

**The Influence of Declarative Processes upon Human Motor
Cortex Physiology**

by

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DEDICATION

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TABLE OF CONTENTS

DEDICATION	ii
ACKNOWLEDGEMENTS	iii
LIST OF TABLES	viii
LIST OF FIGURES	ix
LIST OF ABBREVIATIONS.....	x
ABSTRACT	xi
CHAPTER 1 – Introduction.....	1
1.1. Overview of thesis.....	1
1.2. General objective of thesis	2
1.3. Background	3
1.3.1. Motor cortex and movement	3
1.3.2. Somatosensory cortex contribution to motor skills and motor plasticity	4
1.3.3. Modulatory role of attention.....	5
1.3.4. Intramodal Attention – Vision.....	7
1.3.5. Intramodal Attention – Somatosensation	8
1.3.6. Crossmodal Attention.....	10
1.3.7. Attention and measures of primary motor cortex excitability.....	13
1.3.8. Working memory, motor performance and motor cortex excitability	15
1.4. Specific Hypotheses	18
1.4.1. Study 1 (Chapter 2) – Increasing Working Memory Distraction Enhances Motor Cortical Plasticity	18

1.4.2. Study 2 (Chapter 3) – Verbal Working Memory Modulates Afferent Circuits in Motor Cortex	20
1.4.3. Study 3 (Chapter 4) – Modulation of Short-Latency Afferent Inhibition During Performance of a Discrete Sequence Under Different Foci of Attention.....	22
CHAPTER 2 – Increasing Working Memory Distraction Enhances Motor Cortical Plasticity....	24
2.1. Abstract	24
2.2. Introduction	25
2.3. Methods.....	28
2.3.1. Participants	28
2.3.2. Sternberg scanning task.....	28
2.3.3. Transcranial magnetic stimulation (TMS).....	30
2.3.4. Experimental design and procedure	31
2.3.5. Data analysis.....	31
2.4. Results	32
2.4.1. Sternberg task performance	32
2.4.2. Motor cortex excitability	34
2.5. Discussion	34
CHAPTER 3 – Verbal Working Memory Modulates Afferent Circuits in Motor Cortex	41
3.1. Abstract	41
3.2. Introduction	42
3.3. Methods.....	44
3.3.1. Participants	44
3.3.2. Working memory task.....	44
3.3.3. Transcranial magnetic stimulation (TMS).....	46
3.3.4. Short-latency afferent inhibition (SAI)	47
3.3.5. Somatosensory evoked potentials (SEPs)	48

3.3.6. Experimental design and procedure	48
3.3.7. Data analysis.....	49
3.4. Results	50
3.4.1. Experiment 1 – Monophasic transcranial magnetic stimulation (TMS) during maintenance of varying set size.....	50
3.4.2. Experiment 2 – Somatosensory gating under varying cognitive load.....	52
3.5. Discussion	52
CHAPTER 4 – Modulation of Short-Latency Afferent Inhibition During Performance of a Discrete Sequence Under Different Foci of Attention	58
4.1. Abstract	58
4.2. Introduction	59
4.3. Methods.....	62
4.3.1. Participants	62
4.3.2. Experimental design	62
4.3.3. Discrete sequence production task (DSP)	65
4.3.4. Short-latency afferent inhibition (SAI)	66
4.3.5. Data analysis.....	67
4.4. Results	68
4.4.1. Discrete sequence production performance.....	68
4.4.2. Short-latency afferent inhibition (SAI) at rest.....	68
4.4.3. Short-latency afferent inhibition (SAI) during discrete sequence production (DSP)...	70
4.5. Discussion	70
CHAPTER 5 – General Discussion, Limitations and Conclusions	79
5.1. General discussion.....	79
5.2. Limitations	83
5.3. Conclusion.....	85

BIBLIOGRAPHY.....86

LIST OF TABLES

<i>Table 4.1. Pseudo-randomization table for the relative timing of short-latency afferent inhibition (SAI) and sequence production during the discrete sequence production task (DSP).....</i>	<i>64</i>
<i>Table 4.2. Reaction time and accuracy during the discrete sequence production task (DSP)....</i>	<i>69</i>
<i>Table 4.3. Baseline short-latency afferent inhibition (SAI) in the absence of behavioral task. ..</i>	<i>71</i>

LIST OF FIGURES

<i>Figure 2.1. The timing of the behavioral task and brain stimulation during a single trial.....</i>	<i>29</i>
<i>Figure 2.2. Sternberg working memory task results.....</i>	<i>33</i>
<i>Figure 2.3. Motor cortex excitability following theta burst stimulation (TBS) during the Sternberg working memory task.....</i>	<i>35</i>
<i>Figure 3.1. Example time course of the Sternberg short-term memory task and timing of short-latency afference inhibition (SAI).....</i>	<i>45</i>
<i>Figure 3.2. Experiment 1 – Short-latency afference inhibition (SAI) results.....</i>	<i>51</i>
<i>Figure 3.3. Experiment 2 – Somatosensory evoked potential (SEP) results.....</i>	<i>53</i>
<i>Figure 4.1. The discrete sequence production task (DSP).....</i>	<i>63</i>
<i>Figure 4.2. Short-latency afferent inhibition (SAI) during discrete sequence production task (DSP).....</i>	<i>72</i>
<i>Figure 4.3. Short-latency afferent inhibition (SAI) measured in the abductor pollicis brevis (APB) at SAI-0.....</i>	<i>73</i>

LIST OF ABBREVIATIONS

AMT	Active Motor Threshold
AP	Anterior-Posterior
APB	Abductor Pollicis Brevis
BOLD	Blood-Oxygen-Level Dependent
DSP	Discrete Sequence Production
FDI	First Dorsal Interosseous
fMRI	Functional Magnetic Resonance Imaging
GABA	Gamma-Aminobutyric Acid
IRBMED	Institutional Review Board of the University of Michigan Medical School
NMDA	N-Methyl-D-Aspartate
MNS	Median Nerve Stimulation
MEP	Motor Evoked Potential
PA	Posterior-Anterior
PAS	Paired Associative Stimulation
RMT	Resting Motor Threshold
SAI	Short-latency Afferent Inhibition
SEP	Somatosensory Evoked Potential
TBS	Theta Burst Stimulation
tDCS	Transcranial Direct Current Stimulation
TMS	Transcranial Magnetic Stimulation

ABSTRACT

Skilled movements require the ability to efficiently extract and manipulate incoming sensory information relating to our body and environment to inform motor output. To facilitate efficient sensory to motor transformations humans have developed highly tuned cognitive abilities featuring constructs such as attention and working memory. Such cognitive constructs support the development of declarative knowledge pertaining to skilled actions. Yet, our understanding of how declarative knowledge shapes the function and reorganization of subconscious procedural knowledge about a skill is limited. Importantly, understanding how declarative strategies may influence motor cortical physiology is an essential step towards understanding why some skills benefit from explicit knowledge while others do not. The purpose of this dissertation was to determine how declarative functions, specifically verbal working memory, shape procedural motor control through modulation of sensory afference. Chapter 1 reviews the role of the motor and somatosensory cortices in motor behavior. The role of attention in the activation of the sensorimotor cortex is then described. Finally, the role of verbal working memory in motor performance is discussed. Previous research looked at the role of working memory from a behavioral perspective, but the studies in this thesis investigated the neural substrates, and notably the sensory afference of the interaction of working memory and control of movement. Chapters 2 through 4 detail a series of studies investigating how working memory load and verbal instructions alter motor cortex physiology and plasticity. Specifically, Chapter 2 demonstrates that engaging verbal working memory processes can change the potential for plasticity in the motor cortex, a substrate of the procedural motor system. Chapter 3 demonstrates that working memory acts upon

the motor cortex through intracortical circuits that are distinct from other cognitive functions such as attention. Finally, Chapter 4 extends these results from a model where working memory is a distractor to working memory as a task-relevant construct. Overall, the findings from the studies described in this dissertation demonstrate that working memory has the ability to influence motor cortex physiology through circuits distinct from the circuits affected by attention. Further, the way in which working memory is employed can have important modulatory effects in the motor cortex, which could then impact the acquisition and execution of motor skills. These results lay the groundwork for future studies investigating whether declarative strategies may control and limit procedural learning such that the procedural system serves to perfect the optimal kinematics and dynamics for the imposed strategy even if the imposed strategy results in sub-optimal performance.

CHAPTER 1 – Introduction

1.1. Overview of thesis

Following a description of the overall objective of this thesis, relevant literature will be reviewed pertaining to the role of the motor and the somatosensory cortices in movement, as well as the effect that engaging attention has on sensory afference and motor cortex plasticity. The final section of Chapter 1 will examine the evidence for an effect of working memory on motor performance and motor cortex excitability. In Chapter 2, I will investigate how engaging working memory modulates motor cortex plasticity. In Chapter 3, I will investigate two potential intracortical circuits that might mediate the effect of engaging working memory on motor cortex plasticity. The studies outlined in Chapters 2 and 3 probed working memory influence of sensorimotor brain activity by reducing working memory resource availability from the sensorimotor system. This was achieved by performing a primary visual task, in a dual-task like manner. In Chapter 4, I will investigate changes in a working memory sensitive sensorimotor circuit during a motor task performed under differing instructions. Chapter 4 marks a shift in my approach. In Chapters 2 and 3, working memory was investigated in a dual task-like paradigm in which working memory resources were depleted. In Chapter 4, working memory is investigated as a task-relevant construct in which resource allocation is manipulated through task instruction. Finally, in Chapter 5, I will synthesize my research findings with regards to the objective of the thesis and suggest future directions for research.

1.2. General objective of thesis

Skilled motor performance depends upon accurate, efficient sensorimotor integration across a network of brain areas, including the motor cortex. The motor cortex is the primary source of efferent output to the corticospinal tract. However, its excitability, and in turn its efferent output, is strongly shaped by afferent inputs. In particular, sensory afference has a strong influence over motor cortical excitability and plasticity (Charlton, Ridding, Thompson, & Miles, 2003; Hamdy, Rothwell, Aziz, Singh, & Thompson, 1998; Vidoni, Acerra, Dao, Meehan, & Boyd, 2010). Degraded processing of sensory information plays a role in some disorders of voluntary movement (Patel, Jankovic, & Hallett, 2014). Other intrinsic factors, such as cognition, may also play an important role in determining motor behavior and dysfunction through the facilitation or suppression of sensory afference. Therefore, the declarative memory system may shape voluntary actions thanks to alterations of sensory afference (Paul & Ashby, 2013). Understanding the interactions between cognitive processes, sensory afference, and motor cortical excitability/plasticity will provide important insights into motor control and may offer a framework to interpret conflicting results from past behavioral studies. Long-term, understanding how engaging cognitive processes affect motor plasticity may promote the development of more effective training and rehabilitation protocols in clinical populations, such as individuals who suffered a stroke.

In the following sections, I will highlight the role of the motor cortex and its interactions with the somatosensory cortex for performance and acquisition of motor skills. I will then show how both attention to one sensory modality (intramodal attention) and attention allocated across several modalities (crossmodal attention) change somatosensory cortex activation. I will then discuss evidence of attention's influence over motor cortical processes. Finally, I will describe

how engaging verbal working memory influences motor performance. Most past working memory research is based on behavioral data, while the neural correlates of working memory's influence remain unknown. The studies in this thesis are designed to fill this knowledge gap by measuring how the recruitment of verbal working memory affects activity in the procedural memory system. In particular, these studies will quantify how the potential for plasticity of the motor cortex changes depending upon working memory engagement and will identify which specific sensorimotor cortical circuits may mediate such changes.

1.3. Background

1.3.1. Motor cortex and movement

The primary motor cortex is the main source of efferent projections to the corticospinal tract. It is organized to facilitate skilled motor performance by promoting coordination of muscle synergies and refined muscle contraction. Notably, the primary motor cortex is organized with a broad somatotopy, with different parts of the body controlled by different areas of the brain. However, within this broad somatotopy, a functional somatotopy exists where distal and proximal muscle representations are clustered to promote coordinated activation of the muscles needed to perform smooth and skilled movements (d'Avella, Saltiel, & Bizzi, 2003). Within these representations, movement parameters such as direction (Kettner, Schwartz, & Georgopoulos, 1988) and force (Georgopoulos, Ashe, Smyrnis, & Taira, 1992) are encoded in the combined activity of neuronal populations. The motor cortex has an integral role in consolidating the kinematics and dynamics acquired through practice (Galea, Vazquez, Pasricha, de Xivry, & Celnik, 2011; Muellbacher et al., 2002). The motor cortex's specific role in learning is captured in

its ability to reorganize, known as “neural plasticity”. Studies in both primates (Nudo, Milliken, Jenkins, & Merzenich, 1996) and humans (Karni et al., 1998; Pascual-Leone, Grafman, & Hallett, 1994; Pascual-Leone et al., 1995) show a remarkable ability for change in both the somatotopic representations of muscles as well as neuromuscular gain following skilled learning. However, despite an abundance of research investigating the functional mapping of motor cortex and how this map can be reorganized, relatively little research has focused upon the role of sensory afference in shaping motor cortex function and plasticity.

1.3.2. Somatosensory cortex contribution to motor skills and motor plasticity

That the motor cortex is dependent upon high quality afferent information is highlighted by the similar somatotopic organization of adjacent cortical areas such as the primary somatosensory cortex. Both motor performance and learning benefit from access to somatosensory information (Johansson & Cole, 1992; Manchester, Woollacott, Zederbauer-Hylton, & Marin, 1989; Vidoni & Boyd, 2009). Conversely, lesion studies in animals (Pavlidis, Miyashita, & Asanuma, 1993; Sakamoto, Arissian, & Asanuma, 1989; Xerri, Merzenich, Peterson, & Jenkins, 1998) show that injury to the somatosensory cortex compromises motor control even with the preservation of corticospinal tracts. Likewise, in humans, temporary disruption of the somatosensory cortex using transcranial magnetic stimulation decreases two-point discrimination and continuous tracking performance (Vidoni et al., 2010). Conversely, increasing the strength of somatosensory afference through peripheral stimulation (Celnik, Hummel, Harris-Love, Wolk, & Cohen, 2007) or centrally using transcranial magnetic stimulation (Brodie, Meehan, Borich, & Boyd, 2014; Tegenthoff et al., 2005) enhances tactile discrimination and motor performance. Benefits to motor control are thought to extend beyond simple changes in perception. Peripheral

electrical stimulation not only changes somatosensory cortical processing but leads to both an increased motor cortical representation area and a decreased threshold for contraction of the stimulated muscle at the expense of non-stimulated muscles (Hamdy et al., 1998). The increased size of the cortical representation and increased neural gain are thought to be driven by excitatory projections from the somatosensory to the motor cortex (Iriki, Pavlides, Keller, & Asanuma, 1989; Sakamoto, Porter, & Asanuma, 1987). The above-mentioned studies manipulated the amount of afferent information that reaches the motor cortex in a binary fashion; that is, either no stimulation or a large magnitude was provided. Thus, while these studies demonstrated that extrinsically modulating the strength of afferent information available from the somatosensory cortex is positively correlated with motor performance and motor cortex function, they did so in a coarse fashion. However, the amount of information that is processed can also be modulated intrinsically by attention in a more gradual manner.

1.3.3. Modulatory role of attention

In everyday life, one is bombarded by vast amounts of sensory information spanning multiple sensory modalities. The large amount of sensory information exceeds one's ability to efficiently process every bit of information with the required fidelity to generate skilled motor actions. To facilitate the extraction of high fidelity information most relevant to one's current goals and intentions, humans have evolved the ability to withdraw from processing some sensory afference in favor of focused, intensive processing of other sensory afference. This ability to voluntarily allocate processing resources is known as attention. Several models have been developed to explain the behavioral and neural basis of attention in sensory processing. Early models of attention equated the process to a mechanical filter, or bottleneck that only allowed

stimuli to be processed if necessary to control behavior (Broadbent, 1957, 1958). Sensory information was thought to be stored in a sensory registry with relevant stimuli selected to undergo further processing. Sensory afference in the sensory registry not selected for further processing would degrade and eventually be lost completely. However, evidence that attention was not restricted to the selection of one stimulus but could be divided across multiple sensory stimuli (Moray, 1959) led to a more flexible account of a filter where non-selected sensory afference was not completely shut-off from further processing but that attention served to dampen or attenuate irrelevant information and enhance relevant information (Deutsch & Deutsch, 1963; Treisman, 1960). These filter theories emphasized the role of attention in decreasing the volume of sensory information to be processed. However, there was a shift in conceptualization from a filter to a set of resources that could be flexibly allocated to sensory stimuli to efficiently extract relevant information. For example, Kahneman (1973) framed attention as a limited pool of resources that could be allocated and divided between separate tasks according to an explicit strategy (Kahneman, 1973). In Kahneman's theory, the pool of resources was general and undifferentiated by modality, stage of processing or code (i.e. spatial vs. verbal). Subsequently, Wickens revised the undifferentiated aspect of Kahneman's theory to describe attention as a set of resources specialized by modality, stage and code (Wickens, 1991). Eventually, it was proposed that a circuit involving the pre-frontal cortex, thalamus and sensory cortex formed the neural basis of resource allocation that facilitated relevant stimuli at the expense of irrelevant stimuli (Lalonde, 1995). More recently, contemporary models of attention have begun to distinguish between voluntary or "top-down" attention and involuntary or "bottom-up" attention. Although one possesses the ability to volitionally assign relevance to a stimulus, attention can be oriented in an automatic manner, when a stimulus is salient or unexpected and able to break attention from other previously attended

stimuli (Corbetta & Shulman, 2002). The neural correlates of “top-down” attention are located in a dorsal frontoparietal network (Corbetta, 1998) whereas the correlates of “bottom-up” attention include brain areas in a right ventral frontoparietal network (Corbetta & Shulman, 2002).

Whether top-down or bottom-up, attention can be based on different attributes such as the spatial location of a stimulus, the type of object, or the features of a stimulus. Therefore, attention is a cognitive factor that participates in the efficient processing of sensory afference. The bulk of research on attention has used visual stimuli.

1.3.4. Intramodal Attention – Vision

The study of visual attention has derived from the observation that visual stimuli are processed by a series of brain areas of increasing receptive fields (i.e., larger numbers of stimuli are able to elicit firing in a given neuron) (Smith, Singh, Williams, & Greenlee, 2001). The processing abilities of larger receptive fields are limited; therefore, making the attentional selection of information a necessity. Several attributes drive the selection by attention. Notably, attention to an object (Shomstein & Yantis, 2002) or feature (Rossi & Paradiso, 1995) facilitates detection. Physiologically, attention to features increases the firing rate of neurons of visual area V4 in macaques (Haenny, Maunsell, & Schiller, 1988) and visual cortex in humans (Saenz, Buracas, & Boynton, 2002). Motion is another attribute that can be selectively attended, which leads to improved detection performance, increased gain of motion-sensitive neurons (Treue & Trujillo, 1999) and expansion of activation of the primary visual cortex in response to stimuli (Watanabe et al., 1998). Initial demonstration of the role of attention during visual processing was obtained with spatial attention. Covert attention to a location favors performance of detection tasks as measured by decreased reaction time (Posner, 1980) and increased accuracy (Bashinski &

Bacharach, 1980). At the physiological level, the effect of attention is greater at later stages of visual processing, such as in visual area V4 (Moran & Desimone, 1985). However, as early as the primary visual cortex, attention leads to increased neuronal gain (Moran & Desimone, 1985) and facilitation of early event-related potential components (Hillyard, Vogel, & Luck, 1998). Although the visual system has been a major focus of the attention literature, the other sensory systems have also been investigated, including the somatosensory system.

1.3.5. Intramodal Attention – Somatosensation

The somatosensory system bears similarities with the visual system. Notably, spatial attention improves performance during somatosensory detection tasks and is correlated with increased brain activation. The focus of the following paragraph will be on top-down attention, although attention can also be automatically recruited by stimuli that are highly salient or unexpected, in a bottom-up manner even to an unattended location (Dowman, 2001).

During detection and discrimination tasks, top-down attention or voluntarily orienting attention towards the spatial location of a somatosensory stimulus results in increased perceived intensity and increased accuracy (Sathian & Burton, 1991; van Ede, de Lange, & Maris, 2012). Likewise, attention to a spatial location at which a somatosensory stimulation is expected to appear decreases reaction times in a tactile discrimination task (van Ede et al., 2012). Initial behavioral paradigms used to investigate the neural basis of top-down attention in the somatosensory system were biased towards effects occurring in secondary and higher order areas of the somatosensory pathway. Specifically, these studies demonstrated increased amplitudes of evoked responses in secondary somatosensory cortex to attended stimuli/locations using EEG (Desmedt, Nguyen Tran, & Bourguet, 1983; Desmedt & Robertson, 1977; Michie, Bearparic, Crawford, & Glue, 1987) and

MEG (Mima, Nagamine, Nakamura, & Shibasaki, 1998). However, single unit recordings in macaque monkeys demonstrated increased neuronal gain according to spatial attention as early as in the primary somatosensory cortex (Hyvarinen, Poranen, & Jokinen, 1980). More recently, in humans, functional magnetic resonance imaging (fMRI) evidence showed increased blood-oxygen-level dependent (BOLD) response in primary somatosensory cortex contralateral to the attended hand when it was stimulated compared to when the hand was not attended (Nelson, Staines, Graham, & McIlroy, 2004; Staines, Graham, Black, & McIlroy, 2002) and a concomitant decrease in BOLD response in the ipsilateral cortex (Staines, Graham, et al., 2002). Attention-dependent enhancement of finger representation was also demonstrated using EEG (Noppeney, Waberski, Gobbelé, & Buchner, 1999) and MEG (Braun et al., 2002; Iguchi, Hoshi, & Hashimoto, 2001; Iguchi, Hoshi, Tanosaki, Taira, & Hashimoto, 2002, 2005), as dipole modeling of somatosensory spatial attention was associated with shifts in localization of dipole generators within primary somatosensory cortex. Therefore, unimodal attention to tactile or proprioceptive stimuli affects early sensory processing as indicated by increased performance and modulation of the strength of activation of the primary somatosensory cortex. Further, changes of the strength of the thalamocortical projections to the somatosensory cortex have been demonstrated as described in the following paragraph.

The regulation of somatosensory input to the somatosensory cortex, based upon relevance, has been associated with a dorsolateral prefrontal thalamic gating system. Increasing visual attention requirements to perform a cognitive task is associated with dorsolateral prefrontal cortex activation (Corbetta & Shulman, 2002). Increased dorsolateral prefrontal cortex activity is also observed during voluntary allocation of somatosensory attention and occurs concurrently to increased primary somatosensory cortex activation (Knight, Richard Staines, Swick, & Chao,

1999; Schaefer, Heinze, & Rotte, 2005; Staines, Graham, et al., 2002). In support of a regulatory role for dorsolateral prefrontal cortex, freezing of this area in cats (Skinner & Yingling, 1977) or loss of this area in humans from stroke (Yamaguchi & Knight, 1990) leads to a loss of sensory gating, indexed by increased somatosensory evoked potential (SEP) amplitudes. Evidence for involvement of the thalamus in somatosensory input regulation comes from focal ventroposterior lateral thalamic lesions following stroke where patients are more susceptible to distraction by competing somatosensory inputs (Staines, Black, Graham, & McIlroy, 2002). Patients demonstrate near normal detection ability when the stroke-affected limb is stimulated in isolation, but detection ability decreases in the presence of concurrent stimulation of the non-affected limb (Staines, Black, et al., 2002). Therefore, a dorsolateral prefrontal-thalamic gating system provides a substrate by which cognition can control inputs to somatosensory cortex by facilitating relevant and suppressing irrelevant inputs to enhance signal-to-noise ratio during sensorimotor transformations.

Unimodal studies within vision and somatosensation demonstrate how attention modulates sensory information. However, skilled motor actions result from the integration of percepts related to what one sees, hears and feels. Allocation of attention across modalities can be used to weight how much each percept contributes to the action.

1.3.6. Crossmodal Attention

Perception and action are guided by the integration of concurrent sensory information across multiple sensory modalities. For instance, a car approaching one's position can be seen and heard. The benefit of combining visual and auditory stimuli is to decrease reaction time (Diederich & Colonius, 2004; Hershenson, 1962; Simon, Hinrichs, & Craft, 1970). However, the ability of the brain to integrate stimuli from different modalities is also illustrated by sensory illusions, such

as the ventriloquist effect (the perception of voice coming from a different than the actual source) and the McGurk effect (the fusion of discrepant visual and auditory speech) (McGurk & MacDonald, 1976). Both effects illustrate the dominance of vision over audition, or visual capture, which is not an indication of the superiority of visual input per se but is rather a sign that visual stimuli have a higher resolution and are often easier to localize. The integration between modalities is therefore weighted based on the quality of the sensory information (Alais & Burr, 2004). Although vision and audition are often studied in conjunction, somatosensory information can also be integrated with visual information. The next section will review studies that looked at the processing of somatosensory stimuli in conjunction with other modalities.

At the behavioral level, attending to a physical location for the detection of visual or tactile stimuli improves the detection for both the attended and unattended modalities (Spence, Pavani, & Driver, 2000). Similarly, tactile discrimination is improved with a cue in a different modality (Driver & Spence, 1998). At the physiological level and similar to unimodal attention, crossmodal attention to tactile stimuli leads to increased activation in executive and association cortices, whether the cue was visual or auditory (Eimer & Van Velzen, 2002; Eimer, Van Velzen, & Driver, 2002). In somatosensory modality-specific cortex, activation of the secondary somatosensory cortex was increased in monkeys in response to tactile stimuli compared to visual stimuli (Hsiao, O'Shaughnessy, & Johnson, 1993; Meftah, Shenasa, & Chapman, 2002; Roy, Steinmetz, Hsiao, Johnson, & Niebur, 2007; Steinmetz et al., 2000). In humans, the activation in the secondary somatosensory cortex is not only increased for relevant somatosensory stimuli (Fujiwara et al., 2002; Johansen-Berg, Christensen, Woolrich, & Matthews, 2000) but also when it is irrelevant. In fact, when a task-relevant tactile stimulus is elicited in the vicinity of a location that is attended to

detect a visual stimulation, N140 somatosensory event-related potentials are enhanced (Eimer & Driver, 2000).

Unlike the secondary somatosensory cortex, the involvement of the primary somatosensory cortex during crossmodal attention is not well established. Attending to a tactile stimulus in the form of an electric stimulus to the median nerve failed to increase the magnitude of somatosensory evoked cortical magnetic field deflections generated by the primary somatosensory cortex compared to attending to unrelated auditory stimuli (Fujiwara et al., 2002). When tactile stimuli occurred in a location attended for detection of visual stimuli, the amplitude of early SEPs did not change compared to attending a different location (Eimer & Driver, 2000). However, when tactile stimuli were relevant and required a verbal response, event-related potential amplitude was increased (Eimer & Driver, 2000). Similarly, results with fMRI demonstrated that attending to a location regardless of the modality resulted in increased activation of the primary somatosensory cortex when detection of tactile stimuli was accompanied with a keypress response (Johansen-Berg et al., 2000). Conversely, performing the detection task for visual stimuli acted as an active distractor to tactile sensory processing and reduced activation (Johansen-Berg et al., 2000). Further evidence of the effect of crossmodal attention on the primary somatosensory cortex came from another fMRI study. Being able to see the part of the body that is stimulated increased the activation of the primary somatosensory cortex compared to having vision occluded (Sambo, Gillmeister, & Forster, 2009). Therefore, the activation of the primary somatosensory cortex has been demonstrated in addition to activation in secondary somatosensory cortices and supramodal areas, which proves that crossmodal attention intervenes at early stages of processing of somatosensory information. In sum, attention works across modalities and can alter the processing of afferent information even for unattended modalities.

Controlling the sensory afference that reaches one's cortex can enhance motor actions through efficient integration of information across relevant modalities. The influence of multisensory integration occurs as early as the primary somatosensory cortex. For example, bimodal attention affects the P50, generated in the primary somatosensory cortex (at the border of area 1 and 2) (Hämäläinen, Kekoni, Sams, Reinikainen, & Näätänen, 1990). In fact, the amplitude of the P50 increased when visual and tactile stimuli needed to be integrated for movement performance as opposed to two tactile stimuli (Staines, Popovich, Legon, & Adams, 2014). Staggering the bimodal stimuli further enhanced P50 amplitude (Popovich & Staines, 2014; Staines et al., 2014). In addition, the BOLD response was greater in the primary somatosensory cortex when tracking movements were guided by the position of a visual stimulus compared to the intensity of a vibrotactile stimulus (Meehan & Staines, 2007). Similarly, the amplitude of P27, generated by Brodmann area 1 (Allison, McCarthy, Wood, & Jones, 1991), was greater with visual tracking than with tactile tracking (Meehan, Legon, & Staines, 2009). These increases with visual stimuli are opposite to results cited above that demonstrated increased activation in the somatosensory cortex with somatosensory stimuli (tactile or electric stimuli) compared with stimuli in other modalities.

Therefore, attention to one modality affects activation of areas known to process sensory afference from a different modality. Beyond sensory processing, attention also participates in the control of movements and alters the excitability of the primary motor cortex.

1.3.7. Attention and measures of primary motor cortex excitability

Attention is necessary for the extraction of relevant sensory information during planning and execution of voluntary movements. How one performs dictates how the brain changes. By

extension, attention is expected to play a role in the plasticity of the motor cortex. In accordance with this prediction, previous studies have shown that the potential for plasticity is increased with high levels of attention to the targeted area of the body using plasticity-inducing paradigms such as repetitive transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS) and peripheral nerve stimulation. These stimulation paradigms are beneficial to the study of attention because they induce plasticity over short periods of time, which limits the role of other factors.

Within a session, the level of plasticity, measured by motor evoked potential (MEP) potentiation that was induced by paired associative stimulation (PAS), increased when participants were required to pay attention to the targeted hand compared to when they focused on their opposite hand without vision of their hands in both cases (Stefan, Wycislo, & Classen, 2004). In a second experiment, the researchers introduced a gradation of attention towards the hand by testing 1) seeing and feeling the hand, 2) feeling only and 3) detracting attention with the performance of an arithmetic task. Orienting attention away from the targeted hand reduced the level of plasticity induced in the motor cortex (Stefan et al., 2004). Similarly, attending to the targeted hand increased the MEP potentiation during delivery of excitatory 5 Hz TMS compared to attending to the opposite hand or closing the eyes (Conte et al., 2007). Reducing available attentional resources further by performing a cognitive task, compared to no task, reduced the facilitatory effect of concurrent anodal tDCS upon the motor cortex excitability measured by MEP amplitude (Antal, Terney, Poreisz, & Paulus, 2007). However, these studies failed to adequately control for the recruitment of additional cognitive functions beyond attention, such as working memory, long-term memory, and executive processes (Antal et al., 2007; Stefan et al., 2004), or arousal level (Conte et al., 2007). More recently, Kamke et al. (2012) assessed both PAS and TMS induced

plasticity using a visual detection task that manipulates attention load while maintaining arousal levels and visual information constant (Schwartz et al., 2005). Following both PAS and intermittent theta burst stimulation (TBS), a patterned form of repetitive TMS, MEP potentiation was greater with the low load visual detection condition compared to the high load (Kamke et al., 2012). A low attention load is believed to leave attentional resources available to process somatosensory afference, resulting in greater MEP potentiation (Lavie, 2010). Without taxation of attention resources, the need to suppress incoming somatosensory afference is minimal even at rest (Pfurtscheller, 1992). In contrast, under the high visual attention task, more processing resources are required to complete the visual task leading to a suppression of somatosensory afference to minimize the risk of distraction (Lavie, 2010). We subsequently replicated this result and highlighted the role of somatosensory cortex in this process (Mirdamadi, Suzuki, & Meehan, 2017). The role of attention on induction of plasticity has been studied using a variety of paradigms, but the role of working memory has not been identified despite its contribution to motor performance and learning.

1.3.8. Working memory, motor performance and motor cortex excitability

Memory is generally defined as the ability to retain and recall information. An important dichotomy for memory is the distinction between declarative and procedural memory systems. Each memory system encompasses networks of brain areas that are responsible for different types of information. The declarative memory system is activated for the retention and recall of information that is consciously accessible and can be expressed verbally (Squire, 1992). The procedural system is recruited in a more automatic manner with limited conscious control and has

been defined as “knowing how to do something” without the necessity or the possibility to define it verbally (Reber, 1989).

Memory can also be divided based on length of retention into long-term memory and short-term memory. Long-term memory allows information to be retained over long periods of time without decrement and with resistance to interference. The span of short-term memory is limited to a few hours and is susceptible to interference. The third form of memory is working memory, which is defined as the ability to retain information for its manipulation over the span of a few seconds (Baddeley & Hitch, 1974). Working memory draws upon both short- and long-term memory as sources of information. While earlier models localized the neural correlates of working memory and storage of memories to separate brain areas (Baddeley, 2003), a contemporary model has proposed that working memory and storage are not anatomically distinct (Jonides et al., 2008). This model posits that working memory involves reactivating/engaging brain areas that are responsible for the storage of the information. Therefore, working memory can be viewed as the passage from inactivated to activated memory.

Regardless of the functional neuroanatomy, working memory can be thought of across multiple domains. For instance, working memory is either described as verbal, which deals with verbal information that can be articulated or spatial, which tackles the location of elements in space (Baddeley & Hitch, 1974). Although there is an overlap between the neural correlates of verbal and spatial working memory, the verbal working memory correlates are lateralized to the left hemisphere whereas spatial memory is lateralized to the right hemisphere (Smith, Jonides, & Koeppel, 1996).

Early stages of learning are characterized by processes likely to draw heavily upon attention and working memory (Fitts & Posner, 1967). The verbalization of task goals, rules and movement strategies draws heavily upon verbal working memory (Baddeley & Hitch, 1974). For example, in the early stages of sequence learning, working memory loads individual elements necessary for task performance (Verwey, 2001) to plan and execute voluntary movements (Spiegel, Koester, & Schack, 2013). Similarly, spatial working memory capacity has been correlated in young adults with the rate of visuospatial adaptation (Anguera, Reuter-Lorenz, Willingham, & Seidler, 2010) as well as the rate of explicit (Bo & Seidler, 2009) and implicit sequence learning (Bo, Jennett, & Seidler, 2011). Working memory also influences motor learning through error processing and correction. For example, when a visuospatial adaptation skill has yet to be acquired and movement errors are more prevalent, working memory serves to interpret the error signal and adjust the motor plans (Seidler, Bo, & Anguera, 2012). Yet, the study of the effect of working memory on motor performance and learning relies on the individual difference approach (Anguera et al., 2010; Bo et al., 2011; Bo & Seidler, 2009) or is inferred from imaging studies using motor tasks that do not specifically measure the role of working memory (Jueptner et al., 1997). Despite the behavioral measure of working memory on motor performance, the direct measure of the effect of working memory on neural correlates governing movement is limited.

As the declarative memory system shapes the procedural memory system, it is liable in certain contexts to limit the procedural memory system and decrease motor performance (Masters, 1992; Paul & Ashby, 2013). Determining how this interference takes place at the neurophysiological level has been done by measuring how attention affects motor cortical excitability and potential for plasticity (Antal et al., 2007; Conte et al., 2007; Kamke et al., 2012; Stefan et al., 2004), but the role of working memory remains unknown. However, the perceptual

load theory allows to predict that their impact on somatosensory inputs to the motor cortex would be opposite (Lavie, 2010). Behavioral evidence has shown that high attentional loads prevent the processing of task-irrelevant stimuli (Lavie & Tsal, 1994), whereas high working memory load allows their processing (Lavie, Hirst, De Fockert, & Viding, 2004). In fact, by taxing executive control resources, high working memory loads decrease sensory gating and allow the processing of task-irrelevant stimuli. Therefore, under high working memory load it is predicted that processing of sensory afference would be increased. The purpose of this dissertation is to test this prediction by measuring the effect of working memory task performance on the motor cortex and sensory-to-motor projections.

1.4. Specific Hypotheses

1.4.1. Study 1 (Chapter 2) – Increasing Working Memory Distraction Enhances Motor Cortical Plasticity

Purpose

The purpose of Study 1 was to determine whether working memory influences the potential for motor cortical plasticity induced by TBS. Such influence would provide converging evidence that explicit processes can shape procedural learning.

Approach

The plasticity-inducing TBS was delivered during either the encoding or maintenance of a two- or six-digit memory set. Motor cortical plasticity was assessed by comparing MEP amplitude before and after TBS for each combination of TBS timing and set size. The increase in set size

from two to six digits served to increase the working memory demands of the memory task leaving fewer working memory resources available to govern other critical processes, akin to a dual-task paradigm. Any difference in TBS-induced motor cortical plasticity under the different memory set sizes would provide evidence that working memory demands during encoding, maintenance or both processes shapes motor cortical plasticity. It should be noted that I did not examine the consequences of manipulating working memory demands upon motor performance.

The two-second bouts of TBS, used in Study 1, produce transient periods of motor cortex facilitation in the 20-30 s immediately following the end of stimulation (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). The bouts lead to short-term changes in N-methyl-D-aspartate (NMDA)-mediated potentiation (Cárdenas-Morales, Nowak, Kammer, Wolf, & Schönfeldt-Lecuona, 2010; Huang, Chen, Rothwell, & Wen, 2007) that can be consolidated to produce long-term changes in potentiation (or depression) if delivered in rapid succession (Huang et al., 2005). Critically, the mechanisms underlying potentiation following TBS are similar to the long-term potentiation mechanisms that underlie experience-dependent plasticity (Censor & Cohen, 2011). The changes in MEP amplitude from pre- to post-TBS or changes in gain, were used as a method to index plasticity.

Hypotheses

Hypothesis 1: Reaction time will be shorter, and accuracy will be higher for the low load trials.

Hypothesis 2: Based upon Lavie's model outlining attention and cognitive function under differing load (Lavie, 2005, 2010) I hypothesize that increased engagement of attention in the selection and encoding of the six-digit compared to two-digit memory set will decrease motor cortex gain. Reduced motor cortex gain under high attention demanding conditions is consistent with past work

(Kamke et al., 2012). However, I predict increased motor cortex gain when set size increases from two to six digits during the maintenance phase. This latter prediction is based upon Lavie's model that predicts that maintenance of a larger digit set size will draw greater working memory resources leaving fewer resources to govern the allocation of attention (Lavie, 2005, 2010). The reduction in executive control of attention in turn should reduce gating of somatosensory afference (Meehan et al., 2009; Meehan & Staines, 2007; Staines, Graham, et al., 2002) leading to enhance effectiveness of TBS to induce plasticity.

1.4.2. Study 2 (Chapter 3) – Verbal Working Memory Modulates Afferent Circuits in Motor Cortex

Purpose

The purpose of Study 2 was to probe how verbal working memory affects sensory afference in different circuits that project to the motor cortex using short-latency afferent inhibition (SAI) and SEPs.

Approach

Study 2 was intended to build upon the results from Study 1 by assessing how working memory influences sensorimotor networks that mediate response to TBS. For Study 2, SAI was elicited during the maintenance phase of the Sternberg memory scanning task (Experiment 1). As a control experiment, I also evoked SEPs during the maintenance phase of the memory task in a separate cohort to directly quantify somatosensory afference under the different set sizes (Experiment 2).

SAI is a method to probe the influence of somatosensory afference upon motor cortex excitability (Tokimura et al., 2000). SAI involves single pulse TMS delivered to coincide with the arrival of somatosensory afference evoked by peripheral nerve stimulation. When the peripheral nerve stimulation precedes the TMS stimulus by 18-26 ms, the MEP evoked by the TMS stimulus is reduced (Tokimura et al., 2000). The inhibitory effect of SAI is thought to be mediated by the somatosensory cortex (Ferreri et al., 2012; Kojima et al., 2015; Tsang et al., 2014), with greater sensory afference correlated with greater inhibition (Ni et al., 2011). The level of inhibition was also previously shown to increase with greater spatial attention (Kotb et al., 2005). Therefore, SAI was used in Experiment 1 to assess somatosensory afference during the performance of a working memory task.

One novel aspect of Study 2 – Experiment 1 is that I isolated the effect of working memory on specific intracortical circuits by manipulating the direction of the TMS stimulating current. Changing the current of a monophasic TMS stimulus from posterior-anterior to anterior-posterior recruits distinct neural populations (Ni et al., 2011) linked to specific functions (Hamada et al., 2014; Hamada, Strigaro, et al., 2012). We previously demonstrated that selective attention modulates SAI elicited by an anterior-posterior current (Mirdamadi et al., 2017). Therefore, the different current directions employed here allowed me to differentiate the effect of working memory across the same circuits to contrast against attention.

Experiment 1 assessed sensory afference indirectly through the amplitude of MEPs. Therefore, the second experiment of this study consisted of measuring the SEPs directly after delivery of peripheral nerve stimulation to the median nerve. The resulting potentials measured over the parietal and frontal areas give an indication of the level of sensory gating that occurs between the nerve and the cortical areas. Specifically, changes in N20-P25 amplitude measured

over the parietal cortex are indicative of the level of activity of the primary somatosensory cortex (Allison et al., 1991), while frontal P20-N30 SEP gauges the engagement of premotor and prefrontal cortex (Desmedt & Cheron, 1981).

Hypotheses

Hypothesis 1: The level of SAI is expected to be higher for the high memory load compared to the low load.

Hypothesis 2: The N20-P25 deflection following peripheral nerve stimulation is predicted to be greater over the parietal cortex in the high load condition.

1.4.3. Study 3 (Chapter 4) – Modulation of Short-Latency Afferent Inhibition During Performance of a Discrete Sequence Under Different Foci of Attention

Purpose

The purpose of this study was to determine the effect of focus of attention on the trans-synaptic inhibition from sensory pathways on the motor cortex.

Approach

The first two studies of this dissertation investigated how engaging working memory affects motor cortex activation. In Study 3, the use of cognitive factors moved from being associated with a distractor task to contributing directly to motor performance. In fact, participants received instructions that emphasized either external or internal elements of a discrete sequence production task. During the performance of the sequence, SAI was delivered to determine the level of sensory gating under each type of instructions.

The task performed by the subjects is a variant of the discrete sequence production task (De Kleine & Verwey, 2009), which was selected because instructions can be modified to provide participants information about their body (internal focus of attention) or the keys they press (external focus of attention). The benefit of an external focus has been demonstrated (Wulf, 2013) and associated with the formation of fewer rules (Poolton, Maxwell, Masters, & Raab, 2006). In addition, an internal focus is believed to create an unnatural constraint on the movement (McNevin, Shea, & Wulf, 2003), which I believe is associated with an overemphasis of sensory feedback from a limited number of muscles but this hypothesis remains untested. Therefore, in Study 3, this sensory gating will be measured using SAI and compared between instruction groups.

PA current was selected based on the results of Study 2, which showed a differential effect of current direction during the performance of a distracting working memory task.

Hypotheses

Hypothesis 1: Participants who received information about the key to press (external group) were expected to have a shorter reaction time and higher accuracy compared to participants who received information about their body (internal group). The external group was also predicted to learn more, as expressed by a greater change of reaction time and accuracy.

Hypothesis 2: SAI is expected to be greater in the internal group compared to the external group, reflecting increased sensory afference in the internal group.

CHAPTER 2 – Increasing Working Memory Distraction Enhances Motor Cortical Plasticity

Research question: How does working memory engagement affect the potential for plasticity in the motor cortex?

2.1. Abstract

The brain's ability to reorganize is critical to the performance and acquisition of motor skills. However, little is known about how verbal instruction and declarative strategies may shape such reorganization in the motor cortex. The present study investigated the influence of cognitive load, specifically verbal working memory upon motor cortical plasticity induced by a two-second bout of theta burst stimulation (TBS) delivered during the encoding or maintenance of a digit set. Two- and six-digit sets were used to manipulate cognitive load. Motor evoked potentials (MEPs) elicited using single pulses of transcranial magnetic stimulation were delivered before and after TBS to assess the efficacy of TBS to induce motor cortical plasticity. The expected facilitation of post-TBS MEPs was attenuated during encoding of a six-digit compared to a two-digit memory set. In contrast, during maintenance, the ability of TBS to facilitate MEPs was reduced for a two-digit compared to a six-digit memory set. As the level of plasticity in the motor cortex is related to sensory afference, the current results are consistent with the perceptual load theory that posits that a high perceptual load decreases attention resources leading to suppression of task-irrelevant sensory afference, whereas high working memory load enhances neural processing of a task-irrelevant distractor. Therefore, when encoding six digits (i.e., under high perceptual load), little

somatosensory information is processed, which reduces motor cortex reorganization. However, when maintaining six digits in working memory, cognitive resources are exhausted, and the ability of working memory to guide the allocation of attention is reduced, leading to a reduction in somatosensory gating and greater motor cortex reorganization. These results suggest that perceptual and cognitive demands associated with declarative control of movements interact with procedural control networks in the motor cortex. Such interactions may provide a substrate for declarative strategies to shape motor performance and learning.

2.2. Introduction

The brain's ability to change, known as plasticity, is paramount to the performance and acquisition of skilled motor actions. Plasticity is not a passive process, it is experience-driven and reflects the effort to enhance current ability rather than repetitive use alone (Nudo et al., 1996; Plautz, Milliken, & Nudo, 2000). Although much is known about the role of sensory afference in shaping plasticity (Pavlides et al., 1993; Vidoni et al., 2010), very little is known about how cognitive factors that influence sensory processing alter motor cortical plasticity.

Advances in non-invasive brain stimulation have provided ways to induce cortical plasticity-like states directly. Techniques such as traditional repetitive transcranial magnetic stimulation (repetitive TMS) (Cárdenas-Morales et al., 2010), theta burst stimulation (TBS) (Huang et al., 2007; Teo, Swayne, & Rothwell, 2007) and paired associated stimulation (PAS) (Stefan, Kunesch, Benecke, Cohen, & Classen, 2002) probe N-methyl-d-aspartate (NMDA) mediated-like mechanisms of plasticity known as long-term potentiation and long-term depression. Given these same mechanisms are known to underlie motor learning and plasticity (Censor & Cohen, 2011), non-invasive brain stimulation offers a unique opportunity to investigate

how cognition influences motor cortical plasticity. Few studies have investigated the influence of cognitive factors on motor cortex plasticity and have focused upon perceptual load through attentional manipulations. Stefan et al. (2004) first demonstrated that the ability of PAS to increase motor cortical excitability of the contralateral abductor pollicis brevis muscle (APB) was reduced when participants directed attention to the opposite, non-targeted hand. In the same study, Stefan et al. (2004) demonstrated that motor evoked potential (MEP) amplitude increase was greatest when participants were able to direct both visual and somatosensory attention to the targeted muscle. Finally, plasticity was completely blocked when participants were forced to complete a competing attention task (Stefan et al., 2004). Similar results were demonstrated for traditional 5Hz repetitive TMS (Conte et al., 2007), intermittent TBS (Kamke et al., 2012), as well as facilitatory and inhibitory PAS protocols (Kamke et al., 2012; Kamke et al., 2014). We recently used a shorter two-second bout of TBS, the building block of the cumulative intermittent and continuous TBS protocols, to demonstrate that greater perceptual load decreased responsiveness to stimulation from 2-4 s and 8-12 s post-stimulation (Mirdamadi, Suzuki, & Meehan, In preparation). Critically, these 2-4 s and 8-12 s post-stimulation windows overlap with the inter-burst intervals of the continuous and intermittent TBS protocols respectively. The former involves repeated bouts of the shorter two-second protocol delivered over 40 s while the latter involves bouts of 2 s repeated every 8 s (Huang et al., 2005). Therefore, the reduced efficacy of non-invasive brain stimulation with increasing attention demands is likely explained by a common NMDA receptor-mediated mechanism that is responsive during the two-second burst of stimulation. Further, the effect of the perceptual load has been localized to trans-synaptic circuits (Mirdamadi et al., 2017) known to mediate response to TBS (Hamada, Murase, Hasan, Balaratnam, & Rothwell, 2012). However, despite the emerging understanding of how the allocation of attention

may shape motor cortical function, no research has directly investigated how cognitive load (i.e., working memory demands) influences motor cortical plasticity. While increasing perceptual load decreases behavioral and neural processing of task-irrelevant stimuli (Lavie, 2005), the increased cognitive load is associated with increased behavioral and neural processing to task-irrelevant stimuli (Lavie, 2010). Therefore, increasing working memory demands of a distracting task may have the counter-intuitive effect of increasing plastic potential of motor cortex through disinhibition.

The current study sought to determine whether working memory demands shape motor cortical excitability and identify the time course of the interaction. I used a similar design to past work in the laboratory where two-second bouts of TBS were delivered during either the encoding or maintenance phase of the Sternberg memory scanning task (Sternberg, 1966). As discussed, it is the cumulative effect of these two-second bursts that are the building blocks of the longer traditional intermittent and continuous TBS protocols. However, even the two-second burst alone is capable of inducing a measurable transient change in motor cortex excitability (Huang et al., 2005) and cognitive performance (Demeter, Mirdamadi, Meehan, & Taylor, 2016) lasting on the order of seconds. Therefore, two-second bouts of TBS offer a potential method by which to study changes across time that would shape the response to the traditional intermittent and continuous TBS protocols. Motor cortex excitability was assessed before and after the two-second TBS to assess the potential for plasticity. According to the perceptual load theory and previous studies, I hypothesized that TBS delivered during encoding would be greater for the low working memory load of the Sternberg memory task. However, in the maintenance condition, I predicted that high load would lead to increased motor cortical plasticity.

2.3. Methods

2.3.1. Participants

Sixteen right-handed adults were recruited from the general student body of the University of Michigan (20.5 ± 1.6 years of age; 9 females, 7 males). All participants provided written informed consent. The Institutional Review Board of the University of Michigan Medical School (IRBMED) approved the study protocol.

2.3.2. Sternberg scanning task

Cognitive load was manipulated using a modified version of the Sternberg short-term memory task (Sternberg, 1966) (LabVIEW 2015, National Instruments, Austin, TX). Each trial started with the encoding phase that consisted of sets of two or six digits randomly presented for 2 s on a computer screen 80 cm in front of the participant (see Figure 2.1). The digits of a given memory set were all different. After the encoding phase, the digit set disappeared signaling the start of a 2 s maintenance phase. Following the maintenance phase, a single digit probe appeared. The single digit probe remained visible until participants responded or 2 s elapsed. A trial ended 30 s after the end of the maintenance period. Participants were instructed to respond as fast and accurately as possible as to whether the probe digit was part of the preceding memory set or not. Participants answered by pressing one of two keys under their index and middle fingers. The inclusion probability of the probe was 50%. The performance was assessed using reaction time and accuracy. Reaction time was defined as the time between probe appearance and the participant's response. Accuracy was defined as the number of correct responses expressed as a percentage of the total number of trials. The behavioral data of three participants were not included for analysis due to technical issues.

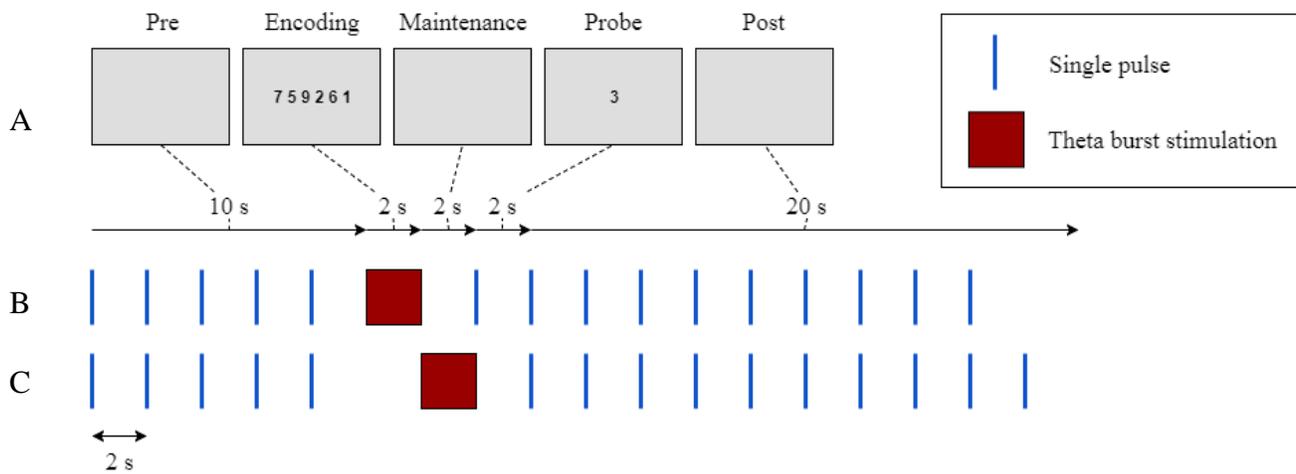


Figure 2.1. The timing of the behavioral task and brain stimulation during a single trial.

A: Example display and timing of the high load variant of the Sternberg memory scanning task. A set of six digits (high load) or two (low load) digits appeared on the screen followed by a single digit probe. Participants were required to respond whether the probe was part of the set or not. Relative timing of the single pulse and theta burst stimulation (TBS) during encoding (B) or maintenance (C) phase of the task. AMT: active motor threshold, RMT: resting motor threshold.

2.3.3. Transcranial magnetic stimulation (TMS)

MEPs evoked by TMS were recorded using LabChart 7 software in conjunction with a Dual BioAmp and PowerLab 8/30 acquisition system (AD Instruments, Colorado Springs, CO). Participants were seated with their right arm resting on a pillow placed upon their lap. Their left arm was bent at about 90° and rested on a table. The left index and middle fingers were situated over the response keypad. Surface electromyography electrodes (Ag-AgCl) were placed over the right first dorsal interosseous (FDI) muscle using a tendon-belly montage. Surface electromyography recording was triggered using a 5V TTL pulse with an epoch of -0.3 to 0.5 s. During acquisition, data were amplified (x 1000), digitized (x 40000 Hz) and filtered (band-pass filtered 5-1000 Hz, notch filter 60 Hz). Surface electromyography data were subsequently down-sampled to 5000 Hz during offline analysis. Any trials in which root mean square error of the baseline of either the targeted or non-targeted muscle exceeded 15 μV were excluded from subsequent analysis.

TMS was delivered using a MagVenture MagPro X100 with option stimulator (MagVenture Inc., Atlanta, GA). Single pulse and TBS were both delivered using a statically cooled figure-8 coil (MCF-B70). The coil was oriented tangentially to the scalp over the left motor cortex with the handle at 45° to the midline in a posterior-lateral orientation. Stimulation consisted of biphasic posterior anterior-anterior posterior (PA-AP) pulses. The FDI motor cortical hotspot was determined as the position that elicited the largest MEP in the targeted contralateral FDI muscle. The position of the coil on the scalp corresponding to the hotspot was recorded using the BrainSight™ stereotactic system (Rogue Research, Montreal, QC). Single pulse stimulation was delivered at 120% of resting motor threshold. The resting motor threshold was defined as the percentage of stimulator output (to the nearest 1%) that elicited an MEP of $\geq 50 \mu\text{V}$ peak-to-peak

on 5 out of 10 trials (Rossini et al., 1994). TBS consisted of three pulses presented at 50 Hz, repeated at 5 Hz for 2 s (30 magnetic stimuli total). Intensity was set to 80% of the active motor threshold (Huang et al., 2005). The active motor threshold was defined as the percentage of stimulator output that elicited an FCR MEP of $\geq 200\mu\text{V}$ peak-to-peak on 5 out of 10 trials during tonic index abduction of 20% of the maximum force production.

2.3.4. Experimental design and procedure

The experiment consisted of a single session during which participants completed 60 trials of the verbal working memory task. A trial included five single TMS pulses at 120% of resting motor threshold prior to the presentation of the memory set. In 30 trials, a two-second bout of TBS was timed to coincide with the encoding phase. In 30 trials, the two-second bout of TBS was timed to the onset of the maintenance phase. Regardless of stimulation phase, TBS was followed by ten additional single pulses of TMS at 120% of resting motor threshold (RMT) every 2 s (Figure 2.1). Within the 30 trials for each stimulation phase (encoding and maintenance), half involved a memory set of two digits (low load), the remaining trials involved a memory set of six digits (high load). The order of memory set size trials was randomized within each stimulation phase.

2.3.5. Data analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows (v24, IBM Corp. Armonk, NY). Response time and accuracy were assessed using a linear mixed model with the factors load (low, high) and period (encoding, maintenance). The factor subject was included as a random effect to account for different intercepts across participants.

The differential impact of working memory demands upon motor cortical plasticity was measured using separate linear mixed models for the encoding and the maintenance data. In all

cases, the dependent variable was raw MEP amplitude whereas the factor subject was included as a random effect to account for different intercepts across participants. First, separate linear mixed models for encoding and maintenance were conducted to compare baseline MEP amplitude across loads (low, high). Second, four separate linear mixed models (i.e., for each combination of period and load) were conducted to compare post-TBS MEP amplitudes to pre-TBS MEP amplitudes. Time (pre, 2 s, 4 s, 6 s, 8 s, 10 s, 12 s, 14 s, 16 s, 18 s, and 20 s) was entered as a fixed factor. *Post hoc* analyses were conducted to compare baseline MEP amplitude to each post-TBS time point for each combination of period and load.

2.4. Results

The influence of working memory on the potential for plasticity was tested by combining the Sternberg working memory task with TBS.

2.4.1. Sternberg task performance

Response time was significantly longer for trials involving a set size of six items to encode and maintain, $F(1,17) = 18.41, p < .001$ (Figure 2.2A). There were no differences in reaction time whether stimulation was delivered during set encoding or maintenance, $F(1,17) = 1.88, p = .19$ (Figure 2.2A). Similarly, accuracy was lower for a set size of six digits compared to a set size of two, $F(1,17) = 4.51, p = .049$ with accuracy not significantly different if stimulation was delivered during encoding or maintenance, $F(1,17) = 1.77, p = .20$ (Figure 2.2B).

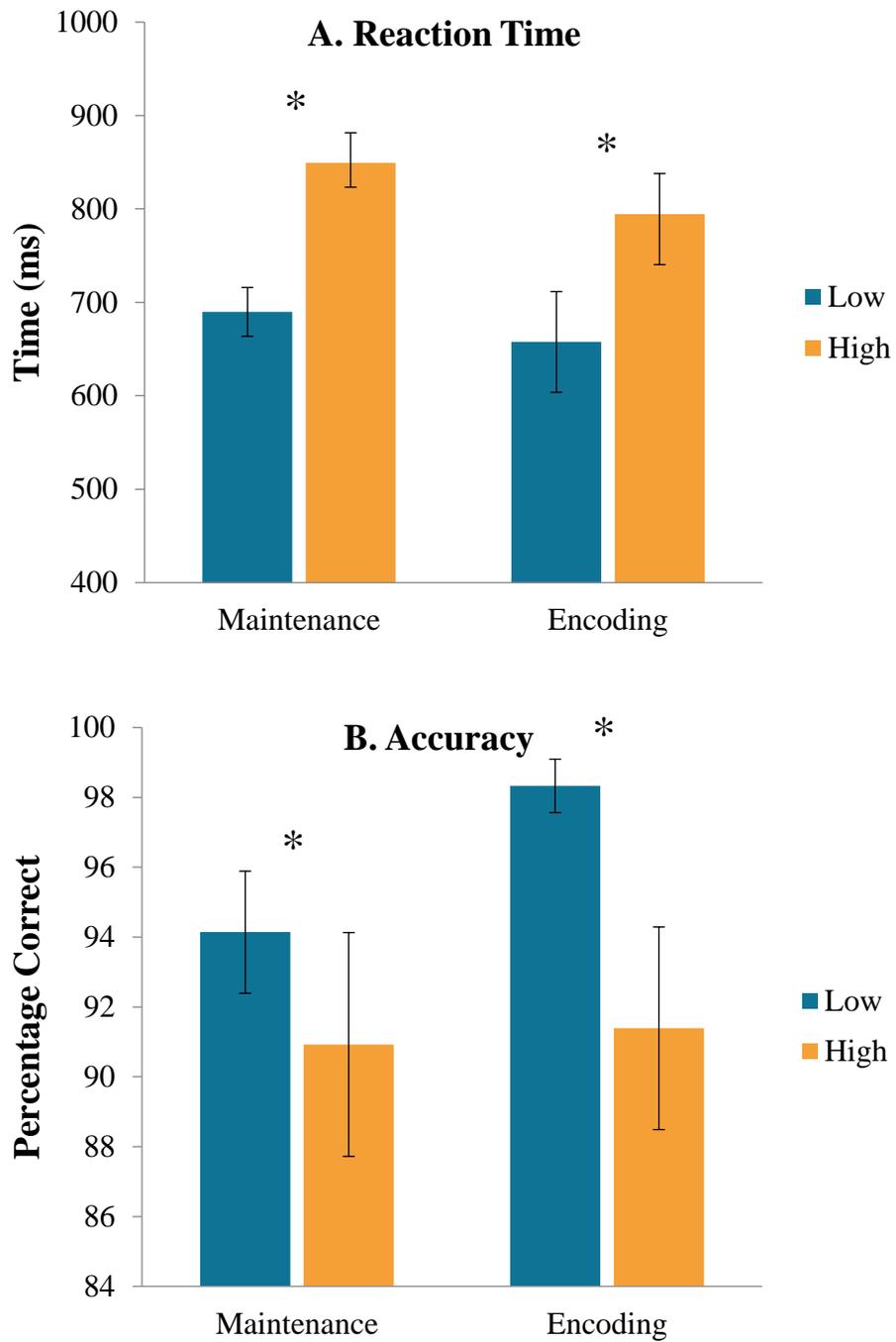


Figure 2.2. Sternberg working memory task results.

Reaction time (A) and accuracy (B) for the Sternberg memory scanning task following theta burst stimulation (TBS) during the encoding and maintenance period of the task. Error bars represent standard error of the mean. * denotes $p < .05$.

2.4.2. Motor cortex excitability

There were no baseline differences in pre-TBS MEP amplitudes across working memory loads for either encoding, $F(1,15) = 4.11$, $p = .06$ (low: $964 \pm 494 \mu\text{V}$, high: $816 \pm 415 \mu\text{V}$) or maintenance, $F(1,15) = 0.61$, $p = .45$ (low: $923 \pm 493 \mu\text{V}$, high: $992 \pm 468 \mu\text{V}$).

The plasticity induced by TBS was greater when encoding the two-digit set compared to baseline with a significant main effect of TBS, $F(10,90) = 2.40$, $p = .014$. Significant facilitation was seen at 2 s ($p = .006$) and 6 s ($p = .046$). None of the other time points reached significance. Encoding the six-digit memory set suppressed the facilitatory effect of TBS across all time points, $F(10,89) = 1.08$, $p = .388$ (Figure 2.3A).

In contrast to encoding, maintenance of the two-digit memory set mitigated the expected facilitatory effect of TBS across all time points, $F(10,91) = 1.25$, $p = .272$, whereas maintenance of the six-digit memory set did not mitigate the facilitatory effect of TBS, $F(10,90) = 2.43$, $p = .013$. Instead, facilitation was observed at 2 s ($p = .02$) and 4 s ($p = .007$) (Figure 2.3B).

2.5. Discussion

The current study is the first to demonstrate that cognitive load, in the form of verbal working memory, influences the potential for motor cortical plasticity. However, the effect of cognitive load is dependent upon the encoding/maintenance phase of the task. During encoding, a larger set size reduces the potential for motor cortical plasticity. In contrast, during set maintenance, the increased cognitive load did not mitigate the potential for motor cortical plasticity to the same extent as only having to rehearse a two-digit set size.

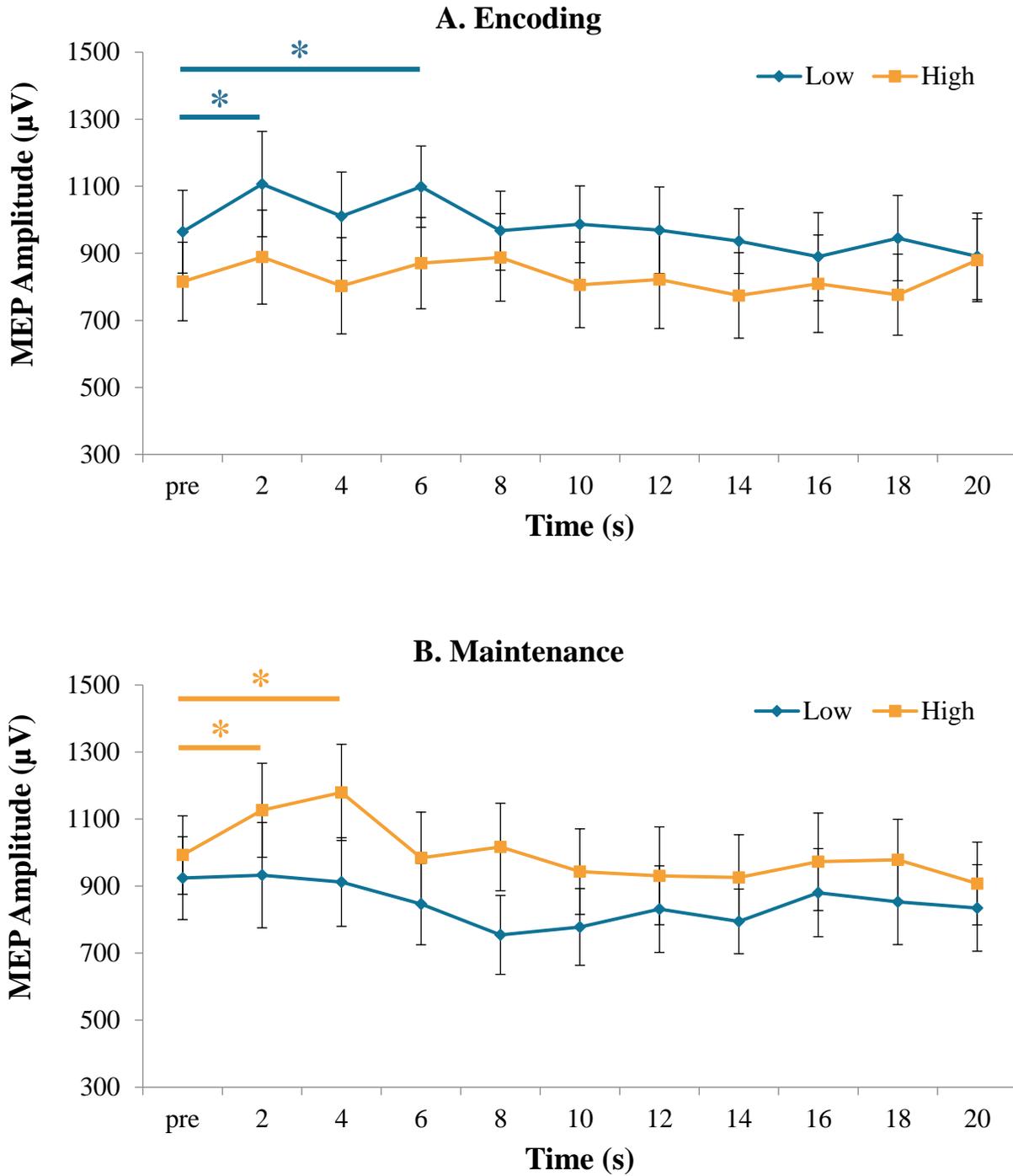


Figure 2.3. Motor cortex excitability following theta burst stimulation (TBS) during the Sternberg working memory task.

Motor evoked potential (MEP) amplitude pre- and post-TBS over motor cortex delivered during the encoding (A) or maintenance (B) phase of the Sternberg memory scanning task. Error bars represent standard error of the mean. * denotes significant contrast comparing MEP amplitude at post-TBS time point to pre-TBS.

The lack of motor cortex facilitation when encoding the larger set size of six digits compared to only two digits is consistent with past work manipulating attention/perceptual demands during PAS (Kamke et al., 2012; Kamke et al., 2014; Stefan et al., 2004), 5 Hz repetitive TMS (Conte et al., 2007), intermittent TBS (Kamke et al., 2012) as well as short-bouts of TBS similar to that delivered here (Mirdamadi et al., In preparation). The current results are also consistent with the load theory of attention and cognitive control (Lavie, 2005, 2010), which states that under low attention demands, spare attentional capacity is available to process concurrent task-irrelevant distractors. In contrast, under higher perceptual loads, greater attentional demands leave less attentional capacity available to process task-irrelevant stimuli that are blocked from further processing at an early stage, akin to sensory gating (Staines, Black, et al., 2002). In the current study, the facilitation of MEPs observed at 2 and 6 s following TBS delivered during two-digit set encoding arises as a result of a lack of penalty to processing irrelevant sensory inputs given lower attention demands and excess attentional capacity. Whereas, the higher perceptual demands imposed by the need to encode six digits result in fewer available attentional resources to process incoming somatosensory input (i.e., the input generated even in the absence of an overt somatosensory stimulus (Pfurtscheller, 1992)). The effect of encoding digits, therefore, reflects attentional demands rather than working memory demands. It should be noted, however, that 2 s of TBS would have been expected to produce effects lasting upwards of 12 to 15 s post-TBS (Huang et al., 2005; Mirdamadi et al., In preparation). The absence of MEP facilitation at 4 s and the reappearance at 6 s for the encoding results are possibly linked to the timing of the task. In fact, the probe appeared at 4 s after the start of TBS and was followed by the motor response. By 6 s after the start of TBS, the working memory trial ended (i.e., probe disappeared, and no motor response could be initiated). Therefore, the absence at 4 s and the reappearance at 6 s may reflect

a response specific effect due to the current behavioral task being performed in conjunction with TBS. In previous work from my laboratory, the behavioral response occurred 20 s post-TBS, after all motor cortical assessments were conducted (Mirdamadi et al., 2017). Alternatively, it is possible that attention demands may vary across the two-second encoding epoch with normalization regardless of set size once the digit set was perceived and encoded.

In contrast to encoding, the active maintenance of the digit set appears to draw upon, at least in part, a distinct neural process from encoding. I observed the expected facilitation up to 4 s after the end of a two-second bout of TBS under higher compared to lower cognitive loads. This effect is not a simple perceptual/attention effect as it runs counter to the direction during encoding, as well as past work investigating spatial attention and perceptual demands (Conte et al., 2007; Kamke et al., 2012; Kamke et al., 2014; Mirdamadi et al., In preparation; Stefan et al., 2004). The dissociation of cognitive from perceptual load effects upon motor cortical plasticity is again consistent with Lavie's load theory (2010). Under the perceptual load theory, the increased plasticity observed under the maintenance of a high memory set is associated with lesser available cognitive resources, which leads to the reduction in somatosensory gating. Interestingly, the high working memory load effect was relatively transient as it did not persist after 4 s post-TBS. Again, this may reflect a methodological choice such that the working memory task would have been completed following 4 s post-maintenance-TBS. The abrupt change in state, caused by the end of the trial, may have mitigated the effects of TBS during maintenance.

The maintenance results observed here are also consistent with behavioral results from studies of motor skill performance and learning in the presence of similar distractor tasks. In experts, automatized skills are improved when cognitive resources are divided by a concurrent tone counting task (Beilock, Carr, MacMahon, & Starkes, 2002). Declarative memory interference

also enhances motor skill acquisition (Brown & Robertson, 2007). Further, suppression of the dorsolateral prefrontal cortex, a cortical area critical to cognitive function, enhances the consolidation of motor skills, a process governed by motor cortex (Cohen & Robertson, 2011; Galea, Albert, Ditye, & Miall, 2009). Finally, concurrent perceptual tasks can suppress motor sequence learning, while increasing cognitive load by requiring memorization of a concurrent color sequence enhances motor sequence learning (Hemond, Brown, & Robertson, 2010). However, the relationship of the increased gain when working memory is pulled towards a distractor task may not directly relate to studies investing the relationship between implicit-sequence learning and working memory. For example, working memory capacity correlates positively with implicit sequence-specific learning in the absence of a concurrent distractor (Bo et al., 2011). While the current study provides evidence that working memory influences motor cortical plasticity, the nature of this influence in a given task may depend upon additional factors such as what working memory is supporting or how it is being used in a task.

Although the current study has demonstrated changes in motor cortical plasticity under differing cognitive loads, I cannot speak to the neural substrate of such effects. One possibility that needs to be examined further is the role of the dorsolateral prefrontal cortex. The dorsolateral prefrontal cortex has been implicated in attention-related sensory gating (Staines, Graham, et al., 2002; Yamaguchi & Knight, 1990) at the level of the thalamus (Staines, Black, et al., 2002). In addition, inhibitory non-invasive brain stimulation protocols over the dorsolateral prefrontal cortex, that theoretically suppress its activity enhance implicit learning (Galea et al., 2009; Zhu et al., 2015). It is possible that these protocols suppress the ability of the working memory neural substrates, such as the dorsolateral prefrontal cortex, to interfere with concurrent procedural motor control much like increased cognitive load enhances performance. However, it is also possible that

other frontal and parietal areas involved in working memory (Curtis & D'Esposito, 2003), such as the premotor cortex may be important mediators. The premotor cortex is often activated during a task delay period (Courtney, Petit, Haxby, & Ungerleider, 1998; D'Esposito et al., 1998; Smith & Jonides, 1999) for motor and non-motor tasks (Simon et al., 2002). In addition to this role as part of the declarative memory system, the premotor cortex is also involved in the timing of learned motor sequences (Halsband, Ito, Tanji, & Freund, 1993) and action recognition (Gallese, Fadiga, Fogassi, & Rizzolatti, 1996). Therefore, the premotor cortex appears to be at the junction of the declarative and procedural memory systems. The reduced plasticity during maintenance of the low load could then be interpreted as an inhibition from the premotor cortex onto the motor cortex. But when the memory load is increased, the premotor cortex is potentially dedicated to the processing of the explicit information and does not influence the motor cortex, resulting in the increased plasticity that is observed here. Future work is needed to understand better which intracortical circuits within motor cortex are affected by cognitive load and what are the extra-motor cortex mediators of such influence (i.e., the connections between areas responsible for working memory task performance and the motor cortex).

One limitation of this study is that working memory engagement was not part of a motor task but instead was part of a distractor task. Therefore, it limits predictions about the beneficial or the detrimental effect of working engagement on motor skill performance and learning. The direction of its influence is however predicted to depend on the type of skill and one's level of expertise. Namely, tasks that require simpler movements might be less affected by working memory engagement compared to tasks that involve more complex kinematics and dynamics.

Overall, the current study demonstrates that working memory has an influence on motor cortical plasticity that is independent of other cognitive constructs such as attention. Drawing

working memory to a distractor or dual-task may enhance the potential for neural plasticity and thereby favor learning by preventing declarative influence over procedural motor control.

CHAPTER 3 – Verbal Working Memory Modulates Afferent Circuits in Motor Cortex

Research question: Which motor circuits are affected by working memory engagement?

3.1. Abstract

Verbal instructions and strategies informed by declarative memory are keys to performance and acquisition of skilled actions. However, it is unknown if the allocation of working memory shapes afferent input to motor cortex. The present study used short-latency afferent inhibition (SAI) to probe the effect of verbal working memory upon afferent circuits converging on corticospinal neurons in the motor cortex. SAI was assessed in the first dorsal interosseous (FDI) muscle while participants mentally rehearsed a two- or six-digit set. SAI was evoked by preceding a suprathreshold transcranial magnetic stimulation (TMS) with electrical stimulation of the median nerve at the wrist. To isolate different afferent intracortical circuits in the motor cortex, SAI was elicited using either posterior-anterior (PA) or anterior-posterior (AP) monophasic currents. In an independent sample, somatosensory processing during the same working memory task was assessed using somatosensory evoked potentials (SEP) elicited by median nerve stimulation. SAI was significantly reduced during maintenance of the six-digit compared to the two-digit memory set in PA and AP circuits. The parietal N20-P25, but not the frontal P20-N30, SEP component was attenuated during maintenance of the six- compared to two-digit memory set. The mirrored reduction in PA SAI and parietal N20-P25 SEP amplitude is consistent with previous reports of a strong positive relationship between the two measures. However, the current results do not support that PA and AP TMS recruit anatomically and functionally distinct neuronal circuits. Therefore,

both PA and AP circuits may be substrates by which cognitive strategies shape sensorimotor processing during skilled movement.

3.2. Introduction

Acquisition and execution of a motor skill are dependent upon the afferent input to the motor cortex. Afferent input can be shaped by volitional strategy through the allocation of cognitive resources. For example, the allocation of attention across space and/or sensory modality can enhance or decline motor performance (Meehan et al., 2009), motor cortex excitability (Ruge, Muggleton, Hoad, Caronni, & Rothwell, 2014) and potential for plasticity (Kamke et al., 2012; Kamke et al., 2014; Stefan et al., 2004). Short-latency afferent inhibition (SAI) (Tokimura et al., 2000) offers a method to probe the modulatory effects of somatosensory afference upon motor cortex excitability and plasticity. SAI involves preceding a transcranial magnetic stimulation (TMS) stimulus over motor cortex by electrical stimulation of the corresponding contralateral afferent peripheral nerve (~20 ms for distal muscles of the hand). The inhibition evoked by the electrical stimulation is thought to be cortical in origin (Ferreri et al., 2012; Kojima et al., 2015; Tsang et al., 2014) and reflect the convergence of somatosensory afference and TMS-induced current upon the corticospinal neurons in the motor cortex (Tokimura et al., 2000). Strong positive relationships between the magnitude of SAI and peripheral stimulus intensity (Bailey, Asmussen, & Nelson, 2016; Fischer & Orth, 2011) support the critical role of somatosensory afferent projections to the motor cortex. In addition to SAI's strong relationship with the extrinsic properties of somatosensory afference (i.e., the positive relationship between peripheral nerve stimulation intensity and level of SAI) (Bailey et al., 2016), SAI is also modified by intrinsic processes. For example, SAI is greater in adjacent muscles not involved in an intended movement

(Asmussen et al., 2014; Dubbioso, Raffin, Karabanov, Thielscher, & Siebner, 2017; Voller et al., 2006). For muscles involved in a movement, SAI decreases during movement planning and onset (Asmussen, Jacobs, Lee, Zapallow, & Nelson, 2013; Asmussen et al., 2014; Voller et al., 2006). The apparent sensitivity of SAI to intrinsic processes makes SAI a potential method to probe the effect of cognition on motor cortex excitability through afferent modulation.

To date, the vast majority of studies have quantified SAI by pairing monophasic posterior-anterior (PA) TMS with the peripheral electrical stimulation. Anatomically, SAI evoked by PA and monophasic anterior-posterior (AP) current index different intracortical sensorimotor circuits (Ni et al., 2011). Functionally, we recently demonstrated that SAI evoked using AP, but not PA, current is reduced by a concurrent visual detection task with high attention demands (Mirdamadi et al., 2017). The sensitivity of the AP interneuron circuit to crossmodal attention represents a motor cortical substrate by which cognition can exert influence over the motor cortex through the intrinsic modulation of sensory afference. However, whether other cognitive systems, such as working memory, have the same impact upon motor cortex and act upon the same motor cortical substrates is unknown.

The current study assessed the effect of short-term memory demands on the specific afferent intracortical motor circuits recruited by different monophasic current directions. SAI was elicited using either PA or AP TMS to preferentially recruit the distinct sensorimotor cortical circuits (Ni et al., 2011) during memory set maintenance in the Sternberg short-term memory task (Sternberg, 1966). Increased working memory demands increase the susceptibility to distraction by task-irrelevant stimuli (Lavie, 2010). The increased susceptibility to distraction is hypothesized to reflect the breakdown of executive attention control when working memory is taxed. Therefore, I hypothesized that increasing the set size to be maintained in working memory would lead to the

breakdown of attention-related suppression of somatosensory afference, thereby increasing SAI in the attention-sensitive AP circuit (Mirdamadi et al., 2017). In a second independent experiment, I quantified the change in the parietal N20-P25 and frontal P20-N30 somatosensory evoked potentials (SEPs) to index the effect of maintaining the different set sizes upon early somatosensory processing. The amplitude of the parietal N20-P25 is positively correlated with the magnitude of PA SAI (Bailey et al., 2016) while we have shown similar attention-related modulation of the P20-N30 and AP SAI (Mirdamadi et al., 2017).

3.3. Methods

3.3.1. Participants

Eighteen self-reported right-handed adults participated in the original TMS experiment assessing SAI during the maintenance of different digit spans (Experiment 1: 6 males, 12 females, 20 ± 2 years). An independent sample of nine self-reported right-handed adults participated in the *post hoc* SEP experiment (Experiment 2: 3 males, 6 females, 20 ± 1 years). All participants across both experiments provided written informed consent; the Institutional Review Board of the University of Michigan Medical School (IRBMED) approved the study protocol.

3.3.2. Working memory task

For both experiments, the working memory task was a modified version of the Sternberg short-term memory task (Figure 3.1) (Sternberg, 1966). Sets of two- or six-digits were randomly presented for 2 s on a computer screen 80 cm in front of the participant (LabVIEW 2015, National Instruments, Austin, TX). After 2 s, the memory set disappeared. Following a 2 s delay consisting of a blank, grey background, a single digit probe appeared. Participants indicated whether the

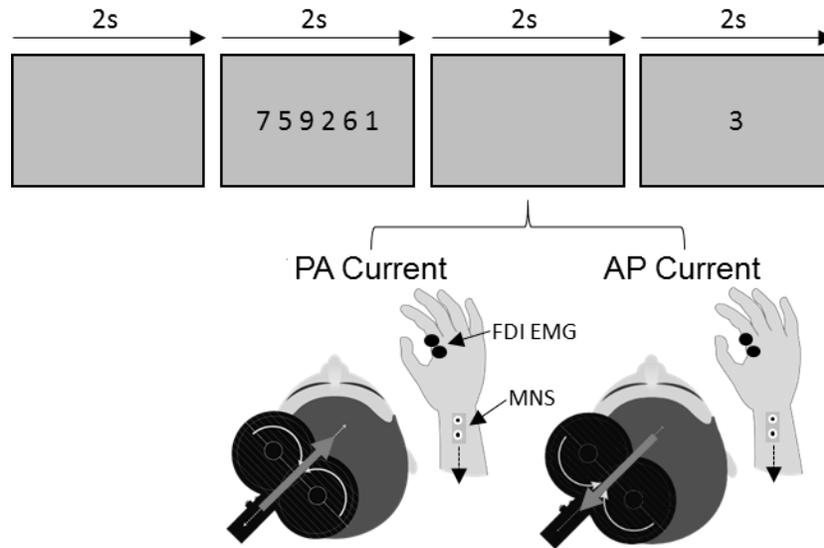


Figure 3.1. Example time course of the Sternberg short-term memory task and timing of short-latency afference inhibition (SAI).

A memory set size consisted of either two or six digits to be encoded and maintained. SAI under different current directions was elicited during the maintenance phase. The dark grey arrows indicate the induced current in the brain. The white curved arrows on the transcranial magnetic stimulation (TMS) coil indicate the direction of the TMS coil current. Note, the induced current in the brain flows in the opposite direction to the coil current. The TMS coil current direction was controlled by the stimulator's onboard software. FDI EMG: first dorsal interosseous electromyography electrode, MNS: median nerve stimulation.

probe was part of the previously presented memory set by pressing one of two response keys located beneath the left index or middle finger. The single digit probe remained visible until participants responded or 2 s elapsed. The inter-trial interval was 2 s. The inclusion probability of the probe was 50%. Response time and accuracy were recorded. Participants completed 15 trials for each combination of phase and memory load.

3.3.3. Transcranial magnetic stimulation (TMS)

For Experiment 1, motor evoked potentials (MEP) elicited by TMS were recorded using LabChart 7 software in conjunction with a Dual BioAmp and PowerLab 8/30 acquisition system (AD Instruments, Colorado Springs, CO). Participants were seated with both arms resting on a pillow placed upon their lap. Surface electromyography electrodes (Ag-AgCl) were placed over the first dorsal interosseous (FDI) muscle using a tendon-belly montage. Surface electromyography recording was triggered using a 5V TTL pulse with an epoch of -0.3 to 0.5s. During acquisition, data were amplified (x 1000), digitized (x 40000 Hz) and filtered (band-pass filtered 5-1000 Hz, notch filter 60 Hz). Surface electromyography data were subsequently down-sampled to 5000 Hz during offline analysis. The MEP was defined as the peak-to-peak amplitude of the maximal electromyography response between 20 to 50 ms post-TMS stimulation. Trials, where baseline root mean square error (-50 to 0 ms) in the FDI muscle exceeded 15 μ V, were excluded from subsequent analysis. Less than 1% of all trials were excluded as a result of excessive muscle activity during the baseline period.

TMS was delivered using a MagVenture MagPro X100 with option stimulator (MagVenture Inc., Atlanta, GA) and a figure-8 coil (MC-B70). Two different current configurations were delivered. For PA stimulation, the coil was held $\sim 45^\circ$ to the midline and

current direction specified as “reverse” using the stimulator’s onboard software (Figure 3.1). For AP stimulation, the coil orientation was identical with that for PA stimulation, but the current direction was set to “normal” via the stimulator’s onboard software (Figure 3.1).

The FDI motor cortical hotspot was defined as the scalp position that elicited the largest and most consistent response following PA stimulation. The location and trajectory of the coil on the scalp at the hotspot was recorded using the BrainSight™ stereotactic system (Rogue Research, Montreal, QC). The same hotspot was used for AP stimulation (Sakai et al., 1997). Resting motor threshold was independently defined for the PA and AP-induced currents as the percentage of stimulator output (to the nearest 1%) that elicited an MEP of $\geq 50 \mu\text{V}$ peak to peak on 10 out of 20 trials (Rossini et al., 2015). TMS intensity for SAI was set to the stimulator output that elicited an MEP of $\sim 1 \text{ mV}$ (in the absence of peripheral stimulation) for each current direction.

3.3.4. Short-latency afferent inhibition (SAI)

SAI consisted of a peripheral electrical stimulus paired with TMS. Electrical stimulation was delivered using a DS7A constant current high voltage stimulator (Digitimer North America LLC, Fort Lauderdale, FL). Stimulation was applied over the median nerve at the right wrist (constant current square wave pulse, 0.2 ms duration, cathode proximal). Electrical stimulation intensity was set to the intensity to produce a slight thumb twitch (i.e., motor threshold) (Abbruzzese, Marchese, Buccolieri, Gasparetto, & Trompetto, 2001). The electrical stimulus intensity was 2.6 ± 0.9 times sensory threshold. Electrical stimulation preceded TMS stimulation by 21 ms, an interstimulus interval known to produce the highest inhibition for PA (Ni et al., 2011; Tokimura et al., 2000) and AP SAI (Ni et al., 2011).

3.3.5. Somatosensory evoked potentials (SEPs)

For Experiment 2, SEPs were derived from electrical stimulation to the right median nerve while the participant completed the short-term memory task. Median nerve stimulation consisted of square wave pulses (0.5 ms duration) delivered through surface electrodes fixed to the wrist (DS-7A constant current stimulator, Digitimer North America LLC, Fort Lauderdale, FL). Median nerve stimulus intensity was set to the motor threshold, and the M-wave was monitored via surface electromyography (EMG) at the thenar eminence (x 2000 amplification, 1-200 Hz band-pass filtered, digitized at 1200 Hz, g.tec g.USBamp, g.tec Neurotechnology, Rensselaer, NY).

Electroencephalographic data were recorded from Fz, Cz, Pz, Oz, C3, C4, Cp3, Cp4 and A1 (g.Sahara active dry electrodes, g.UBSamp, g.tec medical engineering GMBH, Austria). Electrodes were positioned consistent with the international 10-20 system for electrode placement and referenced to average mastoids (< 5 k Ω impedance, x 20000 amplification, 1-200 Hz band-pass filtered, 1200 Hz digitization). SEPs were extracted using the EEGLab toolbox (Institute for Neural Computation, University of California – San Diego, San Diego, CA) for MATLAB v2014b (The MathWorks, Natick, MA) environment. Stimuli occurred during the maintenance period between digit span and probe presentation. Peak-to-peak amplitudes for the frontal P20-N30 and parietal N20-P25 were extracted from Fz and Cp3 respectively.

3.3.6. Experimental design and procedure

Experiment 1 consisted of a single session. SAI was elicited during the two-second maintenance period between the two- or six-digit memory set presentation and probe presentation. During each trial, a single unconditioned or conditioned stimulus was delivered. Fifteen conditioned and 15 unconditioned trials were completed for each digit span length and monophasic

current direction resulting in a total of 120 trials. The order of conditioned/unconditioned epochs, current direction and span length was counterbalanced across participants.

Experiment 2 also consisted of a single session. Participants completed ninety-trials of the Sternberg memory task. Forty-five trials used a set size of two. The remaining 45 trials used a set size of six. The order of the working memory load trials was randomized. Median nerve stimulation was delivered during the two-second period of memory set maintenance. It should also be noted that the Sternberg working memory trials were completed as part of a larger study that also included elicitation of SEPs during the performance of a visual detection task. The order of attention versus working memory task was counterbalanced across participants.

3.3.7. Data analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows (v23, IBM Corp. Armonk, NY). For Experiment 1, behavioral performance was assessed using repeated measures ANOVA with the factors set size (two, six) and current direction (PA, AP).

Motor cortical physiology was assessed in three steps. First, to check that changing the current direction did recruit separate cortical circuits, I conducted a set size (two, six) by current direction (PA, AP) repeated measure ANOVA on the latency data. Second, to confirm that the peripheral conditioning stimulus did have an effect upon MEP amplitude, I conducted separate stimulation type (unconditioned, conditioned) by set size (two, six) repeated measures ANOVAs for each current direction. MEP amplitude was the dependent variable. Third, a current direction (PA, AP) by set size (two, six) repeated measures ANOVA was performed to assess differences in the magnitude of SAI. SAI was the dependent variable. SAI was derived as a percentage of

unconditioned MEP amplitude. Lower values for SAI indicate higher levels of MEP suppression by the somatosensory afferent volley.

For Experiment 2, SEPs were compared for the two- and six-digit set size using separate paired samples t-tests for the N20-P25 and P20-N30 SEP components.

3.4. Results

3.4.1. Experiment 1 – Monophasic transcranial magnetic stimulation (TMS) during maintenance of varying set size

Mean accuracy in the visual detection task was higher for the two- compared to six-digit variation of the working memory task (main effect of set size: $F(1,17) = 26.49$, $p = .00008$; two = 96 ± 1 , six = 89 ± 2 , mean \pm standard error). Accuracy was consistent across current direction as neither the interaction ($F(1,17) = 0.03$, $p = .88$) nor the main effect of current direction ($F(1,17) = 0.35$, $p = .56$) were significant.

Figures 3.2A and 3.2B show the group averaged traces ($n = 18$) of conditioned and unconditioned MEPs for each current direction. Resting motor threshold for monophasic PA stimulation and AP stimulation was 49 ± 6 (mean \pm standard deviation) and $66 \pm 9\%$ of stimulator output respectively. The stimulation intensity to elicit an MEP of 1mV using monophasic PA and AP stimulation was $58 \pm 8\%$ and $78 \pm 10\%$ of stimulator output respectively. Consistent with past work, the latency of MEPs was significantly longer for AP compared to PA stimulation (main effect of current direction: $F(1,17) = 31.11$, $p = .00003$, PA = 22.5 ± 1.1 ms, AP = 24.1 ± 1.1 ms, mean \pm standard error). The longer latencies for AP current were consistent across digit set size

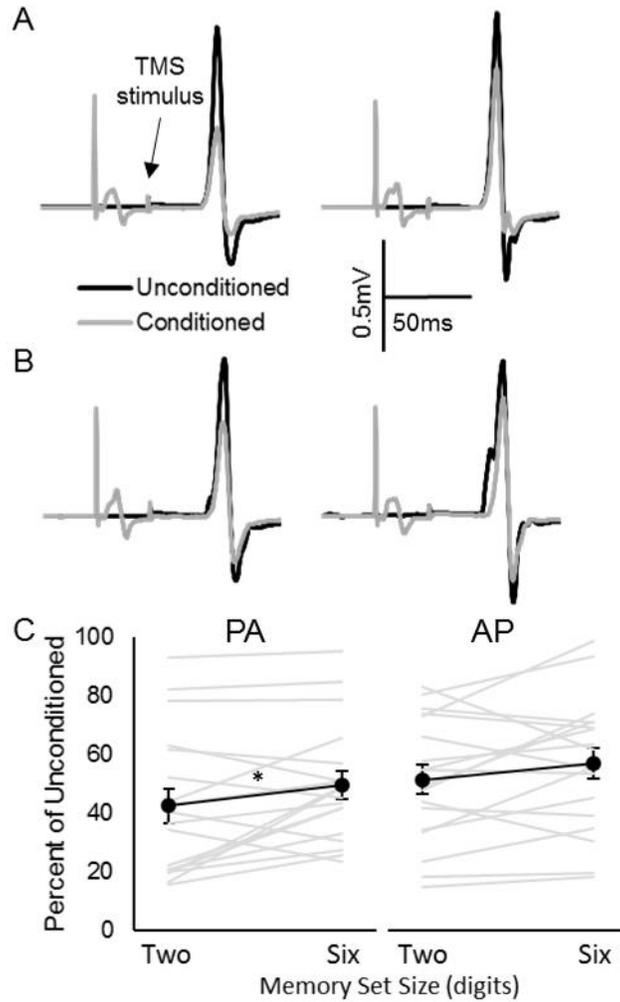


Figure 3.2. Experiment 1 – Short-latency afference inhibition (SAI) results.

A. Unconditioned and conditioned group averaged motor evoked potentials (MEPs) elicited by posterior-anterior (PA) stimulation during the two- (left panel) and six-digit (right panel) conditions. B. Unconditioned and conditioned group averaged MEPs elicited by anterior-posterior (AP) stimulation during the two- (left panel) and six-digit (right panel) condition. C. SAI elicited during maintenance of the two- and six-digit memory sets. Amplitudes are expressed as a percentage of the unconditioned MEP amplitude. Higher values represent lower levels of SAI. The group average across the two- and six-digit set sizes for each current direction (black line) is overlaid on individual data (grey lines). Error bars represent standard error of the mean. * denotes significant contrast ($p < .05$).

given the absence of a significant main effect of set size ($F(1,17) = 2.12, p = .16$) or set size by current direction interaction ($F(1,17) = 0.12, p = .73$).

A stimulation type by set size repeated measures ANOVA confirmed SAI was present across both set sizes for each current direction. In fact, conditioned MEPs were significantly reduced compared to unconditioned MEPs regardless of set size for both the PA (main effect of stimulation type: $F(1,17) = 69.56, p = .0000003$) and AP stimulating currents (main effect of stimulation type: $F(1,48) = 32.36, p = .00003$). Comparison of the magnitude of SAI for each current direction across set size produced a main effect of set size ($F(1,17) = 10.96, p = .004$) with reduced SAI for the 6-digit set size compared to the 2-digit set size (Figure 3.2C). Neither the main effect of current direction ($F(1,17) = 2.74, p = .12$) nor the current direction by set size interaction ($F(1,17) = 0.01, p = .93$) reached significance.

3.4.2. Experiment 2 – Somatosensory gating under varying cognitive load

Figures 3.3A and 3.3B show the group averaged SEPs ($n = 9$) from Fz and Cp3. Parietal N20-P25 peak-to-peak amplitude was significantly reduced during the maintenance of the six-digit compared to two-digit memory set ($t(8) = 3.23, p = .012$) (Figure 3.3C). There were no differences in the frontal P20-N30 SEP amplitude across digit set size ($t(8) = -1.28, p = .24$) (Figure 3.3C).

3.5. Discussion

The current study used SAI to investigate the effect of cognitive load upon PA-sensitive and AP-sensitive afferent intracortical circuits. The novel finding is that higher verbal working memory loads associated with the maintenance of a six- versus a two-digit memory set reduced SAI regardless of whether SAI was evoked using PA or AP stimulating current. Increasing set size

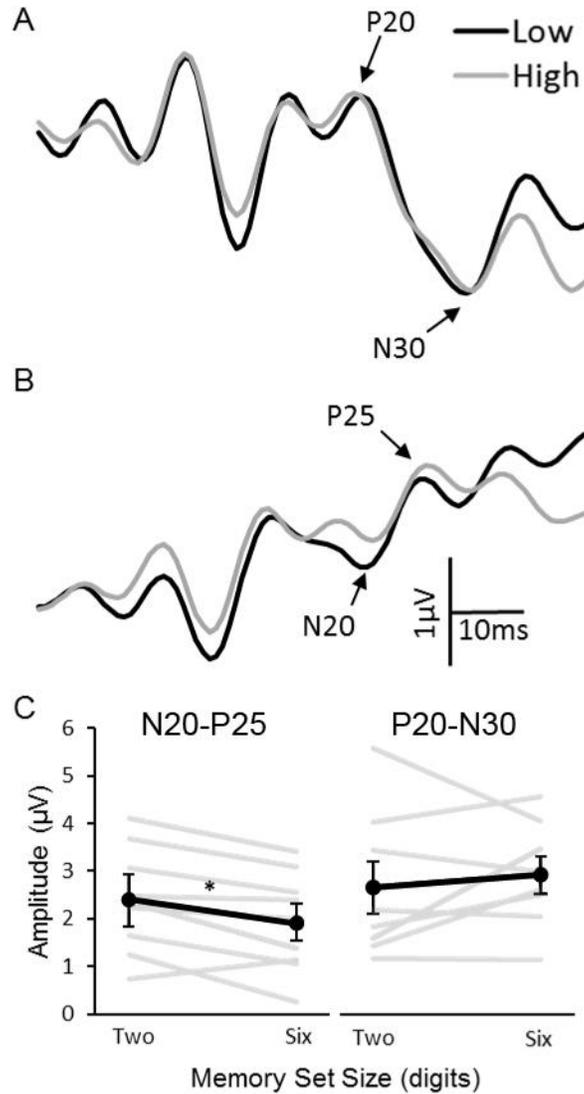


Figure 3.3. Experiment 2 – Somatosensory evoked potential (SEP) results.

A. Grand average SEP waveform recorded from Fz elicited during maintenance of the two- and six-digit memory sets. B. Grand average SEP waveform recorded from Cp3 elicited during maintenance of the two- and six-digit memory sets. C. Peak-to-peak amplitudes of the parietal N20-P25 and frontal P20-N30 during maintenance of the two- and six-digit memory sets. The group average across the two- and six-digit conditions for each SEP component (black line) is overlaid on individual data (grey lines). Error bars represent standard error of the mean. * denotes significant contrast ($p < .05$).

in the same working memory task also reduced the parietal N20-P25 SEP component. The current study is the first study to investigate the effects of verbal working memory upon the corticospinal output generated by SAI.

Previous research has shown that PA and AP circuits are anatomically (Di Lazzaro et al., 2001; Ni et al., 2011) and functionally (Hamada et al., 2014; Mirdamadi et al., 2017) distinct. In particular, we previously demonstrated that the AP but not PA SAI circuit was sensitive to the attentional load imposed by a concurrent visual detection task (Mirdamadi et al., 2017). Given: 1) the AP SAI circuit's sensitivity to attention load, 2) a model that posits increasing working memory loads leads to the breakdown of executive control underlining sensory gating (Lavie, 2005, 2010) and 3) the positive relationship between sensory afference and SAI (Bailey et al., 2016), I hypothesized that increased working memory would specifically increase the magnitude of AP SAI. However, increasing the verbal working memory load of the distractor task equally affected AP and PA SAI. The consistent effect across the PA and AP circuits suggests that contrary to attention, both the PA and AP circuits are sensitive to working memory allocation.

The decrease in SAI across both the PA and AP SAI circuits is also contrary to the direction of the effect I hypothesized. Given the positive relationship between the level of sensory afference and strength of SAI (Bailey et al., 2016), increasing working memory demands of the distractor task did not change sensory afference through the release of somatosensory gating resulting from the breakdown of executive control of attention. The reduction of both the PA and AP SAI with increasing distractor working memory demands is more readily resolved with an action-selection rather than attention-related mechanism. Although studies of the functional significance of the AP SAI circuit are limited, PA SAI is reduced during the preparatory phase immediately preceding finger movement (Asmussen et al., 2013; Voller et al., 2006). Conversely, an increase of PA SAI

is associated with the surround inhibition of digit representations not involved in a planned movement (Asmussen et al., 2014; Dubbioso et al., 2017; Voller et al., 2006). Therefore, the response of at least the PA SAI circuit to verbal working memory load may reflect a mechanism by which working memory influences response selection. Whether the reduction in AP SAI is functionally related to the PA SAI reduction is less clear given that no prior studies have investigated the sensitivity of AP SAI circuits to movement phase. We also cannot rule out the possibility that the AP SAI reduction was driven by increased attention demands, in addition to working memory demands, during maintenance of the six-digit memory set. The reduction in AP SAI is consistent with the reduction observed in this circuit when the attention demands of a visual detection task were increased (Mirdamadi et al., 2017). If AP SAI reduction in the current study is purely working memory sensitive, this would suggest that AP SAI may be involved in both the selection of actions as well as the modulation of a selected action. If the AP SAI effect in the current study reflects an independent attention-related effect, then the AP SAI related attention processes may serve to modulate the properties of a selected movement. Future research is needed to assess task-related changes in PA and AP SAI circuits to elucidate the functional significance of each circuit.

The reduction of sensory afference with a 6-digit set size compared to a 2-digit set size observed in Experiment 1 is confirmed by the results of Experiment 2. In fact, the amplitude of the parietal N20-P25 SEP component, which is known to scale to peripheral stimulation intensity (Bailey et al., 2016), is reduced with the higher working memory load. In addition, the N20-P25 SEP component has been localized to Brodmann Areas 3b/1 of the primary somatosensory cortex and is thought to reflect the thalamocortical relay of somatosensory afference (Allison et al., 1991). Therefore, the task-related reductions in PA SAI and parietal N20-P25 SEP component with

greater verbal working memory load are consistent with the premise that reduced PA SAI is driven by an intrinsic decrease in the thalamocortical relay of somatosensory afference. However, the reduction in AP SAI with a six-digit set size was not associated with a matching reduction of frontal P20-N30; even though we have previously reported that reductions in AP SAI under increasing loads of visual attention are mirrored by reductions in the frontal P20-N30 SEP component (Mirdamadi et al., 2017). It is possible that engagement of attention specifically affects the neural generator of the frontal P20-N30 SEP localized to the supplementary motor area and precentral gyrus (Desmedt & Cheron, 1981) but does not affect the parietal generator of N20-P25. To explain this difference of effect between generators, it is possible that both PA and AP networks receive inputs from the N20-P25 generator, but AP circuit, which is more complex, also receives inputs from the P20-N30 generator. In this case, the AP circuit seems to be influenced by changes to the N20-P25 generator specifically.

One limitation of the current study is that SAIs and SEPs were recorded across two separate samples. Although verbal working memory influenced both PA SAI and the parietal N20-P25 SEP component in a manner consistent with the known relationship between these metrics, the link remains indirect. Another limitation is that there was no quantification of the activation of areas typically associated with working memory engagement such as the frontal and parietal areas (Rottschy et al., 2012). However, these correlates are established and it is doubtful that they would have differed in my sample. Another limitation is that no study to date has measured the relationship between AP SAI and SEP.

The absence of a current effect on SAI independent of working memory demands appears contrary to past work demonstrating that at rest, in the absence of any task, peak SAI is greater for PA compared to AP current (Ni et al., 2011). However, we have previously failed to observe such

stimulating current effects independent of attention load (Mirdamadi et al., 2017). One possible explanation for the absence of different magnitudes of SAI across current directions in the present study is tied to conditioning stimulus intensity. Ni et al. (2011) demonstrated significantly greater SAI for PA compared to AP current starting at a conditioning stimulus intensity of 3 x sensory threshold. I based the stimulation intensity off of motor threshold which equated to 2.6 x sensory threshold in the current work and 2.7 x sensory threshold in past work from my laboratory investigating effects of attention load (Mirdamadi et al., 2017). At conditioning stimulus intensities ranging from 2-3 x sensory threshold, Ni et al. (2011) observed slightly, but not statistically significant, greater SAI for PA compared to AP stimulating current.

The current study reinforces the notion that sensorimotor projections are influenced by the allocation of cognitive resources. The sensitivity of the PA SAI circuit to working memory but not attention allocation suggests a specific role in the selection of action. The sensitivity of the AP SAI circuit to both working memory and attention allocation leaves open the possibility that the AP SAI circuit plays a role in action selection and modulating selected actions. Influence over afferent processing in the PA and AP sensitive circuits may reflect pathways by which declarative strategies may influence procedural processing in motor control and learning.

CHAPTER 4 – Modulation of Short-Latency Afferent Inhibition During Performance of a Discrete Sequence Under Different Foci of Attention

Research question: Does the focus of attention differentially modulate somatosensory gating during sequence learning?

4.1. Abstract

Instructions are integral to the acquisition and performance of motor skills. Explicit instructions emphasizing movement effect on the environment, known as an external focus, generally benefit motor performance relative to explicit instructions emphasizing the control of specific muscles/effectors. The external benefit is believed to originate from increased automatization of sensorimotor control because the focus is put on movement outcomes. In contrast, an internal focus is thought to interfere with automatization through increasing conscious control and over-representation of the specific muscles/effectors being stressed in the explicit instruction. Despite an abundance of behavioral studies, little is known about the physiological correlates associated with using an external or an internal focus of attention. Short-latency afferent inhibition (SAI) was used to probe a possible substrate governing explicit influence over sensorimotor control during a discrete finger keying sequence represented by response key (external focus) or finger (internal focus). Although there was no significant benefit to sequence performance in adopting an external over internal focus, reductions in SAI preceding index finger movement were more prominent under an external focus. With more practice, the difference across groups appeared one movement ahead of the index finger movement. At this preceding element,

the external group demonstrated reduced SAI while the internal group showed increased levels of SAI. These results suggest that performance under both internal and external foci of attention leads to changes in sensorimotor function that can support improved performance. However, the changes under an external focus of attention are consistent with increased proceduralization of the motor sequence that may benefit more complex skills that tax cognitive resources.

4.2. Introduction

Declarative, or explicit knowledge can benefit the performance and the acquisition of motor skills. However, declarative knowledge about a motor skill cannot replace the procedural knowledge that governs movement kinematics and dynamics acquired through experience (Taylor, Krakauer, & Ivry, 2014). In addition, the systems governing declarative and procedural memory may interact in a competitive manner (Galea et al., 2009; Mazzoni & Krakauer, 2006). Therefore, explicit knowledge, whether it is extrinsically provided or intrinsically acquired, needs to be designed to promote efficient performance by limiting this interference. Explicit instructions about a skill that stress control of specific effectors/muscles, known as an internal focus, do not benefit performance to the extent that instructions that emphasize the effect of the movement on a tool or the environment, known as an external focus do (Al-Abood, Bennett, Hernandez, Ashford, & Davids, 2002; Duke, Cash, & Allen, 2011; Wulf, Höß, & Prinz, 1998; Wulf, Lauterbach, & Toole, 1999). However, the generalization of the external focus benefit is still under debate. For some motor skills, it appears that novice performers benefit from an internal focus of attention (Perkins-Ceccato, Passmore, & Lee, 2003).

The proposed penalty of adopting an internal over an external focus of attention is thought to arise from the promotion of conscious control of specific effectors at the expense of the overall

motor autonomy, known as the “constrained action hypothesis” (McNevin et al., 2003). Under an external focus, this model suggests that an external focus does not select or over-represent the individual contribution of a specific effector or set of effectors, instead stressing the net outcome of all contributions. The absence of cognitive constraints promotes the automatization of movements, where an initial assessment of cognitive and sensory cues triggers an efficient and comprehensive feedforward model of the skill. The notion of enhanced efficiency through automaticity is supported by observations of reduced electromyography (EMG) activity (Lohse, Sherwood, & Healy, 2010; Vance, Wulf, Töllner, McNevin, & Mercer, 2004; Wulf, Dufek, Lozano, & Pettigrew, 2010; Zachry, Wulf, Mercer, & Bezodis, 2005) and controlled, energy-efficient movement (Kal, van der Kamp, & Houdijk, 2013).

Despite extensive behavioral and peripheral physiological evidence in support of the constrained action hypothesis, little direct neurophysiological evidence is available. Increased blood-oxygen-level dependent (BOLD) responses in sensorimotor cortex under an external focus of attention is suggested to reflect increased tactile processing of response keys compared to an internal focus (Zentgraf et al., 2009). However, somewhat contradictory to Zentgraf study, the BOLD response in somatosensory cortex has also been shown to increase when shifting from an external to an internal focus of attention (Zimmermann et al., 2012). While a great approach to localizing the effect of attention focus, the BOLD response is ambiguous as it can be either inhibitory or facilitatory, making it difficult to resolve such contradictory findings (Beck & Hallett, 2011). To disambiguate the inhibitory/facilitatory nature of attention focus BOLD responses, a recent paired-pulse transcranial magnetic stimulation (TMS) study demonstrated increased short-interval intracortical inhibition under an external compared to an internal focus (Kuhn, Keller,

Ruffieux, & Taube, 2016). While a useful technique to study gamma-aminobutyric acid (GABA) function, it does not provide insight into whether attention focus alters sensorimotor projections.

The purpose of the current study was to directly assess the effect of attention focus on a sensorimotor circuit known to alter corticospinal output based upon the type of instructions. Short-latency afferent inhibition (SAI) was used to probe the first dorsal interosseous (FDI) sensorimotor circuit at various elements of a 12-element discrete sequence. Like short-interval cortical inhibition, SAI involves the conditioning of motor cortical networks prior to generation of an overt muscular response. However, unlike short-interval cortical inhibition, the conditioning effect is directly attributable to the manipulation of sensorimotor projections by a peripheral conditioning stimulus (Tokimura et al., 2000), with a positive relationship between stimulus intensity and SAI strength (Bailey et al., 2016). In addition, SAI is sensitive to cognition (Kotb et al., 2005; Mirdamadi et al., 2017) and performance of movements (Asmussen et al., 2013; Asmussen et al., 2014; Voller et al., 2006). In light of the positive relationship between sensory afference and strength of SAI, the reduction of SAI during movement is likely due to movement-related inhibition, which occurs during ballistic movements when sensory feedback is not beneficial to performance (Williams, Shenasa, & Chapman, 1998).

I hypothesized that performance would be better in the group that received the external focus of attention instructions (external group) compared to the internal group, as measured by shorter reaction time. I hypothesized that regardless of attention focus, SAI would be reduced at movement onset compared to rest in the task-relevant FDI. However, I hypothesized that the reduction in SAI would be greater for the external compared to the internal focus group, reflective of increased automatization of the discrete sequence and lower reliance on sensory feedback for each individual finger/movement. The relatively greater inhibition in the internal focus group

would be consistent with the attention-related facilitation of somatosensory information coming from fingers that would counter movement-related gating during discrete sequence production (DSP) performance.

4.3. Methods

4.3.1. Participants

Twenty-eight individuals were recruited to participate in the study and divided into two groups: 14 individuals in the external focus of attention instructions (20.1 ± 2.5 years of age; 3 males) and 14 individuals in the internal focus of attention instructions (20.4 ± 2.3 years of age; 3 males). All the participants were right-handed with no history of neurological or psychiatric conditions and met the safety criteria as described by Rossi, Hallett, Rossini, and Pascual-Leone (2009). All participants provided written informed consent; the Institutional Review Board of the University of Michigan Medical School (IRBMED) approved the study protocol.

4.3.2. Experimental design

Participants were seated with the fingers of their right hand resting on the “V”, “B”, “N” and “M” keys. The relevant keys were covered with colored tape (Figure 4.1A). Participants memorized an explicit 12-item sequence (Figure 4.1B) delivered using instructions to stress either an external or internal focus (Figure 4.1C). Participants practiced the sequence 48 times (two blocks of 24 trials). For each sequence, practiced SAI was elicited at three time points during the sequence (see Table 4.1). Each point corresponded to just prior to index finger movement (SAI-0) or the movement immediately preceding index finger movement (SAI-1) or two movements prior to index finger movement (SAI-2).

A



B

Focus	Sequence
External	Green - blue - red - yellow - blue - green - red - blue - yellow - red - green - yellow
Internal	Ring - pinky - index - middle - pinky - ring - index - pinky - middle - index - ring - middle

C

Focus	Instructions
External	Position your fingers over the keys that are covered with tape. A black cross will be flashing on the computer monitor in front of you which indicates the speed of the <u>key presses</u> you have just memorized.
Internal	Position your fingers over the keys that are covered with tape. A black cross will be flashing on the computer monitor in front of you which indicates the speed of the <u>finger movements</u> you have just memorized.

Figure 4.1. The discrete sequence production task (DSP).

A. Position of the fingers on the keyboard. The keys were colored for the external focus group, but all of them were covered with white tape for the internal focus group. The dotted arrows indicate the corresponding position of the fingers and are used for illustration purposes but were not present in the actual set-up. B. Sequences practiced by each instruction group. Although the sequence was worded differently, the item order is the same for both groups. C. Instructions for the two groups.

Table 4.1. Pseudo-randomization table for the relative timing of short-latency afferent inhibition (SAI) and sequence production during the discrete sequence production task (DSP).

Position	1	2	3	4	5	6	7	8	9	10	11	12
Trial 1	③	4	1	2	④	3	1	4	2	①	3	2
Trial 2	3	4	①	2	4	③	1	4	②	1	3	2
Trial 3	3	④	1	2	4	3	①	4	②	1	3	2
Trial 4	③	4	1	2	④	3	1	4	2	①	3	2
Trial 5	3	4	①	2	4	③	1	4	②	1	3	2
Trial 6	3	④	1	2	4	3	①	4	②	1	3	2

○ Single pulse stimulation

⊖ Paired-pulse stimulation

■ Index movement

Notes. The top row indicates the sequence position. Following rows show the alternation between stimulation type (i.e., paired or single). Stimuli can be timed with index movement/keypress of the red key (timing = 0) or earlier by one or two steps (timing = -1 or -2). The corresponding labels are SAI-0, SAI-1 and SAI-2.

4.3.3. Discrete sequence production task (DSP)

Participants learned and practiced a discrete sequence of 12 items using the index, middle, ring and little finger of the right hand (De Kleine & Verwey, 2009). The sequence used in this experiment is a second-order conditioning sequence (3-4-1-2-4-3-1-4-2-1-3-2). It followed a set of rules: no repetitions, same frequency for each cue (each cue occurs three times) and same first-order transition frequency (each cue is preceded by the other three cues only once) (Reed & Johnson, 1994).

Prior to practice, participants were assigned to one of the two types of instructions and were given 5 minutes to memorize the sequence printed on a sheet of paper. The sequence differed per their assigned group (see Figure 4.1B). The external group memorized a sequence that corresponded to the color of the keys of the keyboard placed in front of them (Figure 4.1A). Whereas, the sequence for the internal focus group was designed to provide participants with information about the movement of their fingers.

After this initial learning period, participants were tested on their knowledge of the sequence by reciting it aloud. Once they could repeat it a minimum of 8 out of 10 times without error, they were instructed to perform the sequence three times on the keyboard placed in front of them. Before the start of the practice, each group received different instructions as described in Figure 4.1C. Participants sat in front of a computer screen with their right hand positioned on a computer keyboard. The timing of the keypresses was guided by a cross flashing every 1200 ms on a computer screen placed in front of them. Participants performed the sequence of movements 48 times (two blocks of 24 sequences). This practice was combined with SAI; the specific timing between movements and stimuli is described in the 4.3.4. Short-latency afferent inhibition (SAI) section. Response time and position of the key (keycode) were recorded for each keypress. The

presentation of the crosses and recording of keypresses was controlled by an in-house program written in LabVIEW (National Instruments, Austin, TX).

4.3.4. Short-latency afferent inhibition (SAI)

Transcranial magnetic stimulation measures were derived using a MagVenture MagPro X100 stimulator with option and figure-8 coil (MCF-B70; Farum, Denmark). The coil was oriented tangentially to the scalp over the motor cortex with the handle at 45° to the midline in a posterior-lateral orientation. The current in the coil was delivered in the posterior-anterior (PA) orientation. The motor cortical hotspot was defined for the FDI and recorded using the Brainsight™ stereotactic coil guidance system (Rogue Research, Montreal, Quebec, Canada). Motor evoked potentials (MEP) were recorded using BioAmp coupled with a PowerLab 8/30 unit (AD Instruments, Colorado Springs, CO) connected to surface electrodes applied over the FDI and APB muscles (digitized at 5,000 Hz, amplified x 1000). The motor threshold was determined as the stimulator output that produced MEPs of 1 mV amplitude.

Peripheral stimulations were delivered with a stimulator box (DS-7A stimulator; Digitimer, Welwyn Garden City, England). The bar electrode was applied over the median nerve of the right arm, about 2 cm above the crease of the wrist skin with the cathode located distally. Individual square-wave pulses of 0.5 ms duration and 150 mV were delivered at an intensity sufficient to elicit a visible muscle twitch in the APB, also defined as the motor threshold.

TMS pulses were delivered alone (single pulses) or preceded 21 ms earlier by a peripheral stimulation pulse (paired pulses) (Tokimura et al., 2000). The resulting MEPs were recorded for single and paired stimulations. SAI was calculated as the ratio of the peak-to-peak amplitude of the MEPs for paired pulses to single pulses expressed as a percentage.

Baseline SAI was assessed before DSP practice with the delivery of 24 single and 24 paired pulses. After DSP practice, the baseline was reassessed using the same protocol.

During practice, three single or three paired pulses were delivered during each trial (see Table 4.1). The type of stimulation was alternated every trial. The stimuli were delivered 250 ms prior to the flashing cross in a predefined pattern described in Table 4.1. This pattern was repeated four times per block (for a total of 24 sequences per block). If the stimulus occurred immediately before index movement, the SAI was labeled as SAI-0. When the index movement took place one or two movements later, the trials were classified as SAI-1 or SAI-2 respectively.

4.3.5. Data analysis

Separate mixed-measure ANOVAs were carried out to examine the effect of block (block 1, block 2) and focus (external, internal) on reaction time and accuracy. Block was treated as a repeated measure while the focus was entered as a between groups variable. Reaction time was defined as the time between the appearance of the cross and the keypress. The measure of accuracy was done by comparing the key pressed and the key that should have been pressed during the performance of the DSP.

The SAI analyses were conducted in three steps. First, the absence of difference of SAI at rest was assessed by running a block (pre, post) by focus (external, internal) mixed-measure ANOVA. Second, the reduction of SAI during movement (i.e., movement-related gating) was assessed using a block (pre, block 1, block 2, post) by focus (external, internal) mixed-measure ANOVA. For this analysis, SAI within block 1 and block 2 was averaged across delays (i.e., SAI-0, SAI-1 and SAI-2). Focus was treated as a between-subject factor. Block was treated as a repeated factor. Third, data obtained at each delay were analyzed separately to measure the effect of foci at different levels of movement preparation. Differences in FDI SAI across instructions

during DSP performance were assessed with separate focus (external, internal) by block (block 1, block 2) mixed-measure ANOVAs for each relative position in the sequence (i.e., this analysis was done separately for SAI elicited at different delays between stimulation and FDI response: SAI-0, SAI-1, SAI-2). The focus was treated as a between-subject factor. Block was treated as a repeated factor. The three ANOVAs were corrected for multiple comparisons using the modified Bonferroni correction (Keppel & Wickens, 2004).

To assess the specificity of SAI, the same focus (external, internal) by block (block 1, block 2) mixed-measure ANOVA was repeated for the APB at SAI-0.

4.4. Results

4.4.1. Discrete sequence production performance

Reaction times improved from block 1 to block 2 of sequence performance, as shown by a main effect of block: $F(1,26) = 49.02, p < .0001$ (Table 4.2). However, improved performance was not different across groups as neither the main effect of focus, $F(1,26) = 0.19, p = .671$, nor focus by block interactions, $F(1,26) = 2.01, p = .168$, were significant.

Accuracy was not impacted by either focus group or block. The corresponding two-way analysis for accuracy failed to reveal any significant main effects (block: $F(1,26) = 0.29, p = .595$; focus: $F(1,26) = 1.06, p = .312$) or focus by block interaction ($F(1,26) = 4.07, p = .054$) (Table 4.2).

4.4.2. Short-latency afferent inhibition (SAI) at rest

Baseline SAI, in the absence of the DSP task was not different across focus groups. Neither the main effects (focus: $F(1, 26) = 0.08, p = .777$); block: ($F(1,26) = 0.79, p = .381$), nor the focus

Table 4.2. Reaction time and accuracy during the discrete sequence production task (DSP).

Instructions	External		Internal	
Block	Block 1	Block 2	Block 1	Block 2
Reaction Time (ms)	410 ± 99	326 ± 84	411 ± 111	356 ± 110
Percentage Correct	96 ± 4	97 ± 3	98 ± 2	98 ± 4

Note. Results presented are: mean ± standard deviation.

by block interaction: $F(1, 26) = 0.68, p = .416$) for SAI collected at rest before or after practice were significant (Table 4.3).

4.4.3. Short-latency afferent inhibition (SAI) during discrete sequence production (DSP)

The block (pre, block 1, block 2, post) by focus (external, internal) mixed measure ANOVA revealed that there was a significant main effect of block, $F(3,75) = 15.15, p < .0001, \eta^2 = .36$, but no significant interaction between block and focus on SAI results.

At SAI-0, SAI was significantly reduced for the external compared to the internal group regardless of performance block with a main effect of focus: $F(1,26) = 5.89, p = .02, \eta^2 = 0.24$ (Figure 4.2). For SAI-1 there was a significant focus by block interaction $F(1,26) = 5.63, p = .025, \eta^2 = 0.17$. The interaction was driven by the emergence of a difference across foci during block 2. Although there was no difference between focus groups in block 1, SAI decreased from block 1 to block 2 for the external group but increased from block 1 to block 2 for the internal group (Figure 4.2). There were no significant effects for SAI-2.

For the APB, there were no differences in SAI-0 across focus or block as neither the focus by block interaction ($F(1,25) = 0.42, p = .52$) nor main effects (focus: $F(1,25) = 0.10, p = .75$; block: $F(1,25) = 1.28, p = .27$) were significant (Figure 4.3).

4.5. Discussion

The current study investigated differences in SAI during the motor performance of an explicit discrete sequence under different foci of knowledge. As expected, SAI in the FDI was reduced just prior to movements involving the index finger regardless of whether instructions stressed the finger to be moved (internal focus) or the key to be pressed (external focus). Reduced

Table 4.3. Baseline short-latency afferent inhibition (SAI) in the absence of behavioral task.

Instructions	External		Internal	
Block	Pre	Post	Pre	Post
Percent of Unconditioned	55 ± 25	58 ± 39	43 ± 25	60 ± 61

Notes. SAI elicited with the participant at rest before and after discrete sequence production (DSP) performance. Results presented are: mean \pm standard deviation.

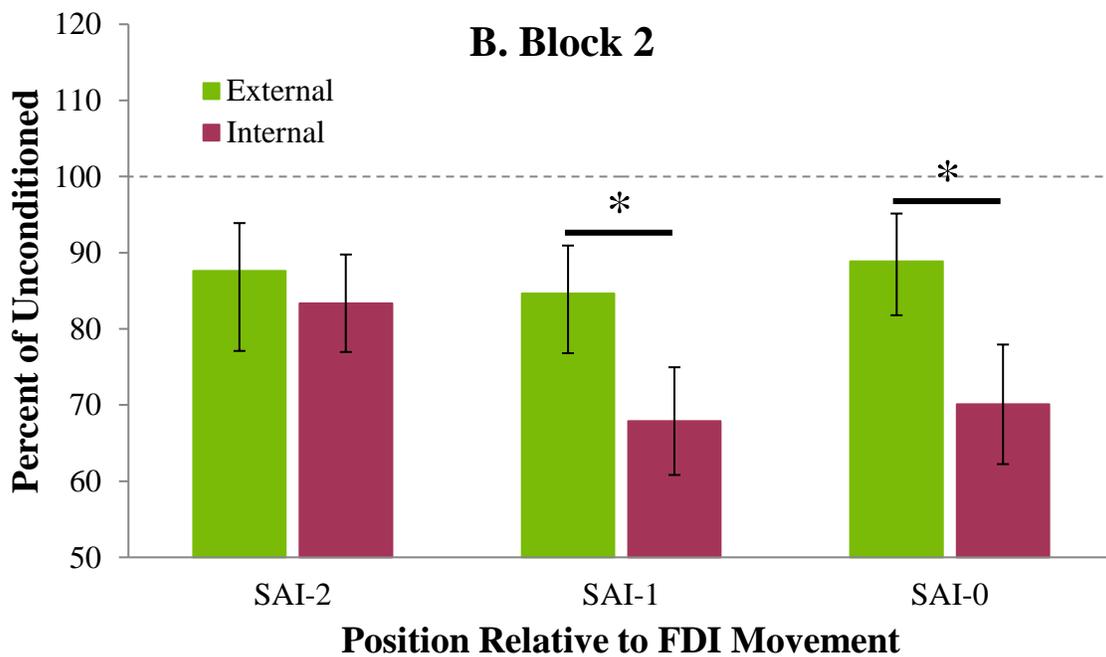
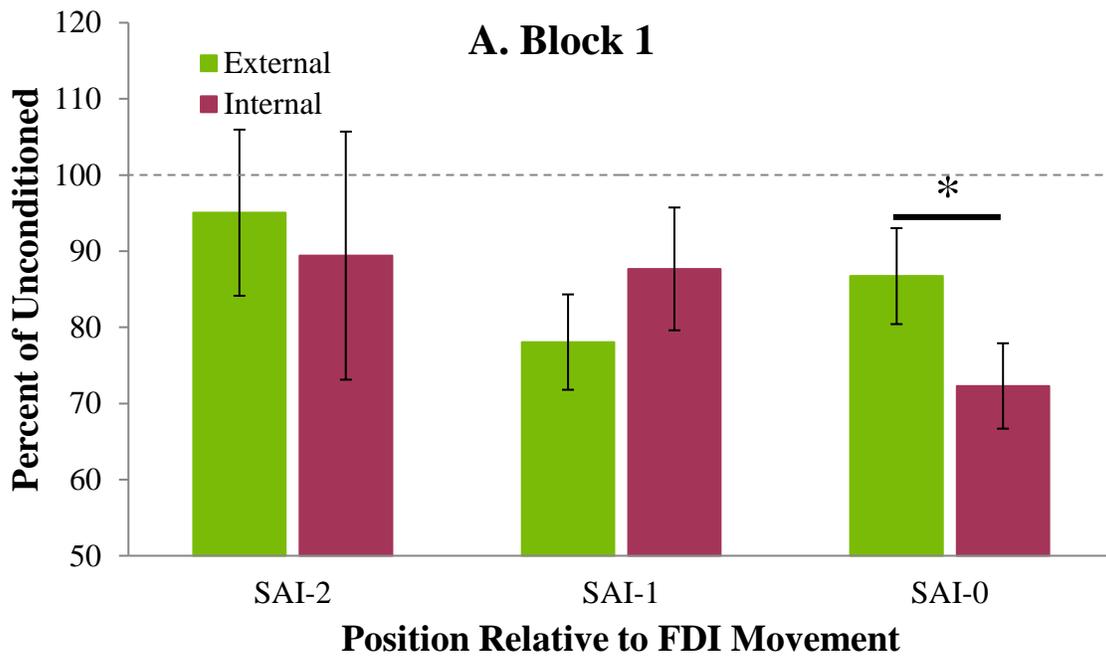


Figure 4.2. Short-latency afferent inhibition (SAI) during discrete sequence production task (DSP).

A. Block 1 of practice. B. Block 2 of practice. The results are split by delay between stimuli: SAI-2 (delay of two movements between stimulus and index movement), SAI-1 (delay of one movement) and SAI-0 (no delay). Error bars represent the standard error of the mean. * denotes $p < .05$.

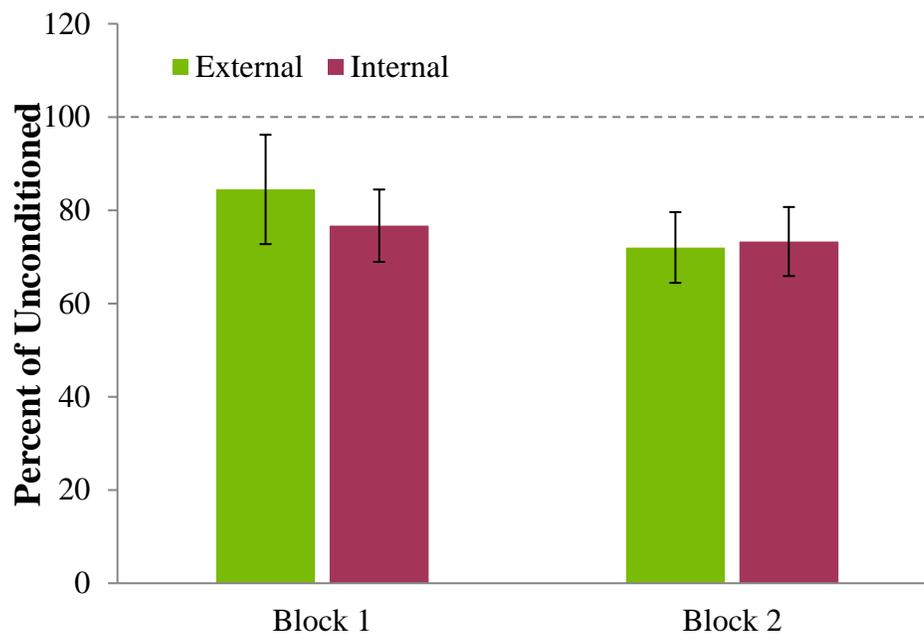


Figure 4.3. Short-latency afferent inhibition (SAI) measured in the abductor pollicis brevis (APB) at SAI-0.

Note. Error bars represent the standard error of the mean.

SAI in the FDI persisted one to two elements prior to index finger movement. In addition to a generalized reduction in SAI, the internal versus external nature of the explicit knowledge differentially impacted SAI depending upon the relative position of the index finger keypress in the discrete sequence. When the index finger key response was imminent (SAI-0), SAI was weaker for the external compared to internal focus group across both performance blocks. The instruction difference was specific to the targeted FDI muscle and was specific to DSP performance. As participants gained more experience performing the discrete sequence the group difference in FDI SAI emerged during movement preparation of the preceding element, an element that did not involve the index finger/key (SAI-1). The emergence of internal-external difference at SAI-1 was driven by a reduction in SAI for the external focus group but an increase in SAI for the internal focus group from performance of block 1 to block 2.

At rest, the level of SAI in the current study was comparable to previous reports SAI elicited using similar parameters (Ferreri et al., 2012; Tokimura et al., 2000). Likewise, the reduction in SAI, regardless of instruction, when index finger movement was imminent (SAI-0) is consistent with past work demonstrating reduced SAI prior to movement onset (Asmussen et al., 2013; Asmussen et al., 2014; Voller et al., 2006). The magnitude of SAI is positively correlated with the intensity of peripheral stimulation, thought to index the strength of the somatosensory volley induced by the peripheral stimulation (Bailey et al., 2016). Therefore, the reduction in SAI preceding impending muscle contraction is hypothesized to represent the suppression of somatosensory afference during ballistic movement, a process called movement-related inhibition (Cohen & Starr, 1987; Tapia, Cohen, & Starr, 1987). While SAI is reduced in the muscle to be moved, SAI is generally reported to be enhanced for muscles not involved in the ballistic movement (Asmussen et al., 2014; Dubbioso et al., 2017; Voller et al., 2006). The pattern of

reduced inhibition for the task-relevant muscle coupled with maintenance of inhibition of the task-irrelevant muscle is suggested to be a surround inhibition mechanism to promote fractionated effector control by preventing unintended spill-over of excitability into surrounding muscle representations. For sequence elements not involving index finger keypresses, I would have expected stable or increased SAI. One explanation for the absence of a surround inhibition-like mechanism in the FDI across the discrete sequence is that explicit knowledge of the sequence promoted links across effectors making all effectors task-relevant. In fact, the DSP consists of a series of ballistic movements where each movement influences the sequential timing of the subsequent movement. Whereas, past work involved isolated discrete ballistic contraction of the FDI in the absence of a task where the remaining muscles of the hand were never required to be contracted or systematically linked to the movement of the other effectors (Asmussen et al., 2013; Asmussen et al., 2014; Voller et al., 2006). Therefore, a degree of movement-related gating may be present across the whole sequence of the DSP in addition to a specific element within the sequence.

The current study is the first to directly measure inhibitory function in the sensorimotor cortex during motor performance depending upon the nature of explicit knowledge (Wulf, 2013). My results demonstrate that the focus of attention shapes sensorimotor circuits above and beyond any generalized effects associated with the movement itself. An external focus of attention is thought to benefit skilled actions by minimizing constraints on the motor system and promoting automaticity (McNevin et al., 2003; Wulf, McNevin, & Shea, 2001). A previous study that investigated the neural basis of attention focus demonstrated BOLD response increases in the primary somatosensory and primary motor cortices (Zentgraf et al., 2009). The increase sensorimotor BOLD response was interpreted as evidence for enhanced processing of tactile input

of the response keys under an external focus of attention. However, the BOLD response cannot differentiate between facilitatory and inhibitory processes as they are both metabolically demanding. Hence, this increased BOLD response could be due to the cortical recruitment of inhibitory networks responsible for movement-related gating.

With practice, reduced SAI in the external compared to internal instruction group appeared earlier in the discrete sequence. The instruction difference was driven by divergence in SAI across the internal and external groups at SAI-1. The changes in SAI, coupled with a general improvement in performance regardless of instruction, suggest that both groups accrued skill across performance trials, but that skill acquisition was driven by a different neurophysiology. The increase in SAI for the internal group is consistent with an attention effect, where directing spatial attention to body part enhances somatosensory afference (Staines, Brooke, & McIlroy, 2000). Since SAI is known to scale the intensity of the strength of peripheral stimulation intensity (Bailey et al., 2016), intrinsic allocation of spatial attention would mitigate movement-related gating and lead to increased SAI. The increased SAI-1 for the internal group would be consistent with the extension of spatial attention to the subsequent effector in addition to the current effector. In contrast, the relative reduction in SAI for the external group is consistent with the development of an implicit movement-related gating mechanism to promote automaticity rather than a cognitively demanding continual shifting of spatial attention across effectors. Such an interpretation is consistent with a prominent psychomotor model of DSP performance, the dual-processor model. The dual-processor model posits that two systems, a cognitive processor and a motor system, support DSP (Abrahamse, Ruitenberg, De Kleine, & Verwey, 2013). During execution of an explicit but still novel sequence, the cognitive processor must load each element of a sequence to be executed to the motor system based upon sensory or cognitive cues. Each element of the sequence is triggered

independently of the preceding or subsequent response. As a sequence becomes more automated with practice, the cognitive processor begins to pre-load multiple movements or “chunks” into a motor buffer (Verwey, 1999). Subsequent movements are primed through integration with the previous response. The reduction of SAI in the external group is consistent with the chunking account of the dual-processor model, while the increase in SAI for the internal group is consistent with increased exploitation of sensory/cognitive cues by the cognitive processor. One question that remains to be addressed is whether the absence of an effect of focus on performance in the current study is due to the discrete nature of the DSP, resulting in the relative ease to implement either strategy. Interestingly, the majority of tasks that benefit from an external focus involved continuous balance (Wulf et al., 1998) or continuous upper limb skills such as a full golf swing (Wulf et al., 1999) or basketball free throw (Zachry et al., 2005). An internal focus of attention may compromise the strategies employed for these complex tasks but might be beneficial for discrete ballistic tasks involving button presses or short, quick movements, such as the one employed in the current study. One caveat is tied to skill level, where novice performers may benefit from an internal focus of attention by reducing degrees of freedom of the skill during early practice (Perkins-Ceccato et al., 2003).

One limitation of the current study is that I did not quantify chunking across the practice. Common practice is to define chunks as a cluster of rapid responses following a slower response (Sakai, Kitaguchi, & Hikosaka, 2003). However, two issues confounded any measure of chunking from my data. First, I had a limited number of sequence trials in each block. Second, suprathreshold TMS stimuli, necessary to elicit MEPs in the FDI, may have also potentially disrupted the measure of chunking by introducing involuntary movements. Future studies should include sham stimulation trials to obtain unconfounded responses times to establish differences in chunking and

correlate the extent of chunking to changes in SAI across groups. In addition, the prediction about the benefit of the external focus of attention based on my physiological results should be tested with tasks involving more complex movements.

Overall, my results show that the focus of attention alters processing in sensorimotor pathways. In the external group, reductions in PA SAI are consistent with increased movement-related gating, a signature of movement preparation and execution that occurred increasingly earlier from movement onset for the task-relevant muscle with practice. The preservation of PA SAI for a task-irrelevant muscle suggests that this phenomenon is effector-specific. Therefore, the reduction in PA SAI during the execution of an explicit discrete sequence may reflect the general benefit of adopting an external focus of attention.

CHAPTER 5 – General Discussion, Limitations and Conclusions

5.1. General discussion

The overall objective of this thesis was to assess the influence of working memory engagement upon motor cortex physiology in an effort to identify potential substrates of declarative-procedural interactions during skilled motor performance. The studies described in Chapter 2 to 4 investigated how the procedural memory system is affected by the use of explicit knowledge unrelated (Chapter 2 and 3) or related to a motor task (Chapter 4). In addition, declarative memory was shown to affect the circuit targeted by both posterior-anterior and anterior-posterior currents short-latency afferent inhibition (PA and AP SAI; Chapter 3).

In the first two studies (Chapter 2 and 3), the declarative-procedural interactions were investigated in the context of the perceptual load theory by changing the level of working memory engagement. Under this approach, the working memory task was task-relevant while somatosensory afference was task-irrelevant. The perceptual load theory predicts that greater attentional load needed for the performance of the task leads to greater suppression of task-irrelevant stimuli, which was confirmed by a previous study involving tactile stimuli (Dalton, Lavie, & Spence, 2009). Conversely, greater working memory load is thought to result in the breakdown of executive functions and attention-mediated control of sensory gating, which in turns allows the processing of irrelevant stimuli. Therefore, increased working memory is believed to lead to increased salience of distractors. Consistent with the perceptual load theory, the efficacy of

theta burst stimulation (TBS) to induce motor cortical plasticity was reduced in Chapter 2 when attentional perceptual demands were greatest (i.e., encoding a six-digit compared to two-digit memory set), hypothetically because the task-irrelevant somatosensory stimulus is suppressed to a greater extent. In contrast, when working memory load was greatest (i.e., maintaining the six-versus two-digit memory set) plasticity induced by TBS was greater. In sum, plasticity in the motor areas of the brain was sensitive to cognitive load. This sensitivity may underlie the important relationship between working memory abilities and the ability to learn new skills or adapt existing skills to changes in the environment. Future studies to understand the functional consequences of the interaction between cognitive load and motor cortex are needed. These studies should address how differing practice structures, instructions and feedback change working memory demands and subsequently the potential for brain reorganization.

Chapter 2 demonstrated that the engagement of working memory during the maintenance phase of the Sternberg task affects the potential for plasticity of the motor cortex, but it did not provide insight into the underlying circuits altered by cognitive load. Therefore, in Chapter 3, I used SAI, a technique that allowed me to test sensory to motor circuits that converge on the motor cortical output neurons projecting to the spinal cord (Ferreri et al., 2012; Tokimura et al., 2000). Within the motor cortex, two anatomically distinct sensorimotor circuits were targeted by changing the current direction of the single pulse transcranial magnetic stimulation (TMS) used in SAI (Mirdamadi et al., 2017; Ni et al., 2011). These circuits are referred to as the PA and AP SAI circuits, where the name denotes the current direction of the monophasic TMS single pulse that is paired with the peripheral electrical stimulation in the SAI protocol. A greater ability to recruit AP in some individuals has been linked to a greater efficacy of TBS to induce plasticity (Hamada, Murase, et al., 2012). The same correlation was not found with PA circuits (Young-Bernier,

Tanguay, Davidson, & Tremblay, 2014). Based on the relationship between the AP circuit and TBS plasticity, and my results from Chapter 2, I had predicted that AP SAI would be altered by the same Sternberg working memory task used in Chapter 2. Further, I hypothesized that AP SAI would be enhanced under high working memory loads due to the breakdown in control of attention-related sensory gating that would allow greater sensory afference to reach motor cortex (Mirdamadi et al., 2017) making it more amenable to plasticity (Hasan et al., 2012; Siebner, 2010). Both PA and AP-sensitive circuits were affected by the working memory load. Greater AP circuit excitability is positively correlated with greater TBS-induced plasticity (Hamada, Murase, et al., 2012). Despite the fact that the AP-sensitive circuit is generally predictive of the type of increased responsiveness to the TBS protocol observed in Chapter 2, the excitability of the AP-sensitive circuit decreased during 6-digit maintenance (Chapter 3). This pattern of results suggests the working memory effects observed in Chapter 3 do not govern the plasticity changes I observed in Chapter 2. Instead the changes in PA and AP SAI are more consistent with an action selection mechanism. PA SAI is known to contribute to the selection of specific muscles by releasing inhibition of muscles about to contract while inhibiting surrounding task-irrelevant muscles to prevent unwanted contractions (Asmussen et al., 2013; Asmussen et al., 2014; Dubbioso et al., 2017; Voller et al., 2006). Although there has been no direct study of AP SAI change during movement phase, the sensitivity of AP SAI to both working memory (Chapter 3) and attention (Mirdamadi et al., 2017) suggests that this relatively more complex circuit may play a role in both selecting action as well as modulating the selected action.

Chapter 4 represented a change of paradigm from engaging working memory to exceed its capacity, to engaging working memory as part of a motor task. In Chapters 2 & 3, working memory was manipulated using a dual-task like paradigm where a distractor task drew away resources away

from intrinsic processes, which are at the origin of procedural system reorganization. In Chapter 4, I investigated the role of PA SAI when cognitive demands were altered in a task-relevant manner. Specifically, I was interested in understanding how different declarative strategies might influence activity in the networks recruited by PA stimulation during explicit discrete sequence production. Within the framework of “Attentional Focus” (Wulf, 2013), I demonstrated that learning the sequence according to fingers to be moved (internal group) versus learning based on the key location (external group) had differential impacts upon PA SAI. The external strategy group consistently demonstrated less PA SAI in the FDI just prior to pressing the key under the index finger. With increasing experience performing the sequence, the onset of decreased SAI occurred increasingly earlier in the sequence relative to the upcoming index finger keypress (i.e., SAI was reduced not only prior to index movement but also at a greater delay). Reduced PA SAI just prior to movement onset is what I expected given past work (Asmussen et al., 2013) while the increasingly earlier onset of this activity suggests increasing proceduralization of the discrete sequence through chunking. Interestingly, anticipated performance differences between the internal and external groups did not materialize. It is possible that the internal group learned differently. I believe the elevated level of PA SAI at movement finger onset is indicative of attention enhancement of somatosensory afference associated with focusing upon the finger rather than the response key. Further, I believe that the earlier onset of this activity in the internal group represents a pre-emptive shift of attention towards the next finger in the sequence during sequence production.

An increased attentional boost of somatosensory afference by an internal focus is at odds with the traditional intentional reduction of expected somatosensory afference associated with feedforward motor control. This reduction, known as movement-related gating, is believed to be

the underlying cause of reduced PA SAI during movement preparation. The pre-emptive shifting of attention suggested by my PA SAI results in the internal focus group suggests this group is invoking a cognitively demanding strategy to shape motor control. The absence of a behavioral consequence is likely attributed to the discrete nature of the keypress sequence. A cursory review of the attention focus literature suggests that the benefits of an external, compared to internal focus, become greater the more complex the movement. It appears that shifting attention from muscle to muscle works during discrete tasks with minimal degrees of freedom and small isolated muscle groups. In such simple tasks, overemphasizing a given muscle through attention-boosting is viable. By contrast, more complex, continuous skills requiring larger muscle synergies are potentially penalized by shifting cognitive resources from muscle to muscle. Such shifts may over-emphasize the muscle of focus at the expense of the larger synergy. The changes in PA SAI in the external group are reflective of increased automaticity and proceduralization of these synergies.

5.2. Limitations

Although this dissertation is the first to demonstrate that the engagement of working memory has an impact on the physiology of the procedural memory system there are a number of limitations that need to be acknowledged.

One limitation of the study presented in Chapter 2 is that the timing of the Sternberg working memory task did not allow for uniform conditions during the stimulation of post-pulses. In fact, during the encoding and the maintenance, the end of the task occurred at 4 s and 2 s post-TBS respectively. One option would have been to delay the motor response until all physiological measures are completed. Another issue is the difference between encoding and maintenance physiological measures as they are shifted in relation to the task (i.e. the point of reference in my

study is the end of TBS but not the relative timing with the task). Although, it is possible to remove this shift by simply using the task as a reference, doing so would create a new confounding factor: the timing in relation to the end of TBS.

In Chapter 3, the separate samples between experiment 1 and experiment 2 limit the comparison between SAI and SEP results as it would have been beneficial to correlate SEP amplitude and level of SAI obtained in the same individuals. However, due to the length of each experiment, it would have been necessary to run the experiments during two separate days, which in itself could have introduced intra-individual differences. To limit differences, it would help to run the experiments at the same time of the day for each participant.

Both Chapter 2 and Chapter 3 are limited by the fact that the working memory was part of a distractor task but was not part of the motor task. The studies of my dissertation are nevertheless a step towards determining that there is a connection between the declarative and the procedural memory systems that can be directly measured in the motor cortex. Future studies will need to investigate how this interaction occurs and in which case it is beneficial or detrimental.

Another limitation of the Chapters 2 and 3 is the lack of assessment of individual differences in terms of working memory capacities, which could explain some of the variability observed in Chapter 3. Without such assessments, it is possible that the influence of inter-individual variability remains unaccounted. However, the participants performed both loads of working memory in an intra-individual design, therefore limiting the impact of inter-individual differences.

In the last study, one limitation is that I did not assess the number and type of explicit rules formed by the participants. It would have allowed me to verify that individuals assigned to the

external and internal groups had different types of knowledge. In addition, it would have allowed me to quantify their use of working memory more adequately.

Measure of chunking would have also been informative, but performance was disrupted by the involuntary twitches caused by the TMS stimulation. The use of sham stimulation would allow to obtain measures not disrupted by twitches but I would not obtain physiological measures. Alternatively, I could have run more participants, who would have been assigned to a sham or an active stimulation group but it would have resulted in an inter-individual design which would have limited the comparison between behavioral and physiological measures.

Another limitation of the study from Chapter 4 is the relative simplicity of the task and the lack of behavioral differences. A more complex task might have been more suited to highlight the benefit of an external focus but motion needs to be limited during stimulation with TMS to ensure that the same area of the brain is stimulated. It might be possible to use other motor tasks using a better stereotactic system that more easily compensate for participants' movements.

5.3. Conclusion

Overall, the three studies presented in Chapters 2, 3 and 4 highlight changes in motor cortical physiology associated with elements of declarative memory. Moving forward, the current work is an important catalyst for future work that will seek to determine how some declarative strategies bootstrap procedural learning and prevent the establishment of optimal kinematics and dynamics, leading to a sub-optimal performance in healthy and clinical populations.

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