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THE CONTRIBUTION OF THE CEREBELLUM TO COGNITION:

AN fMRI STUDY IN VERBAL WORKING MEMORY

A Thesis in

Psychology

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ABSTRACT

Two decades of research support the notion that the cerebellum contributes to cognitive processes such as executive functions and working memory in addition to motor functions. A number of distinct literatures now provide a framework for investigating the hypothesis that the cerebellum contributes to cognition and specifically working memory. First reviewed is evidence from paleontological, comparative and psychological studies demonstrating that the earliest cerebellum-like structures evolved in conjunction with complex senses and presently maintain a role in a wide range of sensory and other nonmotor processes across species. Neuroanatomical studies have revealed several that cortico-cerebellar structural loops integrate an extended network between the frontal and parietal cortices and the cerebellum and findings in modern human development reveal a tight functional relationship between the cerebellum and dorsolateral prefrontal cortex. Studies of executive functions and working memory in neuropsychology and neuroimaging found broad ranging involvement of the cerebellum in many higher order tasks, with pronounced involvement in verbal working memory. These literatures show that the cerebellum has a complex and nuanced functional relationship to the neocortex, but its role in working memory remains poorly explained. For example, the cerebellum's influence on task performance has not been examined in the context of a distributed functional network during a continuous working memory task. It is a goal of the current thesis to review specific evidence supplied by multiple domains of inquiry that provide a framework for understanding the cerebellum's role in modern human cognition, especially in executive functions and verbal working memory. Based upon this review, the current study investigated the contribution of the cerebellum to performance in verbal working memory and

the relationships between activity in the cerebellum to several cortical regions in the context of a continuous verbal working memory task, the n-back, using functional magnetic resonance imaging and functional connectivity analyses. Reaction time was found to decrease during performance of both verbal working memory tasks. In general, the BOLD signal in the cerebellum was highly related to that in the contralateral prefrontal and parietal cortices. Unified structural equation modeling revealed that cerebellar influences on motor and cognitive regions were equivalent with the exception of the early and late portions of the 2-back task, during which the left cerebellum demonstrated high connectivity with the right prefrontal and parietal cortices. These findings suggest that the cerebellum is highly interactive with cognitive regions during verbal working memory, including regions thought to be involved in cognitive control.

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Chapter 1

Introduction

The cerebellum is traditionally thought to be a brain region involved in coordinating human motor activity, but findings from multiple lines of evidence now suggest an important role for the cerebellum in nonmotor functions. A paper by Leiner, Leiner & Dow (1986) proposed a then-controversial hypothesis that the cerebellar cortex may be involved in "skilled mental performance" in addition to the cerebellum's role in skilled motor performance. This hypothesis suggested that the cerebellum is not only critical to acquiring and maintaining fine motor skills, but that it supports the coordination of our thought processes. Thus, while the neocortex is traditionally thought to support many of our higher ordered cognitive abilities, the cerebellum may be responsible for ensuring that these processes run smoothly and efficiently during our daily functioning. Since the initial proposal by Leiner and colleagues, two decades of research support the notion that the cerebellum's role extends beyond motor functioning to various cognitive processes, including evolutionarily recent and complex functions such as executive functions and working memory, and most reliably, verbal working memory. Working memory is a cognitive function that temporarily stores and manipulates a limited amount of information for complex cognitive tasks (see Baddeley, 1992). The most direct work on the cerebellum's contribution to cognition has been conducted in the domain of verbal working memory, and the current thesis will extend this work using modern neuroimaging and functional connectivity modeling.

Thesis Goals

There are several goals in this thesis. First reviewed is evidence from evolutionary, and comparative studies that found that the cerebellum evolved as a sensory region that later expanded substantially during rapid gains in human cognitive ability. Second, neuroanatomical studies in modern humans that revealed the cerebellum's relationship with regions known to be critical to working memory are reviewed. Third, studies of normal and abnormal cognitive development that revealed interplay between the prefrontal cortex and cerebellum during cognitive development are discussed. Fourth, findings from functional neuroimaging revealing the connectivity between the cerebellum and working memory regions during resting conditions are reviewed to characterize cerebellar functional circuits. Taken together, these studies provided a framework for understanding the cerebellum's role in a distributed working memory system that involves a number of cortical regions.

Operating on these findings, many studies of executive functions and working memory in healthy and clinical samples using traditional neuropsychological and neuroimaging techniques found broad ranging involvement of the cerebellum in many higher order tasks, with pronounced involvement in verbal working memory (cf. Stoodley & Schmahmann, 2009 for a meta-analysis and review; see also Chen & Desmond, 2004, Desmond et al., 1997, Desmond et al., 2005, Honey et al., 2000, Kirschen et al., 2005, & Ravizza et al., 2006,). Subregions of the cerebellum are known to be correlated with reaction time and to be responsive to practice during verbal working memory (Honey et al., 2005, Desmond et al., 2005, & Kirschen et al., 2005); however, the cerebellum's direct influence on other regions and

performance has not been examined in the context of a distributed functional network during a task. The logic for these recent efforts in neuroimaging and the current study is that if the cerebellum's relationship with prefrontal brain regions indeed supports cognitive performance, it should bear relationships with performance and neocortical function during cognitive tasks.

It is a goal of the current thesis to review specific evidence from previous studies that provide a framework for understanding the cerebellum's role in modern human cognition, especially in executive functions and verbal working memory. Then, a study is proposed to investigate the contribution of the cerebellum to performance in verbal working memory and the relationships between activity in the cerebellum to several cortical regions in the context of a continuous verbal working memory task, the n-back, using functional magnetic resonance imaging and functional connectivity analyses.

The Cerebellum, Evolution and Comparative Studies

To provide a context for the role the cerebellum in cognition, this section discusses evidence that the cerebellum evolved in tight conjunction with sensory regions and differentially expanded in conjunction with the frontal cortex in recent human evolution. The cerebellum evolved in the earliest vertebrates and has been retained through evolution over the past 500 million years, suggesting an evolutionarily consistent and important role (Bell, Han & Sawtell; Paulin, 2005). Despite its classical definition as a structure supporting motor functions, the cerebellum likely evolved as one of a family of structures responsible for processing vestibular sense, electrosense, and lateral line mechanosense in early predatory

aquatic vertebrates (Paulin, 2005). Bell, Han & Sawtell (2008) discussed the modern family of brain structures that evolved from early "cerebellum-like" forms and indicated that they show remarkable similarity to one another and to the cerebellum neuroanatomically and functionally.

The various cerebellum-like structures discussed have apparent roles in predicting the sensory outcomes of actions in the form of a "forward model" (Kawato, 2003). Kawato demonstrated evidence that the cerebellum compares sensory information resulting from motor actions with a forward model of expected sensory outcomes. The cerebellum then modulates future motor activity based upon matches or mismatches in the expected model Thus, the cerebellum and related structures have evolved to solve a number of sensory processing demands between craniate species that informed directed movements, and maintain an important sensory function today (for an in depth discussion of these hypotheses and cerebellum-like structures, see Bell, Han, & Sawtell, 2008).

Other authors cited evidence of recent expansion of the size and role of the cerebellum in primate species. Similar to Kawato's model, Rilling and Insel (1998) proposed that an enlarged cerebellum confers an ability to modify current movements based upon anticipated future movements. They extended this hypothesis to include an increased capacity for "cognitive representation." Rilling and Insel proposed that higher cerebellum to whole brain volume ratios across primate species may partially contribute to the cerebellum's capacity for cognitive representation (1998).

However, these observations of differences in cerebellar size across species did not provide evidence for the precise mechanisms of cerebellar action or how it may facilitate these operations. One recent study using diffusion tensor imaging found that the prefrontal inputs to the cerebellum in humans are much stronger than in other primates (Ramnani et al., 2006), which supports a case for co-evolution of the neocerebellum and the cognitively important prefrontal cortex in humans.

A human-specific evolutionary examination of cerebellum size may help to understand the role of the cerebellum in modern humans. Weaver (2005) presented data specific to human cerebellar evolution that may offer qualitative insights into possible roles for the cerebellum in modern humans. Data from several different human ancestor species since *australopithecus afarensis* revealed that the cerebellar to whole brain volume ratio of human ancestors was smaller compared to that of modern humans. This trend continued through Cro-Magnon man, in which the cerebellum was the smallest relative to the cerebrum. However, the pattern reversed in recent and modern humans in which the cerebellum was the largest in proportion to the cerebrum (Weaver, 2005). The raw volume of the cerebellum increased steadily after australopithecus, and the small cerebellum volume to cerebrum volume ratio through Cro-Magnon man can be explained by a relatively more rapid cerebral expansion from australopithecus until early archaic homo sapiens. The significant increase in cerebellar volume relative to the cerebrum in recent and modern humans can be explained by both a small decrease in cerebral volume since archaic humans and a large increase in cerebellar volume on a timeline that coincided with pronounced increases in human cognitive abilities.

In light of this trend, Weaver (2005) proposed a three stage model of the evolution of the cerebellum in humans that represents functional shifts in the cerebro-cerebellar networks (see Table 1 for an overview of this model).

Table 1: Weaver's (2005) model of cerebellar development

Stage	Years Ago	Cultural Change	Brain Change
Stage 1	5 million-126,000 years ago	•Increased tool use •Cultural Intensification	•Progressive increase in CB volume •Relatively faster increase in neocorticalvolume
Stage 2	126,000-11,700 years ago	•Increased tool and object use and variety •Increased complex learned behaviors •Increased long-distance transportation of materials	•CB volume remains constant •Continued expansion of NC
Stage 3	11,700 years ago-present	•Increases in technological, social, and cultural complexity	CB volume increases rapidly NC volume decreases slightly

CB: cerebellum, NC: neocortex

Stage 1 (Pliocene, Early to Middle Pleistocene) involved an intensification of the use of stone tools in foraging and food processing that capitalized on the existing cortico-cerebellar relationships in human ancestors, particularly parietal-cerebellar tracts presumed to have been involved in tool making and use that are currently involved in a wide range of memory, working memory, goal-directed, and spatial functions. These cognitive innovations were subserved by a steady increase in cerebellar volume and a relatively faster increase in neocortical volume. Stage 2 saw a leveling of cerebellar volume during the Late Pleistocene and continuing increase in the neocortex that paralleled increases in the variety of objects and sets of objects, complex learned behaviors, pyrotechnology, and long-distance transportations of raw materials. Stage 3 occurred in the terminal Pleistocene and Holocene during continued increases in cultural and social complexity that saw slight decreases in cerebral volume and a rapid expansion of the

cerebellum. In agreement with Kien's (1990) proposal that gross brain size may place upper limits on processing efficiency, Weaver (2005) proposed that this cerebellar expansion supplemented neocortical networking by "providing the infrastructure for rule-based, procedural organization of sequential operations across many cognitive domains in response to cultural pressures." Throughout the evolution of the human cerebellum, the primary regions of cerebellar expansion were the neocerebellum and the dentate nucleus, which are known to have connections with the evolutionarily recent and cognitively critical human prefrontal cortex (Diamond, 2000) as well as every other major anatomical division of the neocortex (Weaver, 2005). Thus, during the course of human evolution, the cerebellum may have retained part of its evolutionarily implied role in sensory processing as well as a varied and novel set of nonmotor contributions in humans. It should be noted that the aforementioned account of cerebellar evolution and presumed functions is retrospective and largely inferred based upon the fossil record. Thus, the specific neurocircuitry and involvement of the cerebellum in neural systems across evolution may differ from previous authors' interpretation of findings. In order to understand modern features of cerebellar motor and cognitive functions, contemporary exploratory and experimental studies provided starting points for understanding the modern cerebellum's role. Importantly, findings in modern human brain anatomy suggested that the interplay between the cerebellum and neocortical regions may facilitate particular cognitive operations in addition to traditionally understood motor functions. These findings and some of their implications for cognitive functioning are discussed in the following section.

Anatomical Substrates Supporting Cognition

Recent work has directly examined the connections between the cerebellum and regions known to be involved in complex cognitive abilities known as executive functions (see Logan, 1985; Norman & Shallice, 1986; and Smith & Jonides, 1999 for specific models of executive functions) and specifically working memory. The circuits that the cerebellum forms with the neocortex and the cerebellum's microcircuitry provide an important context for considering about the cerebellum's role in working memory.

In modern adult humans, the cerebellum receives input fibers via the pons from the temporal, parietal, occipital and frontal lobes, and projects fibers to each of these regions via the thalamus, forming a number of closed loops with neocortical regions within the central nervous system (Leiner, Leiner, & Dow, 1986; Middleton & Strick, 2000; Weaver, 2005). Input fibers from the frontal gyrus originate in primary and supplementary motor areas (Brodmann's areas 6 and 8, respectively) as well as a number of lateral prefrontal regions (Brodmann's areas 8, 9, 10, 44 and 45) (Bellebaum, 2007; Middleton & Strick, 2000; Weaver, 2005). These frontal inputs synapse on cell bodies within the pons, at which point the fibers decussate and enter the cerebellum via the middle cerebellar peduncle and synapse on the dentate nucleus. Frontal fibers tend to synapse more medially and parietal and temporal fibers synapse more laterally within the pons (see Figure 1; Brodal, 1978; Leichnetz et al., 1984; Schmahmann, 1996; Schmahmann and Pandya, 1997a,b; Wiesendanger et al., 1979).

Figure 1: Schematic representation of primary input and output streams of the cerebellum; note inputs relay through the pons and outputs relay through the thalamus.
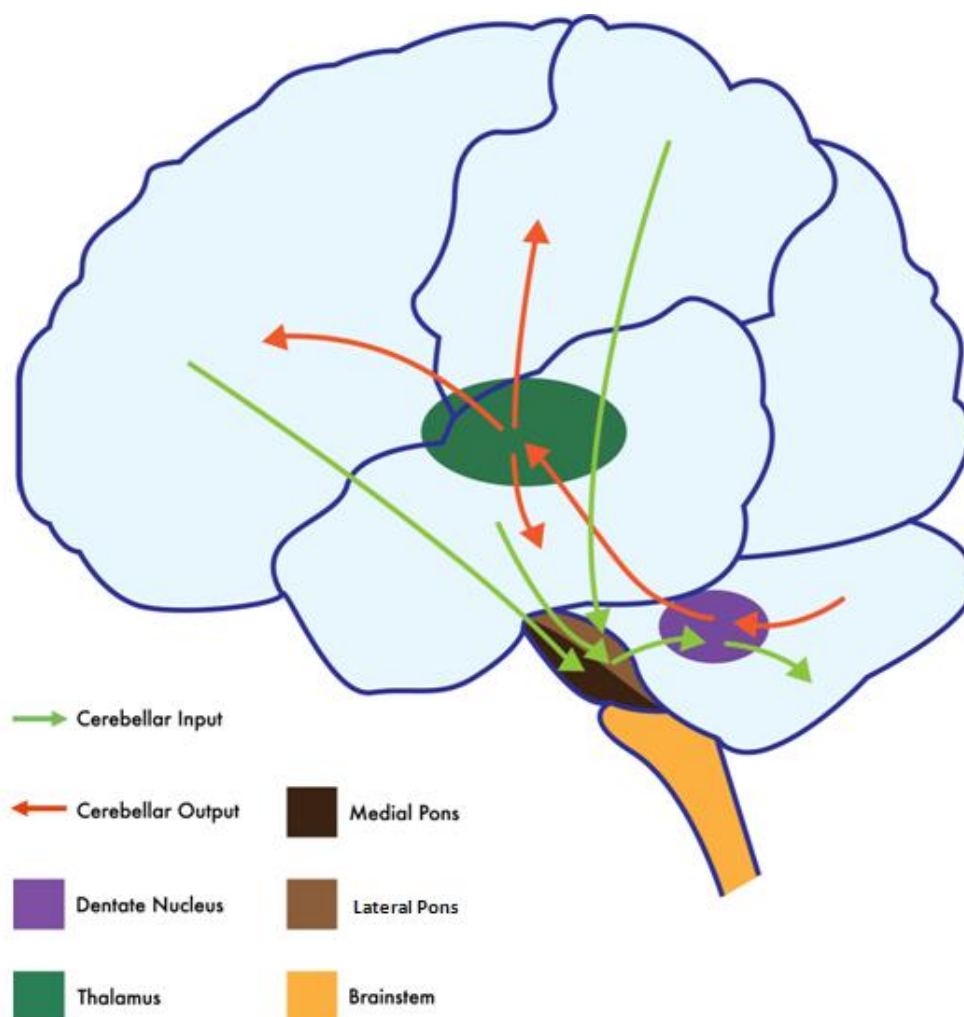
The fibers are additionally segregated at the level of the dentate nucleus: the motor fibers connect with the dorsal dentate nucleus whereas the prefrontal, parietal and temporal fibers connect with the ventral dentate nucleus (see Figure 2; Kelly & Strick, 2003).

Figure 2: Sagittal view of the cerebellum representing the pons, dentate nucleus, and cerebellar peduncles
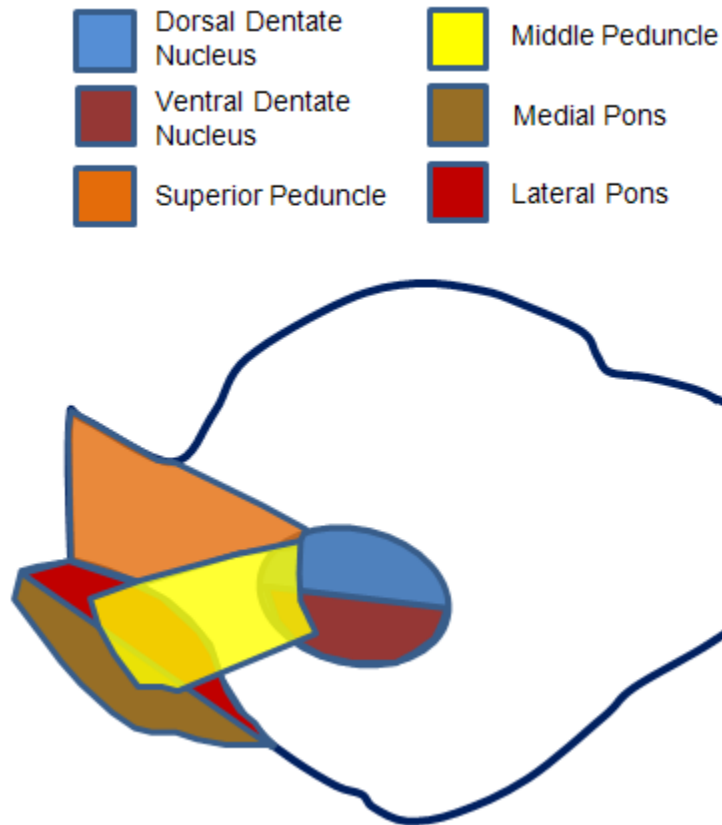
It is notable that the cerebellar connections typically synapse on association regions of the cortex as opposed to primary motor and sensory regions, which may suggest that the cerebellum is relevant to the cognitive and emotional functions these regions are thought to support (Schmahmann & Caplan, 2006).

The uniform cytoarchitecture across the surface of the cerebellum suggests that it has a highly specialized computational role that is performed irrespective of from where input originates. Marr (1969) comprehensively reviewed the microcircuitry of cerebellar structure.

The microcircuitry of the human cerebellum consists of an elaborate configuration of granule cells, stellate cells, basket cells, Golgi cells, and Purkinje cells. The GABAergic Purkinje cells are the sole output of the cerebellar cortex, and synapse on the excitatory deep cerebellar nuclei, which relay signals out of the cerebellum. Every Purkinje cell of the cerebellar cortex receive direct input from a single highly excitatory glutaminergic climbing fiber, which originate solely in the inferior olivary nucleus of the medulla oblongata. The remaining cells of the cerebellar cortex present a more complex set of relationships. Granule cells of the cerebellar glomeruli and the descending dendrites of Golgi cells receive input from weakly excitatory mossy fibers, which originate primarily from the pons and enter the cerebellum via the superior and middle cerebellar peduncles. Granule cells in turn project excitatory parallel fibers perpendicular to the dendritic trees of the Purkinje cells along the cerebellar folia. The parallel fibers synapse with the Purkinje dendrites as well as the inhibitory stellate, basket, and Golgi cells. Stellate and basket cells synapse with Purkinje cells, and Golgi cells synapse in the glomeruli with the granule cells. Additionally, some mossy fibers synapse directly with the deep cerebellar nuclei after entry via the peduncles. Thus, the primary mechanism of cerebellum output is via Purkinje summation, which results in inhibition of the excitatory deep cerebellar nuclei. Purkinje summation is the result of direct climbing fiber excitatory input from the inferior olive and parallel fibers moderated by a complex interplay between the stellate, basket and Golgi cells. Purkinje inhibition on the deep cerebellar nuclei may be further modulated by mossy fiber synapses directly on the nuclei. The cerebellum's microcircuitry suggests that it has high capacity to integrate information: each Purkinje cell receives as many as 200,000 synaptic inputs from parallel fibers, and each parallel fiber synapses on as many as 150 Purkinje cells

(Marr, 1969; See figure 3 for a simplified schematic of cerebellar microcircuitry in a cerebellar folium, adapted from Ramnani et al., 2006; cf. Eccles & Szentagothai, 1967; Marr, 1969). Thus, the cerebellum is capable of performing computations on a large amount of input from the cortex, and this input is used in a consistent manner to influence the rest of the system that the cerebellum connects to.

Figure 3: Schematic of a cerebellar folium and its microcircuitry
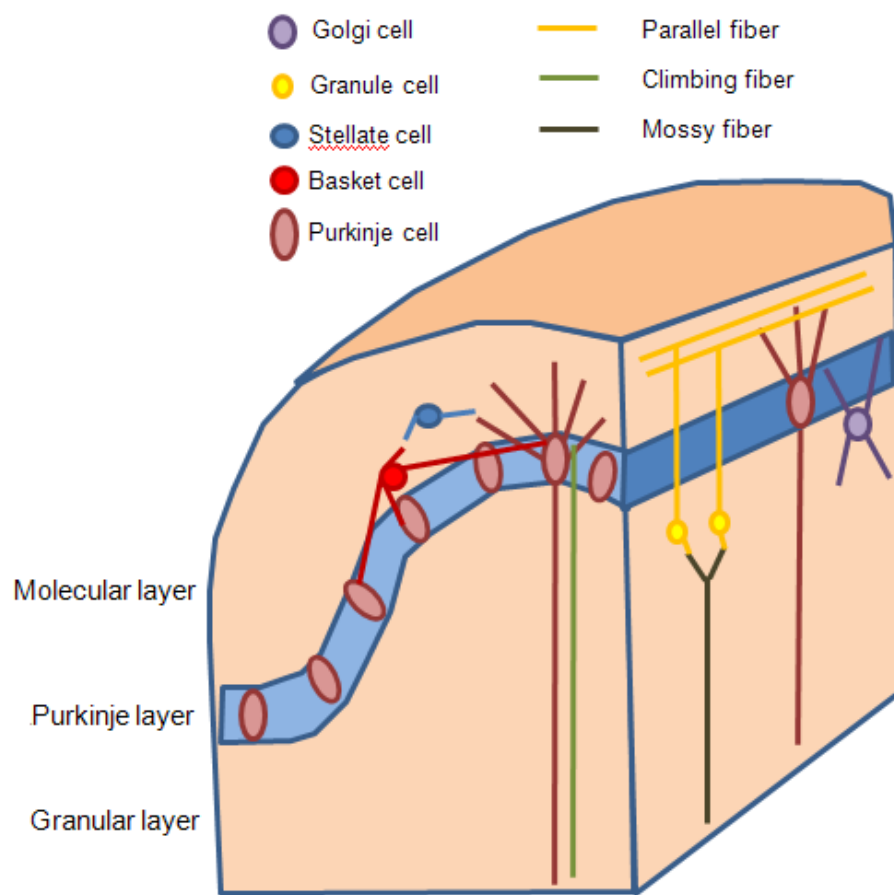
The structure of the cerebellum may hold several implications for its function during working memory. The inhibitory afferents of the Purkinje cells suppress the excitatory outputs of the deep cerebellar nuclei, leading to a net effect of downregulation of activity in target

neocortical structures if Purkinje summation results in a post-synaptic potential. Thus, the output of the Purkinje layer and the cerebellum to the neocortex is ultimately determined by the interplay of excitatory influences from the neocortex and inhibitory influences of the basal ganglia and other subcortical systems. The summation of various inputs from sensory, association, and motor areas in different temporal sequences accounts for forward models of anticipated sensory input for a given motor program (Wolpert, Miall, & Kawato, 1998; Kawato, 2003; Ganguli, 2009) and could represent similar models of anticipated states of cortical regions that can be modulated via Purkinje summation. That is, the cerebellum receives input from the rest of the brain that is compared to information from other brain regions, and may modify the signalling of those regions via Purkinje summation. Purkinje summation as a contributor to network modulation is further consistent with theories that the cerebellum uses internal (Ito, 2005) and forward (discussed above; Kawato, 2003), to inform sequence comparison (Molinari, 2008); that is, detecting patterns in neural activity and modifying cortical activity to optimize the synchronization of information flow between regions. While these models originally were proposed in sensory and motor processes, the cerebellum's uniform structure suggests that it would similarly use input about the neocortex's processes and sequences to calibrate networks involved in cognition (cf., Schmahmann, 2004). The cerebellum may therefore model the expected state of cortical systems based on the present state of the system and make adjustments to the broader network to maintain fluid task performance during working memory. Thus, conditions that affect the cortical regions to which the cerebellum is anatomically connected should influence cerebellar activity, and the cerebellum should in turn

influence those regions in response to "stabilize" the system as it attempts to efficiently perform a task and be more relevant when a task is novel or difficult.

While the anatomical relationships between the cerebellum and neocortex have been explored, investigations that directly implicated the cerebellum in cognition have only recently emerged. Findings from developmental and clinical studies began to demonstrate a tight link between the cerebellum and the neocortex, most particularly the prefrontal cortex.

Development and Clinical Pathology

Findings in cerebellar development in humans further suggest a role in cognition. The cerebellum develops as a part of the dorsal region of the posterior neural tube, also known as the somatic sensory columns, as opposed to the ventral muscle and motor regions (Paulin, 1993; Wang & Zoghbi, 2001). Diamond (2000) reviewed evidence that the neocerebellum matures on a prolonged time table that roughly corresponds to the protracted development of the prefrontal cortex. Structural studies of the brains of adolescents with attention deficit hyperactivity disorder (ADHD) supported the hypothesis that the cerebellum was altered, particularly in the posterior lateral neocerebellum (Berquin et al., 1998; Castellanos et al., 1996; Mostofsky, Reiss, Lockhart, & Denckla, 1998). Diamond (2000) reviewed findings that the greatest difference in brain volume between healthy children and children with ADHD was reduced cerebellum volume in the clinical sample. Thus, as the cerebellum is a common site of abnormality in this disorder, the particular patterns of cognitive discoordination in ADHD may

be at least partially a result of irregular cerebellar development. Additionally, Diamond (2000) reviewed findings of similar irregularities in cerebellar structure in moderate to servere autism, which is known to be marked by significant and pervasive cognitive impairments. The relevance of these findings to cognitive functioning might be investigated by direct examination of anatomical and functional characterstics of the cerebellum during a cognitive task in these populations.

Traumatic brain injury (TBI) is associated with working memory deficits in children (Levin et al., 2002; Levin et al., 2004; Conklin, 2008) and adults (Hillary et al., 2006; Newsome et al., 2009; Vallat-Azouvi et al., 2007), and childhood TBI provides additional evidence of a cerebellum-prefrontal cortex interaction during development. A study of cerebellar volume following TBI in 16 adolescents revealed reduced cerebellar size compared to matched, typically developing adolescents (Spanos et al., 2007). Importantly, significantly reduced white matter volumes were found in cases where no focal cerebellar lesions were present, possibly indicating that altered cortical input disrupts proper cerebellar development or induces cerebellar cell death. Every TBI case exhibited reduced white matter volume relative to its matched control, and all but one TBI case demonstrated reduced gray matter volume in the cerebellum, suggesting that reduced cerebellar volume is a relatively ubiquitous finding in adolescent TBI where cognitive symptoms are prominent.

Thus, normal and abnormal structural fundings suggest that the cerebellum is linked to regions known to be critical to cognitive functioning. An emerging literature examining resting functional connectivity has revealed that these anatomical connections are also represented in functional data.

Modern Neuroimaging and Cerebellar Functional Connectivity

To date, functional connectivity studies of the cerebellum have examined connectivity only during resting states using blood oxygen level dependent functional magnetic resonance imaging (BOLD fMRI; see Logothetis, 2004 for an in-depth review), when no task is presented to subjects. A study by He and colleagues (2004) used a regional homogeneity analysis (cf. Zang, 2004), which examines the correlations between voxels during a task or while at rest, as the basis for defining functional seeds and found bilateral functional clusters in the bilateral anterior inferior cerebellum. He and colleagues (2004) demonstrated significant functional connectivity between these cerebellar functional clusters and the bilateral thalamus, hippocampus, precuneus, temporal lobe, and prefrontal lobe, which conforms to many aforementioned major anatomical substrates of a neocortical-cerebellar network.

A more recent analysis by Krienen and Buckner (2009) employed functional connectivity analysis in eighty healthy individuals at rest and characterized four reciprocal loops between the cerebellum and the frontal cortex based on seeded regions in the bilateral motor areas as well as anterior, medial, and DLPFC. Specifically, seeds placed in the primary motor cortices associated with the contralateral lobules IV, V, VI, and VIIIB of the cerebellum, which conformed to findings of labeled neurons via transneuronal transport of neurotropic viruses implanted in the cerebellum to the cebus monkey primary motor cortex (Kelly & Strick, 2003). (See Figure 4 for a schematic of Schmahmann et al.'s (1999) adaptation of Larsell's (1972) designations of cerebellar lobules).

Figure 4: Schmahmann et al.'s (1999) designations for cerebellar lobules. Sagittal view.
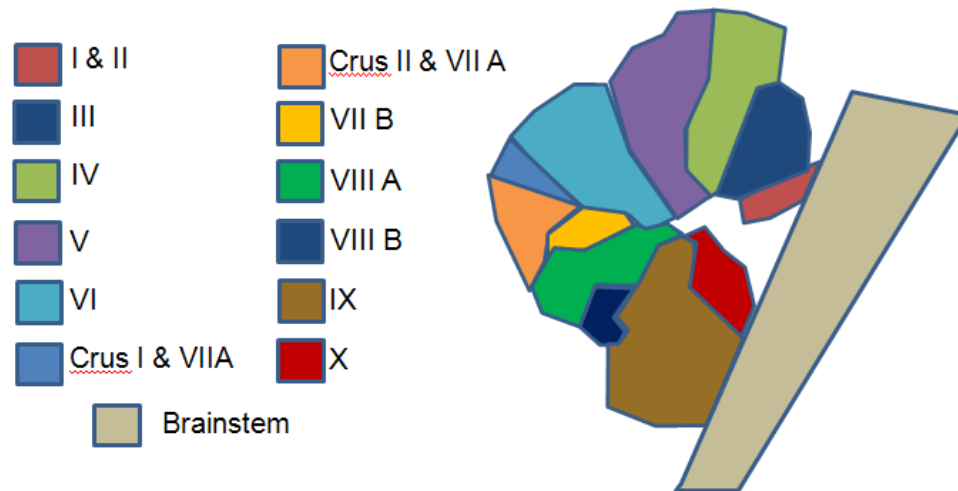
The DLPFC exhibited correlations with the contralateral Crus I and II, which contained the majority of labeled neurons projecting from the cerebellum to the monkey prefrontal area 46 (Kelly & Strick, 2003). Seeds placed in cerebellar regions revealed connectivity between lobules V/VIIIB and the sensorimotor cortex as well as connectivity between Crus I/II, Lobule VI, and Lobule VIIB and distinct frontal regions. Seeds placed in the anterior prefrontal cortex (APFC), medial prefrontal cortex (MPFC) and DLPFC each demonstrated anatomically distinct functional correlations with the cerebellum. MPFC exhibited greater connectivity with Crus I, DLPFC with Crus I and the lateral and ventral extent of Crus II, APFC with lobule VI and ventral VIIB-VIIIA and Crus II at the ansoparamedian fissure. Thus, there were partially dissociable functional networks between the cerebellum and motor and frontal regions during rest. Specifically, the cerebellar lobules Crus I/II and VIIB appeared to be related to the DLPFC and other frontal regions, and the Lobules V and VI appeared more tightly related to the motor cortices.

Krienen and Buckner (2009) found that the frontal connections exhibited predominantly contralateral connectivity as well as modest ipsilateral connectivity that conformed to anatomical findings of ipsilateral frontal lobe to cerebellum white matter tracts. Importantly, when seeds were placed in different cerebellar foci based upon the foci located for the frontal seeds, connectivity analyses indicated distributed cortico-cerebellar connectivity with the dorsal, ventral and medial PFC, as well as the lateral temporal and parietal lobes. That is, specific frontal foci may exhibit dissociable connectivity to anatomically segregated portions of the cerebellum, and these foci are in turn related to an overlapping and distributed network in resting individuals. The authors noted that the network revealed by the cerebellar seed placed in Crus I resembled the theoretical "default" brain network which may be involved in social cognition, episodic memory, and planning for the future as a "resting" brain's attempt at optimizing restful periods when an individual is not engaging in any specific goal-directed activity (Gusnard and Raichle 2001; Svoboda et al. 2006; Buckner and Carroll 2007; Buckner et al. 2008; Spreng et al. 2009).

While these findings converge well with comparative anatomy studies and the functional segregations during cognitive and motor tasks found by Stoodley and Schmahmann (2009; see below for a thorough review), their relevance to how the cerebellum relates to cortical regions during cognitive tasks has not been established. However, if these connections indeed represent distributed functional networks that facilitate cognitive operations, they should demonstrate activation relationships to cortical regions and task performance in the context of cognitive tasks. To date, no investigations of functional connectivity during cognitive tasks have focused on the cerebellum. However, several studies of cerebellar activation have

been conducted in several cognitive domains and provide a foundation for a more extensive understanding of cerebellar contributions to cognition. First described are findings of interactions between cognitive modality and cerebellar region activation in a variety of domains. Then, findings of heavy involvement of the cerebellum in executive functions are discussed. Finally, contributions of the cerebellum to verbal working memory and limits of previous studies are reviewed.

The Cerebellum and Cognition: Findings in Functional Neuroimaging

The Cerebellum and Cognitive Domain-Specific Activation

A recent meta-analysis conducted by Stoodley and Schmahmann (2009) provided evidence for task-dependent regional activation of the cerebellum. The authors selected studies that fit stringent criteria for seven categories: motor, somatosensory, spatial, language, working memory, executive function, and limbic/emotion processes. The spatial, language, working memory, and executive function analyses were separated in order to assist in determining regional participation of the cerebellum that were specific to different cognitive operations. Only the bilateral lobules VI were activated by spatial tasks. Language tasks activated the bilateral lobules VI, Right Crus I and II, and right lobule VIIA. Working memory tasks revealed activation of the bilateral lobules VI, bilateral Crus I, and right VIIIA. Executive function tasks activated the left lobule VI, bilateral Crus I, and left VIIB.

In Stoodley and Schmahmann (2009), each nonmotor category included primarily tasks for which contrasts were generated by subtracting baseline conditions, which typically included motor responses such as button presses, from the cognitive task periods. That is, responses were typically held constant between the baseline and task conditions; thus, the additional activation observed in contrasts such as 2-back versus 1- or 0-back is not solely accounted for by basic motor output processes. Therefore, while the activation observed in motor tasks in lobule VI was present in one or both lobes during cognitive tasks from spatial, language, working memory and executive functioning tasks, that activation was likely not due strictly to motor responses. The bilateral activation observed in lobules V did not appear in the nonmotor categories, and may be more explicitly related to the basic motor processes. It is noteworthy that the working memory tasks all included verbally mediated material and activation of bilateral lobules VI and right Crus I was evident in language tasks as well as working memory tasks, which may partially represent engagement of the phonological loop for both tasks. Overall, the results of the meta-analysis suggested that the bilateral Crus I, Right Crus II, left VIIB, right VIIA and right VIIIA play a role that is not engaged for basic motor output, and that the activation observed in the bilateral lobules VI and right VIIIA is not uniquely accounted for by motor output processes.

As discussed previously, the "uniquely" cognitive cerebellar lobules VIIB, VIIIA and Crus I/II were found to be functionally connected to regions in the prefrontal cortex, including the dorsolateral prefrontal cortex (Krienan & Buckner, 2009). This region is known to be heavily involved in executive functions and working memory. The next section specifically reviews the

literature to date that examined the cerebellum in executive functioning and working memory tasks and describes known relationships between cerebellar activation and performance.

The Cerebellum and Executive Functions

The regions of the lateral PFC that are anatomically and functionally connected to the cerebellum are known to have special significance in a range of "higher-order" faculties that are loosely termed "executive functions" (Kelly & Strick, 2003; Krienen & Buckner, 2009). Three major models propose that executive functions serve a "supervisory" role and coordinate the activities of various sensory and computational networks and become active during planning, novel and/or challenging situations, managing tasks with respect to goals, and execution of strategies (see Logan, 1985; Norman & Shallice, 1986; and Smith & Jonides, 1999 for specific models of executive functions). Particular cognitive components that are regulated by executive functions include spatial and verbal working memory (henceforth referred to as WM), attention, inhibition, task management, and strategy selection and implementation. The differential evolution of executive functions in humans has been cited as a primary source for creativity, intelligence, and the ability to handle environmental and conceptual complexity (Coolidge & Wynn, 2001; Holloway, 1996).

Several recent studies applied traditional neuropsychological measures and neuroimaging techniques to examine executive functions with respect to the cerebellum in both clinical and healthy populations. Schmahmann and Sherman (1998) reported deficits in set shifting, abstract reasoning, verbal flexibility, planning and WM in a sample of 20 individuals

with solely cerebellar damage of various etiologies. Studies of cerebellar contributions to set-shifting or divided attention using the Wisconsin Card Sorting Test (WCST) yielded inconsistent results, where some studies of patients with cerebellar lesions demonstrated deficits (Ravizza & Ivry, 2001), and others did not (Gottwald et al., 2004; Schmahmann & Sherman, 1998; Daum et al., 1993); however, it is likely that specific regions of the cerebellum are more relevant to certain tasks than others as implied by anatomical relationships with the neocortex, so null findings likely are due to variance in the effect of neuropathology on different regions. Studies of multitasking were more consistent: cerebellar patients demonstrated deficits (Gottwald et al., 2004; Lang & Bastian, 2002; but see Heyder, Sucham & Daum, 2004) and healthy individuals demonstrated additional recruitment of the cerebellum during a dual monitoring task (Collette et al., 2005). Additionally, cerebellar patients in one study of spatial fluency in which they were asked to draw as many different figures as possible by connecting five dots demonstrated marked impairments (Gottwald et al., 2004). Thus, the cerebellum appears to have a role in complex executive tasks that require the online management of multiple types of information, attention and the generation of novel responses. One cognitive subfunction thought to be critical to online executive functions is WM, or the ability to temporarily store and manipulate a limited amount of information for complex cognitive tasks (see Baddeley, 1992). The cerebellum has been found to be active during working memory, particularly verbal working memory. The following section will discuss the theoretical components of WM and review neuroimaging findings exploring the role of the cerebellum during WM and some critical limitations of these studies. A study that was conducted to address the need to examine the

cerebellum's role in a distributed neural system during a continuous WM task is then presented and discussed.

Working Memory: Cerebellar involvement and contributions to performance

WM is thought to be comprised of three parts: the phonological loop, which deals with primarily wrote and spoken language, the visuospatial sketchpad, which manipulates visual imagery, and the central executive, which serves as an attentional control mechanism and is a supervisory system that controls the other two subfunctions.   Because WM is thought to contribute heavily to many complex tasks yet is relatively less broadly defined than executive functions, it has received greater attention in functional imaging and behavioral studies of the cerebellum. Current efforts to document the role of the cerebellum in WM have been met with mixed results. A few studies examined the role of the cerebellum in spatial WM. However, the vast majority of WM studies involved verbal WM tasks. These tasks found some relationships between specific regions of the cerebellum, task performance and practice during verbal WM tasks. However, no studies examined the the connectivity of the cerebellum in a distributed network and whether those connections support cognitive performance.

To date, studies have not demonstrated consistent involvement of the cerebellum in spatial WM. Studies that have claimed to assess spatial WM in patients with cerebellar damage have typically used the digit span task (e.g., Daum et al., 1993; Fiez et al., 1992; Ravizza et al., 2006; Reisberg, 2000). However, the digit span task is not thought to exclusively assess the visual domain of WM because numbers require a phonological component and verbalization of stimuli, as do many WM tasks (Baddeley, 1992). A WM study by Hautzel and colleagues (2009)

demonstrated no significant differences in fMRI activation and no laterality effects between an abstract (spatial) and traditional N-back task in the cerebellum in healthy adult males, suggesting that the cerebellum serves a consistent role irrespective of the type of stimuli. The authors suggested that the common cerebellar activation in both conditions represented an auxiliary contribution to executive functions in general, as the N-back design presumably emphasizes operations such as executive control and manipulation of information in addition to internalized stimulus maintenance. However, the study did not present data investigating how cerebellar activation related to task performance measures such as reaction times or how cerebellar activation related to activation of the PFCor parietal cortex.

Involvement of the cerebellum in verbal WM was found in healthy individuals by meta-analyses of fMRI findings (cf. Owen et al., 2005; Stoodley & Schmahmann, 2009) studies of cerebellar tumor cases (Kirschen et al., 2008), lesion patients (Burk et al., 2003; Gottwald et al., 2004; Justus et al., 2005; Ravizza et al., 2006; Silveri et al., 1998), schizophrenia (Mendrek et al., 2004) and transcranial magnetic stimulation (Desmond, Chen & Shieh, 2005). Verbal WM, which depends on the phonological loop of Baddeley's (1992) model, can be further subdivided into two components: the "phonological store", which holds speech-based information for 1 to 2 seconds, and "verbal articulation", which refreshes the phonological store by subvocal repetition.

Desmond and colleagues (1997) presented the first direct evidence that the cerebellum may mediate the theoretical "phonological loop" of verbal WM. Ackermann and colleagues (1998) demonstrated cerebellar involvement during silent mental rehearsal of familiar verbal strings and argued that the cerebellum is involved in primarily articulatory processes, whereas

Ravizza and colleagues (2006) presented evidence that the cerebellum may be involved in initial phonological encoding and strengthening memory traces rather than verbal articulation. As discussed below, it now appears likely that the cerebellum is critically involved in both the articulatory and phonological storage components of the phonological loop, and that different subregions of the cerebellum are involved in different components.

The following section will provide an in-depth exploration of the cerebellum's support of cognitive performance within verbal WM. A critical emphasis will be placed on relationships between cerebellar activation and performance and the limits of these studies for providing information about the cerebellum's role in WM.

The Cerebellum and Performance in Verbal Working Memory

Only a handful of studies directly examining cerebellar activation against performance and practice have been conducted, all with important methodological limitations. Importantly, the cerebellum has been examined in isolation of the rest of the brain, providing little insight into the nature of the cerebellum's contribution to distributed WM systems and how the joint functioning of the neocortex and cerebellum facilitates performance. The next section will review several specific studies that have directly explored relationships between performance and cerebellar activation during verbal WM tasks as a stage for examining the cerebellum's role in a distributed WM network.

A study by Honey and colleagues (2000) investigated relationships between RT and BOLD response during the 2-back and reported significant relationships in the bilateral parietal and supplementary motor areas, and no relationships in other frontal regions. An incidental

finding of activation in the cerebellum was in the right cerebellum and contained only seven active voxels, and the authors did not report whether a cerebellum/RT relationship was examined. Further, the "search volume" for correlations was restricted to 1060 voxels (or approximately 28.6 cm^3) across the brain, which did not allow the possibility of revealing other regions that may be coupled with reaction time but were not identified during initial analyses. The baseline used for this task was a 1-back condition, which may have attenuated signal variance among 2-back responses, thus reducing the power to detect reaction time to activation relationships where they may otherwise exist. Therefore, it is reasonable to assume that while the parietal and supplementary motor regions may have large relationships to reaction time, other relatively weaker relationships may in fact be present when raw activation compared to a different baseline is considered. Additionally, the design made it impossible to discern relationships between task load and activation, which may have provided evidence for task load vs. RT cerebellar responsiveness.

Desmond and colleagues (1997) applied the Sternberg task (or modified delayed-reponse task) during fMRI acquisition and found that activation in the bilateral superior cerebellum was load dependent in both verbal articulatory and WM conditions, and that right inferior cerebellum activation was load-dependent only in the WM condition (Desmond et al., 1997). A later follow-up study by Chen and Desmond (2004) revealed that activation in the inferior parietal lobule and inferior cerebellum was present only during the WM task, whereas superior cerebellum activation was present in both verbal articulation and WM. The authors interpreted their findings as indicative of an articulatory component supported by the frontal

cortex and the superior cerebellum and a phonological storage component subserved by the inferior parietal lobule and right inferior cerebellum.

Desmond and colleagues (2005) extended their earlier work and provided evidence of an RT-cerebellar relationship using transcranial magnetic stimulation (TMS) to eliminate the contribution of the right superior cerebellum (Lobule VI and Crus I) during the Sternberg WM task. Reaction time during WM was significantly higher in the TMS condition that was not found in a sham condition or motor condition, suggesting a role for this region in speeded task performance during WM that cannot be attributed to motor output.

Kirschen and colleagues (2005) conducted analyses of activation, task load, practice and RT using the Sternberg task during fMRI acquisition. Task load was positively correlated with bilateral superior cerebellum activation (Lobules VI and Crus I) and the right inferior cerebellum (Lobules VIIB and VIIIA). Activation that occurred only after task practice was found in the right superior cerebellum (lobule VI) and inferior cerebellum (lobules VIIB and Crus II) in addition to increased activation in session three in the left inferior cerebellum (lobule unspecified). Correlations between reaction time and right inferior cerebellar activation revealed no significant relationship during session 1 and a significant positive relationship during session 3. The authors did not report conducting reaction time correlations for other cerebella regions that exhibited load effects (i.e., the right superior and left inferior cerebellum). The left parietal lobe, from which the right inferior cerebellum receives inputs, exhibited a similar relationship to RT at session 3, though the authors did not conduct analyses relating the activation in one region to the other. As in Honey et al. (2000), reaction times during each session were

confounded with load in the analysis, preventing any determination of the relationships between reaction time and activation at a constant load level.

Thus, several main findings from the fMRI literature appear clear. First, during verbal WM in healthy adults, the right cerebellum generally appears more active than the left in conjunction with the contralateral DLPFC and inferior parietal areas. Second, the right superior cerebellum appears to respond to tasks similarly to the left DLPFC, and the right inferior cerebellum responds similarly to the left inferior parietal area, possibly representing dissociation between Baddeley's (1992) subcomponents of verbal WM. Third, within the superior and inferior cerebellar hemispheres, the dorsolateral features (more specifically, Crus I, Lobule VIIB, VIIA and VI) appear to be the most relevant to verbal WM. Fourth, the cerebellar regions are load sensitive. Fourth, relationships between performance, especially RT, have been confounded with manipulations of WM load level. Finally, there are likely practice effects on cerebellar activation during exposure to a cognitive task.

What remains to be determined is how these cerebellar regions interact with DLPFC and parietal areas during verbal WM task performance. Despite findings demonstrating coactivation of the DLPFC and contralateral cerebellum (Awh et al., 1996; Berman et al., 1995; Desmond et al., 1995; Desmond et al., 1997; deZubicaray et al., 1998; Grasby et al., 1994; Jonides et al., 1997; Nagahama et al., 1996; Paulesu et al., 1995; Paulesu, Frith & Frackowiak, 1993; Raichle et al., 1994; Schlosser et al., 1998) and that the cerebellum is coactive with the dorsolateral and ventralateral prefrontal, frontal pole, thalamus and bilateral parietal cortices during continueous WM during the n-back (Owen et al., 2005), it is unknown how these regions interact with one another during the task (specifically, how their BOLD fMRI signals react to

changes in one region or the other) and how the functional connection between these regions relates to task performance. That is, the functional relationship between regions may be as or more important to performance than the mean activity in the regions and is more representative of WM being supported by a distributed neural system. It is also unknown how cerebellar activation predicts reaction time when load levels are held constant - it is possible that the cerebellum is responsive to inefficiency in the broader network and may increase in activity to establish efficient performance (i.e., faster reaction time) rather than to directly process more difficult task demands per se. Related to this point, the cerebellum's role may change as the network establishes effective routines for completing the task and its relationship with performance may change once the initial routine is established. For example, it is possible that the activation in DLPFC and cerebellum are tightly linked when initially confronted with a task and that these regions become relatively decoupled as an efficient routine is in place. Modern technologies such as BOLD fMRI provide data that can be used to address these areas and advance our understanding of the cerebellum's role in verbal WM.

Summary

This review offers evidence that evolutionary, anatomical, developmental, and clinical studies point to a clear role of the cerebellum in nonmotor aspects of cognition and especially in verbal WM. However, the contribution of the cerebellum to cognition may be nuanced and less central than cortical processes (Molinari, 2007), thus its role may be difficult to detect without proper experimental conditions, control over the condition of a sample's cerebella (e.g., localized damage, healthy cerebella, etc.), and appropriate motor controls. Further, the

hypothesis that the cerebellum may play some part in facilitating the most recent and complex cognitive operations in humans (e.g., Leiner, Leiner, & Dow, 1986; Schmahmann, 2004; Weaver, 2005) such as executive functions and WM, has not been thoroughly assessed.

The persistent question with respect to cerebellar involvement in verbal WM is what role it plays in the broader network and how it assists cognitive performance. While partially dissociable networks between the neocortex and cerebellum were shown to bear relationships with performance and may represent different components of Baddeley's (1992) model of WM, the cerebellum's specific role in networks that support WM and the cerebellum's responsiveness to practice remain poorly clarified. As discussed above, cerebellar involvement early in a task may involve the establishment of new connections representing the practiced skill or task (see Karni, 1995), or more generally a continued and progressive role in calibrating the activities of neocortical regions to the task procedure in order to facilitate efficient task performance and network stability. Thus, it would be expected that while the cerebellum demonstrates detectable activation during many WM tasks, the activation depends upon task novelty and its relationship to load, RT and cortical regions and may change with practice. Furthermore, if the cerebellum directly affects the neocortical regions it shares anatomical connections with during WM, measures of effective connectivity will be instrumental in detecting direct cerebellar influences. A within-subject analysis of BOLD activity during verbal WM may reveal how the cerebellum interacts with the cortex to facilitate task performance and how this role may be modified with task practice.

Current Study

Therefore, the goal of the current study is to clarify the role of the cerebellum with respect to its previously identified activation during WM in a distributed neural system. The current study will examine the relationships between performance, task load, and practice with respect to cerebellar activation during a WM task. An additional goal is to examine the relationship of cerebellar activation to neocortical regions known to participate in WM and motor processes before and after task practice. Finally, the directed influence of the cerebellum on cognitive regions during cognition will be examined. It is hypothesized that:

1) Consistent with previous work in WM (Desmond et al., 1997; Kirschen et al., 2005), there will be a main effect of task load on cerebellar activation, particularly in regions shown to be involved in the subcomponents of Baddeley's (1992) model of WM (e.g., right superior and inferior cerebellum). Additionally, at a given load, reaction time will predict variance in cerebellar activation, and will be positively correlated with activation. This will investigate whether reaction time is associated with cerebellar activity without conflation with load (e.g., in Honey et al., 2000, Kirschen et al., 2005).

2) Activation in the right inferior cerebellum will be positively correlated with reaction time more strongly after practice at a given load level (e.g., as in Kirschen et al., 2005). Given the possibility of multiple semi-independent fronto-cerebellar networks (Krienen et al., 2009), these relationships will be secondarily explored in the left inferior and bilateral superior cerebellum.

3) During a WM task, the right superior cerebellum will correlate with the left frontal cortex, and the right inferior cerebellum will exhibit connectivity with the left inferior

parietal lobe, as suggested by anatomical (Kelly & Strick, 2003; Schmahmann & Pandya, 1998) and resting functional (Krienen & Buckner, 2009) connectivity findings. This effect will exist regardless of load or practice as suggested by their direct anatomical relationships and consistent coactivation during cognitive tasks.

4) Four cerebellar regions of interest (bilateral superior and bilateral inferior cerebellum) will in general have more directed influences on the contralateral prefrontal and parietal regions than on the supplementary motor and primary motor regions as suggested by their activation during cognitive tasks (Schmahmann & Sherman, 2009) and anatomical relationships with the contralateral neocortex (Kelly & Strick, 2003; Schmahmann & Pandya, 1998).

5) The effective connectivity between the right cerebellum and the previously specified (hypothesis 3) left frontal and parietal regions will increase following task practice as the brain routinizes the task, and increased connectivity will be related to increased performance (i.e., decreased reaction time and increased accuracy), as suggested by Karni (1995).

Chapter 2

Methods

Subjects

Subjects included 20 healthy adults between 18 and 55 years of age with no psychiatric or neurological history. Subjects were recruited by word of mouth as matched controls of individuals with traumatic brain injury recruited for an existing protocol examining practice in traumatic brain injury at the Pennsylvania State University.

Task

A well established WM sequential letter task, the n-back (see Chang et al., 2001 and Speck et al., 2000 for examples of earlier administrations of this task) was used to assess WM. Alphabetical letters were presented at a rate of one every two seconds. The subjects were instructed to press a response button as fast as possible whenever the current letter is the same as the one before (1-back task) or two before (2-back task) (Chang et al., 2001; Speck et al., 2000). The task was administered in a periodic task-on/rest ("block") design to determine "task-related" activity. During each 20 second task period, three or four targets were presented at random time points among a string of 10 letters. During the rest period (14 seconds), subjects were instructed to fixate on a small asterisk presented at the center of the display screen. Prior to the task, subjects performed one 10-stimuli block of the 1-back and 2-back to ensure that they understood the task. Subjects performed one run each of the 1-back and 2-back before practice and once again after practice. Subjects engaged in task practice outside of

the scanner between runs in the scanner, during which they completed one run of 1-back and one run of 2-back. Thus, by the beginning of the second in-scanner 1-back and 2-back, each subject had engaged in 17 blocks of each task.

Magnetic Resonance Imaging Procedure

All data were acquired using a Siemens 3T system and a 6-channel SENSE head coil. First, 3-D high resolution T_1-weighted MPRAGE images (9.9 ms / 4.6 ms / 8° repetition time / echo time / flip angle (TR/TE/FA), $240 \times 204 \times 150$ mm^3 field of view (FOV), $256 \times 205 \times 150$ acquisition matrix, 2 averages) were acquired to provide high resolution underlays for functional brain activation. Echo planar imaging (EPI) was used for functional imaging. Imaging parameters for EPI consisted of: 2000 ms/30 ms/89°, TR/TE/FA, 230×230 mm^2 FOV, 80×80 acquisition matrix, 34 4-mm-thick axial slices with no gap between slices.

MRI Data preprocessing

Preprocessing of the fMRI data was performed using SPM5 software (http://www.fil.ion.ucl.ac.uk/spm5). The first nine volumes were removed from analyses in order to control for initial signal instability. The functional data of each run were realigned to the first functional image of that run using affine transformation (Ashburner et al., 1997; Friston et al., 1995). Functional images were co-registered to the individual's T1 MPRAGE and all data will be normalized using a standardized T1 template from the Montreal Neurological Institute (MNI), using a 12 parameter affine approach and bilinear interpolation. Normalized data were smoothed with a Gaussian kernel of 8 x 8 x 10mm^3 in order to minimize anatomical differences

and increase signal to noise ratio.

MRI Data Analyses

SPM Analyses

For each run of each individual a dichotomous vector of interest was used to create individual contrast maps based upon the modeled BOLD signal at the onset of each stimulus presentation. "Activation" was determined using a time-shifted canonical BOLD response to model each block in the design. In order to replicate previous findings, a group random effects analysis ANOVA was conducted to reveal groupwise activation at a significance level of $p<.01$ using correction for false discovery rate.

Defining Regions of Interest

Regions of interest (ROIs) for all analyses were independently defined by the Wake Forest University PickAtlas toolbox for SPM5 (Maldjian et al., 2003; Maldjian et al., 2004) based upon the hypotheses. ROIs will include the bilateral superior (Crus I/Lobule VI) and inferior (Lobules VIIb/VIIIa) cerebellum, bilateral dorsolateral PFC (BA 46), left Brodmann's area (BA44/45), bilateral inferior parietal cortices (BA40), bilateral supplementary motor areas (BA 6), and bilateral primary motor areas (BA 4). See Figure 5 for a schematic representation of the location of ROIs.

Figure 5: Schematic representation of the location of ROIs.
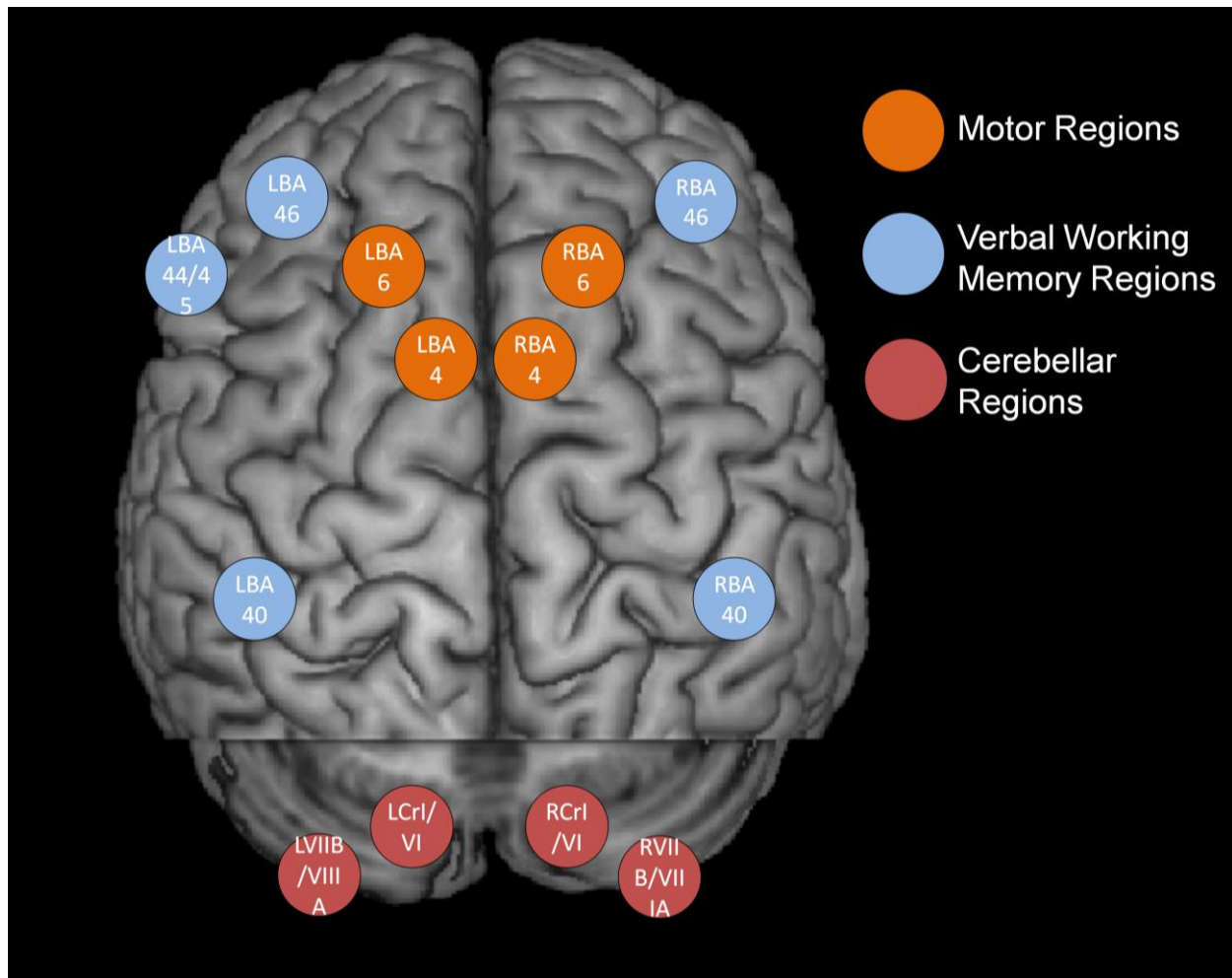
Extracting Activation and Timeseries Data

The SPM5 MarsBaR toolbox (Brett et al., 2002) was used for extraction of raw timecourse data for each ROI for each run of each individual. Percent signal change during the task period compared to baseline was inferred by taking the mean signal change during task periods (shifted 6 seconds to account for latencies in peak BOLD response) and finding the arithmetic change in percentage from off-task to on-task periods.

Performance, Load, and Activation

Testing Hypothesis 1:

Mean reaction times of accurate trials for each block within each run were calculated as well as mean reaction times for entire runs. In order to test the hypothesis that task load has an effect on cerebellar recruitment (hypothesis 1), a two-samples within subjects T-test was performed to compare % BOLD signal change during the 1-back condition to activation during the 2-back for each cerebellar ROI. To test the hypotheses that reaction time was positively correlated with cerebellar activation (hypothesis 1) and that this relationship increased following practice (hypothesis 2), blockwise reaction times were correlated with their respective % signal change values independently at both task load levels before and after practice. Correlation values for this hypothesis and hypotheses 2 and 3 were converted using Fisher's R to Z transformation to normalize the distribution and Z values were submitted to a single-sample t-test to determine if reaction times were correlated with % signal change within each region.

Testing Hypothesis 2:

To test the hypothesis that the relationship between cerebellar activation and RT increases following practice, blockwise reaction times were correlated with their respective % signal change values independently at both task load levels before and after practice. Fisher R to Z converted correlation values were submitted to a 2 X 2 within-subjects ANOVA to test for effects of load and practice on relationships between regions and RT.

Testing Hypothesis 3:

To test the hypothesis that the right superior cerebellum BOLD signal correlates with the left frontal cortex and that the right inferior cerebellum correlates with the right inferior parietal lobe (hypothesis 3), a correlation between the BOLD timeseries of these regions during the task was conducted within each subject and Fisher's R to Z converted correlation coefficients were submitted to one-sample t-tests to determine if they were significantly different from zero.

Testing Hypothesis 4:

To test the hypothesis that the four cerebellar regions of interest relate more significantly to the contralateral prefrontal and parietal regions than to the supplementary motor and primary motor regions (hypothesis 4), each individual's timeseries data from all ROIs were submitted to an exploratory unified structural equation model (uSEM; Kim et al., 2007) via Lisrel (http://www.ssicentral.com/). The betas representing the contemporaneous connectivity between the cerebellum and motor (supplementary and primary) regions were coded as binary (cf., Hillary et al., in press) and submitted to a paired-samples t-test against betas representing the connectivity between the nonmotor (frontal and parietal) regions. To increase power to detect differences, connections were summed into indices representing the total number of cerebellar influences from: 1) each ipsilateral pair of cerebellar ROIs to the contralateral cognitive (parietal and prefrontal) or 2) motor (primary or supplementary) regions; and finally between 3) each pair of ipsilateral cerebellar ROIs to the contralateral cognitive regions and

from the cognitive to the same cerebellar regions and 4) each pair of ipsilateral cerebellar ROIs to the contralateral motor regions and from the motor regions to the same cerebellar regions.

Testing Hypothesis 5:

To test the hypothesis that increased functional connectivity between the left neocortex and right cerebellum is facilitative of performance (Hypothesis 5), on-task BOLD values of each block of the right superior and inferior cerebellum, left Brodmann's areas 44/45 and left inferior parietal cortex were submitted to unified structural equation modeling (Kim et al., 2007) implemented via Lisrel (http://www.ssicentral.com/). The betas between regions from before and after practice were coded as binary (cf. Hillary et al., in press) and submitted to paired samples t-tests to determine if connectivity significantly increased after practice. Further, the changes in betas following practice were correlated with changes in runwise performance (RT and accuracy) within individuals from before to after practice.

<div style="text-align:center">

Chapter 3

Results

</div>

SPM

An ANOVA was conducted to depict the main effect of task on the BOLD signal across the brain. Significant activation was found in the bilateral dorsolateral PFC, lateral temporal lobes, bilateral parietal lobes, and bilateral superior and inferior cerebellum (see Figure 6 for a depiction of average activation during the tasks).

Figure 6: Average activation during the n-back tasks; FDR<.01.
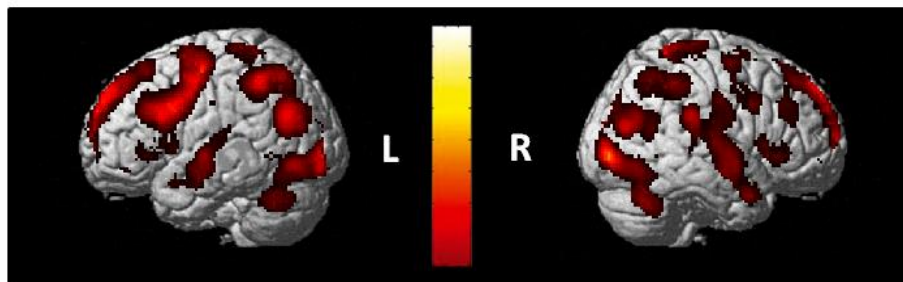
Hypotheses 1 and 2: Cerebellar activation and relationships with reaction time

A 2x2 within-subjects ANOVA was conducted to detect influences of practice and load for each cerebellar ROI. A consistent effect of load was found for all cerebellar ROIs: the left Crus I/Lobule VI of the cerebellum [$F(1,19)=3.61$, p=.073], the left Lobule VIIb/VIIIa [$F(1,19)=5.65$, p=.028], right Crus I/Lobule VI [F(1,19)=5.87, p=.026], and right Lobule VIIb/VIIIa [F(1,19)= 4.24, p=.053]. No effects of practice or a load by time interaction were found for any region of interest.

Table 2: Percent signal change during the n-back for each cerebellar ROI during each portion of the n-back tasks.

	1-back before	1-back after	2-back before	2-back after
Right Crus I/Lobule VI	.097	.062	.238	.126
Right Lobule VIIb/LobuleVIIIa	.009	.049	.117	.093
Left Crus I/Lobule VI	.112	.076	.224	.142
Left Lobule VIIb/LobuleVIIIa	.048	.022	.175	.098

One-sample t-tests were conducted to detect whether correlations conducted between blockwise % signal change and RT were significantly greater than zero across the sample. Blockwise reaction time was nearly significantly correlated with % signal change only in the left Crus I/Lobule VI during the 2-back before practice [t(19)=1.991, p=.061] A paired t-test revealed a trend toward reduction in RT in the 1-back after practice [t(19)= 1.67, p=.11]. A paired t-test revealed a statistically significant reduction in RT in the 2-back after practice [t(19)=2.10, p=.05]. Overall, RT was significantly higher during the 2-back [t(19)= 6.50, p<.001] See Table 3 for mean RT and accuracy values during each phase of the task.

Table 3: Reaction times and accuracy during the n-back tasks.

	1-back before	1-back after	2-back before	2-back after
Mean Reaction Time	572.48	531.85	693.59	641.55
Mean Accuracy	99.4	99.3	90.6	93.6

Hypothesis 2: Effects of practice on cerebellar relationships with reaction time

A 2x2 within-subjects ANOVA was conducted to detect influence of practice and load on the relationship between RT and % signal change. No significant effects of practice were found for any cerebellar ROI. However, a significant effect of load on the relationship between RT and %

signal change was found for the right Crus I/Lobule VI [F(1,19)=4.47, p=.048, from -.11 to .11] and the right Lobule VIIb/VIIIa [F(1,19)=8.68, p=.008, from -.11 to .10].

Hypothesis 3: Relationships between the right cerebellum and contralateral prefrontal and parietal regions

Correlation coefficients between BOLD cerebellar and contralateral neocortical regions were submitted to a one-sample t-test to determine if relationships were significantly different from zero. All cerebellar regions of interest were highly correlated with anatomically connected contralateral prefrontal and parietal regions irrespective of load and practice (see Table 3; see also Figure 7).

Table 4: Correlations between cerebellar ROIs and contralateral neocortical regions

Run	Correlation	t	df	Significance (2-Tailed)
1-back before practice	Right Crus I/Lobule VI with Left BA46	3.507	19	.002*
	Right Lobule VIIb/VIIIa with Left BA40	3.068	19	.006*
1-back after practice	Right Crus I/Lobule VI with Left BA46	4.120	19	.001**
	Right Lobule VIIb/VIIIa with Left BA40	1.900	19	.073
2-back before practice	Right Crus I/Lobule VI with Left BA46	2.989	19	.008*
	Right Lobule VIIb/VIIIa with Left BA40	3.228	19	.004*
2-back after practice	Right Crus I/Lobule VI with Left BA46	3.526	19	.002*
	Right Lobule VIIb/VIIIa with Left BA40	3.736	19	.001**

 * indicates significance at p<.05; ** indicates significance at p<.001

Figure 7: Regions highly correlated to one another during the n-back Task.
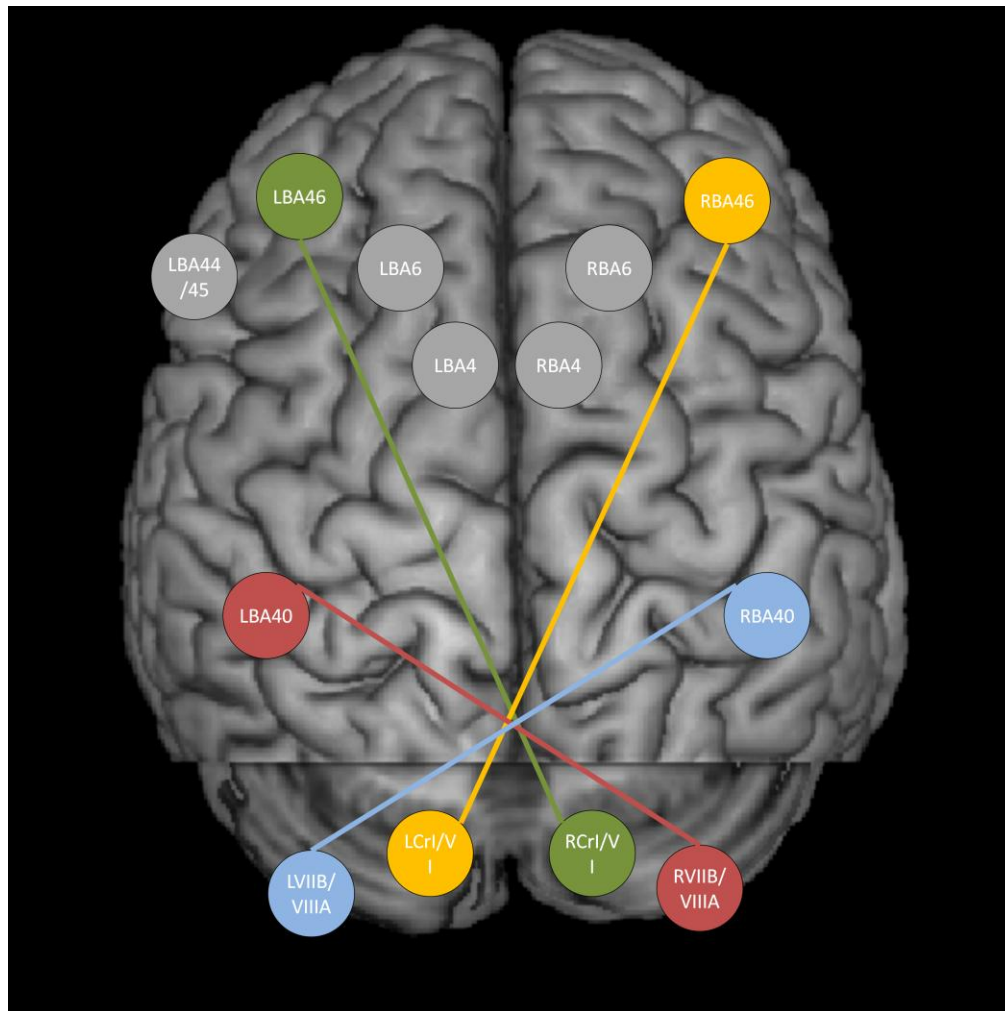
Regions that share matching colors were highly correlated during the n-back tasks.

Hypothesis 4: Cerebellum relationships with associative versus motor regions

Of individual uSEM models estimated within the sample, 3 out of 80 were unable to converge after 1000 iterations and were excluded. Of the remaining models, 83% were a good fit according to RMSEA, NNFI, CFI or SRMR criteria. Within-subjects t-tests were conducted on connections derived from individual uSEM models to test the hypothesis that the cerebellar

regions of interest were more significantly related to associative neocortical regions as opposed to motor and motor planning regions. The left cerebellum (including both left cerebellum ROIs) exerted more "directed" influences on the right neocortical associative (BA 46 and BA 40) regions than on motor regions during the 2-back before practice [t(18)=2.348, p=.031; mean= .58 vs. .21] (see Figure 8).

Figure 8: Schematic representation of the directed influences from the left cerebellum to the right BA 46 and 39 during the 2-back before practice.
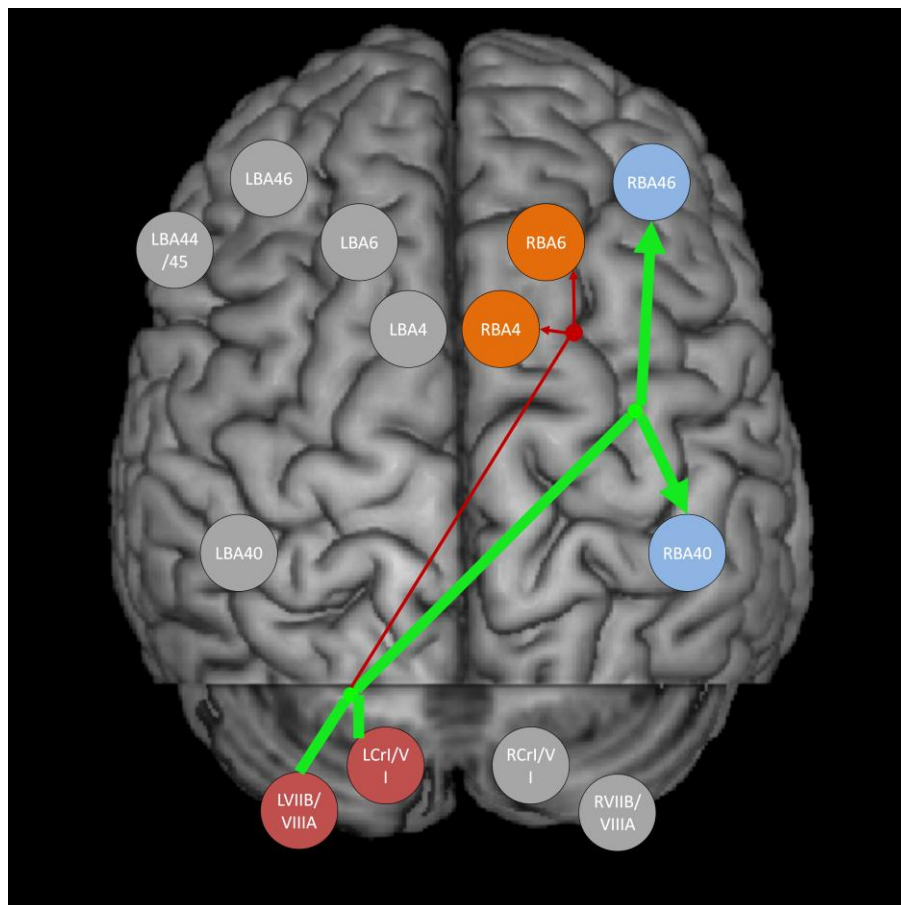
The overall number of connections (in either direction) during the 2-back before practice between the right associative and left cerebellar ROIs was also greater than those between the left cerebellum and motor regions [t(18)=3.314, p=.004; mean= 1.16 vs .53]. The directed influence of the left cerebellum on the right associative regions was no longer greater than motor regions during the 2-back after practice, but the bidirectional influences remained higher between the left cerebellum and right associative regions than those with motor regions during the 2-back after practice [t(19)= 2.405; mean= 1.35 vs .65] (see Figure 9).

Figure 9: Schematic representation of the bidirectional influences between the left cerebellum and the right BA 46 and 39 during the 2-back after practice.
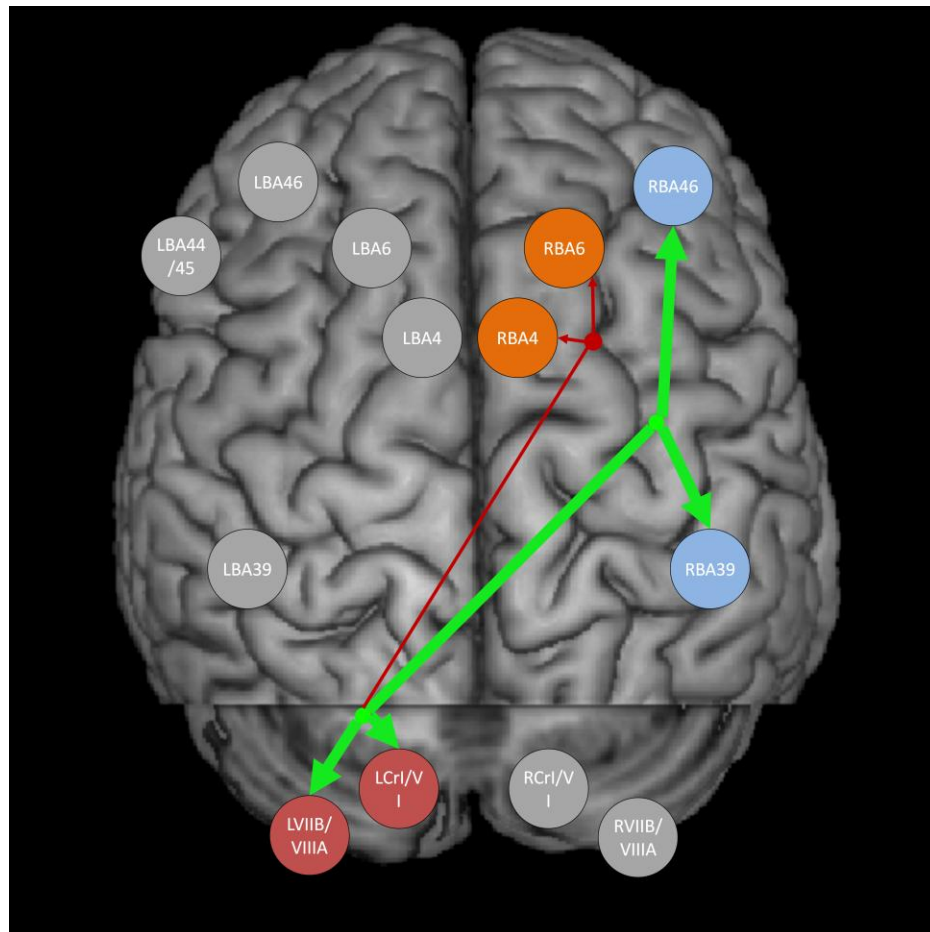
Hypothesis 5: Effects of practice on corticocerebellar connectivity and changes in reaction time

Several within-subjects t-tests were conducted on connections derived from individual uSEM models to detect changes in corticocerebellar connectivity following practice. No main effects of practice were observed on directed influences between the cerebellum and associative regions. There was a nearly significant decrease in the influence of the right Lobules VIIb/VIIIa on the left BA 46 during the 1-back after practice [t(17)=1.84, p=.083; from .22 to .06]. Correlations were conducted between changes in the total bidirectional right cerebellum/left associative region influences and changes in RT for both load levels. No significant correlations were found. In post hoc tests, changes in raw corticocerebellar R values and contralateral associative regions were regressed against changes in RT to test whether changes in covariance between regions significantly predicted changes in performance. No significant results were obtained.

Chapter 4

Discussion

The present study used a verbal WM task to investigate the hypothesis that the cerebellum contributes to cognitive functioning, specifically verbal WM, in a distributed cortico-cerebellar network. Of specific interest was the dissociability of connections between the cerebellum and motor regions versus connections between the cerebellum and associative regions. We extended previous work in verbal WM and functional connectivity analyses to examine the effects of task load and practice on the cerebellum and whether cerebellar activity predicts reaction time. The current work differs from previous investigations in that it uses ROIs defined by a probabalistic anatomical atlas, avoiding known biasing problems in ROI selection (cf. Vul et al., 2009) and providing a conservative approach to the hypotheses. Futhermore, we examined the relationship to reaction time without confounding with load level. We examined two bilateral ROIs: the Crus I/Lobule VI and Lobule VIIb/VIIIa, which have been shown to be active during cognitive tasks (Stoodley & Schmahmann, 2009).

Load affected % signal change in all four cerebellar regions of interest. However, practice was not found to affect cerebellar % signal change in any region of interest. Slight reductions in % signal change were observed during the 2-back, but the effects were subtle, typically in the .1% range. Part of the inability to identify mean signal change changes over time may be due to the relatively large size of the ROIs as neocortical regions may synapse on small areas within specific lobules of the cerebellum

Blockwise reaction time and % signal change were found to be correlated only in the left Crus I/Lobule VI during the 2back before practice. Notably, this is the first time that the

participants encountered the more demanding task. Previous work has shown that one neocortical region with which these lobules are connected, the DLPFC (BA 46), is highly responsive to reaction time (Hillary et al., 2010) and task practice (Medaglia et al., in press). It may be that this cerebellar region is integrally involved in task acclimation and the establishment of subroutines for effective performance in conjunction with this neocortical region. The relationship between this region and reaction time was not observed during the 2-back after practice, which may suggest that the link between these regions is less instrumental after neurally efficient subroutines are in place. Interestingly, the right cerebellar ROI relationships with reaction time were shown to be responsive to load, and relationship between right cerebellum and load switched from a negative correlation in the 1-back to a positive correlation in the 2-back. The change in correlation to RT may also have implications for degree of challenge in the task and how the cerebellum accomodates this difficulty. The correlations, however, were quite small in the current study (accounting for less than 1% of variance), and event-related designs with greater power to detect nuances in relationships with RT may be instrumental to understand contingencies on task difficulty.

The right cerebellar ROI timeseries were all highly correlated with the contralateral neocortical regions (Parietal lobe, DLPFC) with which they share known anatomical substrates. These relationships existed for all phases of the n-back task, demonstrating that the BOLD covariance between the investigated regions was not dissociable across time or load level despite relatively large ROIs. These findings suggest that these regions are very interactive with the cerebellum during cognition in a manner that recapitulates their anatomical connections. Importantly, no changes in overall relationships between regions were found, which indicates

that the cerebellum remains relevant in the extended network despite load differences and exposure to task.

The potential for the cerebellum to serve a directing cognitive role in the distributed network was a point of primary interest in the current study. Exploratory uSEM models including 13 spatially distinct ROIs revealed several features of the "directed" influences within the network and the nature of connections to associative and motor regions. Of note, connections that are considered "directed" in the uSEM estimation are derived from a correlation matrix. Thus, while ROIs that are considered an independent variable in the model predict significant variance in the other region and this connection significantly adds to the model fit, causality cannot be inferred. In the current data, models demonstrated that the left cerebellar ROIs exerted more influences on the right neocortical associative (BA 46 and BA 40) regions than motor regions during the 2-back before practice. When bidirectional influences were considered, the right cerebellum to left associative region connections were greater than the motor connections throughout the entire 2-back. These trends were not found during the 1-back. The dissociation between loads may be critical for understanding a cerebellar contribution to the distributed network in cognition. Motor and cognitive systems are thought to be only partly dissociable, and motor systems may play active and critical roles during some modes of cognition, particularly when responses are required (cf., Rosenbaum, 2005). The 2-back ostensibly requires bits of information to be maintained in WM while the task is executed, and increased reaction time and lower accuracy suggest that it is more cognitively demanding than lower load level n-backs. Thus, the increased connections with associative regions relative to motor regions during the 2-back accompany a manipulation in load, suggesting that while

motor regions are still predicted by the cerebellum and vice versa, the cortico-cerebellar associative relationships become more critical in the higher load to maintain task performance. Notably, the directed influences of the cerebellum on associative regions no longer exceeded the influences on motor regions in the 2-back after practice, which may point to a less active and "controlling" role of the cerebellum after subroutines are established.

Overall, practice did not significantly influence the connections between the right cerebellum and left neocortical associative regions. However, there was a trend toward a reduction in the influence of the right Lobules VIIb/VIIIa on the left Broca's region after practice in the 1-back. The Broca-cerebellar link was not affected during the 2-back. It may be the case that this link becomes more efficient during time when executing the easier WM task, but remains equally critical across time during the more highly activating 2-back.

The current study supports several conclusions. First, the current cerebellar regions are functionally tightly linked with associative regions during the execution of both loads of a verbal WM task. The raw correlations between regions, specifically right cerebellum to left associative neocortical regions, remain constant across loads and time despite any imprecision in ROI selection and the BOLD signal. Second, the cerebellum was also responsive to load across regions, similarly to neocortical regions known to be involved in WM, such as the DLPFC, anterior cingulate cortex and parietal lobe (Medaglia et al., in press). It is unclear why a uniquely motor process should demand additional neural computation during the more cognitively difficult task, suggesting that the cognitive demand influenced cerebellar activity. Third, the relationship between the cerebellum and reaction time may be region, load and time

specific when concerned within accuracy responding in verbal WM, as implied by the finding that only the left Crus I/Lobule IV was correlated with reaction time during the 2-back. This region is anatomically and functionally connected to the contralateral dorsolateral PFC, which may have implications for a role in cognitive control, particularly in novel or demanding situations (Medaglia et al., in press; Ridderinkhof et al., 2004). Despite non-significant first-level correlations with reaction time, the responsiveness to task load of right cerebellar relationships with reaction time may similarly point to its relevance to performance in situations of higher difficulty. Finally, the cerbellar influences on other regions is relatively similar to motor connections in relatively easy WM conditions, but also increases when task challenge is higher, and its direct influence within the cortico-cerebellar system may decline over time within a task. Thus, while motor region influences to and from the cerebellum are present during WM, there are functional effects that cannot be accounted for by motor demands. These novel findings point to a directive role of a cerebellar process during difficult tasks that may be critical in understanding the functional role of the cerebellum (e.g., motor vs. cognitive, spatial vs. verbal, etc). This may involve differential recruitment of the cerebellum's theorized ability in coordinating expected and actual events and the modification of subroutines as the task unfolds and a role of the cerebellum in cognitive control. More difficult tasks may require more neural resources, and thus increased demand on the cerebellum's "universal transform" (cf. Schmahmann, 2004).

Several important limitations apply to the current study. The first concerns the nature of the selection of ROI data. As mentioned previously, probalistically defined ROIs were used to avoid known biasing problems in ROI analysis and to sample data from a standard anatomical

space across individuals. While these ROIs were from regions known to be activated across cognitive tasks, they still encompassed entire lobules of the cerebellum. It may be that cognitively invovled cerebellar regions are considerably more spatially circumscribed within cerebellar lobules. Therefore, the current analysis will be relatively inclusive for both regions involved specifically in the tasks and other regions that may be less relevant. However, it is also difficult to choose one consistent small ROI within the cerebellum because the location of functional nodes may be variable across individuals. Future studies may attempt to localize functional cerebellar nodes within individuals with independent tasks and sample timseries from those nodes for use in tasks intended for connectivity analyses. This limitation also applies to the large ROIs used for neocortical regions. It may be that the current timeseries analyses missed more nuanced relationships between regions and to reaction time because of error in the BOLD signal. Also, only accurate responses of the n-back contributed to measures of reaction time. While this avoids the possibility of a putatively different process (namely, a process that produces incorrect responses) contributing to the behavioral measure, it may reduce the power to detect relationships between the BOLD signal and behavior.

Despite these limitations, the current study provides several key findings that promote our understanding of how specific lobules of the cerebellum are involved in a cognitive task. The current study points to a highly integral and interactive role of specific regions of the cerebellum during verbal WM that appears to extend beyond basic motor processing. We primarily demonstrated several within-subject effects that appear to correspond with findings in neocortical findings of change in the BOLD signal during task performance and direct differences in connectivity between one subregion of the cerebellum and associative versus

motor regions. The current findings indicate that the global activity in the lobules of interest is dynamic and contingent upon task exposure and load, and perhaps more surprisingly may change with respect to how they predict performance depending on difficulty level of a task. Thus, while the specific computation that the cerebellum performs likely remains static as suggested by its cytoarchitecture, how, when and where in the cerebellum this computation is recruited might be variable based on cognitive demand. The use of methods that examine the cerebellum in the context of a distributed brain system and precise anatomical localization of relevant regions may help to specify the unique role of the cerebellum during WM and cognition.

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