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BOSTON UNIVERSITY

GRADUATE SCHOOL OF ARTS AND SCIENCES

Dissertation

CEREBELLAR CONTRIBUTIONS TO VISUAL ATTENTION AND WORKING MEMORY

by

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B.S., University of Oregon, 2013 M.A., Boston University, 2015

Submitted in partial fulfillment of the

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DEDICATION

I would like to dedicate this work to my patient and loving spouse Natalie.

ACKNOWLEDGMENTS

I owe a great debt of gratitude to the many people who contributed in some way to this dissertation. First, I want to acknowledge my advisor, David Somers, who has been an incredible mentor to me these last six years. I would not be where I am today without his constant encouragement, guidance, and insight. I would also like to especially thank Mark Halko who planted the seed that inspired much of this dissertation. His mentorship and advice throughout my graduate career have been invaluable. I want to thank Sam Ling for his insightful feedback on my manuscripts. I also want to thank Chantal Stern for her generous support and advice throughout my time at BU. I want to thank Joe McGuire for his thoughtful comments on my research.

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CEREBELLAR CONTRIBUTIONS TO VISUAL ATTENTION AND WORKING MEMORY JAMES A. BRISSENDEN

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ABSTRACT

Attention and working memory (WM) are processes that enable the efficient prioritization or storage of a subset of available information. Consequently, a substantial body of work has sought to determine the specific brain structures that support attention and WM. To date, this literature has predominantly focused on the contributions of a limited set of cortical areas referred to as the dorsal attention network (DAN). The cerebellum, a subcortical structure traditionally implicated in motor control, has received scant consideration as a locus of attentional control, despite findings of robust anatomical and functional connectivity between cerebellum and DAN areas. This project comprises several functional magnetic resonance imaging experiments aimed at elucidating the role of the cerebellum in attention and WM (n = 38; 20-38 years).

The functional implications of cortico-cerebellar DAN connectivity have received only modest scientific attention. Experiment 1 examined the hypothesis that corticocerebellar DAN functional connectivity predicts recruitment by canonical visual WM and attention tasks. Task-driven responses of DAN-coupled cerebellar areas were found to mirror those of their cortical counterparts. These results argue for the reconceptualization of the DAN as a cortico-cerebellar network. Previous work indicates that the functional topography of the cerebellum is relatively coarse compared with cerebral cortex. Experiment 2 examined the organization of closely related aspects of visual attention and WM within the cerebellum, and found that spatial attention and visual WM recruit overlapping yet dissociable portions of cerebellar lobule VIIb/VIIIa. This functional organization was further shown to be predicted by fine-scale patterns of functional connectivity with occipito-parietal cortex. These findings indicate that the functional specificity of cerebellar cortex mirrors that of cerebral cortex and provides direct empirical support for the hypothesis that functional specialization within the cerebellum arises due to variation in afferent input.

Experiment 3 tested the hypothesis that the cerebellum can be specifically implicated in the persistent representation of information in WM. Lobule VIIb/VIIIa delay-period activity patterns were shown to exhibit stimulus-selectivity, a critical marker of WM storage processes. These results indicate that lobule VIIb/VIIIa contains a robust representation of a stimulus stored in WM, thereby refuting long-standing cortico-centric models of WM maintenance.

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LIST OF ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
aInsula	Anterior Insula
ANOVA	Analysis of Variance
BOLD	Blood Oxygen Level Dependent
CAS-p	Posterior Callosal Sulcus
CCAS	Cerebellar Cognitive Affective Syndrome
CCN	Cognitive Control Network
dACC	Dorsal Anterior Cingulate Cortex
DAN	Dorsal Attention Network
DMN	Default Mode Network
EPI	Echo Planar Imaging
FEF	Frontal Eye Fields
fMRI	Functional Magnetic Resonance Imaging
FOV	Field of View
FWHM	Full-Width Half-Maximum
FWM	Feature Weight Mapping
IFJ	Inferior Frontal Junction
iPCS	Inferior Pre-Central Sulcus
IPS	Intraparietal Sulcus
ITI	Inter-Trial Interval
LIMB	Limbic Network

M1	Primary Motor Cortex
MNI	
MOT	
MPRAGE	Magnetization-Prepared Rapid Acquisition with Gradient Echo
MT+	
RMS	
SOM	Somatomotor Network
sPCS	
SS1	
SS4	
SUIT	
TR	
VAN	
VWM	

CHAPTER ONE: BACKGROUND

Preamble

Attention and working memory are processes that enable the prioritization of a subset of available information in our environment. As such, attention and working memory are thought to critically underlie a broad range of cognitive abilities such as fluid intelligence, reading comprehension, and scholastic aptitude (Cowan et al., 2005; Cowan, Fristoe, Elliott, Brunner, & Saults, 2006; Engle, 2002; Engle, Tuholski, Laughlin, & Conway, 1999; Fukuda, Vogel, Mayr, & Awh, 2010). Much of the research on the neural substrates of attention and working memory suggests these processes are mediated by a small number of frontal and parietal cortical regions (Corbetta & Shulman, 2002a; Ptak, 2012; Scolari, Seidl-Rathkopf, & Kastner, 2015). A limited set of subcortical areas have also historically been implicated in visual attention, namely the superior colliculus and pulvinar nucleus (Ignashchenkova, Dicke, Haarmeier, & Thier, 2004; Müller, Philiastides, & Newsome, 2005; Petersen, Robinson, & Morris, 1987). The majority of subcortical structures, however, have not been traditionally associated with attentional functions. The cerebellum, in particular, has received little consideration as a locus of attentional control. Rather, substantial evidence primarily links the cerebellum with motor control and coordination (Brooks & Thach, 2011; Evarts & Thach, 1969; Gilbert & Thach, 1977; Ito, 1984; Llinás, 1985). Nevertheless, recent research suggests that cerebellar cortex exhibits considerable heterogeneity in its anatomical and functional connections with extracerebellar structures (Buckner, Krienen, Castellanos, Diaz, & Yeo, 2011; Kelly & Strick, 2003). This includes evidence for connectivity between cerebellum

and canonical attention and working memory areas in fronto-parietal cortex (Buckner et al., 2011; Kelly & Strick, 2003; Prevosto, Graf, & Ugolini, 2010; Schmahmann & Pandya, 1989; 1997a). Consequently, a number of studies have found evidence for cerebellar recruitment by a variety of non-motor functions, including attention and working memory (Allen, Buxton, Wong, & Courchesne, 1997; S. A. Chen & Desmond, 2005a; Guell, Gabrieli, & Schmahmann, 2018a; Stoodley & Schmahmann, 2009; Stoodley, Valera, & Schmahmann, 2012). Yet, little is known about the cerebellum's position within the hierarchy of the brain's visual attention circuitry. The experiments detailed in this dissertation are aimed at elucidating the role of the cerebellum in visual attention and working memory processes.

This introduction will first review cerebellar anatomy and the organization of cerebrocerebellar circuits. A review of converging evidence from lesion, functional imaging and brain stimulation studies for cerebellar contributions to attention and working memory will follow. Then, I will summarize various computational theories of cerebellar function. Next, I will review functional characteristics of areas previously implicated in attention and working memory task performance. Lastly, this chapter will end with an overview of the remaining chapters, which describe a series of functional magnetic resonance imaging (fMRI) experiments to investigate cerebellar participation in brain networks responsible for directing visual attention and working memory processes.

Cerebellar Anatomy

The cerebellum, deriving its name from the diminutive of "cerebrum," is located within the posterior cranial fossa lying dorsal to the fourth ventricle, pons and medulla. Cerebellar cortex consists of a tightly folded continuous sheet of gray matter, which if full spread out spans approximately 11 m² in total surface area in humans (Sultan & Braitenberg, 1993). Projections from cerebellar cortex are routed through a set of nuclei lying within the white matter. Cerebellar neuronal structure is highly stereotyped, consisting of the same repeating neuronal elements throughout its extent (Ramnani, 2006). Cerebellar cortex can be organized into 3 layers: the granular layer, the Purkinje cell layer, and the molecular layer. Cerebellar afferents known as mossy fibers synapse on granule cells in the granular layer. The middle layer (Purkinje cell layer) contains Purkinje cell somata, and the topmost layer (molecular layer) contains parallel fibers (granule cell axons), interneurons, and Purkinje cell dendritic arbors. The cerebellum can be grossly subdivided into two hemispheres and a midline region known as the vermis. Each of these structures can be further subdivided into 10 lobules (Figure 1.1; Schmahmann et al., 1999). Cerebellar lobules are organized into an anterior lobe (lobule I-V), a posterior lobe (lobule VI-IX), and a flocculonodular lobe (lobule X).



Figure 1.1 Cerebellar Lobule Organization. Pial surface representation of the cerebellum from superior (top left), anterior (bottom left), inferior (top middle), and posterior (bottom middle) views. Colors denote lobular boundaries. Flatmap representation of the cerebellum is shown on the right with corresponding lobular labels.

Cerebrocerebellar Connectivity

All connections between the cerebral cortex and cerebellum are polysynaptic. Afferent fibers originating from the cerebral cortex reach cerebellar cortex via the pons or the inferior olivary nucleus. Pontocerebellar and olivocerebellar projections are referred to as mossy fibers and climbing fibers, respectively. Mossy fibers innervate both excitatory granule cells and inhibitory golgi cells. Granule cells send axons to the molecular layer where they bifurcate to form parallel fibers. These parallel fibers form synapses with Purkinje cells. Climbing fibers stemming from the inferior olivary nucleus project to both Purkinje cell dendritic arbors and cerebellar nuclei. Each Purkinje cell receives input from a single climbing fiber (Eccles, Llinás, & Sasaki, 1966). Efferent connections are relayed to the cerebral cortex through the cerebellar nuclei and then the thalamus (Evarts & Thach, 1969; Kemp & Powell, 1971; Schmahmann & Pandya, 1997b; Strick, 1985). Thus, both the afferent and efferent limbs of the cerebrocerebellar circuit consist of two stages. The lack of monosynaptic connections between cerebellum and cerebral cortex meant that researchers using traditional tract tracing techniques were limited in their ability to fully characterize cortico-cerebellar circuits (Buckner, 2013). Consequently, for many years there was little anatomical evidence to suggest that the cerebellum communicated with non-motor cortical structures. Schmahmann and Pandya relied on knowledge of the first stage of the feedforward limb of the cerebrocerebellar circuit to specifically examine whether non-motor areas of cerebral cortex project to the cerebellum. In a series of studies, Schmahmann and Pandya injected an anterograde tracer into association areas in posterior parietal, temporal and pre-frontal cortex and then examined terminations in the pons (Schmahmann & Pandya, 1989; 1991; 1997a). They found that these areas do indeed extensively project to the pons (and presumably onto cerebellar cortex). Projections were further shown to be topographically arranged, with each cerebral cortical area projecting to a distinct site within the pons (Schmahmann & Pandya, 1997b). Subsequently, the development of viral tracing techniques that could span multiple synapses allowed Strick and colleagues to examine the organization of both afferent and efferent limbs of the cortico-cerebellar circuit (Kelly & Strick, 2003). They first used a retrograde transneuronal tracer to identify areas of cerebellar cortex that projected to either primary motor cortex (M1) or prefrontal cortex area 46. It was shown that an area located within lobules IV-VI projected to M1 and a distinct area located in Crus II within the lateral cerebellar hemispheres projected to area 46. In a follow-up experiment, they used an anterograde transneuronal tracer to identify cerebellar areas which received input from M1 or area 46. It was shown that lobules IV-VI received projections from M1 and Crus II received projections from area 46. Thus, they showed that regions of cerebellar cortex project back to the same cerebral cortical regions from which they receive input. Furthermore, they demonstrated that circuits connecting cerebellum with motor and non-motor areas of cerebral cortex are segregated. The authors subsequently proposed that "multiple closed-loop circuits represent a fundamental architectural feature of cerebro-cerebellar interactions" (p. 413) (Strick, Dum, & Fiez, 2009). Despite these advances, however, a more complete mapping of cerebrocerebellar organization remained elusive. Buckner and colleagues took advantage of the fact that resting-state fMRI approaches are able to 1) probe indirect connections

between areas; and 2) provide complete coverage of both the cerebral cortex and cerebellum. Resting-state fMRI relies on the fact that low-frequency fluctuations in blood-oxygen level-dependent (BOLD) signal covary between areas that possess either monosynaptic or polysynaptic connections (Biswal, Zerrin Yetkin, Haughton, & Hyde, 1995; Van Dijk et al., 2010). A cluster analysis of a large sample of resting-state scans (N=1000) revealed that the proportion of the cerebellum preferentially coupled with a particular cortical network is proportional to that network's extent in the cerebral cortex (Buckner et al., 2011). Remarkably, it was further shown that the majority of the cerebellum maps to cortical association networks. Thus, it appears that a substantial portion of cerebellum may be involved in domains other than motor processing.

It should be noted that much of the work examining cerebellar connections with cortical association cortex has focused on the cortico-ponto-cerebellar circuit. Projections from neocortex to the inferior olive, which serves as the source of climbing fiber input to the cerebellum, have received little scientific attention. As climbing fiber input figures prominently in computational models of the cerebellum (see below), achieving a better understanding of cerebellar contributions to cognitive processing will require a more complete mapping of cortico-olivary projections.

Neuropsychological Evidence for a Cerebellar Involvement in Cognition Some of the earliest evidence for potential cerebellar contributions to cognition came from studies of patients with cerebellar lesions. Cerebellar cognitive affective syndrome (CCAS), resulting from injury to the cerebellar posterior lobe, is characterized by deficits across a diverse array of cognitive and affective domains (Levisohn, Cronin-Golomb, &

Schmahmann, 2014; Schmahmann & Sherman, 1998). Furthermore, there is substantial evidence for covert attentional deficits resulting from cerebellar damage (Akshoomoff & Courchesne, 1992; 1994; Courchesne et al., 1994; Schweizer, Alexander, Cusimano, & Stuss, 2007; Townsend et al., 1999). These deficits are apparent in patients with acquired cerebellar lesions, as well as in patients with autism and attention deficit hyperactivity disorder (ADHD), disorders known to be associated with cerebellar anatomical abnormalities (Castellanos et al., 2002; Courchesne et al., 1994; Courchesne, Yeung-Courchesne, Hesselink, & Jernigan, 1988). Despite these findings, the notion of cerebellar involvement in attention was still considered controversial, in part due to several studies of cerebellar patients which failed to observe attentional deficits (Dimitrov et al., 1996; Golla, Thier, & Haarmeier, 2005; Haarmeier & Thier, 2007; Ravizza et al., 2006; Yamaguchi, Tsuchiya, & Kobayashi, 1998). One explanation for these divergent findings is the use of heterogeneous patient groups, which vary substantially in the location and extent of cerebellar damage, as well as the source of cerebellar abnormality (lesion or degeneration). The assumption inherent across these conflicting reports is that lesions located anywhere in the cerebellum will produce identical deficits. This would only be true, however, if the cerebellum is functionally homogenous. Recent work suggests that this is not the case. Baier and colleagues (2010) performed lesion-mapping to specifically examine differences in lesion location between patients with and without attentional deficits (Baier, Dieterich, Stoeter, Birklein, & Müller, 2010). They found that only a subset of patients (8/26) exhibited abnormal reaction times in a covert attention task. When compared to patients with normal reaction times, patients with impaired performance were more likely to possess lesions localized to vermal lobule VI and Crus I. A later study found that lesions located in Crus II, lobule VIIb and lobule VIIIa were also associated with attentional impairments (Striemer, Cantelmi, Cusimano, Danckert, & Schweizer, 2015a). These findings provide clear evidence for functional specialization within the cerebellum, with specific cerebellar structures associated with attention deficits.

Functional Imaging

The advent of neuroimaging methods such a PET and fMRI allowed researchers to measures responses elicited by task performance throughout the brain. The increased field of view afforded by these methods meant that activity could be recorded from cerebral cortex and cerebellum simultaneously. Consequently, a number of early neuroimaging studies revealed cerebellar activation in response to non-motor tasks, despite not necessarily setting out to do so. For example, Petersen et al. (1989) found that a word generation task activated the right lateral cerebellum (Petersen, Fox, Posner, Mintun, & Raichle, 1989). Critically, this activation was evident despite motor responses being equated across conditions. Over the next thirty years, numerous studies found evidence for cerebellar recruitment by non-motor paradigms (e.g. Allen et al., 1997; Chen & Desmond, 2005a; Kirschen, Chen, Schraedley-Desmond, & Desmond, 2005; LaBar, Gitelman, Parrish, & Mesulam, 1999; McDermott, Petersen, Watson, & Ojemann, 2003; Rao et al., 1997; Valera, Faraone, Biederman, Poldrack, & Seidman, 2005). A metaanalysis by Stoodley and Schmahmann (2009) detailed the emerging organization of motor, somatosensory, language, verbal working memory, spatial and executive function

within the cerebellum. Their analysis revealed that motor and non-motor functions are topographically organized within the cerebellum. Somatomotor activation was localized to the anterior lobe and lobule VIIIb, consistent with previous somatotopic mapping studies performed in both non-humans and humans (Adrian, 1943; Grodd, Hülsmann, Lotze, Wildgruber, & Erb, 2001; Rijntjes, Buechel, Kiebel, & Weiller, 1999; Snider & Stowell, 1944; Wiestler, McGonigle, & Diedrichsen, 2011). Cognitive and affective activation, on the other hand, was localized to various areas in the posterior lobe. Thus, the topographic arrangement of motor and cognitive functional activation aligns with the organization revealed by connectivity measures (Buckner et al., 2011; Kelly & Strick, 2003).

Several fMRI studies have specifically examined cerebellar recruitment by attention and working memory tasks. Allen and colleagues (1997) found evidence for a double dissociation whereby attention and motor task performance activated distinct portions of the cerebellum. Subjects performed a task in which they were either instructed to selectively attend and count target items of a specific shape or color (attention task), or repeatedly perform a self-paced motor response (motor task). The attention task was found to activate an area located within lobule VI and Crus I, and the motor task activated a distinct area within the anterior lobe (lobule III-V). Another study showed that shifts of attention elicited robust activation of Crus I, as well as a midline region within lobule VII (Le, Pardo, & Hu, 1998). There is also substantial evidence that specific portions of the cerebellum are modulated by working memory load (Chen & Desmond, 2005b; 2005a; Desmond, Gabrieli, Wagner, Ginier, & Glover, 1997; Kirschen et al., 2005). In one study, working memory load was parametrically increased (2-6 visually presented letter stimuli) using a two-alternative forced-choice Sternberg task. Linear load-dependent increases in activation were found in both lobule VI/Crus I and lobule VIIb/VIIIa (Kirschen et al., 2005). Taken together, these studies provide further evidence for the involvement of specific areas within the cerebellum in attention and working memory task performance.

Stimulation of the Cerebellum

Several recent studies employing brain stimulation techniques further argue for the contribution of specific cortico-cerebellar circuits to attention and working memory function. Halko and colleagues (2014) applied intermittent theta-burst stimulation to either lateral Crus I/II or midline lobule VII. These areas exhibit functional connectivity with the default network and dorsal attention network, respectively (Buckner et al., 2011). Stimulation was shown to selectively increase functional connectivity within the network corresponding with each cerebellar target region (default network or dorsal attention network). Although this study did not involve performing a task, these findings indicate that cerebellar network nodes are capable of selectively modulating greater network function. Cerebellar stimulation has also been shown to increase or decrease performance in an attentional blink paradigm, depending on whether the stimulation protocol was excitatory or inhibitory (Arasanz, 2012; Esterman et al., 2017). Moreover, stimulation of right cerebellum has been shown to interfere with short-term memory of novel sequences (Ferrari et al., 2018).

Theories of Cerebellar Computation

There are various theories concerning the computations performed by the cerebellum. The majority of cerebellar models are rooted in the notion of the cerebellum as a supervised learning machine (Koziol et al., 2014; Raymond & Medina, 2018). Early influential models introduced by Marr and Albus proposed that cerebellar circuitry is ideally suited for pattern recognition (Albus, 1971; Marr, 1969). These models are based on several anatomical and physiological features of cerebellar circuitry. Mossy fibers synapse onto an average of ~500 granule cells (Ito, 1984), while up to ~200,000 parallel fibers converge onto a single Purkinje cell (Fox & Barnard, 1957). Excitation from parallel fibers causes Purkinje cells to discharge simple spikes (normal action potentials). In contrast, each Purkinje cell receives input from a single climbing fiber. Climbing fiber input produces a powerful burst of action potentials referred to as a complex spike (Eccles et al., 1966). The divergence and convergence in the mossy fiber pathway is suggested to support a fine-grained representation of context. In both the Marr and Albus models, climbing fiber input is said to provide a "teaching" signal that modulates plasticity at the parallel fiber Purkinje cell synapse. As such, motor commands can be paired with specific contexts. Marr and Albus differed in the exact mechanism by which the synapse was modulated, with Marr proposing a change via potentiation and Albus proposing modulation via depression. Ito and Kano (1982) provided empirical support for Albus' account, showing that conjunctive activation of parallel fibers and climbing fibers produces long-term depression of the parallel fiber-Purkinje cell synapse. Building on these ideas, others have suggested the cerebellum serves to encode input-output

relationships between motor actions and sensory consequences through the generation of internal models (Wolpert, Miall, & Kawato, 1998). Two classes of internal models have been proposed. Forward models generate predictions of the sensory consequences of a motor action, while inverse models generate motor commands necessary to achieve a desired state or goal (Ito, 2008; Wolpert et al., 1998). Regardless of the specific implementation, the hypothesized purpose of cerebellar internal models is to coordinate and fine-tune responses. Similar to the Marr-Albus model, learning is proposed to be mediated by putative error signals transmitted by the climbing fibers. In support of this hypothesis, recent work has shown that complex spikes exhibit error direction tuning (Herzfeld, Kojima, Soetedjo, & Shadmehr, 2015; Soetedjo, Kojima, & Fuchs, 2008). Furthermore, it has been shown that subsequent eye movements following a complex spike are biased in the opposite direction of its preferred error vector (Herzfeld, Kojima, Soetedjo, & Shadmehr, 2018). The cerebellum has also been characterizing as an internal timing device (Braitenberg, 1967; Bullock, Fiala, & Grossberg, 1994; Eccles, 1973; Ivry & Keele, 1989). This idea is based on research indicating that precisely timed responses to a conditioned stimulus depend on the cerebellum (McCormick & Thompson, 1984; Perrett, Ruiz, & Mauk, 1993), as well as work showing that damage to the cerebellum in humans interferes with the performance of tasks that require precise timing (Ivry, 2004; Ivry & Keele, 1989; Ivry, Spencer, Zelaznik, & Diedrichsen, 2002; Keele & Ivry, 1990). A common refrain among various theories of cerebellar function is that due to uniformity of cerebellar microstructure the computations performed by different areas of the cerebellum are mostly likely similarly invariant (Bloedel, 1994; Medina & Mauk, 2000;

Ramnani, 2006; Schmahmann, 2000). This idea is encapsulated by the concept of the "universal cerebellar transform", which proposes that the cerebellum acts to maintain behaviors around a homeostatic baseline regardless of the domain (Schmahmann, 2000). As a consequence, functional heterogeneity in the cerebellum is suggested to arise due to differences in afferent input rather than variation in cytoarchitecture (Ramnani, 2006).

Dorsal Attention Network

Considerable evidence demonstrates that a network of frontal and parietal cerebral cortical areas referred to as the dorsal attention network (DAN) supports visual attention and working memory function (Corbetta & Shulman, 2002; Ptak, 2012; Ptak, Schnider, & Fellrath, 2017; Scolari et al., 2015). The DAN is typically considered to comprise the intraparietal sulcus and superior parietal lobule within the parietal lobe, the superior and inferior pre-central sulcus within lateral frontal cortex, and area MT within occipitotemporal cortex (Corbetta & Shulman, 2002; Fox et al., 2005; Gao & Lin, 2012; Power et al., 2011; Ptak, 2012; Scolari et al., 2015; Szczepanski, Konen, & Kastner, 2010). A substantial body of research has detailed four characteristic properties of functional areas belonging to the visual DAN: 1) recruitment by sustained attention and working memory *paradigms* when contrasted with a sensorimotor control condition (e.g. Corbetta & Shulman, 2002; Culham et al., 1998; Sheremata, Bettencourt, & Somers, 2010; Szczepanski, Konen, & Kastner, 2010); 2) load-dependent activity that increases parametrically with the number of items successfully attended or maintained in working memory (e.g. Culham, Cavanagh, & Kanwisher, 2001; Sheremata et al., 2010; Todd & Marois, 2004a); 3) the representation of the spatial locus of attention and working

memory (e.g. Jerde, Merriam, Riggall, Hedges, & Curtis, 2012; Sprague & Serences, 2013); and 4) *maintenance of stimulus-specific mnemonic representations* over a delay (e.g. Ester, Sprague, & Serences, 2015; Harrison & Tong, 2009; Sprague, Ester, & Serences, 2014). While previous studies have investigated cerebellar recruitment by attention and working memory tasks, no one has systematically examined whether any portion of the cerebellum exhibits each of these characteristics. Such a demonstration would strongly indicate that the dorsal attention network functionally extends to the cerebellum.

Organization of Dissertation

The remainder of this dissertation is organized into four chapters. Chapters 2-4 will describe experimental research aimed at elucidating the cerebellum's role in attention and working memory. Chapter 5 will summarize the research described herein, as well as discuss possible future directions of study.

Chapter 2 presents two neuroimaging experiments designed to investigate whether the dorsal attention network functionally extends to the cerebellum. The first experiment had participants perform a lateralized visual working memory change detection paradigm. In this task, both the hemifield and the number of to-be-remembered items were manipulated. Consequently, this task requires both spatially-specific attention and the maintenance of information in working memory. The second experiment had participants perform a multiple object tracking paradigm, which requires participants to selectively attend targets items among identical distractors. Both paradigms have been shown to robustly recruit cortical dorsal attention network areas (Culham et al., 2001; Sheremata et al., 2010). In both experiments, subjects also underwent several runs of resting-state fMRI to assess the degree of functional connectivity between different portions of the cerebellum and cortical networks.

Chapter 3 presents research aimed at characterizing the topographic organization of visuospatial attention and working memory function within the cerebellum. The cerebral cortex is characterized by a high degree of functional specialization. Current evidence suggests the cerebral cortex contains upwards of 200 specialized areas in each hemisphere (e.g. Glasser et al., 2016; Gordon et al., 2016). The functional specificity of cerebral cortex can in part be explained by differences in cytoarchitecture (Zilles & Amunts, 2010). The microstructural organization of the cerebellum, on the other hand, is relatively homogenous (Bloedel, 1994; Eccles, 2013). Hence, the cerebellum is traditionally viewed as functionally invariant. However, both task and connectivity measures provide evidence for the topographic arrangement of function within the cerebellum (Buckner et al., 2011; Guell, Gabrieli, & Schmahmann, 2018a; Guell, Schmahmann, Gabrieli, & Ghosh, 2018b; Kelly & Strick, 2003; Stoodley et al., 2012; Stoodley & Schmahmann, 2009). Yet, these studies do not provide sufficient evidence to suggest that the cerebellum possesses a similar level of functional specificity as cerebral cortex. Data from the visual working memory change detection paradigm collected for chapter 2 is used to investigate whether any portion of the cerebellum exhibits selectivity for the spatial locus of attention. To further examine whether the cerebellum contains visual field representations, population receptive field mapping was additionally performed (Dumoulin & Wandell, 2008; Swisher, Halko, Merabet, McMains, & Somers, 2007). I then directly compare selectivity for different aspects of attention and working memory (e.g. working memory load and spatial coding) and determine whether differences in selectivity are predicted by resting-state functional connectivity with specific portions of cerebral cortex.

Chapter 4 presents a single fMRI experiment aimed at determining whether any portion of the cerebellum can be implicated in the maintenance of stimulus-specific representations in working memory. There is considerable debate concerning the neural substrates of working memory storage. To date, this research has focused entirely on cerebral cortical sites (Christophel, Klink, Spitzer, Roelfsema, & Haynes, 2017). To investigate working memory stimulus-specificity in the cerebellum, participants performed an event-related visual working memory task in which they were required to maintain the direction of coherent motion of a circular patch of moving dots over a long delay. I then used a generative model-based approach, which incorporates motion direction preferences to estimate the most probable stimulus given the pattern of voxel responses during the delay period.

Lastly, chapter 5 summarizes the findings presented throughout chapters 2-4, as well as discusses the significance of the presented work within the context of the current state of the field. Chapter 5 concludes with suggestions for future avenues of research.

CHAPTER TWO: FUNCTIONAL EVIDENCE FOR A CEREBELLAR NODE OF THE DORSAL ATTENTION NETWORK¹

Introduction

Attention influences neural structures throughout the brain, but is controlled by a more limited architecture (e.g. Kastner & Ungerleider, 2000). Our understanding of the brain structures that control attention has evolved from a unitary parietal locus (Critchley, 1955), to a fronto-parietal network (e.g. Mesulam, 1981; Posner & Petersen, 1989), to multiple networks (e.g. Corbetta & Shulman, 2002; Dosenbach et al., 2007; Michalka, Kong, Rosen, Shinn-Cunningham, & Somers, 2015; Rosen, Stern, Michalka, Devaney, & Somers, 2016; Yeo et al., 2011). Today, there is widespread agreement that a 'dorsal attention network' or 'fronto-parietal network' directs visual attention and short-term memory processes (Courtney, Petit, Maisog, Ungerleider, & Haxby, 1998; Hagler & Sereno, 2006; Ikkai & Curtis, 2011; Sprague & Serences, 2013; Szczepanski, Konen, & Kastner, 2010). Moreover, this network is distinct from a cingulo-opercular cognitive control network (Dosenbach et al., 2007; Power et al., 2011; Yeo et al., 2011). Yet, no consensus has been reached regarding the precise components of the dorsal attention network. On the basis of task-based and resting-state fMRI studies, the dorsal attention network in humans is typically defined to include all or some of the following four regions: 1. Intraparietal sulcus/superior parietal lobule (IPS/SPL); 2. Superior pre-Central sulcus (sPCS) containing the homologue of primate Frontal Eye Fields (FEF); 3. Inferior

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pre-Central sulcus (iPCS), alternately known as inferior frontal junction (IFJ); and 4. The motion-sensitive area MT complex (MT+) (Fox et al., 2005; Gao & Lin, 2012; Power et al., 2011; Ptak & Schnider, 2011; Szczepanski, Konen, & Kastner, 2010; Yeo et al., 2011). While subcortical structures such as superior colliculus and pulvinar are often implicated in attentional functions (e.g. Goldberg & Wurtz, 1972; Saalmann, Pinsk, Wang, Li, & Kastner, 2012), cerebellar structures are not typically discussed among the neural substrates of attention.

Prior work has demonstrated cerebellar activation during working memory and attention tasks (Allen et al., 1997; Desmond et al., 1997; Kellermann et al., 2012; Le et al., 1998; O'Reilly, Mesulam, & Nobre, 2008; Salmi et al., 2010; Stoodley et al., 2012). However, the role of the cerebellum in cognition has long been dismissed (e.g. Glickstein, 2007), and some suggest that cerebellar activation may be a vestige of the evolution of the mammalian brain with little involvement in cognitive processes (Buckner, 2013; Leiner, 2010; Schmahmann, 2010; Strick et al., 2009). Interestingly, both polysynaptic tracing (Kelly & Strick, 2003) and cortico-cerebellar intrinsic functional connectivity studies (Buckner et al., 2011) indicate that the cerebellum is not a unitary structure. Multiple higher-order association networks share intrinsic functional connectivity with distinct cerebellar regions, including the dorsal attention network and default mode network (Buckner et al., 2011; Habas et al., 2009; Krienen & Buckner, 2009; O'Reilly, Beckmann, Tomassini, Ramnani, & Johansen-Berg, 2010). Specifically, Buckner et al. (2011) identified a region spanning cerebellar lobules VIIb and VIIIa that exhibits connectivity with the cortical dorsal attention network and a region within the

lateral-most portion of Crus I and II that couples with the cortical default mode network. In cortex, the dorsal attention and default mode networks competitively interact, such that the dorsal attention network is activated and the default mode network is suppressed during cognitive task performance (Corbetta & Shulman, 2002; Gusnard & Raichle, 2001; Shulman et al., 1997). Furthermore, recruitment of the dorsal attention network reflects the number of items maintained in working memory (Sheremata et al., 2010; Todd & Marois, 2004; Vogel & Machizawa, 2004; Xu & Chun, 2006). It remains unclear whether cerebellar regions coupled with the dorsal attention network and default mode network exhibit similar patterns of activation and interaction as their cortical counterparts.

Here, using fMRI, we observe that cortico-cerebellar connectivity predicts cerebellar activation in individual subjects during visual attention and visual working memory (VWM) task performance. Cerebellar lobules VIIb/VIIIa not only exhibit strong intrinsic functional connectivity with the cortical dorsal attention network, but their task-driven responses mirror those of the cortical dorsal attention network. These findings strongly support the view that the dorsal attention network functionally extends to a portion of the cerebellum.

Materials and Methods

Subjects

Fourteen healthy subjects (eight female) participated in these experiments. All subjects were compensated and gave written informed consent to participate in the study, which was approved by the Institutional Review Board of Boston University. Subjects were

recruited from Boston University and the Greater Boston area. All subjects were righthanded and had normal or corrected-to-normal vision. Nine subjects (three female) participated in experiment 1, and nine subjects (five female) took part in experiment 2. Four subjects participated in both experiments. Subjects in experiment 1 ranged in age from 24 to 38 years, and subjects in experiment 2 ranged in age from 25 to 38 years.

Visual Stimuli and Experimental Paradigm

Experiment 1 (VWM change detection). Stimuli were created in MATLAB (Mathworks, Natick, MA) using the Psychophysics Toolbox extension (Brainard, 1997; Pelli, 1997) and were presented using a liquid crystal display projector illuminating a screen within the scanner bore. Subjects fixated on a centrally located cross, while twelve oriented colored bars were presented (six in each hemifield). The number of bars presented in each hemifield remained constant across trials, but the number of memory targets presented on a given trial varied from 1 to 4. The remaining bars in the display served as distractors (see Figure 2.1A). Targets and distractors were distinguished by color, with targets denoted by red and distractors denoted by blue. Each bar subtended $0.25^\circ \times 2.5^\circ$ of visual angle. Targets were limited to either the right or left hemifield (counterbalanced across blocks). Subjects were instructed to remember the orientation $(0^{\circ}, 45^{\circ}, 90^{\circ}, 135^{\circ})$ of the target items in the display. The memory sample display was presented for 200 ms followed by a 1000 ms delay period. After the sample and delay period, a memory probe was presented for 1800 ms. A 1000 ms fixation period separated each trial. On half of the trials, one of the target bars changed its orientation from the sample period to probe period. On the other half of trials, the memory probe array was identical to the sample array. Subjects could respond during either the memory probe or the inter-trial fixation period by pressing a key to indicate that the orientation of a target had changed, or a separate key if it had not changed. The magnitude of the change was always 90° (e.g. 0° to 90° or 45° to 135°). During sensorimotor control trials, subjects were presented a display consisting entirely of distractors and were instructed to press either key during the probe or inter-trial fixation period.

Experiment 2 (visual attention MOT). Stimuli were generated and presented using Python with the VisionEgg software package (Bettencourt, Michalka, & Somers, 2011; Straw, 2008). The display consisted of two spatially offset rectangular regions, one per hemifield, each containing six white disks and a small centrally located fixation cross (see Figure 2.1B). At the onset of each trial, four target disks were highlighted in red for 1500 ms before changing back to white for 500 ms. In order to encourage subjects to maintain central fixation, two targets were restricted to the left visual hemifield and two were restricted to the right visual hemifield. As a result, holding central fixation is the optimal strategy for tracking all targets. Following the cue period, all disks in the display moved in random directions at a constant speed of 4.8°/s for 12 s. A repulsion algorithm was employed that aggregated the distance between each disk and the edges of each hemifield display to determine the direction of movement. The closer a disk came to these objects, the more strongly it was directed away. As a result, disks repulsed off other disks and the hemifield display edges, preventing any overlap. Subjects were instructed to maintain fixation on the central fixation cross and covertly attend to the cued target disks as they moved around the display. Once the disks stopped moving, a single disk was
highlighted in blue for 3000 ms. Subjects were asked to respond by pressing a key if the probed disk was one of the original targets, or to press a separate key if it was not a target. A 1000 ms blank fixation interval separated each trial. At the onset of sensorimotor control trials, every disk in the display was highlighted in red during the cue period. In this condition, subjects were instructed to refrain from tracking the disks and to press either key during the probe period. Subjects practiced the task prior to scanning. Behavioral data from all but one subject was lost before it could be analyzed. However, 19 additional subjects were previously scanned while performing the same paradigm with a slice prescription that did not include the cerebellum. These subjects in addition to the remaining subject (n = 20) performed the task with a mean accuracy of 63.06%, indicating that although the task was challenging subjects were generally able to perform the task. There is little reason to believe that the two subsets of subjects should differ significantly in their performance.

MR Data Acquisition

Data were acquired from a 3 Tesla Siemens TIM Trio magnetic resonance (MR) imager located at the Center for Brain Science at Harvard University in Cambridge, Massachusetts. A 32-channel head coil was used for all scans. T2*-weighted EPI (BOLD) images were acquired using a slice-accelerated EPI sequence that permits simultaneous multi-slice acquisitions using the blipped-CAIPI technique [TR = 2 s, TE = 30 ms; flip angle = 80°; 6/8 partial-fourier acquisition] (Setsompop et al., 2012). 69 slices were acquired with a slice acceleration factor of 3 and 0% skip, covering the whole brain including the cerebellum. Images were acquired at a nominal 2 mm isotropic spatial resolution (matrix size = $108 \times 108 \times 69$).

In the VWM study (experiment 1), each subject completed eight runs (total time per run = 6 min 16 s). Each run comprised 10 34 s task blocks and 16 s of blank fixation before the first block and after the last block. Each block consisted of a 2 s cue, which indicated the location of the target stimuli (left or right hemifield), followed by 8 4 s trials. In the MOT study (experiment 2), subjects completed four runs (total time per run = 4 min 56 s), each comprising 16 alternating active and sensorimotor control blocks each lasting 18 s. 4 s of blank fixation was presented before and after the task blocks. In both experiments, subjects underwent 2-3 resting-state scans using identical scan parameters (each 180 TRs; 6 min duration). During the resting-state scans, subjects were instructed to let their minds wander while maintaining fixation on a centrally located crosshair.

Data Analysis. Functional and resting-state data were analyzed using the FreeSurfer FS-FAST software package (version 5.3.0) (Charlestown, Boston, MA, USA; Fischl, 2012, <u>http://surfer.nmr.mgh.harvard.edu/</u>). The following preprocessing steps were performed: slice-time correction, motion-correction, spatial smoothing (3 mm FWHM) and spatial normalization to the FreeSurfer "fsaverage" brain (MNI305) using a 6 parameter affine transformation. Single-subject data were analyzed voxel-wise using a general linear model that included a predictor for each task condition (Experiment 1: set size 1 left, set size 1 right, set size 4 left, set size 4 right, sensorimotor control; Experiment 2: attend and sensorimotor control). To control for activation due to cue reorientation, cue time points were included as nuisance regressors in the model. Singular value decomposition reduced the 6 motion correction vectors to 3 eigenvectors, which were also included as nuisance regressors in the model. The task regressors were convolved with a canonical hemodynamic response function prior to fitting. This canonical hemodynamic response was modeled by a γ function with a delay of $\delta = 2.25$ s and a decay time constant of $\tau =$ 1.25 (Boynton, Engel, Glover, & Heeger, 1996). t tests were performed on each voxel to compare differences in activation between conditions. The significance of these activation differences was then overlaid onto the MNI305 template brain, as well as projected onto each hemisphere of the "fsaverage" cortical surface. Significant grouplevel task activation was corrected for multiple comparisons using cluster-based correction in FS-FAST. To generate a null hypothesis dataset, Monte Carlo simulations were performed to generate random volumes of normally distributed values that were smoothed with a FWHM estimated from the group analysis residuals. Significant clusters were identified by thresholding group statistical maps voxel-wise (p < .05) followed by cluster-thresholding at a corrected alpha of p < .05.

Intrinsic Functional Connectivity Analysis

We performed resting-state functional connectivity analysis from cortex to cerebellum, using group averaged cortical network seeds identified from a study of 1000 brains (Yeo et al., 2011) in order to identify cerebellar network ROIs uniquely within each subject. Additionally and independently, we performed a functional connectivity analysis from cerebellum to cortex, using task-evoked activation in the cerebellum to define a seed in order to identify the network of cortical areas intrinsically connected to task-sensitive cerebellar voxels. Resting-state data were further preprocessed in MATLAB. Headmotion regression (6 motion parameters and their 6 temporal derivatives), whole-brain signal regression, and ventricular and white matter signal regression were performed (Van Dijk et al., 2010). We then calculated framewise displacement by taking the sum of the absolute derivatives of the 6 motion parameters for each time point (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). A threshold of 0.5 mm was set to identify time points with excessive motion. To avoid artifact spread during band-pass filtering, high motion time points were replaced using linear interpolation (Carp, 2013). Band-pass filtering was then performed to extract frequencies between 0.01 and 0.08 Hz. After filtering, high-motion time points were removed.

Cortical Seed Connectivity Analysis

For our cortical seeds, we defined 6 composite ROIs using a publicly available parcellation that was originally defined using a cluster-based intrinsic functional connectivity analysis of 1000 subjects (Yeo et al., 2011). Each of these composite seeds comprised all of the ROIs in one of 6 cerebral cortical networks: the dorsal attention network, ventral attention network, cognitive control network, somatomotor network, limbic network, and the default mode network. A seventh network, the visual network, was excluded *a priori* due to the finding that it does not share significant connectivity with the cerebellum (Buckner et al., 2011). Additional analyses used an alternative definition of dorsal attention network from Power et al. (2011). In order to create a bilateral composite ROI, we projected MNI coordinates onto the Freesurfer "fsaverage" cortical surface. These coordinates were then iteratively dilated to a size of 61 vertices

(diameter ~ 8 mm). A mean time course was calculated for each seed ROI. These mean time courses were then correlated against every voxel in the brain including the cerebellum. The resulting correlation maps were then *z*-transformed using Fisher's *r*-to-*z* transformation. To compute the voxel-wise correlation between cerebellar task activation and connectivity we computed the mean *z* value for each cerebellar voxel across subjects.

Cerebellar ROI Creation

To define cerebellar regions-of-interest (ROIs) corresponding with each cortical network in individual subjects, a cerebellar mask was applied to individual subject functional connectivity z-maps (see Figure 2.1C). The extracted data were thresholded at a z of 0.2. To ensure our results were robust to the chosen threshold, additional analyses were performed with ROIs defined with a lower threshold (z > 0.1) and a higher threshold (z > 0.1) 0.3). A winner-take-all procedure was then performed so that each above-threshold voxel was assigned to the network with which that voxel had the strongest correlation. Each network ROI was then binarized to create a volumetric mask. To minimize the inclusion of false-positives in our ROIs, we created a dilated mask that effectively isolated clusters of correlated voxels of sufficient size. To create the dilated mask, network ROIs were iteratively smoothed with a boxcar kernel and thresholded (threshold = 6/27; 5 neighbors). Thus, voxels with less than 5 neighbors were excluded from the dilated mask. This process was repeated three times. The dilated mask was then applied to the unsmoothed ROIs. To be included in the analysis, an ROI had to exceed a threshold of 100 mm³. In experiment 1, the somatomotor network ROI of one subject did not meet this threshold.

To assess the effect of ROI on percent signal change for each contrast, we used the SPSS mixed-model procedure to fit a marginal linear model. In contrast to a more traditional repeated measures ANOVA model, a marginal linear model does not exclude cases with missing values and can flexibly model the dependency introduced by withinsubject measures (West, Welch, & Galecki, 2014). ROI was specified as a repeated measure and subject ID was included as a grouping variable. Within-subject error was modeled using an unstructured covariance structure, which produced a unique variance estimate for each ROI and a unique covariance estimate for each pair of ROIs. A marginal linear model produces valid standard error estimates and more efficient statistical tests of fixed parameters by more accurately modeling the error covariance structure (Littell, Henry, & Ammerman, 1998). It should be noted that SPSS uses the Satterthwaite approximation to calculate degrees of freedom and as a result can produce non-integer values. The model was fitted using maximum likelihood estimation. Post-hoc comparisons were corrected for multiple comparisons using the Holm-Bonferroni method.

Hemispheric ROI Analysis

To examine differences in activation between hemispheres we created hemispherespecific ROIs in the cortex and cerebellum. Cortical ROIs were created by splitting the Yeo dorsal attention network representation into 4 ROIs (iPCS, sPCS, IPS, MT+) in each hemisphere. Hemisphere-specific cerebellar ROIs were created by applying hemispheric masks to the cerebellar ROI defined by connectivity with the cortical dorsal attention network. Mean percent signal change was then extracted from each ROI. Hemispheric differences were assessed by performing paired *t*-tests for each ROI (corrected for multiple comparisons).

Cerebellar Seed Connectivity Analysis

In each experiment we performed an additional and statistically independent functional connectivity analysis. Our goal was to reveal, independent of any presumed cortical network structure, the cerebral cortical regions that exhibit intrinsic functional connectivity with the cerebellar regions strongly recruited during VWM and visual attention task performance. Seed regions within the cerebellum were defined in individual subjects by significant activation (p < .01) within lobules VIIb/VIIIa for the set size 4-sensorimotor control contrast (experiment 1), the set size 4-set size 1 contrast (experiment 1), and the active tracking-sensorimotor control contrast (experiment 2). Our definition of lobules VIIb/VIIIa was obtained from the Spatially Unbiased Infratentorial Template (SUIT; Diedrichsen, 2006; Diedrichsen et al., 2009). A time-course was then averaged across cerebellar voxels included in our seed ROI. A Pearson's correlation coefficient was computed between our cerebellar seed time-course and every vertex on the cortical surface. A random-effects group analysis was then performed and significant group-level correlations were projected onto the inflated cortical surface of the FreeSurfer average (fsaverage) brain (Dale, Fischl, & Sereno, 1999). We computed the overlap between connectivity and cortical task activation by calculating the Simpson overlap coefficient (Fuxman Bass et al., 2013). The Simpson coefficient is defined as the size of the intersection of two sets divided by the minimum size of the two sets. If one set is a perfect subset of the other set the Simpson coefficient is equal to one.

Hierarchical Cluster Analysis

To investigate the network structure of activated regions in the cerebellum and cortex, we performed a hierarchical cluster analysis on seed-to-seed resting-state correlations. Seeds were defined in individual subjects by significant functional activation (p < .01) in the cortex and cerebellum. To ensure functional connectivity seeds did not differ greatly in size we used anatomical masks to constrain our functionally defined ROIs. Cortical masks were taken from a parcellation of the cortex freely available in the FreeSurfer package (Destrieux, Fischl, Dale, & Halgren, 2010; Fischl et al., 2004). Cortical seed ROIs were defined for each hemisphere within IPS, sPCS, iPCS, MT+, dorsal anterior cingulate cortex (dACC), anterior insula (aInsula), and posterior callosal sulcus (CaS-p). To anatomically constrain our cerebellar seed ROI, we again used a mask encompassing cerebellar lobules VIIb and VIIIa obtained from the Spatially Unbiased Infratentorial Template (SUIT: Diedrichsen, 2006; Diedrichsen et al., 2009). If we could not define a seed within a particular mask due to the lack of above-threshold functional activation, we used a seed defined from the group analysis map. To ensure that we could create groupdefined seeds for all regions in which a seed could not be defined in individual subjects, we used a slightly lower threshold (p < .05) to create seeds from the experiment 2 group map. A seed-to-seed correlation matrix was then computed for each subject. To increase statistical power, we collapsed correlation matrices from both studies into a single group correlation matrix. Prior to averaging, correlation values for each subject were transformed using the Fisher r-to-z transformation to address the issue of non-additivity of correlation coefficients. As four subjects participated in both studies, we first computed a mean correlation matrix for each overlapping subject. Due to the discrepancy in the number of resting-state runs between experiment 1 and 2, same-subject correlation matrices were weighted by the number of resting-state TRs in each session. Treating each row of the group correlation matrix as a vector in a 16-dimensional space, we computed pairwise Euclidean distance between each region's pattern of connectivity. We then applied Ward's linkage algorithm to these distances, which forms each new cluster by merging the two clusters that lead to the minimum possible increase in the total sum of squares of the node to centroid distances. Cluster tree branch points were validated using a bootstrapping approach (Dosenbach et al., 2007). 1000 bootstraps were created by randomly sampling with replacement from our pool of 14 individual subject seed-to-seed correlation matrices. Generated bootstrap correlation matrices were averaged to form a mean correlation matrix. Each mean bootstrap matrix was clustered to create 1000 bootstrap cluster trees. Bootstrap confidence values for each branch point were computed by counting the number of iterations in which a subtree consisted of the same ROIs as the original tree.

Eye Movement Monitoring

Subjects were instructed to maintain fixation on a centrally located cross throughout all scans. In experiment 1, eye position was monitored using an EyeLink 1000 from SR research. Eye movement data were analyzed using custom scripts written in MATLAB. To assess whether differential cerebellar activation can be attributed to eye movements, distance from fixation for each trial was calculated by taking the root mean square (RMS) difference of the horizontal and vertical traces from the median value for the trial. These

values were then averaged across trials of each condition to produce an average value for each subject. Due to technical difficulties, eye movement data could not be obtained for one subject.

Results

Experiment 1: Visual Working Memory

Behavior. Subjects performed well in the visual working memory change detection task during fMRI scanning. In the set size 4 (SS4) condition, mean accuracy was 79.64% and subjects effectively held 2.52 objects in VWM (Pashler, 1988). In the set size 1 (SS1) condition, accuracy was 97.57% and subjects effectively held 0.97 objects in VWM.

Subjects held more items in VWM during SS4 vs. SS1, t(8) = 12.74, p < 0.001.

Eye-Tracking. Since the cerebellum is functionally linked to the motor system, it is critical to demonstrate that eye movements did not differ across conditions. We computed the root mean square (RMS) of eye position relative to fixation for each trial. There was no significant difference in mean RMS between conditions (F(2,8) = 2.34, p = 0.158). Pairwise comparisons further revealed no significant difference in RMS between SS4 and both SS1 and the sensorimotor control (*SS4 vs. SS1*: t(8) = -0.40, p = 0.698, uncorrected; *SS4 vs. control*: t(8) = -2.09, p = 0.070, uncorrected). The trend in the SS4-Control comparison reflects greater RMS in the sensorimotor control condition. These measurements demonstrate that any activation observed in the contrast of high-load VWM to low-load VWM and the sensorimotor control condition.

Task-based fMRI and ROI analysis. A random-effects group analysis of the fMRI data contrasting SS4 with the sensorimotor control condition revealed significant clusters of activation located within lobules VIIb/VIIIa bilaterally (MNI coordinates = [-11.5, -85, -100,35.5]; [7.5, -91, -30.5]), consistent with the location of the functional connectivity dorsal attention network representation identified by Buckner et al. (2011). Significant clusters were also identified within lobule VI/Crus I bilaterally (MNI = [-43.5, -81, -22.5], [43.5, -80, -19.5]). In order to better characterize these results, cerebellar ROIs were defined in individual subjects by intrinsic functional connectivity with six cortical networks from the Yeo 7-network parcellation (dorsal attention network (DAN), ventral attention network (VAN), cognitive control network (CCN), somatomotor network (SOM), limbic network (LIMB), default mode network (DMN))(Yeo et al., 2011; see Materials and Methods). Visualization of individual subject cerebellar fMRI activation and resting-state connectivity patterns revealed a similar pattern of cerebellar regions activated by VWM and intrinsically coupled with cortical dorsal attention network regions (Figure 2.2A-C). The ROI analysis revealed that VWM task activation specifically targeted the cerebellar regions coupled with the cortical dorsal attention network (see Figure 2.2D). Mean percent signal change differences between the SS4 condition and the sensorimotor control condition were extracted from each cerebellar network ROI. These values were entered into a marginal linear model. There was a significant effect of ROI (F(5,9) = 11.52, p = .001). Post-hoc comparisons (Holm-Bonferroni corrected) revealed that the cerebellar dorsal attention network ROI exhibited significantly greater activation than every other cerebellar network ROI (DAN vs. VAN: t(9) = 4.50, p = 0.006; DAN vs.

CCN: t(9.01) = 5.40, p = 0.002; *DAN vs. SOM*: t(9.03) = 3.61, p = 0.011; *DAN vs. LIMB*: t(9.01) = 3.35, p = 0.011; *DAN vs. DMN*: t(9) = 4.48, p = 0.006). Only the cerebellar ROIs defined by connectivity with the cortical dorsal attention network and default mode network significantly differed from zero. The cerebellar ROI that coupled with the dorsal attention network exhibited a significant increase in signal, t(9.14) = 3.26, p = 0.048 corrected (uncorrected p < 0.01), and the cerebellar ROI that coupled with the default mode network exhibited a significant decrease in signal, t(9) = -3.92, p = 0.021 corrected (uncorrected p < 0.01). These results were robust to the threshold chosen to define cerebellar ROIs. All comparisons remained significant for ROIs defined with a lower threshold (z > 0.1) or a higher threshold (z > 0.3).

Load-Dependent Responses. A load-dependent response profile (i.e., increasing activation with increasing numbers of items held in VWM) is a defining characteristic of cortical regions implicated in VWM. To assess whether the cerebellar sub-regions exhibit load-dependence, we contrasted SS4 with SS1 within each of our cerebellar ROIs. There was a significant effect of cerebellar ROI, F(5, 8.78) = 39.84, p = 0.000009. Again, this effect was driven by significantly greater percent signal change within the cerebellar ROI coupled to dorsal attention network in relation to every other cerebellar ROI (*DAN vs. VAN*: t(9) = 4.47, p = 0.003; *DAN vs. CCN*; t(9) = 4.08, p = 0.003; *DAN vs. SOM*: t(9) = 5.74, p = 0.0009; *DAN vs. LIMB*: t(9) = 9.55, p = 0.00003; *DAN vs. DMN*: t(9) = 7.94, p = 0.0001; Holm-Bonferroni corrected)(Figure 2.2E). We again found that only the cerebellar ROIs defined by connectivity with the cortical dorsal attention network and with the cortical default mode network exhibited a significant difference in percent signal

change (*DAN*: t(9) = 5.69, p = 0.002, corrected; *DMN*: t(9) = -4.52, p = 0.007, corrected). There was also a significant activation difference within the ROIs defined by connectivity with the VAN and CCN, but this effect was reduced to a trend after correction for multiple comparisons (*VAN*: t(9) = 3.10, p = 0.051 corrected; *CCN*: t(9) = 2.91, p = 0.052 corrected).

Resting-State Functional Connectivity vs. Task Activation. To further quantify the relationship between cerebellar task-evoked activation and intrinsic functional connectivity to cortical networks, we examined, for all cerebellar voxels (independent of the above ROI definitions), the voxel-wise correlation between VWM activation and connectivity to the dorsal attention network and default mode network. We computed the mean normalized activation (SS4 vs. control & SS4 vs. SS1) and mean normalized correlation to the cortical dorsal attention network and default mode network of each cerebellar voxel across subjects and then correlated these two measures. There was a strong positive correlation between VWM-evoked activation and dorsal attention network connectivity (SS4 vs. control: r = 0.60; SS4 vs. SS1: r = 0.62), and a robust negative correlation between VWM activation and default mode network connectivity (SS4 vs. *control*: r = -0.73; SS4 vs. SS1: r = -0.65) (see Figure 2.3). These strong correlations indicate that intrinsic functional connectivity patterns with the dorsal attention network and default mode network are robust predictors of VWM task activation across individual cerebellar voxels.

Hemispheric Bias. A right hemisphere bias is commonly observed in studies of spatial VWM, such that right hemisphere VWM regions exhibit greater activation than left

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hemisphere VWM regions (e.g. Belger et al., 1998; Rypma & D'Esposito, 1999). The cortex is anatomically connected with the contralateral hemisphere of the cerebellum via the pons. Therefore, if a cerebellar region participates in VWM processing, we would expect to observe a left hemisphere bias in the cerebellum. We split the cortical dorsal attention network representation from Yeo et al. (2011) 7-network parcellation into 4 ROIs in each hemisphere (iPCS, sPCS, IPS, MT+). Within all cortical ROIs, the right hemisphere exhibited stronger activation than the left hemisphere (LH vs. RH for SS4 *minus control*: iPCS: t(9) = 3.28, p = 0.029; sPCS: t(9) = 2.94, p = 0.033; IPS: t(9) =5.33, p = 0.002; MT+: t(9) = 2.34, p = 0.044; LH vs. RH for SS4 minus SS1: iPCS: t(9)= 3.22, p = 0.021; sPCS: t(9) = 4.90, p = 0.003; IPS: t(9) = 5.17, p = 0.003; MT+: t(9) = 5.172.23, p = 0.053; Holm-Bonferroni corrected) (Figure 2.4A). To create cerebellar ROIs, we applied hemispheric masks to the cerebellar ROI defined by intrinsic functional connectivity to the dorsal attention network in individual subjects to create a ROI for each hemisphere. We found evidence for hemispheric bias in the cerebellum mirroring the bias observed in the cortex. Within cerebellar regions defined by functional connectivity with the cortical dorsal attention network, the left hemisphere exhibited significantly greater activation than the right hemisphere, (SS4 minus control: t(9) = 5.54,p = 0.002, corrected; SS4 minus SS1: t(9) = 4.21, p = 0.007, corrected) (Figure 2.4B).

Cerebellum-to-Cortex Intrinsic Functional Connectivity. As a further analysis of the interactions between cortex and cerebellum in VWM, we reversed direction and performed a cerebellar-to-cortex intrinsic functional connectivity analysis. The seed regions for this seed-to-vertex intrinsic functional connectivity analysis were defined in

the cerebellum by significant cerebellar VWM activation (SS4 vs. control & SS4 vs. SS1 contrasts) within lobules VIIb/VIIIa (p < .01) in individual subjects. Critically, this seed definition depends only on task activation and is completely independent of the definitions used in the cerebellar ROI analyses of Figure 2.2. We then compared this cortical pattern of intrinsic functional connectivity to each cortical network definition from the Yeo et al. parcellation, as well as to cortical VWM task activation. A randomeffects group analysis of resting-state correlations revealed substantial bilateral overlap between the cortical regions identified by functional connectivity with task-activated cerebellum and the cortical regions directly activated by the VWM task bilaterally (SS4 vs. control: overlap coefficient = 0.59 left hemisphere, 0.62 right hemisphere; SS4 vs. SS1: overlap coefficient = 0.59 left hemisphere, 0.67 right hemisphere) (Figure 2.5; black outlines indicate task activation). There was also remarkable overlap between cerebellum-to-cortex functional connectivity and the cortical dorsal attention network Yeo representation (SS4 vs. control: overlap coefficient = 0.61 left, 0.67 right; SS4 vs. SSI: overlap coefficient = 0.60 left, 0.69 right) and to a lesser degree the cognitive control network Yeo representation (SS4 vs. control: overlap coefficient = 0.18 left, 0.12 right; SS4 vs. SS1: overlap coefficient = 0.20 left, 0.16 right) and ventral attention network Yeo representation (SS4 vs. control: overlap coefficient = 0.19 left, 0.22 right; SS4 vs. SS1: overlap coefficient = 0.21 left, 0.23 right). Overlap with all other network representations did not exceed 0.05. To extend these results, we also computed the overlap between cerebellum-to-cortex functional connectivity and an alternative definition of dorsal attention network from the Power et al. (2011) network parcellation.

There was an even greater degree of overlap between connectivity and the Power dorsal attention network ROIs (*SS4 vs. control*: overlap coefficient = 0.80 left, 0.77 right; *SS4 vs. SS1*: overlap coefficient = 0.77 left, 0.70 right). Therefore, VWM-activated cerebellar regions exhibit a pattern of intrinsic functional connectivity that aligns with multiple definitions of the dorsal attention network and robustly predicts the pattern of cortical VWM activation.

Experiment 2: Sustained Attention

In order to demonstrate the generality of the cerebellar task activation results, we performed a second experiment, using a different attentionally demanding paradigm. In experiment 2, subjects performed a sustained attention multiple object tracking (MOT) task, which required subjects to track cued discs in the presence of identical distractors. The attentional MOT paradigm yielded a similar neural pattern of results to the VWM change detection paradigm of experiment 1. A random-effects group analysis again identified significant clusters of activation within lobules VIIb/VIIIa bilaterally (MNI: [-6.5, -91.0, -28.5]; [32.5, -64.0, -43.5]) and lobule VI/Crus I bilaterally (MNI: [-33.5 -76.0 -21.5]; [46.5 -68.0 -23.5]). Individual subject analyses revealed overlap of cerebellar visual attention task activation (Figure 2.6B) and cortical dorsal attention network seed functional connectivity (Figure 2.6A). An ROI analysis was performed in order to provide a quantitative measure of this within-subject cerebellar spatial correspondence across subjects. ROIs were defined by functional connectivity with the same six cortical networks as described in experiment 1. Mean BOLD percent signal change for the attend condition versus the sensorimotor control condition was obtained

for each of the six cerebellar network ROIs and entered into a marginal linear model. There was a significant effect of ROI (F(5,9) = 69.21, p = 0.000001). Post-hoc comparisons (Holm-Bonferroni corrected) demonstrated that the cerebellar ROI defined by intrinsic functional connectivity with the dorsal attention network exhibited significantly greater activation relative to every other cerebellar network ROI (*DAN vs. VAN*: t(9) = 3.35, p = 0.012; *DAN vs. CCN*: t(9) = 5, p = 0.002; *DAN vs. SOM*: t(9) = 3.58, p = 0.012; *DAN vs. CCN*: t(9) = 5, p = 0.002; *DAN vs. SOM*: t(9) = 0.00002) (Figure 2.6C). Of the six cerebellar network ROIs, only those defined by intrinsic functional connectivity with the dorsal attention network or the default mode network significantly differed from zero. The dorsal attention network-coupled ROI showed a significant increase in signal (*DAN*: t(9) = 4.24, p = .013 corrected), while the default mode network-coupled ROI showed a significant decrease in signal (*DMN*: t(9) = -4.16, p = .013 corrected).

Resting-State Functional Connectivity vs. Task Activation. To further explore the correspondence between attentional activation in the cerebellum and connectivity to cortical networks, we computed the voxel-wise correlation between cerebellar MOT activation and either dorsal attention network or default mode network connectivity. The correlation between task-evoked attentional activation and dorsal attention network connectivity was strongly positive (r = 0.74), while the correlation between task activation and default mode network connectivity was strongly negative (r = -0.77) (Figure 2.6D). Cerebellar voxel-wise connectivity with an alternative seed definition of cortical dorsal attention network (Power et al., 2011) yielded a similarly robust

correlation with voxel-wise MOT activation (r = 0.74). These results closely mirror the results of this analysis for the VWM task.

Cerebellum-to-Cortex Intrinsic Functional Connectivity. To examine whether the cerebellar and cortical regions co-activated during visual attention are also intrinsically coupled during rest, we performed a resting-state functional connectivity analysis using cerebellar seed regions defined by significant MOT activation (p < 0.01) and constrained by an anatomical lobule VIIb/VIIIa mask. We observed robust overlap between connectivity and cortical task-evoked activation (overlap coefficient = 0.51 left hemisphere, 0.64 right hemisphere; see Figure 2.7; black outlines indicate task activation). Additionally, we again observed substantial overlap between connectivity and the cortical Yeo dorsal attention network (overlap coefficient = 0.59 left hemisphere, 0.57 right hemisphere). To a lesser extent, we also found overlap with the cortical Yeo ventral attention network (overlap coefficient = 0.34 left, 0.50 right) and cortical Yeo cognitive control network (overlap coefficient = 0.14 left, 0.14 right). The remaining networks (somatomotor network, limbic network, and default mode network) exhibited negligible overlap (< 0.05) with cerebellum-to-cortex functional connectivity. Additionally, we found a similar degree of overlap between cerebellum-to-cortex functional connectivity and the Power et al. (2011) definition of dorsal attention network (overlap coefficient = 0.69 left, 0.66 right). Similar to the results for VWM, we found that intrinsic resting-state functional connectivity between MOT-activated cerebellar regions and the cortex preferentially aligns with the dorsal attention network and that the pattern of connectivity robustly predicts the pattern of MOT activation in cortex.

Hierarchical Cluster Analysis

Cortical activation in response to both tasks extended beyond the dorsal attention network to include a subset of the cognitive control network, including dorsal anterior cingulate cortex (dACC), anterior insula (aInsula), and posterior callosal sulcus (CaS-p). To investigate whether activated portions of cerebellar lobules VIIb/VIIIa form an intrinsic node of the dorsal attention network we performed agglomerative hierarchical clustering on seed-to-seed resting-state correlations of task-responsive regions in cortex and cerebellum. Hierarchical clustering of the distance (Euclidean) between functional connectivity patterns of task-activated regions revealed two distinct networks (Figure 2.8). Cerebellar lobule VIIb/VIIIa and cortical dorsal attention network regions (iPCS, sPCS, IPS, MT+) formed one network and cognitive control regions (dACC, aInsula, CaS-p) formed another network. A cophenetic correlation of 0.82 indicated that the cluster tree accurately reflected the original dissimilarity matrix. A 1000-iteration bootstrap procedure validated these findings. The cerebellar lobule VIIb/VIIIa ROI clustered with cortical dorsal attention regions on 89.0% of bootstraps. Additionally, on 60.9% of bootstraps, cerebellar regions were closer in distance to frontal and parietal dorsal attention network regions (iPCS, sPCS, and IPS) than MT+. These findings confirm that cerebellar regions recruited by working memory and attention occupy a privileged position within the hierarchy of the dorsal attention network.

Discussion

Cognitive processes such as working memory and attention are typically considered to fall under the purview of the cerebral cortex. In the present study we challenge this notion

and suggest that regions of the cerebellum make a general contribution to working memory and attentional processes as a core component of an attentional network spanning both cortical and subcortical structures. Using resting-state functional connectivity and task-based fMRI, we showed that cerebellar regions intrinsically coupled with the cortical dorsal attention network were robustly recruited by both a VWM paradigm and an attentional paradigm. The observed activation aligns with previous findings of dorsal attention network functional connectivity within cerebellar lobules VIIb/VIIIa (Buckner et al., 2011). Critically, activation in cerebellar lobules VIIb/VIIIa was significantly higher during high-load VWM than during low-load VWM. The observed load-dependent activation exhibited a high degree of specificity. Of the six cerebellar network representations, only the cerebellar regions exhibiting functional connectivity with the cortical dorsal attention network were significantly active across all contrasts. Additionally, we observed that cerebellar regions coupled with the cortical default mode network were suppressed during task performance. To our knowledge, this is the first study to show that the antagonistic relationship between the dorsal attention network and default mode network extends to the cerebellum, providing further evidence for the active participation of cerebellar nodes in whole-brain network function. Finally, we found that the intrinsic functional connectivity of task-activated cerebellar regions was a robust predictor of cortical task activation, indicating that co-activated regions in the cortex and cerebellum also exhibit correlated spontaneous fluctuations during rest. Taken together, our results demonstrate that cerebellar lobules VIIb/VIIIa play an active functional role in the intrinsic network dynamics of the dorsal attention network. We

propose the dorsal attention network should be functionally reconceptualized as a corticocerebellar network that includes cerebellar lobules VIIb/VIIIa.

Evidence for Cerebellar Contributions to Visual Attention and Working Memory

There is accumulating evidence for cerebellar contributions to non-motor function. Cerebellar activation has been reported during visual attention and/or working memory task performance (Allen et al., 1997; Chen & Desmond, 2005a; 2005b; Desmond et al., 1997; Hautzel, Mottaghy, Specht, Müller, & Krause, 2009; Kellermann et al., 2012; Kirschen et al., 2005; Le et al., 1998; O'Reilly et al., 2008; Salmi et al., 2010; Stoodley et al., 2012; Striemer, Chouinard, Goodale, & de Ribaupierre, 2015b; Tomasi, Chang, Caparelli, & Ernst, 2007). Anatomical tracers have been used to identify projections from the prefrontal cortex to the pons (Schmahmann & Pandya, 1997a). Kelly and Strick (2003) further demonstrated the existence of polysynaptic connections between prefrontal cortex and cerebellum, thereby establishing that cognitive regions of the cortex are anatomically connected with the cerebellum. Additionally, closed-loop cortico-cerebellar prefrontal circuits are distinct from cortico-cerebellar motor circuits (Kelly & Strick, 2003) and are substantially larger in humans than in other primates (Ramnani, 2006). These greatly expanded closed-loop circuits between the cerebellum and multimodal association cortex provide an anatomical basis for cerebellar contributions to human cognition and participation in greater network function.

Clinical work has further substantiated the notion of cerebellar involvement in cognitive processing. Cerebellar lesions, even in the absence of cortical damage, have been shown to produce a variety of cognitive deficits (Schmahmann, 2004; Schmahmann

& Sherman, 1998), including impairment of visual attention processes (Baier et al., 2010; Schweizer et al., 2007; Striemer, Cantelmi, Cusimano, Danckert, & Schweizer, 2015a). The cerebellum has also been linked to attention deficit hyperactivity disorder (ADHD). ADHD is associated with reduced cerebellar volume (Castellanos et al., 2002; Mackie et al., 2007; Stoodley, 2014), decreased cerebellar activation during the performance of cognitive tasks (Suskauer et al., 2008; Valera et al., 2005; 2010), and abnormal intrinsic functional connectivity (Cao et al., 2009; Fair et al., 2012; Kucyi, Hove, Biederman, Van Dijk, & Valera, 2015; Tian et al., 2006).

Dorsal Attention Network

This study demonstrates that cerebellar regions functionally connected to the dorsal attention network are recruited by working memory and attention. Our results align with a rich body of research implicating the cortical dorsal attention network in these processes (e.g. Corbetta & Shulman, 2002; Hagler & Sereno, 2006; Szczepanski, Konen, & Kastner, 2010). However, despite growing evidence for cerebellar contributions to attention and working memory, mention of the cerebellum has been noticeably absent from the dorsal attention network literature. On the other hand, resting-state fMRI studies have revealed connectivity between cerebral cortical networks and the cerebellum (Buckner et al., 2011; Habas et al., 2009; Krienen & Buckner, 2009; O'Reilly et al., 2010). Most recently, one member of our team observed that transcranial magnetic stimulation of the cerebellar midline can lead to increases in cortico-cortical functional connectivity of the dorsal attention network, indicating that cerebellar nodes of cortical networks are capable of modulating greater network function (Halko et al., 2014). Until

now, the functional relevance of these cerebellar network nodes to task processing has not been established. Our results confirm that cerebellar regions actively contribute to working memory and attentional processing as part of a cortico-cerebellar attention network.

Outside of VIIb/VIIIa

Previous work has implicated cerebellar regions beyond lobules VIIb/VIIIa in working memory and attentional functions, namely lobule VI/Crus I (Allen et al., 1997; Baier et al., 2010; Chen & Desmond, 2005a; 2005b; Kirschen et al., 2005; Striemer, Cantelmi, Cusimano, Danckert, & Schweizer, 2015a; Striemer, Chouinard, Goodale, & de Ribaupierre, 2015b; Townsend et al., 1999). Here, group analyses of task activation revealed clusters in lobule VI/Crus I bilaterally; however, only a portion of this activation exhibited functional connectivity with cortical dorsal attention network and the extent was less than half of the size of clusters observed in lobules VIIb/VIIIa. Although this location is consistent with resting-state observations (Buckner et al., 2011), our findings suggest that lobule VI/Crus I activation may reflect recruitment of multiple cerebellar network nodes. However, further investigation is needed uncover the full range of cerebellar contributions to human visual cognition.

The Visuo-Motor Cerebellum and Ocular-Motor Vermis

The role of the cerebellum has long been established in the control of ocular movements, particularly reflexive eye movements, saccades and smooth pursuit (Voogd et al., 2012). Regions within the cerebellar vermis (lobules VI/VII), Crus I/II and floccular lobe

indirectly receive and send projections to superior parietal eye movement areas and the frontal eye fields (Voogd, Schraa-Tam, van der Geest, & De Zeeuw, 2010). Electrical stimulation to these regions in the cerebellum can evoke eye movements (Fujikado & Noda, 1987; Ron & Robinson, 1973). In patients, eye movement deficits arise from lesions in these locations (Baier, Stoeter, & Dieterich, 2009). In the current study, activation differences were primarily observed in the cerebellar hemispheres, and an analysis of eye movements did not reveal any differences between conditions. Consequently, it is unlikely that the observed cerebellar activation differences can be strongly attributed to cerebellar involvement in ocular control. Furthermore, a recent study directly investigated the relationship between working memory load and eye movements in the cerebellum and found no correlation (Peterburs, Cheng, & Desmond, 2015). Our results suggest that a broader definition of the role of the cerebellum should be assigned, and that the regions connected to frontal and parietal attention regions do far more than simply control eye movements.

Cerebellar Computation

While our results demonstrate that cerebellar sub-regions are a functional component of the dorsal attention network, it is unclear what computation these cerebellar regions perform. Cerebellar cytoarchitecture is remarkably uniform (Bloedel, 1994). Consequently, it has been proposed that the computations performed by the cerebellum are similarly invariant across processing domains (Ramnani, 2006; Schmahmann, 1991). As a result, we can look to existing models of motor control in the cerebellum for intuition as to how the cerebellum may contribute to attention and working memory. Some researchers implicate the cerebellum in coding of prediction error (Ito, 2001; 2006; Kawato & Gomi, 1992), while others have characterized the cerebellum as an internal timing device (Bullock et al., 1994; Ivry, 1997; Ivry & Keele, 1989). Allowing for both these possibilities, it has been proposed that the cerebellum is critical for the development of internal models (see Ito, 2008 for review). Internal models formed by the cerebellum are thought to facilitate adaptive control necessary for mental activity (Doya, 2000; Ito, 2008). The present study cannot distinguish between these possibilities. However, the use of individual subject intrinsic connectivity to identify regions of the cerebellum recruited by working memory and attention lays the groundwork for clarifying the computations the cerebellum performs during working memory and attentional tasks.

Concluding Remarks

The present study characterizes the role of cerebellar lobules VIIb/VIIIa in VWM and attention tasks, and shows that cerebellar regions functionally connected to the dorsal attention network, as opposed to other networks, are preferentially recruited during task performance. Typically considered to be the domain of the cortex, the present work suggests that working memory and attentional processes are supported by a dynamic interaction between cortical and cerebellar regions. Taking this into account, we propose a reconsideration of the dorsal attention network as a cortical network, and suggest it be reconceived as a cortico-cerebellar attention network.



Figure 2.1 Experimental stimuli and methods. (A) Visual working memory (VWM) change detection paradigm. Participants were asked to maintain central fixation and remember the orientation of target bars (red) and ignore distractor bars (blue). An array of oriented bars was presented (200 ms), then a blank screen (1000 ms), and finally a second array of bars (1800 ms) that was either identical or differed in the orientation of a single target bar (change on 50% of trials). Participants indicated with a key press whether or not a change occurred in the display. (B) Visual attention multiple object tracking (MOT) paradigm. Participants were presented a cue display which highlighted 4 out of 12 total disks for 1.5 s. Participants were instructed to maintain central fixation while attentively tracking cued disks (2 in left visual field, 2 in right visual field) as they moved around the display. After 12 s, the disks stopped moving and participants indicated whether a single highlighted disk was one of the original targets. (C) Cerebellar ROIs defined by intrinsic resting-state functional connectivity with cortical networks. Mean time-courses were extracted from six cortical networks (Yeo et al., 2011) and correlated with every cerebellar voxel. ROIs were created via a winner-take-all procedure that assigned each above-threshold voxel to the network with which it had the strongest correlation.



Figure 2.2 Experiment 1: Visual working memory (VWM) and functional connectivity results. (A) Cerebellar voxels that exhibit significant positive correlation with cortical dorsal attention network (hot colors) in one subject. (B) VWM task activation in cerebellum for the same subject, contrasting the set size 4 (SS4) condition (hot colors) versus sensorimotor control (cool colors). (C) Cerebellar VWM activation contrasting the SS4 condition (hot colors) versus the set size 1 (SS1) condition (cool colors) (D & E) Group-analysis of task activation in cerebellum. Cerebellar ROIs for individual subjects were defined by intrinsic functional connectivity with cortical networks. (D) Bars represent mean percent signal change (n = 9) for the SS4 condition. Error bars reflect within-subject SEM. (E) Mean percent signal change (n = 9) for the SS4 condition. Error bars reflect within-subject SEM. DAN, dorsal attention network; VAN, ventral attention network; CCN, cognitive control network; SOM, somatomotor network; LIMB, limbic network; DMN, default mode network.



Figure 2.3 (A) Relationship between mean normalized task activation (SS4 vs. sensorimotor control) and mean normalized correlation with the cortical dorsal attention network (left) and the cortical default network (right) for every voxel in the cerebellum. (B) Relationship between voxel-wise mean normalized activation (SS4 vs. SS1 contrast) and mean normalized correlation with the cortical dorsal attention network (left) and the cortical default network (right). DAN, dorsal attention network; DMN, default mode network.



Figure 2.4 Hemispheric asymmetry in VWM activation reflects contralateral corticocerebellar structural connectivity. (A) Cortical regions of the dorsal attention network exhibit a right hemisphere activation bias. (B) A left hemisphere activation bias occurs in the cerebellar ROIs defined by functional connectivity with the cortical dorsal attention network. Bars represent average percent signal change for SS4 condition compared with sensorimotor control for each hemisphere. Error bars reflect within-subject SEM. iPCS, Inferior Precentral Sulcus; sPCS, Superior Precentral Sulcus; IPS, Intraparietal Sulcus; MT+, area MT complex.



Figure 2.5 Intrinsic functional connectivity of task-responsive cerebellar regions predicts cortical task activation. For this functional connectivity analysis, cerebellar lobule VIIb/VIIIa ROIs were defined by VWM activation (*SS4 vs. sensorimotor control* and *SS4 vs. SS1* contrasts). (A) Color map displays cortical regions that exhibit significant (p < .01, group level) intrinsic functional connectivity with cerebellar regions activated by SS4 vs. sensorimotor control contrast. Cortical VWM task activation (cluster-corrected, SS4 vs. sensorimotor control) is denoted by the black outlines. (B) Cortical regions that exhibit significant (p < .01, group level) intrinsic functional connectivity with cerebellar regions that exhibit significant (p < .01, group level) intrinsic functional connectivity with cerebellar regions that exhibit significant (p < .01, group level) intrinsic functional connectivity with cerebellar sensorimotor control) is denoted by the black outlines. (B) Cortical regions that exhibit significant (p < .01, group level) intrinsic functional connectivity with cerebellar regions activated by SS4 vs. SS1 contrast. Black outlines denote significant SS4 vs. SS1 activation (cluster-corrected). iPCS, Inferior Precentral Sulcus; sPCS, Superior Precentral Sulcus; IPS, Intraparietal Sulcus; MT+, area MT complex; aInsula, Anterior Insula; dACC, Dorsal Anterior Cingulate Cortex; CAS-p, Posterior Callosal Sulcus.



Figure 2.6 Experiment 2: MOT sustained attention and functional connectivity results. (A) Cerebellar voxels that exhibit significant positive correlation with cortical dorsal attention network (hot colors) in one subject. (B) MOT task activation in cerebellum for the same subject, contrasting the "attend" condition (hot colors) versus sensorimotor control (cool colors). (C) Group-analysis of task activation in cerebellum. Cerebellar ROIs for individual subjects were defined by intrinsic functional connectivity with cortical networks. Bar graph shows mean percent signal change for the attend condition versus the sensorimotor control condition. Error bars reflect within-subject SEM. (D) Relationship between mean normalized task activation (attend vs. sensorimotor control) and mean normalized correlation with the cortical dorsal attention network (left) and the cortical default network (right) for every voxel in the cerebellum. DAN, dorsal attention network; VAN, ventral attention network; CCN, cognitive control network; SOM, somatomotor network; LIMB, limbic network; DMN, default mode network.



Figure 2.7 Intrinsic functional connectivity of MOT-responsive cerebellar regions aligns with cortical task activation. Cerebellar lobule VIIb/VIIIa ROIs defined by significant MOT activation (p < .01; tracking vs. sensorimotor control). Color map displays cortical regions that exhibit significant (p < .01, group level) intrinsic functional connectivity with cerebellar regions activated by MOT. Black outlines denote significant group-level cluster-corrected MOT task activation. iPCS, Inferior Precentral Sulcus; sPCS, Superior Precentral Sulcus; IPS, Intraparietal Sulcus; MT+, area MT complex; aInsula, Anterior Insula; dACC, Dorsal Anterior Cingulate Cortex; CAS-p, Posterior Callosal Sulcus.



Figure 2.8 Cerebellar lobule VIIb/VIIIa ROI groups into cortical dorsal attention network. Hierarchical cluster tree based on the Euclidean distance between seed-to-seed resting-state functional connectivity patterns of task-responsive regions in cortex and cerebellum. Values next to each branch point represent confidence values based on the percentage of bootstraps in which a subtree consisted of the same ROIs (See Materials and Methods). Green indicates cortical dorsal attention network. Orange indicates cortical cognitive control network. MT, area MT complex; sPCS, Superior Precentral Sulcus; iPCS, Inferior Precentral Sulcus; IPS, Intraparietal Sulcus; aInsula, Anterior Insula; dACC, Dorsal Anterior Cingulate Cortex; CAS-p, Posterior Callosal Sulcus.

CHAPTER THREE: TOPOGRAPHIC CORTICO-CEREBELLAR NETWORKS REVEALED BY VISUAL ATTENTION AND WORKING MEMORY²

Introduction

Dating back to the seminal work of Brodmann, a substantial body of research has sought to parcellate the cerebral cortex on the basis of cytoarchitecture, connectivity and function (e.g. Brodmann, 1909; Glasser et al., 2016; Yeo et al., 2011). This work has led to the conclusion that the cerebral cortex comprises a large number of functionally specialized areas. The cerebellum, on the other hand, has traditionally been viewed as functionally homogenous. For much of the last century, the cerebellum was primarily thought to contribute to motor control and coordination (Evarts & Thach, 1969; Ito, 1984; Llinás, 1985). In recent years, functional neuroimaging has revealed evidence linking the cerebellum to cognitive functions, including attention and working memory (Allen et al., 1997; Brissenden, Levin, Osher, Halko, & Somers, 2016; Chen & Desmond, 2005a; Sokolov, Miall, & Ivry, 2017; Stoodley et al., 2012). Working memory, language, executive function and affective tasks have been shown to elicit non-overlapping patterns of activation within cerebellar cortex (Guell, Gabrieli, & Schmahmann, 2018a; Stoodley et al., 2012; Stoodley & Schmahmann, 2009). Additionally, neuroanatomical tracing in primates (Kelly & Strick, 2003) and functional connectivity analyses in humans (Brissenden et al., 2016; Buckner et al., 2011) indicate that regions of cerebral association cortex communicate with specific, non-motor portions of the cerebellum.

² This work has been previously published as Brissenden J.A., Tobyne S.M., Osher D.E., Levin E.J., Halko M.A. and Somers D.C. (2018). Topographic cortico-cerebellar networks revealed by visual attention and working memory. *Current Biology*.

Despite the exquisitely regular local circuit organization of the cerebellum, the topography of polysynaptic connections with association areas of cerebral cortex has evaded accurate description. Current evidence suggests that the cerebellum possesses a coarse functional organization that does not mirror the fine-scale specificity observed in cerebral cortex.

Here, we perform detailed investigations of closely related aspects of visuospatial attention. The current work extends prior human cerebellar research (Allen et al., 1997; Brissenden et al., 2016; Chen & Desmond, 2005a; Stoodley et al., 2012) in performing a more detailed functional mapping of the topographic organization of visuospatial attention and working memory function within the cerebellum. We observe that the dorsomedial portion of cerebellar lobule VIIb/VIIIa represents working memory targets in the ipsilateral visual field. Using population receptive field mapping, we confirm that this portion of cerebellum represents the ipsilateral visual field. While somatotopic representations are well documented within the cerebellum, the finding of cerebellar visuospatial representations is novel. A closer examination reveals that working memory load processes recruit an overlapping but more ventrolaterally positioned portion of lobule VIIb/VIIIa. Similarly, within the cerebral cortex's dorsal attention network we observe overlapping but dissociable patterns of activation for spatial coding and for working memory load. Remarkably, these differential patterns of visual attentional functional recruitment within the cerebral cortex are strongly predicted by functional connectivity with visuospatial and working memory load processing domains in

cerebellar lobule VIIb/VIIIa. These findings reveal a high degree of specificity in the functional organization of the cerebellum and cortico-cerebellar circuitry.

Materials and Methods

Subjects

20 healthy subjects participated in this study. The Institutional Review Board of Boston University approved the study. All subjects were compensated and gave written informed consent to participate in the study. Subjects were recruited from Boston University and the Greater Boston area. All subjects were right-handed and had normal or corrected-tonormal vision. 10 subjects participated in experiment 1. Due to a large displacement in head position, functional data from a large portion of the cerebellum was irretrievably lost in one subject. As a result, this subject was removed from further analysis, leaving us with 9 subjects (3 female). Resting state data from an additional 5 subjects (5 female) were used in a subset of analyses. 5 subjects (3 female) participated in experiment 2. 3 subjects participated in both experiments. Subjects in experiment 1 ranged in age from 24 to 38 years, and subjects in experiment 2 ranged in age from 27 to 35 years. All subjects were screened for MRI contraindications prior to scanning.

Magnetic Resonance Image Acquisition

Experiment 1. Data were acquired from a 3 Tesla Siemens TIM Trio magnetic resonance imager located at the Center for Brain Science at Harvard University in Cambridge, Massachusetts. A 32-channel head coil was used for all scans. A high-resolution $(1.0 \times 1.3 \text{ mm})$ magnetization-prepared rapid gradient-echo (MPRAGE) sampling
structure scan was acquired for each subject. The cerebral cortical surface of each hemisphere was then computationally reconstructed from this anatomical volume using Freesurfer software (version 5.3.0; <u>http://surfer.nmr.mgh.harvard.edu/;</u> Fischl, 2012). T2*-weighted EPI (BOLD) images were acquired using a slice-accelerated EPI sequence that permits simultaneous multi-slice acquisitions using the blipped-CAIPI technique [TR = 2 s, TE = 30 ms; flip angle = 80°; 6/8 partial-fourier acquisition] (Setsompop et al., 2012). A total of 69 slices were acquired with a slice acceleration factor of 3 and 0% skip, covering the whole brain, including the cerebellum. Images were acquired at a nominal 2mm isotropic spatial resolution (matrix size = $108 \times 108 \times 69$).

Experiment 2. Data were acquired from a 3 Tesla Siemens Prisma scanner located at the Center for Brain Science at Harvard University in Cambridge, Massachussetts using a 64-channel head coil. High-resolution T1-weighted multiecho MPRAGE (Sagittal; TR = 2780 ms; TE = 1.32 ms, 3.19 ms, 5.11 ms, 7.03 ms; FA = 7°; 0.8 mm isotropic voxels; 224 slices; FOV = 256 mm × 256 mm × 180 mm; in-plane GRAPPA acceleration 2) and T2-weighted (Sagittal; TR = 3200 ms; TE = 564 ms; 0.8 mm isotropic voxels; 224 slices; FOV = 256 mm × 180 mm; in-plane GRAPPA acceleration 2) structural images were acquired. Functional data were acquired using a multi-band gradient-echo echo-planar pulse sequence (Feinberg et al., 2010; Moeller et al., 2010; Xu et al., 2013) with the following acquisition parameters: TR = 650 ms; TE = 34.8 ms; FA = 52°; 2.3 mm isotropic voxels; FOV = 207 mm × 207 mm × 148 mm. A short TR was chosen in order to increase the number of time points recorded, as this was expected to enhance the quality of the pRF mapping. The increase in temporal sampling rate required a modest

increase in voxel size relative to experiment 1. A total of 64 slices were acquired with a slice acceleration factor of 8 and 0% skip, fully covering the cerebral cortex and cerebellum. Spin echo field maps were also acquired with opposite phase encoding directions (Anterior-to-Posterior; Posterior-to-Anterior) and matching parameters to the gradient-echo EPI fMRI timeseries.

Magnetic Resonance Image Preprocessing

Experiment 1. Task and resting-state data were preprocessed using the Freesurfer FS-FAST software package (version 5.3.0) (Charlestown;

http://surfer.nmr.mgh.harvard.edu/) (Fischl, 2012). The following preprocessing steps were performed: slice-time correction, motion-correction, and spatial normalization to a spatially unbiased infratentorial template (SUIT) of the human cerebellum and brainstem using a non-linear deformation (Diedrichsen, 2006; Diedrichsen et al., 2009). Data were then spatially smoothed with a 3 mm FWHM Gaussian kernel. Smoothing was constrained to only occur within cerebellar cortex as defined by the SUIT anatomical atlas (Diedrichsen et al., 2009). Resting state data were then further preprocessed in MATLAB using custom scripts. We performed nuisance signal regression of headmotion (6 motion parameters and their 6 temporal derivatives), whole-brain signal, and ventricular and white matter signals (Van Dijk et al., 2010). We then calculated framewise displacement by taking the sum of the absolute derivatives of the 6 motion parameters for each time point (Power et al., 2012). A threshold of 0.5 mm was set to identify time points with excessive motion. To avoid artifact spread during bandpass filtering, high motion time points were replaced using linear interpolation (Carp, 2013).

Band-pass filtering was then performed (0.01–0.08 Hz). After filtering, high-motion time points were removed.

Experiment 2. Functional task data first underwent the Human Connectome Project's 'minimal' preprocessing pipeline, which comprises gradient nonlinearity distortion correction, motion correction, EPI image distortion correction, and co-registration with the subject's T1-weighted image (Glasser et al., 2013). The transforms involved in each step of this pipeline were concatenated into a single nonlinear transformation and performed as a single resampling step to reduce interpolation related blurring (Glasser et al., 2013). Following these preprocessing steps, functional images were further nonlinearly transformed to the SUIT template (Diedrichsen, 2006; Diedrichsen et al., 2009). Data were then spatially smoothed within cerebellar cortex with a 3 mm FWHM Gaussian kernel.

Visual Stimuli and Experimental Paradigm

Experiment 1 – VWM change detection paradigm. Stimuli were generated using the Psychophysics Toolbox extension (Brainard, 1997; Pelli, 1997) in MATLAB (Mathworks, Natick, MA), and displayed using a liquid crystal display projector that back-projected onto a screen within the scanner bore. Subjects fixated on a centrally located crosshair, while 12 oriented colored bars were presented (six in each hemifield). While the number of presented bars in each hemifield was held constant across trials, the number of to-be-remembered items presented within a given block was either 1 or 4. The remaining bars in the display served as distractors. Target and distractors were distinguished by color, with targets shown in red and distractors shown in blue. Each bar

subtended 0.25° x 2.5° of visual angle. The stimulus display subtended 25.6° x 19.2° of visual angle. Targets were limited to either the right or the left hemifield (counterbalanced across blocks). All bars in the display were randomly oriented at one of four possible angles (0°, 45°, 90°, 135°). Each subject completed 8 runs (total time per run = 6 min 16 s). Each fMRI task run contained 10 34 s task blocks and 16 s of blank fixation before and after the task blocks. Each block of trials consisted of a 2 s cue indicating the location of the target stimuli (left or right hemifield), followed by 8.4 s trials. On each VWM trial, a memory sample display was presented for 200 ms. Subjects were instructed to maintain the orientations of the presented target items over a 1000 ms delay period. After the sample and delay period, a memory probe was presented for 1800 ms. A 1000 ms fixation period separated each trial. On 50% of trials one of the target bars changed its orientation from the sample period to the probe period, while the on the other 50% of trials no changed occurred. Subjects could respond during either the memory probe or the inter-trial fixation period by pressing a key to indicate that the orientation of the target had changed, or a separate key if it had not changed. The magnitude of the change on change trials was held constant at 90° (e.g. 0° to 90° or 45° to 135°). During sensorimotor control blocks, subjects were presented a display consisting entirely of distractors (all blue) and were instructed to press either key during the probe or inter-trial fixation period. Subjects also underwent 2-3 resting-state scans using identical scan parameters (each 180 TRs; 6 min duration). During the resting-state scans, subjects were instructed to let their minds wander while maintaining fixation on a centrally located crosshair.

Experiment 2 – Population receptive field mapping procedure. Stimuli were generated and presented using Python with the PsychoPy software package (Peirce, 2007; 2008). The paradigm was adapted from the procedure described in (Mackey, Winawer, & Curtis, 2017). Stimulus presentation was confined to a $16.2^{\circ} \times 16.2^{\circ}$ field of view. The stimulus consisted of a bar aperture which subtended 16.2° in length and subtended either 1°, 2°, or 3° in width. The use of different bar widths can aid the estimation of pRF size. The width of the bar aperture was held constant within each run. Functional time-series of runs consisting of the same bar width were averaged prior to pRF modeling. The bar aperture comprised 3 equally sized rectangular patches of moving dots. Dot patches swept across the visual field in a discrete manner, changing location every 1.95 s (3 TRs). The step size of each change in location was 1.1 degrees. There were four possible sweep directions: left to right, right to left, top to bottom, and bottom to top. Each sweep consisted of 13 steps/trials. A full sweep of the visual display was followed by a 9.75 s blank fixation interval (15 TRs). Each patch spanned 5.2 ° along the side perpendicular to the sweep direction. A 0.3° gap separated each patch. Patches of width 1°, 2°, and 3° contained 100, 200, and 300 dots, respectively. Dots moved at 1.5 deg/s and updated their position 60 times per second.

At each location, observers discriminated which of the two flanking patches contained dots moving in the same direction as the middle patch. Only one of the flanker patches moved in the same direction as the middle patch on each trial. Dot motion within the middle patch was always 100% coherent. Coherent dots moved along the length of the patch opposite to the sweep direction (left or right for vertical sweeps and up or down for horizontal sweeps). The coherence of the flanker patches' dot motion was staircased using a 1-up 3-down procedure. Moving dots had a limited lifetime of 10 frames (167 ms). Each noise dot moved in a random direction for the extent of its lifetime.

Quantification and Statistical Analysis

Multivariate pattern analysis. Patterns of cerebellar BOLD activity were obtained by temporally averaging the middle 9 TRs (18 s) of each VWM task block (34 s; set size 1 and 4 conditions) for each voxel in the cerebellum, thus ensuring independence of activity patterns between blocks. Support vector machines (SVM) were trained to discriminate the direction of attentional deployment using a leave-one-run-out crossvalidation procedure. Analyses were performed in R 3.2.3 (R Core Development Team, 2015) using the caret (version 6.0-68; Kuhn, 2008) and kernlab (version 0.9-25; Karatzoglou, Smola, Hornik, & Zeileis, 2004) packages. Classifier performance was assessed by predicting the class labels of each hold-out run. Classification accuracies were then averaged across hold-out sets to yield an overall accuracy for each ROI and subject. The cost parameter C, which is a regularization parameter that controls the biasvariance tradeoff (Hastie, Friedman, & Tibshirani, 2001), was tuned by performing an inner leave-one-run-out cross-validation loop on each training set. The search space of C ranged from 2⁻² to 2⁴. Nested cross-validation schemes provide an unbiased method for selecting model hyperparameters (Haynes, 2015; Pereira, Mitchell, & Botvinick, 2009; Varma & Simon, 2006). Significance was evaluated using permutation tests (Golland & Fischl, 2003). To estimate a null distribution, a data-wise permutation scheme was employed in which class labels were permuted within-run prior to crossvalidation (Etzel & Braver, 2013). This procedure was performed 1000 times. On each respective permutation, the same permutation scheme was used for each subject. A permuted group-level accuracy was computed by averaging individual subject accuracies (Etzel, 2015). We then compared our constructed null distribution to the decoding accuracy obtained with the true class labeling. A p-value was computed as [(# of permutation accuracies \geq true accuracy) + 1]/(N permutations + 1) (Phipson & Smyth, 2010).

Multivariate feature weight mapping. To finely localize spatially selective attentional responses within the cerebellum, we performed a multivariate feature weight mapping analysis on whole-cerebellum BOLD activity patterns (Mourão-Miranda, Bokde, Born, Hampel, & Stetter, 2005; Stelzer et al., 2014; Wang, Childress, Wang, & Detre, 2007). The SVM algorithm defines a discriminant function that can be used to predict the class of new samples:

$$g(x) = wx + b,$$

where *w* is a vector of weights, *x* is a vector of voxel BOLD amplitude values, and *b* is a bias term. The weight vector (*w*) reflects the contribution of each voxel to the classification decision. By submitting whole-cerebellum multi-voxel activity patterns to the classification procedure, we obtained weights for every voxel in the cerebellum for each cross-validation fold. To reduce computation time on our computing cluster, PCA was used to orthogonally transform our original features (all cerebellar voxels) into principal components (# PCs = # samples – 1). The SVM classifier was then trained on this dimensionality-reduced matrix. The resulting principal component weight vector

could then be transformed back to the original feature space by reversing the PCA transformation (e.g. Mourão-Miranda et al., 2005; Stelzer et al., 2014; Z. Wang et al., 2007), thus resulting in a weight for each feature (voxel). Final weights were computed by averaging weights across cross-validation folds. We then generated an empirical null distribution of weights for each voxel in the cerebellum by training the whole-cerebellum classifier 1000 times with permuted class labels. We could then assess the discriminative value of a voxel by computing the probability of obtaining a weight that is at least as extreme as the observed weight given the voxel's null weight distribution. Probabilities were computed for all cerebellar voxels in the original weight map as well for each permuted weight map. Each voxel probability was then subtracted from 1 to generate a cumulative probability and then converted to a z-score using MATLAB's norminv function. To maintain information about the direction of discriminance, voxel z-scores were signed according to the direction of the effect (left or right tail of null distribution). Actual discriminance z-maps and permuted z-maps were then submitted to a 2nd-level group analysis. To control family-wise error rate, we employed threshold-free cluster enhancement (TFCE) (Smith & Nichols, 2009) and non-parametric randomization tests (Nichols & Holmes, 2002). First, group statistic maps were generated via voxel-wise ttests with variance smoothing ($\sigma = 4$ mm) followed by TFCE transformation as implemented by FSL's randomise tool (www.fmrib.ox.ac.uk/fsl/randomise; (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012; Smith et al., 2004)). A null distribution was then generated by recording the image-wise maximum TFCE statistic for each permuted group map (Eklund, Nichols, & Knutsson, 2016; Nichols & Holmes, 2002).

Using this maximum statistic null distribution, the original group map was thresholded at p < 0.05, two-sided. In order to compare our cerebellar results with regions with well-documented spatial selectivity in the cerebral cortex, we additionally performed feature weight mapping on whole-cortex activity patterns. As FSL's *randomise* tool is not compatible with Freesurfer functional surface files, we used the CoSMoMVPA analysis package's surface-based implementation of TFCE (Oosterhof, Connolly, & Haxby, 2016).

Eye movement control analysis. As the cerebellum has previously been implicated in eve movements, subjects were instructed to maintain fixation on a centrally located cross while performing the task using covert attention. All subjects were experienced visual psychophysical observers. Additionally, subjects practiced holding central fixation while performing the task prior to scanning. During scanning, eve position was monitored using an EyeLink 1000 from SR research. Eye tracking data could not be obtained for one of our subjects in Experiment 1 due to technical difficulties. To examine the relationship between any residual eye movements and cerebellar activation, we used linear support vector regression (SVR) ($\varepsilon = 0.1$) (Drucker, Burges, & Kaufman, 1997) to predict a continuous measure of eye movements from the pattern of BOLD activity extracted from a cerebellar ROI. Our cerebellar ROI included any cerebellar voxel that was considered significant at the group level of the multivariate feature weight mapping analysis (p < p0.05 FWE corrected, two-sided). Model performance assessment and hyperparameter tuning were carried out using the same nested cross-validation procedure described previously. For each trial within a block, we quantified the magnitude of eye movement

by computing the root mean square deviation from the median gaze position for the trial. We also computed the average horizontal gaze position for each trial. These values were averaged across trials to generate a mean value for each block. Some blocks had missing eye position data as a result of the eye tracker being unable to locate the subject's pupil (excessive eye blinks or interference from eye lids). Consequently, for some subjects training or test sets contained different number of samples across different cross-validation folds. The accuracy of SVR predictions was assessed by computing a cross-validated coefficient of determination or R^2 .

$$R^{2}_{cv} = 1 - \frac{\sum_{i=1}^{htest} (y_{i} - \hat{y}_{i})^{2}}{\sum_{i=1}^{htest} (y_{i} - \bar{y}_{train})^{2}}$$

where \hat{y}_i denotes the SVR prediction for the *i*th test set observation and \bar{y}_{train} indicates the response mean of the training set. In cases where explained variance is very low, R^2_{cv} can be negative (Nichols et al., 2017). Negative values of R^2_{cv} indicate that the fitted model performs worse than a null model in which the response of each test set observation is predicted to be the mean response of the training set.

VWM load/spatial coding selectivity analysis. Cortico-cerebellar VWM load activation was identified by fitting a voxel-wise general linear model that included a predictor for each task condition. Model fitting was performed using the Freesurfer FS-FAST software package (version 5.3.0) (Charlestown; <u>http://surfer.nmr.mgh.harvard.edu/</u>) (Fischl, 2012). To control for activation due to cue reorientation, cue time points at the beginning of each block were included as nuisance regressors in the model. Singular value decomposition reduced the 6 motion correction vectors obtained during

preprocessing to 3 eigenvectors, which were also included as nuisance regressors in the model. Task regressors were convolved with a canonical hemodynamic response function prior to fitting. The hemodynamic response was modeled by a Y function with a delay of $\delta = 2.25$ s and a decay time constant of $\tau = 1.25$ (Boynton et al., 1996). *t* tests were performed voxel-wise, contrasting the set size 4 condition with the set size 1 condition. Individual subject *t*-statistic maps were then submitted to 2nd-level group analysis. Mirroring the feature weight group analysis, voxel-wise *t*-tests were performed with variance smoothing ($\sigma = 4$ mm). The resulting *t*-statistic map then underwent TFCE transformation (Smith & Nichols, 2009). To correct for multiple comparisons, the maximal test statistic was retained for all possible permutations or sign-flips (n=512) (Eklund et al., 2016; Nichols & Holmes, 2002). Using this null distribution, the group VWM load map was thresholded at p < 0.05, one-sided.

To assess the relative strength of load activation and spatial selectivity within the cerebellum and cerebral cortex, uncorrected group *t*-statistic maps from spatial and load analyses were normalized across either the cerebellum or cerebral cortex. Prior to normalization, we took the absolute value of the spatial *t* map, as both extremes of the distribution indicate spatial selectivity. We then directly contrasted the normalized VWM load activation map and normalized spatial coding discriminance map via subtraction. After taking the difference of the two maps, any voxel/vertex that did not survive correction for multiple comparisons in both analyses was masked out.

A similar procedure was performed on resting-state correlation maps to contrast the connectivity of spatial and load sensitive portions of the ventral cerebellum. Restingstate data collected across 18 sessions and 14 subjects (4 subjects scanned twice) were included in this analysis. Spatial- and load-selective seed ROIs were defined in each hemisphere of lobule VIIb/VIIIa by the intersection of a hemispheric lobule VIIb/VIIIa anatomical mask and the multiple comparison corrected group map of each analysis. Mean time courses extracted from these ROIs were then correlated with every vertex from the contralateral hemisphere of cerebral cortex. Cerebral cortical correlation maps were normalized using Fisher's *z* transformation. For subjects with multiple sessions, *z* maps were averaged prior to the 2^{nd} -level group analysis. We then performed the same procedure previously carried out on the spatial and load selectivity group maps (normalization, subtraction, and masking). To assess the relationship between task selectivity and cortico-cerebellar connectivity we computed the spatial correlation between the task difference map and the connectivity difference map.

Population receptive field modeling. pRF analysis was performed using the analyzePRF MATLAB toolbox (Kay, Winawer, Mezer, & Wandell, 2013). Voxel time-series were modeled with a compressive summation model (Kay et al., 2013), which is an extension of the pRF model described by (Dumoulin & Wandell, 2008). This model includes an additional exponent parameter to account for subadditive spatial summation (Kay et al., 2013). The model is formally expressed as:

$$r(t) = g \times \left[\int S(x, y)G(x, y)dxdy\right]^n$$

where r(t) is a voxel's predicted response, g is a gain parameter, S is a binary stimulus mask, and G is a 2-dimensional isotropic Gaussian expressed as:

$$G(x, y) = e^{-\frac{(x-x_0)^2 + (y-y_0)^2}{2\sigma^2}}$$

where x_0 and y_0 are parameters defining the position of the Gaussian, and σ is a parameter defining the standard deviation of the Gaussian. Prior to fitting, functional time-series of runs consisting of the same experimental bar size $(1, 2 \text{ or } 3^\circ)$ were averaged. The original pRF model described by (Dumoulin & Wandell, 2008) involved a two-stage fitting procedure: an initial coarse grid-fit followed by an exhaustive non-linear optimization procedure using seed parameters from the grid-fit. However, a recent study found that the full optimization procedure did not outperform the coarse grid-fit when predicting independent, left-out data (Mackey et al., 2017). It was argued that the grid-fit procedure is more robust to noise and better able to predict the responses of frontoparietal voxels with large pRFs (Mackey et al., 2017). As cerebellar lobule VIIb/VIIIa possesses similar profiles of connectivity and task recruitment as fronto-parietal regions, we only performed the initial grid-fit procedure. This analysis was restricted to the ventral cerebellum. The grid-fitting procedure iterated over 7720 possible parameter combinations (16 angles, 13 eccentricities, 8 widths, and 5 exponents). A 3-fold crossvalidation procedure was used to determine which voxels were further analyzed. Each fold included all three experimental bar sizes. We excluded voxels that did not exceed a cross-validated predicted-actual correlation of 0.2.

Results

To investigate spatial coding of visual attention within the cerebellum, we asked participants (n = 9) to perform a lateralized visual working memory task in an fMRI scanner (Figure 3.1A). At the beginning of each block, participants were cued to covertly

attend either the left or right visual hemifield while holding central fixation. Participants were instructed to maintain in working memory the orientation of briefly presented (200 ms) target items (red bars) in the attended hemifield over short delays. VWM load also was varied, by presenting 1 or 4 targets in different blocks (results presented in figure 3.4A). Distractor stimuli (blue bars) were included to equate visual stimulation between attended and unattended hemifields. The locus of attention (left vs. right) did not influence behavioral measures of accuracy (*d*'; *t*(8) = 0.0066, *p* = 0.995) or reaction time (*t*(8) = 0.0017, *p* = 0.999). We observed that the location of covert attentional deployment (left or right visual hemifield) could be decoded from whole cerebellum multi-voxel BOLD activity patterns. Mean classification accuracy was 60.42% (\pm 1.54% S.E.M.) relative to chance performance of 50%. Non-parametric permutation tests showed that the mean classification accuracy produced by the whole-cerebellum region of interest (ROI) fell outside the bounds of the 95% confidence interval of the generated null distribution (p = 0.001).

Visuospatial Selectivity Within Cerebellar Lobule VIIb/VIIIa

To localize the cerebellar regions that exhibit attentional spatial sensitivity, we performed a multivariate feature weight mapping (FWM) analysis on whole cerebellum BOLD activity patterns (see STAR Methods for details). Submitting individual subject feature weight discriminance maps to a 2nd-level group analysis revealed clusters of discriminative voxels in both left and right cerebellar lobule VIIb/VIIIa (Figure 3.1B; MNI152/SUIT coordinates: [-6.5, -70.2, -42.5]; [9.0, -71.1, -41.4]). The clusters of significant feature/voxel weights in each hemisphere were oppositely signed, indicating

that these clusters influenced the classification decision towards different classes (i.e. hemifields). The cluster in left lobule VIIb/VIIIa was found to weight the decision function towards the left hemifield attentional locus and the cluster in right lobule VIIb/VIIIa was found to weight the decision function towards the right hemifield attentional locus. Thus, these cerebellar responses code for attentional processing within the ipsilateral visual hemifield, while cerebral cortical regions encode contralateral visual field representations (Swisher et al., 2007). This relationship is consistent with the hemispheric crossing of poly-synaptic neuronal pathways connecting cerebral cortex and cerebellum; the cortico-ponto-cerebellar and cerebello-thalamo-cortical fiber tracts each cross the midline via the decussation of the middle and superior cerebellar peduncle, respectively. Cerebral cortical sensitivity to the locus of spatial attention estimated by FWM is shown in Figure 3.2A. Cortical spatial sensitivity was found to be largely restricted to extrastriate cortex and the intraparietal sulcus (IPS), consistent with prior observations (Jerde et al., 2012; Kalberlah, Chen, Heinzle, & Haynes, 2011; Serences & Yantis, 2006; Swisher et al., 2007; Szczepanski, Konen, & Kastner, 2010).

Eye Movement Control

The cerebellum has been implicated in oculomotor control, and some have argued that cerebellar attentional activation reflects oculomotor behavior rather than true involvement in attention (e.g. Haarmeier & Thier, 2007). Therefore, it is critical to examine whether our finding of visuospatial sensitivity in the cerebellum simply reflects eye movement related processing. All subjects possessed extensive experience at performing psychophysical tasks while maintaining fixation on a central crosshair. Inscanner eye tracking confirmed that subjects tightly held central fixation through all conditions; there was no significant difference between attend-left and attend-right trials in root mean square (RMS) deviation from fixation (t(7) = 0.84, p = 0.43) or horizontal eye position (t(7) = 1.54, p = 0.17). To further examine oculomotor factors as a possible source of cerebellar spatial selectivity, we investigated whether cerebellar BOLD signal predicted eye movements or eye position. We employed a support vector regression model trained on the cerebellar voxels identified as spatially discriminative by the multivariate feature weight mapping analysis (see STAR Methods). Model performance was assessed by computing a cross-validated coefficient of determination (see STAR Methods). Predictions yielded a negative coefficient of determination for both RMS deviation and average horizontal gaze position, indicating that both models performed no better than a null model in which the response of each test set observation was predicted to be the mean response of the training set (RMS deviation $R^2_{cv} = -1.65 \pm 0.42$ S.E.M.; X coordinate $R_{cv}^2 = -1.48 \pm 0.55$ S.E.M.). Therefore, we find that cerebellar BOLD signal was not predictive of eye movements or position.

Cerebellar Visual Field Representations

As a further examination of visuospatial sensitivity in cerebellar lobule VIIb/VIIIa, we conducted a second experiment to investigate whether lobule VIIb/VIIIa contains visual field representations. The task required participants (n = 5) to covertly attend to a rectangular stimulus that moved slowly across the visual field in different directions. Thus, the entire visual field was parametrically mapped across multiple stimulus sweeps. The stimulus was divided into three segments, each containing random dot motion

stimuli (see Fig 3.3A). On each trial subjects were asked to report which of the two outer segments exhibited the same global motion direction as that of the inner segment. This task, which combines both spatially specific attention and visual stimulation has previously been employed to map visual field representations in the cerebral cortex (Mackey et al., 2017). We performed population receptive field (pRF) modeling (see STAR Methods for details) on the resulting data for ventral cerebellum. Polar angle analysis revealed a representation of ipsilateral visual hemifield within dorsomedial lobule VIIb/VIIIa (Figure 3.3B), consistent with the findings of the hemifield classification. To reveal the representation of the visual field in lobule VIIb/VIIIa across all subjects, we computed a visual field coverage density map. This entails averaging the pRFs of above-threshold voxels ($r_{cv} > 0.2$) within an anatomical region-of-interest (anatomical lobule VIIb and VIIIa mask) within and across subjects. Lobule VIIb/VIIIa coverage density showed a clear bias towards ipsilateral visual hemifield locations (Figure 3.3C). Additionally, the extent and laterality of visual field coverage in lobule VIIb/VIIIa mirrors the visual field coverage of attention areas in fronto-parietal cortex (see Figure 6 in (Mackey et al., 2017)). Lobule VIIb/VIIIa also appears to contain an over-representation of the lower visual field, similar to that observed in the visuotopic areas of intraparietal sulcus (Wang, Mruczek, Arcaro, & Kastner, 2015); the dorsal subdivisions of early visual cortical areas V1, V2, and V3 code only the lower visual field and a lower field bias persists throughout the dorsal visual pathway in the cerebral cortex. Experiment 2 replicates the Experiment 1 finding of visuospatial selectivity within the dorsomedial portion of cerebellar lobule VIIb/VIIIa. Furthermore, these

findings critically demonstrate that cerebellar representations of the visual field mirror those previously reported in parietal and frontal cerebral cortices.

Visuospatial Functional Specificity Within Cerebellar Lobule VIIb/VIIIa

To further examine the fine-scale functional organization of visuospatial attention processing within cerebellar lobule VIIb/VIIIa, we compared the locus of visuospatial selectivity with the locus of sensitivity to visual working memory load within ventral cerebellum. The visual working memory experiment (see figure 3.1A; STAR Methods; Brissenden et al., 2016) manipulated the number of items held in visual working memory (VWM load) and the hemifield of the targets, while keeping stimulus drive equivalent across conditions. Overlapping but different regions were found to be sensitive to visuospatial location and to VWM load. VWM load activation extended much farther ventrolaterally within lobule VIIb/VIIIa than did the spatial sensitivity (Figure 3.4A). Working memory load has also been shown to activate additional areas located in dorsal cerebellum (lobule VI and Crus I) (Brissenden et al., 2016; Chen & Desmond, 2005a). However, as we did not observe spatial selectivity in dorsal cerebellum, subsequent analyses comparing VWM load and spatial coding were restricted to ventral cerebellum (dorsal cerebellum is masked in Figure 3.4A and 3.4B). Cerebral cortical sensitivity to VWM load is shown in Figure 3.2B. To more closely examine the degree of specificity for spatial coding and VWM coding within lobule VIIb/VIIIa, we normalized the uncorrected group statistic map of each analysis across cerebellar lobule VIIb/VIIIa and then contrasted (via subtraction) the normalized spatial coding map with the normalized VWM load map. The resulting difference map was masked to exclude voxels that did not survive multiple comparison correction in both analyses. This analysis revealed a functional gradient for visuospatial attention running from dorsomedial to ventrolateral across lobule VIIb/VIIIa (Figures 3.4B, 3.5).

In order to better characterize the anatomical distinctions within lobule VIIb/VIIIa between spatial coding and VWM load coding, we constructed probability density functions of the spatial-dominant (spatial > load) and of the load-dominant (load > spatial) voxels for each of the X, Y, and Z MNI anatomical axes (See Figures 3.4C, 3.4D, and 3.6). The distinction between these two populations is very clear across both the X (mediolateral) and Z (dorsoventral) axes. Spatial coding more strongly recruits the dorsomedial portion of lobule VIIb/VIIIa bilaterally, while VWM load more strongly recruits the ventrolateral portion of lobule VIIb/VIIIa bilaterally.

Within dorsomedial lobule VIIb/VIIIa many voxels exhibited both significant spatial coding and significant load coding (Fig 3.4A, 3.4B). To examine the relationship between visual field representations and space vs. load coding, we constructed separate visual field coverage density maps weighted by load effect size and by spatial effect size. This analysis, which was limited to the subjects who participated in both studies (N=3), used all voxels with significant visual pRF fits ($r_{cv} > 0.2$). The weighted visual field representations closely matched each other and the unweighted representation (Figure 3.7), although in the right hemisphere spatial coding emphasized the peripheral ipsilateral visual field more so than did load coding.

Topographically Organized Cortico-Cerebellar Networks

The fine-scale functional organization within cerebellar lobule VIIb/VIIIa mirrored the organization observed in the cerebral cortex. Spatial selectivity was stronger within extrastriate cortex and along the medial bank of intraparietal sulcus, which dovetails with previous work identifying retinotopic maps within these areas (Mackey et al., 2017; Swisher et al., 2007; Wang et al., 2015). VWM load activation, on the other hand, dominated in the more anterior and ventral portions of the intraparietal sulcus (Figure 3.8A).

The observation of similar functional gradients in cerebellar lobule VIIb/VIIIa and parieto-occipital cortex raises the question of whether highly specific functional subnetworks for visuospatial attention processing exist between cerebellum and the cerebral cortex. To address this question, we examined whether resting-state functional connectivity with cerebellar lobule VIIb/VIIIa could predict the functional organization in parieto-occipital cortex. Spatial coding seed and VWM load seed ROIs in lobule VIIb/VIIIa were defined in each hemisphere using the multiple comparison corrected group map from each analysis. These ROIs included any lobule VIIb/VIIIa voxel that survived correction for multiple comparisons in each respective analysis (Load: p < 0.05FWE corrected, one-sided; Spatial: p < 0.05 FWE corrected, two-sided) (Figures 3.1B and 3.4A). No constraints were placed on the overlap between load and spatial coding ROIs. For each cerebellar ROI, we extracted average resting-state time courses and then computed their correlations with the resting-state time course from each vertex from the contralateral hemisphere of cerebral cortex, using data from 14 subjects (see STAR Methods). A difference analysis of spatial and load seed connectivity yielded a prediction of parieto-occipital functional organization (Figure 3.8B). Spatially selective cerebellar voxels exhibited stronger functional connectivity with extrastriate cortex and the medial bank of IPS, while load-activated cerebellar voxels exhibited stronger functional connectivity with anterior IPS and frontal areas. This functional gradient, produced from resting-state functional connectivity, closely matches the actual functional gradient observed in the task data (Figure 3.4A). Spatially correlating the connectivity difference map with the task recruitment difference map yielded very strong correlations for each hemisphere (RH: r = 0.84, p < 0.000001, LH: r = 0.70, p < 0.000001). These results provide evidence for fine-grained functional subnetworks for visual attention and working memory spanning both cerebellar lobule VIIb/VIIIa and parieto-occipital cortex.

Discussion

These findings reveal a highly specific functional organization for visuospatial attention and working memory within cerebellar lobule VIIb/VIIIa. Here, for the first time we demonstrate that the cerebellum encodes representations of the visual field. Spatially selective responses were found in cerebellar lobule VIIb/VIIIa across two independent tasks that required allocating attention to different portions of the visual display. Additionally, a functional gradient for visuospatial attention processing was observed running from dorsomedial to ventrolateral within lobule VIIb/VIIIa. The dorsomedial portion of lobule VIIb/VIIIa was more strongly recruited by spatial aspects of the task, while ventrolateral lobule VIIb/VIIIa was reflected in the connectivity of these areas with cerebral cortex. Seed-based intrinsic functional connectivity analyses showed that cortico-cerebellar connectivity of load- and space-sensitive portions of cerebellar lobule VIIb/VIIIa precisely predicted the specialization observed in cortex. Taken together, these findings indicate the existence of fine-scale cortico-cerebellar networks that differentially encode key functional aspects of visual attentional processing.

Our findings extend prior work demonstrating the specificity of cortico-cerebellar connections. Anatomical tracer studies performed in non-human primates have shown that cerebellar regions project to the same cerebral cortical regions from which they receive input forming closed-loop circuits (Kelly & Strick, 2003). Additionally, cortico-cerebellar circuits connecting cerebellum with pre-frontal cortex area 46 are shown to be distinct from circuits connecting cerebellum with M1 (Kelly & Strick, 2003). There is also evidence for anatomical projections from cerebellar output nuclei to specific portions of posterior parietal cortex (Prevosto et al., 2010). Work in humans using resting-state fMRI provides complementary evidence for extensive cortico-cerebellar projections that can be segregated into motor and cognitive domains (Buckner et al., 2011; Habas et al., 2009; O'Reilly et al., 2010).

Due to the uniformity of cerebellar cytoarchitecture, it has been suggested that differences in information processing across cerebellar cortex arise from differences in connectivity (Ramnani, 2006). Indeed, cerebellar intrinsic coupling with foot, hand and tongue areas of primary motor cortex precisely predicts task-based estimates of cerebellar somatomotor topography (Buckner et al., 2011). We previously showed that corticocerebellar resting-state functional connectivity can also predict cerebellar recruitment by cognitive tasks. Cerebellar functional connectivity with fronto-parietal cortex was found to be strongly associated with the magnitude of cerebellar activation by working memory and attention (Brissenden et al., 2016). In the current study, we showed that two regions within cerebellar lobule VIIb/VIIIa exhibited differential connectivity patterns with cerebral cortex and that these differences precisely mirrored the specialization observed in parieto-occipital cortex.

It should be noted that we cannot definitively attribute our set size effect to VWM storage processes. The VWM change detection task used here employed a block design. Consequently, the load contrast could potentially reveal differences during selection, encoding, maintenance periods and/or probe periods of a trial; future studies will be needed to isolate which VWM task components specifically contribute to the observed load effects.

Cerebellar somatomotor representations have been extensively mapped in both non-humans and humans (Adrian, 1943; Buckner et al., 2011; Grodd et al., 2001; Rijntjes et al., 1999; Snider & Eldred, 1952; Snider & Stowell, 1944; Wiestler et al., 2011). The cerebellum contains two full body maps. An inverted map is found in lobules IV and V within the anterior lobe, and a second upright map is found in lobule VIIIb within the posterior lobe (Buckner et al., 2011; Grodd et al., 2001). No prior work has investigated whether non-motor topographic representations exist within the portion of the cerebellum intervening these areas. Here, we find strong evidence for an ipsilateral visual hemifield representation within lobule VIIb/VIIIa, mirroring the ipsilateral representation of the body within the two cerebellar somatomotor maps. Future work will need to determine whether a more fine-grained topographic organization exists within these hemifield representations. It is possible that cerebellar lobule VIIb/VIIIa may contain fine-scale representations of within-hemifield locations but may not be retinotopically organized. Physiological studies have shown that nearby areas of somatotopic cerebellar cortex respond to stimulation of distinct portions of a particular body part. This disordered representation has been referred to as "fractured somatotopy" (Kassel, Shambes, & Welker, 1984; Schlerf, Wiestler, Verstynen, & Diedrichsen, 2014; Shambes, Gibson, & Welker, 1978). Nevertheless, local voxel patterns in both cerebellar motor maps have been shown to discriminate the stimulation or movement of individual fingers, indicating the existence of finger representations in these areas (Wiestler et al., 2011). Consequently, fine-scale representations of within-hemifield locations may exist in dorsomedial lobule VIIb/VIIIa, even in the absence of an orderly organization.

Prior work has reported that verbal working memory recruits cerebellar lobule VII (Chen & Desmond, 2005a). The combination of the present and prior findings suggests that lobule VII may support generalized working memory functions. Alternatively, modality-specific subdomains of lobule VII could exist to support different forms of working memory, similar to recent observations in lateral frontal cortex (Michalka et al., 2015). A broad range of cerebellar contributions to visual perception have been observed (e.g., Baumann et al., 2015). Patients with lesions to lobule VIIb/VIIIa (and to Crus I/II) exhibit covert attention deficits (Striemer, Cantelmi, Cusimano, Danckert, & Schweizer, 2015a) and lesions to left hemisphere lobule VIIb/VIIIa have been associated with deficits in visual processing of biological motion (Sokolov, Gharabaghi, Tatagiba, & Pavlova, 2010), consistent with a functional role in dorsal attention network processing. Increasing evidence points to an association between reduced cerebellar grey matter volume, particularly within cerebellar lobule VIIb, and psychiatric disease (Moberget et al., 2018; Romer et al., 2018). These studies are largely consistent with our finding of attentional organization within lobule VIIb/VIIIa. However, the relationship between cerebellar measures and clinical symptom severity has not been examined at the level of granularity of within-system organization we report here.

Within posterior parietal cortex, dorsomedial portions of the intraparietal sulcus (IPS) contain robust visual field representations (Mackey et al., 2017; Swisher et al., 2007; Wang et al., 2015) and are also activated by VWM load (Sheremata et al., 2010; Sprague et al., 2014; Todd & Marois, 2004), while the adjacent ventral and lateral portions of IPS exhibit VWM load-dependence, but do not possess clear visual field representations. Similarly, within cerebellar lobule VIIb/VIIIa we observed that the dorsomedial portion contains robust visual field representations and is activated by VWM load, while the ventrolateral portion is strongly recruited by VWM load but lacks clear visual field representations. Further research is needed to differentiate the functional contributions of dorsomedial and ventrolateral portions of cerebellar lobule VIIb/VIIIa from those of their cerebral cortical counterparts. The uniformity of cerebellar cytoarchitecture has led to proposals that cerebellar computations are similarly uniform (Ramnani, 2006; Schmahmann, 1991). One prominent theory, paralleling well-established ideas concerning the role of the cerebellum in motor learning (Albus, 1971;

Doya, 1999; Ito, 1984; Marr, 1969; Wolpert et al., 1998), proposes that cerebellar regions form internal models that coordinate and refine cognitive operations (Ito, 2008; Sokolov et al., 2017). In the motor domain, cerebellar internal models are conceptualized as predicting the sensory consequences of a motor action (forward model) or as generating the motor commands necessary to achieve a desired state or goal (inverse model) (Ito, 2008; Wolpert et al., 1998). Ultimately, the hypothesized purpose of these models is to enable the efficient coordination of motor actions necessary for skilled behavior. Consequently, the cerebellum may play a similar role in attentional processing, serving to refine the precise spatio-temporal deployment of visuospatial attention in familiar contexts.

These findings not only have implications for our understanding of how the brain's circuitry precisely controls the deployment of limited visual attentional resources, but also provide evidence for the existence of highly specific cortico-cerebellar functional networks for cognitive processing. We hypothesize that similarly precise corticocerebellar networks exist for many other aspects of cognition and that the observed functional and connective specificity may reflect a general governing principle of corticocerebellar topographic organization. In order to observe such networks, it may prove useful to follow the methodological approach that was employed here by combining high-resolution functional connectivity analysis with multiple task-based fMRI paradigms that target closely related cognitive processes.



Figure 3.1 Visuospatial working memory. (A) Task Configuration. Participants held central fixation while covertly performing a spatially lateralized visual working memory task, in which they were asked to encode the orientation of 1 or 4 target stimuli (red) and to report whether the orientation of any bar changed (one bar changed on 50% of trials, no change on other 50% of trials) across a brief delay interval. Target stimuli alternated visual hemifields across blocks of trials. (B) Cerebellar spatial classification discriminance group map (n=9) produced by a multivariate feature weight mapping analysis (FWM). Hot or cool colors indicate voxels/features that influenced the classification decision towards the right or left hemifield attentional locus, respectively. Map is thresholded at p <0.05 FWE corrected, two-sided. VI -Lobule VI; CrI – Crus I; CrII – Crus II; VIIb - Lobule VIIb; VIIIa - Lobule VIIIa



Figure 3.2 Group level results for spatial coding, working memory load, and cerebellar seed functional connectivity analyses. Superimposed black lines mark ROI boundaries from a probabilistic retinotopy atlas (Wang et al., 2015). (A, B) Group average task analysis maps (A) Cerebral cortical spatial classification discriminance group map, p < 0.05 FWE corrected, two-sided (B) Group results for contrast of working memory set size 4 versus set size 1, p < 0.05 FWE corrected, one sided. (C, D) Group average resting-state functional connectivity maps (C) Cerebellar lobule VIIb/VIIIa spatial coding seed group average functional connectivity map, p < 0.05 FWE corrected, one-sided (compare to A). (D) Cerebellar lobule VIIb/VIIIa working memory load seed group functional connectivity map, p < 0.05 FWE corrected, one-sided (compare to B).



Figure 3.3 Visual Stimulation and visual attention. (A) Participants held central fixation while bar-like apertures containing moving dot stimuli were slowly swept across the visual field in each of four cardinal directions. The task was to report which of the two outer sections possessed dot motion in the same direction as the inner section. This task was repeated for each step in the visual field sweep. fMRI responses were used to estimate the population receptive field for each ventral cerebellar voxel. (B) Polar angle visual field mapping in ventral cerebellum of one participant revealed ipsilateral visual field representations within the dorsomedial portion of cerebellar lobule VIIb/VIIIa. VI – Lobule VI; CrI – Crus I; CrII – Crus II; VIIb – Lobule VIIb; VIIIa – Lobule VIIb/VIIIa. (C) Group-average (n=5) visual field coverage maps for cerebellar lobule VIIb/VIIIa also revealed coding of ipsilateral visual space. Note that X and Y axes represent visual field position, while the color map reflects the density of visual field coverage.



Figure 3.4 Visuospatial functional specificity within cerebellar lobule VIIb/VIIIa. (A) Visual working memory (VWM) load (set size 4 vs. set size 1, irrespective of stimulus hemifield) drove activity broadly across cerebellar lobule VIIb/VIIIa. Black outlines indicate the extent of spatial coding from Figure 1B. (B) Normalized comparison of spatial location coding and VWM load coding revealed complementary gradients, for which spatial coding is more robust dorsomedially and VWM load coding is more robust ventrolaterally. (C, D) Probability density curves for VWM load coding (orange) and for spatial coding (blue) showed separable profiles in the X- and Z- dimensions (MNI coordinates).



Figure 3.5 Observation of cerebellar functional gradient is robust to analysis details. (A) Voxel-wise comparison of load and spatial effect size maps computed using multivariate feature-weight mapping (FWM). (B) Voxel-wise comparison of load and spatial effect size maps computed using univariate GLM analysis.



Figure 3.6 Spatial profile of cerebellar VWM load and spatial coding in Y-dimension. Probability density curve of MNI Y-dimension for VWM load coding (orange) and for spatial coding (blue) cerebellar lobule VIIb/VIIIa voxels.



Figure 3.7 Relationship between cerebellar lobule VIIb/VIIIa VWM load/spatial coding specificity and retinotopic visual field location preference. (A) Unweighted visual field coverage density map for 3 subjects who participated in Experiments 1 and 2. (B) Visual field coverage weighted by VWM load *z*-scores. Values have been normalized and thus reflect probability densities of locations in the visual field. (C) Visual field coverage weighted by spatial coding *z*-scores. (D) Difference between VWM load and spatial coding visual field coverage probability density maps.



Figure 3.8 Specificity of cortico-cerebellar sub-networks. (A) Normalized comparison of spatial coding and VWM load coding in the cerebral cortex revealed a gradient in parieto-occipital cortical regions. Areal boundaries from a probabilistic retinotopy atlas (Wang et al., 2015) are overlaid. Within parietal cortex, dorsomedial retinotopic areas IPS0, IPS1, IPS2, IPS3, IPS4 and IPS5 exhibited varying degrees of spatial bias, while the ventrolateral portion of IPS was biased for VWM load coding (B) Contrast between resting-state functional connectivity of cerebellar lobule VIIb/VIIIa spatial coding and VWM load coding seeds accurately reflected the functional gradient observed in the task data of panel A.

CHAPTER FOUR: CEREBELLUM ENCODES STIMULUS-SPECIFIC REPRESENTATIONS DURING VISUAL WORKING MEMORY Introduction

Visual working memory (VWM) can be defined as the temporary maintenance of visual information independent of the constant influx of perceptual input. Investigating the neural mechanisms of VWM is of considerable interest to the neuroscience community as performance on VWM tasks has been shown to be highly correlated with broader measures of intellectual ability such as fluid intelligence, reading comprehension, and scholastic aptitude (Engle, 2002; Engle et al., 1999; Fukuda et al., 2010). The question of where working memory contents are stored in the brain is the subject of ongoing debate. Based on electrophysiological recordings in non-human primates and neuroimaging in humans, it has long been asserted that parietal and pre-frontal cortices support working memory maintenance (Courtney et al., 1998; Funahashi, Bruce, & Goldman-Rakic, 1989; Mendoza-Halliday, Torres, & Martinez-Trujillo, 2014). On the other hand, the sensory recruitment hypothesis posits that working memory storage is mediated by the same areas involved in the initial sensory processing of stimuli and that parietal and pre-frontal areas instead serve as a source of top-down biasing signals (D'Esposito & Postle, 2015; Pasternak & Greenlee, 2005). Recently, it has been suggested that working memory contents are distributed across number of cerebral cortical areas including both sensory and pre-frontal regions (Christophel et al., 2017; Ester et al., 2015; Serences, 2016). Despite the progress that has been made in characterizing the neural substrates of working memory encoding and storage, the involvement of subcortical structures has

received little consideration. Recent work suggests that portions of the cerebellum are actively involved in attention and working memory task performance (Brissenden et al., 2016; 2018). However, as these studies either did not include a VWM maintenance component or employed a block design in which sample, delay and probe responses could not be distinguished, it is unclear whether the cerebellar contribution to these tasks reflects working memory storage processes or rather a more generalized attentional control mechanism. In the current study, we sought to directly investigate whether specific portions of the cerebellum contribute to the encoding and maintenance of mnemonic representations.

Early research aimed at determining where working memory contents are stored in the brain was primarily informed by either lesion-induced deficits in working memory task performance or the observation of sustained, elevated activity over extended delays (Courtney et al., 1998; Funahashi et al., 1989; Postle, Zarahn, & D'Esposito, 2000; Wager & Smith, 2003). However, as noted in number of recent reviews (Christophel et al., 2017; D'Esposito & Postle, 2015; Serences, 2016), working memory deficits following the lesioning of an area or elevated delay period activity could simply indicate an area influences storage in other areas and does not necessarily mean that an area contains a representation of working memory contents. More recently, researchers have employed multivariate methods to determine whether an area exhibits activity patterns that are selective for the specific stimulus stored in working memory (Christophel, Iamshchinina, Yan, Allefeld, & Haynes, 2018; Ester et al., 2015; Harrison & Tong, 2009; Lee, Kravitz, & Baker, 2013; Riggall & Postle, 2012). As a result, content-specificity is now argued to
be the critical marker of information storage in VWM (Christophel et al., 2017). Contentselective activity has been revealed across distributed network of cerebral cortical regions (Christophel et al., 2017, 2018; Ester et al., 2015). Here, we used an event-related delayed recall paradigm and a multivariate encoding model to investigate whether this distributed network extends to the cerebellum.

Materials and Methods

Participants

16 healthy adult volunteers (9 female) participated in this study. The Institutional Board of Boston University approved the study. All subjects gave written informed consent and were compensated to participate in this study. Subjects were recruited from Boston University and the Greater Boston area. All subjects possessed normal or corrected-to-normal vision. All subjects completed a ~30 minutes behavioral session prior to being scanned in order to familiarize them with the task. One subject's behavioral accuracy was found to not significantly differ from chance performance and was excluded from further analysis, leaving us with 15 subjects (9 female).

Magnetic Resonance Image Acquisition

Data were acquired from a 3 Tesla Siemens Prisma scanner located at the Cognitive Neuroimaging Center at Boston University in Boston, Massachusetts using a 64-channel head coil. High-resolution T1-weighted multiecho MPRAGE (Sagittal; TR = 2780 ms; TE = 1.32 ms, 3.19 ms, 5.11 ms, 7.03 ms; FA = 7°; 0.8 mm isotropic voxels; 224 slices; FOV = 256 mm × 256 mm × 180 mm; in-plane GRAPPA acceleration 2) and T2weighted (Sagittal; TR = 3200 ms; TE = 564 ms; 0.8 mm isotropic voxels; 224 slices; FOV = 256 mm × 256 mm × 180 mm; in-plane GRAPPA acceleration 2) structural images were acquired. Functional data were acquired using a multi-band gradient-echo echo-planar pulse sequence (Feinberg et al., 2010; Moeller et al., 2010; Xu et al., 2013) with the following acquisition parameters: TR = 2000 ms; TE = 35 ms; FA = 80°; 2.2 mm isotropic voxels; FOV = 207 mm × 207 mm × 152 mm; SMS = 3. A total of 69 slices were acquired with 0% skip, fully covering the cerebral cortex and cerebellum. Spin echo field maps were also acquired with opposite phase encoding directions (Anterior-to-Posterior; Posterior-to-Anterior) and matching parameters to the gradient-echo EPI fMRI timeseries for subsequent EPI distortion correction.

Visual Stimuli and Experimental Paradigm

Stimuli were generated and presented using Python with the PsychoPy software package (Peirce, 2007; 2008) and were projected with a PROPixx digital light processing LED projector (VPixx Technologies Inc., Saint-Bruno-de-Montarvile, QC, Canada) onto a screen within the scanner bore. Each trial consisted of a trial start cue period (1 s), sample period (1 s), retro-cue and delay period (10 s), and probe period (5 s) (See Figure 4.1). The beginning of each trial was denoted by the white fixation cross briefly changing to red for 500 ms. A 500 ms fixation interval separated the trial start cue and the sample period. During the sample period, subjects were presented with two circular random dot kinematograms (one in each hemifield) each spanning 8° in diameter. Dots within each patch were 0.05° in size and possessed a density of approximately 2 dots per square degree. The dot motion patches were centered 6° to the left or right from fixation along

the horizontal meridian. Dots moved with 100% coherence at 1.5% and had a limited lifetime of 10 frames (167 ms). The direction of coherent motion on a trial within each patch was drawn from a uniform distribution over 0°-315° in 45° increments. A small $\pm 1^{\circ}$ -10° angular jitter was added randomly to the motion direction on each trial to minimize verbal coding of stimuli. 250 ms following the offset of the sample, an arrow appeared pointing either to the left or right. This 'retro-cue' indicated which of the two motion directions subjects should maintain over the subsequent 9.75 s delay period. On 20% of trials, an 'X' was presented indicating that both items should be dropped. Following the delay period, subjects were presented with a probe display (5 s). The probe display consisted of a circle (8° diameter) centered at fixation and a line extending from the center of the display to a location on the circumference of the circle. Subjects were instructed to rotate the line so that it aligned with the remembered direction of motion. Subjects pressed one key to incrementally rotate the line 10° clockwise, another key to rotate the line 10° counter-clockwise, and a third key to flip the line 180°. The initial position of the line segment was selected randomly, with the constraint that the initial location was within a multiple of 10° of the to-be-remembered motion direction. On drop trials, subjects were instructed to make a random number of responses. Trials were separated by a 7 s inter-trial interval. Each fMRI run comprised 20 trials (16 store trials + 4 drop trials; 482 s total). Subjects completed 8 runs during the session. Stimulus directions and locations (left or right visual hemifield) were fully crossed within a run. Additionally, the motion directions of cued and non-cued stimuli were fully crossed across all 8 runs.

fMRI Data Preprocessing and Regions of Interest

Functional task data first underwent the Human Connectome Project's 'minimal' preprocessing pipeline, which comprises gradient nonlinearity distortion correction, motion correction, EPI image distortion correction, co-registration with the subject's T1weighted image, and nonlinear transformation to MNI152 space (Glasser et al., 2013). The transforms involved in each step of this pipeline were concatenated into a single nonlinear transformation and performed as a single resampling step to reduce interpolation related blurring (Glasser et al., 2013). Voxel timeseries within each run were then standardized and detrended with a 3rd order polynomial. Multivariate analyses were performed on the average response of individual voxels across three TRs beginning 6 s, 8 s, and 10 s (TRs 4, 5, and 6) after the start of each trial, consistent with previous working memory decoding studies (Harrison & Tong, 2009; Ester et al., 2015). Additionally, we generated stimulus reconstructions across time by applying our decoding model to a sliding window of the average response across three consecutive TRs (0-4 s, 2-6 s, etc.)

Resting-state data underwent additional preprocessing using custom scripts in MATLAB. The following preprocessing steps were performed: linear interpolation across high-motion time-points (> 0.5 mm FD; Power et al., 2012; Carp, 2013), application of a fourth-order Butterworth temporal bandpass filter to extract frequencies between 0.009 and 0.08 Hz, mean 'grayordinate' signal regression (MGSR; Burgess et al., 2016), and censoring of high-motion time-points (Power et al., 2012).

Regions of interest (ROIs) were defined from publicly available atlases. Cortical ROIs corresponding with a combined IPS0-IPS3 ROI and a combined V1-V3 ROI were defined in each hemisphere from a probabilistic retinotopy atlas (Wang et al., 2015). An ROI corresponding with the superior pre-central sulcus (sPCS), which is presumed to encompass the human homolog of the frontal eye fields, was defined from the 6a label from the Glasser multi-modal parcellation in both hemispheres (Glasser et al., 2016). The cerebellar spatially unbiased infratentorial template (SUIT) atlas was used to define an ROI for each lobule within the cerebellum in each hemisphere (Diedrichsen et al., 2009). As our prior work indicates that an area spanning both lobule VIIb and lobule VIIIa is recruited by attention and working memory tasks in concert with fronto-parietal areas (Brissenden et al., 2016; Brissenden et al., 2018), we also created a combined lobule VIIb/VIIIa ROI. We further created ROIs subdividing VIIb/VIIIa using resting-state functional connectivity. A resting-state correlation with each cortical ROI (V1-3, IPS0-3, sPCS) was computed for each voxel within lobule VIIb/VIIIa. We then created ROIs corresponding with the top 25%, 10% or 5% of correlations within lobule VIIb/VIIIa for each cortical seed.

Statistical Analysis

Event-Related Analysis. Following preprocessing, we examined univariate fMRI response amplitudes for both store and drop trials. To account for retinotopic preferences, response amplitudes were averaged for each ROI's preferred hemifield (contralateral for cortical ROIs and ipsilateral for cerebellar ROIs) and then averaged across hemispheres. As the task structure and inter-trial interval (ITI) did not include a sufficient amount of fixation to estimate a baseline response, event-related blood-oxygen level-dependent (BOLD) timecourses were baseline-corrected by taking the difference between the average response amplitude at each time point and the minimum of the averaged response across the first 3 TRs. This baseline was estimated separately for each condition and ROI. Differences between store and drop trials were examined using a bootstrap resampling procedure. Trial average ROI BOLD amplitude values for each timepoint were sampled with replacement from our pool of subjects 10,000 times and averaged to generate an empirical distribution of the sample mean. A p-value was computed for each timepoint as the proportion of bootstraps in which the difference between conditions was less than or equal to 0 e.g. (([store amplitude – drop amplitude] \leq 0) + 1) / (N bootstraps + 1). Correction for multiple comparisons was performed using the Holm-Bonferroni procedure (Holm, 1979).

Generative Model. We employed a generative model-based approach developed by van Bergen et al. (2015). This model assumes voxel responses can modeled as the linear weighted sum of 8 motion direction selective neuronal populations or channels. Each channel was represented as a half-wave rectified (co)sinusoid raised to the 5th power:

$$R_k(\theta) = \max(0, \cos(\pi \frac{\theta - \theta_k}{180})^5)$$

where θ_k indicates the preferred direction of the *k*th population or channel. Channel basis functions were maximally tuned at one of eight equally spaced angles (0°, 45°, 90°, 135°, 180°, 225°, 270°, or 315°).

The model was fit using a 8-fold leave-one-run-out cross-validation scheme, which iteratively partitions the data into a training set (B_1) and a test set (B_2) . The

training set was expressed as an $n \times m$ matrix B_1 , where n is the number of trials in the training set and m is the number of voxels. We then created an $n \times k$ hypothetical channel output matrix C_1 (where k is the number of channels), which represents the idealized channel responses for each trial given the remembered motion direction. A $k \times m$ channel weight matrix W related the observed voxel responses to hypothetical channel responses via a general linear model of the form:

$$B_1 = C_1 W$$

The weight matrix was estimated via ordinary least squares estimation as follows:

$$W = (C_1^{\ T} C_1)^{-1} C_1^{\ T} B_1$$

Then for each trial in the test set, we used Bayes rule to obtain a posterior probability distribution over motion direction indicating which stimulus value was most probable given the observed pattern of BOLD responses.

$$p(s|b_2) \propto p(b_2|s)p(s)$$

where *s* denotes a particular stimulus value and b_2 indicates a single trial/row of test set BOLD matrix (B_2). The prior, p(s), was set to 1 for all angles as each stimulus value was presented equally often and we did not want to bias decoding towards particular motion directions (van Bergen, Ma, Pratte, & Jehee, 2015). To avoid numerical underflow, we compute log-probability rather than probability. The conditional log-probability of a voxel activation pattern given a specific stimulus value was defined as:

$$\ln(p(b_2|s)) = -\frac{1}{2} [\ln(|\Sigma|) + m \ln(2\pi) + (b_2 - c_2 W)^T \Sigma^{-1} (b_2 - c_2 W)]$$

where c_2 denotes a single row/trial of the test set channel matrix C_2 and Σ denotes the $m \times m$ voxel covariance matrix estimated from the training set. As computing the above conditional probability requires computing the inverse of the voxel covariance matrix, we performed a procedure described in Naselaris et al. (2009) if Σ was non-invertible. First, we performed principal component analysis on the predicted responses (\hat{B}_1) for the training set. *p* components were chosen with the constraint that each component explained at least 5% of the total variance. Using the resulting $n \times p$ projection matrix, we then projected the predicted (\hat{B}_1) and actual (B_1) responses from the training set onto the first *p* principal components. These dimensionality-reduced responses were then normalized to unit length.

$$\hat{b}_{1}^{*} = \frac{P^{T} \hat{b}_{1}}{\|P^{T} \hat{b}_{1}\|}$$
$$b_{1}^{*} = \frac{P^{T} b_{1}}{\|P^{T} b_{1}\|}$$

where *P* represents the computed projection matrix. The voxel covariance matrix was then computed as

$$\Sigma^* = cov(B_1^* - \hat{B}_1^*)$$

where Σ^* is a $p \times p$ matrix. During the testing phase, the same procedure (projection onto the first *p* components followed by normalization) was performed on the predicted and actual responses for the test set. Thus, the conditional log-probability of the dimensionality-reduced pattern of voxel responses given a specific stimulus value was reexpressed as

$$\ln(p(b_2^*|s)) = -\frac{1}{2} [\ln(|\Sigma^*|) + m \ln(2\pi) + (b_2^* - \hat{b}_2^*)^T \Sigma^{*-1} (b_2^* - \hat{b}_2^*)]$$

To assess whether an area contains stimulus-specific information across trials, we then circularly shifted trial log-posterior distributions so that the center value corresponded with the presented stimulus on that trial. We then averaged these shifted distributions across trials to yield a subject-level log-posterior probability distribution. Finally, subject log-posterior distributions were averaged to form a group-level log-posterior distribution for each region-of-interest. The group-level log-posterior probability distribution was then exponentiated and divided by a normalization constant to yield a probability distribution. To assess the degree to which ROI activity patterns contained information about the presented stimulus, we performed non-parametric permutation tests comparing the probability of the presented stimulus (corresponding with $p(0^{\circ}|b)$ for circularly shifted distributions) to an empirical null distribution (Golland & Fischl, 2003). To estimate a null distribution, we permuted the motion direction labels within each run prior to model fitting and testing. This procedure was repeated 1000 times, yielding a probability for each permutation. We then compared our constructed null distribution to the probability obtained with the true class labeling ($\alpha < 0.05$, one-sided). A p-value was computed as $[(\# of permutation probabilities \geq true probability) + 1] / (N permutations + 1)$ 1) (Phipson & Smyth, 2010).

Results

To investigate working memory stimulus-specificity in the cerebellum, we had participants perform a delayed motion direction recall task while measuring BOLD responses using fMRI (Figure 4.1). On each trial, participants were simultaneously presented with two patches of dot motion (100% coherence), presented to the right and left of fixation. After stimulus offset, participants were retroactively cued to maintain the direction of motion of one of the patches over a blank delay interval (9.75 s) or drop both items. Following the delay period, participants then adjusted a probe stimulus to match the remembered direction of motion. Behavioral performance was assessed by computing a distribution of recall errors over trials for each subject (Figure 4.2). Trial errors were found to be clustered around the cued direction of motion, indicating that participants were able to successfully maintain the direction of motion of the cued item. The average mean absolute value of the angular difference between reported and actual motion directions was $16.75^\circ \pm 0.07^\circ$ SD.

Event-Related Analysis

We next examined persistent delay period responses in areas previously implicated in working memory maintenance. IPS0, IPS1, IPS2 and IPS3 visuotopic regions in the intraparietal sulcus were combined into a single ROI (IPS0-3). IPS0-3 and the superior pre-central sulcus (sPCS) each exhibited elevated delay-period BOLD responses for trials in which participants were cued to store one of the presented items ('store' trials) relative to trials in which they were cued to drop both items ('drop' trials) (Figure 4.3A & B). Visual cortex (V1-3 combined ROI), on the other hand, exhibited greater delay period activation for drop trials relative to store trials (Figure 4.3C). This effect could potentially be driven by an unanticipated stimulus confound introduced during the delay-period. The centrally presented retro-cue on each trial persisted for the entire delay-period and was larger for drop trials than active trials (X vs. < or >). To test this possibility, we masked

out the portion of the V1-3 ROI corresponding with approximately 0-3° eccentricity. Estimates of eccentricity preferences were derived from the human connectome project (HCP) retinotopy dataset (Benson et al., 2018). When the representation of the fovea was masked out of our V1-3 ROI, drop trial delay-period responses were no longer significantly different from active trial responses (Figure 4.3D), indicating that the previously observed difference was driven by foveal stimulation and not the peripherally presented target items. Thus, we observed elevated delay-period responses in frontoparietal cortex, but not in visual cortex, consistent with prior studies (Emrich, Riggall, LaRocque, & Postle, 2013; Lee et al., 2013; Riggall & Postle, 2012; Sreenivasan, Vytlacil, & D'Esposito, 2014b).

Lobule VIIb/VIIIa delay-period responses across conditions were found to depend on which portion of lobule VIIb/VIIIa was examined. The entire anatomically defined VIIb/VIIIa ROI exhibited an event-related response similar to the V1-3 ROI (including foveal representation), with drop trials eliciting greater responses during the delay period than active trials (Figure 4.4A). As eccentricity preferences are not well characterized in cerebellum, we could not simply mask out the foveal representation as we did in visual cortex. Instead, we subdivided our VIIb/VIIIa ROI on the basis of functional connectivity with each cortical ROI (see methods). Functional connectivity subdivisions of VIIb/VIIIa showed markedly different response patterns. While the V1-3-coupled VIIb/VIIIa ROI exhibited delay-period activity indicative of the stimulus confound (Figure 4.4D), VIIb/VIIIa ROIs defined by functional connectivity with IPS0-3 and sPCS exhibited significantly greater delay-period activation for store trials than drop trials (Figure 4.4B & C). Furthermore, the magnitude of the difference between active trial and drop trial activation was shown to depend on the functional connectivity strength, with stronger functional connectivity with IPS and sPCS associated with more elevated delay-period responses (IPS0-3 coupled VIIb/VIIIa: F(2, 30) = 17.09, p = 0.00001; sPCS coupled VIIb/VIIIa: F(2, 32) = 32.06, p = 0.0000004; Figure 4.4E). Thus, areas of lobule VIIb/VIIIa that are intrinsically coupled with fronto-parietal cortex exhibit elevated responses when a stimulus is stored in working memory rather than dropped. While these results extend prior work linking the cerebellum to working memory processes (e.g. Brissenden et al., 2016) by showing that elevated activation extends into the delay period, they do not show that cerebellar activity patterns are selective for the stored stimulus.

Stimulus Encoding Model

To quantify feature selectivity during working memory, we employed a generative model-based decoding approach. This analysis approach uses information about voxel motion direction preferences to produce a posterior probability distribution over motion direction for each trial given the observed pattern of voxel responses during the delay period (see methods). The mode or peak of this distribution served as our prediction of the stimulus on that trial. To produce a group-level reconstruction of the probability of a particular stimulus given the observed responses, we circularly shifted trial posterior probability distributions so 0° corresponded with the presented motion direction and then averaged the shifted distributions across trials and participants. If an ROI contains feature-selective information about the remembered direction of motion then this averaged posterior distribution should peak at or near 0°. We first present our decoding

results for the last 3 TRs of the delay period (TRs beginning 6-10 s after trial onset), consistent with previous working memory decoding studies (Harrison & Tong, 2009; Ester et al., 2015). Centered and averaged posterior distributions for V1-3, IPS0-3, and sPCS are shown in Figure 4.5. Each cortical ROI was found to contain a robust representation of the direction of motion maintained in working memory (IPS0-3: p = 0.001 uncorrected, 0.012 corrected; sPCS: p = 0.001 uncorrected, 0.012 corrected; V1-3: p = 0.001 uncorrected, 0.012 corrected). We next examined whether lobule VIIb/VIIIa delay-period responses are also selective for a stimulus stored in working memory. A group-level reconstruction of the probability of a stimulus given the pattern of voxel responses in lobule VIIb/VIIIa was found to peak at the remembered direction of motion (p = 0.001 uncorrected, 0.012 corrected; Figure 4.6A). We also found a significant, albeit weak, representation of the non-remembered stimulus in lobule VIIb/VIIIa (p = 0.036uncorrected; Figure 4.6B). To test whether the strength of representation was stronger for remembered or non-remembered stimuli we compared the observed difference in probability for remembered and non-remembered items to a null probability difference distribution. The probability of the remembered stimulus given the observed pattern of lobule VIIb/VIIIa voxel responses was significantly greater than the probability of the non-remembered stimulus (p = 0.005). Taken together, these findings indicate that the representation of the remembered stimulus in VIIb/VIIIa during the delay period is working memory specific and cannot be explained by residual sample related responses.

Working memory stimulus specificity was further found to be restricted to lobule VIIb/VIIIa within the cerebellum. For each other cerebellar lobule, we were unable to

reconstruct the remembered stimulus (all p > 0.05 corrected) (Figure 4.7). Thus, it appears that the encoding of stimulus-specific mnemonic representations is limited to lobule VIIb/VIIIa within the cerebellum.

Time-resolved stimulus probability reconstructions for both remembered and nonremembered items were produced by applying our encoding model to a sliding window consisting of three consecutive TRs. Due to the coarse temporal resolution of this analysis, we note that we are limited in terms of detecting fine-scale differences in the time-course of working memory stimulus-specificity. Questions concerning temporal differences in stimulus-specificity could potentially be better addressed using fMRI sequences that allow for sub-second sampling intervals (e.g. Lewis, Setsompop, Rosen, & Polimeni, 2016). Nevertheless, we observe some potentially informative differences in the stimulus reconstruction time-course between areas. Lobule VIIb/VIIIa (Figure 4.8D) exhibits a robust representation of the remembered stimulus starting at the 1st TR window (TRs 1, 2 and 3). This representation persists through the 5th TR window (TRs 5, 6 and 7). A representation of remembered stimulus is not apparent for the 6th TR window. which consists of last timepoint of the delay and the first 2 timepoints of the probe display. For cortical ROIs, a representation of the remembered stimulus does not emerge until later points in the trial (IPS0-3: TRs 3, 4 and 5; sPCS: TRs 2, 3 and 4; V1-3: TRs 4, 5 and 6) and this representation persists until the last TR window (Figure 4.8A-C). This discrepancy between lobule VIIb/VIIIa and cortical areas could indicate that cerebellum and cerebral cortical regions contribute to different aspects of working memory encoding and maintenance (see discussion).

Discussion

The findings presented here demonstrate that cerebellar lobule VIIb/VIIIa exhibits several markers of working memory processes. Our prior work found that lobule VIIb/VIIIa is recruited by working memory and attention tasks (Brissenden et al., 2016, 2018). However, these prior studies could not determine whether lobule VIIb/VIIIa is driven by involvement in working memory storage processes or rather more generalized attentional processes. In the current study, we used an event-related paradigm with an extended delay period so that we could specifically examine cerebellar responses associated with the maintenance period of the task. Each trial presented two stimuli simultaneously followed by a post-stimulus retro-cue indicating which stimulus to maintain in working memory; this aspect of the experimental design permitted us to distinguish between stimulus-driven responses and working memory responses. We demonstrated that portions of lobule VIIb/VIIIa that exhibit resting-state functional connectivity with fronto-parietal regions show elevated responses during the delay period when a stimulus is stored in VWM. An encoding model of motion direction further revealed that lobule VIIb/VIIIa robustly represented the remembered stimulus. Moreover, the representation of the remembered stimulus was significantly stronger than the representation of the non-remembered stimulus, indicating that this representation can be attributed to a working memory trace rather than a perceptual one.

The current results provide further evidence for cerebellar contributions to cognitive function. It has become increasingly clear that cerebellar function is not limited to the motor domain and that substantial functional heterogeneity exists within cerebellar

cortex (Brissenden et al., 2016; 2018; Buckner et al., 2011; Guell, Gabrieli, & Schmahmann, 2018a; Guell, Schmahmann, Gabrieli, & Ghosh, 2018b; Stoodley et al., 2012; Stoodley & Schmahmann, 2009). Indicative of this heterogeneity, we found that lobule VIIb/VIIIa was the only cerebellar region implicated in the storage of VWM representations. Along with recent work demonstrating the existence of visual field representations in lobule VIIb/VIIIa (Brissenden et al., 2018), this study also demonstrates that the cerebellum possesses considerable representational specificity for items within the focus of attention or working memory. It remains to be seen whether areas of the cerebellum associated with other cognitive domains exhibit similar specificity in terms of their representational content.

The time-course of elevated and feature-selective delay period activity in lobule VIIb/VIIIa exhibited several key differences with cortical areas. In fronto-parietal cortex, delay-period activation remained elevated for the full extent of the delay period. Lobule VIIb/VIIIa, on the other hand, was elevated only at time-points 4-6 seconds following retro-cue onset before returning to baseline. Similarly, stimulus-selective activity was present earlier and fell off earlier than cortical ROIs. This pattern potentially argues for cerebellar involvement in processes active immediately following the presentation of the retro-cue. Working memory research has shown that the working memory storage process comprises several phases. These include the initial selection of items, encoding/consolidation of those items into working memory, attentional prioritization of items within working memory (if required), and maintenance or retention of information over extended delays (Awh, Vogel, & Oh, 2006; Myers, Stokes, & Nobre, 2017; Todd, Han, Harrison, & Marois, 2011; Woodman & Vogel, 2005; Ye et al., 2017). Each of these processes could potentially elicit content-specific activity within an area. The earlier onset and offset of a robust representation in lobule VIIb/VIIIa is potentially consistent with a role in the feature-specific attentional prioritization of the cued stimulus within working memory immediately following the presentation of the retro-cue. In contrast, the later onset and persistence of the representation in cortical areas could reflect these areas' primary involvement in the subsequent maintenance or rehearsal of items stored in working memory. However, future studies employing fast fMRI sequences would be better equipped to make conclusions regarding cerebellar contributions to specific phases of working memory storage.

A substantial body of work has attempted to identify the locus or loci of a working memory storage buffer. Our results extend recent proposals that working memory contents are distributed across a number of areas (Serences, 2016; Christophel et al., 2017) by showing that working memory representations are additionally encoded in the cerebellum. Central to the distributed working memory network hypothesis is the notion that storage across different areas reflects different levels of representational abstraction (Christophel et al., 2017). It is suggested that a sensory to frontal gradient exists which serves to transform detailed feature representations into a format that can guide subsequent behavior (Christophel et al., 2017). The current results leave untested where the cerebellum lies within this hierarchy. Follow-up work will need to more finely probe the nature of representations in cerebellum to elucidate its unique role in working memory storage processes.

As the cerebellum has been extensively implicated in oculomotor processes (Baier et al., 2009; Fujikado & Noda, 1987; Ron & Robinson, 1973; Voogd & Barmack, 2006), an alternative explanation for our findings is that VIIb/VIIIa activity patterns reflect saccades rather than a VWM representation. This interpretation is unlikely for several reasons. First, participants were experienced observers who extensively practiced maintaining fixation prior to scanning. Second, our findings cannot be explained by the two most obvious saccade strategies. One strategy would be to make eye movements during stimulus presentation along a vector parallel to the direction of motion. However, as participants did not know which dot motion patch would be cued, there is no reason that eye movements would be selective for the direction of motion of the subsequently cued item and not the non-cued item. Thus, if saccades during the sample period drove the content specificity observed in lobule VIIb/VIIIa, then we would expect to be able to recover both remembered and non-remembered items. However, only the remembered item was robustly reconstructed from lobule VIIb/VIIIa activity patterns, indicating that saccades prior to the retro-cue are unlikely to have produced the observed stimulusselectivity. Another strategy would be to make a saccade to the cued hemifield following the presentation of the cue. Yet, as motion direction and hemifield were dissociated from one another, a saccade towards the cued hemifield would not be predictive of stimulus identity. A less obvious strategy would be to refrain from making eye movements during the presentation of coherent motion and then make a saccade parallel to the direction of motion of the cued item following the presentation of the cue. Lobule VIIb/VIIIa stimulus-specificity could potentially be explained by this scenario. Concurrent eyetracking during fMRI scanning would allow future studies to explicitly rule out this possibility.

A recent study in mice presented evidence suggesting that the persistent representation of information in frontal cortex depends on the cerebellum (Gao et al., 2018). Head-fixed mice were presented with a sample stimulus that cued one of two actions (left or right lick) to be made following a delay period. Neurons in both frontal cortex and the cerebellar fastigial nucleus were shown to exhibit selectivity for the cued action during the delay period. Critically, optogenetic silencing of fastigial neurons abolished selectivity in frontal cortex and resulted in incorrect behavioral choices. In the current study, we explicitly dissociated motor planning from VWM storage by randomizing the start position of the probe stimulus relative to the remembered stimulus. As a consequence, subjects were unable to prospectively plan their responses. Thus, our results suggest that the cerebellum is involved in the sustained representation of information in working memory even when stored items are not related with specific actions. Stimulation protocols such as TMS could be used to investigate whether inactivation of specific cerebellar areas in humans similarly interferes with cortical representations of remembered stimuli, as well as behavioral performance.

Cortico-centric models of cognition are pervasive in cognitive neuroscience. Our findings highlight the shortcomings of a narrow focus on cerebral cortex in characterizing the neural mechanisms of working memory storage. The more expansive characterization of the neural substrates of working memory storage suggested by the current results could

provide new insights into a wide range of goal-directed behaviors that are known to rely on working memory.



Figure 4.1 Behavioral task paradigm. Participants were presented with two patches of moving dots. 250 ms following the offset of the stimulus presentation period participants were post-cued to remember the direction of motion of the moving dots. Following a 10 s delay, participants were given 5s to adjust an oriented line segment to match the remembered direction of motion with key presses. The initial orientation of the line segment was randomized with respect to the memorized direction of motion on each trial.



Figure 4.2 Behavioral Performance. Histograms and kernel density estimates of recall error for each participant. Subject 9 was excluded from further analysis due to poor behavioral performance.



Figure 4.3 Cortical ROI blood-oxygen level-dependent (BOLD) timecourses. (A) IPS0-3 ROI average BOLD timecourse for store and drop trials. (B) sPCS ROI average BOLD timecourse. (C) V1-3 ROI average BOLD timecourse. (D) V1-3 ROI with foveal representation (0-3° eccentricity) masked out. Gray shaded area denotes timepoints averaged for subsequent encoding model analysis of delay-period activity. Shaded ribbon represents bootstrap standard error of the mean (SEM). Horizontal bars along the top of each panel indicate points for which there is a significant difference between store and drop trials (p < 0.05 corrected; red: store > drop; blue: drop > store). Boxes along x-axis denote onset and duration of trial events.



Figure 4.4 Lobule VIIb/VIIIa BOLD timecourses. (A) Anatomically defined lobule VIIb/VIIIa ROI average BOLD timecourse for store and drop trials. (B) Average BOLD timecourse for ROI defined by resting-state connectivity with IPS0-3 seed in individual subjects (top 10% of correlations within lobule VIIb/VIIIa). (C) Average BOLD timecourse for ROI defined by connectivity with sPCS seed. (D) Average BOLD timecourse for ROI defined by connectivity with V1-3 seed. (E) BOLD amplitude difference between store and drop trials (store – drop) as a function of percentile threshold (top 25%, 10% or 5%). Boxplots show mean (diamond), median (bar), quartiles (boxes), range (whiskers), and outliers (circles). Shaded ribbon in panels A-D represents bootstrap SEM. Horizontal bars along the top of each panel (A-D) indicate points in which there is a significant difference between store and drop trials (p < 0.05 corrected; red - store > drop; blue - drop > store). Boxes along x-axis (A-D) represent trial events.



Figure 4.5 Group-level cortical encoding model results. Shifted and averaged posterior probability distributions over motion direction indicating which stimulus is most probable given the observed pattern of voxel responses during the delay period for (A) IPS0-3, (B) sPCS, and (C) V1-3. Shaded ribbon reflects bootstrap SEM.



Figure 4.6 Lobule VIIb/VIIIa encoding model results. (A) Posterior probability of the stimulus for remembered stimuli. (B) Posterior probability distribution for non-remembered stimuli. Shaded ribbon reflects bootstrap SEM.



Figure 4.7 Cerebellar lobule encoding model results. Group-level posterior probability distributions for cerebellar lobules outside of lobule VIIb/VIIIa. Inset shows flatmap representation of cerebellum demarcating lobular boundaries (Diedrichsen & Zotow, 2015).



Figure 4.8 Time-resolved encoding model results. Posterior probability distributions of the remembered (right) and nonremembered (left) stimulus for (A) IPS0-3, (B) sPCS, (C) V1-3, and (D) lobule VIIb/VIIIa. Each row of the heat map represents a probability distribution generated by applying an encoding model to a window of three consecutive TRs. tr123 – TRs 1, 2, 3; tr234 – TRs 2, 3, 4; tr345 – TRs 3, 4, 5; tr456 – TRs 4, 5, 6; tr567 – TRs 5, 6, 7; tr678 – TRs 6, 7, 8.

CHAPTER FIVE: SUMMARY AND DISCUSSION

Restatement of Original Goals

The goal of the experiments presented here was to determine whether brain networks responsible for directing visual attention and working memory processes include cerebellar structures. To do so, I carried out three experiments in which we examined 1) the relationship between cerebellar recruitment by canonical attention and working memory tasks and resting-state functional connectivity with the cortical dorsal attention network; 2) the specificity of cerebellar contributions to multiple components of attention and working memory function; and 3) the role of the cerebellum in the encoding and maintenance of stimulus-specific mnemonic representations.

Summary of Findings

In chapter 2, we sought to characterize the relationship between cerebellar functional coupling with cortical dorsal attention network areas and functional responses to a visual working memory task and a visual attention task. Across two experiments, participants either performed a visual working memory change detection paradigm or a multiple object tracking paradigm. The change detection task manipulated the number of items held in working memory, while the multiple object tracking task required sustained attention to a subset of moving target items among identical distractors. In each experiment, participants additionally underwent several runs of resting-state fMRI. In the first experiment, we demonstrated a strong relationship between resting-state correlations with the cortical DAN and recruitment by VWM when contrasted with a passive sensorimotor control condition. Moreover, DAN-coupled cerebellar areas were shown to

be modulated by working memory load such that maintaining four items in VWM elicited greater activation than maintaining one item. This convergence of DAN functional connectivity and VWM activation was primarily localized to an area spanning cerebellar lobules VIIb and VIIIa. In the second experiment, we demonstrated that sustained selective attention also robustly recruits portions of the cerebellum that are functionally coupled with the DAN. Lastly, a hierarchical cluster analysis performed on seed-to-seed functional connectivity measures showed that working memory and attention task responsive portions of the cerebellum within lobule VIIb/VIIIa form a network with co-activated dorsal attention network areas as opposed to co-activated cognitive control network regions.

In chapter 3, we aimed to answer two questions: 1) Does the cerebellum contain a representation of the spatial locus of attention?; and 2) what is the specificity with which the cerebellum is recruited by closely related aspects of visual attention and working memory function, such as spatially specific attention and working memory load-dependence? To address the first question, we performed two separate experiments. The first experiment employed the same lateralized visual working memory change detection paradigm used in chapter 2. In addition to varying the number of to-be-remembered items, this task also manipulated the hemifield to which attention was deployed. Stimuli were presented bilaterally, but working memory target items were restricted to one visual hemifield. Voxels located in the dorsomedial portion of lobule VIIb/VIIIa were found to be selective for attentional loci located in the ipsilateral visual hemifield. This ipsilateral bias mirrors the well-documented contralateral bias observed throughout the cortical

DAN (Jerde et al., 2012; Mackey et al., 2017; Sheremata et al., 2010; Sheremata & Silver, 2015; Swisher et al., 2007; Szczepanski, Konen, & Kastner, 2010), and is consistent with the crossing of cortico-cerebellar fiber tracts at the cerebellar peduncles (Middleton & Strick, 2001; Schmahmann & Pandya, 1997b). In the second experiment, participants performed a task that required them to covertly attend a rectangular stimulus that moved slowly across the visual field in different directions (Mackey et al., 2017). A population receptive field analysis confirmed the existence of an ipsilateral visual hemifield representation within the dorsomedial portion of lobule VIIb/VIIIa. Thus, dorsomedial cerebellar lobule VIIb/VIIIa accurately encodes the spatial locus of attention in a similar manner to cortical attention areas. We then examined the specificity of cerebellar recruitment by spatial attention and working memory by comparing effect size estimates for spatial coding (attend left vs. attend right) and VWM load (set size 4 vs. set size 1) within lobule VIIb/VIIIa. Different portions of lobule VIIb/VIIIa were found to be selective for spatial coding and working memory load. The dorsomedial portion of lobule VIIb/VIIIa was more strongly recruited by spatial coding, and an area shifted ventrolaterally was more strongly activated by VWM load. This functional organization was shown to mirror the organization of these processes in cerebral cortex. Furthermore, we observed that the specificity of task recruitment could be explained by fine-scale differences in connectivity between cortex and cerebellum. Resting-state functional connectivity of space- and load-selective portions of lobule VIIb/VIIIa with cerebral cortex differed and this differential connectivity accurately predicted differences in functional selectivity across occipito-parietal cortex. These findings indicate that, at least

in the attentional domain, cerebellar cortex exhibits fine-scale functional specialization similar to the degree of specialization observed in cerebral cortex. Moreover, the observed specificity is reflected by fine-scale patterns of cortico-cerebellar functional connectivity.

In chapter 4, I investigated whether the cerebellum can be specifically implicated in the persistent representation of items in working memory. Participants performed an event-related delayed-recall paradigm that required them to maintain the coherent direction of motion of moving dot patterns over an extended delay period. Fronto-parietal areas, along with portions of cerebellar lobule VIIb/VIIIa that exhibit intrinsic connectivity with these areas, showed elevated delay period responses on trials in which a stimulus was stored in working memory. We then employed a motion direction encoding model to demonstrate that the pattern of lobule VIIb/VIIIa delay period responses was selective for the remembered stimulus. This content-selectivity was found to be specific to lobule VIIb/VIIIa within the cerebellum. We were unable to recover the remembered stimulus from every other cerebellar lobule. Taken together, these findings provide strong evidence for the involvement of lobule VIIb/VIIIa in working memory storage processes and provide further confirmation for functional specialization within the cerebellum.

Discussion

The notion of cerebellar contributions to cognitive processes is steadily gaining acceptance within the field. However, this acknowledgment is far from universal and the study of cerebellar involvement in cognition remains a niche topic of research. The current evolution in the field's understanding of the cerebellum's role in cognitive

processes can be likened to a similar progression in our view of basal ganglia function. A few decades ago, the basal ganglia were widely thought to be limited to providing support for motor control function; however, today the basal ganglia are understood to make major contributions to a vast array of emotional and cognitive processes (Brown, Schneider, & Lidsky, 1997; Frank, Loughry, & O'Reilly, 2001; Graybiel, 1997; Middleton & Strick, 2002). Due to the homogeneity of cerebellar cortical circuit organization and the lack of monosynaptic connections between cerebral cortex and cerebellum, progress in understanding the functional specificity of the cerebellum has long been stalled. However, recent advances in resting-state fMRI connectivity analysis and in polysynaptic anatomical tracing find evidence for fine-scale specificity in corticocerebellar networks similar to the specificity observed in cortico-striatal networks (Brissenden et al., 2018; Buckner et al., 2011; Kelly & Strick, 2003; Middleton & Strick, 2002). I argue that each cerebral cortical network functionally extends to a specific cerebellar component. The anatomical regularity of cerebellar circuitry suggests that each cerebellar region plays a consistent computational role in parallel cortico-cerebellar networks, and that functional differences between cerebellar regions arises due to variation in the specific cortical sites with which they are connected (Ramnani, 2006). Future cognitive neuroscience studies should investigate cerebellar contributions to a wide range of functions previously thought to be predominantly, if not exclusively, mediated by cerebral cortical regions.

The results presented here extend prior work on cerebellar contributions to cognition in several respects. Throughout this dissertation we have demonstrated a close

link between connectivity measures and functional responses to tasks. This relationship argues for a network-level interpretation of cerebellar involvement in attention and working memory task performance. There have been a number of previous demonstrations of cerebellar recruitment by attention and working memory tasks (Allen et al., 1997; Baier et al., 2010; Chen & Desmond, 2005a; Desmond et al., 1997; Kirschen et al., 2005; Le et al., 1998; Striemer, Chouinard, Goodale, & de Ribaupierre, 2015b). However, many of these prior studies were quite limited in the scope of their inferences concerning a cerebellar role in attention and working memory. For example, it has been argued that the cerebellum is recruited specifically by attentional shifts but not sustained attention (Akshoomoff & Courchesne, 1992; 1994; Allen et al., 1997; Le et al., 1998). Our findings instead argue for a more general cerebellar contribution to attention and working memory memory function. In our view, if a particular task recruits cortical DAN structures then it will also recruit the cerebellar component of the DAN. The specificity of recruitment by different aspects of attention and working memory presented in chapter 3 could explain the more narrow interpretation of prior studies. As we show, different cortico-cerebellar subnetworks can support different intra-domain components of attention and working memory, such as spatial coding versus working memory load or shifting versus sustained attention. Consequently, previous work may have localized a node of a particular attentional sub-network responsible for one aspect of attention (e.g. shifting attention) and failed to identify nodes belonging to other sub-networks dedicated to other aspects of attention (e.g. sustained attention). Given the known challenges of cerebellar functional imaging, including greater susceptibility to physiological noise

(Diedrichsen, Verstynen, Schlerf, & Wiestler, 2010), early reports of null findings for certain contrasts are not unexpected.

Chapter 3 provides the first demonstration of the existence of visual field representations in the cerebellum. Dating back to the last century, somatomotor representations in the cerebellum have been extensively characterized (Adrian, 1943; Buckner et al., 2011; Grodd et al., 2001; Rijntjes et al., 1999; Snider & Stowell, 1944; Wiestler et al., 2011). Despite growing interest in cerebellar involvement in non-motor function, as well as observations of connectivity with cortical areas that contain visual maps, no one had previously investigated whether the cerebellum contains representations of the visual field. This novel finding raises a number of questions for future research concerning the organization of these visuospatial representations (detailed in following section).

The current work indicates that the topographic organization of cerebellar recruitment by cognition is far more precise than previously demonstrated. This finescale functional topography highlights a fundamental difference between cerebellum and cerebral cortex. In the cerebral cortex, functional selectivity is tightly linked with microstructure (Amunts, Schleicher, & Zilles, 2007). In contrast, cytoarchitecture is essentially invariant across cerebellar cortex (Bloedel, 1994; Schmahmann, 2000). Thus, functional specialization within the cerebellum appears to be independent of variation in cytoarchitecture, providing support for the hypothesis that cerebellar computations are invariant across functional domains.

In chapter 4, we provide the first demonstration that a portion of the cerebellum encodes working memory representations. This finding represents a radical departure from previous studies of working memory storage. There is currently an ongoing debate as to where working memory contents are stored in the brain. A number of cortical areas have been proposed to act as storage buffers. Some researchers argue that working memory storage is mediated by feature-selective neuronal populations in sensory cortex (D'Esposito & Postle, 2015; Sreenivasan, Curtis, & D'Esposito, 2014a). Others argue that representations stored in sensory cortex would be susceptible to overwriting by incoming perceptual information and that working memory contents are instead stored by frontoparietal areas previously implicated in attentional control (Bettencourt & Xu, 2015). A third view suggests that information can be stored across both sensory and fronto-parietal cortices depending on task demands (Christophel et al., 2017; Serences, 2016). Our results indicate that information can also be temporarily maintained in cerebellar lobule VIIb/VIIIa along with cortical areas. Another line of research focuses on the specific mechanisms by which information is persistently maintained in working memory. In addition to content-specific persistent activity patterns, it is suggested that representations can also be maintained via activity-silent mechanisms which involve the reconfiguration of synaptic weights (Stokes, 2015). The present results presumably reflect persistent activity as synaptic plasticity mechanisms cannot be identified using fMRI. It is currently unclear whether representations can additionally be stored in an activity-silent manner in the cerebellum.
Future Directions

The specific computational role of the cerebellum in visual attention and working memory tasks remains to be revealed. The cerebellum's structural homogeneity and connectional heterogeneity suggests that computation it performs is invariant across domains (Bloedel, 1994; Ramnani, 2006; Schmahmann, 2000). Consequently, insights acquired in one domain can inform theories of cerebellar function in other domains. Future work should examine whether well-established theories of cerebellar contributions to motor control can explain cerebellar involvement in attention and working memory tasks. Substantial empirical evidence suggests the cerebellum instantiates internal models that serve to coordinate and refine motor actions (Herzfeld et al., 2015; 2018; Ito, 2008; Raymond & Medina, 2018; Wolpert et al., 1998). Additionally, the cerebellum has been implicated in sub-second temporal processing (Braitenberg, 1967; Ivry, 2004; Ivry & Keele, 1989). Consequently, the cerebellum may instantiate internal models that serve to coordinate and refine the spatio-temporal deployment of attention and working memory resources in well-trained contexts.

Chapter 3 revealed the existence of an ipsilateral visual hemifield representation in the dorsomedial portion of lobule VIIb/VIIIa bilaterally. From this result we can conclude that the cerebellum possesses a coarse representation of space. Conversely, visual and parietal areas have been shown to contain a continuous topographic representation of the visual field (Silver & Kastner, 2009; Swisher et al., 2007; Wandell, Dumoulin, & Brewer, 2007). It is unclear whether cerebellar visual field representations exhibit a more fine-scale topographic organization beyond the demonstrated hemifield representation. Cerebellar somatotopy is known to be disorganized relative to somatomotor cortex (Bower & Woolston, 1983; Kassel et al., 1984; Schlerf et al., 2014; Shambes et al., 1978). In spite of this disorderly organization, cerebellar activity patterns have been shown to be selective for the stimulation or movement of individual fingers (Wiestler et al., 2011). Consequently, the cerebellum may contain fine-scale representations of visual space, but these representations may not be organized into continuous maps. Fine-scale representations could be revealed with an encoding model approach similar to that described in chapter 4. If cerebellar activity patterns can accurately reconstruct the location of a stimulus or attentional focus within a hemifield it would suggest that the cerebellum contains a fine-grained representation of space, even in the absence of a map-like organization.

Chapter 2 examined the participation of cerebellar nodes within the DAN. Along with the DAN, additional networks have been shown to be recruited during attentional task performance. These include the ventral attention network (VAN), which is implicated in exogenous attention (Corbetta & Shulman, 2002), and the cognitive control network (CCN), which is thought to coordinate broader executive functions (Cole & Schneider, 2007; Dosenbach et al., 2007). These networks have also been shown to exhibit robust connectivity with the cerebellum (Buckner et al., 2011). Distinct types of attention tasks are known to recruit the DAN, VAN, and CCN, respectively. Tasks requiring sustained attentional control and/or working memory preferentially recruit the DAN, while exogenous attention tasks such as the Posner cuing paradigm and oddball paradigm recruit the VAN (Corbetta & Shulman, 2002; Scolari et al., 2015). The CCN,

on the other hand, is shown to be recruited by long-term memory (LTM) guided attention tasks (Rosen et al., 2016; Rosen, Stern, Devaney, & Somers, 2017). Rosen et al. (2017) found that a bilateral region located within lobule VI/Crus I was activated by a contrast of LTM-guided attention versus endogenous cue-guided attention. This area was shown to overlap substantially with the cognitive control network functional connectivity representation as defined by Buckner et al. (2011). These findings suggest that the cerebellum can be further subdivided on the basis of connectivity and recruitment by various attentional paradigms. The approach used in chapter 3 of comparing effect size estimates across tasks could be used to more finely detail the organization of different attention networks in the cerebellum.

Another potential avenue of research concerns differences between intra-network nodes. Functional connectivity parcellations of cerebellar cortex reveal additional regions outside of lobule VIIb/VIIIa that map onto the DAN (Buckner et al., 2011). It is suggested that each cortical association network possesses three distinct representations in the cerebellum (Guell, Gabrieli, & Schmahmann, 2018a). In addition to lobule VIIb/VIIIa, functional connectivity measures reveal cerebellar DAN nodes in lobule VI/Crus I and lobule VIIIb/IX (Buckner et al., 2011). More research will have to be performed to delineate the shared and unique functional contributions of each of these nodes.

Conclusions

The results presented in this dissertation further our understanding of the neural mechanisms of visual attention and working memory processing. Attention and working

memory critically underlie a diverse array of cognitive behaviors. The findings presented here indicate that distributed networks that include both cortical and cerebellar areas mediate attention and working memory processes. This more detailed characterization of the neural substrates of attention and working memory has the potential to aid the diagnosis and treatment of neurological disorders associated with attention and working memory deficits, as well as inform the development of cognitive interventions and brain stimulation protocols aimed at improving cognitive performance across a broad range of contexts.

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