellar Crus II. This activation pattern is strikingly lateralised.

5.4.3. PREDICTION-RELATED ACTIVATIONS AND THEIR RELATION TO OTHER CONDITIONS

In other to determine whether the clusters which were more active during processing of a predictive sentence stem than processing a neutral sentence stem were also engaged in other processes, the activation pattern was compared with a number of other contrasts. In addition, the parameter estimates for each condition for the four identified clusters were visualised (see Figure 5.7). These parameter estimates illustrate the relative recruitment of these four clusters in each of the conditions.

5.4.3.1. *Parameter* estimates

Inspection of the parameter estimates in the four predictive clusters reveals that their overall recruitment during the context event is relatively low. Consistent with the fact that they came up in the contrast of interest, these clusters are more active during the sentence stem event of a predictive trial than a neutral trial. However, for the inferior frontal cluster in BA45 this difference is driven by a lower activation in the neutral condition. The cluster in BA47 and the more posterior cluster are most consistent with what could be expected in regions engaged in forward model prediction. They show higher levels of BOLD when an online prediction is made during the stem sentence event. Moreover, they are engaged when the assumed prediction is compared with the outcome of the sentence, and even more engaged when this prediction is incorrect.

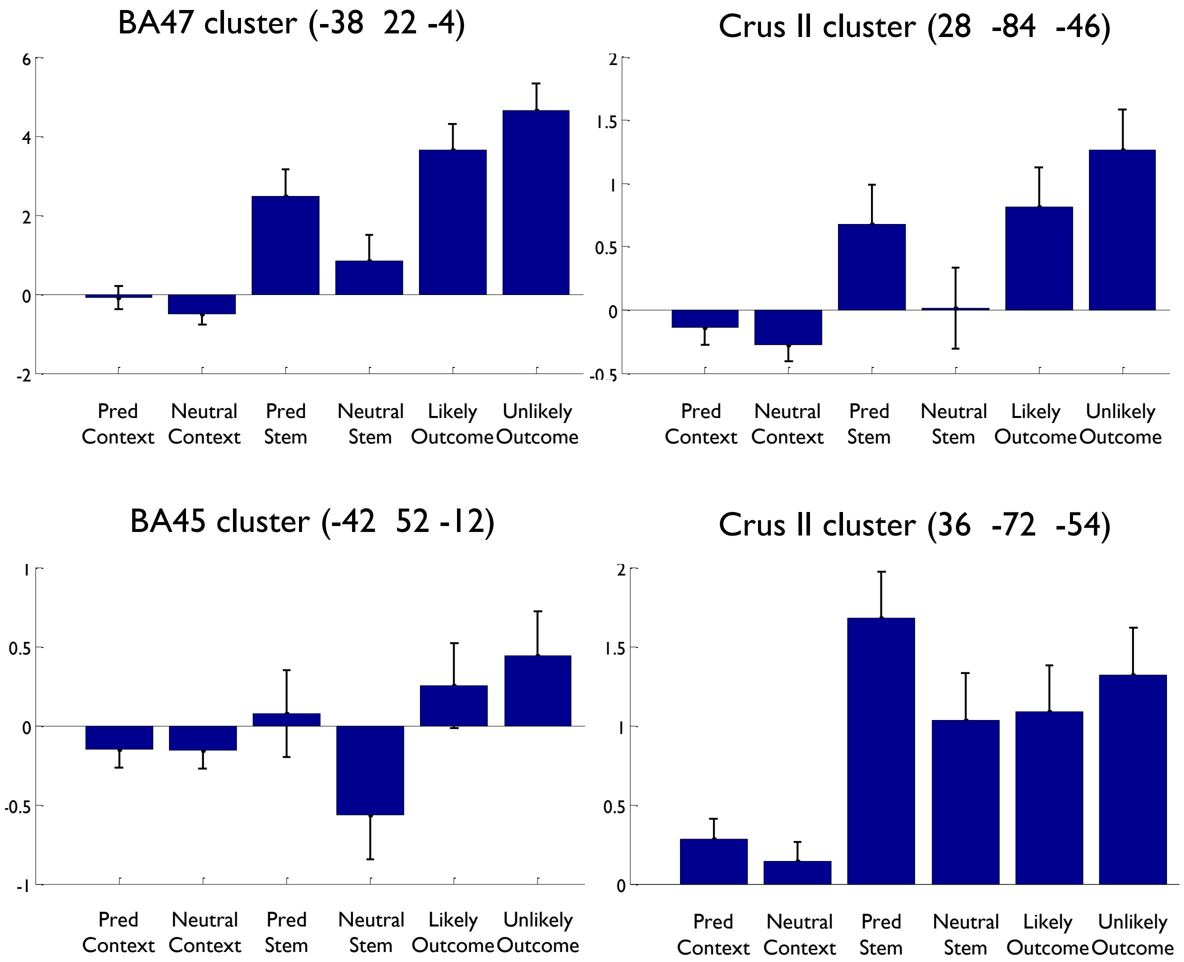

Figure 5.8. Bar graphs indicating the parameter estimates for the four clusters identified in the contrast of interest (stem ^{predictive} - stem ^{neutral}). First column shows the BA47 cluster (top). and the BA45 cluster (bottom). Second column shows the Crus II cluster at MNI (28,-84,-46, top) and the Crus II cluster at MNI (36,-72,-54; bottom). Error bars indicate +/- 1 SE.

5.4.3.2. *Overlapping activation patterns*

First, a comparison was made with other conditions in the event-related prediction experiment. The contrast of interest was compared with three other contrasts, namely the conjunction between predictive and neutral context sentence, the conjunction between a predictive and neutral stem sentence, and the difference between the context sentences in the predictive condition versus the neutral condition (see Figure 5.9). No clusters in the regions of interest areas were more active in the neutral condition compared with the predictive condition for either the context event or the stem event. In the inferior frontal gyrus, the "predictive" cluster borders activation which is common to both conditions in the context events, and overlaps considerably with regions which are more active during the context event in the predictive condition. Activity common to both conditions in the stem event does not overlap with the prefrontal clusters. For the cerebellar activations, it seems that one cluster is unique to the predictive condition in the stem event, and one overlaps with activity common to both conditions in the stem event. Neither of the "predictive" Crus II clusters overlaps with activations during the context event. The conjunction of both conditions in the context event does activate a posterolateral cerebellar region, which overlaps with the conjunction at the stem event.

Second, the activation pattern in the (stem $^{\text{predictive}}$ - stem $^{\text{neutral}}$) was compared with activation patterns during the outcome event (see Figure 5.10). This comparison could shed light on whether the clusters activated by the contrast of interest are also significantly active when participants see the outcome of the sentence, make a judgment about whether or not the outcome is plausible, and press a button to indicate whether it is. The contrast of interest was compared with the conjunction between likely and unlikely outcomes, which should include motor activity related to the button press, and with the contrast between unlikely and likely outcome, which should bring out brain regions sensitive to prediction errors. The opposite contrast (outcome $^{\text{likely}}$ - outcome $^{\text{unlikely}}$) did not yield any activation in the regions of interest and was therefore not displayed. The overlapped activation maps show that both inferior frontal gyrus clusters overlap with areas more active when processing implausible outcomes than when processing plausible outcomes, and that the more posterior inferior frontal gyrus cluster overlaps with activity common to both conditions in the outcome event. Neither of the "prediction" clusters in Crus II overlapped with areas more engaged in processing an implausible versus a plausible outcome, but the most anterior cerebellar cluster bordered the conjunction between likely and unlikely outcomes, as it did with the conjunctions of the stem event.

Third, the contrast of interest was compared with activity on the three control tasks (see Figure 5.11.) This comparison can shed some light on the overlap between structures which are more engaged in predictive than neutral sentence processing on the one hand, and structures recruited when attention is paid to semantic, phonological, and visual properties of visually presented stimuli. In the inferior frontal region of interest, the contrast of interest overlaps slightly with a cluster in the semantic matching contrast and it borders a cluster which is recruited in the phonological matching task. In Crus II, the more anterior "prediction" cluster overlaps with an activation cluster for the phonological matching task and the semantic matching task. The most posterior cluster does not overlap with any of the three tasks. The visual matching task did not elicit any activation near the inferior frontal and right cerebellar activations in the contrast of interest.

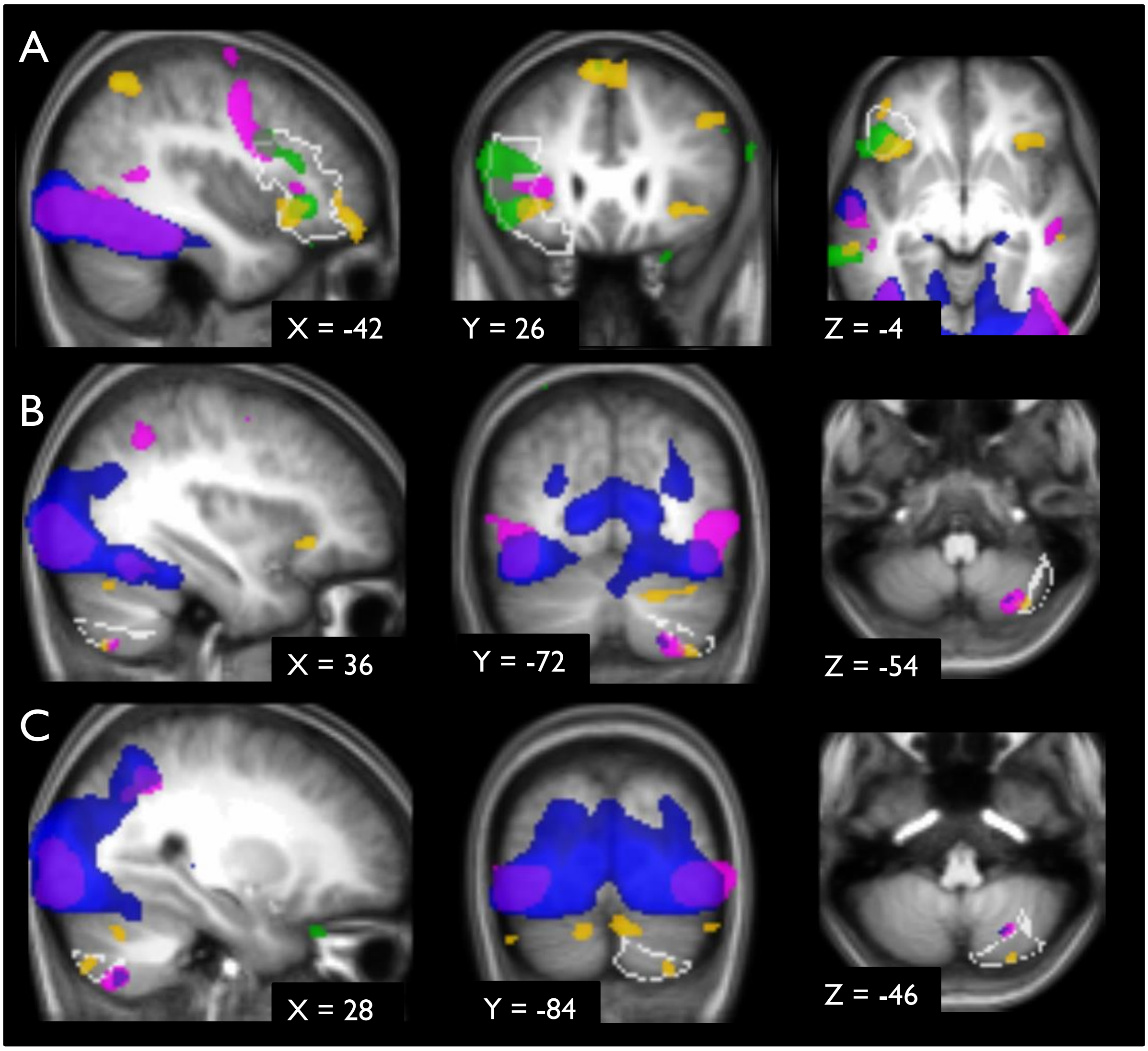

Figure 5.9. Overlap between contrast of interest (stem ^{predictive} - stem ^{neutral}; orange) and the conjunction between stem ^{predictive} and stem ^{neutral} (violet), the conjunction between context ^{predictive} and context ^{neutral} (blue), and areas more active during the context sentence in the predictive condition than in the neutral condition (context ^{predictive} - context ^{neutral}; green). White lines indicate regions of interest. A. Overlap with inferior fontal gyrus activations. B. Overlap with posterior Crus II activation. C. Overlap with posterior Crus II activation. Dotted lines indicate areas outside of the regions of interest. Slices displayed onto the mean of all 17 normalised T1 images. Left is displayed on the left.

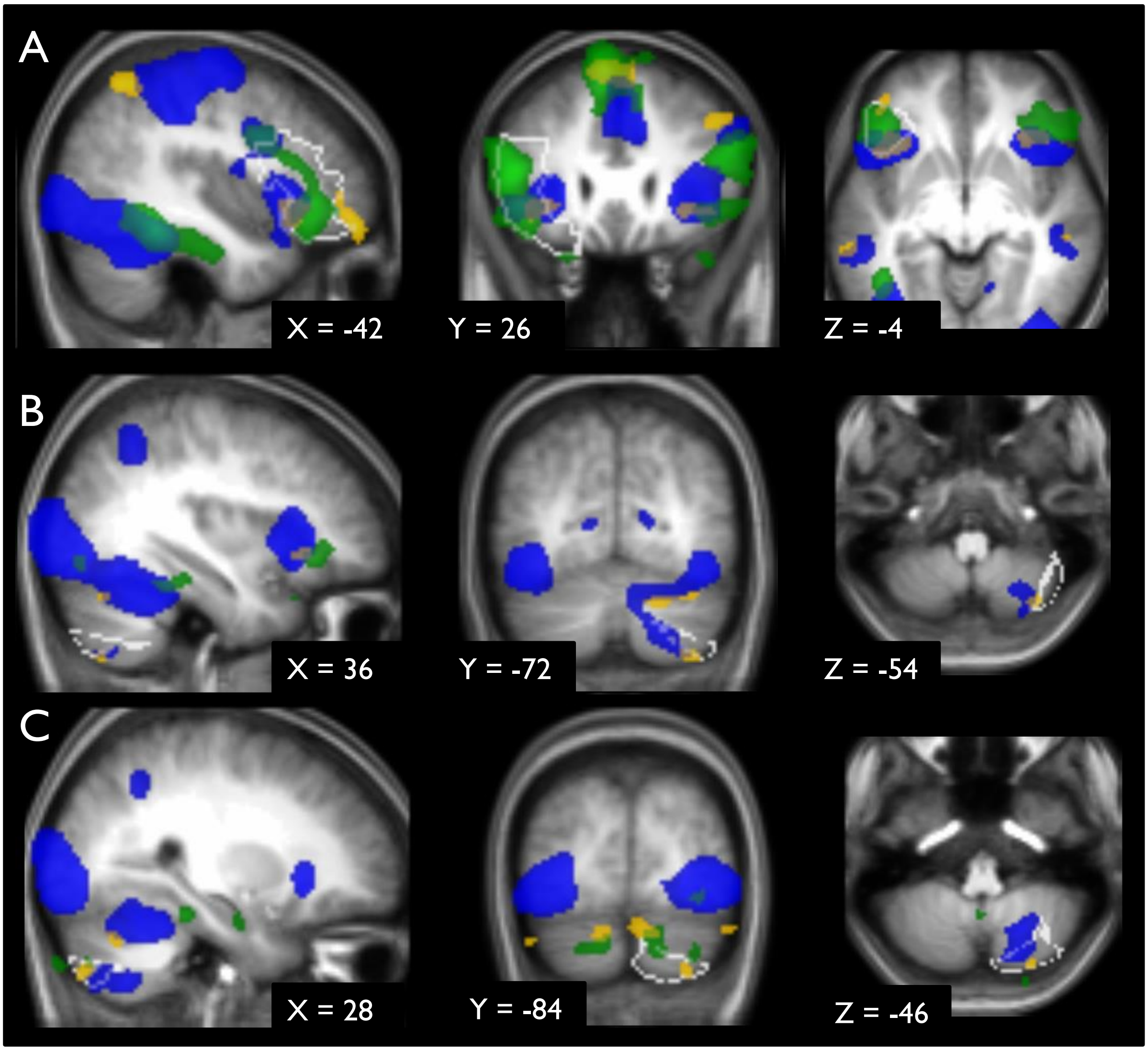

Figure 5.10. Overlap between contrast of interest (stem ^{predictive} - stem ^{neutral}; orange) and conjunction between outcome ^{unlikely} and outcome ^{likely} (blue), and areas more active when the outcome was implausible then when it was plausible (outcome ^{unlikely} - outcome ^{likely}; green). White lines indicate regions of interest. A. Overlap with inferior fontal gyrus activations. B. Overlap with posterior Crus II activation. C. Overlap with posterior Crus II activation. Dotted lines indicate areas outside of the regions of interest. Clusters overlaid onto average of 17 normalised structural scans. Left is displayed on the left.

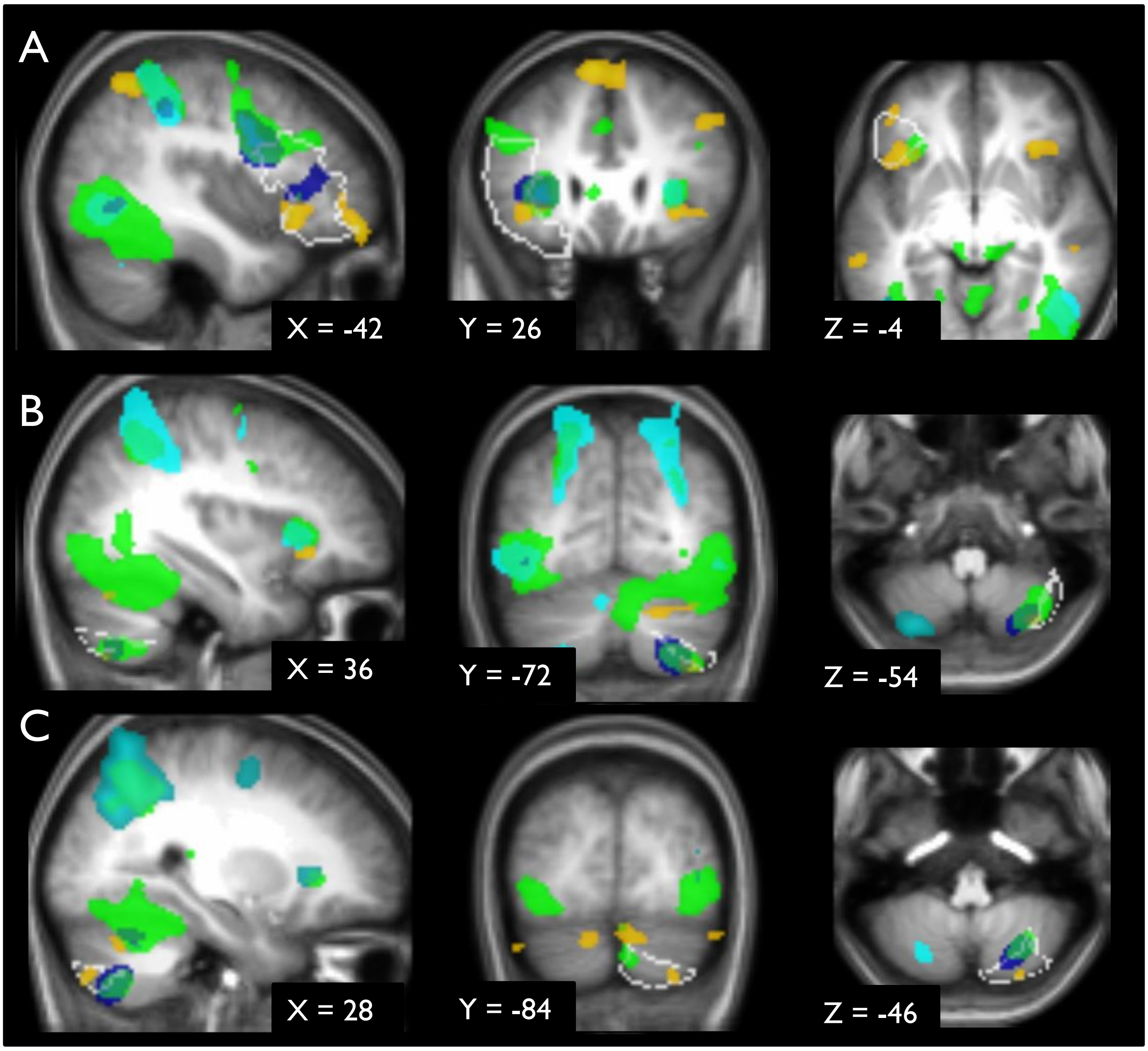

Figure 5.11. Overlap between contrast of interest (orange) and activation maps for the semantic matching task (green), the phonological matching task (blue) and the visual matching task (cyan). White lines indicate regions of interest. A. Overlap with inferior fontal gyrus activations. B. Overlap with posterior Crus II activation. C. Overlap with posterior Crus II activation. Dotted lines indicate areas outside of the regions of interest. Clusters overlaid onto average of 17 normalised structural scans. Left is displayed on the left.

5.5. DISCUSSION

In this chapter, an event-related fMRI study was designed to look at the neural loci of online prediction of an upcoming word during sentence comprehension. We test the hypothesis that the right cerebellum is involved in semantic prediction during sentence comprehension, and would therefore be differentially activated depending on the predictability of upcoming sentence content. Instances where a strong prediction could be made about the final word of a sentence were compared with instances where such a prediction was not possible. Consistent with our hypothesis, right posterolateral areas of the cerebellum were more active when a strong prediction could be made, as were clusters in the left inferior frontal gyrus. However, it is worth noting that these differences between the predictive and neutral conditions were modest, and could only be detected using a small volume correction.

Due to the complexity of language comprehension as a process, it is difficult to disentangle semantic prediction from the myriad of other processes going on concurrently. Activation patterns from the prediction contrast were therefore compared with those during tasks where attention was directed at semantic, phonological and visual aspects of a visual stimulus, as well as with activation patterns from a series of control contrasts in the prediction experiment. Commonalities in the observed activation patterns could shed light on the functions of the activated regions. The spatial relationship of these clusters can also elucidate whether a different area is recruited when making a linguistic prediction, or whether the same tissue is recruited to a larger extent. Two clusters in left inferior frontal gyrus were more active when processing highly predictable sentences versus neutral sentences. The largest of these had its peak in BA47 and extended into the anterior insula.

This area was also recruited at the time of the outcome, which is evident from both the parameter estimates and the overlap with a conjunction analysis of both likely and unlikely outcomes. In addition, this BA47 cluster partially overlapped with a cluster which was more active in the predictive than the neutral condition at the time of the context sentence, with a cluster more active when an unlikely outcome was processed than a likely outcome, and with activity during the semantic matching task. Most of these overlapping conditions have in common that they have an element of evaluation, or that there is an increased attention for anomalies. This is the case at the time of the outcome, where final word must be evaluated in light of the rest of the sentence. It is perhaps even more the case when the final word is unlikely and a prediction error occurs. In the semantic matching task too, the participant is on the lookout for objects in the same semantic category as the previous stimulus. The contrast between predictive context and neutral context does not fit this description, but the parameter estimates for these conditions indicate that while the difference between the conditions may have been significant, the absolute recruitment of the BA47 cluster during both the context event was lower than baseline, and the only pattern present is a small further de-activation in the neutral condition. All of the overlapping contrasts have a semantic aspect to them, as evidenced by the absence of overlapping clusters with the visual and phonological matching task. In summary, the BA47 region is engaged when an upcoming word is predicted, when the end of the sentence is evaluated, and when semantic features of a word are attended to. At first glance, this pattern would seem to be in line with the proposed role in inner speech or automatic pre-articulatory processes (Ackermann & Riecker, 2004). However, if this were the case, the strongest activity would be expected during the context sentence, which was not the case here.

A more anterior prediction cluster in the inferior frontal region of interest was found in BA45, with the activation extending into BA10. However, parameter estimates indicate that rather than being more engaged in the predictive condition, this region was less engaged in the neutral condition than at baseline. Therefore, it seems less likely that the BA45 cluster would be engaged in online linguistic prediction. This area showed a small overlap with a region more active when responding to an implausible than a plausible outcome. There was no overlap with any of the other contrasts it was compared to.

In right cerebellar Crus II, two clusters were identified which were more engaged when a prediction could be made than when no prediction could be made. The more anterior of these clusters bordered areas recruited commonly in all conditions at the time of the presentation of the stem and at the time of the outcome. The parameter estimates from the prediction task indicate that this region was involved when the sentence stem was presented and when the outcome was presented, with the most prominent recruitment when the stem of a highly predictive sentence was presented. This cluster also overlapped with activity in the rhyming task (phonological matching task) and bordered activity in the semantic matching task. The overlapping clusters have in common that the phonological properties of written words were considered. The more posterior Crus II cluster did not overlap with any of the contrasts it was compared to. This cluster was only significantly activated in the contrast of interest, when a linguistic prediction about upcoming content could be made. This right Crus II activation and the left BA47 activation closely match the activation pattern one might expect from regions that are engaged in a forward model prediction. That is, their metabolic demands are elevated when an online prediction can be made, and when it is compared against the observed outcome. The left inferior frontal gyrus is functionally connected to the right posterolateral cerebellum (Buckner et al., 2011; see also Chapter 4, Section 4.4.3.1). It is therefore possible that there areas might interact to support linguistic prediction.

This is the first fMRI study to investigate semantic prediction in the cerebellum during written sentence comprehension. However, Desmond, Gabrieli, and Glover (1998) have previously manipulated single word predictability in an fMRI study using a word stem completion task. There it was found that words with few possible endings, where the stem was therefore very predictable of the target word, engaged the right posterolateral cerebellum and cerebellar vermis, whereas word stems with a wider array of possible alternatives engaged middle frontal gyrus and the caudate nucleus. Like in the present chapter, right cerebellar activity was linked with higher predictability. Other fMRI investigations have looked at semantic priming, and have reported right posterolateral cerebellar and left inferior frontal gyrus activations in high-cloze versus low-cloze contrasts (Sass et al., 2013; Ulrich, Hoenig, Grön, & Kiefer, 2013). The overall activation pattern for these two studies matched remarkably well with that of the prediction contrast reported here. Two others studies manipulate cloze probability in semantic priming paradigms, but do not report high-cloze versus low-cloze contrasts (Dien et al., 2008; Obleser & Kotz, 2010). Yet others report semantic priming contrasts, which activate the left anterior insula but do not include the cerebellum in their field of view (Rossell, Bullmore, Williams, & David, 2001). It is not always clear whether the cerebellum was included in the field of view, which makes it difficult to determine the prevalence of cerebellar activation in linguistic predictability contrasts, despite the wealth of imaging paradigms on semantic priming or prediction.

The topography of cerebellar activations found here is in line with existing literature on cerebellar contributions to cognitive and linguistic tasks, and with connectivity data (Bernard et al., 2012; Buckner et al., 2011; Habas et al., 2009). Cerebellar clusters were found in Crus II, an area implicated in cognitive and linguistic tasks (Stoodley, 2012). Also consistent with functional divisions characterised in previous works (E et al., 2012; Scott et al., 2001; Stoodley & Schmahmann, 2009a, 2010), activation patterns for the visual matching task showed a reverse lateralisation (stronger activity in the left cerebellum than the right) compared to those in the semantic and phonological task. Interestingly, activity in the posterior vermis was present during both the semantic and visual matching tasks, but not during the phonological matching task. This pattern could indicate that working memory tasks with a strong visual component (attending to line drawings in the semantic task, attending to unfamiliar characters in the visual task) elicits vermal and paravermal activation. Conversely, the right posterolateral component was most pronounced in the working memory tasks with a strong phonological component (rhyming judgment, attending to line drawings and their associated phonemic representation in the semantic task). Such a distinction would be consistent with the role of the posterior vermis in eye movements and the proposed right posterolateral cerebellar role in phonological processing (Marvel & Desmond, 2010). Perhaps this could be an interesting further distinction when topographical differentiation of the cerebellar cortex is considered.

A major strength of the current study is its event-related design, where the differential contextual properties of the trial are isolated to a context sentence, and the response and prediction error processes are isolated to the outcome of the sentence, while the event of interest is identified by a carefully controlled stem sentence. This ensured that observed differences at the level of the sentence stem are due to the predictability of the final word of the sentence, and cannot be attributed to other differences between the conditions. The previous fMRI investigation where linguistic predictability in the cerebellum was assessed used a block design, where it was not possible to pinpoint predictive processes to a certain part of the trial (Desmond & Fiez, 1998). For example, this study had a (covert) response component, which may have confounded uniquely semantic and predictive activations with response preparation. In other instances, the sentence elements that made a certain item predictive may have confounded the effect of prediction per se. By contrast, in the current study differences between the presented stimuli were only present in the context sentence, while the sentence stems were matched between conditions. A limitation of this study is that it was not possible to avoid semantic prediction in other aspects of the task. If, as is hypothesised, the cerebellum is engaged in continuous prediction of upcoming content, this process will not be limited to the end of the stem sentence. Areas engaged in semantic prediction should be recruited to a larger extent in the predictive condition, but should be present to some extent throughout the trial.

Interestingly, the parameter estimates for the significant clusters show a markedly smaller recruitment during the presentation of the context sentence than during the other events. This difference is present in all clusters that were more engaged during the predictive stem condition than during the neutral stem condition. This pattern seems at odds with the idea of a continuous prediction throughout sentence processing. One might expect the level of activation to be modulated by the level of constraint imposed by the information thus far. This would me maximal when the predictive stem is processed, and might explain how these regions were more active during the predictive stem even than during the presentation of the context sentence. However, this does not explain why recruitment is not equally low when the neutral stem is processed. Alternatively, the length and nature of the event may have had an effect on the activation strength. The context sentence was presented for three seconds, while the other events presented for one second. Moreover, the stem sentence was presented in serial visual presentation format (word per word, in quick succession), while the context sentence was displayed in its entirety. Both these factors may have led to differences in attentional modulation that might explain the lower activations during the context events. However, it is worth noting that whatever differences were present between the context sentence and the sentence stem, these do not affect the comparison between the sentence stem in both conditions.

An issue to address is whether the right posterolateral cerebellar recruitment in this task can be explained by varying working memory demands. There is a close relation between working memory and the feedforward predictive processed studied here, and previous fMRI investigations of cerebellar language function have confounded linguistic demands and working memory demands. Areas which respond to verbal working memory tasks overlap with areas engaged in linguistic tasks (E et al., 2012; Stoodley & Schmahmann, 2009a), and right posterolateral cerebellar areas are connected to both language and executive control networks of the neocortex. Bearing in mind the linguistic task requirements of a verbal working memory task and the working memory requirements of many language tasks, this structural and functional overlap is perhaps not surprising. A sensible hypothesis to consider is therefore whether verbal working memory requirements can account for cerebellar activations in this task. fMRI studies on working memory load have shown that the right cerebellum is more heavily recruited when verbal working memory load is higher (Desmond et al., 1997; Hayter et al., 2007), but the cerebellum is also engaged when the working memory load is very low. For example, right cerebellar activations are observed when hearing or reading sentences (Fedorenko et al., 2010) or viewing single words (Petersen et al., 1989). Crucially, results from Desmond and Fiez (1998) and from the current chapter show larger cerebellar activation when there are few alternatives or in a highly constraining context. From a working memory point of view, this is the less demanding condition, because no selection needs to be made and no array of alternatives must be kept online. Therefore, working memory demands alone cannot account for the right cerebellar activations observed in this task.

Nevertheless, a notion worth considering may be that both verbal working memory and language processes both rely on inner speech processes. Interestingly, the anterior insula and right neocerebellum are both implicated in inner speech processes (Ackermann, Mathiak, & Riecker, 2007; Marvel & Desmond, 2013). Importantly, inner speech does not reduce to articulatory processes; it is likely to operate at a more abstract level of representation and has different properties than overt speech (Oppenheim & Dell, 2011). Inner speech is faster than overt speech (MacKay, 1992); overt speech can be disrupted without affecting inner speech (Aziz-Zadeh, Cattaneo, Rochat, & Rizzolatti, 2005); inner speech is not eliminated by articulatory suppression (Wheeldon & Levelt, 1995), and inner speech is not sensitive to the same systematic errors as overt speech is (Oppenheim & Dell, 2008). Pickering and Garrod (2013) and Oppenheim (2013) have suggested that inner speech may be a by-product of or a closely related process to linguistic forward models. Thus verbal working memory and linguistic prediction could both require inner speech processes, without one explaining the other. Whether and how inner speech processes could contribute to linguistic prediction remains to be determined.

We interpret these fMRI findings in the context of a theoretical model of language comprehension where forward model prediction plays a key role (Pickering & Garrod, 2013), with the specification that these forward models are present in the cerebellum. Where Chapter 2 demonstrated delayed prediction-driven eye-movements following disruption of the right cerebellum, the present chapter shows increased right posterolateral cerebellar activity in linguistic prediction. Together, these results provide evidence that the cerebellum is engaged in linguistic prediction, and support the notion that the posterolateral cerebellum may be responsible for forward model predictive processes in language. The current data cannot address whether these linguistic predictions stem from a forward model or another type of prediction. However, evidence for linguistic forward model prediction is emerging. For example, evidence for lexical-semantic forward model prediction was recently reported in a language comprehension task using an EEG paradigm with items in sign language (Hosemann et al., 2013). Participants showed an N400 effect when a sentence had an unexpected ending. Interestingly, this effect originated before the unexpected final sign, during a phase where the signer was making a transition towards signing the unexpected word. These data provide support for forward model semantic prediction, whereby visual input which does not match the expected movement elicits a prediction error, even before the unexpected sign occurs. Not only did the comprehender expect that a certain word/sign would follow, but this prediction also included the expected visual input. An interesting avenue for further research would be to determine whether such N400 responses are linked with right posterolateral cerebellar activity.

While the present results indicate a cerebellar role in semantic prediction, it is not clear what the nature of the proposed linguistic representations in the cerebellum is. Argyropoulos (2010) has proposed that the cerebellum houses semantic associations which can serve predictive processes in language comprehension and production. In support of this notion, there is evidence for a right cerebellar role in semantic association and for semantic association deficits in cerebellar patients (De Smet et al., 2013). In addition, the vocabulary learning data in Chapter 4 suggest that the acquisition of novel associations involves the cerebellum. Alternatively, rather than storing associations between items, the cerebellum could store multiple facets of a semantic item, which would include (at least) its syntactic, phonological and orthographic features. Depending on the context (for example, written versus spoken versus sign language), some or all of these facets could be predicted. Other possibilities are that the cerebellum helps retrieve neocortical linguistic representations, or that it weights the probability of alternative options. However, the data in this chapter and the results from Desmond et al (1998) show less cerebellar involvement when many alternatives are competing, which argues against the latter explanation, At this point, it is unclear whether other types of linguistic predictions are also cerebellar-dependent. Pickering and Garrod (2013) proposed that linguistic forward models should entail all levels of representation, including syntactic, phonological and orthographic representations. This notion is consistent with the study by Hosemann et al (2013) where a specific visual expectation was generated by a lexico-semantically driven forward model.

Another remaining question concerns how exactly the cerebellum interacts with other brain regions to achieve a linguistic prediction. Our results have identified inferior prefrontal

(BA47 extending into anterior insula) and cerebellar clusters which are selectively active at the time a linguistic prediction is made, i.e. when a specific stimulus is predicted. It is not clear which elements of this predictive process recruit the cerebellum. It is not necessary that this fronto-cerebellar system is responsible for searching plausible semantic targets and selecting one amongst those. For example, it is possible that initial contextual priming (search) can occur in the left superior temporal sulcus and left/or inferior frontal gyrus (here: when the context sentence was presented). Later, when the sentence stem was presented, more specific expectations can be generated by the right cerebellum and left inferior frontal gyrus. This specific prediction, governed by the cerebellum, might then entail semantic, phonological, and visual representations, as well as a precise expectation of when the stimulus is meant to appear. For example, left-lateralised semantic regions, could select one or several relevant semantic concepts and the right cerebellum could create a detailed forward model prediction of a specific word spoken by a specific voice at a specific time, which is compared with the actual perceived sound. Such a conceptualisation would be very close to the model of language comprehension proposed by Pickering and Garrod (2013; see Chapter 1, Section 1.6), whereby the comprehension implementer and covert imitation are governed by left-lateralised core language networks, and the forward model prediction of the upcoming spoken word takes place in the cerebellum.

In sum, the left inferior frontal gyrus and right posterolateral cerebellum were selectively recruited when participants made an online prediction about upcoming content. These results are suggestive of a role in linguistic prediction in right Crus II, which can be separated from semantic, phonological or visual linguistic requirements. Along with Chapter 2, the present chapter demonstrates that the cerebellum is engaged in linguistic predictions during language comprehension. The results also are in line with accounts of a unified cerebellar algorithm, whereby the predictive function of the cerebellum can be extended from motor control processes to cognitive domains such as language processing (Ito, 2008; Leiner et al., 1991; Ramnani, 2006).

CHAPTER 6

GENERAL DISCUSSION

This thesis set out to explore the role of the cerebellum in predictive language processing. Recent psycholinguistic accounts have proposed the notion of forward model prediction in language (Hickok, 2012; Pickering & Garrod, 2013). Pickering and Garrod (2013) propose that forward models of syntactic, semantic and phonological representations are used for online predictive processing, both during speech production and during comprehension, which is achieved by covert imitation of the perceived linguistic input and online prediction of input to come. One of the strengths of this proposal is that it accounts for the observed speed and flexibility of everyday linguistic communication, and that it fits well with the considerable overlap between the neural circuitry activated in both receptive and predictive language processes. Forward model accounts of language function are based on forward models in motor control, which are thought to be governed by the cerebellum (Miall, 1998).

While the cerebellum is best known for its role in motor control, it is also implicated in nonmotor processes, including language and working memory (Strick et al., 2009). Anatomical, neuroimaging, and clinical evidence in support of a cerebellar role in language processing has accumulated over the last decades. Posterolateral cerebellar regions are functionally connected to cortical language regions (Buckner et al., 2011), neuroimaging studies often find right cerebellar activity in language contrasts probing semantic processing (Price, 2012), and clinical studies report linguistic deficits in cerebellar patients (De Smet et al., 2013). The highly conserved and uniform architecture of the cerebellar cortex suggests a uniform computation throughout the cerebellar tissue (Leiner et al., 1986) and previously, Ramnani (2006) and Ito (2008) have proposed that internal forward and inverse models such as those used in motor control may also be present in cerebellar domains which project to cortical association areas, thus supporting cognitive and language functions. Therefore, there is some support for the notion that forward models in the cerebellum can be extended to language processing, but very little research has investigated the cerebellum in nonmotor prediction. The goal of this thesis was to explore the cerebellar role in predictive language processing. The theoretical framework which underlies the experiments presented here is that linguistic forward model prediction takes place in the right posterolateral cerebellum, and (tentatively) that these predictions are based on semantic associations. The initial literature review and the experimental studies that make up this thesis address cerebellar involvement in online semantic prediction and during the acquisition of linguistic associations.

In this final chapter of the thesis, the empirical evidence gathered will be summarised and reviewed against the theoretical framework tested. Strengths and weaknesses of the set of experiments will be considered. Implications of the results will be discussed and future directions will be outlined.

6.1. SUMMARY OF THE RESULTS

This thesis addresses the cerebellar contribution to language processing, using a number of different methods. In Chapter 2, performance in a linguistic prediction task was assessed before and after right cerebellar processing was experimentally disrupted with repetitive transcranial magnetic stimulation. In Chapter 3, the same task was used to investigate whether cerebellar patients are similarly impaired at linguistic predictions. In Chapter 4, the contribution of the right posterolateral cerebellum during the acquisition of a novel lexicon was assessed with functional imaging (fMRI) using a standard block design, and learning-induced changes in resting state functional connectivity were addressed. Finally, in Chapter 5 an event-related fMRI design was used to assess right posterolateral cerebellar activation during online linguistic prediction. The main results of these experiments are summarised below.

Chapter 2 reports a test of the hypothesis that a virtual lesion of the right cerebellum would lead to a linguistic prediction deficit. To this end, the visual world paradigm (Altmann & Kamide, 1999), an eye-tracking task which captures online sentence processing and probes predictive language processing, was used in conjunction with repetitive transcranial magnetic stimulation (rTMS). Predictive eye movements to targets were delayed following right cerebellar rTMS, but not following rTMS over a control site (the vertex) or after a non-TMS control. Importantly, low-level eye movement characteristics were not changed after cerebellar TMS, nor was fixation behaviour in the non-predictive condition affected. Thus, a selective deficit was induced, which affected online linguistic prediction, without affecting linguistic processing per se.

In Chapter 3, I initiated an experiment to test whether natural lesions of the cerebellum would result in a similar deficit as reported in Chapter 2. Here, the visual world task was performed by a group of cerebellar patients and a group of neurologically healthy control participants. Unfortunately, insufficient data has yet been acquired in this ongoing study to address the hypothesis adequately. In the group tested thus far, patients did not show a selective impairment making predictive eye movements. A broad-span cognitive assessment did detect language impairments in the patient group. The preliminary results do not allow us to conclude whether or not cerebellar patients have selective predictive language impairments, but data acquisition will continue beyond this thesis. Based on a power analysis of the data in Chapter 2, a minimum of 17 participants in each group would allow the hypothesis to be addressed with sufficient power.

Chapter 4 addressed the possibility that linguistic prediction is based on semantic associations which are acquired by and stored in the cerebellum (Argyropoulos, 2010). If this is the case, one might expect the cerebellum to be engaged in learning associations between words. An fMRI experiment was conducted to investigate whether the right posterolateral cerebellum is engaged in the acquisition of a novel vocabulary, and whether possible connectivity changes following learning involve the right posterolateral cerebellum. In an fMRI paradigm, resting state scans were acquired before and after participants learnt a 25-word lexicon, and before and after they performed a control task which did not involve learning. Analysis of the learning task identified a region in right cerebellar Crus II (amongst other activated regions) which was more active when learning unknown words compared to a matched task where known associations were probed. The resting state connectivity maps demonstrated decreased connectivity between left hippocampus and both the inferior frontal gyrus and right Crus II. Connectivity from other seed regions, in inferior frontal cortex and right Crus II, did not show connectivity changes following learning, but they do emphasise the connectivity of the right posterolateral cerebellum with other language regions in the cerebrum.

Finally, in Chapter 5 the hypothesis that the right posterolateral cerebellum is engaged in predictive language processing was further tested using fMRI to support the rTMS data reported in Chapter 2. An event-related fMRI study looked for differential activation when processing the stem of a sentence delivered within a predictive context versus a non-predictive context, whilst carefully controlling for other features of the sentence stem. Clusters in right Crus II and the inferior frontal gyrus were found to be more active when participants processed highly predictable sentences. Interestingly, one of the right posterolateral cerebellar clusters was specifically active when an online prediction was elicited, and when the prediction was evaluated, but not during other phases of the trial or during any of the three control experiments aimed at capturing attention to phonological, semantic and visual aspects of language processing. This chapter's results are complimentary to those of Chapter 2, and further support a role for online linguistic prediction in the cerebellum.

6.2. STRENGTHS AND LIMITATIONS

6.2.1. STRENGTHS

One of the strengths of the set of experiments presented in this thesis is that a variety of methods are used to address the same question. Notably the experimental methods in Chapter 2 and Chapter 5 can overcome each other's weaknesses. Strengths of fMRI include its relatively precise localisation and the fact that the entire brain can be covered. However, the change in metabolic demand captured in fMRI is but an indirect measure of neuronal activity. Moreover, the BOLD response is slowed by several seconds with respect to neuronal activity (Aguirre, Zarahn, & D’esposito, 1998). A further limitation is that BOLD is a correlational measure, and it is not possible to draw a causal link between the metabolic recruitment in a given areas and a task-related process. Conversely, TMS allows causality to be assessed through an experimental manipulation of the site of interest. On the downside, it is blind to the possible contribution of other nodes in the network and has poor spatial resolution. By addressing the same question with both methods, a more complete picture of the process at hand could be obtained.

Another way in which the methods of Chapters 2 and 3 and those in Chapter 5 were complementary was that predictive processing was addressed using different experimental tasks. The visual world paradigm used in Chapters 2 and 3 uses eye movements as a dependent measure and uses auditory and pictorial stimuli. The dependent measure therefore relied on the auditory system and the oculomotor system, even though neither was directly relevant for the hypothesis. In Chapter 5, the stimuli were visually presented words, and the dependent measure was the BOLD response at the time a prediction was assumed to occur. Despite these methodological differences, the right cerebellum was found to be engaged in online linguistic prediction in both chapters. This strengthens the confidence that the right cerebellum is recruited in online linguistic prediction, regardless of input modality, and regardless of whether the oculomotor system is involved in the response.

The set of experiments presented in this thesis also contributes to the literature by applying techniques which are relatively new to the neuroscience of language processing with a focus on the cerebellum. For example, the study presented in Chapter 2 is one of the first to use cerebellar TMS in a language paradigm, and the first to do so in a linguistic prediction paradigm. Similarly, the experiments in Chapters 4 and 5 are the first to control for possible confounds of breathing and heart rate in a nonmotor functional imaging paradigm of the cerebellum. Heart rate and breathing traces have been regressed out sporadically in studies of motor control with a cerebellar focus, and in one particular study it changed the results dramatically (Schlerf et al., 2012). Finally, the prediction experiment in Chapter 5 was the first to investigate the role of the cerebellum in predictive sentence processing using an event-related design, which enabled us to specifically address the critical phase of the trial at which predictions were evoked.

6.2.2. LIMITATIONS

A limitation of the presented studies in this thesis is that they were not able to test for the presence of forward models. While the results of Chapters 2, 4 and 5 are consistent with forward model prediction in language, none of the experiments could determine whether the prediction was supported by the simulation of expected linguistic input, or whether predictions were made through another process. Evidence for lexical forward models in language comprehension has been found (Hosemann et al., 2013), and if the cerebellum subserves a role in linguistic prediction, its structure would suggests that this would be through internal models. However, this cannot be concluded on the basis of the evidence presented in this thesis.

Another limitation is that the experiments presented here do not address which type of linguistic feature was predicted. What was predicted in the tasks in Chapters 2, 3 and 5 could have been either the semantic, the phonological or the syntactic properties of the predicted word. It has yet to be clarified whether cerebellar linguistic prediction is an exclusively semantic process, as is suggested by Argyropoulos and Muggleton (2013), or whether phonological and/or syntactic features are also processed, as is proposed by Pickering and Garrod (2013).

An obvious limitation in Chapter 3 is the incomplete data acquisition; with the limited number of participants we cannot reliably assess whether performance in the visual world paradigm is affected in patients with cerebellar lesions. Thus far, we failed to find evidence for a predictive language deficit in cerebellar patients, but we should wait for a complete dataset to draw firm conclusions.

6.3. IMPLICATIONS OF THE RESULTS

The studies outlined in all four experimental chapters confirm that the cerebellum is involved in receptive language processing. Chapter 2 showed a disruption of performance in a language comprehension task. In Chapter 4, a conjunction revealing areas active both when processing known words and learning new words activated the right posterolateral cerebellum. Moreover, analysis of the resting state signals showed functional connectivity between left inferior frontal gyrus and the right posterior cerebellum. In Chapter 5, robust posterior cerebellar activity was found linked to processing semantic information whilst reading sentences and during tasks where attention to semantic, phonological or orthographic features of a stimulus was required. Throughout this thesis, the right cerebellum has been implicated whenever linguistic stimuli were processed. These findings are in line with previous research, showing right posterior cerebellar activity during sentence comprehension (Fedorenko et al., 2010), single word reading (Petersen et al., 1989), and attention to the semantic properties of figures (Vandenberghe et al., 1996). Though not new, these findings have considerable implications for current neurobiological models of language processing, which largely ignore the cerebellum. One clear suggestion would be to consistently include the cerebellum in the field of view for fMRI and MEG investigations, and to report cerebellar activations when found.

Together, the empirical evidence gathered here is in line with a cerebellar role in linguistic prediction. Both chapters 2 and 5 found evidence for cerebellar involvement in the online prediction of upcoming sentence content. In a visual world paradigm fixations on predictable targets are consistently earlier than those to targets that cannot be predicted. In Chapter 2 experimental disruption of the right cerebellum delayed gaze fixations on figures which represented upcoming content, specifically under predictive conditions. Language comprehension in this experiment was not obliterated, but slightly delayed. This finding fits a model where the comprehension apparatus is functional, but forward model prediction is disrupted. That is, if the cerebellum aids comprehension by rapid short-term predictions, the loss of this capacity should not have detrimental effects on language processing. Rather, comprehension would be expected to be slightly slower. Such effects might only be noticeable under highly controlled experimental settings or, in a real-life setting, lead to subtle disturbances during rapid conversation. My interpretation is therefore that following posterolateral rTMS, participants were less able to profit from cerebellar-generated short-term predictions of upcoming content. In Chapter 5, the cerebellum was further found to be engaged when a strong prediction could be made about upcoming sentence content. In addition, a region in the left inferior gyrus extending into the left insula was also more engaged when a prediction could be made. Together, these results implicate the cerebellum in predictive language comprehension, and suggest that studies of prediction in language could include the cerebellum as a region of interest.

In this thesis, the idea of a universally predicting cerebellum was used as a backdrop for the experimental hypotheses and study designs. However, it should be clear that the experiments in this thesis do not address how this prediction was achieved. Because forward models are a well-accepted process in the cerebellum, these are used as a hypothetical mechanism. However, other types of prediction could underlie cerebellar linguistic prediction.

Forward model prediction maps most readily onto prediction in language comprehension if the latter is achieved through imitation. That is, if efference copies of the simulated input evoke a prediction of the upcoming stimulus, and if this prediction is compared with the perceived stimulus whereby a discrepancy will have an impact on future predictions, then this would constitute forward model prediction. Within this framework there is wide array of possibilities concerning which features of a concept are represented and how exactly these are triggered. At its core, a forward model can be conceived of as a table of input-output relations, and this model can be very simple or very complicated (Koziol et al., 2014). There are indications that the motor apparatus is used for language perception (Fadiga, Craighero, Buccino, & Rizzolatti, 2002; Wilson et al., 2004), but this is not clear whether all language comprehension is mediated through simulation.

Conversely, predictive processes that do not rely on simulation would not be forward model based. Prediction could then simply be based on associative principles. The probabilistic relation between different words (or certain features of words), can underlie the expectancy of one following the other without requiring simulation through the language production apparatus. In Chapters 2, 3, and 5, the relationship between the contextual or linguistic cues and the target words were be the basis of the prediction, and in Chapter 4, this relationship was learnt. That is, a predictions investigated in this thesis can rest on the statistical relation between contextual and linguistic information without the need for a forward model.

A recent theoretical conceptualisation of sensory and motor processing is the free-energy framework, which places a great emphasis on prediction. This framework entails predictive coding models which can be applied to variety of different processes. The free-energy framework posits that predictions occur at many hierarchical levels of processing, and that prediction errors drive the optimisation of the predictive process (Noppeney, Josephs, Hocking, Price, & Friston, 2008). For example, motor control processes have been rewritten into the free-energy framework (Friston, Daunizeau, Kilner, & Kiebel, 2010), and this formulation retains most of the core concepts referred to here: efference copies, forward and inverse models, reafference cancellation and the use of the resulting error signal to update the model. In this sense, forward models can be thought of as a special case of a predictive coding model. Whether or not linguistic prediction of upcoming content occurs through simulation, a predictive coding model can be written to account for prediction in language, so long as prediction errors optimise future predictions. Therefore, forward models and predictive coding models would not necessarily lead to differential predictions.

Non-predictive hypotheses about the role of the cerebellum in language and cognition generally expand on other cerebellar models of motor control (see Section 1.5). For example, the cerebellar role in precise timing, or the cerebellar role in sequential processing have been expanded to the language domain (Leggio et al., 2011; Mariën et al., 2013). It is not straightforward to derive differential predictions from other hypotheses about the cerebellar role in language, as these models generally do not oppose the existence of forward models in the cerebellum. One theoretical model that does not make reference to cerebellar motor control highlights the cerebellar role in verbal working memory, inner speech and phonological loop processes (Mariën et al., 2013; Marvel & Desmond, 2010). However, this model cannot account for the findings in Chapter 2 and Chapter 5, as the predictive conditions did not require more phonological loop processes or verbal working memory.

Chapter 4 did not assess linguistic prediction per se, but addressed the possibility that associative relations between words may be represented in the cerebellum. Indeed, the cerebellum is implicated in associative motor learning such as eye blink conditioning (Gerwig, Kolb, & Timmann, 2007), in fear conditioning (Sacchetti, Scelfo, & Strata, 2005) and cognitive associative learning (Timmann et al., 2010). Here, the right cerebellum and the cerebellar vermis (along with core language and cognitive frontoparietal networks) were more active when unknown Basque words were learned to be associated with known English words than when known associations were processed. Activation in Crus II related to associative learning is in line with the role of the cerebellum in cognitive associative learning (Balsters & Ramnani, 2011). From the lexical learning task used we cannot tell which aspects of these words were associated. This learned association may have been semantic (the meaning of the word was learnt), or it may have been phonological (the sounds of both words were learnt), or it may have been merely orthographic (the written forms of both words were associated). It is likely that a combination of these representations were encoded, and this would be consistent with comparison of the areas active during vocabulary learning and the activation patterns of the various matching tasks in Chapter 5, which show a strong degree of overlap with the semantic and phonological matching tasks. However, we can exclude that a motor response was associated with a new word, as the required response varied from trial to trial. Whatever the precise nature of the associations, the presence of the Basque word was associated with the English word. These results implicate the cerebellum in lexical learning, and might underpin the semantic predictions discussed above.

Co-activation of the inferior frontal gyrus, notably left BA47 and the anterior insula, was striking throughout the fMRI experiments in Chapters 4 and 5. In Chapter 4, left BA47 was found to be functionally connected with the right posterolateral cerebellum, as well as other language areas. Moreover, the cerebellar connectivity changes observed after learning were present in areas functionally connected with left BA47, but not with left BA44 or BA45. In Chapter 5, the right cerebellum and left ventral inferior frontal cortex were active in all matching tasks, and in more active when processing predictive sentences than non-predictive sentences. Indeed, the left anterior insula and right posterolateral cerebellum have been found to be engaged in similar tasks, but are typically associated with over speech and articulation (Ackermann & Riecker, 2004; Riecker et al., 2005). However, the absence of overt speech in any of the contrasts used in Chapter 4 and 5 seems at odds with that characterisation. It is possible that these regions encode inner speech or else that they carry phonological information.

6.4. FUTURE DIRECTIONS

The findings presented here indicate a number of directions for future research. A first avenue for further investigation could be to use TMS or transcranial direct current stimulation (tDCS) to assess the contribution of other brain areas in linguistic prediction.

Specifically, it would be useful to apply rTMS to areas such as left inferior frontal gyrus, left middle temporal gyrus, and left angular gyrus in a visual world paradigm. This could elucidate the specific contribution of each of these areas to online linguistic prediction.

Second, future experiments could aim to differentiate predictions based on phonological, semantic and syntactic information. Some patient and neurostimulation research suggests that certain linguistic associations are governed by the cerebellum (e.g. phonological associations, semantic phrasal associations) but others are not (e.g. semantic categorical associations; Argyropoulos & Muggleton, 2013; Leggio, Silveri, Petrosini, & Molinari, 2000). This would result in the differential recruitment of the cerebellum in different types of predictive tasks.

Another interesting avenue for further investigation might be the relation between the N400 response and cerebellar-based linguistic prediction. The N400 component is inversely related to predictability, with larger N400 amplitudes indicating larger deviations from the expected. The violation of a lexical forward model prediction has been shown to elicit N400 responses (Hosemann et al., 2013). If such a lexical forward model is generated by the cerebellum, the cerebellum could be part of the network that underlies the N400. Such a link has been reported in a non-linguistic paradigm, where an N400 response was reported in expert basketball players who observed a rule violation. The N400 response was linked to activity in fronto-parietal networks, higher-order visual cortex and the cerebellum (Proverbio, Crotti, Manfredi, Adorni, & Zani, 2012). It would be interesting to see whether right posterolateral areas of the cerebellum are part of the network that gives rise to the N400 response, for example in response to a linguistic prediction error. Currently the origins of the N400 are unclear, with the component usually located over centro-parietal regions with a slight right-ward bias. It is thought to be governed by a distributed network of semantic regions (Lau et al., 2008). If the cerebellum truly is engaged in predictive language processing, there should be a close link between cerebellar error processing and modulation of the N400 component.

In the fMRI studies in Chapters 4 and 5, the cerebellar vermis was identified in cognitive contrasts. Interestingly, when comparing activation patterns between visual, semantic and phonological matching tasks, tasks where visual features were more important (visual and semantic tasks) had larger vermal and paravermal contribution and tasks where phonological processing was important had larger right posterolateral contributions. Therefore, it would be interesting to see whether this posterior vermis activity evoked during linguistic prediction is modality-specific. For example, it would be interesting to see whether a vocabulary learning task using auditory stimulus would evoke the same response in the vermis.

Finally, and most importantly, further research could aim to determine whether forward models underlie the cerebellar contribution to linguistic prediction. The empirical data presented in this thesis indicate that the right cerebellum is engaged when a linguistic prediction is made. The prediction of an upcoming word is a complex process which likely consists of several phases which engage different brain areas. It is not clear where exactly in this process the right cerebellum contributes. The fact that right cerebellar activity was found using both spoken (in the visual world paradigm) and written language (in the prediction task in Chapter 5), argues against a mere sensory-based prediction. Here, a framework outlined by Pickering and Garrod (2013) was used as theoretical backdrop for the experiments performed, with the specification that the cerebellum performs the proposed forward model predictions. However, this framework remains largely untested. Further research could aim to isolate different components of this model and to determine which brain regions interact to achieve prediction in language comprehension.

6.5. CONCLUSIONS

This thesis addressed the role of the right posterolateral cerebellum in receptive language processing, specifically in linguistic prediction and the acquisition of a new lexicon. Throughout this work, it is apparent that the cerebellum plays a role in language processing. Neurostimulation and neuroimaging results indicate that the right posterolateral cerebellum has a specific role in the online prediction of upcoming sentence content, and neuroimaging evidence indicates that the cerebellum is involved when learning linguistic associations. Overall, the findings are consistent with a fundamentally predictive cerebellar role which spans motor and nonmotor territories, but additional studies remain to be done to test this theory comprehensively.

APPENDICES

APPENDIX 1: STIMULI USED IN THE VISUAL WORLD TASK

			CONTROL	PREDICTION		TARGET	DISTRACTERS		
The	boy	will	move	eat	the	cake.	toy car	hat	ball
The	woman	will	try	drink	the	wine.	cake	chair	celery
The	woman	will	touch	bathe	the	baby.	plant	kettle	nail
The	boy	will	throw	bounce	the	ball.	paper plane	acorns	match
The	man	will	draw	climb	the	mountain.	deer	cactus	moon
The	woman	will	wash	fry	the	mushrooms.	coat	baby	jug
The	woman	will	check	inject	the	child.	microscope	TV	letter
The	woman	will	dust	play	the	piano.	book	desk	telephone
The	woman	will	shut	read	the	book.	door	window	bag
The	man	will	notice	repair	the	washing machine.	child	dog	lolly
The	girl	will	kick	ring	the	bell.	drum	bricks	duck
The	man	will	watch	sail	the	boat.	mountain	bird	car
The	man	will	collect	smoke	the	cigarette.	diary	briefcase	glasses
The	boy	will	feed	grow	the	plant.	clown	hen	dog
The	man	will	forget	wear	the	hat.	sweet	wine	wallet
The	boy	will	stroke	ride	the	horse.	hair	toy bear	hand
The	woman	will	sample	cook	the	chicken.	lipstick	ice cream	perfume
The	man	will	admire	drive	the	car.	church	watch	piano
The	woman	will	clean	boil	the	kettle.	table	plate	washing machine
The	boy	will	pass	smash	the	plate.	cushion	chicken	balloon
The	man	will	buy	chew	the	sweet.	carrot	car	cigarette
The	man	will	fetch	light	the	match.	milk	pepper	remote
The	woman	will	ignore	kiss	the	man.	radio	cooker	chicken
The	girl	will	steal	lick	the	lolly.	book	ball	toy bear
The	woman	will	break	sharpen	the	pencil.	bottle	telephone	computer
The	woman	will	polish	cut	the	nail.	car	glass	bell
The	man	will	smell	plant	the	flower.	cheese	candle	perfume
The	boy	will	avoid	taste	the	celery.	fire	snake	man
The	man	will	carry	fasten	the	coat.	guitar	pencil	mushrooms
The	girl	will	receive	write	the	letter.	medal	flower	parcel
The	boy	will	spot	chop	the	carrot.	horse	motorbike	owl
The	girl	will	sketch	wipe	the	desk.	plant	fire	boat

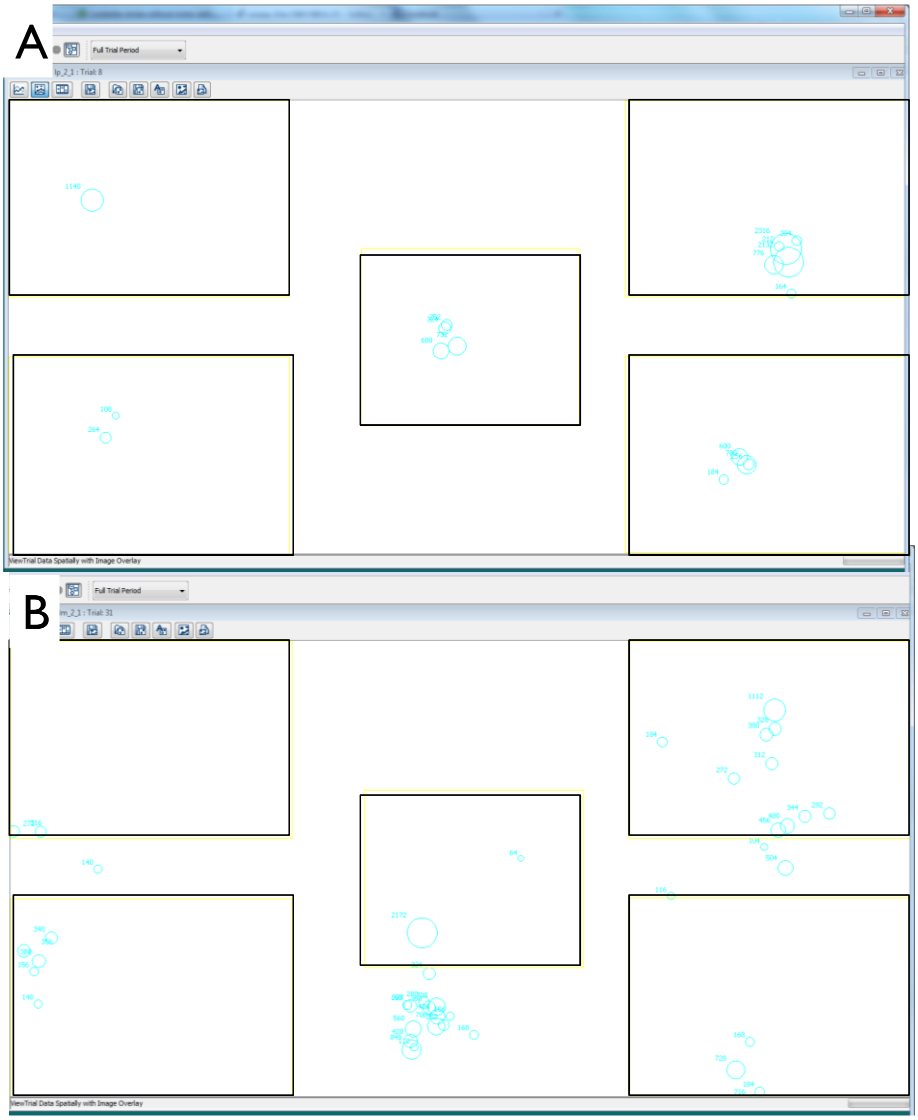

Figure 1. Fixation record of a visual world trial. Fixations indicated in cyan, interest areas in yellow (overlaid with black for clarity) A. A typical trial; fixations largely fall into the interest areas, no systematic deviations. From the fixation density, it is clear that the target was in the upper right-hand corner. B. In this trial, fixations are systematically lower than the interest areas, indicating calibration problems. Here the target is in the upper right-hand corner, which means no target fixations have been lost. The fixation record was moved up.

APPENDIX 3: STIMULI USED IN THE VOCABULARY LEARNING TASK

Basque		Synonym	
Stimulus	Target	Stimulus	Target
laranjak	oranges	glasses	specs
behia	cow	ball	sphere
loreak	flowers	bush	shrub
haurra	baby	knife	scalpel
jantzi	dress	adhesive	glue
hartza	bear	chair	seat
aterki	umbrella	dog	hound
logela	bedroom	field	meadow
gazta	cheese	bag	satchel
baso	forest	truck	lorry
arkatza	pencil	monitor	screen
anaia	daughter	scent	odour
tapiza	rug	money	cash
zorro	wallet	picture	image
arrain	fish	tin	can
horma	wall	cylinder	tube
izarrak	stars	twig	branch
katilua	cup	stream	brook
aita	father	house	home
sagua	mouse	fire	blaze
elurra	snow	author	writer
ogia	bread	woman	lady
otsoa	wolf	sea	ocean
leiho	window	bloke	guy
koilara	spoon	frock	gown

APPENDIX 4: CONJUNCTION ANALYSIS VOCABULARY LEARNING TASK

Table 1. Table of results: conjunction between Basque and Synonym learning task (FWE corrected at P<0.05). If a cluster spans several regions, the total cluster volume is reported and numbered according to the activation strength of the sub-cluster.

Gross anatomical location	Volume (mm3)	T-value	MNI x	coordinate y	z	Cytoarchitectonic region
Frontal						
Left Middle Frontal Gyrus	168732 (10)	9.97	-30	-2	52	BA8
Left Precentral Gyrus	168732 (8)	10.09	-38	-6	66	BA6
Right Middle Frontal Gyrus	2925	7.47	30	2	54	BA8
Parietal						
Left Postcentral Gyrus	168732 (3)	11.78	-46	-34	52	BA2
Left Superior Parietal Lobule	168732 (7)	10.40	-28	-60	52	BA7
Right Superior Parietal Lobule	2664	6.91	30	-58	52	BA39
Right Intraparietal Cortex	432	5.98	48	-30	46	n/a
Occipital						
Left Inferior Occipital Gyrus	168732 (1)	13.85	-36	-82	-8	BA19
Left Fusiform Gyrus	168732 (2)	12.36	-38	-64	-18	BA19/BA37
Left Inferior Occipital Gyrus	168732 (4)	11.73	-20	-96	-6	BA19
Right Middle Occipital Gyrus	909	6.83	32	-70	28	BA19
Temporal						
Left Inferior Temporal Gyrus	168732 (5)	11.29	-42	-42	-18	BA37
Cerebellum						
Right Cerebellum	168732 (6)	11.17	32	-52	-25	Lobule HVI
Right Cerebellum	168732 (9)	10.00	18	-60	-47	Lobule HVIII
Left Cerebellum	801	5.85	-22	-34	-43	Lobule HX
Other subcortical						
Left caudate nucleus	2790	7.60	-14	-8	14	n/a

APPENDIX 5: PREDICTION TASK ITEMS

An additional study was performed in order to make sure that the manipulation of predictability used in this experiment was effective. The items used in the prediction task were therefore used in a web-based sentence completion task. Participants were 43 students at the University of Birmingham which participated in exchange for course credit. One participant had indicated that they had not taken the task seriously, and their data were discarded. All participants were native English speakers. Cloze probability was used as a proxy for predictability. An item's cloze probability is the probability of the item being completed with one particular word. Participants were asked to complete each sentence with the word that came to mind. The frequency of each response was calculated, and the proportional occurrence of the most frequently chosen word for each item (the cloze probability) was compared between conditions.

Cloze probability was higher for the Predictive condition (mean = 0.76, SE = 0.04) than for both the Semi-predictive (mean = 0.58, SE = 0.06) and the Neutral conditions (mean = 0.38, SE = 0.04). Independent samples t-tests between the three conditions showed significant differences between all conditions (Predictive vs. Neutral: $t(58) = 7.54$, $p < 0.001$; Predictive vs. Semi-predictive: $t(46) = 2.80$, $p = 0.007$; Semi-predictive vs. Neutral: $t(46) = 3.04$, $p = 0.004$). These results demonstrate that the predictability manipulation was effective.

Table 2. Items in the Predictive condition.

Predictive Condition Context sentence	Sentence stem	Probe	Answer
Trains were cancelled and Susie had to use the replacement service.	She waited for the	bus	likely
Two months after his move, Matt discovered the local library.	He picked up several	books	likely
Jen's eyesight had been poor since childhood.	That's why she wore	glasses	likely
As a teenager Peter spent hours in front of the mirror.	He spent ages on his	hair	likely
It was Carl's turn to put the children to bed.	He told them a	story	likely
Leigh heard a chirping noise and looked up.	There she saw the	bird	likely
Sonja wanted to avoid a sunburn in this hot weather.	She had brought some	sunscreen	likely
Greg went home for Christmas dinner.	His mum always cooked a	turkey	likely
Carl liked to entertain his friends down the pub.	He told them a	joke	likely
Jen scalded her hand whilst trying to pour the kettle.	She had spilled the	water	likely
Nick had been working for hours on his project.	He really needed a	break	likely
Amy got out of the shower and wanted to dry herself.	She picked up a	towel	likely
Matthew thought he was a good comedian.	He was often telling	jokes	likely
After the marathon Donald was dehydrated.	He quickly drank the	water	likely
Dane was securely wrapping the Christmas presents.	He used lots of	tape	likely
Lee wanted something to melt on his toast.	He had bought some	porridge	unlikely
Caleb needed to chop up some vegetables.	He picked up a	spoon	unlikely
Jo came home and put the kettle on.	She drinks lots of	wine	unlikely
Lyndsey had a wedding coming up so she went shopping.	She bought a nice	cookbook	unlikely
Harry was working on his model aeroplane.	He used lots of	glitter	unlikely
Natasha is scared of eight-legged creatures.	She screamed at the	puppy	unlikely
Sue had been for a walk and her arms were cold.	She put on a	skirt	unlikely
The kids were playing football when Ben heard a loud crash.	He looked at the	clown	unlikely
Andrew was thirsty after hiking all morning.	So he bought a	teddybear	unlikely
Albert caught the lovely smell of the woman as she walked past.	She was wearing a	coverall	unlikely
Nathan regretted moving to a noisy apartment building.	He was kept up by his	goldfish	unlikely
David wanted to change the colours in his bedroom.	He first bought some	pencils	unlikely
Becky was afraid to walk to the other side of the river.	She dreaded crossing the	desert	unlikely
Russel had hurt his hand in the door of the car.	He had trapped his	toes	unlikely
The public was warned to avoid the armed criminal.	He was holding a	pear	unlikely

Table 3. Items in the neutral condition.

Neutral Condition Context sentence	Sentence stem	Probe	Answer
Chris arrived home from work after a busy day.	He took off his	boots	likely
Sue went upstairs and opened her wardrobe.	She quickly put on a	pound	likely
Russel was in a lot of pain and went to the hospital.	He had trapped his	finger	likely
As always Sandra was well-prepared for the summer mountain hike.	She had brought some	sunscreen	likely
Dane was excited about his new crafts project.	He used lots of	tape	likely
Sandra was sitting in the park enjoying the nice weather.	She had brought some	sunscreen	likely
Rosie needed a new wardrobe so she went clothes shopping.	She bought a nice	dress	likely
Lee wanted to have a mid-morning snack.	He had bought some	cheese	likely
Ronald opened his cupboard.	He took out the	bread	likely
Nathan had been sleeping horribly since he moved house.	He was kept up by his	neighbours	likely
Bob had to get up early for a doctor's appointment.	He had pain in his	neck	likely
The weatherman warned people not to go outside this afternoon.	There was a lot of	wind	likely
Lee wanted to have a mid-morning snack.	He had bought some	cheese	likely
Jo came home and made herself a drink.	She drinks a lot of	tea	likely
John noticed a beautiful lady in the hotel lobby.	She was wearing a	perfume	likely
Ben was in the kitchen making dinner for his family.	He prepared a nice	speech	unlikely
Greg hurt himself when he was in the kitchen this morning.	He spilled some of the	toast	unlikely
Laura came out of the station and looked up.	There she saw the	shrub	unlikely
Andrew walked into the busy corner shop.	There he bought a	racecar	unlikely
Caleb needed to prepare a three course meal.	He picked up a	todler	unlikely
Jen liked to look good at the office.	That's why she wore	rags	unlikely
Luke was reading a football magazine in the garden.	He looked at the	soldier	unlikely
David had taken a day off to work on his house.	But first he bought	bread	unlikely
It was a sunny Saturday and Becky went out for a walk.	She dreaded crossing the	ocean	unlikely
Douglas opened the fridge and took out the bottle.	He quickly drank the	tea	unlikely
Greg went home to visit his family.	His mum always cooked a	speech	unlikely
After a long argument, Heather gave up with Jason.	He remained the only	snorkler	unlikely
Harry was working on a new art project.	He used lots of	water	unlikely
Kyle got up very early in the morning.	He liked to have	arguments	unlikely
Mark enjoyed his job because he loved being outside.	He loved being by the	water	unlikely

Table 4. Items in the semi-predictive condition. These items were not incorporated in the imaging analysis.

Semi-predictive condition			
Context sentence	Sentence stem	Probe	Answer
After two busy weeks, Will finally had an evening off.	He played his favourite	music	likely
Ben is a good chef, but his pasta was very dry.	He prepared a nice	sauce	likely
Bob arrived home after walking in the muddy field.	He took off his	boots	likely
Kyle put some bread under the glowing grill.	He liked to have	toast	likely
Bob had a bit of a whiplash after the car accident.	He had hurt his	neck	likely
Andrew has always been a fearful person.	He screamed at the	spider	likely
Peter annoyed his sister when he was younger.	He spent ages on his	hair	likely
It was Carl's turn to put the children to bed.	He told them a	story	likely
Jason decided never to give up his unmarried life.	He remained the only	bachelor	likely
When Paul moved out and gave away all his stuff, Matt was glad.	He picked up several	books	likely
The baker opened his oven.	He took out the	brick	unlikely
Zoe was warned not to go outside during a hurricane.	There was lots of	sun	unlikely
It was Jodie's turn to go get snacks at the bar.	So she bought some	trousers	unlikely
Roger saw a strange man hiding in the forest.	He was holding a	dolphin	unlikely
It had been a long day's work and Susie was on her way home.	She waited for the	carnaval	unlikely
Matt found the lounge in a horrible mess after the party.	He picked up several	books	unlikely
Frank enjoyed his job as a lifeguard by the sea.	He loved being by the	paintbrush	unlikely
When she got home, Claire rummaged through her bag for 10 minutes.	She was looking for her	cat	unlikely

Table 5. Context sentences were matched for length between the conditions.

	N Syllables		N words	
	Mean	SE	Mean	SE
Predictive	11.95	2.01	8.62	1.77
Neutral	12.23	2.44	8.88	1.61
Semi-predictive	12.33	2.74	8.78	2.28

APPENDIX 6: ITEMS MATCHING TASKS

ਮੁਕਤਾਰ	ਖਿੜਕੀ
ਟੈਲੀਫ਼ੋਨ	ਕੋਕੁਰਸੀ
ਲਮਾਰੀ	ਪੈਂਹਾਮੇਜ਼
ਕਕੋਮੀਜ਼	ਜੁਰਾਟਬ
ਕੰਮਪਿਟ	ਅਫ਼ਰਿੱਜ

Figure 2: Stimuli for the visual matching task.

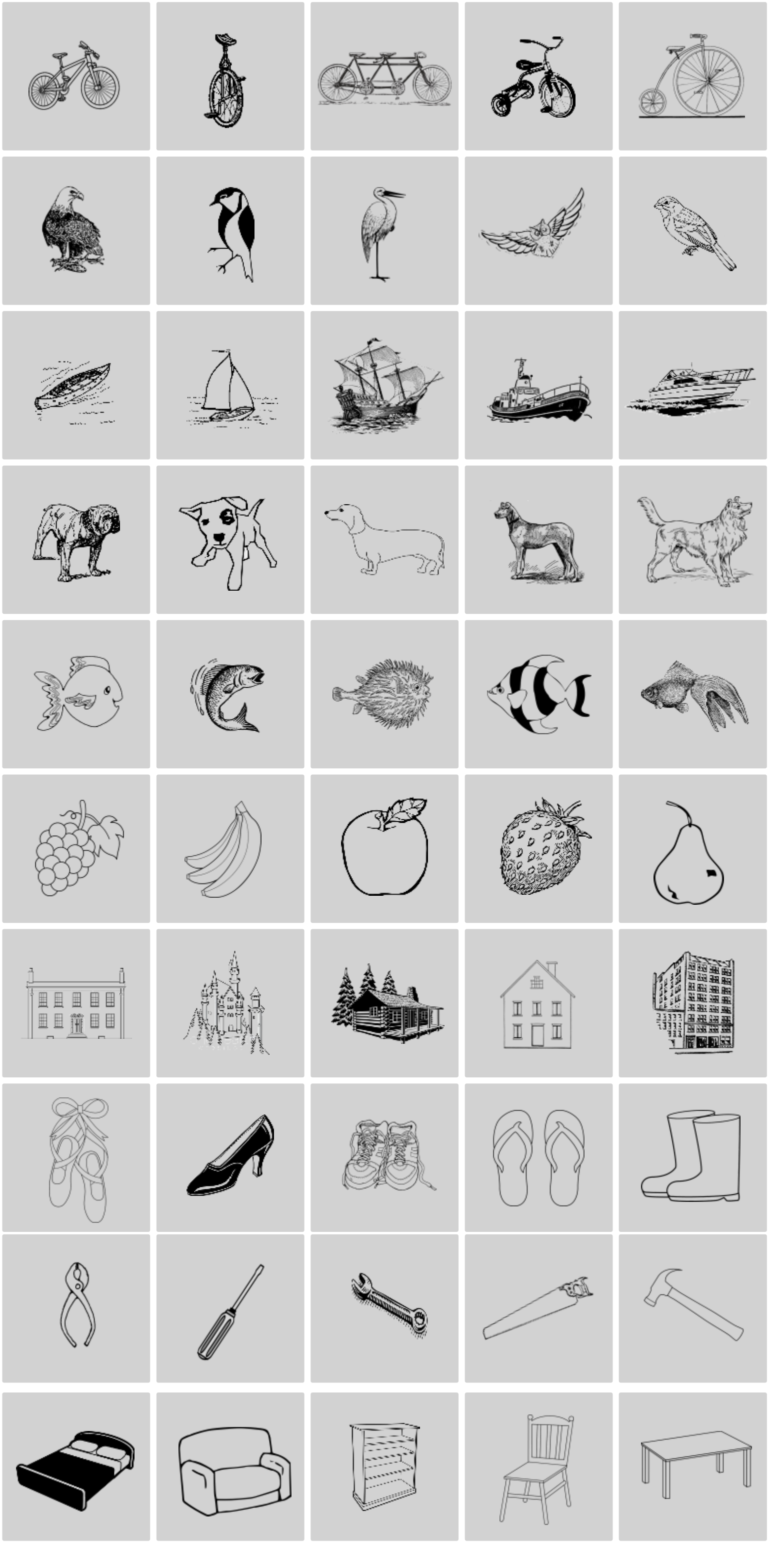

Figure 3. Stimuli for the semantic matching task.

Table 6: Stimuli presented in the phonological 1back task.

Block	Presented word in 1back condition									
Block 1	scoff	promo	slime	nurse	floor	score	prude	agent	doors	boars
Block 2	error	feist	shark	puree	decay	block	wharf	beers	tears	royal
Block 3	psych	spike	psalm	lingo	melon	lobby	merge	surge	kayak	debts
Block 4	lousy	skull	grass	honey	sunny	vocal	micro	drugs	towel	scowl
Block 5	kneel	steal	joint	flick	leach	guest	chest	unity	widow	irony
Block 6	rehab	spark	under	float	quote	otter	throw	dough	queue	hobby
Block 7	poppy	lurch	birch	alibi	cobra	sails	wales	mercy	arson	mafia
Block 8	learn	churn	germs	japan	stock	knack	tooth	tunes	small	crawl
Block 9	scone	sync	wink	attic	ankle	adder	start	heart	gloom	usual
Block 10	frock	novel	label	table	lotus	smile	aisle	idiot	odour	solve
Block 11	laser	razor	short	enrol	organ	toxic	forum	crisp	quite	sight
Block 12	layer	mayor	brick	alien	cigar	swamp	wraps	lapse	udder	cheek
Block 13	peace	niece	rolls	pixel	spite	night	opium	intro	stone	least
Block 14	rapid	mango	flake	hippo	still	quill	while	enemy	while	style
Block 15	glass	notch	glove	shove	drink	timer	quick	slick	gravy	actor

Table 7: Stimuli presented in the phonological 0back task.

Block	Presented word in 0back condition									
Block 1	robot	press	guide	bicep	learn	ninja	mango	rifle	salsa	press
Block 2	plasm	order	press	vinyl	hedge	older	press	peach	zebra	depth
Block 3	press	still	jerks	wires	jewel	atlas	press	photo	offer	peers
Block 4	hiker	dream	shawl	ferry	ocean	press	acres	older	yeast	press
Block 5	pizza	press	tango	swamp	extra	score	grant	press	trial	whale
Block 6	hotel	wreck	press	monks	proof	coins	nudge	mouse	jokes	press
Block 7	loser	quark	nanny	leafy	press	sleep	ratio	youth	press	human
Block 8	input	press	onion	imply	spoon	press	email	quirk	watch	flask
Block 9	sting	value	icing	thorn	curry	press	years	point	orbit	press
Block 10	froth	press	paste	image	noble	river	press	biker	dizzy	judge
Block 11	press	tulip	drape	gloom	panic	enjoy	trend	press	oasis	dread
Block 12	mossy	press	baron	class	zones	press	merit	cobra	fires	voice
Block 13	essay	lease	roast	press	saint	skirt	banjo	humor	press	pawns
Block 14	close	regal	press	vowel	think	apple	rigid	fewer	karma	press
Block 15	limit	press	horse	berry	exact	ivory	panda	press	daily	blast

APPENDIX 7: TABLES OF RESULTS CHAPTER 5

Table 8. Table of results: Predictive stem > Neutral stem contrast (uncorrected at p<0.001).

Gross anatomical location	Volume	T-value	MNI	coordinate		Cytoarchitectonic
	(mm3)		x	y	z	region
Frontal						
Left Supplementary Motor Area	3420	4.22	-8	22	64	BA6/BA8
Left Inferior Frontal Gyrus/insula	3042	4.06	-36	22	-4	BA44 / BA45/ n/a
Left Inferior Frontal Gyrus	1665	3.83	-42	54	-14	BA47
Left Precentral Gyrus	603	3.43	-54	12	42	BA4
Left Anterior Insula	225	3.42	-48	14	14	n/a
Right Pre-SMA	1809	3.91	4	38	40	BA6
Right Middle Frontal Gyrus	1044	3.6	46	24	38	BA44
Right Frontal Operculum	945	3.70	34	26	-4	n/a
Parietal						
Left Superior Parietal Lobule	6606	4.49	-50	-56	58	BA39
Right Inferior Parietal Lobule	315	3.33	54	-56	50	BA39
Temporal						
Right Middle Temporal Gyrus	936	4.11	56	-26	-10	BA20
Right Middle Temporal Gyrus	576	3.76	68	-40	-12	BA20
Left Middle Temporal Gyrus	567	3.69	-62	-34	-2	BA21
Cerebellum						
Right Cerebellum	2907	3.88	12	-78	-28	Lobule VII Crus I
Right Cerebellum	270	3.44	28	-84	-46	Lobule HVII Crus II
Right Cerebellum	252	3.55	36	-72	-54	Lobule HVII Crus II
Left Cerebellum	567	3.51	-14	-82	-28	Lobule VII Crus I
Other subcortical structures						
Right caudate nucleus	324	3.43	14	-6	20	n/a

Table 9. Table of results: Semantic 1back > Semantic 0back (FWE corrected at P<0.05). If a cluster spans several regions, the total cluster volume is reported and numbered according to the activation strength of the sub-cluster.

Gross anatomical location	Volume (mm3)	T-value	MNI x	coordinate y	z	Cytoarchitectonic region
Frontal						
Left SMA	4482 (1)	9.66	-6	10	48	BA6
Left Precentral Gyrus	4482 (2)	8.88	-40	10	30	BA44
Left Precentral Gyrus	4482 (3)	8.35	-48	-2	42	BA6
RightPrecentral Gyrus	184	6.85	50	6	36	
Right Middle Frontal Gyrus	136	6.26	50	32	30	BA44
Insula						
Left Insula Lobe	656	9.74	-32	26	2	n/a
Left Rolandic Operculum	34	5.61	-48	8	2	n/a
Right Insula Lobe	245	6.78	32	28	4	n/a
Parietal						
Left Supramarginal Gyrus	2127 (1)	7.69	-34	-54	54	BA40
Left Superior Parietal Lobule	2127 (2)	7.56	-26	-60	50	BA7
Right Inferior Parietal Lobule	996	8.23	34	-56	50	BA7
Temporal						
Right Inferior Temporal Gyrus	6389 (1)	9.00	34	-56	-24	BA37
Left Inferior Temporal Gyrus	3694	8.74	-40	-48	-18	BA37
Right Middle Temporal Gyrus	6389 (3)	7.80	50	-74	-2	BA19
Cerebellum						
Right Cerebellum	6389 (2)	8.06	34	-68	-50	Lobule HVII Crus II
Cerebellar Vermis	6389 (4)	6.57	6	-82	-36	Lobule VII vermis
Other subcortical						
Left Thalamus	187	6.38	-16	-30	2	n/a
Right Caudate Nucleus	40	5.56	20	-20	24	n/a
Left Hippocampus	94	5.79	8	-30	-4	n/a

Table 10. Table of results: Phonological 1back > Phonological 0back (FWE corrected at $p<0.05$).

Gross anatomical location	Volume (mm3)	T-value	MNI x	coordinate y	z	Cytoarchitectonic region
Frontal						
Left Inferior Frontal Gyrus	12114	9.54	-44	4	24	BA44
Left Inferior Frontal Gyrus / insula	8838	6.90	-28	28	2	BA45/BA47/ n/a
Left Supplementary Motor Area	3024	7.12	-6	12	58	BA6
Parietal						
Left Supramrginal Gyrus	2340	6.66	-48	-38	46	BA40
Left Superior Parietal Lobule	657	5.52	-30	-56	52	BA7
Temporal						
Left Middle Temporal Gyrus	2115	6.76	-48	-64	-2	BA37
Left Inferior Temporal Gyrus	279	5.49	-48	-50	-14	BA20
Cerebellum						
Right Cerebellum	4257	8.23	28	-68	-48	Lobule HVII Crus II
Right Cerebellum	864	6.22	26	-64	-24	Lobule HVI

Table 11. Table of results: Visual 1back > Visual 0back (FWE corrected at p<0.05). If a cluster spans several regions, the total cluster volume is reported and numbered according to the activation strength of the sub-cluster.

Gross anatomical location	Volume (mm3)	T-value	MNI coordinate			Cytoarchitectonic region
			x	y	z	
Frontal						
Left SMA	466	7.22	-6	10	52	BA6
Left Superior Frontal Gyrus	390	7.68	-28	-6	62	BA6
Right Precentral Gyrus	326	7.59	50	6	36	BA44 / BA6
Right Precentral Sulcus	175	6.16	26	-6	52	BA6
Left Precentral Gyrus	174	6.22	-46	2	32	BA44 / BA6
Left Inferior Frontal Gyrus	109	6.16	-32	22	4	BA47
Right Middle Frontal Gyrus	49	5.52	50	30	32	BA45
Insula						
Right Anterior Insula	233	6.51	32	22	4	n/a
Left Anterior Insula	233	6.51	-32	22	4	n/a
Parietal						
Right SupraMarginal Gyrus	3591 (1)	9.10	36	-50	50	BA40
Right Superior Parietal Lobule	3591 (2)	8.34	30	-70	36	BA7
Left Superior Parietal Lobule	2573 (1)	8.56	-22	-68	60	BA7
Left Inferior Parietal Lobule	2573 (2)	7.57	-36	-44	46	BA40
Occipital						
Left Middle Occipital Gyrus	609	8.06	-52	-68	-2	BA19
Temporal						
Right Inferior Temporal Gyrus	490	7.22	58	-58	-8	BA37
Cerebellum						
Left cerebellum	335	7.88	-28	-74	-52	Lobule HVII
Left Cerebellum	236	6.31	-6	-76	-22	Lobule VI (vermis)
Left Cerebellum	164	6.34	-26	-62	-30	Lobule HVI
Right Cerebellum	22	5.28	26	-76	-52	Lobule HVII

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